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Individualised Anaesthesia and Analgesia in Surgery

Mogianos, Krister

2026

Document Version:

Publisher's PDF, also known as Version of record

[Link to publication](#)

Citation for published version (APA):

Mogianos, K. (2026). *Individualised Anaesthesia and Analgesia in Surgery*. [Doctoral Thesis (compilation), Department of Clinical Sciences, Malmö]. Lund University, Faculty of Medicine.

Total number of authors:

1

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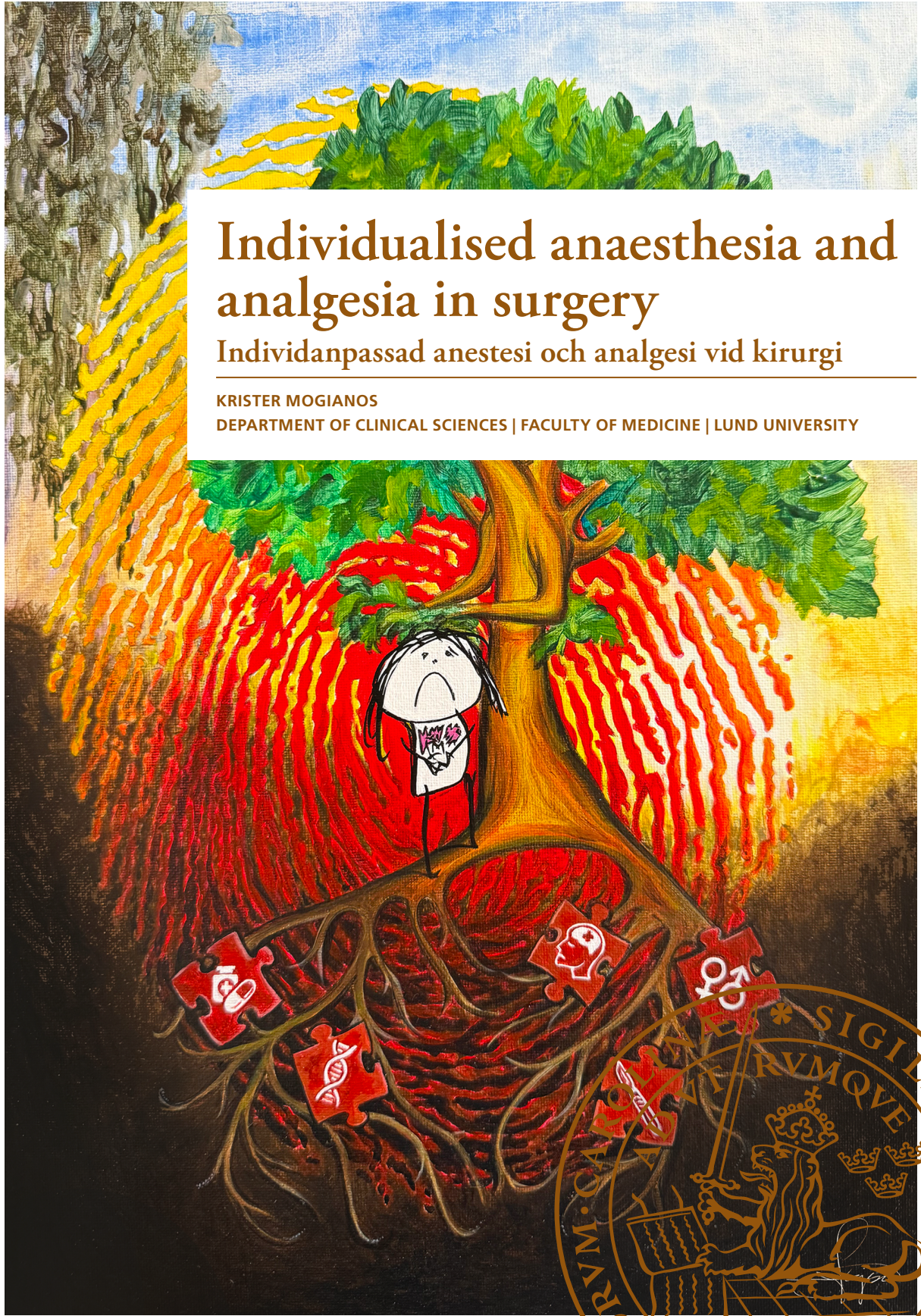
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Individualised anaesthesia and analgesia in surgery

Individanpassad anestesi och analgesi vid kirurgi

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FACULTY OF MEDICINE

Department of Clinical Sciences

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2026:111

ISBN 978-91-8021-909-9

ISSN 1652-8220



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Krister Mogianos



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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on Friday 2nd of October 2026 at 09.00 in Beartling's Hall, Department of Clinical Sciences Malmö.

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Organization: LUND UNIVERSITY

Document name: Doctoral dissertation

Date of issue 2026-10-02

Author(s): Krister Mogianos

Sponsoring organization:

Title and subtitle: Individualised anaesthesia and analgesia in surgery: Individanpassad anestesi och analgesi vid kirurgi

Abstract:

Background: The idea of individualised patient care is not new, and there is a growing trend in perioperative medicine to integrate individualised approaches. However, no evidence-based recommendations currently exist for individualised perioperative care. This doctoral thesis aims to develop the concept of individualised anaesthesia and analgesia in surgery, focusing on pharmacological interventions based on individual risk, while also introducing a broader framework for personalised perioperative care that may complement and strengthen existing enhanced recovery recommendations.

Methods: Predicting pain in surgical patients requires structured methods and solid evidence to guide clinical decision-making. It is essential not only to identify patients at risk for postoperative pain but also to intervene accordingly. In these trials, patients who were risk-stratified for postoperative pain were randomised to different multimodal anaesthesia regimens or standard care, with the aim of achieving improved, or at minimum comparable, pain outcomes while also considering additional recovery benefits. We also investigated whether pain during venous cannulation could serve as a simple preoperative tool to predict postoperative pain vulnerability. Lastly, this work provides preliminary support for future studies examining whether real-time processed electroencephalography could contribute to more individualised perioperative management, both within validated anaesthesia protocols and in the growing area of opioid-free anaesthesia.

Results: The thesis' findings indicate that individual pain prediction is well-studied. However, of all the studied methods, only a few might be ready for patient stratification in clinical trials. For high-risk patients, adding esketamine and clonidine did not improve outcomes. Opioid-free anaesthesia is feasible for low-risk patients, and was non-inferior to standard of care, but did not enhance recovery outcomes. Pain assessment during venous cannulation can predict acute postoperative pain in the "unadjusted" real-life patient but was influenced by gender and the intensity of current preoperative pain at the day of surgery. Patients under general anaesthesia with opioid-free protocols and real-time electroencephalography monitoring showed different quantitative values and power spectrograms compared to routine anaesthesia.

Conclusion: This thesis identifies knowledge gaps in terms of methods for individual preoperative pain prediction. However, some methods that are pragmatic and promising might be ready to test in clinical trials. Multimodal anaesthesia regimens are key to improving pain outcomes for patients at varying risks. Although the clinical trials did not show significant benefits, other factors beyond receptor modulation need exploration for enhanced outcomes. Some unexplored aspects of individualised anaesthesia and analgesia might unlock opportunities to further enhance perioperative outcomes. Processed electroencephalography can be used in opioid-free anaesthesia, but different target values should be expected compared to routine methods.

Key words: Acute postoperative pain, Individualised perioperative medicine,

Language English

ISSN and key title: 1652-8220

ISBN: 978-91-8021-909-9

Number of pages: 146

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Individualised Anaesthesia and Analgesia in Surgery

Individanpassad anestesi och analgesi vid kirurgi

Krister Mogianos



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Funding information: This work was financially supported by grants from the Scientific Council, Region Halland, Southern Health-Care Region and Sparbanksstiftelsen.

Cover image by: Kajsa Henricsson

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Published by:

Department of Clinical Sciences

Faculty of Medicine

Lund University

ISBN 978-91-8021-909-9

ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University, Lund 2026



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MADE IN SWEDEN 

*For my copper-crowned trio, whose
brilliance outshines any thesis*

Table of content

List of Papers	9
Other manuscripts related but not included in the thesis	10
Abstract	11
Populärvetenskaplig sammanfattning	13
Abbreviations	15
AI Statement	17
Introduction	18
The physiology of perioperative pain.....	18
Conduction of nociception.....	18
Neuromodulation of pain	21
Pharmacologic aspects of perioperative analgesia	25
Paracetamol	26
Peripheral de-sensitisation	27
Opioid receptor modulation	29
N-methyl D-aspartate (NMDA) receptor antagonism.....	30
Gabapentinoids	32
GABA _A -agonism	32
Alfa ₂ -agonism	32
Activation of descending pathways	34
Drug synergism and multimodal anaesthesia.....	35
Individualised aspects of pharmacologic management.....	36
Practical aspects of perioperative pain	38
Definition of acute and persistent postoperative pain	38
Nociception - the unconscious relative to pain	39
Individual preoperative prediction methods for postoperative pain	44
Demographic and lifestyle related	44
Psychometric analysis.....	49
Quantitative sensory testing.....	52
Procedural sensory testing	54
Real-time nociception monitoring	56
Serologic biomarkers	64
The concept of Individualised anaesthesia and analgesia in surgery.....	65
Predicting risk.....	66
Goals with care	67
Patient expectations	68

Aim.....	74
Ethical considerations	76
Patients and methods.....	79
Paper I	80
Methodological framework and Registration	80
Search strategy.....	80
Literature review.....	80
Paper II.....	82
Methodological framework.....	82
Study design and Setting	82
Eligibility criteria.....	82
Interventions	82
Outcomes	83
Sample size and Statistical analysis.....	84
Data Collection and Management.....	84
Allocation and blinding	84
Protocol Adherence and Monitoring.....	84
Paper III.....	86
Study design	86
Participants	86
Pain Sensitivity Assessment	86
Randomisation and Blinding	86
Anaesthetic Protocols	86
Outcome Measures	87
Statistical Analysis.....	87
Paper IV	88
Study design	88
Participants	88
Pain Sensitivity Assessment	88
Randomisation and Blinding	88
Anaesthetic Protocols	88
Outcome Measures	89
Statistical Analysis.....	89
Paper V.....	90
Study Design and Setting.....	90
Patient Selection and Grouping	90
Anaesthesia Protocols.....	90
Monitoring and Data Collection	90
Outcomes	90
Statistical analysis.....	91
Paper VI	92
Study Design.....	92
Patient Selection and Grouping	92
Anaesthesia Protocols.....	92
Outcome Measures	92
Statistical analysis.....	92

Results.....	94
Paper I	94
Psychometric methods	94
Quantitative sensory testing.....	95
Combined techniques of testing.....	95
Other techniques of testing	95
Genetic testing	96
Biochemical testing	96
Paper III.....	97
Condensed version of results from the study	98
Paper IV	99
Condensed version of results from the study	100
Paper V.....	101
Quantitative outcomes	101
Descriptive outcomes.....	102
Paper VI	103
Discussion	105
IAAS cornerstone: Individualised Pain Prediction -	
Current Limitations and Clinical Implications	105
Insights From the POPIT Trial: Stratification, Interventions, and Outcomes	106
Methodological Challenges in Risk Stratification and Prediction Tools.....	107
IAAS cornerstone: Pain as Predictive Processing -	
Expectations, Variability, and Clinical Relevance	109
IAAS cornerstone: Shared Decision Making and Patient -	
Centred Perioperative Care	111
Opioid Stewardship, Nociception vs Pain, and the Role of processed EEG	112
Conclusions.....	117
Future perspectives.....	119
Acknowledgements	123
References.....	125
Appendices, Paper I-VI	145

List of Papers

Paper I

Mogianos K, Åkesson J, KM Persson A. **Systematic review of methods for individual prediction of postoperative pain.** *Pain Research and Management* 2025; 2025: 1331412

Paper II

Mogianos K, Undén J, Persson A: **Effect of individualized anesthesia and analgesia on postoperative pain in patients stratified for pain sensitivity: A study protocol for the PeriOperative individualization trial randomized controlled trial.** *Acta Anaesthesiologica Scandinavica* 2024;68: 153¹2-40

Paper III

Mogianos K, Holgersson J, Undén J, KM Persson A. **The additive effect of esketamine and clonidine in patients at high risk for acute postoperative pain undergoing laparoscopic surgery: A randomised controlled trial.** *Journal of Clinical Anesthesia* 2026;108

Paper IV

Mogianos K, Holgersson J, Undén J, KM Persson A. **Opioid-free versus opioid-based anaesthesia and analgesia for patients at low risk for acute postoperative pain undergoing laparoscopic surgery: A randomised controlled trial.** *Journal of Clinical Anesthesia.* 2026;108

Paper V

Mogianos K, KM Persson A. **Anesthesia depth monitoring during opioid free anesthesia – a prospective observational study.** *BMC Anesthesiology* 2025; 25: 37

Paper VI

KM Persson A, Mogianos K. **Venous Cannulation Pain as a Marker of Postoperative Pain Vulnerability: A Pre-specified Secondary Analysis of a Randomized Controlled Trial.** *Journal of Personalized Medicine* 2026; 16, 1, s. 1-13

Other manuscripts related but not included in the thesis

Paper I

Mogianos K, KM Persson A. **The role of intraoperative real-time nociceptive monitoring in individualised anaesthesia and analgesia and where to head next; A narrative review.** *Journal of Clinical Anesthesia* 2026; 110, 112162

Paper II

Mogianos K, KM Persson A. **A Conceptual Framework for Understanding Patient Expectations in Individualised Anaesthesia and Analgesia: A Narrative Review and Future Directions.** *Journal of Personalized Medicine* 2026; 16 (4), 191.

Paper III

Mogianos K, KM Persson A. **Individualised anaesthesia and analgesia in surgery: a conceptual framework for improving postoperative pain.** *British Journal of Anesthesia* 2026

Abstract

Background: Acute and persistent postoperative pain (APOP, PPOP) are common and burdensome for patients and healthcare systems. Traditionally, perioperative care has focused on the surgical procedure rather than individual risk factors for postoperative pain. Thus, there is a growing demand and trend in perioperative medicine to integrate individualised approaches. It is essential to not only identify patients at risk for postoperative pain but also to intervene accordingly.

Aim: Overall, this doctoral thesis aims to develop the concept of Individualised Anaesthesia and Analgesia in Surgery, with specific focus on pharmacological interventions based on individual risk for postoperative pain.

Methods: In Paper I, a systematic review was conducted to compile evidence on preoperative pain prediction at the bedside. Paper II describes the methodology used in a randomised controlled trial in which patients who were risk-stratified for postoperative pain were allocated to different anaesthesia and analgesia strategies. In Paper III, patients at high risk of postoperative pain were randomised to multimodal opioid-based with additive esketamine and clonidine (EC) or to standard of care (SOC). The primary outcome was APOP in the post-anaesthesia care unit (PACU) and secondary outcome included APOP at 24 h, early recovery, opioid consumption, postoperative nausea and vomiting (PONV) as well as persistent postoperative pain (PPOP) at 3 and 6 months respectively. In Paper IV, patients at low risk of postoperative pain were randomised to opioid-free anaesthesia (OFA) or SOC, with outcomes identical to those in Paper III, but with a non-inferiority design. In Paper V, patients were observed prospectively with perioperative processed electroencephalography (pEEG). They were grouped according to the anaesthesia strategy used: OFA or SOC, the latter with either total intravenous anaesthesia (TIVA) or volatile anaesthesia. In Paper VI, the primary focus was to evaluate pain assessment during venous cannulation (VCP) as a preoperative prediction method for APOP and PPOP, and to examine its association with other preoperative risk factors. This was performed as a pre-specified *post hoc* analysis of the trial described in Paper II.

Results: (I) Qualitatively, individual pain prediction is well-studied. Generally, no single predictive method is sufficiently accurate to forecast postoperative pain. However, some methods may be suitable for use in interventional clinical trials.

(III) There was no difference in APOP (difference in NRS 0.2, 95% CI -0.8 - 1.1, $p = 0.78$), APOP at 24 h ($p = 0.35$), PONV ($p = 0.80$), opioid consumption ($p = 0.47$), early recovery ($p = 0.92$) or PPOP ($p = 0.72$, $p = 0.12$) between patients randomised to EC or SOC.

(IV) Similarly, there was no difference in APOP (difference in NRS 0.1, 95% CI -0.8 - 1.2, $p = 0.67$), APOP at 24 h ($p = 0.11$), PONV ($p = 0.52$), early recovery ($p = 0.44$) or PPOP ($p = 0.52$, $p = 0.72$) between patients randomised to OFA or SOC. However, there was a difference in opioid consumption (difference in intravenous morphine milligram equivalents 1.7 mg, 95% CI 0.1 – 3.4, $p = 0.04$) between OFA and SOC.

(V) Quantitative variables for pEEG were significantly different between OFA, TIVA and volatile groups; PSI ($p < 0.001$), SEF ($p < 0.001$). At anaesthetic steady-state after skin incision, DSA was different in OFA compared to TIVA and volatile groups. Most notably, a high-powered spectrum in theta (4 - 8 Hz) and sporadic elements of high-powered beta activity (13 – 30 Hz) were seen.

(VI) Patients with $VCP \geq 2.0$ (VAS units) had more APOP in the PACU (difference NRS 0.9, $p = 0.005$) and at 24 h (difference NRS 0.6, $p = 0.021$) and worse recovery ($p = 0.008$).

Conclusions: The thesis findings show that individual pain prediction is well-studied, and several methods appear ready for patient stratification in clinical trials. For high-risk patients, EC did not improve postoperative outcomes. Opioid-free anaesthesia was feasible in low-risk patients but did not enhance recovery. Patients receiving OFA displayed higher pEEG values and distinct spectral patterns, suggesting that different target ranges may be needed for this technique. Pain during venous cannulation was predictive of APOP but not for PPOP. Female gender and current preoperative pain influenced as confounders for VCP. Overall, the thesis highlights several conceptual avenues for Individualised Anaesthesia and Analgesia, but further clinical trials are needed before firm recommendations can be made.

Populärvetenskaplig sammanfattning

Smärta i samband med kirurgi är vanligt och förknippat med både allvarliga och kostsamma komplikationer för den enskilde patienten. Hittills, har omhändertagandet på operationsdagen mestadels fokuserats kring att möta kraven som operationen ställer på individen snarare än att tillgodose individens behov. Mycket forskningsresurser har lagts på att identifiera riskfaktorer associerade med akut, och i förlängningen långvarig postoperativ smärta. Det är emellertid fortfarande svårt att i förväg identifiera patienter som förväntas uppleva mer intensiv smärta efter en operation. Tack vare tidigare forskning vet vi att det finns individer, som är mer känsliga för smärta.

Individanpassad anestesi och analgesi vid kirurgi är ett koncept som bygger på en helhetssyn, med brännpunkten på den enskilde individen. Idén med detta koncept är inte ny, utan handlar snarare om att omorientera sig mot att nyckeln till framgång ligger hos varje enskild patient.

Även om tanken kring individanpassat omhändertagande i samband med kirurgi florerat de senaste åren, finns idag inga rekommendationer om hur ett individanpassat omhändertagande ska se ut. Förutom att vara nyfikna och kartlägga individuella sårbarheter måste vi också ta reda på hur individer med en viss risk ska omhändertas. Då smärta är en invecklad process tror vi att smärtlindrande läkemedel enkom bör ses som *en* av flera grundpelare i individanpassad anestesi och analgesi vid kirurgi. Kirurgiska och sövningsrelaterade faktorer, borde också inverka i helheten. Förutom detta, är det också viktigt att sätta rätt förväntningar samt ha en samsyn på de mål man vill uppnå med operationen.

I avhandlingen har vi gjort ett försök att samla och kategorisera all den forskning som utförts kring att testa metoder förutspå smärta efter kirurgi. Detta är utfört i *delprojekt ett* som en systematisk litteraturgenomgång. I *delprojekt två* till *fyra* har patienterna indelats utifrån deras risk för smärta efter kirurgi samt lottats till att sövas och smärtbehandlas med en av två anestesimetoder beroende på om de har hög respektive låg risk för smärta. Syftet med studien på gruppen med hög risk var att utröna om vi kunde förbättra smärtutfallet efteråt.

Strategin för lågriskgruppen var att se om de här individerna mår generellt bättre samt uppnår snabbare återhämtning utan att för den delen uppleva mer smärta efteråt. Vidare, valde vi att titta närmre på andra metoder med potential att kunna individanpassa smärtlindring fortlöpande hos patienter som sover och genomgår ett

kirurgiskt ingrepp. I *delprojekt fem* studerade vi patienter som anestesi behandlades enligt tre olika protokoll: opioidfri anestesi samt två etablerade standardmetoder, för att undersöka om kontinuerlig hjärnövervakning uppvisade skillnader under operationen. Syftet med detta delprojekt var att, för första gången, titta på hur en kombination av anestesiläkemedel, utan opioideffekter, påverkar den kontinuerliga hjärnövervakningen jämfört med traditionella standardmetoder för sövning.

Slutligen, i *delprojekt sex*, har vi tittat närmre på *smärtskattning vid nålsättning* som metod att hitta individer som löper större risk för smärta efter sin operation.

Genom detta avhandlingsarbete har vi kommit fram till att flertalet väl beforskade metoder, för att förutspå vilka patienter som kommer uppleva mer smärta efter kirurgi, inte har någon framtid i konceptet om individanpassad anestesi antingen för att de inte är tillräckligt bra eller att de är tidsödande och inte praktiskt tillämpbara. Idag finns dessutom ingen enskild metod för detta ändamål utan hoppet ligger för tillfället på enskilda oberoende riskfaktorer. Omvänt kan flera nya men mindre beforskade metoder vara intressanta i framtiden.

I den kliniska prövningen på högriskgruppen var det inte någon skillnad i smärta efter kirurgi, även om de sövdes på olika sätt. Patienter med låg risk för smärta hade inte mer ont efter operationen. I ingen av de kliniska prövningarna var det någon skillnad i tidig återhämtning, illamående eller förekomst av långvarig smärta. I högriskgruppen var det ingen skillnad i given opioiddos, något vi däremot såg skiljde sig något i lågriskgruppen.

Gällande den kliniska prövningen av kontinuerlig hjärnövervakning fann vi att en kombination av sövnings- och smärtlindringsläkemedel utan opioder påverkade både siffervärden och utseendet på själva hjärnövervakningen.

Smärta vid nålsättning kunde inte själv förutspå smärta efter kirurgi.

Implikationerna av resultaten i denna avhandling är flerfaldiga. Övergripande har ett första steg tagits mot att konceptualisera idén om individanpassad anestesi och smärtlindring i samband med kirurgi. Idén att läkemedel kan påverka flera steg i smärtsignaleringssystemet förefaller rimlig, men behöver fortsatt utvärdering. Däremot tror vi att andra aspekter med läkemedelskombinationer, såsom läkemedelssamverkan, doser och sättet hur dessa ges måste tas i beaktande. Vi förslår här förslag på hur framtida kliniska prövningar kan designas för detta ändamål. I avhandlingen kan man för första gången få en inblick vad som kan förväntas från kontinuerlig hjärnövervakning hos patienter som sövs och smärtbehandlas med en kombination av läkemedel utan opioideffekter. Detta tror vi är viktigt då sövning och smärtlindring på detta sätt kommer ha en etablerad plats inom anestesi. Således är det viktigt att denna metod valideras gentemot ny medicinteknisk utrustning.

Abbreviations

AP	Action potential
AKI	Acute kidney injury
ACP	Advanced care planning
AM404	<i>N</i> -arachidonoyl phenolamine
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AVP	Arginine vasopressin in plasma
BPS	Behavioural pain scale
CNS	Central nervous system
CPOT	Critical-care pain observation tool
COX	Cyclooxygenase
cAMP	cyclic adenosine monophosphate
DAMP	Damage associated molecular patterns
DRG	Dorsal root ganglion
EC	Multimodal anaesthesia and analgesia with esketamine and clonidine
GABA	Gamma-aminobutyric acid
GPCR	G-protein coupled receptors
pEEG	processed electroencephalography
IAAS	Individualised anaesthesia and analgesia in surgery
IL-1	Interleukin 1
IASP	International Association for the Study of Pain
OFA	Opioid-free anaesthesia
SOC	Standard of Care
NMDA	N-methyl-D-aspartate

NMBA	Neuro muscular blocking agents
NSAID	Non-steroidal anti-inflammatory drugs
NRS	Numeric rating scale
VAS	Visual analogue scale
SDM	Shared decision making
SPI	Surgical pleth index
SG	Substantia gelatinosa
NOL	Nociception level
qNOX	Quantitative nociception index
OPRM1	Mu-opioid receptor gene 1
ORAS	Opioid-related adverse side-effects
PAG	Periaqueductal grey
PTI	Pain threshold index
PNS	Peripheral nervous system
PONV	Postoperative nausea and vomiting
SC	Skin conductance
SSRI	Selective serotonin reuptake inhibitor
SNRI	Serotonin-noradrenaline reuptake inhibitors
SG	Substantia gelatinosa
TCA	Tricyclic antidepressant
TENS	Transcutaneous nerve electrical stimulation
TRP	Transient receptor potential
TLR	Toll-like receptors
TNF	Tumor necrosis factor
VR1	Vanilloid receptor 1
VGCC	Voltage-gated calcium channels
VGPC	Voltage-gated potassium channels
VGSC	Voltage-gated sodium channels
5-HT	Serotonin

AI Statement

I, the author of this dissertation, have used Microsoft Copilot solely for English-language review. The AI tool was employed exclusively to assist with grammar, syntax, and linguistic clarity, and it was not used for any other aspect of the dissertation's development. After using Copilot, I carefully reviewed and edited all content to ensure accuracy, coherence, and overall clarity.

Introduction

The physiology of perioperative pain

Since Friedrich W. Sertürner first isolated morphine in 1806, the study of pain and its treatment has evolved considerably, driven by sustained research and expanding therapeutic possibilities. Landmark achievements include Felix Hoffmann's synthesis of aspirin in 1897 and David Julius's identification of the vanilloid receptor 1 (VR1) in 1999, discoveries that have each been recognised with Nobel Prizes.

Over the past 220 years, such breakthroughs have transformed our understanding of pain and nociception. Yet the physiology of pain remains only partly understood. Much of our current knowledge is derived from in vitro studies and functional imaging, which provide valuable insights but still leave important questions unanswered¹.

Before examining the details of pain physiology and its neuroanatomical pathways, it is important to acknowledge the psychological factors that shape these processes. These factors influence neuroplasticity, neurotransmitter release, and receptor modulation. It is therefore useful to view pain signalling both as a holistic phenomenon and as a series of interconnected pathways, much like appreciating both the forest and the individual trees. This introductory chapter will focus on pain within the perioperative context.

Conduction of nociception

Nociceptive transmission typically begins with a painful stimulus arising from the skin, visceral organs, or both. These tissues are interwoven with specialised free nerve endings known as nociceptors, which differ from other sensory nerve endings in two key aspects¹: they respond to thermal, chemical and mechanical stimuli in an undifferentiated manner, and they possess a higher threshold for generating an action potential (AP). This ensures that normal touch and temperature are not misinterpreted as painful or harmful.

Extensive research has been devoted to understanding how nociceptors are activated. A major milestone was the identification and characterisation of the

transient receptor potential (TRP) receptor family, a group of non-selective ligand-gated cation channels embedded in the cell membrane². These receptors have deepened our understanding of nociceptive signalling and represent promising therapeutic targets.

The cell bodies of nociceptors are located in the dorsal root ganglia (DRG) of the spinal cord and in the trigeminal ganglion within the brainstem. These structures form the key peripheral components of the nociceptive pathway¹. Once an AP is generated, it propagates relatively slowly along the dendritic and axonal projections of the nociceptor until reaching the preterminal junction at the synaptic cleft (figure 1)^{3,4}. Depolarisation occurs when a noxious stimulus reaches threshold, triggering the opening of voltage-gated sodium channels (VGSCs) in an all-or-nothing fashion¹. The resulting AP travels along either A δ - or C-fibres, the former conducting more rapidly, producing sensations typically described as sharp or, alternatively, dull and diffuse.

Potassium efflux through voltage-gated potassium channels (VGPCs) plays a crucial counterbalancing role by hyperpolarising the membrane and preventing uncontrolled or repetitive firing¹. Following each AP, the sodium-potassium ATPase restores the resting membrane potential, enabling the nociceptor to respond to subsequent stimuli. This framework clarifies that the intensity of a noxious stimulus is encoded by the frequency of APs rather than their amplitude, as each AP is generated by the same ionic shifts regardless of stimulus strength⁵.

While sodium and potassium fluxes are essential for establishing and propagating the AP, calcium is critical for initiating and sustaining neurotransmitter release at the preterminal junction⁶. At this interface, nociceptive signalling transitions from an electrical to a chemical form before being converted back to an electrical signal in the postsynaptic neuron.

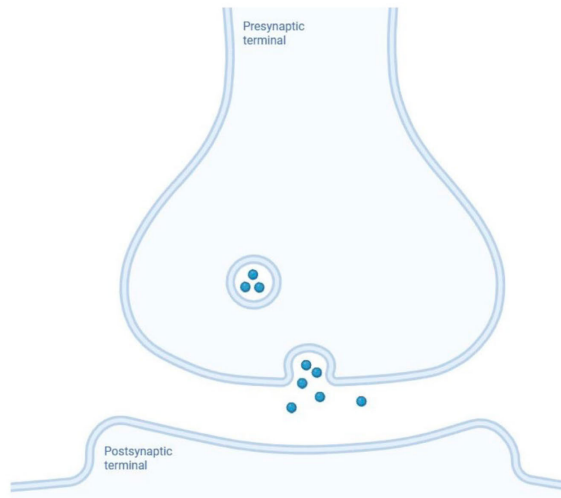


Figure 1. Calcium-induced release of neurotransmitter at the synaptic cleft. As an action potential reaches the preterminal junction, calcium influx triggers a cascade of events that culminates in the exocytosis of neurotransmitter.

The reasons why synapses exist are not entirely understood, but one theory suggests that they enable neuromodulatory changes, supporting the sophisticated sensory processing characteristic of more complex animals⁷. Synapses also ensure unidirectional conduction of APs, functioning in a manner analogous to a valve⁷.

The release of neurotransmitters is a highly complex process, influenced by numerous interactions from other modulatory neurons (interneurons) at the site of transmission, particularly within the substantia gelatinosa (SG) of the dorsal horn of the spinal cord⁸. The SG is a gelatinous-appearing cluster of neurons located in lamina II of the dorsal horn⁸. It is here that additional neuromodulatory changes occur, driven by both ascending and descending signalling pathways.

The ascending noxious stimulus, first generated peripherally, then propagates along the second-order neuron of the contralateral spinothalamic or trigeminothalamic tract within the central nervous system (CNS) towards the thalamus in the midbrain¹. The thalamus subsequently relays this information to the primary somatosensory cortex, where the precise origin of the stimulus is identified, and to the anterior cingulate cortex, where the affective or aversive component of pain is processed and initiated⁹.

This description typically outlines the pathway of painful stimuli from the peripheral to the central nervous system via the spinothalamic tract. However, similar ascending pathways exist for other dimensions of pain, as localisation represents only one aspect. These include the spinomesencephalic, spinoreticular and

spinohypothalamic tracts, which convey signals to the periaqueductal grey (PAG), reticular formation and hypothalamus, respectively. These structures modulate endogenous pain inhibition, arousal and autonomic responses to pain¹.

Ascending noxious stimuli from the visceral organs are less well defined, as afferent nerves from each organ are widely distributed throughout the internal organs and vasculature. These signals are conveyed primarily through sympathetic fibres in the spinal ganglia, as well as through the parasympathetic glossopharyngeal and vagal nerves¹.

Neuromodulation of pain

The International Association for the Study of Pain's (IASP) definition of pain proclaims in its first note: *pain is a response to noxious stimuli when impeding tissue damage occur*¹⁰. It is essential that this response is prioritised so that ongoing tissue damage is minimised and tissue repair can begin effectively. Within seconds and minutes of the initial noxious stimulus, an intricate and highly coordinated process of pain modulation develops, driven largely by neurological and chemical changes.

In its 2020 update, the IASP added a second note: *pain can also occur in response to the perception of tissue damage*¹⁰. This addition acknowledges that painful sensations can occur in the absence of actual tissue injury, an important consideration in understanding chronic pain syndromes.

At the site of tissue damage, inflammation develops within minutes¹¹. This process serves two key purposes:

1. to draw attention to the injured area, prompting goal-directed behaviours aimed at preserving life, limb or tissue and, when appropriate, removing the offending stimulus.
2. to initiate tissue repair, including haemostasis and coagulation, clearance of debris, and subsequent fibrotic healing^{11,12}.

Tissue damage almost invariably leads to cell rupture, resulting in the release of intracellular molecules known as damage-associated molecular patterns (DAMPs)¹³. Evolution has ensured that higher species possess an innate response to these molecules, as DAMPs bind to a relatively non-specific receptor family called toll-like receptors (TLRs)¹³. These receptors are expressed on circulating immune cells, which scavenge DAMPs at the site of injury, as well as on endothelial cells.

For the purposes of this text, the binding of DAMPs to TLRs can be understood as initiating the production and release of pro-inflammatory mediators and the recruitment of additional immune cells from both the innate and adaptive immune system¹². To facilitate this recruitment, increased blood flow and vascular

permeability are essential, alongside the release of chemotaxins, e.g. the chemical cues that guide immune cells towards the site of injury¹⁴.

At this point, the inflammatory process is fully established at the injured site. It is important to recognise that inflammation typically causes further tissue disruption before the subsequent phases of healing and repair begin to dominate.

The painful component of inflammation is known as peripheral sensitisation, or primary hyperalgesia. This refers to a state in which the same noxious stimulus produces a heightened painful response over a larger area and at a lower threshold for generating APs¹⁵. As a result, even normal touch in and around the injured region may evoke pain, as nociceptors become more easily activated. Although much of the evidence for peripheral sensitisation originates from animal models and in vitro studies, it remains a well-supported clinical concept¹⁶.

In parallel with the development of inflammation, pain-inducing and pain-modulating molecules (neuropeptides) such as prostaglandins, histamine and Substance P are released¹⁷. In addition, intracellular ions, beyond DAMPs, such as potassium act as potent pain-inducing agents. The importance of fundamental molecular research is exemplified by the discovery of aspirin and the subsequent development of more advanced cyclo-oxygenase (COX) inhibitors.

Cyclo-oxygenase is an enzyme within immune cells that metabolises arachidonic acid, a precursor of prostaglandin E₂, which is present in cell membranes¹⁷. Prostaglandin E₂ then binds to specific G-protein-coupled receptors (GPCRs), activating a signalling cascade that increases cyclic AMP (cAMP) production. This, in turn, activates protein kinase A, which phosphorylates VGSCs and TRPV1 channels, making them more susceptible to activation¹⁷. Inhibiting COX, particularly COX-2, remains one of the most effective strategies for treating postoperative pain and is generally recommended for all patients who can safely tolerate it.

Apart from the chemical environment that promotes peripheral sensitisation, a complex network of interneurons also influences pain signalling and its upward transmission from the dorsal horn of the spinal cord. This concept was first proposed by Melzack and Wall nearly 50 years ago and is known as the gate control theory (figure 2), named for its intuitive explanatory framework¹⁸.

In essence, small (C and A δ) and large (A β) first-order sensory neurons synapse with second-order sensory neurons in the substantia gelatinosa (SG) of the dorsal horn, as previously described. Within the gate control theory, these second-order neurons are referred to as transmission cells (T-cells)(Figure 2)¹⁹. Interneurons within the SG can inhibit the synaptic transmission of noxious stimuli at the preterminal junction between first-order neurons and T-cells. Theoretically, this inhibition occurs through hyperpolarisation of the preterminal junction by gamma-aminobutyric acid (GABA) or other inhibitory neurotransmitters, reducing

the likelihood of calcium influx and the subsequent release of excitatory neurotransmitters into the synaptic cleft. However, this mechanism has not been directly demonstrated in experimental research¹⁹.

According to the gate control theory, inhibitory interneurons are themselves modulated by first-order sensory neurons, either enhancing or diminishing their inhibitory influence on synaptic transmission. Large sensory fibres (associated with touch and proprioception) activate both inhibitory interneurons and T-cells, resulting in reduced transmission of noxious stimuli, the gate is “closed” (Figure 2). Conversely, small sensory fibres (associated with nociception) activate T-cells while inhibiting the inhibitory interneurons. The disinhibition of interneurons allows more robust transmission of noxious signals, e.g. the gate is “open”.

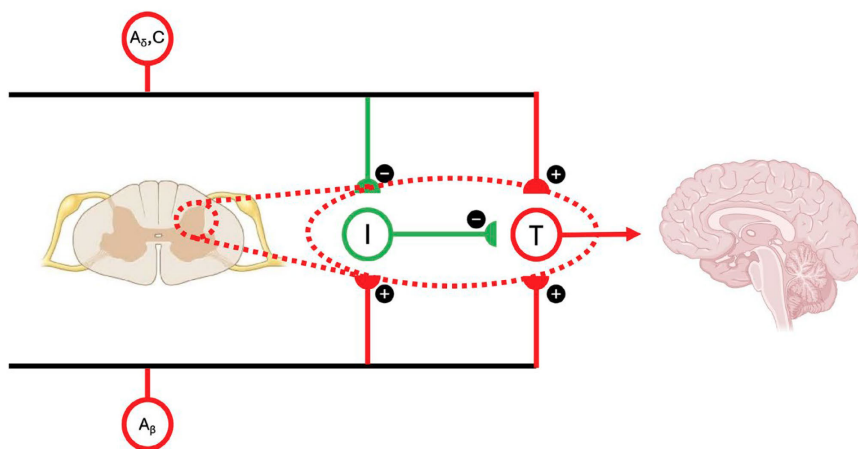


Figure 2. Graphic depiction of the gate control theory. Action potentials conveying noxious stimuli travel along nociceptors (A δ , C). Second order neurons (T) are stimulated to convey the noxious stimuli further to the central nervous system where a more complex neuronal processing will take place. In the dorsal horn of the spinal cord, the noxious stimuli will inhibit inhibitory interneurons (I), effectively disinhibiting the second order transmission neuron – the gate is open for noxious stimuli to reach higher structures in the brain. Larger-calibre first order nerve fibres (A β), mainly transmitting stimuli of normal touch, stimulate both second-order neurons (T) and inhibitory neurons (I), effectively alleviating the simultaneously incoming noxious stimuli from A δ and C, fibers - The gate is closed for noxious stimuli to reach the brain. Clinically, light normal touch or transcutaneous electrical nerve stimulation can alleviate pain by “closing the gate” for incoming noxious stimuli.

Transcutaneous electrical nerve stimulation (TENS) utilises the gate control theory by effectively “closing the gate” to ascending noxious stimuli through the activation of large proprioceptive nerve fibres in muscle spindles²⁰. Similar principles underlie simple clinical observations, such as rubbing the skin around a painful area or applying a light tap, both of which can reduce discomfort.

Central sensitisation, or secondary hyperalgesia, is another pain-enhancing process and is central to understanding persistent postoperative pain (PPOP). Although PPOP is a long-lasting condition, central sensitisation begins shortly after the initial noxious stimulus²¹. In more advanced stages, even normal touch can provoke pain, resulting in allodynia (e.g. normal touch perceives as painful).

Following a skin incision, noxious APs travel through the dorsal horn via activation of AMPA receptors, which mediate onward transmission to higher structures in the CNS. If these stimuli are continuous and unrestrained, pre- and postsynaptic NMDA receptors (NMDAR) become activated, amplifying nociceptive signalling²². In their inactive state, NMDAR are blocked by Mg^{2+} . Repetitive nociceptive input from first-order neurons dislodges Mg^{2+} from the receptor channel, allowing calcium influx, which increases the likelihood of postsynaptic depolarisation and further transmission²². Electrophysiological studies show that NMDAR are slow to activate but remain open long after the nociceptive stimulus has ceased²³. A stark historical example of central sensitisation is the so-called Chinese water torture, which relied on this mechanism for its effect. Subjects were restrained while water droplets were repeatedly applied to the forehead; over time, the sensation intensified dramatically, eventually becoming excruciating.

Understanding central sensitisation is crucial, particularly as many patients may already present with an advanced degree of this process before surgery. Central sensitisation underscores the importance of an individualised approach to anaesthesia and analgesia, as such patients are more likely to experience unnecessary discomfort and postoperative pain-related complications if managed in the same way as individuals with less up-regulated pain pathways.

The final modulatory process discussed in this introductory chapter is that of descending inhibitory pathways. Like many modulatory mechanisms, descending inhibition operates within the dorsal horn of the spinal cord and serves as a potent endogenous analgesic system²⁴. This pathway can be viewed as a highly complex, multi-level negative feedback loop originating in neurons of the PAG, which receive ascending noxious input via the spinomesencephalic tract. The PAG subsequently activates multiple subcortical structures in the midbrain and brainstem, producing a convergent descending inhibitory signal that acts on second-order sensory neurons conveying noxious stimuli²⁵. Although this process involves numerous neurotransmitters, serotonin (5-HT) and noradrenaline play particularly important roles, with potential clinical implications.

To relate these theoretical aspects of nociceptive transmission and modulation to the principles of individualised anaesthesia and analgesia, it is important to acknowledge that there is currently no robust framework for understanding how these processes interact in individual patients, nor how they might be assessed clinically. Pragmatic bedside tests, such as evaluating pain during peripheral venous cannulation or during infiltration of local anaesthesia, can only identify an

up-regulated pain response as a surrogate marker for underlying neuromodulatory changes. While promising and clinically relevant, these approaches remain crude, offer limited insight into the complexity of pain modulation, and require further refinement before individualised anaesthesia and analgesia can be reliably implemented in routine practice.

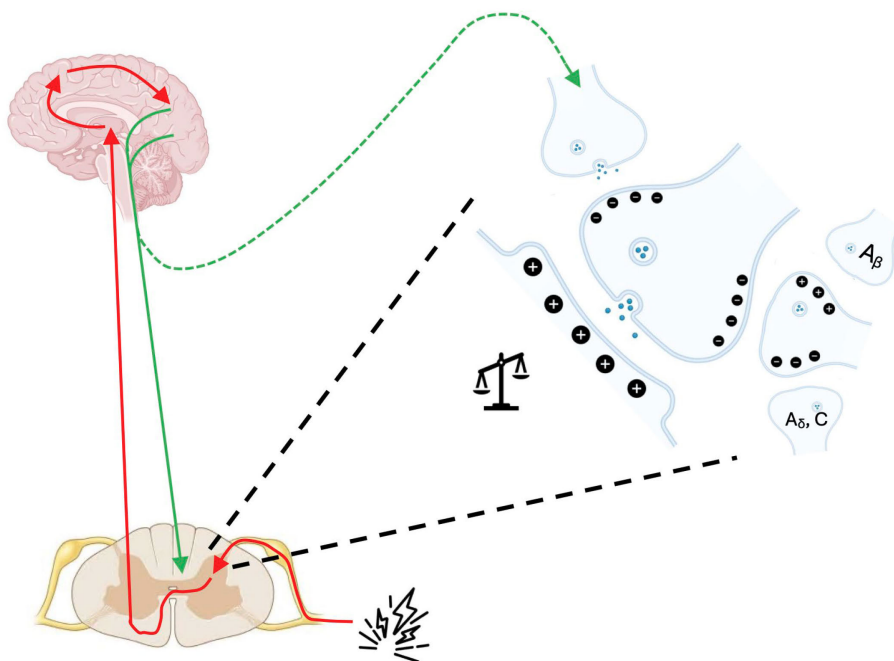


Figure 3. Simplified graphical depiction of the endogenous neuromodulation of pain. This process can be viewed as a balance between pro-nociception and anti-nociception mechanisms. When a noxious stimulus occurs (red arrowed path) first-order neurons send signals to the dorsal horn of the spinal cord, where they synapse with second-order neurons (T-cells). These neurons then relay the signal to the thalamus on the contralateral side. The thalamus further transmits the signal via third-order neurons to the somatosensory cortex and other complex regions in the CNS. If the noxious stimulus is intense and prolonged, pro-nociceptive processes (open-gate, peripheral- and central sensitisation) shifts the balance towards increased and prolonged pain intensity. Conversely, depending on the effectiveness of anti-nociceptive processes (closed-gate, descending inhibition [green filled and dashed arrow], exogenous analgesia) the balance shifts towards reduced pain intensity. The scales in the figure represent the likelihood of post-synaptic excitation, which depends on whether the membrane potential at the preterminal junction favours hyperpolarisation or depolarisation.

Pharmacologic aspects of perioperative analgesia

When moving from the complex nature of pain physiology to its clinical implications, it becomes clear that decades of scientific discovery have laid the

foundation for therapeutic interventions in perioperative medicine. Despite major advances in surgical techniques, many patients continue to experience moderate to severe APOP²⁶. Over time, we have learned to manipulate receptors and neural circuits to improve pain outcomes, and, as with many other conditions, a multimodal approach is generally preferred over high-dose, single-target strategies.

Discussions of multimodal anaesthesia and analgesia often focus on receptor-level mechanisms. However, other pharmacological considerations, such as drug dosing, drug–drug interactions, and the mode of administration (bolus versus continuous infusion), may be equally important. These factors become particularly relevant when interpreting current evidence, as the heterogeneity among published studies is substantial.

Paracetamol

Although paracetamol has been available commercially since the 1950s, its exact mechanism of action has not been fully elucidated. Current evidence suggests that paracetamol acts through several complementary pathways:

- Prostaglandin inhibition via COX-3 suppression. Cyclo-oxygenase-3 is an isoenzyme of COX-1, located primarily within the central nervous system rather than the periphery. This distinction explains why paracetamol functions as a systemic analgesic and antipyretic, yet lacks meaningful anti-inflammatory effects at the site of injury^{27,28}.
- Activation of descending inhibitory pathways via 5-HT. Administration of 5-HT antagonists, such as ondansetron, partially abolishes the antinociceptive effect of paracetamol, supporting this mechanism²⁹.
- Endocannabinoid modulation. Within the CNS, paracetamol is metabolised to p-aminophenol, which conjugates with arachidonic acid to form N-arachidonoyl-phenolamine (AM404). AM404 inhibits the reuptake of endocannabinoids, ultimately activating cannabinoid receptors and producing a relaxing, and in some individuals, mildly euphoric, effect²⁸.

Paracetamol is available in all formulations except cutaneous preparations, which broadens its clinical utility. Its analgesic and opioid-sparing effects are well supported by current research and guidelines, which recommend paracetamol as a first-line agent for all patients who can safely receive it³⁰. In terms of tolerability, paracetamol can generally be administered safely even in patients with liver disease; however, caution and dose reduction are advised in cases of severe malnutrition, advanced hepatic impairment, prolonged fasting, or a lean body mass below 50 kg³¹.

In perioperative practice, a common regimen involves a pre-emptive loading dose of 1000 - 1500 mg (i.v – p.o), followed by 1000 mg every six hours³². Pooled data indicate a number needed to treat (NNT) of 3.8 across mixed surgical procedures,

with dental extractions showing the greatest benefit³³. Furthermore, postoperative opioid consumption is reduced by approximately 20 %.

Oral paracetamol offers advantages in cost-effectiveness and avoids unnecessary intravenous fluid load. However, its bioavailability is variable (63–89%)³⁴, introducing uncertainty in achieving therapeutic plasma concentrations³⁵. Earlier studies have shown that patients receiving 1000 mg orally before day-surgery achieved median plasma concentrations of 2.7 mg/L and 4.8 mg/L at 40 and 80 minutes, respectively³⁶. This stands relative to the overall accepted minimal plasma concentration of 10 mg/L for pain control³⁵

Peripheral de-sensitisation

Non-steroidal anti-inflammatory drugs (NSAID)

Tissue inflammation is partly driven by prostaglandins produced via COX activity. NSAIDs constitute a group of analgesic agents that inhibit COX-1 and/or COX-2, thereby exerting anti-inflammatory and antinociceptive effects. Within this class, both non-selective COX inhibition and selective COX-2 inhibition can be achieved.

In a meta-analysis (n = 76 RCTs; 58,451 participants), NSAIDs reduced APOP by 0.62 NRS units³⁷. A Cochrane review and meta-analysis demonstrated that a single dose of a selective COX-2 inhibitor produced a low NNT for achieving a 50% reduction in APOP³⁸. Etoricoxib (a COX-2 inhibitor) was particularly effective as a single agent (NNT 1.8), comparable to paracetamol + oxycodone 1000 mg/10 mg (NNT 1.8) and paracetamol + ibuprofen 1000 mg/400 mg (NNT 1.5).

Given their efficacy, NSAIDs should be strongly considered for inclusion in individualised anaesthesia protocols. As with paracetamol, they represent one of the few analgesic classes that should be administered to all patients who can safely tolerate them. However, several important considerations remain, including the risks of acute kidney injury (AKI), gastrointestinal bleeding, and cardiovascular events³⁹. Surgical concerns have also included potential increases in intraoperative bleeding, bowel anastomotic leakage, and impaired bone healing³⁹.

A large meta-analysis (n = 151,000) found no association between NSAID use and intraoperative bleeding, regardless of whether the drug was administered preoperatively, intraoperatively, or postoperatively⁴⁰. Similar conclusions were reached regarding bone healing⁴¹. Evidence for bowel anastomotic leakage, however, suggests a possible association, particularly with non-selective NSAIDs (OR 1.68, 95% CI 1.25–2.24)⁴². Importantly, this association was driven by observational data as randomised controlled trials did not show a significant effect, indicating potential bias. In subgroup analyses, the association was not observed for COX-2 inhibitors (OR 1.67, 95% CI 0.90–3.13). Furthermore, selective COX-2

inhibitors do not provoke bronchospasm in hyperreactive individuals, a recognised concern with non-selective NSAIDs⁴³.

Lidocaine

Intravenous lidocaine has become an important adjunct in multimodal anaesthesia and analgesia strategies. As a local anaesthetic, lidocaine inhibits the propagation of APs by blocking VGSCs. In addition, lidocaine exhibits anti-inflammatory properties by inhibiting GPCRs on neutrophils, thereby reducing their ability to amplify the inflammatory response to tissue injury⁴⁴. There is also evidence suggesting that lidocaine interacts with NMDA receptors (NMDAr) in the brainstem, enhancing antinociception and attenuating arousal⁴⁵.

Although the rationale for using lidocaine as an adjunct in perioperative pain management is compelling, the supporting evidence is not unequivocal. A review and sequential analysis demonstrated modest improvements in pain scores, opioid consumption, and bowel function, with particular benefit in abdominal surgery⁴⁶. However, due to the risk of bias in the included trials, the authors concluded that the overall certainty of evidence for perioperative lidocaine remains low. More recently, the ALLEGRO trial (n = 590) failed to demonstrate a benefit of lidocaine for return of bowel function after laparoscopic colonic surgery⁴⁷. Notably, this study has been criticised for methodological limitations, including higher perioperative opioid use in the lidocaine group, an important confounder given opioids' well-known inhibitory effects on bowel motility. Interestingly, in terms of postoperative analgesia, lidocaine infusion was found to be non-inferior to thoracic epidural analgesia during the first 24 hours following major open abdominal surgery⁴⁸.

A 2021 consensus statement recommends using intravenous lidocaine with caution and only in carefully selected patients. When administered, dosing should be based on ideal body weight, avoided in individuals weighing less than 40 kg, and should not exceed 120 mg/h⁴⁹. A commonly suggested regimen includes a bolus of no more than 1.5 mg/kg followed by an infusion of 1.5 mg/kg/h for less than 24 hours⁴⁹.

Corticosteroids

Corticosteroids have a wide range of indications in the perioperative setting. For patients receiving chronic corticosteroid therapy, a stress dose of 100 mg hydrocortisone (added to normal daily dose) is recommended to mitigate the risk of adrenal insufficiency during surgical stress⁵⁰. In addition, guidelines support the use of corticosteroids to reduce the risk of PONV⁵¹. Dexamethasone is the most extensively studied agent within this class, although differences between corticosteroids may exist. For example, in elective breast surgery, betamethasone (8 mg) produced only a small effect size compared with placebo for PONV prevention⁵².

Corticosteroids exert their effects by modulating intracellular gene expression, influencing several key processes:

- Inhibition of phospholipase A₂, thereby reducing the conversion of arachidonic acid into prostaglandins⁵³.
- Suppression of lymphocyte chemotaxis, which would otherwise contribute to inflammation and peripheral sensitisation⁵³.
- Inhibition of pro-inflammatory mediators, including interleukin-1 (IL-1) and tumour necrosis factor (TNF), released by macrophages and monocytes⁵³.

Corticosteroids have a documented analgesic effect^{54,55}. Pooled data (n = 2,751) demonstrated that intermediate dosing (dexamethasone 0.11–0.20 mg/kg) improved pain outcomes and reduced opioid consumption, with an acceptable safety profile⁵⁴. A more recent meta-analysis (47 RCTs) evaluating dexamethasone and methylprednisolone found reductions in opioid consumption (11 mg/24 h), although the effect on APOP was modest (VAS reduction of 6–9 mm at 24 h)⁵⁵.

Opioid receptor modulation

Opioids are potent antinociceptive agents with a wide range of clinical applications. Numerous drugs fall within this class, and their effects vary considerably depending on their pharmacological properties. Therapeutically, opioids target three principal receptor types: the μ - (MOR), δ - (DOR), and κ - (KOR) receptors. These receptors are distributed throughout multiple regions of the central nervous system, including the PAG, spinal cord, amygdala, rostral ventral medulla, and cortex, as well as in peripheral tissues^{56,57}. Their analgesic effects are mediated through several mechanisms:

- Inhibition of afferent nociceptive transmission to the spinal cord by reducing VGCC activity and opening inward-rectifying potassium channels, thereby decreasing the probability of synaptic transmission⁵⁸.
- Enhancement of descending inhibitory pathways originating in the PAG⁵⁹.
- Modulation of the emotional component of pain through actions on the amygdala⁶⁰.

In anaesthesia, opioids also exert adjunctive effects on arousal by inhibiting cholinergic circuits in the brainstem and thalamus⁶¹, contributing to the concept of balanced anaesthesia.

Beyond their analgesic and anaesthetic properties, opioids have well-recognised side effects across multiple organ systems. These include respiratory depression and cardiovascular compromise due to sympathicolysis. In the perioperative setting, opioids may also cause bowel obstruction⁶², urinary retention⁶³, PONV⁶⁴ and shivering⁶⁵. Notably, and of growing concern, perioperative opioid use has been

associated with cancer recurrence after surgery⁶⁶⁻⁶⁸. One proposed mechanism is opioid-induced immunosuppression, particularly through reduced natural killer (NK) cell activity, impairing tumour cell clearance⁶⁹.

Despite their widespread use, opioids can paradoxically induce rapid tolerance and increase postoperative opioid requirements⁷⁰. This phenomenon is particularly pronounced with remifentanyl compared with other perioperative opioids. Additionally, opioid dependence and tolerance have gained increasing attention, as perioperative opioid exposure contributes to the development of substance use disorders and preventable overdose deaths⁷¹. However, this relationship is complex. Efforts to reduce perioperative opioid use without adequate alternatives may lead to unintended consequences, including increased postoperative pain and higher opioid consumption⁷².

N-methyl D-aspartate (NMDA) receptor antagonism

Ketamine/esketamine

Ketamine exists as two enantiomers: R-ketamine (ketamine) and S-ketamine (esketamine). Its pharmacodynamic profile makes it particularly useful in anaesthesia, as NMDA receptors are widely distributed throughout the human body. However, this broad receptor distribution also contributes to unwanted effects when ketamine is not used judiciously, hence its occasional, somewhat pessimistic description as a “dirty drug”.

During the perioperative period, ketamine and esketamine are primarily used for their non-competitive NMDA receptor antagonism, which contributes to the dissociative state characteristic of ketamine-based general anaesthesia. At lower doses, these agents block NMDA receptors in the spinal cord, potentially preventing central sensitisation and effects of uncontrolled ascending nociceptive input. Esketamine has a three- to four-fold higher affinity for the NMDA receptor compared with ketamine, which accounts for its greater potency⁷³.

Although ketamine and esketamine, in equipotent dosing, produce similar clinical effects, their data are often analysed separately in meta-analyses. One such analysis demonstrated that esketamine, used as an adjunct during general anaesthesia, reduced APOP for up to 24 hours and lowered opioid requirements over the same period⁷⁴. Similarly, ketamine has been shown to reduce APOP, decrease opioid consumption, and improve postoperative recovery^{75,76}.

It is important to note that the overall reduction in APOP is modest, which complicates clinical decision-making given the risk of psychotropic side effects. The risk–benefit balance may shift in favour of ketamine in patients expected to experience severe postoperative pain after major surgery⁷⁷. A unique clinical advantage of ketamine is its ability to attenuate rapid opioid tolerance⁷⁷, making it

particularly valuable when high opioid doses have been administered or when patients already exhibit opioid tolerance⁷⁸.

Magnesium

Magnesium (Mg^{2+}) is one of the most abundant cations in the human body and plays a key role in a wide range of physiological processes⁷⁹. Clinically, Mg^{2+} has diverse therapeutic applications, particularly in obstetrics, where it is widely used in the management of pre-eclampsia⁸⁰. In perioperative medicine, interest in Mg^{2+} has increased over the past decade. Similar to ketamine, Mg^{2+} modulates NMDA receptors through ion-channel blockade, as described earlier⁸¹.

Since its introduction into clinical trials, Mg^{2+} has been evaluated in numerous small RCTs for its role in postoperative pain management. A meta-analysis of 43 RCTs concluded that Mg^{2+} reduces APOP and opioid consumption, with pooled effect sizes corresponding to a 9.2 mm reduction on the VAS and a 3.6 mg reduction in opioid use⁸². Subgroup analysis suggested that a bolus-only regimen provided the greatest benefit compared with bolus plus infusion or infusion alone. However, substantial heterogeneity was introduced due to the wide dosing range (30–50 mg/kg). Similar findings were reported in another meta-analysis⁸³.

In terms of optimal dosing, one RCT compared three different regimens and found that a bolus of 40 mg/kg followed by an infusion of 10 mg/kg/h significantly reduced postoperative opioid consumption⁸⁴. Higher infusion doses did not improve analgesic outcomes and were associated with more haemodynamic adverse events.⁸⁴.

Although Mg^{2+} is a naturally occurring ion, its use as an analgesic adjunct requires caution. High doses may cause hypotension, respiratory and neurological depression, and bradyarrhythmia. However, in terms of hemodynamics, findings in one RCT suggests that intraoperative Mg^{2+} has a dose-dependent reductions in MAP and systemic vascular resistance, while cardiac output remained stable⁸⁵. Interestingly, plasma arginine vasopressin (AVP) levels were highest in the control group and lowest in the high-dose Mg^{2+} group, suggesting that magnesium may exert sympatholytic effects that reduce surgical stress rather than causing true flow-dependent haemodynamic compromise. Put into context, a lower SVR and MAP due to decreased stress may be more beneficial if blood-flow and tissue perfusion remain the same or increased.

For anaesthesiologists, it is also important to note that Mg^{2+} enhances neuromuscular blockade, necessitating careful monitoring of train-of-four (TOF) responses when used alongside neuromuscular blocking agents (NMBAs)⁸⁶.

Gabapentinoids

As the name suggests, gabapentinoids are structurally similar to γ -aminobutyric acid (GABA). However, their mechanism of action does not involve GABAergic transmission. Instead, they inhibit ion flux through presynaptic voltage-gated calcium channels (VGCCs), thereby reducing excitatory neurotransmitter release and diminishing synaptic transmission⁸⁷. The two most widely used gabapentinoids, gabapentin and pregabalin, have traditionally been employed in the management of persistent neuropathic pain.

Evidence for their perioperative use has been inconsistent, largely due to methodological limitations across studies. However, one recent trial demonstrated benefit when 600 mg intravenous gabapentin was administered preoperatively to women undergoing caesarean section⁸⁸. Although several RCTs have shown reductions in postoperative pain and opioid consumption, there remains no clear consensus regarding which agent to use, the optimal dose, or which patient groups are most likely to benefit. Importantly, gabapentinoids exert depressant effects on both respiration and the central nervous system. This raises safety concerns when they are combined with other sedative agents, particularly opioids, making their routine perioperative use questionable and potentially unsafe.

GABA_A-agonism

Although pure anaesthetic agents do not directly modulate pain-signalling pathways, they can influence the perception of incoming afferent noxious stimuli⁸⁹. In essence, these agents act on GABA_A receptors located on interneurons within the CNS, thereby reducing the activity of pyramidal neurons in the cortex, thalamus, brainstem, striatum, and spinal cord^{90,91}. In addition to propofol and benzodiazepines, volatile anaesthetics also exert effects on NMDA receptors⁹¹.

Appropriate anaesthetic depth is reflected in characteristic neuronal oscillatory patterns on the electroencephalography (EEG). Under adequate anaesthesia, EEG power is predominantly concentrated in the slow/delta (0–4 Hz) and alpha (8–12 Hz) frequency bands⁹². With volatile anaesthetics, increasing the minimum alveolar concentration (MAC) above 1.0 is associated with a shift towards greater power in the theta frequency range⁹².

Alfa₂-agonism

Dexmedetomidine

Like ketamine and lidocaine, dexmedetomidine has emerged as a reliable adjunct in multimodal anaesthesia strategies, particularly within OFA. Pharmacodynamically,

dexmedetomidine is an analgesedative that exerts its effects through agonism at presynaptic α_2 -receptors. Its antinociceptive properties primarily arise from the enhancement of descending inhibitory pathways. This occurs through activation of inhibitory interneurons, which subsequently synapse onto second-order neurons in the dorsal horn of the spinal cord⁹³.

The sedative effects of dexmedetomidine, however, are attributed to inhibition of noradrenaline release from the locus coeruleus, ultimately contributing to loss of consciousness⁹⁴. Compared with its pharmacodynamic relative clonidine, dexmedetomidine has a markedly higher $\alpha_2:\alpha_1$ receptor affinity (1600:1 vs 200:1) and a shorter elimination half-life (approximately 2 hours vs 8–12 hours)⁹⁵.

The most prominent side effects of dexmedetomidine are reductions in blood pressure and heart rate, particularly when administered as a bolus rather than an infusion⁹⁶. These haemodynamic changes may be related to decreased plasma concentrations of noradrenaline and adrenaline⁹⁷. Since its introduction, dexmedetomidine has also been regarded as relatively sparing of respiratory drive, which contributes to its popularity in critical care settings⁹⁸.

A meta-analysis comparing dexmedetomidine with remifentanyl found that dexmedetomidine provided superior control of APOP, with an effect size corresponding to a 0.7-point reduction on the NRS⁹⁹.

Clonidine

Clonidine is an analgesedative originally developed for blood pressure control in 1966¹⁰⁰. Compared with dexmedetomidine, clonidine has lower affinity for both α_2 - and α_1 -receptors and a longer elimination half-life⁹⁵. It is available in both oral and intravenous formulations, broadening its use beyond the intensive care unit and operating theatre¹⁰¹.

A RCT investigated the optimal perioperative dose of clonidine for postoperative pain management in patients undergoing extensive spinal fusion¹⁰². Patients received loading doses of 5 $\mu\text{g}/\text{kg}$, 3 $\mu\text{g}/\text{kg}$, 2 $\mu\text{g}/\text{kg}$, or placebo, followed by a fixed infusion of 0.3 $\mu\text{g}/\text{kg}/\text{h}$ for 12 hours. All clonidine groups demonstrated dose-dependent improvements in APOP and reductions in opioid consumption. Similar findings were reported in open cholecystectomy procedures¹⁰³. However, in the highest-dose group, significantly more patients required vasopressor support during the first postoperative hour, without additional analgesic benefit compared with lower doses.

For intrathecal administration, pooled data indicate that adding clonidine reduces postoperative opioid consumption and prolongs time to first analgesic request, though at the cost of increased intraoperative hypotension and sedation^{104,105}.

Activation of descending pathways

Antidepressants

Modern anaesthesia increasingly relies on multimodal strategies for both hypnosis and analgesia, ensuring safety and efficacy throughout the perioperative period. As our understanding of the physiological mechanisms underlying perioperative pain and nociception has expanded, new therapeutic opportunities have emerged, including the repurposing of established medications. Among these, antidepressants, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin–noradrenaline reuptake inhibitors (SNRIs), have attracted considerable interest for their potential analgesic effects.

1. TCAs inhibit monoamine oxidase, increasing central concentrations of 5-HT and noradrenaline. This enhances activity within descending inhibitory pathways, thereby suppressing ascending nociceptive transmission from the spinal cord¹⁰⁶. TCAs reach peak plasma concentrations within 2–6 hours and have an elimination half-life of approximately 24 hours, making them less suitable for acute perioperative use¹⁰⁷.

In addition to their primary pharmacodynamic actions, TCAs block postsynaptic histaminergic, cholinergic, and muscarinic receptors, contributing to a broad side-effect profile¹⁰⁶. Before initiating therapy, a thorough cardiovascular assessment is essential, as TCAs may cause QT prolongation, tachyarrhythmias, and even cardiac arrest. This limits their perioperative utility, particularly given that several commonly used perioperative drugs, such as antibiotics and antiemetics, also prolong the QT interval¹⁰⁸.

2. SNRIs increase synaptic availability of 5-HT and noradrenaline by inhibiting their reuptake transporters, thereby enhancing descending inhibitory pain pathways¹⁰⁶. In the perioperative setting, duloxetine is the most extensively studied agent. It is well absorbed and has an elimination half-life of 12–15 hours. Duloxetine is a significant inhibitor of the cytochrome P450 enzyme CYP2D6, which has clinical implications: active metabolites of certain opioids may accumulate more readily, and concomitant use with other antidepressants or synthetic opioids increases the risk of serotonin syndrome¹⁰⁸.
3. SSRIs exert similar effects on pain modulation to SNRIs and TCAs, though with fewer side effects due to greater receptor selectivity. Peak plasma concentrations are reached within 1–8 hours. The most clinically relevant perioperative concern is their association with increased intraoperative bleeding and higher transfusion requirements. This risk is amplified when SSRIs are combined with non-selective NSAIDs or anticoagulants¹⁰⁸.

Randomised controlled trials over the past decade have primarily evaluated duloxetine versus placebo. Overall, a 60 mg (duloxetine) dose has demonstrated beneficial effects on APOP, opioid consumption, and time to first analgesic request¹⁰⁹⁻¹¹¹. However, caution is warranted: the literature is limited by heterogeneity in dosing regimens, timing of administration, and surgical populations, making firm conclusions difficult.

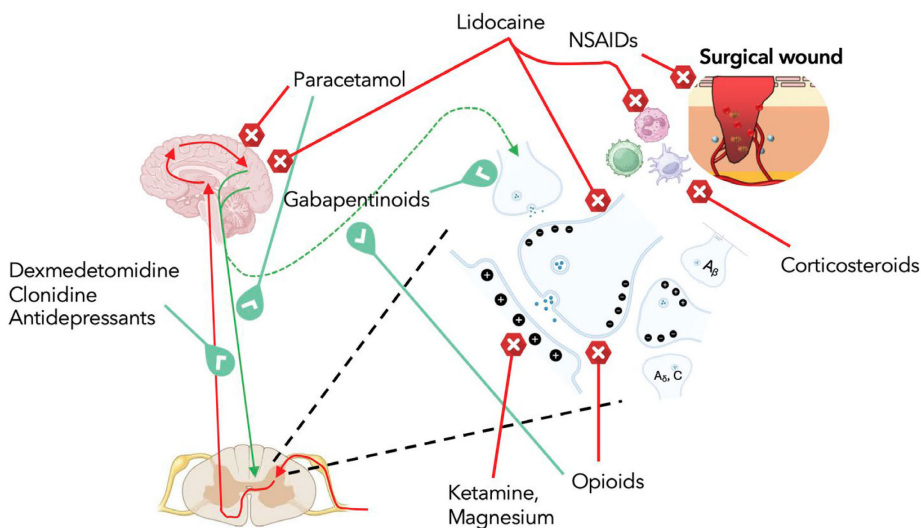


Figure 4. Graphical depiction of the site of action where pharmacologic agents in anaesthesia exert their effect in terms of analgesia and anti-nociception. Red lines illustrate an inhibitory effect and green lines illustrate an excitatory effect, both ultimately leading to anti-nociception described in text in previous sections.

Drug synergism and multimodal anaesthesia

Pharmacology of anaesthetic and analgesic drugs are complex. If pharmacokinetics and safety are considered first, to exclude therapies that are deemed unsafe for the individual patient, pharmacodynamic properties, such as receptor modulation, are as important to consider when setting up an effective individualised multimodal strategy. Drug synergism is a term that basically can be described as when two or more drugs potentiate each other to achieve a more potent effect than if each are used in isolation ($A + B = C$). In contrast, agent additivity is a more relevant description when the combined effect of two or more drugs is equal to the sum of their individual effect ($A + B = AB$)¹¹².

The fundamental principle of multimodal anaesthesia is to achieve better outcomes, or similar pain results with additional benefits and safety, by targeting multiple

receptor mechanisms and pain signalling pathways using smaller doses, rather than fewer pathways with higher doses. Furthermore, there are numerous instances in anaesthesia where anaesthetic drugs play both explicit and implicit roles, which can be effectively utilised⁸⁹.

Remifentanyl is used explicitly to achieve nociceptive control, but contributes implicitly to anti-arousal. Conversely, ketamine at higher doses is used for anti-arousal but contributes to anti-nociception. Magnesium is used for nociceptive control but have implicit effect on muscle relaxation. Modern anaesthesia draws advantages of the benefits from such multifaceted effects of the drugs used. Therefore, it is crucial for clinicians to have a profound understanding of pain physiology and the unique characteristics of each patient and drug therapy.

Empirically, there are significant differences between theory and practice. Theoretically, it is desirable to utilise drug synergism, although it is essential to establish clinical evidence for such advantages since theoretical association might not be intuitive. A small RCT (n = 30 each group) randomly allocated patients to control (remifentanyl), infusion magnesium, infusion lidocaine or infusion magnesium + lidocaine to investigate potential drug synergy between the two latter. Despite the small sample size and the fact that it was a secondary outcome, APOP was significantly lower in the magnesium + lidocaine group compared to the other groups¹¹³. However, these findings precluded the authors to draw any conclusions whether the combination acted as additive or synergistic to each other.

Individualised aspects of pharmacologic management

In the context of clinical trials, it is important to recognise that findings may not be universally generalisable to all patients. As with most research, this limitation underscores the need for clinicians to carefully consider how best to tailor treatment to the individual in front of them. There is also a risk of cognitive bias when excessive emphasis is placed on the surgical procedure itself, rather than adapting therapy to the patient's unique physiological profile, comorbidities, and preferences. The preceding discussion has outlined the current evidence supporting each pharmacological agent. To achieve truly individualised perioperative management, clinicians must integrate population-level data with patient-specific factors, including physiological variability and contextual nuances. Such an approach enables more precise and patient-centred therapeutic decisions.

Paracetamol is widely regarded as one of the most broadly applicable analgesic agents, with very few contraindications across diverse patient groups. As several studies suggest, the primary clinical challenge lies not in safety but in ensuring that therapeutically effective plasma concentrations are achieved. Underdosing remains a recognised issue that may compromise analgesic efficacy. Ondansetron, commonly used as a first-line antiemetic, has been shown to interfere with one of

paracetamol's proposed mechanisms of action, raising important considerations regarding its routine use. This suggests that ondansetron should be administered more judiciously and reserved for cases with clear clinical indications. In the future, therapeutic drug monitoring (TDM) may help optimise dosing as such technologies become more accessible in routine practice.

Non-steroidal anti-inflammatory drugs, particularly selective COX-2 inhibitors, should be administered to all patients who can safely tolerate them. Postoperative AKI remains a significant concern, with long-term consequences that are only beginning to be fully understood. The contribution of NSAIDs administered within the first 24 hours to postoperative AKI is not yet clearly defined, nor is it known whether they act as mediators in the context of perioperative hypotension. This uncertainty is one reason why NSAIDs are generally restricted to patients with normal or near-normal renal function¹¹⁴. Within an individualised anaesthesia framework, the default should be to include COX-2 inhibitors, with omission reserved for cases where patient-specific comorbidities warrant caution. The surgical procedure itself is not a valid reason to avoid NSAIDs. Indeed, guidelines for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC), a procedure associated with a 32% incidence of AKI, still recommend NSAIDs as part of postoperative analgesia^{115,116}.

The use of lidocaine is now both empirically and scientifically supported. In abdominal surgery, this multifaceted drug has some of the strongest evidence for benefit. As with other potent agents, its use should be limited to clinicians with anaesthesia training and remain within current dosing recommendations⁴⁹.

Corticosteroids have a well-established role in multimodal anaesthesia protocols, offering a multifaceted and appealing profile with a high degree of safety¹¹⁷. Most patients, including those with diabetes, may benefit from perioperative corticosteroid administration. A single high dose is typically well tolerated and should be considered standard practice. Current evidence predominantly supports dexamethasone, which has demonstrated efficacy in improving postoperative outcomes

Opioids have historically been central to anaesthetic practice, yet their use is associated with a wide range of adverse effects. The adoption of balanced and multimodal anaesthesia strategies has markedly reduced reliance on opioids. In contrast to foundational agents that should form the base of a bottom-up multimodal approach, opioids are increasingly viewed from a top-down perspective, reserved for selected cases where their use is clearly indicated.

Ketamine and esketamine appear to be gaining prominence as core components of multimodal anaesthesia strategies, particularly when opioid avoidance or reduction is desired. Although theoretically beneficial for patients with preoperative central sensitisation, chronic high-dose opioid dependence, or morbid obesity, large RCTs have not conclusively demonstrated superior outcomes in these subgroups.

It remains unclear whether specific patient populations derive greater benefit from magnesium as an analgesic adjunct compared with a universal approach. No clinical trials have stratified patients by postoperative pain risk. It would also be valuable to determine whether synergistic interactions exist between ketamine/esketamine and magnesium, potentially producing supra-additive NMDA receptor antagonism. Current findings suggest that magnesium's effect size is modest but comparatively favourable relative to other adjuncts, with a low risk of adverse events.

Dexmedetomidine is an analgesic and sedative alternative with relatively strong scientific support. For example, substituting remifentanyl with dexmedetomidine may offer a more favourable risk profile regarding postoperative respiratory complications without compromising analgesic outcomes. However, many aspects of its use in individualised anaesthesia remain insufficiently explored. Concerns regarding hypotension and bradycardia necessitate careful patient selection and dosing, the latter of which is not yet fully elucidated.

Antidepressants appear to be efficacious but carry important side-effect considerations. Tricyclic antidepressants have well-documented benefits for persistent and neuropathic pain, making them particularly suitable for patients at high risk of developing persistent postoperative pain or undergoing high-risk procedures such as mastectomy, thoracotomy, or major joint arthroplasty. In other contexts, TCAs may offer little benefit and pose unnecessary risk. Current evidence suggests that SSRIs do not meaningfully influence APOP and have not been extensively studied in this setting. Their association with increased bleeding risk is particularly relevant in perioperative care. Duloxetine, an SNRI, has accumulating evidence supporting its role in reducing APOP at relatively low and well-tolerated doses. However, more high-quality clinical trials are needed to determine how SNRIs can be optimally integrated into individualised anaesthesia and analgesia strategies.

Practical aspects of perioperative pain

Definition of acute and persistent postoperative pain

The International Association for the Study of Pain (IASP) defines pain (2020) as: “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”¹⁰.

Acute pain arises suddenly and is typically sharp or intense. It serves as a protective warning signal of disease or bodily threat and is commonly triggered by injury, surgery, illness, trauma, or painful medical procedures. Acute pain generally lasts

from a few minutes to less than three to six months and usually resolves once the underlying cause has been treated or has healed¹¹⁸.

Persistent pain, often referred to as chronic pain, is defined as pain that persists or recurs for longer than three months. It may be continuous or intermittent and can arise from an initial injury, an ongoing pathological process, or may have no clearly identifiable cause¹¹⁹. The temporal overlap between acute and persistent pain presents a challenge in perioperative pain research, contributing to substantial heterogeneity in study populations and outcomes.

There is broad agreement that moderate to severe APOP, commonly defined as an NRS ≥ 4 or a VAS score ≥ 40 mm, poses the greatest concern regarding postoperative complications. However, the precise definition and severity thresholds for PPOP remain subjects of ongoing debate.

According to the IASP publication¹⁰, pain is inherently a personal experience shaped by a complex interplay of biological, psychological, and social factors. Importantly, pain must be distinguished from nociception, as pain cannot be inferred solely from sensory neuron activity. Individuals develop their understanding of pain through life experiences, and a person's self-report of pain should be respected. While pain often serves an adaptive function, it can also adversely affect functional capacity, social participation, and psychological well-being. Verbal expression is only one of many ways to communicate pain; the inability to verbalise does not preclude the presence of a painful experience.

Nociception - the unconscious relative to pain

An individual may be subjected to nociception without experiencing pain, just as pain may occur in the absence of nociception. In anaesthesia, these terms are often used interchangeably, which can be misleading. According to the IASP, *nociception* refers to the neural processes involved in the detection, transduction, and transmission of noxious stimuli within the peripheral and central nervous systems¹²⁰. This definition also notes that autonomic responses (e.g., increased blood pressure and heart rate) and motor responses (e.g., withdrawal reflexes) are frequent consequences of nociception.

Pain, by contrast, is a subjective and conscious experience that cannot be fully explained by neural activity alone. It is something the individual perceives, interprets, and "owns". Without awareness, pain cannot exist, although the body may still display nociceptive responses such as tachycardia or hypertension. This distinction is crucial for anaesthesiologists, who must determine whether physiological signs of stress, in the anaesthetised patient, reflect nociception requiring intervention, or whether they are managing a conscious patient reporting pain in the PACU.

Clinically, consider a healthy young individual under general anaesthesia whose heart rate and blood pressure increase by 10% following skin incision. This represents a nociceptive response. Whether treatment is appropriate depends on factors beyond nociception alone. For example, intervention may be justified in a patient with subcritical coronary artery stenosis, where haemodynamic instability could have harmful consequences. In the otherwise healthy patient, however, administering high-dose opioids may cause more harm than benefit due to their side-effect profile.

Now consider the awake, young, and healthy individual in the PACU who reports significant APOP. If all treatment options have been exhausted, side effects such as opioid-related respiratory compromise begin to emerge, and surgical complications have been ruled out, it may be reasonable to accept a higher pain level ($\text{NRS} \geq 4$). This is acceptable only if the physiological stress is tolerable for that individual. However, this approach remains controversial and does not fully account for the psychological distress such pain may cause. In these rare situations, clear communication, trust-building, and setting realistic expectations are essential.

Pain assessments

Pain as an ordinal or continuous scale?

The debate over whether commonly used pain assessment tools, such as the NRS, VAS, and Likert scales, should be treated as ordinal or continuous measures is longstanding and complex within both pain research and statistics¹²¹.

Arguments for treating these scales as *ordinal* emphasise that they provide ranked data without guaranteeing equal intervals between points. A rating of 4 indicates more pain than 3, but the difference between 3 and 4 may not be equivalent to the difference between 4 and 5.

Conversely, some argue that pain scales can be treated as *continuous*, particularly when data are aggregated across large populations. This perspective assumes that intervals between scale points can be considered approximately equal. The implications for statistical analysis are substantial: continuous treatment allows the use of parametric tests (e.g., independent t-tests, ANOVA), which are generally more robust and powerful. Ordinal treatment requires non-parametric tests (e.g., Mann–Whitney U), which are less sensitive because they rely on ranked rather than raw data. Continuous treatment also permits calculation of means and standard deviations, offering more detailed insights into data distribution. Ordinal treatment relies on medians and modes, which are statistically safer when interval equality is uncertain but provide less granularity. As in clinical medicine, statistics is more a matter of nuances of grey rather than being seen as black or white, which puts significant pressure on reasoning and a prespecified statistical plan.

In practice, a compromise has emerged between statistical pragmatism and clinical reality. Researchers frequently analyse pain scores using parametric testing, yet clinicians recognise that the difference between NRS 3 and 4 is not equivalent to the difference between 9 and 10. This discrepancy complicates the translation of research findings into individual patient care. For example, a treatment that reduces APOP by 1 NRS unit may have very different clinical implications depending on whether pain decreases from NRS 4 to 3 or from NRS 10 to 9. Such nuances raise ethical considerations that are difficult to define but important to acknowledge.

Because counterfactual reasoning is challenging in everyday clinical practice, clinicians must rely on the assumption that evidence derived from rigorous methodology is likely to benefit the patients they treat. Recent perioperative literature suggests that the minimal clinically important difference (MCID) after surgery ranges between 1.2 and 1.6 NRS units¹²². However, baseline pain intensity appears to significantly influence what patients perceive as a meaningful change.

Verbal assessment tools

Numeric Rating Scale

The NRS is one of the most commonly used tools in clinical practice for assessing pain intensity. It is a unidimensional measure, focusing solely on the intensity of the pain experience. The scale typically consists of a horizontal line marked from 0 to 10, where 0 represents *no pain* and 10 represents *the worst pain imaginable*. Patients select the number that best reflects their pain at a given moment or over a specified period, such as the previous 24 hours. Responses may be provided verbally, graphically (marking a printed scale), or digitally.

The NRS is widely used because it is quick, simple, reliable, and valid¹²³. However, its limitations stem from its unidimensional nature: pain is inherently multidimensional, and intensity alone may not capture important qualitative aspects. This is particularly evident in neuropathic pain, where descriptors such as burning sensations are not conveyed by intensity ratings alone. Additionally, temporal fluctuations in pain may go unnoticed if assessments are infrequent.

Visual Analogue Scale

The VAS is another widely used tool for assessing subjective experiences, including pain intensity, in both research and clinical practice. It typically consists of a 100-mm horizontal line with endpoints labelled “no pain” and “worst pain imaginable”. Patients mark a point on the line corresponding to their perceived pain, and the score is measured in millimetres from the left endpoint.

The VAS is valued for its simplicity, its ability to be used without verbal communication, and its sensitivity to small changes in pain intensity. It produces quantifiable, continuous data that are easily interpreted in both clinical and research settings. However, its limitations mirror those of the NRS: it captures only one

dimension of the pain experience, is subject to interpersonal variability, and may fail to reflect temporal variability if used infrequently.

Non-verbal assessment tools

Although a consciously given response remains the gold standard for pain assessment, certain clinical scenarios require objective measures. This is particularly relevant for patients who are unable to communicate effectively, such as those who are intubated, sedated, or delirious. In these situations, non-verbal assessment tools have been developed and validated to support clinical decision-making.

It is essential to recognise that vital signs, such as blood pressure, heart rate, and respiratory rate, are neither sensitive nor specific indicators of pain nor nociception¹²⁴. Despite this long-established understanding, vital signs are still frequently and incorrectly used as surrogate markers of pain in clinical practice. Some studies have even compared their assessment tools against vital signs as if these were equivalent comparators¹²⁵, which is methodologically flawed and should not be the focus of postoperative pain research.

Nevertheless, in certain challenging clinical situations, such as patients who are extremely difficult to manage despite adequate analgesic strategies, vital signs may still provide limited insight into sympathetic stress driven by nociception. In these rare cases, it may be reasonable to intervene to reduce physiological stress, even if the relationship to pain is uncertain. However, this approach carries a potential risk of psychological strain and should be used cautiously.

Behavioural pain scale (BPS)

The BPS consists of three domains regarding “facial expression”, “upper limb” and “compliance with ventilation”. Each domain contains four descriptive characteristics scored from 1 to 4, generating a total score ranging from 3 to 12, with higher scores indicating greater pain. A score of ≤ 5 is generally considered acceptable before treatment is recommended¹²⁶. Originally developed for intubated patients, the BPS has since been adapted for non-intubated individuals by replacing the “compliance with ventilation” domain with “vocalisation”.

Since the definition for pain clearly states that the sensation of pain is subjective and completely governed by the patient, the issue of validity is problematic in the unconscious patient. However, for all assessment tools used on unconscious patients this becomes highly important since the results are used to create a trajectory of pain relief associated with treatment. Because pain is defined as a subjective experience, the issue of validity becomes inherently complex in unconscious patients. Nonetheless, for all non-verbal assessment tools, validity is crucial, as these scores guide treatment decisions and shape the trajectory of analgesic management. The BPS has demonstrated high validity in this context¹²⁷. Inter-rater reliability,

reflecting the degree to which different observers assign similar scores, has been shown to be substantial, with weighted kappa coefficients ranging from 0.67 to 0.76¹²⁸. In terms of reliability, one study (n = 864) found that BPS scores varied depending on the type of painful procedure performed¹²⁹. Endotracheal tube repositioning, venous cannulation and tracheal suctioning had a Cronbach's alpha value (e.g. statistic measure showing how well items on a scale consistently measure the same construct, between 0 and 1) of 0.89, 0.87 and 0.70 respectively, corresponding to good and acceptable reliability.

Table 1. The Behavioral pain scale depicted with its domains and their descriptive characteristics used to assess pain in a non-communicable patient. Each domain is graded from 0 to 4, which mounts up to a total score of 3 to 12. A score of ≤ 5 mandates treatment as this could imply significant pain.

Domain	Description	Score
Facial expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation most of the time	2
	Fighting ventilation	3
	Unable to control ventilation	4

Critical care Observation Tool (CPOT)

The CPOT was originally developed to assess pain in critically ill patients who are unable to communicate verbally. It evaluates four behavioural domains, each comprising three observable indicators. Each indicator is scored from 0 to 2, with higher values indicating greater pain intensity. The total CPOT score therefore ranges from 0 to 8, and a score > 2 suggests clinically significant pain warranting further analgesic intervention.

Despite being based on subjective behavioural observations, the CPOT has demonstrated high inter-rater reliability¹³⁰. Regarding validity, studies have shown variable but significant associations between CPOT scores and other pain assessment tools, as well as with physiological indicators of pain. However, when compared with patient self-reported pain, the correlation is weak ($r_s = 0.26$)¹³¹. This is not unexpected, given that pain is inherently subjective and cannot be fully captured through behavioural proxies.

Table 2. The Critical care Observation Tool depicted with its domains and their descriptive characteristics used to assess pain in a non-communicable patient. Each domain is graded from 0 to 2, which mounts up to a total score of 0 to 8. A score of > 2 mandates treatment as this could imply significant pain.

Domain	Behavioural indicators	Score
Facial expression	No muscular tension observed	Relaxed, neutral - 0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense - 1
	All of the above facial movements plus eyelid tightly closed	Grimacing - 2
Body movements	Does not move at all	Absence of movements - 0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection - 1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness - 2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed - 0
	Resistance to passive movements	Tense, rigid - 1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid - 2
Compliance with ventilation OR	Alarms not activated, easy ventilation	Tolerating ventilation or movement - 0
	Alarms stop spontaneously	Coughing but tolerating - 1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator - 2
Vocalisation (extubated patients)	Talking in normal tone and sound	Talking in normal tone or sound - 0
	Sighing, moaning	Sighing, moaning - 1
	Crying out, sobbing	Crying out, sobbing - 2

Individual preoperative prediction methods for postoperative pain

Demographic and lifestyle related

Non-modifiable risk-factors

Patients present with a wide range of risk factors during the perioperative period. Some of these can be modified with timely intervention, whereas others cannot. Nonetheless, recognising non-modifiable risk factors remains essential, as they allow anaesthesia providers to anticipate challenges, tailor perioperative care, and potentially reduce postoperative pain and related complications.

Gender

A substantial body of research has examined predictors of preoperative and postoperative pain¹³². Across these studies, female gender consistently emerges as an independent risk factor for worse postoperative pain outcomes^{133,134}. A large international study spanning 17 countries found that 45% of women reported experiencing pain at some point in their lives, compared with 31% of men¹³⁵.

Hormonal influences are frequently proposed as an explanation for these differences. In general pain research, fluctuations in pain sensitivity across the menstrual cycle and around menopause have been observed¹³⁶. Women receiving hormone replacement therapy have also been shown to experience heightened pain sensitivity¹³⁷.

Genetic factors may also contribute. A specific allele of the OPRM1 gene, which encodes the μ -opioid receptor, has been associated with increased pain sensitivity in women and reduced sensitivity in men¹³⁸.

However, biological explanations alone are insufficient. Social and psychological factors, including gender norms surrounding emotional expression and pain reporting, also influence both the experience and communication of pain¹³⁹. These factors may likely contribute to the observed gender differences in postoperative pain outcomes.

Age

Age is another well-established predictor of postoperative pain. Research consistently shows that younger patients report higher levels of postoperative pain compared with older individuals¹³⁴. Several mechanisms have been proposed:

- Degeneration of peripheral nerve fibres with age, including A δ , C, and A β fibres, may reduce the ability to transmit noxious stimuli such as heat and pressure¹⁴⁰. The point at which this becomes clinically significant remains unclear.
- Age-related changes in inflammatory responses to surgical trauma may alter postoperative pain perception¹⁴¹.
- Neurophysiological changes affecting neurotransmitters, receptors, and both ascending and descending pain pathways may also contribute¹⁴².

Importantly, although older adults may have reduced pain sensitivity, their pain tolerance is often lower due to high frailty and common comorbidities such as obstructive lung disease, obstructive sleep apnoea (OSAS), and coronary artery disease. These conditions increase vulnerability to pain-related complications, highlighting the need for careful, individualised anaesthesia planning¹⁴³.

Modifiable risk-factors

Body mass index

Body weight is a complex and multifaceted factor in perioperative medicine, influencing both risk and postoperative outcomes. Obesity is associated with an increased prevalence of preoperative comorbidities and postoperative complications, including desaturation, wound infections, and greater intraoperative blood loss^{144,145}. Paradoxically, however, several studies have demonstrated that overweight and mildly obese individuals may have lower mortality rates than those who are underweight, a phenomenon commonly referred to as the obesity paradox¹⁴⁶.

In a large cohort where complications were graded by severity rather than type, obesity did not emerge as an independent predictor of adverse outcomes¹⁴⁵. With respect to postoperative pain, research has not established a consistent association between obesity and pain intensity^{147,148}.

Opioid consumption is often used as a surrogate marker for APOP, but this approach is problematic in obese patients. Their larger volume of distribution naturally requires higher opioid doses, introducing bias and complicating interpretation. At the same time, clinicians often exercise greater caution with opioids in this population due to the heightened risk of postoperative pulmonary complications.

Although findings remain inconsistent, some hypotheses suggest that obesity-related inflammation and comorbidities, such as osteoarthritis, may influence pain modulation¹⁴⁹. Opioid-free anaesthesia may be a viable option for these patients, as it has been shown to be comparable to standard care while theoretically reducing opioid-related side effects¹⁵⁰.

Given these complexities, a holistic and individualised approach to anaesthesia and analgesia is essential. This includes multimodal anaesthetic strategies, vigilant respiratory monitoring, and coordinated multidisciplinary efforts to promote early postoperative mobilisation.

Sleep quality

Sleep is fundamental to overall health and well-being. Poor sleep quality has been associated with an increased risk of APOP, with a clustered odds ratio of 2.7 (95% CI 2.0–3.6)¹⁵¹. However, further clinical research is needed to fully elucidate this relationship.

The Pittsburgh Sleep Quality Index (PSQI) is a widely used self-report questionnaire that assesses sleep quality over a one-month period¹⁵². The PSQI evaluates seven key components of sleep: 1. Subjective sleep quality, 2. Sleep latency (time it takes to fall asleep), 3. Sleep duration, 4. Habitual sleep efficiency

(ratio of total sleep time to time spent in bed), 5. Sleep disturbances (frequency of sleep interruptions), 6. Use of sleep medication, 7. Daytime dysfunction¹⁵².

Each component is scored from 0 to 3, yielding a total score of up to 21, with higher scores indicating poorer sleep quality. A PSQI score of ≥ 5 is commonly used to categorise individuals as having poor sleep quality in research settings¹⁵¹.

If poor sleep can be identified and improved before surgery, postoperative pain outcomes may be enhanced. For example, one study investigated the effect of administering 10 mg of zolpidem the night before surgery. Despite a small sample size, the intervention group demonstrated improvements in both APOP and opioid consumption¹⁵³. Currently, the American Society of Anaesthesiologists (ASA) provides guidelines for optimising perioperative care in patients with obstructive sleep apnoea (OSAS)¹⁵⁴, but no specific recommendations exist for preoperative sleep optimisation in the general population.

Although evidence suggests that sleep quality influence postoperative pain, improving sleep preoperatively is not straightforward. A systematic review of 47 studies examining preoperative sleep interventions found inconsistent results¹⁵⁵. Moreover, studies reporting positive effects were graded as having low to very low certainty of evidence. This indicates that, while poor sleep might be risk factor for postoperative pain, effective intervention may be more challenging than anticipated.

Preoperative pain

Preoperative pain is a well-established and powerful risk factor for both APOP and PPOP^{134,156}. In a large cohort study ($n = 4,733$), preoperative pain was associated with an odds ratio of 1.21 (95% CI 1.10–1.32) for developing moderate to severe APOP¹³⁴. A qualitative synthesis of 48 studies ($n = 23,037$) similarly identified preoperative pain as one of the most consistent and independent predictors of APOP¹⁵⁷.

While postoperative pain is strongly linked to preoperative pain, it is essential to distinguish this association from the underlying physiological mechanisms in order to establish true causation. Until such mechanisms are fully elucidated, preoperative pain should be viewed as a surrogate marker of an upregulated pain system rather than a causal factor in itself.

Mechanistically, preoperative pain is thought to sensitise ascending nociceptive pathways, particularly within the dorsal horn of the spinal cord, where enhanced NMDA-receptor signalling plays a central role. Psychosocial stressors may further potentiate, but do not independently initiate, this sensitisation¹⁵⁸. Conversely, persistent pain conditions can lead to depression, which is known to alter central 5-HT-signalling^{158,159}. Disruption of 5-HT pathways may impair descending inhibitory control, thereby amplifying pain perception.

Persistent pain and memory share overlapping neurobiological mechanisms. The hippocampus, amygdala, and anterior cortex are involved in encoding and consolidating both memory and pain experiences¹⁶⁰. Persistent pain is thought to arise, in part, from memory-induced neuroplasticity within limbic–cortical circuits. Functional imaging studies have demonstrated spatiotemporal reorganisation, with neural activity shifting from sensory regions to emotional centres within the limbic system. This supports the concept that persistent pain may represent the persistence of a “pain memory”¹⁶⁰. Completing this pain–memory cycle, chronic pain syndromes intensify the emotional salience of nociceptive inputs, making it increasingly difficult to extinguish maladaptive pain memories. It is therefore plausible that multimodal strategies, combining multimodal anaesthesia with preoperative cognitive interventions, may offer synergistic benefits in preventing or attenuating PPOP¹⁶¹.

Smoking

Tobacco use is well known to increase the risk of cardiovascular disease and cancer¹⁶². In perioperative medicine, smoking is associated with elevated risk across virtually all types of surgical procedures and contributes to a range of postoperative complications¹⁶². Smoking has also been linked to APOP^{134,163}. A meta-analysis including 15,764 patients demonstrated an increased risk of APOP among smokers, with an odds ratio of 1.33 (95% CI 1.09–2.21)¹³⁴.

The mechanisms underlying this association remain incompletely understood. One hypothesis is that smoking impairs tissue healing and perfusion, thereby increasing nociceptive input. Preclinical work has shown that smokers exhibit higher levels of inflammatory markers, including C-reactive protein (CRP), fibrinogen, and interleukin-6 (IL-6), alongside reduced natural killer cell activity and increased regulatory T-cell levels¹⁶⁴. These immunological alterations may contribute to dysregulated inflammation and heightened pain sensitivity.

Given that smoking is a modifiable risk factor, preoperative cessation appears to be a logical strategy. A meta-analysis of 16 randomised controlled trials (n = 2,940) found that patients receiving structured cessation support were significantly more likely to stop smoking before surgery (OR 1.64, 95% CI 1.30–2.07)¹⁶⁵. However, substantial heterogeneity ($I^2 = 76\%$) limits the generalisability of these findings. Notably, secondary outcomes, including postoperative pulmonary complications and ICU admissions, did not differ significantly between groups. Importantly, postoperative pain outcomes were not assessed, leaving uncertainty regarding whether smoking cessation improves APOP¹⁶⁵.

These gaps highlight the need for future studies to evaluate effective preoperative interventions for active smokers, particularly with respect to pain outcomes and perioperative recovery.

Psychometric analysis

Psychological strain is a broad and somewhat imprecise term encompassing common psychological constructs such as anxiety, depression, and catastrophic thinking. These factors have been extensively studied in relation to postoperative pain, as researchers attempt to understand how mental health influences recovery. However, the evidence remains inconsistent and difficult to interpret, largely due to substantial heterogeneity across studies.

A major challenge lies in how psychological strain is measured. Most studies rely on validated self-report questionnaires. Although these tools provide standardised assessment, they introduce several limitations. Respondents may misinterpret questions or struggle to capture the complexity of their emotional state within fixed-choice formats. Various forms of response bias, such as acquiescence bias or socially desirable responding, may further distort results. Additionally, ambiguous or broadly phrased items can lead to divergent interpretations, undermining the validity of the constructs being measured¹⁶⁶. These methodological issues complicate efforts to draw firm conclusions about the role of psychological strain in postoperative pain.

Pain catastrophising

Pain catastrophising is a psychological construct describing an exaggerated negative orientation toward actual or anticipated pain. It comprises three core components: rumination (persistent focus on pain), magnification (overestimation of pain severity), and helplessness (a sense of being unable to manage pain).

Individuals with high levels of catastrophising tend to dwell on their discomfort, perceive pain as more threatening, and feel powerless in response to it¹⁶⁷.

The most widely used tool for assessing this construct is the Pain Catastrophising Scale (PCS)^{167,168}. This 13-item self-report questionnaire asks individuals to rate the frequency of pain-related thoughts and feelings on a scale from 0 (“not at all”) to 4 (“all the time”). Higher scores indicate greater catastrophising, and the scale is structured to reflect the three subdomains described above.

Although several small studies have reported associations between PCS scores and postoperative pain, findings have been inconsistent and often arise from secondary analyses¹³². Certain elements, particularly the helplessness subdomain, may influence postoperative pain perception, but the overall predictive value of the PCS appears limited. Consequently, its clinical utility in perioperative medicine remains uncertain.

Mood disorder – Depression

Depression can profoundly affect an individual’s engagement with daily life, impairing emotional resilience, cognitive function, and physical well-being.

Neurobiologically, depression is associated with disrupted 5-HT and noradrenergic signalling within the CNS. Such disruptions weaken descending inhibitory pain pathways, potentially lowering pain thresholds and amplifying pain perception¹⁶⁹. Cognitive symptoms, including impaired concentration and decision-making, may further hinder a patient's ability to adhere to postoperative instructions, increasing the risk of complications and heightened pain experience¹⁷⁰.

A large meta-analysis examining the relationship between preoperative depression and postoperative pain outcomes drew on 60 clinical trials involving more than 500,000 patients¹⁷¹. The included studies varied substantially in design (42 prospective, 18 retrospective) and in the tools used to assess depression, such as the Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), CES-D, Hamilton Depression Scale, and the 12-item Short Form Survey. This heterogeneity limits the certainty of the findings. Nonetheless, the analysis identified a statistically significant association between preoperative depression and APOP, with a standardised mean difference of 0.97 (95% CI 0.37–1.56, $p = 0.009$) NRS-units¹⁷¹.

No clear association was found between depression and PPOP at 3–6 months. However, when follow-up extended beyond 6 months, a modest association emerged (mean difference 0.45, 95% CI 0.23–0.68, $p < 0.001$). Importantly, these results were not adjusted for key confounders such as age, gender, comorbidities, surgical variables, anaesthetic technique, or other psychological factors, introducing a significant risk of bias¹⁷¹. A more recent meta-analysis focusing on spinal surgery (44 studies, $n = 21,452$) did not find a consistent association between preoperative depression and postoperative pain in this subgroup¹⁷².

Although depression may be associated with postoperative pain outcomes, its precise impact remains uncertain. Depression is a multifaceted condition that cannot be fully captured by brief questionnaires, and its severity, duration, and context vary widely, particularly in vulnerable populations such as children and the elderly. External factors, including social support, socioeconomic status, and pre-existing chronic pain, further complicate interpretation. While depression is undoubtedly relevant to surgical recovery, its exact role in shaping postoperative pain requires more nuanced and controlled investigation¹⁷³.

Mood disorders – Anxiety

Anxiety and depression are often grouped together in clinical discussions due to their frequent co-occurrence and overlapping features. However, it is important to recognize their distinct characteristics, especially in the context of surgical care, as they may influence perioperative outcomes in different ways. Depression typically manifests as persistent sadness, anhedonia, low energy, and fatigue, whereas anxiety is characterised by excessive worry, fear, restlessness, and hyperarousal¹⁷⁴. Although both conditions share common aetiological factors and respond to similar

therapeutic approaches, their clinical presentations and physiological consequences differ.

Preoperative anxiety is highly prevalent, though reported rates vary depending on the assessment tool used^{174,175}. Common instruments include the State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), Hospital Anxiety and Depression Scale–Anxiety (HADS-A), Amsterdam Preoperative Anxiety and Information Scale (APAIS), Perioperative Anxiety Scale-7 (PAS-7), and the Yale Preoperative Anxiety Scale (YPAS).

Patients with preoperative anxiety often require up to 20% more anaesthetic agents, which can lead to delayed emergence from anaesthesia (by approximately 15 minutes) and increased intraoperative haemodynamic instability, around 30% more events compared with non-anxious patients^{174,176}. These individuals also tend to experience more intense postoperative pain¹⁷⁴.

Given these findings, identifying and managing preoperative anxiety is crucial. Interventions such as preoperative counselling, anxiolytic medication, and individualised anaesthetic planning may help mitigate the adverse effects of anxiety. Proactive management has the potential to improve patient comfort, reduce postoperative pain, and shorten hospital stays. However, implementing routine psychological assessment in preoperative care remains challenging. Uncertainty persists regarding which screening tools to use, optimal timing, and how best to interpret results. Additionally, the resources required for multidisciplinary psychological support may be difficult to implement in low-resource settings, limiting the feasibility of such interventions.

Self-expected postoperative pain

Self-expected pain refers to the level of pain an individual anticipates experiencing in a specific context, such as undergoing surgery. These expectations may influence the actual pain experienced postoperatively, reflecting the psychological principle that expectations shape perception, a phenomenon often described as a self-fulfilling prophecy¹⁷⁷.

Self-expected pain is typically assessed using self-report tools. Patients may be asked to rate their anticipated pain on the Numerical Rating Scale (NRS) from 0 to 10, where 0 represents no pain and 10 the worst pain imaginable. Alternatively, the Pain Self-Efficacy Questionnaire (PSEQ) has been validated for this purpose¹⁷⁸. Although originally designed to measure confidence in managing pain, PSEQ scores also reflect patients' expectations regarding their ability to cope with postoperative pain¹⁷⁹. Other validated instruments include the Expectation for Treatment Scale (ETS)¹⁸⁰ and the Treatment Expectation Questionnaire (TEX-Q)¹⁸¹.

Preoperative pain self-efficacy, as measured by the PSEQ, is increasingly recognised as a predictor of postoperative outcomes. Higher PSEQ scores are associated with lower postoperative analgesic requirements. For example, in patients undergoing bilateral knee replacement, greater self-efficacy was linked to significantly lower NSAID use three months after surgery ($\beta = -0.27$, $p = 0.04$)¹⁸². Patients with low PSEQ scores (< 22) were twice as likely to use opioids daily before surgery¹⁸³ and also reported higher levels of pain, disability, fatigue, and depression. These findings support psychological models emphasising coping confidence as a key determinant of pain recovery¹⁸⁴. Although most evidence is observational and direct links to opioid use remain limited, the PSEQ shows promise as a screening tool to identify at-risk patients and guide targeted interventions. It has even been proposed for inclusion in a core outcome set for perioperative clinical trials¹⁸⁵.

Several studies illustrate the impact of pain expectations. In a prospective study ($n = 996$), patients who expected moderate pain ($\text{NRS} \geq 4$) had significantly higher rates of APOP and opioid consumption, and women reported greater anticipated pain (adjusted OR 1.52; 95% CI 1.13–2.06)¹⁸⁶. More recent studies have concluded that expected pain was the only independent predictor of moderate to severe APOP during the first three postoperative days^{187,188}. Treatment expectations, measured by TEX-Q, also influence pain outcomes in patients with lower back pain¹⁸⁹. Notably, one causal analysis suggested that treatment expectations may act as a mediator between depression and pain intensity.

Quantitative sensory testing

Quantitative sensory testing (QST) is a method designed to assess individual variations in pain signalling by applying controlled noxious stimuli of different modalities at various anatomical sites and time points. Patients then report their subjective experience of these stimuli, allowing researchers to calculate pain thresholds. These thresholds have been associated, albeit inconsistently, with the risk of developing both APOP and PPOP¹³². QST has been used in research exploring individual pain prediction, but almost exclusively as a secondary outcome in observational clinical trials. Its value as a predictive tool has been questioned due to several practical and methodological limitations. QST demonstrates substantial intra-individual variability, lacks standardised protocols across studies, is time-consuming to administer, and has produced inconsistent results¹⁹⁰. These issues limit its feasibility and reliability in routine clinical practice.

The qualitative evidence presented in this thesis represents the first attempt to systematically compile and evaluate the role of QST as a predictive method for postoperative pain¹³². While the concept remains scientifically appealing,

particularly in the context of personalised pain medicine, current evidence suggests that QST is not yet ready for widespread clinical implementation.

Cold QST

Cold-based quantitative sensory testing is commonly performed using the cold pressor test, in which a participant immerses a limb into a container of cold water maintained at 0–4 °C¹⁹¹. The Cold Pain Threshold (CPT_h) is determined by asking the participant to report the moment the cold stimulus becomes painful, typically defined as reaching an NRS score of ≥ 4 . Cold Pain Tolerance (CPT) is the duration for which the participant can keep the limb immersed before the pain becomes intolerable¹⁹¹. For both CPT_h and CPT, the outcome measure is the time to pain, recorded in seconds.

Heat QST

Heat-based QST is performed using a thermode applied to a predefined skin area. Participants are first exposed to a non-painful baseline temperature of 32 °C, after which the temperature increases gradually at 1 °C per second to a maximum of 50 °C to avoid tissue injury. From this, two measures are derived: the Heat Pain Threshold (HPT_h) and Heat Pain Tolerance (HPT). These values are frequently used in research exploring individual pain sensitivity and postoperative pain prediction¹⁹².

Pressure QST

Pressure-based QST assesses pain sensitivity, central sensitisation, and the function of descending inhibitory pathways. A commercial algometer is typically used to apply pressure at a controlled rate (30–50 kPa/s) to a prespecified anatomical site until the participant reports the sensation as painful. The pressure at this point is recorded as the Pressure Pain Threshold (PPT_h)¹⁹³.

Standard blood pressure cuffs have also been used as an alternative method¹⁹⁴. In this protocol, the cuff is inflated to 60 mmHg, followed by a steady increase in pressure at 20 mmHg/s until the participant reports pain corresponding to NRS ≥ 4 . The PPT_h is then extrapolated from the inflation pressure that elicits the painful sensation.

Electric QST

Electric-based quantitative sensory testing follows the same principles as other QST modalities. The primary outcomes are the Electric Pain Threshold (EPT_h) and Electric Pain Tolerance (EPT)¹⁹⁵. The test is typically performed using surface electrodes placed on a predefined body area. A low-intensity electrical stimulus is initiated, after which the pulse intensity is increased in incremental steps.

The EPTh is determined by instructing the participant to report when the stimulus first becomes painful, commonly defined as reaching an NRS score of ≥ 4 . The EPT represents the point at which the participant can no longer tolerate the electrical stimulus due to its painful intensity.

Temporal summation of pain

Temporal summation of pain (TSP) is a phenomenon in which repeated noxious stimuli of identical intensity lead to a progressively increased perception of pain. It is considered an experimental model of central sensitisation.

One common method for assessing TSP involves applying a metal pinprick stimulator of standardised weight to a predefined skin area¹⁹⁶. After an initial single stimulus, a sequence of identical stimuli is delivered in rapid succession. Participants then compare their pain experience from the first and final stimulus. An increase in perceived pain indicates the presence of temporal summation, reflecting heightened CNS responsiveness.

Conditioned pain modulation

Conditioned pain modulation (CPM) is used to evaluate the function of the descending inhibitory pain pathways¹⁸⁰. The method involves applying a test stimulus to a predefined body area and recording the associated pain rating. A second, more intense conditioning stimulus is then applied to a different body region. The test stimulus is subsequently repeated, and the participant again rates the pain.

The difference in pain ratings before and after the conditioning stimulus serves as a surrogate measure of endogenous pain inhibition. A reduction in perceived pain following the conditioning stimulus suggests effective descending inhibitory control, whereas little or no reduction may indicate impaired modulation¹⁸⁰.

Procedural sensory testing

Procedural sensory testing represents a pragmatic variant of QST, using routine clinical procedures to elicit a controlled painful stimulus. The aim is to identify individuals with an up-regulated pain signalling pathway, thereby offering a practical alternative to laboratory-based QST. As with other predictive tools, these methods do not directly assess the underlying mechanisms of inadequate pain modulation, such as impaired descending inhibition, central sensitisation, or mismatched patient expectations. Instead, they infer a phenotype associated with heightened pain responsiveness. This reduction in mechanistic resolution has important implications for interpreting how best to manage individuals identified as high risk.

Venous cannulation pain

Venous cannulation is performed daily in anaesthetic practice and, when combined with a validated pain assessment scale, has been explored as a potential method for identifying patients at increased risk of APOP. Several independent observational studies have reported a significant association between venous cannulation pain (VCP) and subsequent APOP, most notably in laparoscopic surgery but also in mixed surgical populations¹⁹⁷⁻¹⁹⁹.

Additionally, anticipatory pain, whether a patient expects the procedure to be painful, may influence the reported pain intensity and vary over time within the same individual.

Standardising or statistically adjusting for all these variables would improve internal validity but at the cost of substantially reducing external validity, limiting the generalisability of findings to real-world clinical practice. As such, while venous cannulation pain shows promise as a pragmatic screening tool, its methodological constraints must be carefully considered.

Local anaesthesia infiltration

Local anaesthetics (LA) are weak bases formulated in an acidic solution to maintain stability and solubility. When an unbuffered LA is injected into tissue, both chemical and mechanical nociceptors are activated, producing a noxious stimulus²⁰⁰. Because LA infiltration is routinely performed in many institutions prior to procedures, it presents an appealing opportunity for pragmatic assessment in clinical trials.

When 2.5 ml of lidocaine was injected prior to spinal anaesthesia placement, a positive correlation was observed between pain during infiltration and APOP following caesarean section ($r_s = 0.53$, $p < 0.001$)²⁰¹. Moreover, this method demonstrated strong predictive performance for severe APOP, with a sensitivity of nearly 92% and a specificity of approximately 93% at a cut-off of $\text{NRS} \geq 7.0$. These findings have recently been reproduced in the same surgical population ($r_s = 0.58$, $p < 0.001$)²⁰².

These results suggest that pain during LA infiltration may serve as a practical surrogate marker for heightened pain sensitivity and increased risk of APOP. However, further research is needed to determine its generalisability across different procedures and patient populations.

Real-time nociception monitoring

Skin conductance

Skin conductance (SC, MedStorm Innovation AS, Oslo, Norway) is a physiological measure reflecting sympathetic nervous system activity in response to nociceptive stimuli. The principle behind SC is that nociception and stress increase sweating, which alters the electrical conductance of the skin²⁰³.

Activation of the sympathetic nervous system stimulates eccrine sweat glands, primarily located on the palms and soles. This increases sweating and enhances the skin's electrical conductance. By applying a small electrical current and measuring conductance changes, sympathetic tone can be extrapolated as a surrogate for nociception in the intraoperative setting.

In a 2006 study, SC was compared with NRS in 25 PACU patients²⁰⁴. For each NRS score, the number of SC fluctuations per second (NFSC) was recorded by an unblinded assessor. SC itself did not correlate with APOP, but NFSC showed a moderate correlation ($r = 0.625$, $p < 0.01$)²⁰⁴. The authors concluded that SC outperformed HR and BP in detecting pain, although this comparison is limited since HR and BP are not appropriate reference standards. In a subsequent intraoperative study of 73 patients, NFSC again correlated with APOP ($r = 0.477$, $p < 0.01$), whereas HR and BP did not²⁰⁵. In both studies, fentanyl administration produced a significant decrease in NFSC, an effect not observed in HR or BP^{204,205}.

Despite these findings, using SC to measure intraoperative nociception is challenging. Many anaesthetic drugs, including propofol and sevoflurane, suppress sympathetic tone and thereby reduce SC fluctuations, affecting reliability. Individual variability in drug response, influenced by factors such as age, weight, and baseline sympathetic activity, further complicates interpretation²⁰⁶. External factors can also interfere with SC readings; for example, changes in room temperature or humidity may alter conductance independently of nociception. Procedures involving abrupt temperature shifts, such as HIPEC, can therefore produce misleading SC values²⁰⁷.

Nociception level

The Nociception Level (NOL) index is a non-invasive technology (Medasense, Ramat Gan, Israel) developed to continuously and objectively quantify intraoperative nociception in real time. It is based on a multiparameter composite of autonomic signals, including HR variability (photoplethysmography), SC, movement (accelerometer), and temperature²⁰⁸. The displayed value is generated through random forest analysis and machine-learning algorithms, producing a unitless score from 0 to 100, where values above 25 indicate substantial nociceptive input²⁰⁹.

A recent meta-analysis examined whether NOL-guided intraoperative analgesia improved postoperative pain outcomes²¹⁰. A total of 662 patients were included, with heterogeneity of $I^2 = 48\%$ for APOP and $I^2 = 15\%$ for opioid consumption. Clustered data showed small but statistically significant reductions in APOP (mean difference NRS -0.46 , 95% CI $-0.88 - 0.03$) and opioid consumption (mean difference -1.04 mg, 95% CI $-1.94 - 0.15$). However, these differences were not clinically meaningful. Secondary outcomes, including PONV and PACU stay, showed no improvement.

Individual RCTs have produced mixed findings. In one study, NOL guidance resulted in higher intraoperative fentanyl administration without improving APOP²⁰⁸. In prostatectomy, NOL-guided analgesia reduced opioid consumption (lower than control and SPI, but higher than pupillary pain index), yet was associated with greater cortisol and ACTH release at lower remifentanyl rates, without clear recovery benefits²¹¹. In thoracic surgery, NOL detected major sympathetic tone changes but did not predict postoperative outcomes²¹². In ICU patients, NOL detected nociception better than chance (weighted prediction probability 0.67 vs 0.50) but performed worse than RASS and Patient state index (Masimo Corporation, Irvine, CA)²¹³.

NOL offers continuous, non-invasive monitoring of nociception and may support more individualised intraoperative opioid titration. However, its clinical benefit remains uncertain. Predictive accuracy is moderate, threshold values lack robust validation, and effects on opioid consumption and stress responses are inconsistent. Until procedure-specific protocols and adaptive algorithms are developed, NOL should be viewed as a complementary tool rather than a replacement for clinical judgement and multimodal monitoring.

Surgical pleth index

The Surgical Pleth Index (SPI, GE HealthCare, Chicago, Illinois, USA) is a monitoring tool used to assess nociception in the intraoperative setting. It is derived from photoplethysmographic signals measured by a pulse oximeter. SPI is calculated by normalising the plethysmographic pulse wave amplitude (PPGA) and the heart beat interval (HBI, the time between heartbeats in milliseconds, reflecting sympathetic tone), and combining these values using the formula: $SPI = 100 - (0.33 \times HBI + 0.67 \times PPGA)^{214}$.

Several studies have randomised patients to receive intraoperative analgesia guided by SPI or by conventional parameters such as HR and BP^{215,216}. Overall, these studies favoured SPI, reporting reduced intraoperative opioid use, shorter extubation times, improved recovery, and lower rates of APOP. However, most of these trials were small. In contrast, a larger study comparing 246 SPI-guided patients with 248 controls found no significant benefit of SPI in the intraoperative setting²¹⁷.

A proposed SPI cut-off of 30 for predicting APOP has shown poor diagnostic performance, with sensitivity of 0.61, specificity of 0.58, and an AUC of 0.59, essentially comparable to MAP, HR, and BP based on ROC analysis²¹⁸. One observational study reported that SPI > 50 predicted both postoperative fentanyl use and APOP in the PACU and at 24 hours²¹⁹.

As with any device reliant on vital parameters, SPI has notable limitations. Its reliability is significantly influenced by age-related differences in HR variability and vascular properties²¹⁴. In paediatric patients, higher vascular compliance and baseline HR may lead to underestimation of SPI values, whereas increased arterial stiffness in older adults affects SPI in the opposite direction. These differences suggest that age-specific reference ranges are necessary for accurate interpretation.

The effectiveness of SPI-guided analgesia also varies with anaesthetic technique. In clinical studies, total intravenous anaesthesia (TIVA) tends to reduce opioid use, while inhalational agents such as sevoflurane produce mixed results²¹⁴. Furthermore, SPI shows considerable discrepancies when compared with the clinical gold standard, verbal NRS/VAS, raising questions about its validity²²⁰. To be fair, SPI is intended to measure nociception rather than pain itself, but the mismatch remains a potential concern.

Processed electroencephalography

Electroencephalography (EEG) is a diagnostic method used to detect various brain disorders by measuring the electrical activity generated by neurons in the brain²²¹. When large groups of neurons fire synchronously, electrodes placed on the scalp can detect their combined electrical activity as voltage fluctuations. Electrode placement follows standardised systems such as the International 10–20 system²²², which ensures consistent positioning and reproducible measurements.

Interpreting raw EEG requires several processing steps: filtering to remove frequencies outside the range of interest, segmentation into epochs, feature extraction (including amplitude, frequency, and phase), and frequency analysis to examine power distribution across delta, theta, alpha, beta, and gamma bands²²¹. Full interpretation of EEG signals demands specialised expertise that most anaesthesia providers do not possess.

To make EEG more accessible in the perioperative setting, raw EEG is processed (pEEG) into simplified indices using proprietary algorithms. These indices reflect the depth of anaesthesia or sedation and are derived from parameters such as the EEG power spectrum. Several devices are designed specifically for perioperative use, including BIS (Medtronic, Minneapolis MN), Entropy (GE Healthcare, Chicago IL), Narcotrend (MT MonitorTechnik GmbH & Co, Hannover, Germany), and Sedline (Masimo Corporation, Irvine CA). Typically, electrodes are placed only on the forehead, meaning that pEEG reflects activity exclusively from the prefrontal cortex.

In the perioperative setting, pEEG is used to monitor anaesthetic depth and reduce the risk of both under- and over-sedation, with emphasis on the latter²²³. When individualising anaesthesia depth, clinicians interpret the algorithm-generated index alongside additional features such as the spectral edge frequency (SEF), colour spectrograms, raw-EEG signatures and measures of burst suppression.

Spectral edge frequency (SEF) is a measure used in EEG analysis to determine the frequency below which a specified percentage of the total power of the oscillating signal is contained²²⁴. The value is derived from cumulative power calculations, typically using Fourier Transform methods, to identify the frequency below which a given proportion of the total power lies (for example, SEF90 or SEF95)²²⁵. During general anaesthesia with agents such as GABA_A-agonists and opioids, a high-power spectrum in the slow/delta and alpha ranges is expected, corresponding to an SEF95 of approximately 8–12 Hz²²⁴.

The colour spectrogram is a visual representation of EEG power distribution over time²²⁴. To make interpretation more intuitive, power is colour-coded from high to low (red to blue) and plotted across the relevant frequency bands. Under general anaesthesia with GABA_A-agonists and opioids, adequate anaesthetic depth is typically reflected by high power (red) in the slow/delta and alpha bands, and low power (green to blue) in the theta, beta, and gamma bands. Importantly, the colour spectrogram is interpreted in conjunction with other pEEG parameters. A coherent picture of appropriate anaesthetic depth includes a device-specific index within the recommended range, an SEF95 between 8 and 12 Hz, absence of burst suppression, and stable vital signs. Only when these elements align can the spectrogram be reliably interpreted as indicating adequate anaesthesia.

When a patient is under general anaesthesia, certain colour spectrogram patterns have been associated with nociception. These include brief, high-frequency activation bursts that tend to appear during surgical stimulation²²⁶. Three phenomena are commonly described in this context: delta arousal (a transient increase in delta-oscillation activity), alpha dropout (a temporary loss of alpha oscillations), and beta arousal (a transient increase in beta-oscillation activity). All typically occur during periods of intense surgical stimulation.

In the intensive care setting, these EEG changes have been shown to differentiate pain, as assessed by the Behavioural Pain Scale, more effectively than traditional clinical signs of increased sympathetic tone²²⁷. However, these patterns are not specific to nociception. Similar changes can result from artefacts, lighter levels of sedation, or pharmacodynamic shifts. Interpretation becomes even more challenging in opioid-free or non-GABA-based regimens, where cortical activity signatures differ substantially²²⁸.

During recent years, pEEG has gained ground in the operating theatre. The rationale for its use has been to individualise anaesthesia and reduce the risk of postoperative cognitive dysfunction²²⁹. However, these devices are not without limitations. Aside

from requiring a certain level of expertise, pEEG indices and colour spectrograms show substantial inter-individual variability²³⁰, particularly with respect to age. Furthermore, pEEG devices are typically validated for traditional opioid-based anaesthesia using GABA_A-agonists²³¹. This has led to general recommendations aiming for an SEF95 of 8–12 Hz and a high-powered slow/delta–alpha pattern on the DSA, with some variation depending on the device-specific algorithm. As multimodal anaesthesia techniques become more common, including regimens with reduced or absent opioid use, the interpretation of pEEG has become increasingly uncertain.

Frequently used agents in multimodal anaesthesia, such as ketamine/esketamine and dexmedetomidine, influence the raw-EEG in ways that differ markedly from GABA_A-based anaesthesia²²⁴. Ketamine administration typically increases SEF95 values due to its enhancement of high-frequency oscillations, particularly in the gamma range (30–100 Hz)^{224,232}. On the colour spectrogram, this appears as increased power intensity (red) in the gamma band. Conversely, ketamine tends to reduce power in the delta (0.5–4 Hz) and theta (4–8 Hz) ranges²²⁴, which is reflected as reduced colour power (blue or green) in these lower frequencies.

Dexmedetomidine produces the opposite pattern. It enhances low-frequency oscillations in the delta and theta bands while reducing high-frequency activity, resulting in a decrease in SEF95^{224,233}. On the colour spectrogram, dexmedetomidine increases power (red) in the delta and theta ranges^{224,234}, while reducing power (blue or green) in the beta (13–30 Hz) and gamma (30–100 Hz) frequency spectra. Conversely, dexmedetomidine reduces high-frequency oscillations, particularly in the beta (13–30 Hz) and gamma (30–100 Hz) frequency spectra^{224,234}. These characteristic shifts illustrate why pEEG interpretation becomes more complex when anaesthetic regimens deviate from traditional opioid- and GABA_A-based approaches.

Only a few studies have investigated the impact of pEEG-guided anaesthesia and analgesia on the risk of developing APOP. Most available evidence focuses on postoperative delirium, and postoperative pain has generally been assessed only as a secondary outcome. One RCT evaluating raw-EEG-guided anaesthesia in elderly patients (n = 141) found no difference in APOP²³⁵. Methods using simplified pEEG-derived indices, such as the Quantum Nociception Index (qNOX, Quantum Medical S.L., distributed by Fresenius Kabi) and the Pain Threshold Index (PTI, Medasense, Ramat Gan, Israel), have shown some promise in predicting APOP. In this regard, PTI has demonstrated better discriminability than SPI (AUC 0.772, 95%CI 0.661–0.860)²³⁶. Similarly, a study of 80 children undergoing laparoscopic surgery found that PTI predicted APOP (AUC 0.80, 95%CI 0.69–0.90) more effectively than SPI²³⁷. However, more high-quality clinical trials, and a deeper understanding of the underlying mechanisms, are needed before these devices can be recommended for broader implementation.

Given its potential to capture individual neurophysiological signatures, the rationale for using pEEG in individualised anaesthesia and analgesia is compelling. If we can more accurately determine anaesthetic depth and acknowledge the limitations of relying solely on vital signs for intraoperative pain management, it may be possible to reduce the use of high-dose opioids in favour of non-opioid alternatives. This is clinically relevant, as high-dose opioids are known to contribute to rapid postoperative opioid tolerance and adverse events²³⁸. However, this theory has not yet been tested, and high-quality, protocolised, randomised trials are required.

It is also essential that pEEG devices are validated for multimodal anaesthesia techniques, which often combine several anaesthetic agents and may produce cortical activity patterns that differ substantially from traditional opioid- and GABA_A-based regimens. The data presented in this thesis represent the first findings on OFA as an anaesthetic method²²⁸.

Looking ahead, it would be particularly interesting to explore whether pEEG could serve as a broad, overarching monitor to guide anaesthesia at a general level, while more nuanced adjustments are made using the raw-EEG signature itself. Such an approach could combine the accessibility of simplified indices with the precision of detailed cortical pattern interpretation, potentially offering a more refined and individualised method for titrating both anaesthesia and analgesia.

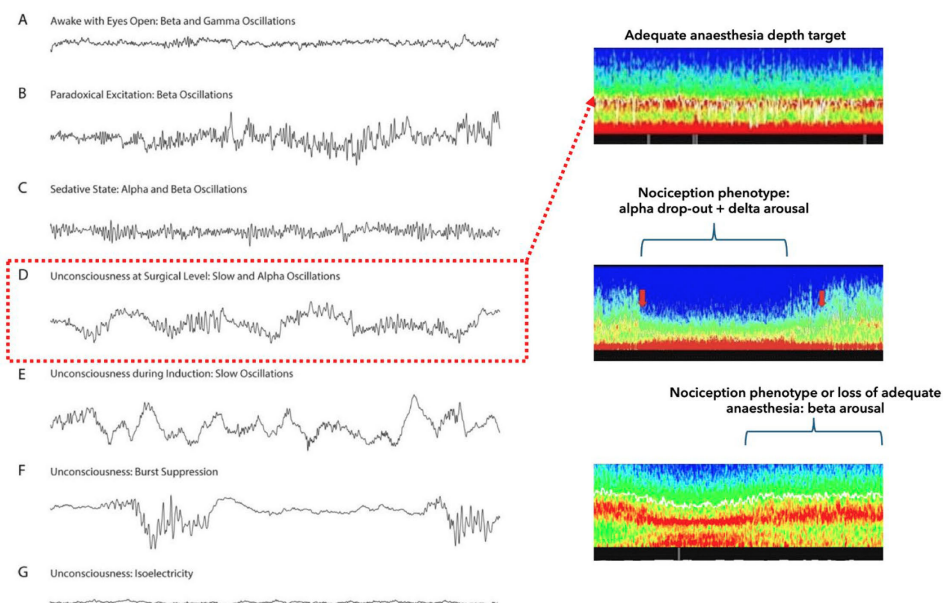


Figure 5. On the left; a depiction of raw-EEG signatures associated with different clinical states. In the use of traditional anaesthesia methods, a slow-wave with delta and alpha activity is recommended (D). On the right; three different colour spectrogram signatures. On the top, adequate anaesthesia is depicted since high power (red) reside in the aforementioned oscillating frequency spectra. The middle and lower image depicts two distinct colour spectrogram signatures associated with nociception: alpha drop-out + delta arousal and beta arousal respectively. *Left part of image reproduced, not altered or used for commercial purposes, from Purdon et al., 2015, Anesthesiology, Vol. 123, No. 4²²⁴.*

Table 3. A comprehensive table comparing intraoperative real-time monitors in terms of mechanism, predictive performance of intraoperative nociception, performance in guiding anaesthesia, predicting postoperative acute pain and opioid consumption. ✓ - Qualitative assessment showing positive association and potential clinical applicability, △ - Qualitative assessment showing positive association but questionable clinical applicability, ✗ - Qualitative assessment showing negative association and no clinical applicability. APOP: Acute postoperative pain, ANI: Anti-Nociception Index, HBI: Heart beat interval, HRV: Heart rate variability, NOL: Nociception Level, NFSC: number of fluctuations of skin conductance per second, NRS: Numeric rating scale, PPI: Pupillary Pain Index, qNOX: quantum Nociception Index, SPI: Surgical Pleth Index. Reproduced, not altered or used for commercial purposes, from *Moghanas et al., 2026, Journal of Clinical Anesthesia, Vol. 110, No. 1. Licensed under CC BY 4.0*³³

Method	Mechanism	Predicting intraoperative nociception	Guiding intra-op treatment	Predicting postoperative pain	Postoperative opioid consumption
ANI	HRV (parasympathetic tone), 0–100	✓ Sensitivity/specificity 0.81/0.93, AUC 0.77, OR 2.32 ✗ No difference in ANI after fentanyl bolus	△ Remifentanyl reduction, SMD -0.262 △ Correlated with lower doses remifentanyl, $r = 0.959$, $p = 0.01$ △ Decreased remifentanyl in ANI-group, 447µg vs 191 µg ✗ No association with opioid dose	△ Sensitivity/specificity 0.90/0.51, OR 3.3 ✓ Less APOP at 24 h, effect NRS 1.0 △ Correlation with APOP, $r = 0.312$, $p = 0.001$ △ Correlation with APOP, $r = -0.075$, $p = 0.034$ ✗ Could not discriminate between NRS 0 and NRS 6–10, AUC 0.43	✗ No difference in opioid dose
SPI	Multiparametric (HR/HB/PPG/skin conductance/temp/motion), 0–100	△ Sensitivity/specificity 0.81/0.93, AUC 0.77, OR 2.32 ✗ No difference in ANI after fentanyl bolus	△ Less intraoperative opioids, SMD -0.41 (-0.70 – (-)0.11) ✗ No difference in fentanyl dose, 450 vs 400 (SPI) ✗ No difference in sufentanil dose, $p = 0.906$ ✗ No difference in remifentanyl dose, $p = 0.14$	△ Sensitivity/specificity 0.71/0.58, AUC 0.72 ✗ No difference in APOP ✗ No correlation with APOP △ SPI 30 predicted APOP, sensitivity/specificity 0.61/0.58, $p = 0.036$ ✓ Difference between groups at PACU $p = 0.006$ and 24 h, $p = 0.007$ △ SPI > 30 before arousal predicted APOP, NPV 50%, PPV 88%	✗ No difference in proportion needing rescue dose ✗ No correlation with rescue dose △ ΔSPI 23 predicted fentanyl IV-PCA, sens/spec – 0.67/0.68 and 817 µg vs 573 µg, $p = 0.008$
NOL	Photoplethysmography: normalised heartbeat interval + PPGA, 0–100	✓ Discriminates noxious vs non-noxious events; ΔNOL AUC 0.95 △ Discriminability AUC 0.68 △ Prediction AUC 0.80, Detection AUC 0.68 in the ICU	✗ NOL resulted in more cortisol excretion but less remifentanyl ✗ More intraoperative fentanyl 300µg vs 500µg ✗ No association with opioid dose	✗ No association with APOP △ Machine-learning discriminability, AUC 0.75 △ NOL-guidance - SMD -0.44 (-)0.03 △ Discriminated dichotomised APOP, AUC 0.66, $p = 0.038$	✗ No association with opioid dose, $p = 0.06$ ✗ NOL-guidance – difference -1.5 mg (-8.3 – 5.3) ✓ Decreased opioid dose, 3.3 mg vs 7.7 mg
Skin conductance	Sympathetic activity indicator via sweat gland response	✗ Does not predict changes in stress hormone level		✓ NFSC distinguished levels of APOP, sens/spec 0.89/0.73 ✓ NFSC discriminability NRS > 3, sens/spec 0.89/0.68 ✗ NFSC discriminability NRS > 3 and NRS > 6, AUC 0.55 and AUC 0.56 ✗ No difference in NFSC between pain groups, $p = 0.59$, $p = 0.30$	
Pupillometry	Stimulus-evoked pupillary reflex dilation → PPI 0–10	△ PPI increase with sympathetic stimulus; decrease after opioids, $p < 0.001$	△ Decreased intra-op remifentanyl, $p < 0.001$ △ Decreased intra-op sufentanyl, $p = 0.04$ △ Decreased intra-op opioids, SMD -2.44 mg (-4.35 to -0.52)	✓ Pre-extubation PPI $f_5 = 0.62$, $p = 0.002$ with APOP ✗ No difference in APOP	✗ No difference in opioid dose
qNOX	EEG-derived probability of response to noxious stimuli	✗ Discriminability AUC 0.52 △ Predicted movement after noxious stimuli, $p < 0.001$	✗ No difference in qNOX between low and high intra-op opioids after noxious stimuli △ Association with intra-op remifentanyl and qNOX > 60, AUC 0.66	✗ Discriminability NRS > 3, AUC 0.50	

Serologic biomarkers

Serologic biomarkers are measurable indicators found in blood that can provide valuable insights into various physiological and pathological processes. In the context of postoperative pain, these biomarkers hold potential for predicting pain outcomes and guiding individualised anaesthesia and analgesia strategies. One example is variation in the Mu-Opioid Receptor (OPRM1), which can influence responsiveness to certain opioids²⁴⁰.

Current evidence on the use of serologic biomarkers for preoperative pain prediction remains highly uncertain and is almost exclusively derived from studies where pain was a secondary outcome¹³². In these studies, associations have been identified through group-based comparisons using predefined numerical thresholds, as well as through correlation analyses involving continuous pain measures making it unclear if the effect holds clinical value¹³².

It is important to recognise biomarkers as a complex research field on its own. As with all prediction methods, biomarkers involve trade-offs between specificity and sensitivity, and they must meet standards of reliability and validity. Moreover, each biomarker has its own fluctuating dynamic, influenced by biological rhythms, comorbidities, medications, and perioperative stress responses²⁴¹. These factors complicate interpretation and limit the generalisability of findings

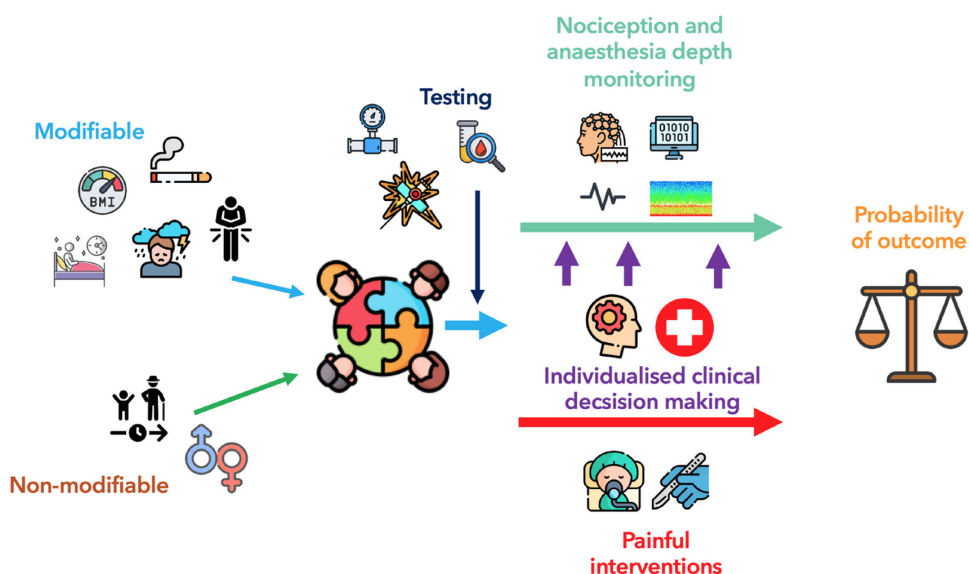


Figure 6. Graphical depiction of how intraoperative real-time monitoring might support individualised decision making. Each patient presents with unique risk factors that, together with surgical and intraoperative variables, may influence postoperative pain. Real-time monitoring could help maintain adequate anaesthetic depth and reduce the risk of undertreating nociceptive input. “Testing” refers to assessing pain sensitivity using biomarkers and/or brief procedural pain responses (e.g pain assessment during venous cannulation, infiltration of local anaesthetics). Purple arrows illustrate ongoing intraoperative adjustments that are data-informed but still guided by clinical judgement. *Reproduced, not altered or used for commercial purposes, from Mogianos et al., 2026, Journal of Clinical Anesthesia, Vol. 110, No. 1. Licensed under CC BY 4.0²³⁹.*

The concept of Individualised anaesthesia and analgesia in surgery

The idea of individualised perioperative anaesthesia and analgesia is compelling, and the ongoing debate is fuelled by the persistently high incidence of moderate-to-severe APOP. Why this remains such a challenge has understandably occupied clinicians and researchers for many years. Traditionally, preoperative planning has centred on the surgical procedure and its expected physiological stress rather than on individual predictors of postoperative pain. Although numerous recommendations exist for different types of surgery, individual patient factors remain underrepresented in these guidelines.

Individualised anaesthesia and analgesia in surgery (IAAS) is a broad perioperative concept that acknowledges the intricate role of individual characteristics in shaping patient-centred outcomes and satisfaction. The concept rests on three cornerstones:

- Risk factors, recognising that this includes not only high-risk individuals but the full spectrum of patient variability.
- Goals of care, involving multiple healthcare professionals throughout the perioperative process.
- Patient expectations regarding pain outcomes.

Predicting risk

Individual

In previous sections, several individual risk factors were highlighted for their association with worse pain outcomes. Some of these factors are modifiable, while others are not. The value of modifiable factors lies in their potential to both identify patients at increased risk of postoperative pain and serve as targets for interventions aimed at reducing that risk. Unfortunately, even when factors such as smoking or poor sleep are addressed preoperatively, improvements have not consistently translated into reduced postoperative pain.

A substantial amount of research has explored preoperative prediction methods for postoperative pain, yet no single approach is currently capable of reliably distinguishing high- from low-risk individuals¹³². A more promising direction may be the development of a robust prediction model that integrates clinically relevant risk factors, easy-to-use predictive tools, real-time intraoperative data, and biomarkers. Such a multimodal strategy may offer a more accurate and individualised understanding of each patient's likely pain trajectory.

Procedure related

Although this thesis focuses on individual approaches to managing postoperative pain, surgical risk factors cannot be overlooked. The type of surgery has a strong influence on postoperative pain outcomes. Thoracotomy, mastectomy, caesarean section, and joint arthroplasty are examples of procedures repeatedly shown to be associated with high postoperative pain²⁴². Despite the existence of ERAS pathways for many of these surgery types, pain outcomes often remain suboptimal.

For certain procedures, such as thoracotomy or major abdominal surgery, their characteristic postoperative pain trajectories have prompted the adoption of countermeasures, including regional anaesthesia techniques²⁴². A common feature among some high-pain procedures is the risk of nerve injury, which can have substantial consequences for the patient²⁴³. One contributing factor may be that neuropathic pain is more difficult to recognise and treat once established.

Other procedural factors influencing postoperative pain include the length of the skin incision, the degree of invasiveness, and the duration of surgery, all of which

affect the extent of tissue damage and physiological stress to which the patient is exposed^{156,244}.

Anaesthesia related

Anaesthesia techniques have become increasingly refined, with a wide range of options available across both regional and pharmacological approaches. When it comes to postoperative pain, certain anaesthetic choices can influence pain intensity and outcomes such as opioid consumption. Failure to use multimodal anaesthesia and analgesia in favour of a single agent is associated with worse postoperative pain outcomes^{245,246}. The rationale for modulating multiple receptors within the nociceptive pathway, rather than relying on only one or two, is widely accepted. However, the term “multimodal anaesthesia and analgesia” is broad and non-specific, and its use alone does not guarantee improved outcomes. A recent consensus statement has attempted to address this by offering recommendations on what to include in a pharmacological regimen²⁴⁷.

Opioids remain a double-edged sword. They are effective for nociceptive pain, yet they are also associated with a range of complications described earlier. Moreover, opioids are well known to induce rapid tolerance in the perioperative setting, which can contribute to increased postoperative pain and higher opioid requirements²⁴⁸.

Goals with care

Healthcare is grounded in the principles of healing, comforting, and avoiding harm. As modern medicine advances, these values are increasingly tested. Expanding clinical capabilities push the boundaries of what is possible, bringing new challenges in their wake. In perioperative medicine, these challenges are particularly evident. Changing demographics, evolving lifestyles, and advances in surgical techniques have reshaped the field, while healthcare systems face growing pressure to reduce costs and shorten treatment duration. Patients today are more informed and rightly expect high-quality care, yet they still rely on clinicians to guide them towards decisions that align with their health goals. Surgery, although often life-enhancing or lifesaving, remains one of the most invasive interventions in medicine, aimed at restoring function and prolonging life, but not without risk.

Advanced care planning (ACP) is a process that supports adults in understanding and communicating their personal values, life goals, and preferences for future medical care. Its purpose is to ensure that treatment aligns with these values²⁴⁹. In the perioperative setting, ACP often includes not-for-resuscitation orders, goals-of-care discussions, and preferences regarding life-sustaining treatments. While surgery is typically the focus, postoperative care must also be considered to achieve outcomes that are meaningful to the patient. The topic is complex, and concerns have been raised that ACP may be associated with higher mortality

through self-fulfilling expectations or reduced intervention, yet evidence remains inconsistent²⁴⁹. Importantly, ACP should not be limited to mortality-related decisions; it also encompasses postoperative symptoms such as pain. Many patients have strong preferences regarding pain control, tolerance for sedation, or fears of inadequate analgesia, and these concerns can only be addressed proactively. Incorporating pain expectations and analgesic preferences into ACP allows clinicians to deliver care that is more closely aligned with the patient's goals, while reducing anxiety and potentially improving satisfaction.

Open, interprofessional discussions about goals of care are essential, and these conversations must be genuinely centred on what matters most to the patient. To make them meaningful, clinicians need to be transparent and move beyond general guidelines, offering opinions tailored to the individual rather than the broader population. Understanding a patient's values is crucial to avoid causing unnecessary harm. This understanding is best established before surgery, with both surgical and anaesthesia teams involved. Since their perspectives may differ, early collaboration helps ensure that care is aligned with the patient's expectations from the outset.

Patient expectations

When approaching pain as an entity, the research community has often divided this complex phenomenon into smaller, more manageable fields (e.g. postoperative pain, acute non-surgical pain, chronic pain syndromes, cancer related pain, experimental pain) to aid understanding. Historically, several models of pain development have been proposed, many of which still hold relevance. In pain research, considerable effort has been devoted to isolating the painful component of a stimulus, as fear and expectations are well-known modulators of self-reported pain intensity, even when the stimulus itself remains unchanged.

One example is the motivation-decision model, first proposed by Howard Fields in 2006²⁵⁰. This theory suggests that the brain continuously evaluates whether attending to a painful stimulus is the most adaptive and safest option. Other theoretical frameworks have explored how expectations interact with nociception. For instance, fear-avoidance and negative expectations can lead to behavioural inhibition and may contribute to the persistence of pain, which is a significant factor in the development of chronic pain states^{251,252}.

A Bayesian model of pain perception conceptualises pain as a process in which noxious stimuli are integrated with prior expectations to generate subjective pain experiences²⁵³. This model is grounded in the idea that the brain continually updates its understanding of the world by combining incoming nociceptive input with beliefs about how painful a stimulus is likely to be. Together, these elements shape the actual experience of pain. When there is a mismatch between expected and actual

sensory input, a prediction error occurs, prompting the individual to adjust their behaviour. This, in turn, informs and updates future expectations²⁵³.

Thus, expectations may be a potent modulator of treatment effects and perceived pain. One clinical example is placebo treatment, which appears to produce moderate reductions in reported pain without corresponding changes in neurological pain signatures²⁵⁴. This suggests that expecting analgesia may exert its influence through networks other than standard nociceptive pathways. Pollo et al. explored this by administering buprenorphine to patients three days after thoracotomy, alongside an infusion of normal saline²⁵⁵. Patients were divided into three groups: a natural-history group receiving no information about the infusion; a double-blinded group told that the infusion contained either a strong analgesic or placebo; and a deceptive group told that the infusion contained a strong analgesic. Although all groups reported similar analgesia scores, opioid requirements were significantly lower in the deceptive group compared with the natural-history group, and lower in the double-blinded group compared with the natural-history group. Analgesic treatment was therefore identical, but postoperative opioid use differed, leading the authors to conclude that expectations of analgesia can produce distinct placebo analgesic effects

When individuals hold optimistic expectations, anticipating a low-intensity nociceptive stimulus (e.g. VAS 30) but receiving a more intense stimulus (e.g. VAS 50), the resulting perception, according to the Bayesian model of pain, reflects a weighted integration of the two, producing an intermediate percept (e.g. VAS 40). Conversely, if expectations are pessimistic and a high-intensity stimulus is anticipated (e.g. VAS 70), the same VAS 50 stimulus may be perceived as more intense (e.g. VAS 60), driven by the higher expectancy of pain (figure 6A). A sense of control may act as a powerful modulator of perceived pain, largely through its influence on expectations. This is well documented in clinical contexts such as patient-controlled analgesia, where patients who self-administer analgesics frequently report lower pain intensities without receiving greater overall analgesic doses²⁵⁶.

In earlier experimental research, the concept of control has varied considerably across studies and includes dimensions such as control over stimulus occurrence, intensity, duration, onset, and offset²⁵⁷. Within a Bayesian framework, control is thought to influence pain perception through two primary mechanisms. First, control can increase the precision of prior expectations, meaning the brain assigns greater confidence to its predictions (figure 6B). Second, control can shift the mean of prior expectations towards lower anticipated pain intensities. Both mechanisms alter how expectations and nociceptive input are integrated, thereby modulating the final pain percept.

In experimental research, control over the occurrence, duration, or intensity of a noxious stimulus has been suggested to increase the precision of prior expectations.

When precise priors predict lower pain (optimistic expectations) than the stimulus actually induces, perceived pain may still be attenuated. Conversely, if precise priors predict higher pain (pessimistic expectations), perceived pain may be amplified even when the actual stimulus is less intense (figure 6B). A clinical example is a patient undergoing a procedure who has previously had a traumatic experience with similar pain. They expect the procedure to be very painful (pessimistic expectation) and are confident in that expectation (high precision). Even if the procedure is objectively less painful, the brain gives greater weight to the prior, resulting in amplified pain perception. This mechanism may help explain the association between preoperative self-expected pain ratings, assessed using PROMs, and APOP¹⁷⁷⁻¹⁷⁹.

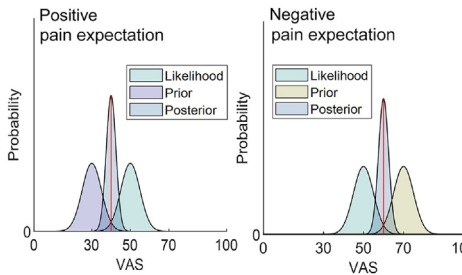
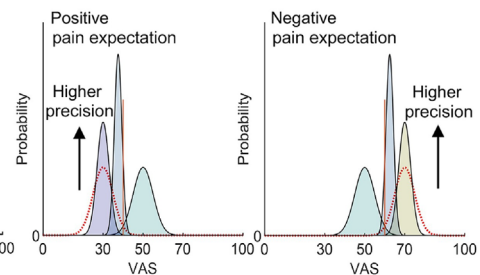
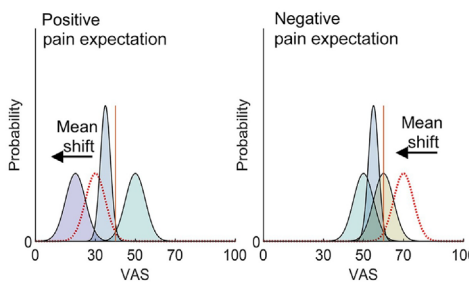
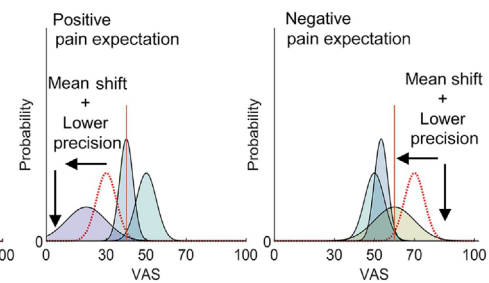
Control over stimulus onset, offset, or treatment initiation (e.g. being able to stop pain or initiate analgesia) may reduce perceived pain by shifting expectations towards lower pain intensities. In this case, control modulates pain by shaping expectations, regardless of whether those expectations are optimistic or pessimistic (figure 6C). A clinical example is a diabetic patient self-administering insulin, who may experience less pain than if the injection were administered by someone else.

When a person initiates a painful stimulus (e.g. by pressing a button), they typically feel more in control, which can reduce perceived pain. However, if there is a delay between the action and the onset of pain, this diminishes the effect of control, a phenomenon referred to as induced temporal uncertainty (figure 6D). In theory, temporal uncertainty reduces the precision of prior expectations, forcing the brain to rely more heavily on raw nociceptive input. If initial expectations are optimistic, predictability allows the brain to weight the expectation more strongly, reducing perceived pain. When the stimulus becomes unpredictable, the brain must weight sensory input more heavily, increasing perceived pain and diminishing the benefit of optimistic expectations. Conversely, if prior expectations are pessimistic, temporal uncertainty reduces their influence, thereby attenuating the amplification of pain. A simple clinical example is venous cannulation: knowing a patient's mental orientation allows clinicians to decide whether to announce the moment of insertion. For optimistic patients, signalling may reduce the perceived procedural pain; for pessimistic patients, avoiding such cues may be more beneficial. In this way, perceived pain can be modulated and individualised.

In summary, expectations and noxious stimuli may integrate to shape perceived pain, while mismatches between the two help form future expectations. Although this model has been more extensively explored in chronic pain²⁵⁷, it offers a useful conceptual framework for the perioperative setting. Here, patients typically have limited control over their environment and may approach surgery with broadly optimistic, pessimistic, or ambivalent expectations. With this in mind, it seems reasonable for clinicians to aim to enhance the patient's perceived sense of control and to clarify what they can expect. It also follows that expectations should ideally be addressed before the painful experience occurs, meaning preoperatively. Such

information is most effective when delivered by a knowledgeable clinician with credibility, ensuring that expectations are shaped in a realistic and supportive manner.

It is important to emphasise that this model is largely derived from experimental research. How these mechanisms translate into real-world clinical settings, particularly the perioperative environment, remains uncertain. Patients undergoing surgery face a multitude of contextual, emotional, and physiological factors that differ substantially from experimental paradigms, making direct application of the model challenging. This theoretical framework should therefore be viewed as a conceptual aid rather than a validated clinical tool, and its relevance to perioperative pain modulation requires further investigation.

(A) The Bayesian pain model**(B) Control over stimulus occurrence
Control over stimulus intensity and duration****(C) Control over stimulus onset
Control over stimulus offset or treatment onset****(D) Control over stimulus onset / offset
with induced (temporal) uncertainty**

Trends in Cognitive Sciences

Figure 7. Graphical depiction of the Bayesian model of pain as a framework for the development and modulation of acute postoperative pain. A. Optimistic expectations result in decreased subjective perception of pain, whereas pessimistic expectations increase the subjective perception of pain. B. Control (stimulus occurrence, intensity or duration) influence expectations, making them precise. Being optimistic, results in a higher probability that the subjective perception of pain further match these expectations, shifting perceived pain further to the left. The opposite occurs if being pessimistic (higher precision, increased pain), shifting perceived pain to the right. C. Control (stimulus onset/offset or treatment offset) influence and reassures the individual, shifting both expectations and subjective perception of pain towards lower intensities (optimistic), or higher intensities (pessimistic). D. Control (stimulus onset/offset) but with induced temporal uncertainty causes the brain to rely on raw sensory input since the precision of the expectations is decreased. In optimistic orientation the potential benefit of control gets abolished if uncertainty is introduced. In pessimistic orientation, decreased precision align the subjective perception of pain with the intensity of the raw noxious stimulus, influencing positively on the outcome. *Reproduced, not altered or used for commercial purposes, from Habermann et al., 2025, Trends in Cognitive Sciences, Vol. 29, No. 1. Licensed under CC BY-NC-ND 4.0*²⁵⁷.

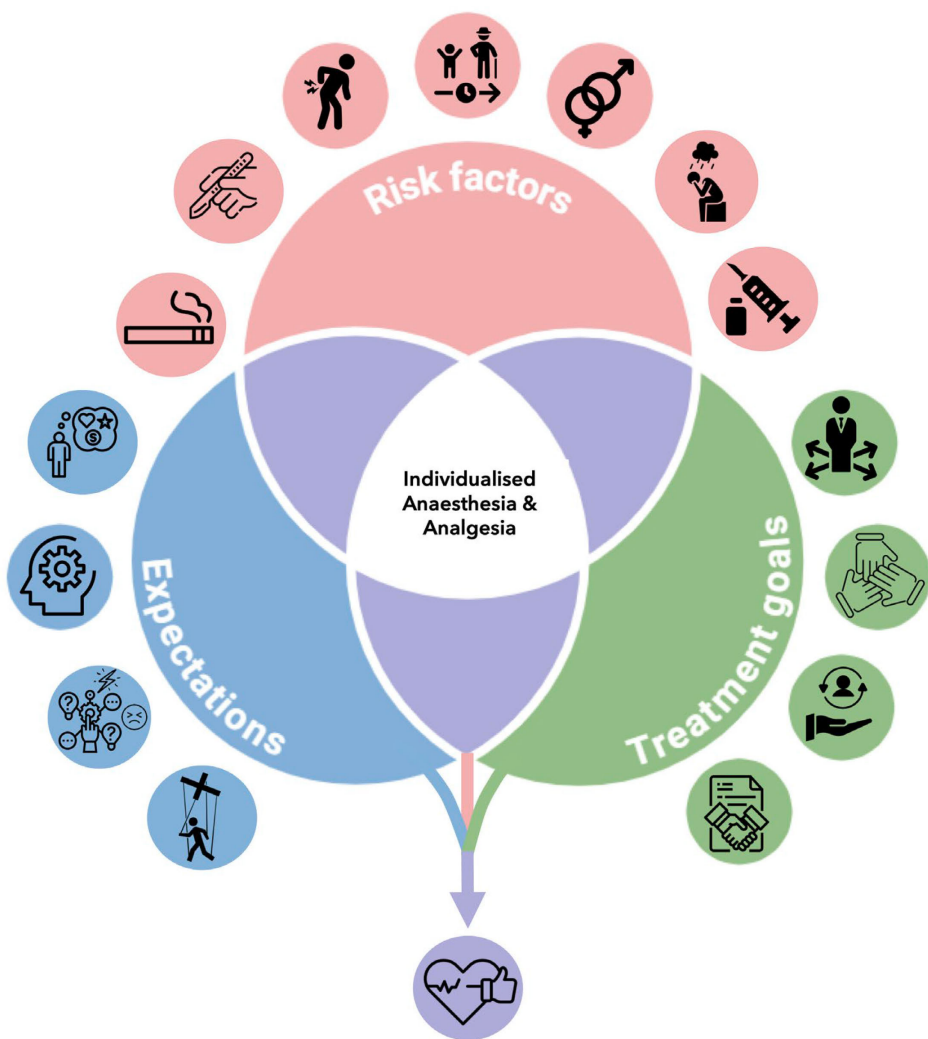


Figure 8. Individualised anaesthesia and analgesia in surgery explained in graphical terms, including the framework of risk, individual expectations, and overall patient-centred strategy. As the scientific foundation for this approach continues to evolve and the conceptual framework becomes more refined, the overarching aim is to enhance postoperative outcomes, including improved pain control and accelerated recovery.

Aim

This thesis aims to explore the concept of individualised management in perioperative medicine and introduce the framework of Individualised Anaesthesia and Analgesia in Surgery. In brief, this involves compiling current evidence on preoperative methods for predicting postoperative pain, conducting clinical trials in which patients at increased risk of APOP have been exposed to different anaesthetic strategies, and examining the role of pEEG in OFA as well as VCP as an individual-level risk-stratification method.

Paper I

To qualitatively and systematically compile evidence from preoperative prediction methods for postoperative pain.

Paper II

To develop a study protocol for the PeriOperative Individulisation Trial (POPIT), in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. We also strived to publish the protocol article before analysing the data from the clinical trial.

Paper III

To determine whether pain-sensitive patients benefit from multimodal anaesthesia and analgesia adding esketamine and clonidine, with APOP as the primary outcome and PPOP, PONV, early recovery, and postoperative rescue opioid requirements as secondary outcomes.

Paper IV

To investigate whether OFA is non-inferior to standard care in pain-tolerant patients undergoing laparoscopic surgery. Acute postoperative pain was the primary outcome, with PPOP, early recovery, PONV, and postoperative rescue opioid requirements as secondary outcomes.

Paper V

To evaluate pEEG, specifically patient state index (PSI), SEF95, and density spectral array (DSA), during general anaesthesia with OFA, and to compare these values with those observed during routine GABA_A- and opioid-based anaesthesia using either volatile agents or TIVA.

Paper VI

To present data on venous cannulation pain as a potential stratification method for APOP and PPOP, and to examine its association with other known risk factors such as gender, age, psychological variables, and preoperative pain.

Ethical considerations

Vulnerable population

Although POPIT (Paper III, Paper IV, Paper V, Paper VI) recruited adult patients undergoing elective laparoscopic surgery, typically considered a low-risk population, ethical vigilance was maintained throughout. Inclusion criteria were restricted to ASA class I–II, thereby excluding individuals with significant comorbidities or pregnancy.

Participants were stratified by pain sensitivity using a method with established scientific merit (VCP). While this stratification supports individualisation, being labelled as ‘pain-sensitive’ may introduce psychological vulnerability by increasing anxiety or expectations of pain. To mitigate this, all patients, irrespective of group allocation, were closely monitored in the PACU to ensure that no participant was undertreated or exposed to unnecessary discomfort. Since the study was blinded for both patients and assessors, information about risk phenotype was not available to either party.

In the anaesthesia-depth study (Paper V), patients were recruited from the pain-tolerant arm of POPIT to avoid confounding EEG effects from non-GABAergic agents. This approach ensured a more homogeneous cohort for neurophysiological monitoring and reflects an ethical decision to minimise both risk and variability.

Data protection

All studies adhered to strict data-protection procedures. POPIT used the Entermedic platform, certified under ISO 27000:1 and fully compliant with GDPR and Swedish patient-data legislation. Data were stored on secure servers located in Sweden, with no outsourcing permitted. The system automatically sent follow-up reminders and ceased communication once data collection was complete. Investigators manually monitored data completeness daily to maintain high data integrity. Since the clinical trials in this thesis enrolled participants from POPIT, the data-protection procedures were consistent across studies.

Informed consent

Informed consent was obtained both orally and in writing for all studies included in this thesis. In POPIT, patients received study information via text message 1–7 days before surgery and were given time to review it upon arrival at the hospital. Consent was verified before proceeding with pain sensitivity stratification. Participation was voluntary, and patients were free to withdraw at any time.

Ethical permit

Ethical permission was sought from the regional ethical board in Uppsala and approved on 2020-12-16 with Dnr 2020-06178. For the follow-up study regarding anaesthesia depth monitoring another application was submitted and approved in Uppsala 2023-01-05 with Dnr 2022-07156-02.

Benefit to participants

Therapeutic misconception, the belief that participation in research will provide personalised therapeutic benefit, was an important consideration in these studies. To minimise this risk, all participants were clearly informed that the interventions were part of a research protocol and not guaranteed to improve their individual clinical outcomes. Study information emphasised the distinction between standard clinical care and research procedures, and patients were explicitly told that allocation to different anaesthetic strategies was based on study design rather than clinical need. Investigators avoided language that could imply direct benefit, and consent discussions focused on the purpose of generating generalisable knowledge. Furthermore, because the studies were blinded, neither patients nor assessors knew the risk phenotype or treatment allocation, reducing the likelihood that participants would interpret study participation as tailored therapeutic decision-making.

Although direct clinical benefit was not guaranteed, all clinical trials in this thesis aimed to improve perioperative care through individualised approaches. In POPIT, patients received tailored anaesthesia and analgesia based on their pain sensitivity, with the intention of reducing APOP (e.g. Paper III) or achieving secondary benefits without increasing pain intensity (e.g. Paper IV). This approach has the potential to support improved recovery and reduced opioid exposure.

In the anaesthesia-depth study, patients contributed to the evaluation of processed EEG monitoring in opioid-free anaesthesia, helping to establish reference values and characteristic patterns for safe intraoperative monitoring. These contributions

may ultimately enhance anaesthetic safety and precision for future patients, but in the present studies they did not result in any direct benefit or harm for individual participants.

Patients and methods

This thesis consists of six papers based on three underlying studies. In Paper I, a qualitative assessment and systematic review of the current literature was conducted. Paper II presents a structured description of the POPIT study protocol. Papers III and IV apply a pragmatic quantitative interventional design. Paper V uses a quantitative observational design, and Paper VI is a quantitative pre-specified post hoc analysis of POPIT, on which Papers II–IV are based (table 4).

Table 4. Overview of the included studies in this thesis categorised in respects to methodological principles. DSA; Density Spectral Array, NRS; Numeric rating scale, PONV; Postoperative nausea and vomiting, PSI; Patient State Index, QoR; Quality of recovery, SEF95; Spectral Edge Frequency below 95 %, VCP; pain assessment during venous cannulation.

	Design	Data collection	N	Analysis
Study I	Systematic review	Bibliographic search with PICO in PubMed, Embase, CINAHL, selected reference list	107	Qualitative analysis
Study II	Study protocol	-	-	-
Study III	RCT	NRS, PONV, QoR, rescue dose opioids	125	Statistical comparative analysis
Study IV	RCT	NRS, PONV, QoR, rescue dose opioids	154	Statistical comparative analysis
Study V	Prospective observational	PSI, SEF95, DSA	30	Statistical comparative analysis, descriptive analysis
Study VI	Prospective pre-specified secondary analysis	NRS, QoR, pre-operative risk factors, VCP	271	Statistical comparative analysis, multivariate logistic regression model

Paper I

Methodological framework and Registration

The first study¹³² aimed to survey the field of preoperative prediction of postoperative pain and to summarise what had been published between 2016 and 2022. We conducted a systematic review that included peer-reviewed and published articles from the PubMed, EMBASE (Elsevier), and CINAHL Complete (EbscoHost) databases. The study protocol was preregistered in PROSPERO (PROSPERO 2022 CRD42022298479) before the systematic literature search was undertaken.

Search strategy

The search strategy followed the PICO format: *Population* – adult patients aged ≥ 18 years undergoing surgery, regardless of country; *Intervention* – measurement of postoperative pain; *Comparison* – none; *Outcome* – methods for individual bedside prediction of postoperative pain. Only randomised controlled trials and prospective or retrospective observational studies were included, thereby excluding unpublished studies, editorials, meta-analyses, and all forms of review articles. The research question guiding the review was: *Which bedside methods and techniques for predicting the intensity of APOP or PPOP have been reported between 2016 and 2022?*

Literature review

After the literature search, two researchers independently screened all abstracts identified in the initial search using the systematic screening and data-collection tool Covidence. Any abstract deemed potentially relevant by at least one researcher was advanced to full-text assessment. The same two researchers then independently evaluated the full-text articles against the predefined inclusion and exclusion criteria. Agreement between both assessors was required for an article to be included in the final review. Any disagreement prompted a structured discussion, after which a joint decision was made regarding inclusion.

Due to substantial heterogeneity in the methods identified, no meta-analysis or other quantitative synthesis was performed. A risk-of-bias assessment using the Newcastle–Ottawa Scale had been planned; however, given the large number of included studies ($n = 107$), completing and presenting such an assessment was deemed impractical, primarily due to space and publication constraints.

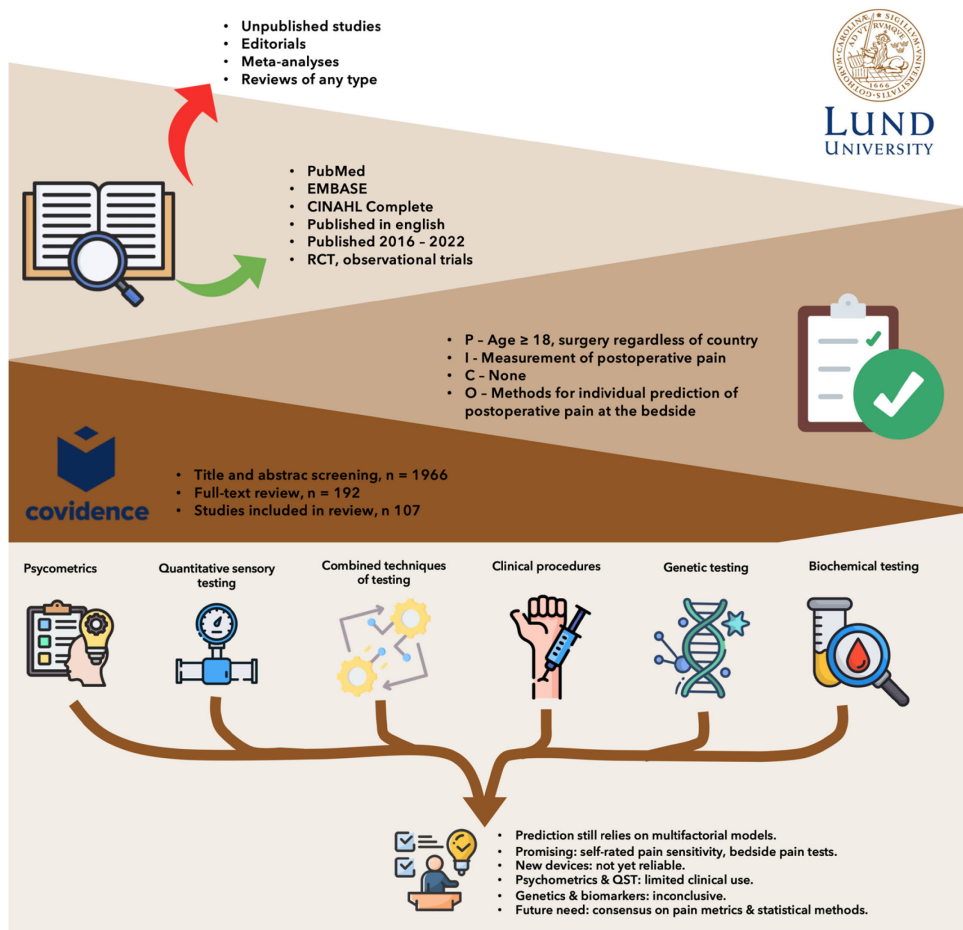


Figure 9. A graphical depiction of the methodology, result and conclusion of the systematic review (Systematic Review of Methods for Individual Prediction of Postoperative Pain¹³²) on preoperative bedside methods used to predict acute and persistent postoperative pain.

Paper II

Methodological framework

The PeriOperative Individualisation Trial (POPIT)²⁵⁸ was a pragmatic, single-centre, randomised, controlled, patient- and assessor-blinded clinical trial (figure 11), which study protocol was presented in accordance with the SPIRIT 2013 (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. The protocol included all essential components required to ensure transparency, reproducibility, and methodological integrity.

Study design and Setting

POPIT employed a parallel-group design with 1:1 simple randomisation. The trial was conducted at Halland Hospital Halmstad, a non-tertiary hospital performing approximately 9,000 anaesthesia procedures annually. The study population consisted of adult patients scheduled for elective laparoscopic surgery.

Eligibility criteria

Inclusion criteria were age >18 years, ASA physical status I–II, and the ability to understand and provide informed consent. Exclusion criteria included pregnancy, NSAID allergy, refusal to participate, and conversion to open surgery. These criteria were clearly defined to ensure internal validity and patient safety, in accordance with SPIRIT item 10.

Interventions

Preoperative pain sensitivity was assessed using VCP. Based on VCP scores, patients were stratified into two independent cohorts (figure 10):

- High-risk patients ($VCP \geq 2.0$) were randomised to multimodal anaesthesia with opioids (EC) or standard of care (SOC).
- Low-risk patients ($VCP < 2.0$) were randomised to OFA or SOC.

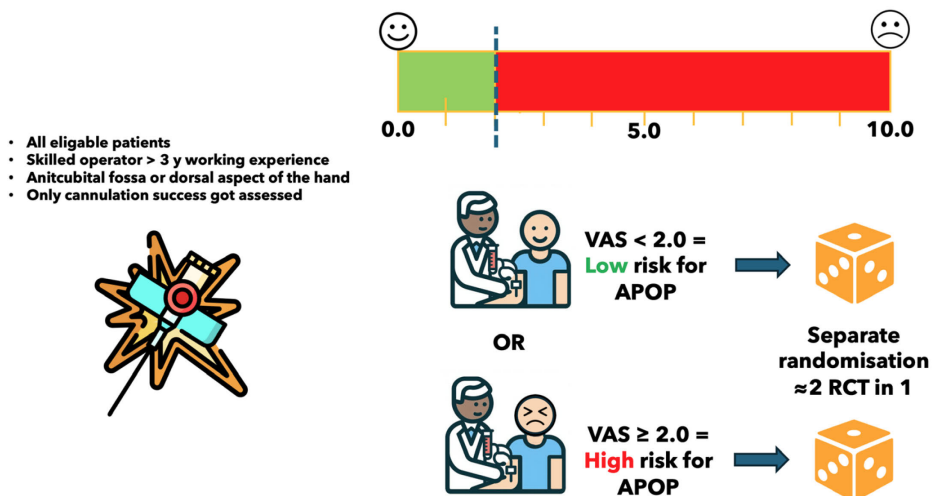


Figure 10. Detailed graphical description of the pain-sensitivity stratification method, pain assessment during venous cannulation. APOP; Acute postoperative pain, VAS; Visual analogue scale.

Outcomes

The primary outcome was worst APOP in the PACU (NRS).

Secondary outcomes included

- Proportion of patients with NRS ≥ 4 in the PACU
- Worst APOP (NRS) at rest and during movement at 24 hours
- Proportion of patients with NRS ≥ 4 at rest and during movement at 24 hours
- Worst PPOP (NRS) at rest and during movement at 3 and 6 months respectively
- Proportion of patients with NRS ≥ 1 at rest and during movement at 3 and 6 months respectively
- Postoperative recovery, using total QoR-15 score at 24 hours
- Proportion of patients having PONV in the PACU
- PONV, measured with PONV-NRS at 24 hours.

Exploratory outcomes include

- Postoperative rescue dose of opioids in the PACU, presented as intravenous morphine equivalents.

All outcomes, except for the exploratory outcome, were pre-specified and measured using validated instruments, fulfilling SPIRIT items 12 and 18.

Sample size and Statistical analysis

Sample-size calculations were based on clinically meaningful differences in NRS scores, resulting in a target of 280 patients to account for a worst-case anticipated drop-out rate of 20 %. Statistical analyses included two-sided independent t-tests for the primary outcome and continuous secondary outcomes and chi-square tests for binary secondary outcomes. All analyses followed intention-to-treat principles, in accordance with SPIRIT item 20.

Data Collection and Management

Data were collected via secure electronic questionnaires and SMS follow-ups using Entermedic®, a GDPR-compliant and ISO 27001-certified platform. The system automates reminders and ensures data completeness. Data management procedures are aligned with SPIRIT item 19.

Allocation and blinding

A simple randomisation was performed, stratified by VCP group (figure 9). Patients and outcome assessors were blinded to group allocation. Due to safety considerations, anaesthesia providers were not blinded. Blinding procedures were clearly documented, in accordance with SPIRIT item 17.

Protocol Adherence and Monitoring

Regular training sessions were held for clinical staff to ensure protocol adherence. No interim analysis was planned, and no Data Monitoring Committee was appointed, as the interventions were considered low-risk. Monitoring procedures were described in line with SPIRIT item 21.

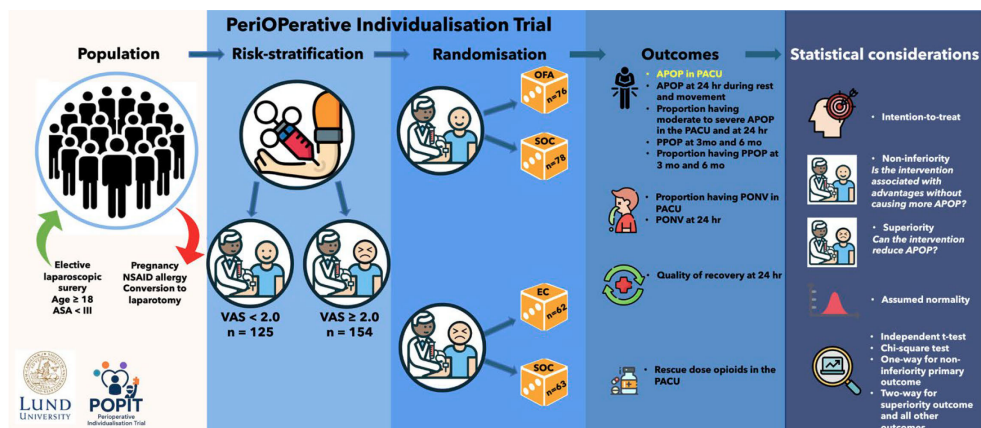


Figure 11. Graphical abstract of the PeriOperative Individualisation Trail and aspects in terms of inclusion, risk-stratification, randomisation, results and statistical methodology.

Paper III

Study design

This trial was conducted as a single-centre, randomised controlled superiority trial with parallel groups (figure 12). Both participants and outcome assessors were blinded to group allocation. Ethical approval was granted by the Swedish Ethical Review Authority, and the study manuscript adhered to the Declaration of Helsinki and CONSORT guidelines. The protocol was preregistered and published for transparency²⁵⁸.

Participants

Eligible patients were adults scheduled for elective laparoscopic surgery, aged over 18 years, with ASA classification I-II. Participants were required to comprehend study details and be stratified as high risk for APOP. Exclusion criteria included refusal to participate, pregnancy, NSAID allergy, and conversion to open surgery.

Pain Sensitivity Assessment

On the day of surgery, pain sensitivity was evaluated using a visual analogue scale during peripheral venous cannulation. Patients scoring ≥ 2.0 were deemed high risk for APOP and eligible for randomisation.

Randomisation and Blinding

Participants were randomly assigned in a 1:1 ratio to receive either SOC or additional intraoperative esketamine and clonidine. Randomisation was performed by nurses in the preoperative clinic. Patients and outcome assessors were blinded to allocation, while anaesthesia staff remained unblinded for safety reasons.

Anaesthetic Protocols

EC: Preoperative: Etoricoxib, paracetamol, oxycodone, ondansetron. Induction: Propofol and remifentanyl; maintenance with propofol or sevoflurane with remifentanyl. Additional agents: Esketamine bolus 0.25 mg/kg (intervention), betamethasone, ropivacaine infiltration and clonidine 1 µg/kg (intervention). Postoperative: Paracetamol every 6 hours; rescue analgesia with oxycodone if NRS ≥ 4 .

SOC: Identical preoperative and induction medications as EC. No intraoperative esketamine or clonidine administered. Postoperative: Paracetamol every 6 hours; rescue analgesia with oxycodone if NRS ≥ 4 .

Outcome Measures

As described in Paper II

Statistical Analysis

A clinically meaningful difference of 1.5 NRS units was defined as the *superiority* margin. Sample size calculations indicated 112 participants were required, increased to 140 to account for potential dropouts. Independent t-tests and chi-square tests were applied as hypothesis-testing for parametric and non-parametric data respectively. Analyses were conducted on an intention-to-treat basis, with supplementary per-protocol results provided.

Figure 12. Graphical abstract depicting the methodology, results and conclusion of paper III; *The additive effect of esketamine and clonidine in patients at high risk for acute postoperative pain undergoing laparoscopic surgery: A randomised controlled trial*²⁵⁹.

Paper IV

Study design

This was a single-centre, randomised controlled non-inferiority trial with a parallel-group design (figure 13). The study manuscript adhered to the Declaration of Helsinki and was approved by the Swedish Ethical Review Authority.

Participants

Adult patients, ASA I-II, scheduled for elective laparoscopic surgery were eligible if they were classified as low risk for APOP, based on pain experienced during venous cannulation ($VAS < 2.0$). Exclusion criteria included refusal to participate, pregnancy, NSAID allergy, and conversion to open surgery.

Pain Sensitivity Assessment

On the day of surgery, pain sensitivity was assessed using a visual analogue scale during venous cannulation. Patients with scores below 2.0 were deemed low risk and eligible for randomisation.

Randomisation and Blinding

Participants were randomly assigned in a 1:1 ratio to receive either OFA or SOC. Allocation was concealed from patients and outcome assessors, though anaesthesia providers were not blinded due to safety considerations.

Anaesthetic Protocols

OFA: Orally administered pre-emptive medications included etoricoxib, paracetamol, and ondansetron. Induction involved propofol, esketamine, and dexmedetomidine, with maintenance using sevoflurane, esketamine, betamethasone and dexmedetomidine. Postoperative analgesia included paracetamol, lidocaine, and esketamine, with opioids only if necessary, as rescue if pain relief NRS < 4 was not achieved.

SOC: Orally administered pre-emptive medications included etoricoxib, paracetamol, oxycodone, and ondansetron. Induction used propofol and remifentanyl, with maintenance via sevoflurane or propofol, betamethasone and

remifentanyl. Postoperative analgesia included oxycodone and paracetamol, with rescue doses of oxycodone.

Outcome Measures

As described in Paper II

Statistical Analysis

A non-inferiority margin of 1.5 NRS units was predefined. Sample size was calculated to detect clinically meaningful differences, with 140 patients enrolled to account for potential dropouts. Analyses were conducted on an intention-to-treat basis using appropriate parametric (Independent t-test) and non-parametric tests (Chi-square).

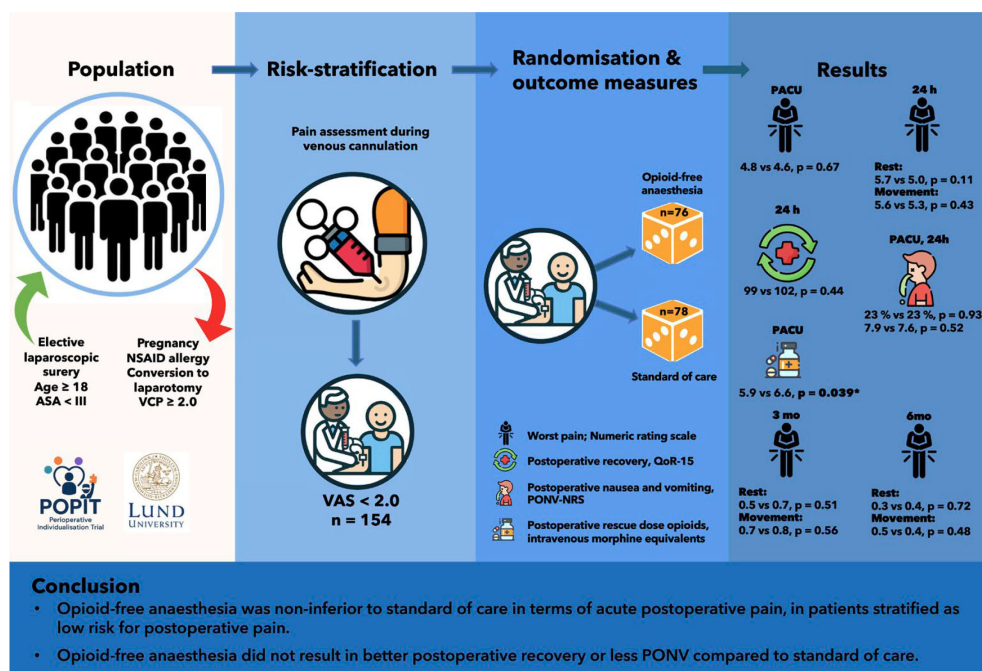


Figure 13. Graphical abstract depicting the methodology, results and conclusion of paper IV; *Opioid-free versus opioid-based anaesthesia and analgesia for patients at low risk for acute postoperative pain undergoing laparoscopic surgery: A randomised controlled trial*²⁶⁰.

Paper V

Study Design and Setting

This prospective observational cohort study was conducted at Halland Hospital in Halmstad, Sweden. It included 30 adult patients (ASA I–II) undergoing elective laparoscopic surgery (figure 14). Ethical approval was obtained, and the study was registered on ClinicalTrials.gov (NCT06227143; 24 January 2024).

Patient Selection and Grouping

Participants were recruited from the PeriOperative Individualisation Trial, an RCT in which patients were stratified by pain sensitivity. Only low-risk patients (VCP < 2.0) were included to avoid confounding effects from esketamine in the control groups and because the aim was specifically to characterise the appearance of OFA on pEEG. Patients were allocated into three groups; OFA, SOC-volatile anaesthesia, and SOC-TIVA, with 10 patients in each group.

Anaesthesia Protocols

As described in Paper IV. Anaesthesia providers were blinded to EEG data and relied on conventional clinical signs.

Monitoring and Data Collection

Processed electroencephalography was used to monitor brain activity during anaesthesia with the SedLine® monitoring system (Masimo Corporation, Irvine, CA, USA). Metrics included PSI, SEF95, and DSA. Data were collected after 20 minutes of anaesthetic steady state following skin incision, with standardised DSA settings.

Outcomes

The primary outcome was the Patient State Index (PSI) at anaesthetic steady state after skin incision, compared between groups. The secondary outcome was SEF95 at the same predefined steady-state time point. A descriptive outcome involved visual comparison of DSA patterns between OFA and routine anaesthesia techniques (e.g. SOC-volatile anaesthesia, SOC-TIVA).

Statistical analysis

Sample size was calculated to detect PSI differences using one-way ANOVA. Normality and variance assumptions were tested, and post hoc comparisons were made using Tukey's test. A p-value below 0.05 was considered statistically significant.

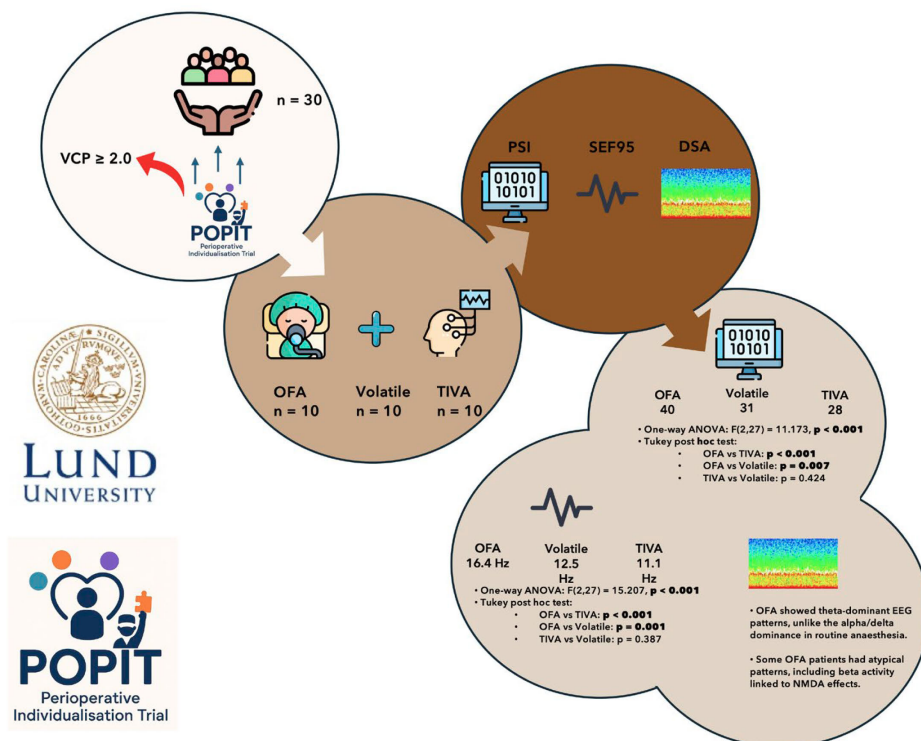


Figure 14. Graphical abstract of paper V depicting patient selection and allocation, outcome and results. Original paper: *Anesthesia depth monitoring during opioid free anesthesia – a prospective observational study*²²⁸.

Paper VI

Study Design

This was a pre-specified secondary analysis on the POPIT cohort. The primary aim was to evaluate the predictive performance of VCP as a surrogate measure of pain sensitivity in relation to APOP in the POPIT cohort (figure 15).

Patient Selection and Grouping

To maximise statistical power, the full cohort ($n = 271$) was included, as the main trial did not demonstrate statistically significant differences in APOP in either the high- or low-risk groups^{259,260}. To address potential contamination from the OFA and EC intervention groups, parallel analyses were conducted using only the SOC groups in the high- and low-risk cohorts, as pre-specified in Paper II. Group allocation based on VCP-derived pain sensitivity is described in Papers II–IV.

Anaesthesia Protocols

As described in Paper III and IV.

Outcome Measures

Worst APOP in the PACU and after 24 h (during rest and movement) between the high- ($VCP \geq 2.0$) and low-risk ($VCP < 2.0$) cohorts in the full cohort ($n = 271$) and SOC-cohorts ($n = 142$). Worst PPOP at 3 and 6 months (during rest and movement) between the high- and low-risk cohorts in the full cohort and SOC-cohorts. Independent risk-factors for APOP and independent modulators for VCP.

Statistical analysis

Continuous variables were compared using two-sided independent t-tests. Dichotomised pain outcomes were analysed using chi-square tests applied to contingency tables.

The predictive performance of VCP for APOP (defined as $NRS \geq 4$, dependent variable) was evaluated using stepwise multivariable logistic regression. Candidate predictors, limited to clinically relevant and previously validated variables such as PCS, were first examined in univariate regression, with variables meeting a

threshold of $p < 0.1$ considered for inclusion. Independent predictors in the final model were identified at $p < 0.05$.

A separate multivariable logistic regression model was used to explore factors associated with $VCP \geq 2.0$ (dependent variable). The same stepwise procedure and significance thresholds were applied to ensure consistency across analyses.

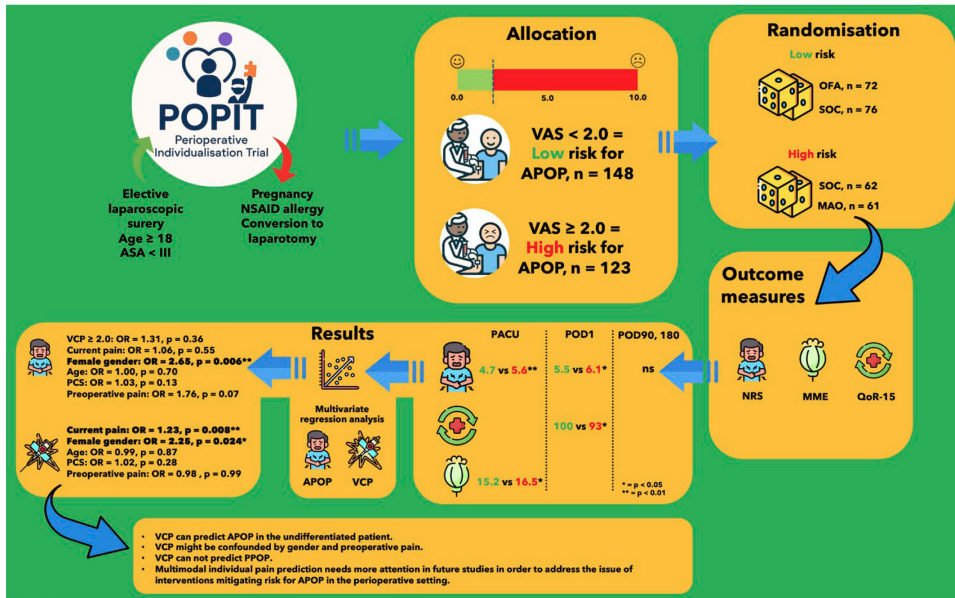


Figure 15. Graphical abstract depicting the methodology, results and conclusion of paper VI; *Venous Cannulation Pain as a Marker of Postoperative Pain Vulnerability: A Predefined Secondary Analysis of a Randomized Controlled Trial.*

Results

Paper I

A total of 1,950 records were identified through database searches. After screening, 192 articles underwent full-text review, with 16 additional studies included via citation tracking. Exclusions were made for the following reasons: study protocol (n = 1), absence of pre-operative testing (n = 21), non-English language (n = 1), irrelevant outcomes (n = 31), ineligible study design (n = 25), and paediatric populations (n = 6). Ultimately, 107 studies met all inclusion criteria and were incorporated into the systematic review.

Psychometric methods

Psychometric assessment: The Hospital anxiety and depression scale (HADS) and pain catastrophising scale (PCS) show inconsistent results in predicting postoperative pain. HADS is more often linked to APOP, while PCS shows mixed associations across surgery types. Depression measures and alexithymia also show limited or variable predictive value.

Self-expected pain: has been shown to predict moderate-to-severe APOP after thoracoscopic and mixed surgeries and is also associated with PPOP.

Self-reported pain sensitivity: The Pain Sensitivity Questionnaire (PSQ) and pain self-efficacy questionnaire (PSEQ) show mixed results in predicting APOP and PPOP. The Central Sensitisation Inventory (CSI) is more consistently linked to long-term pain, especially after joint and breast cancer surgeries.

Evaluation of anxiety and stress: Anxiety, helplessness, and emotional stress are linked to APOP. Tools like the State-Trait Anxiety Inventory (STAI), brief measure of emotional preoperative stress (B-MEPS), fear of Pain Questionnaire (FOP-9), and the national comprehensive cancer network (NCCN) Distress Thermometer show mixed but sometimes significant associations. Machine learning has identified psychometric items that may help exclude persistent pain with high certainty.

Sleep quality: Poor sleep quality is linked to increased APOP and PPOP, as well as longer hospital stays, though findings are not consistent. Obstructive sleep apnea (OSAS) does not appear to predict postoperative pain.

Quantitative sensory testing

Evaluation of sensitivity to temperature-induced pain: Cold and heat-based QST show inconsistent associations with postoperative pain. Some studies link suprathreshold cold and hot stimuli to APOP, while others report no predictive value for cold pain threshold or heat QST across various types of surgeries.

Evaluation of sensitivity to pressure-induced pain: Pain pressure threshold (PPT) has shown mixed results in predicting APOP. While it has been linked to APOP after knee, pancreatic, and other major surgeries, other studies found no association with acute or persistent pain, opioid use, or hospital stay across various procedures.

Evaluation of sensitivity to electrically induced pain: Electrical pain threshold (EPT) generally shows no association with APOP across various surgeries, though one study found a correlation in women undergoing laparoscopic cholecystectomy.

Dynamic evaluation of pain: Temporal summation of pain (TSP) may predict APOP after knee replacement, but findings are inconsistent in breast cancer surgery. Conditioned pain modulation (CPM) has been linked to persistent pain after knee arthroplasty, though several studies report no predictive value for TSP or CPM in PPOP.

Combined techniques of testing

Combining predictors improves accuracy in identifying patients at risk of APOP and PPOP. High preoperative pain, expected pain, and surgical extent predict APOP. Combinations like low PPT with high PCS, or preoperative pain with CPM and PCS, enhance prediction of PPOP. The Risk Index for Chronic Pain (RICP) predicts PPOP with good sensitivity and specificity. Other models using multiple risk factors or machine learning also show promising predictive accuracy, but lack clinical feasibility, for PPOP and opioid consumption.

Other techniques of testing

Evaluation of painful routine procedures: Simple clinical procedures like pain assessment during local anaesthetic infiltration and venous cannulation pain (VCP) have been associated with APOP and opioid consumption, offering practical tools for identifying high-risk patients.

Evaluation with commercial techniques: New nociceptive monitoring tools show mixed results in predicting APOP. For nociception, the SPI and PTI have shown some predictive value, particularly during specific surgical phases. EEG-based measures like qNOX have not been reliable, while NOL shows limited predictive accuracy, with timing of measurement being critical.

Genetic testing

Genetic predictors of postoperative pain remain limited and inconsistent. SNPs in genes such as ABCB1, COMT, NAV3, BDNF, and inflammatory markers (IL6, TNF, CXCL8) have shown associations with APOP, PPOP and opioid use in some studies, but findings are not yet conclusive.

Biochemical testing

Biomarkers such as circulating mRNA, blood cell ratios, receptor activity (μ -opioid, angiotensin II), and cerebrospinal fluid components (Substance P, endorphins) have shown associations with APOP and PPOP. A UVB-induced gene expression–based inflammation index was also negatively correlated with APOP.

Paper III

From March 2022 to February 2024, 299 of 424 patients were eligible for pain sensitivity stratification (VCP). Twenty (n = 20) patients did not undergo this stratification and were not included. 154 were low risk (VCP < 2.0); 125 high risk (VCP ≥ 2.0) This paper focused on the high-risk cohort where patients were randomised to EC (n = 62) or SOC (n = 63). Data were analysed as intention-to-treat (n = 125). Three patients had laparotomy conversion during index surgery; two protocol violations occurred. Per-protocol analysis (n = 120).

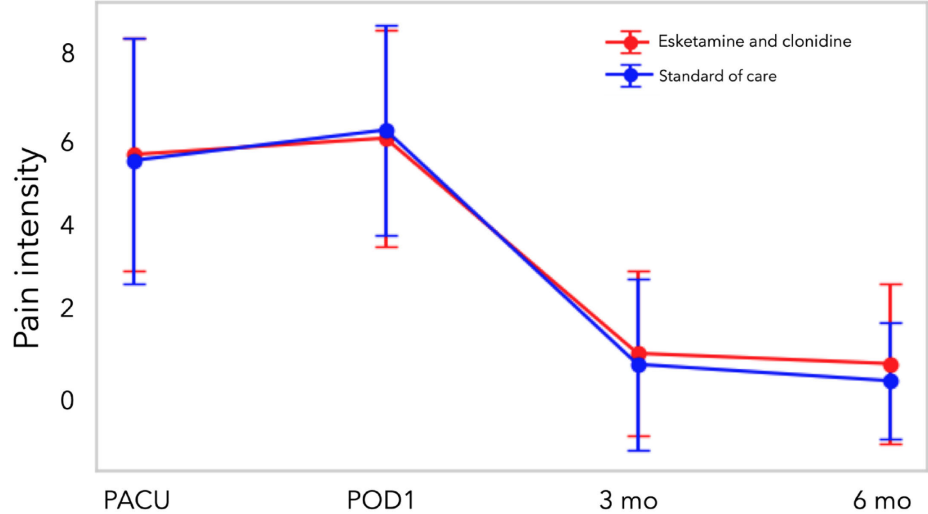


Figure 16. Pain trajectory depicting worst pain score during movement at four different time-points. Whiskers reflect the standard deviation on each time-point measurement respectively. PACU; Post anaesthesia care unit, POD1; Postoperative day one.

Condensed version of results from the study

- Group-based APOP score and group difference in worst APOP in the PACU: 5.7 ($\pm$ 2.7) and 5.5 ($\pm$ 2.8)(figure 15) NRS units for EC and SOC groups respectively $\rightarrow$ **non-significant difference of 0.2 NRS units (95%CI – 0.8 to 1.1, $P = 0.78$)** (Figure 16).
- Group-based APOP score and group difference in APOP at 24 hours: EC; 5.6 ($\pm$ 2.5) NRS units at *rest*, 6.0 ($\pm$ 2.5) during *movement*. SOC; 6.1 ($\pm$ 2.6) at *rest*, 6.2 ($\pm$ 2.4) during *movement* $\rightarrow$ **non-significant difference of 0.5 (95% CI –1.4 to 0.5, $P = 0.35$) NRS units at rest, non-significant difference of 0.2 (95% CI –1.1 to 0.7, $P = 0.68$) NRS units during movement.**
- Group-based PONV-NRS and group difference in PONV-NRS at 24 hours: 7.0 ($\pm$ 3.3) and 6.9 ($\pm$ 3.3) PONV-NRS units for EC and SOC groups respectively $\rightarrow$ **non-significant difference of 0.1 (95% CI –1.1 to 1.4, $P = 0.80$).**
- Proportion of PONV in the PACU: 34 % vs 29 % for EC and SOC groups respectively $\rightarrow$ **non-significant difference ($P = 0.53$).**
- Postoperative recovery at 24 hours: 93 ($\pm$ 23) vs 94 ($\pm$ 23) QoR-total score for EC and SOC groups respectively $\rightarrow$ **non-significant difference of 1.0 (95%CI –9.0 to 8.0, $P = 0.92$).**
- Postoperative rescue dose opioid in the PACU, in intravenous morphine equivalents: 5.9 mg ($\pm$ 4.9) and 6.6 mg ($\pm$ 5.6) for EC and SOC groups respectively $\rightarrow$ **non-significant difference of 0.7 mg (95%CI –2.5 to 1.2, $P = 0.92$).**
- Group-based PPOP score and group difference in PPOP at 3 months: EC; 0.9 ($\pm$ 1.7) NRS at *rest*, 1.1 ($\pm$ 1.9) during *movement*. SOC; 0.8 ($\pm$ 1.8) NRS at *rest*, 0.9 ($\pm$ 2.0) during *movement* $\rightarrow$ **non-significant difference of 0.1 (95%CI – 0.5 to 0.7, $P = 0.72$) NRS at rest, non-significant difference of 0.2 (95%CI – 0.4 to 0.9, $P = 0.48$) NRS during movement.**
- Group-based PPOP score and group difference in PPOP at 6 months: EC; 0.8 ($\pm$ 1.8) NRS at *rest*, 0.9 ($\pm$ 1.8) during *movement*. SOC; 0.3 ($\pm$ 1.0) NRS at *rest*, 0.5 ($\pm$ 1.3) during *movement* $\rightarrow$ **non-significant difference of 0.5 NRS (95%CI – 0.1 to 1.0, $P = 0.12$) at rest, non-significant difference of 0.4 NRS (95% CI – 0.2 to 1.0, $P = 0.18$) during movement.**

Paper IV

From March 2022 to February 2024, 299 of 424 patients were eligible for pain sensitivity stratification (VCP). Twenty (n = 20) did not undergo this stratification and were not included. 154 were low risk (VCP < 2.0); 125 high risk (VCP ≥ 2.0) This paper focused on the low-risk cohort where patients were randomised to OFA (n = 76) or SOC (n = 78). Data were analysed as intention-to-treat (n = 154). Four patients had laparotomy conversion during index surgery; six protocol violations occurred. Per-protocol analysis (n = 144).

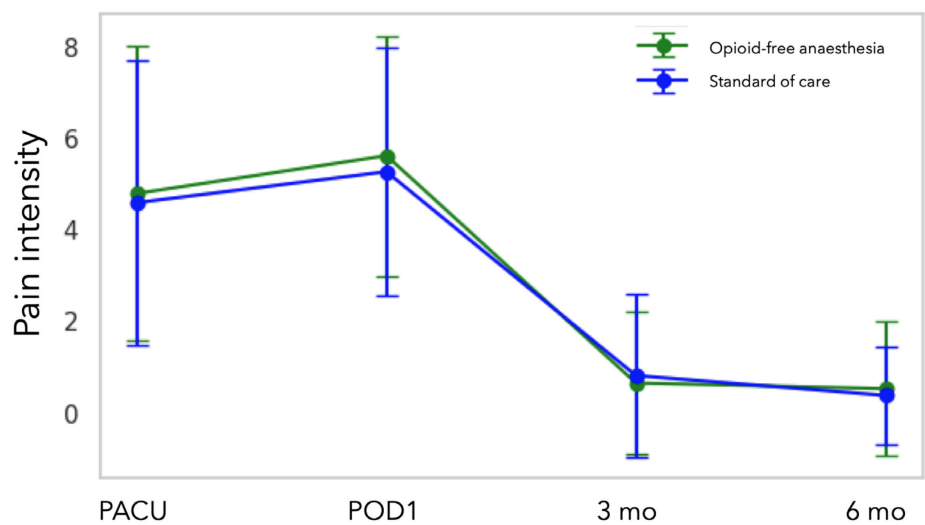


Figure 17. Pain trajectory depicting worst NRS during movement at four different time-points. Whiskers reflect the standard deviation on each time-point measurement respectively. PACU; Post anaesthesia care unit, POD1; Postoperative day one.

Condensed version of results from the study

- Group-based APOP score and group difference in APOP in the PACU: 4.8 (± 3.2) NRS and 4.6 (± 3.1) NRS units for OFA and SOC groups respectively $\rightarrow$ **non-significant difference of 0.2 (95%CI -0.8 to 1.2, $P = 0.67$)** (figure 17).
- Group-based APOP score and group difference in APOP at 24 hours: OFA; 5.7 (± 2.7) NRS at rest, 5.6 (± 2.6) during movement (figure 17). SOC; 5.0 (± 2.8) NRS at rest, 5.3 (± 2.7) during movement $\rightarrow$ **non-significant difference of 0.7 NRS (95% CI - 0.2 to 1.7, $P = 0.11$)** at rest, **non-significant difference of 0.3 NRS (95%CI - 0.5 to 1.2, $P = 0.43$)** during movement.
- Group-based PONV-NRS and group difference in PONV-NRS at 24 hours: 7.9 (± 3.0) and 7.6 (± 3.0) PONV-NRS units for OFA and SOC groups respectively $\rightarrow$ **non-significant difference of 0.3 (95% CI -0.7 to 1.3, $P = 0.52$)**.
- Proportion of PONV in the PACU: 23 % vs 23 % for OFA and SOC groups respectively $\rightarrow$ **non-significant difference ($P = 0.93$)**.
- Postoperative recovery at 24 hours: 99 (± 26) vs 102 (± 24) QoR-total score for OFA and SOC groups respectively $\rightarrow$ **non-significant difference of 3.0 (95%CI -11.0 to 5.0, $P = 0.44$)**.
- Postoperative rescue opioid consumption in the PACU, in intravenous morphine equivalents: 3.4 mg (± 5.1) and 5.1 mg (± 5.3) for OFA and SOC groups respectively $\rightarrow$ **non-significant difference of 1.7 mg (95%CI -0.1 to 3.4, $P = 0.039$)**.
- Group-based PPOP score and group difference in PPOP at 3 months: OFA; 0.5 (± 1.3) NRS at rest, 0.7 (± 1.5) during movement (Figure 16). SOC; 0.7 (± 1.5) NRS at rest, 0.8 (± 1.8) during movement $\rightarrow$ **non-significant difference of 0.2 NRS (95%CI - 0.6 - 0.3, $P = 0.51$)** at rest, **non-significant difference of 0.1 NRS (95%CI - 0.7 to 0.4, $P = 0.56$)** during movement.
- Group-based PPOP score and group difference in PPOP at 6 months: OFA; 0.3 (± 1.0) NRS at rest, 0.5 (± 1.5) during movement. SOC; 0.4 (± 1.1) at rest, 0.4 (± 1.1) during movement $\rightarrow$ **non-significant difference of 0.1 NRS (95%CI - 0.4 - 0.3, $P = 0.72$)** at rest, **non-significant difference of 0.1 NRS (95% CI - 0.3 - 0.6, $P = 0.48$)** during movement (Figure 16).

Paper V

Table 5. Descriptive data of enrolled patients. Oneway ANOVA comparison between groups in terms of quantitative study outcome and clinical parameters. *Indicating a significant difference between study groups. The standard deviation is reported within the brackets.

	Volatile	TIVA	OFA	p - value
Number of patients	10	10	10	
Age, years	55 (18.4)	49 (16.4)	65 (18.2)	0.142
Female gender	8/10	7/10	7/10	
Heart rate	63 (12.7)	62 (10.1)	71 (10.3)	0.176
Systolic blood pressure	109 (18.5)	100 (37.7)	100 (17.9)	0.661
Diastolic blood pressure	67 (10.0)	63 (11.6)	68 (6.4)	0.510
Patient state index	31 (3.9)	28 (3.7)	40 (8.5)	<0.001*
Spectral edge frequency, Hz	12.5 (1.8)	11.1 (1.3)	16.4 (3.1)	<0.001*

Quantitative outcomes

Patient state index

The OFA group had a significantly higher PSI (40.0 ± 8.5) compared to the volatile group (31.0 ± 3.9) and the TIVA group (28.0 ± 3.7) (One-way ANOVA: $F(2,27) = 11.173$, $p < 0.001$)(table 5). A F-value of 11.173 indicates that the variability between the group means is much larger than the variability within the groups, demonstrating a strong overall group effect. Post hoc analysis confirmed the difference between OFA and both control groups ($p < 0.001$, $p = 0.007$), but not between TIVA and Volatile groups ($p = 0.424$).

Spectral edge frequency

The OFA group had a significantly higher SEF95 (16.4 ± 3.1) compared to the volatile group (12.5 ± 1.8) and the TIVA group (11.1 ± 1.3) (One-way ANOVA: $F(2,27) = 15.207$, $p < 0.001$)(table 5). A F-value of 15.207 indicates that the variability between the group means is much larger than the variability within the groups, demonstrating a strong overall group effect. Post hoc analysis confirmed the difference between OFA and both control groups ($p < 0.001$, $p = 0.001$), but not between TIVA and Volatile groups ($p = 0.387$).

Descriptive outcomes

Patients in OFA-group typically exhibited theta-dominant EEG patterns (Figure 18D), differing from the alpha/delta dominance seen in routine anaesthesia. A few OFA patients showed atypical patterns: Two patient had high beta activity (B: SEF95 = 19.0 Hz, PSI = 46, C: SEF95 = 19.4 Hz, PSI = 52), two patients (exemplified by A in figure 18) showed more typical alpha/delta patterns (figure 18). TIVA and volatile groups consistently displayed expected alpha/delta frequency dominance. No patients in any group reported intraoperative awareness, an EMG interference was minimal.

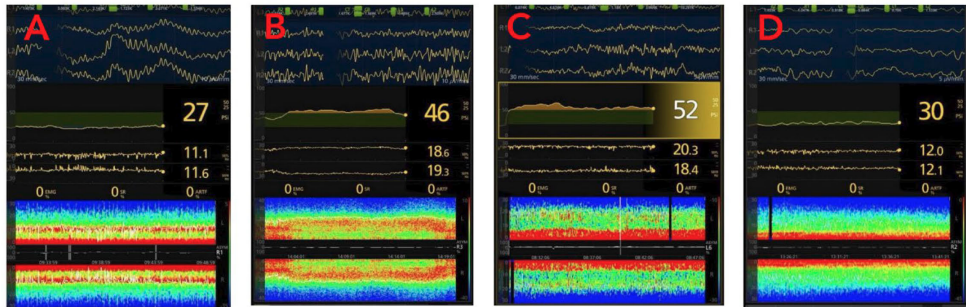


Figure 18. Descriptive outcome. Data from processed electroencephalography and density spectral array (DSA) for four patients in the study. A (control); Patient under clinical anaesthetic steady-state after skin incision with total intravenous anaesthesia (propofol, remifentanyl). This patient follows the recommended pEEG signature, with high power in slow/delta and alpha frequency spectrum. B; Patient under clinical anaesthetic steady-state after skin incision with opioid-free anaesthesia. This patient had almost exclusively high power in the beta frequency spectrum without any clinical signs of arousal or awakening. C; OFA patient who's EEG signature exhibited a patchy breakthrough pattern with high-powered beta-activity as well as a continuous theta frequency pattern. D; OFA patient with a predominantly high-powered theta frequency pattern.

Paper VI

In this pre-specified secondary analysis, 271 patients were included in the full cohort (FC) and 138 in the standard-of-care cohort (SOC). Within the FC, the high-risk and low-risk groups comprised 123 and 148 patients, respectively. When restricting the analysis to patients who received only SOC anaesthesia, the high-risk and low-risk groups included 62 and 76 patients, respectively.

Across both cohorts, significant between-group differences were observed in the proportion of female patients (FC: $P = 0.006$; SOC: $P = 0.04$), the presence of preoperative pain on the day of surgery (FC: $P < 0.001$; SOC: $P < 0.001$), and VCP (FC: $P < 0.001$; SOC: $P < 0.001$). In the SOC cohort only, the prevalence of longstanding preoperative pain lasting ≥ 3 months differed significantly between risk groups ($P = 0.047$). Conversely, in the FC, but not the SOC cohort, pain catastrophising differed significantly between high-risk and low-risk groups ($P = 0.046$) (Table 6).

Table 6. Postoperative outcomes and group-based comparison between the high-risk and low-risk groups in both the full cohort and standard of care only cohort. Mean values with standard deviation.

	Full cohort				Standard of care groups only			
	VCP < 2.0	VCP $\geq$ 2.0	p-value	95 % CI	VCP < 2.0	VCP $\geq$ 2.0	p-value	95 % CI
APOP _{PACU}	4.7 (3.1)	5.6 (2.7)	0.009**	0.2 - 1.6	4.5 (3.1)	5.6 (2.8)	0.047*	0.0 - 2.0
APOP _{24h,rest}	5.3 (2.8)	5.9 (2.5)	0.063	0.0 - 1.2	4.9 (2.8)	6.1 (2.6)	0.016*	0.2 - 2.1
APOP _{24h,mov}	5.5 (2.7)	6.1 (2.4)	0.048*	0.0 - 1.3	5.3 (2.7)	6.2 (2.4)	0.039*	0.0 - 1.8
QoR _{24h}	100 (25)	93 (23)	0.018*	1 - 13	102 (24)	94 (23)	0.048*	0 - 17
PPOP _{3mo,rest}	0.6 (1.4)	0.9 (1.7)	0.146	-0.1 - 0.7	0.7 (1.5)	0.8 (1.7)	0.593	-0.4 - 0.7
PPOP _{3mo,mov}	0.7 (1.7)	1.0 (1.9)	0.267	-0.2 - 0.7	0.8 (1.8)	0.9 (2.0)	0.831	-0.6 - 0.7
PPOP _{6mo,rest}	0.3 (1.1)	0.5 (1.4)	0.264	-0.1 - 0.5	0.4 (1.1)	0.3 (1.0)	0.990	-0.4 - 0.4
PPOP _{6mo,movement}	0.5 (1.3)	0.6 (1.5)	0.335	-0.2 - 0.5	0.4 (1.1)	0.5 (1.3)	0.562	-0.3 - 0.5
Postoperative opioids MME	10.0 (8.3)	17.5 (5.9)	<0.001**	5.8 - 9.2	15.2 (6.5)	17.5 (6.5)	0.048*	0.1 - 4.5

Abbreviations; APOP; Acute postoperative pain, MME; morphine milligram equivalents, NRS; Numeric rating scale, QoR; Quality of recovery. Statistically significant difference is marked by an asterisk (*) in conjunction with the absolute value. *Statistical significance at 0.05 level. ** Statistical significance at the 0.01 level.

Table 7. Stepwise multivariable logistic regression, for acute postoperative pain (NRS ≥ 4) in the PACU as dependent variable as the primary sample size based outcome in the PeriOperative Individualisation Trial²⁵⁸. Predefined variables were selected in terms of clinical significance and earlier scientific merits (PCS). Significance level for univariate logistic regression $p < 0.1$ and highlighted in bold digits and single asterisk (*). For the multivariate model, only female gender acted as an independent risk factor for acute postoperative pain (NRS ≥ 4) in the PACU, here with the significance level of $p < 0.05$, highlighted as bold digits and with double asterisk (**).

Variable	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
VCP ≥ 2.0	1.76 (1.02 – 3.04)	0.043*	1.31 (0.73 – 2.36)	0.361
Current pain	1.22 (1.03 – 1.45)	0.022*	1.06 (0.88 – 1.27)	0.551
Female gender	3.21 (1.75 – 5.89)	<0.001*	2.65 (1.33 – 5.29)	0.006**
Age	0.98 (0.97 – 0.99)	0.039*	1.00 (0.98 – 1.02)	0.699
PCS	1.04 (1.01 – 1.07)	0.019*	1.03 (0.99 – 1.06)	0.133
BMI	1.01 (0.98 – 1.03)	0.675	-	-
Preoperative pain	2.29 (1.32 – 3.98)	0.003*	1.76 (0.95 – 3.24)	0.071

Table 8. Stepwise multivariable logistic regression, for VCP ≥ 2.0 as dependent variable, with predefined variables in terms of clinical significance and earlier scientific merits (PCS). Significance level cut-off for univariate logistic regression $p < 0.1$ and highlighted in bold digits and single asterisk (*). For the multivariate model female gender and current pain influence VCP ≥ 2.0 , with the significance level of $p < 0.05$, highlighted as bold digits and with double asterisk (**).

Variable	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Current pain	1.28 (1.14 – 1.44)	<0.001*	1.23 (1.05 – 1.43)	0.008**
Female gender	2.65 (1.56 – 4.52)	0.003*	2.25 (1.11 – 4.55)	0.024**
Age	0.99 (0.97 – 0.99)	0.068*	0.99 (0.98 – 1.02)	0.868
PCS	1.03 (1.00 – 1.05)	0.050*	1.02 (0.99 – 1.04)	0.279
BMI	0.99 (0.97 – 1.01)	0.501	-	-
Preoperative pain	1.53 (1.02 – 2.29)	0.084*	0.98 (0.58 – 1.72)	0.990

Discussion

IAAS cornerstone: Individualised Pain Prediction - Current Limitations and Clinical Implications

The concept of individualised medicine is not new, although its implementation has progressed more rapidly in other medical fields than in the perioperative setting. As demonstrated in Paper I of this thesis, there has been considerable scientific interest over the past decade in individual perioperative pain prediction. Despite this growing body of evidence, current prediction strategies remain largely reliant on single-model approaches, which often exhibit limited accuracy and questionable clinical applicability. Although efforts to develop more high-performing models are ongoing, a fundamental question persists: how should clinicians interpret and act upon the information these models provide to achieve improved outcomes?

In this context, a more nuanced discussion of test performance is essential, especially for interventional trials where identified risk serves as the basis for targeted actions intended to optimize postoperative pain outcomes. It is essential to consider what level of predictive performance is currently acceptable. This is not merely a statistical matter but one of patient safety and clinical advancement. To illustrate; consider cancer screening programs, where tests with near-perfect sensitivity are required to reliably identify individuals with a disease. Anything less is often deemed unacceptable. Similarly, high specificity is necessary to avoid unnecessary and potentially harmful diagnostic procedures (e.g ultrasound-guided prostate biopsies after a high PSA) and to ensure efficient use of healthcare resources.

Postoperative pain is associated with several complications with negative effect on patients, health care systems and society at large^{261,262}. However, currently we must be open to the fact that some individuals will suffer postoperatively, which will mandate having a structured plan for their recovery. This is where enhanced recovery protocols come into play. In the meanwhile, it can be argued that many patients are potentially salvageable today, if an individualised pre-, intra- and postoperative approach is applied. Today, no such recommendations exist. Maybe it is time to accept current performance levels and discriminability to progress in the field of individualised interventions that can potentially improve postoperative outcomes. Meanwhile, the field of postoperative pain prediction must continue to advance and provide better models that can be challenged in clinical interventional trials.

Insights From the POPIT Trial: Stratification, Interventions, and Outcomes

The POPIT sought out to risk-stratify participants for postoperative pain with a pragmatic preoperative method. The participants got stratified to either high- or low-risk in terms of individual pain sensitivity. Subsequently, they were randomised to different interventions, each designed with distinct hypotheses and objectives in mind.

The low-risk participants either got OFA or standard of care. The purpose was to determine whether the individuals, in OFA-group, may be managed without having more postoperative pain, while possibly gaining other benefits compared to those treated with conventional opioid-based approaches. Although opioids are potent analgesics, their use is well-known to be associated with a range of postoperative complications, including respiratory depression, gastrointestinal dysfunction, central nervous system effects, and the early development of tolerance⁶²⁻⁶⁸. These side-effects, discussed in detail in the introduction, can collectively have a detrimental impact on postoperative outcomes.

As a first step, this trial focused on evaluating potential positive outcomes. The findings indicated that while OFA was non-inferior to standard care in terms of acute pain outcomes, it did not confer any additional advantages. A more comprehensive interpretation of these results, one that includes the negative consequences of opioid administration, may yield a more nuanced and informative conclusion. Unfortunately, no such outcomes were addressed in that trial.

The high-risk cohort was presumed to consist of individuals with an increased pain sensitivity, which was also shown in paper VI, i.e patients who are likely to require greater resources and more intensive postoperative management. In this cohort, the aim was to improve postoperative outcomes by incorporating modulation of NMDA and alpha-2 adrenergic receptors, based on the hypothesis that these individuals may process noxious stimuli through more complex or varied mechanisms. However, the results demonstrated no significant differences in either acute or persistent pain outcomes, nor in associated measures of pain or recovery.

At first glance, these findings may appear disappointing to clinicians and researchers who advocate for the feasibility of individualised perioperative management. Anaesthesia providers, as experts in patient safety and pharmacological modulation of physiology, are naturally inclined to seek pharmacological strategies to alleviate pain. However, if pain is to be understood in its full complexity, the study design and its findings must be interpreted within a broader conceptual framework. A critical starting point is to distinguish between nociception and pain at the bedside. Nociception refers to the neural processing of noxious stimuli, whereas pain encompasses not only sensory input but also

emotional and cognitive dimensions, including memory¹¹⁸. Current definition acknowledges that pain cannot be experienced during an unconscious state and that it may occur even in the absence of nociceptive input. Given this complexity, is it reasonable to expect that the addition or omission of a few anaesthetic or analgesic agents would significantly alter postoperative pain outcomes?

This raises further questions about the nuances of pharmacological management that may not have been fully explored in the POPIT or other trials. Pharmacology involves not only pharmacodynamics, such as receptor modulation, but also pharmacokinetics, including drug distribution, metabolism, and excretion. Therefore, identifying the optimal titration of anaesthetic and analgesic agents involves considerations of dosage, drug synergy, and the mode of administration. In this context, it is relevant to consider the numerous trials and meta-analyses that have attempted to quantify the effect sizes of individual analgesic agents. As referenced in the introduction, the pooled effect sizes of currently available agents typically range from 0.5 to 1.0 NRS units on a population level^{46,74,82,99}. However, it remains unclear what these average effects translate to for the individual patient. This ambiguity suggests that optimal utilisation strategies are yet to be fully elucidated and supports the argument for moving beyond a one-size-fits-all approach towards individualised perioperative strategies. In POPIT we wanted to achieve an effect size that would have made a clinical difference. As an outcome, the minimal meaningful clinical difference varies significantly in acute pain. However, recommendations are to achieve a pain reduction around 30 %^{263,264}, which is pretty much in line with a recent publication on a perioperative population¹²². It is possible that the statistical analysis would have rendered different results if a larger sample were collected in POPIT. Furthermore, subgroup analyses with different sample effect, matching a 30 % APOP reduction, is also feasible but statistically more advanced.

Methodological Challenges in Risk Stratification and Prediction Tools

Going back to the conclusion from Paper I, prediction of postoperative pain has many aspects that need discussion in the anaesthesia society. Ideally, the prediction method should be 100 % sensitive, 100% specific, instantaneous and non-invasive, non-harm-full, inexpensive or free, universally available and unaffected by confounders. It goes without stating that no such method will ever exist. In light of this, all existing prediction tools will have negative after-effects on interventions in clinical trials, decreasing the resolution of the outcome data as a consequence. Pain during venous cannulation is appealing since its pragmatic and theoretically can be seen as a marker for pain-sensitivity phenotype. Furthermore, it has previous

scientific merits¹⁹⁷⁻¹⁹⁹. Even though these factors speak to its utility, we do not fully understand the extent to how it introduces bias. In Paper VI, we tried to investigate this using one more exact and one pragmatic statistical approach, comparing SOC-groups and the full cohort from POPIT respectively. We saw that $VCP \geq 2.0$ could discriminate patients in an unadjusted group comparison. However, when controlling for clinically significant variables, VCP was not an independent predictor and was influenced by female gender and increased preoperative pain on the day of surgery. When looking at the cohort in POPIT, we found that female gender and the presence of preoperative pain was overrepresented. Since the cutoff of VAS 2.0 is extrapolated from other perioperative cohorts, the cohort skewness in POPIT might have led to VCP having poor sensitivity towards the majority class (e.g. high-risk for postoperative pain), introducing a type II error (e.g. false negatives) resulting in high-risk patients missed and classified as low-risk. Subsequently, this bias would supposedly be more influential in the low-risk cohort²⁶⁰. In theory, this could have been mitigated if using a different methodological design including:

- Oversampling - artificially generating more samples of patients with low postoperative pain, balancing the dataset. However, oversampling also risks amplifying noise and artefacts in an already biased dataset, and because it only supports predictive modelling rather than causal inference, it cannot meaningfully correct imbalance introduced at the design stage²⁶⁵.
- Balance the dataset - using a design to recruit equal numbers of patients expected to have high and low pain. This approach depends on deliberately incorporating patients with a lower-risk profile, defined by one or more relevant preoperative factors (e.g. lower surgical invasiveness, male gender, higher age etc)
- Adjust the decision threshold – using other cut-off other than $VAS \geq 2.0$ and thereby increasing sensitivity or high-pain predictions, reducing Type II errors. We analysed this post hoc and found that a VCP cut-off 1.35 provided the best balance between sensitivity and specificity in the POPIT cohort. This in turn suggests that patients in the POPIT cohort reached the “high-risk” pain category at lower VCP scores, meaning the population was generally more pain-sensitive or had a higher baseline risk for postoperative pain.

In hindsight these solutions in designs might be sound but difficult to predefine in practice when designing a clinical trial and without introducing other types of Type I and II errors. The investigation in Paper VI shines new light on the results from Paper III²⁵⁹ and IV²⁶⁰, with the conclusion that we cannot confidently state that these interventions wouldn't have had a real impact on the defined postoperative outcomes in other surgical populations or with a more balance in gender in the total study population.

IAAS cornerstone: Pain as Predictive Processing - Expectations, Variability, and Clinical Relevance

It is widely recognised that individuals experience pain differently, and that this variability is somewhat context dependent²⁶⁶. For instance, the reported intensity of pain during venous cannulation prior to surgery can vary significantly between individuals. In contrast, when observing others in pain, we may be susceptible to a cognitive bias, assuming that pain is a uniform experience solely determined by the external stimulus, rather than shaped by internal factors.

The Bayesian model of pain proposes that the brain generates predictions about impending pain, which in turn influence the actual perception of pain^{267,268}. This framework, known as predictive coding, suggests that perception is not a passive process but is actively shaped by prior expectations, especially when those expectations are held with high precision. As stated in the introduction, the precision can be influenced by the sensation of control or uncertainty. According to this concept, expectations (priors) and noxious sensory input (likelihood) are combined to shape the actual pain perception (posterior).

A small psychobiological study (n = 45) was conducted to investigate how different models on pain expectations influence pain perception using the Bayesian framework, and to explore individual differences in sensitivity to these expectations²⁶⁷. Basically, all participants got to choose between two visual cues (pie charts or playing cards), each representing different probabilities of receiving varying intensities of noxious stimulation. Next, participants received a mild electric stimulus based on the cue they picked, after which they were asked to rate their perceived pain on a scale between 0 and 100. The statistical analysis incorporated six models, each representing increasing levels of complexity regarding the influence of participants' expectations on their pain perception:

1. *Assumptions - Baseline model*: Pain perception depends only on the actual noxious stimulus. This model acted as a reference point to be able to see if adding expectations improved predictions.
2. *Assumptions - Multimodal prior model*: Pain perception depends on the intensity of noxious stimuli + information about the cue. This assumes that people form expectations based on all possible intensities of the noxious stimuli, shown in the cue.
3. *Assumptions - Mean-only model*: Pain perception depends on the intensity of noxious stimuli + information about the mean value of the cue. This assumes that people simplify the cue and expect an average pain intensity. For example, if the cue states that it is 50 % chance of VAS 40 and 50 % chance of VAS 70, the expected pain is VAS 55.

4. *Assumptions - Mean and variance model:* Pain perception depends on the intensity of noxious stimuli + the mean and variance of the cue. This basically assumes that people consider both the average pain intensity of the cue (as in mean-only model) but also its variance. If the cue states that there is a 25 % chance of VAS 30 and 75 % chance of VAS 70, uncertainty is introduced leading to a reduced influence of the expectations (less control = less precision).
5. *Assumptions - Full model:* Pain perception depends on the intensity of noxious stimuli + independent cue information + trait-like features (pessimism vs optimism). This assumes that someone who always expects high pain, regardless of the cue, will perceive pain more intensely.
6. *Assumptions - Hierarchical model:* Pain perception depends on the intensity of noxious stimuli + cue information (average pain + uncertainty) + trait-like features. This assumes real-life scenarios where people are different: one may be sensitive to pain cues, another have strong pessimistic bias, a third may be less influenced by expectations altogether. Thus, these variables were allowed to vary freely.

In this study expectations influenced perceived pain more than the baseline model²⁶⁷. However, when uncertainty was introduced into the experimental paradigm, the influence of expectations on perceived pain was attenuated. Moreover, stable individual traits, such as dispositional optimism or pessimism, were found to significantly modulate pain perception, suggesting that trait-like biases in pain expectation play a meaningful role. Among the models tested, the hierarchical model was best at capturing individual differences in expectation sensitivity.

Despite the study's limitations, namely its small sample size and the uncertainty surrounding its generalisability to perioperative contexts, these findings offer valuable insights but remain hypothesis-generating. They highlight the potential impact of preoperative psychological preparation on postoperative outcomes. Specifically, the results suggest that patients' expectations may either facilitate or hinder recovery, depending on how these expectations are shaped prior to surgery.

Predictive processing of nociceptive input offers a promising framework for identifying individuals who are particularly sensitive to expectation effects. This, in turn, could inform a more individualised approach to preoperative patient education and support the development of quantitative frameworks for future clinical trials²⁶⁸. For example, trials could stratify participants into groups with high versus low expectation sensitivity to examine whether certain interventions are particularly effective for those whose pain responses are strongly shaped by expectations.

Similarly, postoperative recovery studies could statistically control for individual differences in pain expectations to better isolate the true effect of an intervention.

A Bayesian perspective provides one way to formalise this process. In such a model, priors represent patient expectations, likelihood reflects the expected nociceptive load based on surgical, individual and biological factors, posterior corresponds to the predicted pain outcome, and prediction error captures the discrepancy between predicted and observed pain. Priors can be estimated using brief expectation measures and past surgical experiences, while likelihood can be approximated from routine perioperative variables such as surgical invasiveness, comorbidities, demographics, preoperative pain, opioid tolerance, analgesic technique, and intraoperative nociception indices. These components can be weighted according to their predictive precision to generate an individualised posterior pain estimate. Prediction errors may then be used both to identify patients who require additional support and to refine the model by updating the relative influence of priors and likelihood.

Before the influence of prior expectations on perioperative pain is fully understood, it is essential to critically evaluate whether our current perioperative approach is setting up patients for failure or success.

IAAS cornerstone: Shared Decision Making and Patient - Centred Perioperative Care

Independent of individual, surgical, anaesthesia-related or prior patient expectations, surgery is in many times an extreme measure aiming to benefit the patient. Ideally, the goal with surgery should align with the patient's and their families own goals. Shared decision making (SDM), in this context is essential, especially in elderly and in more complex procedures where stakes are higher²⁶⁹. Over the years, evidence has suggested that SDM has the potential benefits in potentiating satisfaction and trust, reduce decisional conflict and regret but also align surgical interventions with quality-of-life outcomes and functional goals²⁷⁰⁻²⁷². Furthermore, SDM may reduce unnecessary procedures and healthcare costs that comes from postoperative complications and readmissions²⁷³. However, implementing this framework is not without challenges, some of which include patients with cognitive impairment, communication barriers (sensory deficits, language, and health literacy issues), cultural differences (varying expectations), time-constraints and system-level barriers (lack of interdisciplinary coordination). Time-constraints, particularly in emergency settings when the patient's life is at risk, are situations where clinicians may feel that time-pressure leave little room for meaningful discussions²⁷⁴. In order to be effective there are some evidence-based

structural aids for SDM, such SHARE, stepwise SDM model and the Three-talk model, the former for the general population and the two latter being more tailored to elderly patients²⁶⁹. Context specific tools for anaesthesia are not yet readily available, even though the My anaesthesia Choice-HF has recently been developed for anaesthesia in hip fracture surgery²⁷⁵.

Shared decision-making may have potential benefits for postoperative pain by helping patients enter surgery with clearer expectations and a better understanding of their analgesic options. When patients feel more informed and involved, this could reduce uncertainty and anxiety, factors that are thought to influence pain perception. SDM also might support more tailored perioperative pain plans by incorporating individual preferences, previous pain experiences, and concerns, which in turn may improve engagement with analgesic strategies. Although evidence is still emerging, SDM represents a plausible pathway through which patient involvement could contribute to more satisfactory postoperative pain experiences.

As patient's values are subjected to more focus, future studies aimed at facilitating the implementation of SDM is important. One specific potential lay within technology-enhanced SDM, i.e evaluation/development of mobile apps, telemedicine platforms, and video-based tools for their usability and impact on decision quality.

Opioid Stewardship, Nociception vs Pain, and the Role of processed EEG

Within perioperative care, the overarching objective should be to optimise patient outcomes. As stated in the introduction, inadequately managed postoperative pain can impose a substantial burden, not only on individual patients, but also on healthcare systems and society at large. Some of the immediate consequences relate to impaired respiratory function and delayed ambulation, both of which can hinder recovery and increase the risk of additional complications. Similarly, some of our interventions are associated with actual harm. Opioids, for example, which has a historically natural role in anaesthesia, is well-known to cause multiple postoperative complications that are in direct conflict with enhanced recovery protocols. Aside from opioid-related adverse side-effects (ORAS), early tolerance development is getting increased attention since it carries its own set of risks in the long-term²⁷⁶. This highlights a critical opportunity for anaesthesia providers to exercise opioid stewardship, ensuring that opioids are used appropriately and in alignment with best practices.

Returning to the distinction between nociception and pain, it is essential for anaesthesiologists to remain aware that these are not interchangeable concepts. Misinterpreting physiological markers of sympathetic activation, such as tachycardia or hypertension, as indicators of pain rather than nociception may lead to unnecessary opioid administration. This cognitive bias risks causing harm, particularly when it results in overtreatment. While nociception and pain are clearly related, they are distinct phenomena and must be treated as such in clinical decision-making.

In this context, real-time intraoperative monitoring may serve as a valuable adjunct, offering clinicians enhanced capability to distinguish between inadequate anaesthetic depth, potentially resulting in pain perception, and nociceptive input occurring under insufficient anaesthesia. Specifically, pEEG that integrates both quantitative indices and power-spectrogram analysis may currently be one of the most promising approaches, as most other purely intraoperative real-time nociception monitors carry substantial limitations²³⁹. When used appropriately in conjunction with traditional clinical signs, pEEG may support more appropriate intraoperative opioid administration. Although this approach warrants further investigation, one plausible hypothesis is that improved opioid stewardship, guided by accurate assessment of anaesthetic depth and nociceptive activity, could lead to better postoperative outcomes. This strategy include; 1. administering multimodal anaesthesia including opioids to patients exhibiting inappropriately high sympathetic tone, 2. Ensuring confidence in the anaesthesia depth, thereby enabling clinicians to interpret physiological responses as nociceptive rather than painful and withhold inappropriately high opioid doses that can have negative effect postoperatively.

This can be exemplified by two cases: 1. *A young patient under appropriate general anaesthesia depth whose MAP and heart rate increases 20 % after skin incision. In an otherwise healthy individual, it may be more harmful to give opioids in this situation than adapting a restrictive attitude.* 2. *An elderly patient with stable angina and undertreated coronary artery disease whose mean arterial pressure and heart rate increases with 20 % who is under appropriate anaesthesia depth. This patient is at increased risk for perioperative cardiac injury, which mandates a more aggressive anti-nociception strategy.*

To support these hypotheses, a study on 64 critically ill patients in the ICU sought out to explore whether pEEG can detect signs of nociceptive processing after noxious stimulation (tracheal suctioning)²²⁷. Main aim was to identify and describe pEEG signatures to this stimulus in a clinical setting. The study protocol involved three key steps: 1. Application of a pEEG monitoring device (SedLine Monitor, Masimo Corporation, Irvine, CA, USA) on the patient's forehead. 2. Induce the noxious stimulus. 3. Pain assessment using the BPS. For statistical analysis they dichotomised the cohort into weak ($BPS \leq 6$) or strong ($BPS \geq 7$) responders. After stimulation, strong responders had significantly increased power in the delta

frequency spectrum and decreased power in the alpha frequency spectrum. Furthermore, changes in pEEG indices and colour spectrogram were more sensitive to nociceptive processing compared to signs of increased sympathetic tone (MAP, heart rate). These changes in colour spectrogram reflect previously described neurophysiological phenomena referred to as alpha drop-out and delta arousal (figure 19).

Alpha drop-out, a sudden reduction/disappearances of alpha frequency power, is suggestive of a disruption of cortical stability in the prefrontal cortex²²⁶. Delta arousal, a transient increase in power in delta frequency spectrum, is suggestive of cortical activation²²⁶. Both phenomena have been proposed as markers of insufficient analgesia. However, their clinical interpretation requires contextual judgement, particularly in distinguishing between analgesia and anti-nociception. These findings suggest that pEEG may serve as a non-invasive, real-time indicator of nociceptive processing, with potential applications in individualised analgesic and anti-nociceptive management strategies. Nevertheless, the study's limitations, including its small sample size, retrospective design, and the heterogeneity of ICU patients (many of whom may have metabolic encephalopathy), underscore the need for further clinical research to validate and expand upon these results.

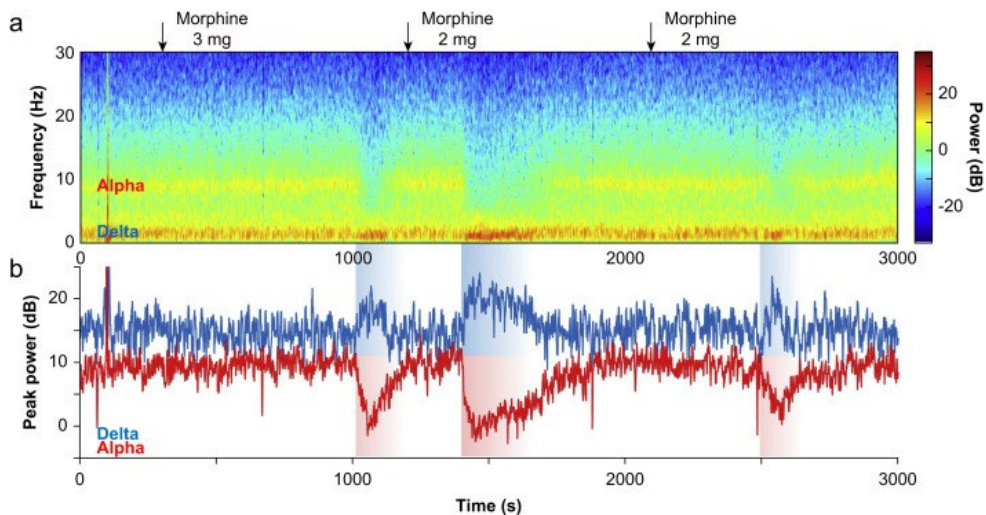


Figure 19. Image depicting the power spectrogram (a) and peak power in the delta and alpha frequency spectrum (b) on a patient undergoing laparotomy during general anaesthesia using sevoflurane as maintenance. During maintenance phase there is an appropriate anaesthesia depth defined as a high- powered spectrum in the alpha and delta frequency range. At timepoints $t_1 = 1000$ s, $t_2 = 1500$ s, $t_3 = 2600$ s, the patient was subjected to noxious stimulus, followed by clear delta arousal and alpha drop-out. In (a) the power spectrogram an interruption in the alpha spectrum band and a more intense focus in the delta spectrum band. In (b) this is made clearer as contrast enhancement decreases and increases for alpha and delta frequencies respectively. *Reproduced, not altered or used for commercial purposes, from García et al., 2021, British Journal of Anaesthesia, Vol. 126, No. 2. Licensed under CC BY-NC-ND 4.0* ²²⁶.

Opioid-free anaesthesia is now a well-researched approach to general anaesthesia but has currently not been shown to be more advantageous than other multimodal anaesthesia strategies²⁷⁷. This may reflect a broader shift in anaesthetic practice, where increasing awareness of the importance of balanced anaesthesia has led to more nuanced clinical decision-making. Alternatively, it may indicate that OFA is not universally applicable and should not be considered a one-size-fits-all approach. This argues further for IAAS and clinical research on risk-stratified patients for postoperative pain.

A growing concern with OFA, particularly as perioperative monitoring technologies advance, is that many commercial monitoring devices have not been validated for use within this framework. For pEEG, the reliance on NMDA-antagonists and alpha-2-agonists in OFA presents a specific challenge. These pharmacological agents are known to significantly alter neurophysiological parameters, yet their combined effects within an OFA regimen have not been systematically studied. As a result, the use of pEEG in this context may be unreliable and even unsafe.

In the light of this, paper V of this thesis aimed to take the first step toward aligning OFA with traditional anaesthetic techniques in terms of monitoring validity²²⁸. Subsequently, the findings from this study are hypothesis-generating and may inform the design of future research, both in validating OFA protocols and in exploring individualised anaesthesia strategies for risk-stratified cohorts.

Processed EEG has the potential to give the clinician a true scope on what is going on in the brain when under general anaesthesia. Even though complex, the use of raw-EEG patterns together with colour spectrograms have the potential to refine and increase the resolution of data that are put into clinical judgement and decision making. As a start, actionable thresholds should be defined and used in clinical interventional trials; Burst suppression → decrease sedation. Sudden loss of alpha → increase sedation. Loss of alpha + gain in delta + new noxious stimulus → consider anti-nociception if appropriate. Increased delta with volatile anaesthetic → consider decreasing MAC if high. Beta-breakthrough burst (beta arousal) → consider antinociception if appropriate anaesthesia depth or consider increased sedation if arousal. To have such a design, the monitoring device must be recordable so that the investigator can go back and objectively cross-check so that treatment algorithms were followed. Although this technology exist, this poses a significant challenge in high-powered, high-quality trials.

Taken together, the work in this thesis supports a pragmatic path toward IAAS: ❖ use good enough preoperative phenotyping to stratify risk; ❖ recognise that OFA was noninferior for APOP in low-risk patients but not superior in the outcomes assessed, arguing for selective use; ❖ acknowledge that in high-risk patients the specific NMDA/ α 2 strategy tested did not improve acute or persistent pain under the studied conditions, indicating the need to refine targets, dosing, and

timing rather than abandon individualisation; ❖ be cautious with $VCP \geq 2.0$ as a sole triage tool given important pain biases, and consider other design solutions in future trials; ❖ and to use pEEG together with structured intraoperative algorithms to separate nociception from pain, support opioid stewardship, and reduce large “prediction mismatches” that may worsen postoperative pain.

Conceptually, a predictive processing view helps in explaining patient to patient variability and motivates combining bottom up (antinociception, desensitisation) with top down measures (expectation informed communication, anxiety management) across the pre-, intra-, and postoperative pathway. This is the core of IAAS, e.g. a workflow that aligns individual risk and expectations with monitoring guided titration and coherent recovery plans. External commentary has underscored this trajectory. In an editorial titled “*From risk stratification to precision analgesia — What the POPIT trials teach us*”²⁷⁸ Yurttas et al frame POPIT as a step from risk stratification toward precision analgesia, emphasising the potential value of phenotype guided, stratified designs and the need to interpret neutral findings as prompts to refine targeting, dosing, and endpoints rather than to abandon individualisation.

Conclusions

This thesis examined multiple components of individualised anaesthesia and analgesia, spanning preoperative pain prediction, multimodal anaesthetic strategies, OFA, intraoperative nociception monitoring, and psychobiological mechanisms. Across six studies, the collective findings show that while several approaches hold promise, their clinical impact varies, and meaningful individualisation will require a combination of refined prediction tools, selective pharmacological strategies, and improved intraoperative monitoring.

Preoperative phenotyping emerged as useful for stratifying risk, even when prediction accuracy was modest. Methods such as self-rated pain sensitivity and pain during venous cannulation showed potential, but their performance was influenced by factors such as sex and preoperative pain, underscoring the need for multifactorial rather than single-method approaches. The work also highlights that commonly used thresholds, such as $VCP \geq 2.0$, may embed systematic biases, reinforcing the importance of design-level considerations in future trials.

In high-risk patients, the tested NMDA/ $\alpha 2$ -based multimodal strategy did not improve APOP or PPOP, suggesting that the concept of individualisation remains valid, but the specific targets, timing, and dosing require refinement. In contrast, OFA was noninferior to standard care in low-risk patients and reduced postoperative rescue opioid requirements, supporting its selective, not universal, use. These findings collectively argue for tailoring anaesthetic strategies to patient risk profiles rather than applying uniform protocols.

The thesis also shows that pEEG can offer meaningful insight into a patient's intraoperative nociceptive state. At the same time, these devices should be used with caution, as multimodal anaesthesia techniques may produce patterns that differ from those seen with routine anaesthesia.

Beyond physiological and pharmacological factors, this thesis also acknowledges the potential importance of psychobiological variables, such as pain expectations and predictive coding, in shaping perioperative pain responses. Although these mechanisms were not directly tested in the included studies, they represent compelling avenues for future research and may ultimately play a key role in advancing truly individualised anaesthesia.

In summary, this thesis supports a pragmatic, evidence-based approach to IAAS: one that uses risk stratification, selective opioid-free strategies, refined multimodal analgesia, and advanced monitoring, while recognising the limitations of current prediction tools and the need to integrate emerging psychobiological insights. The path forward lies not in a single method, but in combining complementary strategies to improve postoperative pain outcomes and move closer to genuinely individualised perioperative care.

Future perspectives

To truly advance the field of individualised anaesthesia and analgesia, researchers must align around and try to close existing knowledge gaps. The concept of IAAS is not meant to draw attention from already established concepts like ERAS. Instead, IAAS shifts the focus toward tailoring postoperative pain management and recovery to the individual, rather than solely on the type of surgery. In research, IAAS can serve as a guiding mindset, encouraging clinical trials and methodologies which prioritise the patient's unique needs. While we have made progress in predicting who might experience more postoperative pain, we still lack effective interventions to reduce that risk. Individualised approaches to anaesthesia and postoperative pain relief may help fill this gap. Importantly, this concept does not only focus on pharmacologic therapy but also non-pharmacologic values, such as how and when to set fair expectations and define care goals with patients. These aspects are crucial but often hard to measure in clinical trials. In terms of these values, the implementation requires a broader organisational change that align with each institution's structure, making it difficult to apply one-size-fits-all recommendations.

It is important to advocate for trials that go beyond a one-size-fits-all approach. Future research should focus on stratifying patients based on their individual risk for postoperative pain and then tailoring interventions accordingly. This would allow for more precise and effective treatment strategies, ensuring that patients receive care that matches their specific needs and risk profiles.

Assessing APOP remains a persistent challenge, not least because the tools most commonly used, numerical or visual analogue scales, capture only a narrow part of the patient experience. In clinical trials, these scales offer tidy, quantifiable endpoints that suit statistical analysis. Yet in everyday practice, pain is rarely so neatly packaged. Patients struggle to translate complex, fluctuating sensations into a single number, and clinicians often interpret those numbers through the lens of time pressure, expectations, or institutional norms. The result is a mismatch between the controlled clarity of trial data and the messy reality of postoperative care.

Building on these measurement challenges, clinical trial methodology introduces further complications. When postoperative pain is assessed across multiple domains, the volume of statistical testing increases substantially, raising the risk of false-positive findings. Traditional approaches often rely on family-wise error rate

corrections, which, while statistically rigorous, can dilute apparent treatment effects and obscure clinically meaningful signals. Composite outcomes offer one potential solution by combining several pain-related endpoints into a single measure, but they are only as robust as the components chosen. Without a coherent framework, composites risk blending outcomes of unequal importance or masking divergent effects across domains.

These methodological issues reinforce a broader point: reducing pain to a single score risks overlooking dimensions that matter deeply to patients. Functional recovery, emotional distress, sleep disruption, and the wider impact on daily activities often remain invisible when pain is captured solely through intensity scales. A patient who reports “4 out of 10” may still be unable to mobilise, breathe deeply, or participate in rehabilitation, outcomes that are clinically meaningful but not reflected in traditional measures.

Against this backdrop, a core outcome set offers a constructive way forward. By defining a standardised, balanced group of domains; pain intensity, physical function, side-effects, emotional wellbeing, and patient satisfaction, it encourages a more holistic understanding of postoperative recovery. Such an approach not only strengthens the interpretability of composite outcomes and reduces unnecessary multiplicity, but also aligns research with real-world priorities. Ultimately, it ensures that interventions are judged not only by how much they reduce pain scores, but by how well they support patients in returning to their lives.

Thus, this point-by-point list serves as a suggestive call for research in this demanding field:

- Prospective investigational clinical trials using predefined preoperative prediction methods or models that are clinically available and feasible to implement.
- A nuanced discussion or Delphi consensus on what level of predictive performance is currently acceptable for identifying patients at increased risk of postoperative pain.
 - Depending on the agreed performance threshold, a clear methodological and statistical strategy should be proposed to mitigate any loss of outcome granularity arising from limitations in model performance.
- Pragmatic randomised controlled trials of interventions, pharmacological or non-pharmacological, that have the potential to mitigate postoperative pain in participants with different postoperative pain risk phenotypes.
 - These trials should be powered to detect a minimally clinically meaningful difference in postoperative pain and should assess not only pain intensity but also functional and emotional outcomes¹⁸⁵.

- A rigorous statistical framework that uses fair family-wise grouping and structured gatekeeping procedures, with conditional Hochberg correction applied within each family to control error rates while preserving power.
- As an alternative, carefully constructed composite outcomes may be employed, provided that components are clinically coherent and hierarchically ordered; in such cases, a win-ratio approach with gatekeeping can offer a transparent and interpretable way to prioritise clinically meaningful differences.
- Pragmatic randomised controlled trials and systematic reviews employing a Bayesian framework for predictive coding of pain, to explore how preoperative expectations, and interventions designed to shape these expectations, influence postoperative pain. Suggested statistical plan and methodology:
 - Step 1 – Estimate prior expectations: Use brief tools such as anticipated pain NRS, PSEQ, TEX-Q, and previous surgical experiences to quantify expectations.
 - Step 2 – Approximate the likelihood (nociceptive load): Use routine perioperative variables; surgical invasiveness, comorbidities, demographic and pain-related risk factors, analgesic technique, and intraoperative nociception indices.
 - Step 3 – Integrate priors and likelihood: Fit separate models for expectations and nociceptive factors, calculate residual variances, and convert these into normalised precision weights. Combine these weighted components to generate an individualised posterior prediction of postoperative pain or APOP risk for stratification and individualised analgesic planning.
 - Step 4 – Calculate prediction error: Compute prediction error as *observed pain minus predicted pain*. Large positive or negative errors may flag individuals needing tailored analgesic or expectation-focused interventions, while systematic model-level errors can guide iterative updating of weights and variable selection.

- Implementation science studies aimed at overcoming organisational barriers to introducing structured advance care planning in the perioperative setting.
 - A hybrid implementation–effectiveness design may be used to test strategies that address these barriers while simultaneously evaluating the impact of structured advance care planning on perioperative care.

Acknowledgements

This thesis exists thanks to the unwavering support and encouragement of many individuals. Before being specific, I would like to acknowledge all the participants, who were included in the studies, without whom this book would never exist.

Specifically, I would direct my deepest gratitude to my main supervisor **Anna Persson**, who's valuable insights and companionship helped me throughout my work and especially during the tougher periods. Anna's profound knowledge in perioperative pain has been inspiring and throughout the years has become a dear friend.

My co-supervisor, **Johan Undén**, who's profound experience and suggestions at times was groundbreaking and helpful.

Anna Tjärnqvist, Ursula Carlstrand, Carita Nilsson, Marianne Orring deserves my deepest gratitude and respect since their enthusiasm and work-ethics lead to the rigorous inclusion of participants and data collection in the preoperative preparation phase.

Hanna Svensson, helped me with administrative tasks and having an oversight on grants and their dead-line, with a rigorous energy and professionalism.

Josefin Holgersson, a co-author in paper III and IV, who helped me with data collection and analysis and proved to be a talented researcher.

Professor **Jonas Åkeson**, who provided his valuable insights and experience when writing paper I.

Peter Asplund, Malin Larsson, and Hanna Johansson, my closest line managers during these years, showed great belief in my work and provided me support in completing this thesis. I cannot understate the importance their support has given me and my family by giving me time and space to perform this work.

All my **colleagues at the department of anaesthesia and intensive care**, Halmstad Hospital, for their understanding and respect during the clinical trial phases. Especially, I would like to applaud their curiosity and, at times, enthusiasm (☺) when phased with relatively new approaches to their clinical practice, like opioid-free anaesthesia did.

The **department for science and innovation (FIC)** at Hallands Hospital, **Lund University**, and **Region Halland** for scientific and financial support, and **Sparbanksstiftelsen** for their generous grants.

Entergate AB, for excellent cooperation and support in managing Entermedic, which made data collection, safety and structure manageable.

Lastly, to my wife **Felicia**, and children **Juni**, **Arvid** and **Ester** who gave me warmth, energy and stability at times in need. Especially, I would like to give all my love to **Felicia** who has always been supportive even though her interest in research and my work not always has been totally apparent (☺).

References

1. Cao B, Xu Q, Shi Y, Zhao R, Li H, Zheng J, Liu F, Wan Y, Wei B. Pathology of pain and its implications for therapeutic interventions. *Signal Transduction and Targeted Therapy* 2024; 9: 155.
 2. Clapham DE. TRP channels as cellular sensors. *Nature* 2003; 426: 517-24.
 3. Karcz M, Abd-Elseyed A, Chakravarthy K, Aman MM, Strand N, Malinowski MN, Latif U, Dickerson D, Suvar T, Lubenow T, Peskin E, D'Souza R, Cornidez E, Dudas A, Lam C, Farrell Ii M, Sim GY, Sebai M, Garcia R, Bracero L, Ibrahim Y, Mahmood SJ, Lawandy M, Jimenez D, Shahgholi L, Sochacki K, Ramadan ME, Tieppo Francio V, Sayed D, Deer T. Pathophysiology of Pain and Mechanisms of Neuromodulation: A Narrative Review (A Neuron Project). *J Pain Res* 2024; 17: 3757-90.
 4. Yam MF, Loh YC, Tan CS, Khadijah Adam S, Abdul Manan N, Basir R. General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation. *Int J Mol Sci* 2018; 19.
 5. Eilers H, Schumacher MA. Mechanosensitivity of Primary Afferent Nociceptors in the Pain Pathway. In: Kamkin A, Kiseleva I, eds. *Mechanosensitivity in Cells and Tissues*. Moscow: Academia
- Copyright © 2005, Academia Publishing House Ltd., 2005.
6. Südhof TC. The presynaptic active zone. *Neuron* 2012; 75: 11-25.
 7. Nadim F, Bucher D. Neuromodulation of neurons and synapses. *Curr Opin Neurobiol* 2014; 29: 48-56.
 8. Merighi A. The histology, physiology, neurochemistry and circuitry of the substantia gelatinosa Rolandi (lamina II) in mammalian spinal cord. *Prog Neurobiol* 2018; 169: 91-134.
 9. Sun G, McCartin M, Liu W, Zhang Q, Kenefati G, Chen ZS, Wang J. Temporal pain processing in the primary somatosensory cortex and anterior cingulate cortex. *Mol Brain* 2023; 16: 3.
 10. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* 2020; 161: 1976-82.
 11. Soliman AM, Barreda DR. Acute Inflammation in Tissue Healing. *Int J Mol Sci* 2022; 24.
 12. Ward PA, Lentsch AB. The acute inflammatory response and its regulation. *Arch Surg* 1999; 134: 666-9.

13. Rani M, Nicholson SE, Zhang Q, Schwacha MG. Damage-associated molecular patterns (DAMPs) released after burn are associated with inflammation and monocyte activation. *Burns* 2017; 43: 297-303.
14. Mañes S, Gómez-Moutón C, Lacalle RA, Jiménez-Baranda S, Mira E, Martínez AC. Mastering time and space: immune cell polarization and chemotaxis. *Semin Immunol* 2005; 17: 77-86.
15. Sandkühler J. Understanding LTP in pain pathways. *Mol Pain* 2007; 3: 9.
16. Li Y, Lock A, Fedele L, Zebochin I, Sabate A, Siddle M, Cainarca S, Röderer P, Montag K, Tarroni P, Brüstle O, Shaw T, Taams L, Denk F. Modelling inflammation-induced peripheral sensitization in a dish-more complex than expected? *Pain* 2025.
17. Ronchetti S, Migliorati G, Delfino DV. Association of inflammatory mediators with pain perception. *Biomedicine & Pharmacotherapy* 2017; 96: 1445-52.
18. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965; 150: 971-9.
19. Mendell LM. Constructing and deconstructing the gate theory of pain. *Pain* 2014; 155: 210-16.
20. Boensch S. Stimulation-produced analgesia: TENS, acupuncture and alternative techniques. *Anaesthesia & Intensive Care Medicine* 2011; 12: 28-30.
21. Gao YJ, Ji RR. c-Fos and pERK, which is a better marker for neuronal activation and central sensitization after noxious stimulation and tissue injury? *Open Pain J* 2009; 2: 11-17.
22. Zhou HY, Chen SR, Pan HL. Targeting N-methyl-D-aspartate receptors for treatment of neuropathic pain. *Expert Rev Clin Pharmacol* 2011; 4: 379-88.
23. Maio VD, Ventriglia F, Santillo S. Stochastic, structural and functional factors influencing AMPA and NMDA synaptic response variability: a review. *Neuronal Signal* 2017; 1: Ns20160051.
24. Millan MJ. Descending control of pain. *Prog Neurobiol* 2002; 66: 355-474.
25. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care* 2014; 8: 143-51.
26. Liu Y, Xiao S, Yang H, Lv X, Hou A, Ma Y, Jiang Y, Duan C, Mi W. Postoperative pain-related outcomes and perioperative pain management in China: a population-based study. *Lancet Reg Health West Pac* 2023; 39: 100822.
27. Smith HS. Potential analgesic mechanisms of acetaminophen. *Pain Physician* 2009; 12: 269-80.
28. Mattia C, Coluzzi F. What anesthesiologists should know about paracetamol (acetaminophen). *Minerva Anesthesiol* 2009; 75: 644-53.
29. Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Leone S. Paracetamol: new vistas of an old drug. *CNS Drug Rev* 2006; 12: 250-75.
30. Anekar AA HJ, Cascella M. (2023) WHO Analgesic Ladder. [www document] <https://www.ncbi.nlm.nih.gov/books/NBK554435/> [accessed on 17th November 2025]

31. Hayward KL, Powell EE, Irvine KM, Martin JH. Can paracetamol (acetaminophen) be administered to patients with liver impairment? *Br J Clin Pharmacol* 2016; 81: 210-22.
32. Gregoire N, Hovsepian L, Gualano V, Evene E, Dufour G, Gendron A. Safety and pharmacokinetics of paracetamol following intravenous administration of 5 g during the first 24 h with a 2-g starting dose. *Clin Pharmacol Ther* 2007; 81: 401-5.
33. Oscier CD, Milner QJ. Peri-operative use of paracetamol. *Anaesthesia* 2009; 64: 65-72.
34. Rawlins MD, Henderson DB, Hijab AR. Pharmacokinetics of paracetamol (acetaminophen) after intravenous and oral administration. *Eur J Clin Pharmacol* 1977; 11: 283-6.
35. van der Westhuizen J, Kuo PY, Reed PW, Holder K. Randomised controlled trial comparing oral and intravenous paracetamol (acetaminophen) plasma levels when given as preoperative analgesia. *Anaesth Intensive Care* 2011; 39: 242-6.
36. Holmér Pettersson P, Jakobsson J, Owall A. Plasma concentrations following repeated rectal or intravenous administration of paracetamol after heart surgery. *Acta Anaesthesiol Scand* 2006; 50: 673-7.
37. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, Trelle S. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2017; 390: e21-e33.
38. Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2015; 2015: Cd008659.
39. Halvey EJ, Haslam N, Mariano ER. Non-steroidal anti-inflammatory drugs in the perioperative period. *BJA Educ* 2023; 23: 440-47.
40. Bongiovanni T, Lancaster E, Ledesma Y, Whitaker E, Steinman MA, Allen IE, Auerbach A, Wick E. Systematic Review and Meta-Analysis of the Association Between Non-Steroidal Anti-Inflammatory Drugs and Operative Bleeding in the Perioperative Period. *Journal of the American College of Surgeons* 2021; 232: 765-90e1.
41. Chuang PY, Yang TY, Tsai YH, Huang KC. Do NSAIDs affect bone healing rate, delay union, or cause non-union: an updated systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 2024; 15: 1428240.
42. Jamjittong S, Matsuda A, Matsumoto S, Kamonvarapitak T, Sakurazawa N, Kawano Y, Yamada T, Suzuki H, Miyashita M, Yoshida H. Postoperative non-steroidal anti-inflammatory drugs and anastomotic leakage after gastrointestinal anastomoses: Systematic review and meta-analysis. *Ann Gastroenterol Surg* 2020; 4: 64-75.
43. Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials. *J Allergy Clin Immunol* 2014; 134: 40-5.
44. Karnina R, Arif SK, Hatta M, Bukhari A. Molecular mechanisms of lidocaine. *Ann Med Surg (Lond)* 2021; 69: 102733.

45. Gronwald C, Vegh V, Hollmann MW, Hahnenkamp A, Garaj V, Hahnenkamp K. The inhibitory potency of local anesthetics on NMDA receptor signalling depends on their structural features. *Eur J Pharmacol* 2012; 674: 13-9.
46. Weibel S, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, Eberhart LH, Poepping DM, Afshari A, Kranke P. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. *Br J Anaesth* 2016; 116: 770-83.
47. Paterson H, Vadiveloo T, Innes K, Balfour A, Atter M, Stoddart A, Cotton S, Arnott R, Aucott L, Batham Z, Foo I, MacLennan G, Nimmo S, Speake D, Norrie J. Intravenous Lidocaine for Gut Function Recovery in Colonic Surgery: A Randomized Clinical Trial. *Jama* 2025; 333: 39-48.
48. Casas-Arroyave FD, Osorno-Upegui SC, Zamudio-Burbano MA. Therapeutic efficacy of intravenous lidocaine infusion compared with thoracic epidural analgesia in major abdominal surgery: a noninferiority randomised clinical trial. *Br J Anaesth* 2023; 131: 947-54.
49. Foo I, Macfarlane AJR, Srivastava D, Bhaskar A, Barker H, Knaggs R, Eipe N, Smith AF. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. *Anaesthesia* 2021; 76: 238-50.
50. Woodcock T, Barker P, Daniel S, Fletcher S, Wass JAH, Tomlinson JW, Misra U, Dattani M, Arlt W, Vercueil A. Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency: Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK. *Anaesthesia* 2020; 75: 654-63.
51. Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, Habib AS, Jin Z, Kovac AL, Meyer TA, Urman RD, Apfel CC, Ayad S, Beagley L, Candiotti K, Englesakis M, Hedrick TL, Kranke P, Lee S, Lipman D, Minkowitz HS, Morton J, Philip BK. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. *Anesth Analg* 2020; 131: 411-48.
52. Olanders KJ, Lundgren GA, Johansson AM. Betamethasone in prevention of postoperative nausea and vomiting following breast surgery. *J Clin Anesth* 2014; 26: 461-5.
53. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol* 2017; 17: 233-47.
54. De Oliveira GS, Jr., Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology* 2011; 115: 575-88.
55. Laconi G, Coppens S, Roofthoof E, Van De Velde M. High dose glucocorticoids for treatment of postoperative pain: A systematic review of the literature and meta-analysis. *J Clin Anesth* 2024; 93: 111352.
56. Waldhoer M, Bartlett SE, Whistler JL. Opioid receptors. *Annu Rev Biochem* 2004; 73: 953-90.
57. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med* 1995; 332: 1685-90.

58. Weiss N, Zamponi GW. Opioid Receptor Regulation of Neuronal Voltage-Gated Calcium Channels. *Cell Mol Neurobiol* 2021; 41: 839-47.
59. Lubejko ST, Livrizzi G, Buczynski SA, Patel J, Yung JC, Yaksh TL, Banghart MR. Inputs to the locus coeruleus from the periaqueductal gray and rostroventral medulla shape opioid-mediated descending pain modulation. *Sci Adv* 2024; 10: eadj9581.
60. Veinante P, Yalcin I, Barrot M. The amygdala between sensation and affect: a role in pain. *J Mol Psychiatry* 2013; 1: 9.
61. Mortazavi S, Thompson J, Baghdoyan HA, Lydic R. Fentanyl and morphine, but not remifentanyl, inhibit acetylcholine release in pontine regions modulating arousal. *Anesthesiology* 1999; 90: 1070-7.
62. Venara A, Neunlist M, Slim K, Barbieux J, Colas PA, Hamy A, Meurette G. Postoperative ileus: Pathophysiology, incidence, and prevention. *Journal of Visceral Surgery* 2016; 153: 439-46.
63. Baldini G, Bagry H, Aprikian A, Carli F. Postoperative urinary retention: anesthetic and perioperative considerations. *Anesthesiology* 2009; 110: 1139-57.
64. Smith HS, Laufer A. Opioid induced nausea and vomiting. *European Journal of Pharmacology* 2014; 722: 67-78.
65. Nakasuji M, Nakamura M, Imanaka N, Tanaka M, Nomura M, Suh SH. Intraoperative high-dose remifentanyl increases post-anaesthetic shivering. *Br J Anaesth* 2010; 105: 162-7.
66. Maher DP, Wong W, White PF, McKenna R, Rosner H, Shamloo B, Louy C, Wender R, Yumul R, Zhang V. Association of increased postoperative opioid administration with non-small-cell lung cancer recurrence: a retrospective analysis. *British Journal of Anaesthesia* 2014; 113: i88-i94.
67. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* 2006; 105: 660-4.
68. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology* 2008; 109: 180-7.
69. Maher DP, Walia D, Heller NM. Morphine decreases the function of primary human natural killer cells by both TLR4 and opioid receptor signaling. *Brain Behav Immun* 2020; 83: 298-302.
70. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth* 2014; 112: 991-1004.
71. prevention USCFdca. (2025) Understanding the Opioid Overdose Epidemic. [www document] <https://www.cdc.gov/overdose-prevention/about/understanding-the-opioid-overdose-epidemic.html> [accessed on 4th November 2025]
72. Santa Cruz Mercado LA, Liu R, Bharadwaj KM, Johnson JJ, Gutierrez R, Das P, Balanza G, Deng H, Pandit A, Stone TAD, Macdonald T, Horgan C, Tou SLJ, Houle TT, Bittner EA, Purdon PL. Association of Intraoperative Opioid Administration With Postoperative Pain and Opioid Use. *JAMA Surg* 2023; 158: 854-64.

73. Kawczak P, Feszak I, Bączek T. Ketamine, Esketamine, and Arketamine: Their Mechanisms of Action and Applications in the Treatment of Depression and Alleviation of Depressive Symptoms. *Biomedicines* 2024; 12: 2283.
74. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: A systematic review and meta-analysis. *J Clin Anesth* 2021; 68: 110071.
75. Hung KC, Kao CL, Ho CN, Hsing CH, Chang YJ, Wang LK, Liao SW, Chen IW. The impact of perioperative ketamine or esketamine on the subjective quality of recovery after surgery: a meta-analysis of randomised controlled trials. *Br J Anaesth* 2024; 132: 1293-303.
76. Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen V. Perioperative intravenous ketamine for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2018; 12: Cd012033.
77. Wu L, Huang X, Sun L. The efficacy of N-methyl-D-aspartate receptor antagonists on improving the postoperative pain intensity and satisfaction after remifentanyl-based anesthesia in adults: a meta-analysis. *J Clin Anesth* 2015; 27: 311-24.
78. Barreveld AM, Correll DJ, Liu X, Max B, McGowan JA, Shovel L, Wasan AD, Nedeljkovic SS. Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: results of a prospective, randomized, double-blind study. *Pain Med* 2013; 14: 925-34.
79. Do SH. Magnesium: a versatile drug for anesthesiologists. *Korean J Anesthesiol* 2013; 65: 4-8.
80. Cunningham FG, Nelson DB. Magnesium sulfate for the prevention of seizures in preeclampsia: origin, experimental basis, clinical studies, and the evolution in obstetrical practice. *Am J Obstet Gynecol* 2025.
81. Mathew AA, Panonnummal R. 'Magnesium'-the master cation-as a drug—possibilities and evidences. *BioMetals* 2021; 34: 955-86.
82. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. *Anaesthesia* 2013; 68: 79-90.
83. De Oliveira GS, Jr., Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology* 2013; 119: 178-90.
84. Seyhan TO, Tugrul M, Sungur MO, Kayacan S, Telci L, Pembeci K, Akpir K. Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery. *Br J Anaesth* 2006; 96: 247-52.
85. Tan W, Qian DC, Zheng MM, Lu X, Han Y, Qi DY. Effects of different doses of magnesium sulfate on pneumoperitoneum-related hemodynamic changes in patients undergoing gastrointestinal laparoscopy: a randomized, double-blind, controlled trial. *BMC Anesthesiol* 2019; 19: 237.
86. Dahake JS, Verma N, Bawiskar D. Magnesium Sulfate and Its Versatility in Anesthesia: A Comprehensive Review. *Cureus* 2024; 16: e56348.

87. Wesche D, Bockbrader H. A pharmacokinetic comparison of pregabalin and gabapentin. *The Journal of Pain* 2005; 6: S29.
88. Moore A, Costello J, Wiecezorek P, Shah V, Taddio A, Carvalho JC. Gabapentin improves postcesarean delivery pain management: a randomized, placebo-controlled trial. *Anesth Analg* 2011; 112: 167-73.
89. Brown EN, Pavone KJ, Naranjo M. Multimodal General Anesthesia: Theory and Practice. *Anesth Analg* 2018; 127: 1246-58.
90. Franks NP. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nat Rev Neurosci* 2008; 9: 370-86.
91. Hemmings HC, Jr., Akabas MH, Goldstein PA, Trudell JR, Orser BA, Harrison NL. Emerging molecular mechanisms of general anesthetic action. *Trends Pharmacol Sci* 2005; 26: 503-10.
92. Hagihiro S. Changes in the electroencephalogram during anaesthesia and their physiological basis. *Br J Anaesth* 2015; 115 Suppl 1: i27-i31.
93. Kamibayashi T, Maze M. Clinical uses of alpha2 -adrenergic agonists. *Anesthesiology* 2000; 93: 1345-9.
94. Brown EN, Purdon PL, Van Dort CJ. General anesthesia and altered states of arousal: a systems neuroscience analysis. *Annu Rev Neurosci* 2011; 34: 601-28.
95. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. *Drugs* 2000; 59: 263-8; discussion 69-70.
96. Wang CY, Chen F, Wu J, Fu SY, Xu XM, Chen J, Jiang YF, Lian Q, Liu HC. The association of the optimal bolus of dexmedetomidine with its favourable haemodynamic outcomes in adult surgical patients under general anaesthesia. *Br J Clin Pharmacol* 2020; 86: 85-92.
97. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; 77: 1134-42.
98. Devlin JW, Al-Qadheeb NS, Chi A, Roberts RJ, Qawi I, Garpestad E, Hill NS. Efficacy and safety of early dexmedetomidine during noninvasive ventilation for patients with acute respiratory failure: a randomized, double-blind, placebo-controlled pilot study. *Chest* 2014; 145: 1204-12.
99. Grape S, Kirkham KR, Frauenknecht J, Albrecht E. Intra-operative analgesia with remifentanyl vs. dexmedetomidine: a systematic review and meta-analysis with trial sequential analysis. *Anaesthesia* 2019; 74: 793-800.
100. Stähle H. A historical perspective: development of clonidine. *Best Practice & Research Clinical Anaesthesiology* 2000; 14: 237-46.
101. Gregoretto C, Moglia B, Pelosi P, Navalesi P. Clonidine in perioperative medicine and intensive care unit: more than an anti-hypertensive drug. *Curr Drug Targets* 2009; 10: 799-814.
102. Marinangeli F, Ciccozzi A, Donatelli F, Di Pietro A, Iovinelli G, Rawal N, Paladini A, Varrassi G. Clonidine for treatment of postoperative pain: a dose-finding study. *Eur J Pain* 2002; 6: 35-42.

103. Bharti N, Dontukurthy S, Bala I, Singh G. Postoperative analgesic effect of intravenous (i.v.) clonidine compared with clonidine administration in wound infiltration for open cholecystectomy. *Br J Anaesth* 2013; 111: 656-61.
104. Allen TK, Mishriky BM, Klinger RY, Habib AS. The impact of neuraxial clonidine on postoperative analgesia and perioperative adverse effects in women having elective Caesarean section-a systematic review and meta-analysis. *Br J Anaesth* 2018; 120: 228-40.
105. Engelman E, Marsala C. Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. *BJA: British Journal of Anaesthesia* 2012; 110: 21-27.
106. Micó JA, Ardid D, Berrocoso E, Eschalier A. Antidepressants and pain. *Trends Pharmacol Sci* 2006; 27: 348-54.
107. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol* 2007; 151: 737-48.
108. Hanson AM. Perioperative Pain Management: Springer Nature, 2024.
109. Baradwan S, Alshahrani MS, Alkhamis WH, Allam HS, AlSghan R, Ghazi A, Ragab B, Elmazzaly SMM, Aboshama RA, Ismail RA, Dahshan SA, Al-Touny AA, Daghash NH, Abdelhakim AM, Abbas AM, Fouda AA, Ezzat Abdelfattah L. Preoperative duloxetine on postoperative pain after laparoscopic gynecological surgeries: A systematic review and meta-analysis of randomized controlled trials. *J Gynecol Obstet Hum Reprod* 2022; 51: 102305.
110. Branton MW, Hopkins TJ, Nemec EC. Duloxetine for the reduction of opioid use in elective orthopedic surgery: a systematic review and meta-analysis. *Int J Clin Pharm* 2021; 43: 394-403.
111. Hetta DF, Elgalaly NA, Mohammad MAF. The Efficacy of Preoperative Duloxetine in Patients Undergoing Major Abdominal Cancer Surgery: A Randomized Controlled Trial. *Clin J Pain* 2021; 37: 908-13.
112. Shafer SL, Hendrickx JF, Flood P, Sonner J, Eger EI, 2nd. Additivity versus synergy: a theoretical analysis of implications for anesthetic mechanisms. *Anesth Analg* 2008; 107: 507-24.
113. Mendonça FT, Pellizzaro D, Grossi BJ, Calvano LA, de Carvalho LSF, Sposito AC. Synergistic effect of the association between lidocaine and magnesium sulfate on peri-operative pain after mastectomy: A randomised, double-blind trial. *Eur J Anaesthesiol* 2020; 37: 224-34.
114. Bell S, Rennie T, Marwick CA, Davey P. Effects of peri-operative nonsteroidal anti-inflammatory drugs on post-operative kidney function for adults with normal kidney function. *Cochrane Database Syst Rev* 2018; 11: Cd011274.

115. Hübner M, Kusamura S, Villeneuve L, Al-Niaimi A, Alyami M, Balonov K, Bell J, Bristow R, Guiral DC, Fagotti A, Falcão LFR, Glehen O, Lambert L, Mack L, Muenster T, Piso P, Pocard M, Rau B, Sgarbura O, Somashekhar SP, Wadhwa A, Altman A, Fawcett W, Veerapong J, Nelson G. Guidelines for Perioperative Care in Cytoreductive Surgery (CRS) with or without hyperthermic IntraPERitoneal chemotherapy (HIPEC): Enhanced Recovery After Surgery (ERAS®) Society Recommendations — Part II: Postoperative management and special considerations. *European Journal of Surgical Oncology* 2020; 46: 2311-23.
116. Liesenfeld LF, Wagner B, Hillebrecht HC, Brune M, Eckert C, Klose J, Schmidt T, Büchler MW, Schneider M. HIPEC-Induced Acute Kidney Injury: A Retrospective Clinical Study and Preclinical Model. *Ann Surg Oncol* 2022; 29: 139-51.
117. Toner AJ, Ganeshanathan V, Chan MT, Ho KM, Corcoran TB. Safety of Perioperative Glucocorticoids in Elective Noncardiac Surgery: A Systematic Review and Meta-analysis. *Anesthesiology* 2017; 126: 234-48.
118. Pain IAftSo. (2021) "IASP Terminology." [www document] <https://www.iasp-pain.org/resources/topics/acute-pain/> [accessed on Accessed 23 Feb 2025.]
119. Pain IAftSo. (2021) IASP terminology. [www document] <https://www.iasp-pain.org/advocacy/definitions-of-chronic-pain-syndromes/> [accessed on 23 February 2025]
120. Group ITW. (2011) Nociception. [www document] <https://www.iasp-pain.org/resources/terminology/> [accessed on May 1st 2025]
121. Kim TK. Practical statistics in pain research. *Korean J Pain* 2017; 30: 243-49.
122. Vollert J, Egert VM, Segelcke D, Fletcher D, Kalso E, Kemp H, Lavand'homme P, Komann M, Weinmann C, Meissner W, Pogatzki-Zahn EM. Minimal Clinically Important Changes of Patient-reported Outcome Measures for Acute Postsurgical Pain. *Anesthesiology* 2026; 144: 143-53.
123. Berthier F, Potel G, Leconte P, Touze MD, Baron D. Comparative study of methods of measuring acute pain intensity in an ED. *Am J Emerg Med* 1998; 16: 132-6.
124. Shahiri TS, Gélinas C. The Validity of Vital Signs for Pain Assessment in Critically Ill Adults: A Narrative Review. *Pain Manag Nurs* 2023; 24: 318-28.
125. Ledowski T. Objective monitoring of nociception: a review of current commercial solutions. *Br J Anaesth* 2019; 123: e312-e21.
126. Chanques G, Jaber S, Barbotte E, Violet S, Sebbane M, Perrigault PF, Mann C, Lefrant JY, Eledjam JJ. Impact of systematic evaluation of pain and agitation in an intensive care unit. *Crit Care Med* 2006; 34: 1691-9.
127. Dehghani H, Tavangar H, Ghandehari A. Validity and reliability of behavioral pain scale in patients with low level of consciousness due to head trauma hospitalized in intensive care unit. *Arch Trauma Res* 2014; 3: e18608.
128. Ahlers SJ, van Gulik L, van der Veen AM, van Dongen HP, Bruins P, Belitser SV, de Boer A, Tibboel D, Knibbe CA. Comparison of different pain scoring systems in critically ill patients in a general ICU. *Crit Care* 2008; 12: R15.
129. Kirshner D. Validity and Reliability of the Behavioral Pain Scale (BPS) for Assessing Pain in Non-Communicative Chronically Ventilated Patients. *Journal of Gerontology & Geriatric Medicine* 2020.

130. Gélinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. *Am J Crit Care* 2006; 15: 420-7.
131. Keane KM. Validity and reliability of the critical care pain observation tool: a replication study. *Pain Manag Nurs* 2013; 14: e216-e25.
132. Mogianos K, Åkeson J, Persson AKM. Systematic Review of Methods for Individual Prediction of Postoperative Pain. *Pain Research and Management* 2025; 2025: 1331412.
133. Pereira MP, Pogatzki-Zahn E. Gender aspects in postoperative pain. *Curr Opin Anaesthesiol* 2015; 28: 546-58.
134. Yang MMH, Hartley RL, Leung AA, Ronksley PE, Jetté N, Casha S, Riva-Cambrin J. Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. *BMJ Open* 2019; 9: e025091.
135. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, Borges GL, Bromet EJ, Demyttenaere K, de Girolamo G, de Graaf R, Gureje O, Lepine JP, Haro JM, Levinson D, Oakley Browne MA, Posada-Villa J, Seedat S, Watanabe M. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain* 2008; 9: 883-91.
136. Gulati M, Dursun E, Vincent K, Watt FE. The influence of sex hormones on musculoskeletal pain and osteoarthritis. *Lancet Rheumatol* 2023; 5: e225-e38.
137. Fillingim RB, Edwards RR. The association of hormone replacement therapy with experimental pain responses in postmenopausal women. *Pain* 2001; 92: 229-34.
138. Fillingim RB, Kaplan L, Staud R, Ness TJ, Glover TL, Campbell CM, Mogil JS, Wallace MR. The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. *J Pain* 2005; 6: 159-67.
139. Bernardes SF. (2024) Sex/Gender Biases in Pain Research and Clinical Practice. [www document] <https://www.iasp-pain.org/resources/fact-sheets/sex-gender-biases-in-pain-research-and-clinical-practice/>
140. Zhi Y, Zhang Y, Zhang Y, Zhang M, Kong Y. Age-associated changes in multimodal pain perception. *Age and Ageing* 2024; 53.
141. Di Vita G, Balistreri CR, Arcoleo F, Buscemi S, Cillari E, Donati M, Garofalo M, Listì F, Grimaldi MP, Patti R, Candore G. Systemic inflammatory response in elderly patients following hernioplastical operation. *Immun Ageing* 2006; 3: 3.
142. Gibson SJ, Farrell M. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. *Clin J Pain* 2004; 20: 227-39.
143. Shellito AD, Dworsky JQ, Kirkland PJ, Rosenthal RA, Sarkisian CA, Ko CY, Russell MM. Perioperative Pain Management Issues Unique to Older Adults Undergoing Surgery: A Narrative Review. *Ann Surg Open* 2021; 2: e072.
144. Haslam DW, James WP. Obesity. *Lancet* 2005; 366: 1197-209.
145. Dindo D, Muller MK, Weber M, Clavien PA. Obesity in general elective surgery. *Lancet* 2003; 361: 2032-5.

146. Tjeertes EK, Hoeks SE, Beks SB, Valentijn TM, Hoofwijk AG, Stolker RJ. Obesity--a risk factor for postoperative complications in general surgery? *BMC Anesthesiol* 2015; 15: 112.
147. van Helmond N, Timmerman H, van Dasselaar NT, van de Pol CC, Olesen SS, Drewes AM, Vissers K, Wilder-Smith OH, Steegers MA. High Body Mass Index Is a Potential Risk Factor for Persistent Postoperative Pain after Breast Cancer Treatment. *Pain Physician* 2017; 20: E661-e71.
148. Liu QR, Dai YC, Ji MH, Liu PM, Dong YY, Yang JJ. Risk Factors for Acute Postsurgical Pain: A Narrative Review. *J Pain Res* 2024; 17: 1793-804.
149. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci* 2017; 13: 851-63.
150. Olausson A, Jildenstål P, Andréll P, Angelini E, Stenberg E, Wallenius V, Öhrström H, Thörn SE, Wolf A. Effects of an opioid-free care pathway vs. opioid-based standard care on postoperative pain and postoperative quality of recovery after laparoscopic bariatric surgery: A multicentre randomised controlled trial. *Eur J Anaesthesiol* 2025; 42: 714-26.
151. Niklasson A, Finan PH, Smith MT, Forsberg A, Dietz N, Kander T, Werner MU, Irwin MR, Kosek E, Bjurström MF. The relationship between preoperative sleep disturbance and acute postoperative pain control: A systematic review and meta-analysis. *Sleep Med Rev* 2025; 79: 102014.
152. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28: 193-213.
153. Xiao Z, Long B, Zhao Z. The Effect of Improving Preoperative Sleep Quality on Perioperative Pain by Zolpidem in Patients Undergoing Laparoscopic Colorectal Surgery: A Prospective, Randomized Study. *Pain Res Manag* 2022; 2022: 3154780.
154. apnea ASoATFoPMopwos. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. *Anesthesiology* 2014; 120: 268-86.
155. Sibley D, Sellers D, Randall I, Englesakis M, Culos-Reed SN, Singh M, Mina DS. Evaluating the effect of preoperative interventions on sleep health in the perioperative period: a systematic review. *J Sleep Res* 2024; 33: e14124.
156. Rosenberger DC, Pogatzki-Zahn EM. Chronic post-surgical pain - update on incidence, risk factors and preventive treatment options. *BJA Educ* 2022; 22: 190-96.
157. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology* 2009; 111: 657-77.
158. Young G, Thielen H, Samuelson K, Jin J. Neurobiology of Chronic Pain, Posttraumatic Stress Disorder, and Mild Traumatic Brain Injury. *Biology* 2025; 14: 662.

159. Huang C, van Wijnen AJ, Im H-J. Serotonin Transporter (5-Hydroxytryptamine Transporter, SERT, SLC6A4) and Sodium-dependent Reuptake Inhibitors as Modulators of Pain Behaviors and Analgesic Responses. *The Journal of Pain* 2024; 25: 618-31.
160. McCarberg B, Peppin J. Pain Pathways and Nervous System Plasticity: Learning and Memory in Pain. *Pain Med* 2019; 20: 2421-37.
161. Powell R, Scott NW, Manyande A, Bruce J, Vögele C, Byrne-Davis LM, Unsworth M, Osmer C, Johnston M. Psychological preparation and postoperative outcomes for adults undergoing surgery under general anaesthesia. *Cochrane Database Syst Rev* 2016; 2016: Cd008646.
162. Gräsbeck HL, Reito ARP, Ekroos HJ, Aakko JA, Hölsä O, Vasankari TM. Smoking is a predictor of complications in all types of surgery: a machine learning-based big data study. *BJS Open* 2023; 7.
163. Armstrong AD, Hassenbein SE, Black S, Hollenbeak CS. Risk Factors for Increased Postoperative Pain and Recommended Orderset for Postoperative Analgesic Usage. *Clin J Pain* 2020; 36: 845-51.
164. Elisia I, Lam V, Cho B, Hay M, Li MY, Yeung M, Bu L, Jia W, Norton N, Lam S, Krystal G. The effect of smoking on chronic inflammation, immune function and blood cell composition. *Sci Rep* 2020; 10: 19480.
165. Alsanad M, Aljanoubi M, Alenezi FK, Farley A, Naidu B, Yeung J. Preoperative smoking cessation interventions: a systematic review and meta-analysis. *Perioper Med (Lond)* 2025; 14: 5.
166. Runze J, van IMH. Response bias is genetically biased: Another argument for Kagan's philippic against questionnaires in developmental psychology. *Dev Psychol* 2024; 60: 2008-15.
167. Sullivan MJL, Bishop, S. R., & Pivik, J. The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment* 1995; 7: 524 - 32.
168. Lyckner S, Böregård IL, Zetterlund EL, Chew MS. Validation of the Swedish version of Quality of Recovery score -15: a multicentre, cohort study. *Acta Anaesthesiol Scand* 2018; 62: 893-902.
169. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. *Molecular Psychiatry* 2023; 28: 3243-56.
170. Ghoneim MM, O'Hara MW. Depression and postoperative complications: an overview. *BMC Surg* 2016; 16: 5.
171. Lee S, Xue Y, Petricca J, Kremic L, Xiao MZX, Pivetta B, Ladha KS, Wijesundera DN, Diep C. The impact of pre-operative depression on pain outcomes after major surgery: a systematic review and meta-analysis. *Anaesthesia* 2024; 79: 423-34.
172. Javeed S, Benedict B, Yakdan S, Saleem S, Zhang JK, Botterbush K, Frumkin MR, Hardi A, Neuman B, Kelly MP, Steinmetz MP, Piccirillo JF, Goodin BR, Rodebaugh TL, Ray WZ, Greenberg JK. Implications of Preoperative Depression for Lumbar Spine Surgery Outcomes: A Systematic Review and Meta-Analysis. *JAMA Netw Open* 2024; 7: e2348565.

173. Hsu CJ, Fok MN, Wei JC. Confounders in anaesthesia-related depression outcomes. *Anaesthesia* 2025.
174. Baagil H, Baagil H, Gerbershagen MU. Preoperative Anxiety Impact on Anesthetic and Analgesic Use. *Medicina (Kaunas)* 2023; 59.
175. Zemła AJ, Nowicka-Sauer K, Jarmoszewicz K, Wera K, Batkiewicz S, Pietrzykowska M. Measures of preoperative anxiety. *Anaesthesiol Intensive Ther* 2019; 51: 64-69.
176. Ahmetovic-Djug J, Hasukic S, Djug H, Hasukic B, Jahic A. Impact of Preoperative Anxiety in Patients on Hemodynamic Changes and a Dose of Anesthetic During Induction of Anesthesia. *Med Arch* 2017; 71: 330-33.
177. Sipilä RM, Haasio L, Meretoja TJ, Ripatti S, Estlander AM, Kalso EA. Does expecting more pain make it more intense? Factors associated with the first week pain trajectories after breast cancer surgery. *Pain* 2017; 158: 922-30.
178. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. *Eur J Pain* 2007; 11: 153-63.
179. Briet JP, Bot AG, Hageman MG, Menendez ME, Mudgal CS, Ring DC. The pain self-efficacy questionnaire: validation of an abbreviated two-item questionnaire. *Psychosomatics* 2014; 55: 578-85.
180. Ramaswamy S, Wodehouse T. Conditioned pain modulation-A comprehensive review. *Neurophysiol Clin* 2021; 51: 197-208.
181. Shedden-Mora MC, Alberts J, Petrie KJ, Laferton JAC, von Blanckenburg P, Kohlmann S, Nestoriuc Y, Löwe B. The Treatment Expectation Questionnaire (TEX-Q): Validation of a generic multidimensional scale measuring patients' treatment expectations. *PLoS One* 2023; 18: e0280472.
182. Sonobe T, Nikaido T, Sekiguchi M, Kaneuchi Y, Kikuchi T, Matsumoto Y. High Pain Self-Efficacy Reduces the Use of Analgesics in the Early Postoperative Period After Total Knee Arthroplasty: A Retrospective Cohort Study. *J Pain Res* 2025; 18: 1407-15.
183. Mo KC, Gupta A, Movsik J, Covarrubius O, Greenberg M, Riley LH, 3rd, Kebaish KM, Neuman BJ, Skolasky RL. Pain Self-Efficacy (PSEQ) score of <22 is associated with daily opioid use, back pain, disability, and PROMIS scores in patients presenting for spine surgery. *Spine J* 2023; 23: 723-30.
184. Dubé MO, Langevin P, Roy JS. Measurement properties of the Pain Self-Efficacy Questionnaire in populations with musculoskeletal disorders: a systematic review. *Pain Rep* 2021; 6: e972.
185. Pogatzki-Zahn EM, De Lucia S, Weinmann C, Heitkamp H, Hummelshoj L, Liedgens H, Meissner W, Vincent K, Vollert J, Zahn P, Kaiser U, Rosenberger DC. A core outcome set of measurement instruments for assessing effectiveness and efficacy of perioperative pain management: results of the international IMI-PainCare PROMPT Delphi consensus process. *Br J Anaesth* 2025; 134: 1460-73.
186. Chang WS, Hsieh YT, Chen MC, Chang SC, Chen TS, Chang YC, Tsai YC, Lam CF. Characterization of self-anticipated pain score prior to elective surgery - a prospective observational study. *BMC Anesthesiol* 2021; 21: 85.

187. van Boekel RLM, Bronkhorst EM, Vloet L, Steegers MAM, Vissers KCP. Identification of preoperative predictors for acute postsurgical pain and for pain at three months after surgery: a prospective observational study. *Sci Rep* 2021; 11: 16459.
188. Bayman EO, Parekh KR, Keech J, Larson N, Vander Weg M, Brennan TJ. Preoperative Patient Expectations of Postoperative Pain Are Associated with Moderate to Severe Acute Pain After VATS. *Pain Med* 2019; 20: 543-54.
189. Levenig CG, Hasenbring MI, Günnewig L, Titze C, Elsenbruch S, Schulte TL. Treatment Expectations and You Get What You Expect; and Depression Plays a Role. *The Journal of Pain* 2024; 25.
190. Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. *Pain* 2007; 129: 256-59.
191. MacLachlan C, Shipton EA, Wells JE. The Cold Pressor Test as a Predictor of Prolonged Postoperative Pain, a Prospective Cohort Study. *Pain Ther* 2016; 5: 203-13.
192. Malmström EM, Stjerna J, Högestätt ED, Westergren H. Quantitative sensory testing of temperature thresholds: Possible biomarkers for persistent pain? *J Rehabil Med* 2016; 48: 43-7.
193. Antonaci F, Sand T, Lucas GA. Pressure algometry in healthy subjects: inter-examiner variability. *Scand J Rehabil Med* 1998; 30: 3-8.
194. Edwards RR, Campbell C, Schreiber KL, Meints S, Lazaridou A, Martel MO, Cornelius M, Xu X, Jamison RN, Katz JN, Carriere J, Khanuja HP, Sterling RS, Smith MT, Haythornthwaite JA. Multimodal prediction of pain and functional outcomes 6 months following total knee replacement: a prospective cohort study. *BMC Musculoskelet Disord* 2022; 23: 302.
195. Braun M, Bello C, Riva T, Hönemann C, Doll D, Urman RD, Luedi MM. Quantitative Sensory Testing to Predict Postoperative Pain. *Curr Pain Headache Rep* 2021; 25: 3.
196. Overstreet DS, Michl AN, Penn TM, Rumble DD, Aroke EN, Sims AM, King AL, Hasan FN, Quinn TL, Long DL, Sorge RE, Goodin BR. Temporal summation of mechanical pain prospectively predicts movement-evoked pain severity in adults with chronic low back pain. *BMC Musculoskelet Disord* 2021; 22: 429.
197. Persson AK, Pettersson FD, Dyrehag LE, Åkeson J. Prediction of postoperative pain from assessment of pain induced by venous cannulation and propofol infusion. *Acta Anaesthesiol Scand* 2016; 60: 166-76.
198. Persson AKM, Åkeson J. Prediction of Acute Postoperative Pain from Assessment of Pain Associated With Venous Cannulation. *Pain Pract* 2019; 19: 158-67.
199. Peng F, Li Y, Ai Y, Yang J, Wang Y. Application of preoperative assessment of pain induced by venous cannulation in predicting postoperative pain in patients under laparoscopic nephrectomy: a prospective observational study. *BMC Anesthesiol* 2020; 20: 86.
200. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001; 413: 203-10.

201. Orbach-Zinger S, Aviram A, Fireman S, Kadechenko T, Klein Z, Mazarib N, Artiuch A, Reuveni A, Ioscovich A, Eidelman LA, Landau R. Severe pain during local infiltration for spinal anaesthesia predicts post-caesarean pain. *Eur J Pain* 2015; 19: 1382-8.
202. Nimmaanrat S, Wongwiwattananon W, Siripreukpong S, Chongsuvivatwong V, Jensen MP. A prospective observational study to investigate the relationship between local anesthetic infiltration pain before spinal anesthesia and acute and chronic postsurgical pain in women undergoing elective cesarean delivery. *International Journal of Obstetric Anesthesia* 2021; 45: 56-60.
203. Storm H. Changes in skin conductance as a tool to monitor nociceptive stimulation and pain. *Curr Opin Anaesthesiol* 2008; 21: 796-804.
204. Ledowski T, Bromilow J, Paech MJ, Storm H, Hacking R, Schug SA. Monitoring of skin conductance to assess postoperative pain intensity. *Br J Anaesth* 2006; 97: 862-5.
205. Ledowski T, Bromilow J, Wu J, Paech MJ, Storm H, Schug SA. The assessment of postoperative pain by monitoring skin conductance: results of a prospective study. *Anaesthesia* 2007; 62: 989-93.
206. Norbeck DW, Lindgren S, Wolf A, Jildenstål P. Reliability of nociceptive monitors vs. standard practice during general anesthesia: a prospective observational study. *BMC Anesthesiol* 2025; 25: 51.
207. Kongsgaard UE, Menchini RJ, Larsen SG, Juul-Hansen KE. Skin conductance algesimeter is unreliable during sudden perioperative temperature increases. *Scand J Pain* 2024; 24.
208. Ruetzler K, Montalvo M, Bakal O, Essber H, Rössler J, Mascha EJ, Han Y, Ramachandran M, Keebler A, Turan A, Sessler DI. Nociception Level Index-Guided Intraoperative Analgesia for Improved Postoperative Recovery: A Randomized Trial. *Anesth Analg* 2023; 136: 761-71.
209. Ben-Israel N, Kliger M, Zuckerman G, Katz Y, Edry R. Monitoring the nociception level: a multi-parameter approach. *J Clin Monit Comput* 2013; 27: 659-68.
210. Bornemann-Cimenti H, Lang-Illievich K, Kovalevska K, Brenna CTA, Klivinyi C. Effect of nociception level index-guided intra-operative analgesia on early postoperative pain and opioid consumption: a systematic review and meta-analysis. *Anaesthesia* 2023; 78: 1493-501.
211. Funcke S, Pinnschmidt HO, Brinkmann C, Wessler S, Beyer B, Fischer M, Nitzschke R. Nociception level-guided opioid administration in radical retropubic prostatectomy: a randomised controlled trial. *Br J Anaesth* 2021; 126: 516-24.
212. Dziodzio T, Jurth C, Schmid JC, Weber LM, Lichtner G, Neudecker J, von Dincklage F. Utility of the nociception level index to monitor intraoperative nociception and predict acute postoperative pain in thoracic surgery. *J Clin Monit Comput* 2025.
213. Bublitz V, Ringat T, Jurth C, Lichtner G, von Dincklage F. Performance of the Nociception Level Index and the PainSensor to predict and detect responsiveness to nociceptive procedures in critical care patients. *Journal of Critical Care* 2025; 88: 155090.

214. Oh SK, Won YJ, Lim BG. Surgical pleth index monitoring in perioperative pain management: usefulness and limitations. *Korean J Anesthesiol* 2024; 77: 31-45.
215. Chen X, Thee C, Gruenewald M, Wnent J, Illies C, Hoecker J, Hanss R, Steinfath M, Bein B. Comparison of Surgical Stress Index-guided Analgesia with Standard Clinical Practice during Routine General Anesthesia: A Pilot Study. *Anesthesiology* 2010; 112.
216. Bergmann I, Göhner A, Crozier TA, Hesjedal B, Wiese CH, Popov AF, Bauer M, Hinz JM. Surgical pleth index-guided remifentanyl administration reduces remifentanyl and propofol consumption and shortens recovery times in outpatient anaesthesia. *Br J Anaesth* 2013; 110: 622-8.
217. Gruenewald M, Harju J, Preckel B, Molnár Z, Yli-Hankala A, Roskopf F, Koers L, Orban A, Bein B. Comparison of adequacy of anaesthesia monitoring with standard clinical practice monitoring during routine general anaesthesia: An international, multicentre, single-blinded randomised controlled trial. *Eur J Anaesthesiol* 2021; 38: 73-81.
218. Ledowski T, Schneider M, Gruenewald M, Goyal RK, Teo SR, Hruby J. Surgical pleth index: prospective validation of the score to predict moderate-to-severe postoperative pain. *Br J Anaesth* 2019; 123: e328-e32.
219. Jung K, Park MH, Kim DK, Kim BJ. Prediction of Postoperative Pain and Opioid Consumption Using Intraoperative Surgical Pleth Index After Surgical Incision: An Observational Study. *J Pain Res* 2020; 13: 2815-24.
220. Choi BM, Shin H, Lee JH, Bang JY, Lee EK, Noh GJ. Performance of the Surgical Pleth Index and Analgesia Nociception Index in Healthy Volunteers and Parturients. *Front Physiol* 2021; 12: 554026.
221. Singh J, Ebersole JS, Brinkmann BH. From theory to practical fundamentals of electroencephalographic source imaging in localizing the epileptogenic zone. *Epilepsia* 2022; 63: 2476-90.
222. Myslobodsky MS, Coppola R, Bar-Ziv J, Weinberger DR. Adequacy of the International 10-20 electrode system for computed neurophysiologic topography. *J Clin Neurophysiol* 1990; 7: 507-18.
223. Mulvey DA, Klepsch P. Use of Processed Electroencephalography in the Clinical Setting. *Curr Anesthesiol Rep* 2020; 10: 480-87.
224. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical Electroencephalography for Anesthesiologists: Part I: Background and Basic Signatures. *Anesthesiology* 2015; 123: 937-60.
225. Szeto HH. Spectral edge frequency as a simple quantitative measure of the maturation of electrocortical activity. *Pediatr Res* 1990; 27: 289-92.
226. García PS, Kreuzer M, Hight D, Sleigh JW. Effects of noxious stimulation on the electroencephalogram during general anaesthesia: a narrative review and approach to analgesic titration. *British Journal of Anaesthesia* 2021; 126: 445-57.
227. Bublitz V, Jurth C, Kreuzer M, Lichtner G, von Dincklage F. Electroencephalogram-based prediction and detection of responsiveness to noxious stimulation in critical care patients: a retrospective single-centre analysis. *Br J Anaesth* 2023; 130: e339-e50.

228. Mogianos K, Persson AKM. Anesthesia depth monitoring during opioid free anesthesia – a prospective observational study. *BMC Anesthesiology* 2025; 25: 37.
229. Sumner M, Deng C, Evered L, Frampton C, Leslie K, Short T, Campbell D. Processed electroencephalography-guided general anaesthesia to reduce postoperative delirium: a systematic review and meta-analysis. *Br J Anaesth* 2023; 130: e243-e53.
230. Kim MC, Fricchione GL, Brown EN, Akeju O. Role of electroencephalogram oscillations and the spectrogram in monitoring anaesthesia. *BJA Educ* 2020; 20: 166-72.
231. Purdon PL, Pavone KJ, Akeju O, Smith AC, Sampson AL, Lee J, Zhou DW, Solt K, Brown EN. The Ageing Brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. *Br J Anaesth* 2015; 115 Suppl 1: i46-i57.
232. Akeju O, Song AH, Hamilos AE, Pavone KJ, Flores FJ, Brown EN, Purdon PL. Electroencephalogram signatures of ketamine anesthesia-induced unconsciousness. *Clin Neurophysiol* 2016; 127: 2414-22.
233. Zhang L, Li H, Deng L, Fang K, Cao Y, Huang C, Gu E, Li J. Electroencephalogram Mechanism of Dexmedetomidine Deepening Sevoflurane Anesthesia. *Front Neurosci* 2022; 16: 913042.
234. Sleight JW, Vacas S, Flexman AM, Talke PO. Electroencephalographic Arousal Patterns Under Dexmedetomidine Sedation. *Anesth Analg* 2018; 127: 951-59.
235. He Z, Zhang H, Xing Y, Liu J, Gao Y, Gu E, Zhang L, Chen L. Effect of raw electroencephalogram-guided anesthesia administration on postoperative outcomes in elderly patients undergoing abdominal major surgery: a randomized controlled trial. *BMC Anesthesiol* 2023; 23: 337.
236. Wang R, Deng Y, Zhou S, Zhang J. EEG-derived pain threshold index for prediction of postoperative pain in patients undergoing laparoscopic urological surgery: a comparison with surgical pleth index. *J Clin Monit Comput* 2021; 35: 1395-402.
237. Lv J, Zhang J, Zhang K, Zheng J. Predictive value of EEG-derived pain threshold index for acute postoperative pain in children. *Front Pediatr* 2022; 10: 1052532.
238. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 2011; 14: 145-61.
239. Mogianos K, Persson AKM. The role of intraoperative real-time nociceptive monitoring in individualised anaesthesia and analgesia and where to head next; A narrative review. *J Clin Anesth* 2026; 110: 112162.
240. Ho KWD, Wallace MR, Staud R, Fillingim RB. OPRM1, OPRK1, and COMT genetic polymorphisms associated with opioid effects on experimental pain: a randomized, double-blind, placebo-controlled study. *Pharmacogenomics J* 2020; 20: 471-81.
241. McDermott JE, Wang J, Mitchell H, Webb-Robertson BJ, Hafen R, Ramey J, Rodland KD. Challenges in Biomarker Discovery: Combining Expert Insights with Statistical Analysis of Complex Omics Data. *Expert Opin Med Diagn* 2013; 7: 37-51.

242. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013; 118: 934-44.
243. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *The Lancet* 2006; 367: 1618-25.
244. Xu J, Brennan TJ. Comparison of skin incision vs. skin plus deep tissue incision on ongoing pain and spontaneous activity in dorsal horn neurons. *Pain* 2009; 144: 329-39.
245. Cheng L, Liu J, Qin S, Geng X, Jing L, Fang S. Safety and effectiveness of multimodal opioid-free anaesthesia for pain and recovery after laparoscopic surgery: a systematic review and meta-analysis. *BMJ Open* 2025; 15: e085988.
246. Fernandes RM, Pontes JPJ, Rezende Borges CE, de Brito Neto DR, Pereira AdJ, Carvalho VP, Gomes LG, Prado Silva FCd. Multimodal Analgesia Strategies for Cardiac Surgery: A Literature Review. *Hearts* 2024; 5: 349-64.
247. El-Boghdady K, Levy NA, Fawcett WJ, Knaggs RD, Laycock H, Baird E, Cox FJ, Eardley W, Kemp H, Malpus Z, Partridge A, Partridge J, Patel A, Price C, Robinson J, Russon K, Walumbe J, Lobo DN. Peri-operative pain management in adults: a multidisciplinary consensus statement from the Association of Anaesthetists and the British Pain Society. *Anaesthesia* 2024; 79: 1220-36.
248. Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia—when is enough too much? A review of opioid-induced tolerance and hyperalgesia. *The Lancet* 2019; 393: 1558-68.
249. Keon-Cohen Z, Loane H, Romero L, Jones D, Banaszak-Holl J. Advance care planning and goals of care discussions in perioperative care: a scoping review. *Br J Anaesth* 2025; 134: 1318-32.
250. Fields H. A motivation-decision model of pain: the role of opioids. *Proceedings of the 11th world congress on pain*. 2006: 449–59.
251. Vlaeyen JW, Kole-Snijders AM, Rotteveel AM, Ruesink R, Heuts PH. The role of fear of movement/(re)injury in pain disability. *J Occup Rehabil* 1995; 5: 235-52.
252. Büchel C. The role of expectations, control and reward in the development of pain persistence based on a unified model. *Elife* 2023; 12.
253. Büchel C, Geuter S, Sprenger C, Eippert F. Placebo analgesia: a predictive coding perspective. *Neuron* 2014; 81: 1223-39.
254. Zunhammer M, Bingel U, Wager TD. Placebo Effects on the Neurologic Pain Signature: A Meta-analysis of Individual Participant Functional Magnetic Resonance Imaging Data. *JAMA Neurol* 2018; 75: 1321-30.
255. Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F. Response expectancies in placebo analgesia and their clinical relevance. *Pain* 2001; 93: 77-84.
256. Thomas V, Heath M, Rose D, Flory P. Psychological characteristics and the effectiveness of patient-controlled analgesia. *Br J Anaesth* 1995; 74: 271-6.
257. Habermann M, Strube A, Büchel C. How control modulates pain. *Trends in Cognitive Sciences* 2025; 29: 60-72.

258. Mogianos K, Undén J, Persson A. Effect of individualized anesthesia and analgesia on postoperative pain in patients stratified for pain sensitivity: A study protocol for the PeriOPerative individualization trial randomized controlled trial. *Acta Anaesthesiol Scand* 2024.
259. Mogianos K, Holgersson J, Undén J, Persson AKM. The additive effect of esketamine and clonidine in patients at high risk for acute postoperative pain undergoing laparoscopic surgery: A randomised controlled trial. *J Clin Anesth* 2025; 108: 112059.
260. Mogianos K, Holgersson J, Undén J, Persson AKM. Opioid-free versus opioid-based anaesthesia and analgesia for patients at low risk for acute postoperative pain undergoing laparoscopic surgery: A randomised controlled trial. *Journal of Clinical Anesthesia* 2026; 108: 112058.
261. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. *Anesthesiol Clin North Am* 2005; 23: 21-36.
262. Odor PM, Bampoe S, Gilhooly D, Creagh-Brown B, Moonesinghe SR. Perioperative interventions for prevention of postoperative pulmonary complications: systematic review and meta-analysis. *Bmj* 2020; 368: m540.
263. Olsen MF, Bjerre E, Hansen MD, Hilden J, Landler NE, Tendal B, Hróbjartsson A. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med* 2017; 15: 35.
264. Bahreini M, Safaie A, Mirfazaelian H, Jalili M. How much change in pain score does really matter to patients? *Am J Emerg Med* 2020; 38: 1641-46.
265. He H, Garcia EA. Learning from Imbalanced Data. *Knowledge and Data Engineering, IEEE Transactions on* 2009; 21: 1263-84.
266. Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. *Pain* 2017; 158 Suppl 1: S11-s18.
267. Hoskin R, Berzuini C, Acosta-Kane D, El-Deredy W, Guo H, Talmi D. Sensitivity to pain expectations: A Bayesian model of individual differences. *Cognition* 2019; 182: 127-39.
268. Mogianos K, Persson AKM. A Conceptual Framework for Understanding Patient Expectations in Individualised Anaesthesia and Analgesia: A Narrative Review and Future Directions. *Journal of Personalized Medicine* 2026; 16: 191.
269. Weiss Y, Zarour S, Neuman MD, Politi MC, Tang VL, Gisselbaek M, Berger-Estilita J, Saxena S. Shared decision-making for older adults in the peri-operative setting: A narrative review. *Eur J Anaesthesiol* 2025.
270. Pel-Littel RE, Buurman BM, van de Pol MH, Twisk JWR, Tulner LR, Minkman MM, Scholte Op Reimer WJM, van Weert JCM. Effects of a shared decision making intervention for older adults with multiple chronic conditions: the DICO study. *BMC Med Inform Decis Mak* 2023; 23: 42.
271. Rosca A, Karzig-Roduner I, Kasper J, Rogger N, Drewniak D, Krones T. Shared decision making and advance care planning: a systematic literature review and novel decision-making model. *BMC Medical Ethics* 2023; 24: 64.
272. Montori VM, Ruissen MM, Hargraves IG, Brito JP, Kunneman M. Shared decision-making as a method of care. *BMJ Evid Based Med* 2023; 28: 213-17.

273. Légaré F, Thompson-Leduc P. Twelve myths about shared decision making. *Patient Educ Couns* 2014; 96: 281-6.
274. van der Horst DEM, Garvelink MM, Bos WJW, Stiggelbout AM, Pieterse AH. For which decisions is Shared Decision Making considered appropriate? - A systematic review. *Patient Educ Couns* 2023; 106: 3-16.
275. Neuman MD, Elwyn G, Graff V, Schmitz V, Politi MC. My anesthesia Choice-HF: development and preliminary testing of a tool to facilitate conversations about anesthesia for hip fracture surgery. *BMC Anesthesiology* 2024; 24: 165.
276. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. *JAMA Intern Med* 2016; 176: 1286-93.
277. Feenstra ML, Jansen S, Eshuis WJ, van Berge Henegouwen MI, Hollmann MW, Hermanides J. Opioid-free anesthesia: A systematic review and meta-analysis. *J Clin Anesth* 2023; 90: 111215.
278. Yurttas T, Royse C, Luedi MM. From risk stratification to precision analgesia - What the POPIT trials teach us. *J Clin Anesth* 2026; 108: 112069.

Appendices, Paper I-VI

Paper I



Review Article

Systematic Review of Methods for Individual Prediction of Postoperative Pain

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Received 17 July 2024; Accepted 31 December 2024

Academic Editor: Massimiliano Valeriani

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Background: Acute postoperative pain is a common problem in clinical practice and merits attention considering its potential long-term adverse effects. This systematic review covers current knowledge on methods for individual prediction of postoperative pain.

Methods: A systematic literature search was conducted using the PubMed, EMBASE, and CINAHL databases for original studies with adult patients published in English between 2016 and 2022. Inclusion required assessment of risk factors preoperatively and assessment of postoperative pain. No reviews, meta-analyses, or study protocols were included, nor studies with outcomes other than pain or where risk factor analysis was not performed preoperatively. A two peer-reviewed system was utilized using the screening and data collection tool Covidence, with a focus on new tools for preoperative pain prediction. The results were only analyzed qualitatively.

Results: The search yielded 1950 abstracts to be screened. In total, 208 articles were subjected to full-text review, and 107 articles were included in the data synthesis of this review. The evaluated scientific methods were grouped and analyzed separately. Psychometric questionnaires and methods for quantitative sensory testing are still being studied. New methods proposed include the evaluation of pain induced by tourniquet inflation, venous cannulation, or pin-prick stimulation, the analgesia/nociception index, electroencephalographic recording, and other new equipment developed for this purpose.

Conclusion: Various screening methods have been proposed to identify patients prone to postoperative pain. The focus has shifted from procedure-specific to individualized strategies to improve early management of pain. However, many traditional predictive methods still have a questionable role in clinical practice.

Trial Registration: ClinicalTrials.gov identifier: CRD42022298479

Keywords: acute postoperative pain; pain sensitivity; persistent postoperative pain; postoperative pain; postsurgical pain; prediction of postoperative pain

1. Background

Known risk factors for acute postoperative pain (APOP) are female sex, smoking, young age, preoperative pain and opioid consumption, and psychosocial factors such as anxiety and depression, functional disability, certain types of surgery (specifically surgery involving nerve damage), and

a large skin incision [1–8]. Although young age is a risk factor for postoperative pain, high frailty in older patients is associated with the risk of developing persistent postoperative pain (PPOP) [9]. None of these risk factors are strong enough to be used alone for individual prediction of the risk for severe APOP. Various preoperative screening methods have been proposed to identify patients prone to

severe APOP, and focus has shifted from procedure-specific to individualized strategies to improve early management of APOP and/or PPOP [10, 11]. Historically, the methods proposed and most extensively studied are psychometric evaluations, quantitative sensory thresholds (QSTs), genetics, and methods combining individual risk factors with these evaluations [8, 12].

Approximately 80% of patients who undergo surgery experience acute pain, less than half of whom report adequate pain relief [13], and persistent pain, i.e., pain continuing for more than 3 months after surgery, affects 10%–50% of patients [6, 14]. Despite recent advances in pain prediction and treatment, APOP remains insufficiently relieved [15]. Improved management of this common surgical complication is crucial for preventing stress, promoting early recovery, and reducing the risk of potentially harmful complications [16]. No predictive model has yet shown good enough results in combination with feasibility to merit use in standard anesthesia routines.

This systematic review was designed to compile current knowledge on methods recently proposed for the individual prediction of acute and PPOP intensity.

2. Methods

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. The search strategy and inclusion criteria were registered in the PROSPERO database on December 15, 2021, and published on January 15, 2022. The search strategy was developed in accordance with the PICO format in the PubMed database and was carried out on December 15, 2021, based on relevant MeSH and free-text terms. The search terms were adapted and used for the PubMed, EMBASE (Elsevier), and CINAHL Complete (EbscoHost) databases. Manual searches of the reference lists of the included papers were also carried out.

Covidence, a systematic screening and data collection tool, was used to perform literature searches to screen abstracts and subsequently review full texts. We included original randomized controlled trials and retrospective and prospective observational studies published in English between 2016 and 2022, comprising adult patients who underwent surgery regardless of country and for whom preoperative factors in combination with the intensity of postoperative acute or persistent pain and/or the use of postoperative analgesics were reported. We considered all studies with an association between preoperative factors and postoperative pain. Unpublished studies, congress abstracts, review articles, meta-analyses, or letters to the editor were considered ineligible, as were studies using postoperative outcomes more vaguely associated with postoperative pain per se, i.e., postoperative recovery, eating habits, and synovitis. There are multiple definitions of both APOP and PPOP, and in this review, we decided to include all since we believe there is value in trying to sum up current knowledge despite differences in methods.

Two researchers (K.M. and A.P.) independently screened abstracts of papers obtained in the original search for

potential eligibility. Any abstract deemed relevant by at least one researcher was included for full-text assessment. The same two researchers then independently assessed the full texts of the articles with respect to the inclusion and exclusion criteria. Due to the large number of full-text articles, assessments of study quality and bias were conducted on a case-by-case basis without a specific tool, by looking at confounding factors, information bias, and selection bias. This was performed independently by the reviewers, and when conflicts arose, a consensus was reached after discussion. Both reviewers had to consent to include the article in the final systematic review. No meta-analyses or other summary measures were carried out. For a better overview, and due to category heterogeneity, the methods reported were categorized into psychological methods, quantitative sensory testing, combined, genetic, biochemical, and “other techniques” for the prediction of pain. The category structure was decided on post hoc. No effect measures were used to compare studies; rather, the results were analyzed qualitatively. For the qualitative comparison of results, we present whichever outcome measure the specific study used as the primary outcome.

3. Results

3.1. Literature Search. The search terms used identified 1950 items, of which 192 articles were selected for full-text review, and an additional 16 relevant studies were added after citation screening. One study protocol was excluded as well as studies without any actual preoperative test method ($n = 21$), not written in English ($n = 1$), outcomes not being postoperative pain or opioid consumption ($n = 31$), study design not met by the inclusion criteria ($n = 25$), and including pediatric population ($n = 6$). After exclusion, 107 studies passed full-text screening and were included in this systematic review (Figure 1).

3.2. Psychological Methods

3.2.1. Psychometric Evaluation. The *Hospital Anxiety and Depression Scale* (HADS) has been used in research on pain prediction with conflicting results, and except for one study [17], its ability to predict PPOP has recently failed to be confirmed statistically. For APOP, the HADS score has been reported to be associated with pain intensity [18–22]. However, one study failed to show an association between acute pain and HADS after total knee arthroplasty [23].

Another psychometric assessment for depression only revealed an association between preoperative depression and severe acute pain after cardiac surgery [24]. In the same study, the preoperative depression score showed only weak correlations with APOP. Furthermore, the *Beck Depression Inventory II* Questionnaire failed to associate depression with PPOP in a mixed surgery cohort [25].

Regarding the *Pain Catastrophizing Scale* (PCS) [26], one of the most studied psychometrics in the current systematic review, results remain contradictory (Table 1). Several recent studies have correlated PCS with acute pain after cardiac surgery [27], upper extremity surgery [28], breast cancer

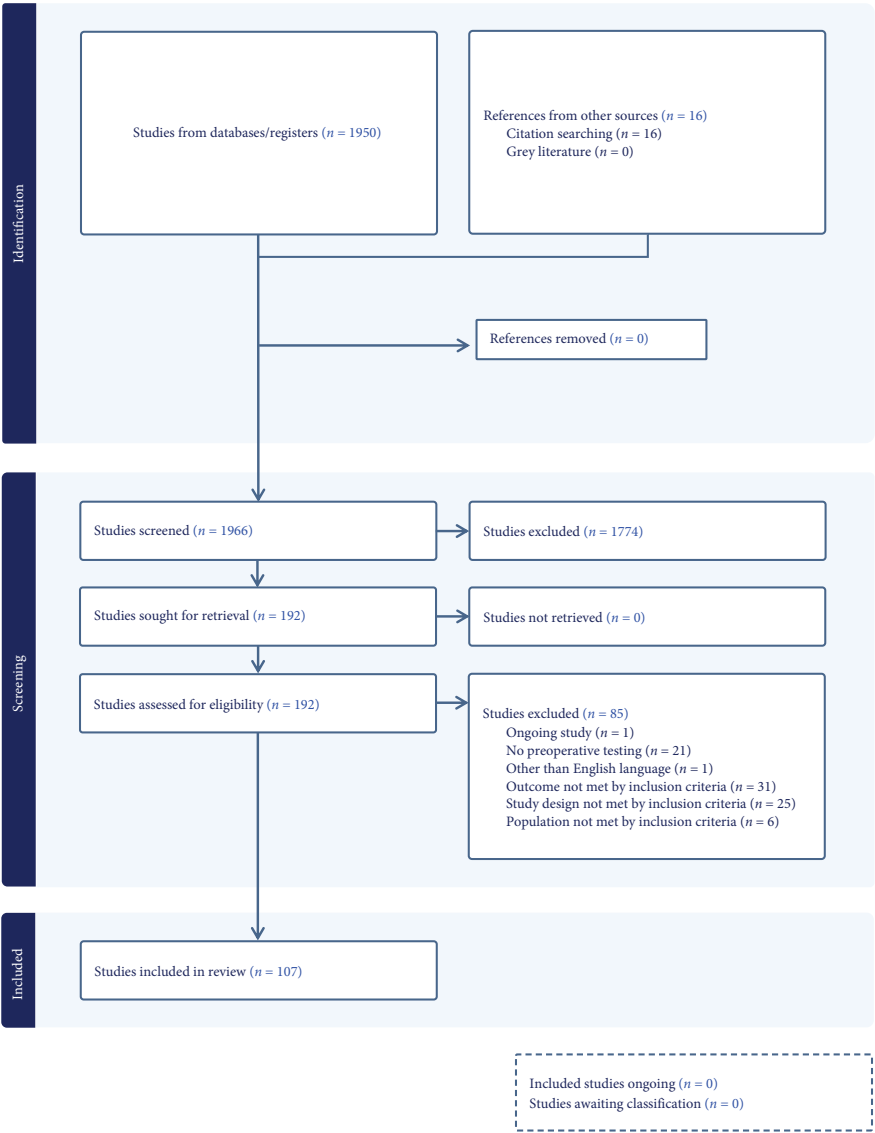


FIGURE 1: Consort diagram.

surgery [29, 30], and high pain trajectories following major elective surgery [31]. Furthermore, studies also suggest that PCS is associated with persistent pain after total knee arthroplasty [32], hysterectomy [33], mixed surgery [34], and breast cancer surgery [35]. However, the PCS has not been found to predict pain in a large number of other recent studies [29, 36–44]. The PCS has shown better prediction of

postoperative pain when related to experimental pain, compared to just any pain experience [45].

One study examined alexithymia, the inability to identify emotions within oneself and others, in patients undergoing bariatric surgery. In this study, patients who were positive for alexithymia had higher APOP and postoperative opioid consumption [46] (Table 1).

TABLE 1: Summary of studies covering psychometric techniques for prediction of postoperative pain and published between 2016 and 2022.

Method of testing	Kind of surgery	Number of patients	Outcomes	Statistics	Outcome measure and result (95% confidence interval)	Reference
Hospital Anxiety and Depression Scale	Knee surgery	104	APOP	Correlation	Anxiety: $r = 0.35^*$; Depression: ns	Thomaszau 2016
	Caesarean section	1062	APOP	Logistic regression	Anxiety: OR 1.60 (1.22–2.30); Depression: ns	Borges 2016
	Mixed elective surgery	304	APOP	Correlation	Anxiety: $r = 0.18^{**}$; Depression: $r = 0.22^{**}$	Bradshaw 2016
	Knee arthroplasty	220	PPOP	Dichotomous groups ^a	Anxiety: ns; Depression: ns	Chen 2021
	Orthopedic trauma	229	PPOP	Dichotomous groups ^a	PPOP vs no PPOP, ns	Edgley 2019
	Knee/hip arthroplasty	184	APOP/PPOP	Dichotomous groups ^a	PPOP vs no PPOP, ns	Giusti 2022
				Multiple logistic regression	Anxiety: OR 2.07 (1.36–2.25)	Han 2017
	Hysterectomy	870	PPOP	Multiple logistic regression	Depression: OR 2.21 (1.19–4.12)	Liu 2022
	Gastrointestinal surgery	282	APOP	Multiple linear regression	Anxiety: $\beta = 0.07$ (0.01–0.14); Depression: ns	Liu 2022
	Gastrointestinal surgery	282	PPOP	Multiple linear regression	Anxiety: OR 5.28 (1.59–17.54); Depression: ns	Liu 2022
Hamilton Anxiety and Depression Scale	Thoracoscopic surgery	67	APOP	Dichotomous groups ^b	Anxiety: ns; Depression: ns	Han 2021
	Thoracoscopic surgery	188	APOP	Linear regression	Anxiety: ns; Depression: ns	Lindberg 2017
	Knee arthroplasty	188	APOP	Multivariate logistic regression	Anxiety: OR 1.24 (1.04–1.54); Depression: ns	Nishimura 2017
	Breast cancer surgery	68	APOP	Multivariate logistic regression	Anxiety: OR 1.24 (1.04–1.54); Depression: ns	Nishimura 2017
	Bariatric surgery	116	Opioid use	Correlation	Anxiety: $r = 0.52^{***}$; Depression: $r = 0.52^{***}$	Aceto 2016
	Orthopedic surgery	118	APOP	Correlation	$r = 0.28^*$	Alkozaï 2019
	Knee/hip arthroplasty	124	APOP	Correlation	THA, ns; TKA, 0.26^*	Pinto 2018
	Knee arthroplasty	126	APOP	Correlation	$r = 0.02$, ns	Albrecht 2019
	Video-assisted thoracoscopic surgery	82	APOP	Dichotomous groups ^b	ns	Bayman 2019
	Thoracic surgery	104	PPOP	Logistic regression	OR 1.11 (0.95–1.30)	Hom–Hofmann 2018
Pain Catastrophizing Scale	Laparoscopic hysterectomy	73	APOP	Correlation	$r = 0.23$, ns	Scheel 2017
	Thoracic surgery	42	APOP	Correlation	ns	Grosen 2016
	Thoracotomy/-scopy	99	PPOP	Dichotomous groups ^a	ns	Bayman 2017
	Hysterectomy	200	APOP	Binary logistic regression	1.38 (1.09–1.75)	Benlolo 2021
	Hysterectomy	200	PPOP	Binary logistic regression	1.04 (1.01–1.08)	Benlolo 2021
	Knee arthroplasty	220	PPOP	Dichotomous groups ^a	ns	Chen 2021
	Breast cancer surgery	166	PPOP	Correlation	$r = 0.25^{***}$	Dams 2022
	Knee/hip arthroplasty	184	PPOP	Multiple linear regression	$\beta = 0.678^{***}$	Giusti 2022
	Orthopedic trauma	303	APOP	Multivariable logistic regression	OR 0.99 (0.95, 1.03)	Edgley 2019
	Orthopedic trauma	229	PPOP	Multivariable logistic regression	OR 0.98 (0.94, 1.03)	Edgley 2019
Asking the patient/expected pain	Breast cancer surgery	124	APOP	Multivariate logistic regression	OR 1.08 (1.02–1.14)	Habb 2019
	Knee arthroplasty	71	PPOP	Dichotomous groups ^a	ns	Hovik 2016
	Mixed elective surgery	284	PPOP	Multiple regression	$\beta = 0.153^{**}$	Mi 2021
	Knee arthroplasty	248	PPOP	Multivariable linear regression	Estimate 0.02 (0.002–0.05) [†]	Edwards 2022
	Thoracic surgery	107	PPOP	Dichotomous groups ^a	ns	Bayman 2017
	Cardiac surgery	100	APOP	Correlation	$r = 0.65^{**}$	Tai 2021
	Mixed elective surgery	363	APOP	Multinomial logistic regression	OR 1.03 (0.98–1.09)	Vasilopoulos 2021
	Breast cancer surgery	228	APOP	ANOVA	Association ^{c†}	Wilson 2021
	Knee arthroplasty	60	APOP	Multivariate logistic regression	OR 1.06 (1.01–1.13)	Luna 2017
	Upper extremity surgery	118	APOP	Multivariate logistic regression	OR 1.06 (1.01–1.13)	Luna 2017
Asking the patient/expected pain	Thoracoscopy	82	APOP	Correlation	$r = 0.28^*$	Alkozaï 2019
	Mixed elective surgery	304	APOP	Correlation	$r = 0.43^{***}$	Bayman 2019
	Knee arthroplasty	220	PPOP	Multiple logistic regression	$r = 0.28^{***}$	Bradshaw 2016
	Breast cancer surgery	139	PPOP	Dichotomous groups ^a	OR 1.01 (0.99–1.02)	Chen 2021
					Yes, if expected NRS $\leq 6^{**}$	Dereu 2018

TABLE 1: Continued.

Method of testing	Kind of surgery	Number of patients	Outcomes	Statistics	Outcome measure and result (95% confidence interval)	Reference
Pain Sensitivity Questionnaire	Cardiac surgery	419	PPOP	Linear mixed model	$\beta = -0.16$ (0.06–0.26) ^{†††}	Byrnes 2018
	Breast cancer surgery	198	APOP	Multivariable logistic regression	OR 1.03 (1.01–1.05) ^{††}	Rehberg 2017
	Hysterectomy	200	PPOP	Correlation	$r = 0.09$, ns	Benlolo 2021
	Breast cancer surgery	139	PPOP	Dichotomous groups ^a	ns	Dereu 2018
	Knee arthroplasty	248	PPOP	Dichotomous groups ^a	ns	Edwards 2022
Pain Self-Efficacy Questionnaire	Mixed surgery	259	APOP	Logistic regressions	OR 0.96 (0.93–1.00)	Wang 2018
	Knee/hip arthroplasty	184	APOP/PPOP	Multiple regression	No predictor in model	Giusti 2022
Sleep quality	Caesarean section	245	APOP	Multivariable logistic regression	OR 2.64 (1.2–6.0)	Orbach-Zinger 2017
	Breast cancer surgery	108	APOP	Dichotomous groups ^b	Good sleep vs poor sleep ^{††}	Wang 2019
	Hip arthroplasty	163	PPOP	Correlation	$r = 0.05$, ns	Boye Larsen 2021
	Hip arthroplasty	52	POP	Multivariable linear regression	$\beta = 0.091$ (0.001–0.181), $R^2 = 0.35^*$	Biurström 2021
PROMIS	Thoracotomy/-scopy	99	PPOP	Dichotomous groups ^a	3 months, ns 6 months ^{††}	Bayman 2017
WOMAC	Knee arthroplasty	220	PPOP	Multiple logistic regression	OR 0.98 (0.95–1.01)	Chen 2021
Pain Detect Questionnaire	Knee arthroplasty	220	PPOP	Multiple logistic regression	OR 1.15 (1.01–1.30)	Chen 2021
Central Sensitization Inventory	Breast cancer surgery	166	PPOP	Correlation	$r = 0.30^{\dagger\dagger\dagger}$	Dams 2022
	Knee/hip arthroplasty	184	PPOP	Multiple regression	$\beta = 0.547^{\dagger\dagger}$	Giusti 2022
	Knee arthroplasty	68	PPOP	Correlation	$r = 0.32^{\dagger\dagger}$	Kim 2019
Brief Pain Inventory	Breast cancer surgery	139	PPOP	Dichotomous groups ^a	PPOP vs no PPOP ^{†††}	Dereu 2018
	Knee/hip arthroplasty	229	PPOP	Multivariable logistic regression	ns	Edgley 2019
	Knee/hip arthroplasty	184	PPOP	Multiple regression	$\beta = 0.047$, ns	Giusti 2022
	Foot surgery	49	APOP/PPOP	Dichotomous groups ^{ab}	High pain trajectory vs low pain trajectory ^{††}	Guichard 2019
	Knee surgery	104	APOP	Correlation	$r = 0.40^{\dagger\dagger\dagger}$	Thomazeau 2016
Beck Depression Inventory	Breast cancer surgery	139	PPOP	Dichotomous groups ^a	PPOP vs no PPOP ^{†††}	Dereu 2018
	Mixed elective surgery	371	PPOP	Dichotomous groups ^a	PPOP vs no PPOP ^{††}	Hah 2019
State-Trait Anxiety Inventory	Breast cancer surgery	139	PPOP	Dichotomous groups ^a	Trait: PPOP vs no PPOP ^{††}	Dereu 2018
	Caesarean section	527	PPOP	Dichotomous groups ^a	State: PPOP vs no PPOP ^{†††}	Jin 2016
Kessler Psychological Distress Scale	Cardiac surgery	100	APOP	Correlation	State: PPOP vs no PPOP, ns State: PPOP vs no PPOP, ns	Tai 2021
	Foot surgery	49	APOP/PPOP	Dichotomous groups ^{ab}	$r = 0.48^{\dagger\dagger}$	Guichard 2019
	Orthopedic trauma	303	APOP/PPOP	Multivariable logistic regression	High pain trajectory vs low pain trajectory ^{††}	Edgley 2019
	Cardiac surgery	98	APOP	Multivariable logistic regression	OR 1.04 (1.00–1.08)	Gohari 2022
	Bariatric surgery	116	APOP	Correlation	OR 1.02 (0.98–1.06)	Aceto 2016
Fear of Pain Questionnaire	Thoracic surgery	98	APOP	Correlation	$r = 0.38^{\dagger\dagger}$	Luo 2022
National Comprehensive Cancer Network	Breast cancer surgery	956	APOP	Multivariable logistic regression	$r = 0.29^{\dagger\dagger}$	Pak 2022

Note: Significance level for regression models are shown within confidence intervals.

Abbreviations: APOP, acute postoperative pain; NRS, numeric rating scale; OR, odds ratio; PPOP, persistent postoperative pain; PROMIS, patient-reported outcomes measurement information system; WOMAC, Western Ontario-McMaster Universities Osteoarthritis Index.

^aPPOP vs no PPOP.

^bModerate to severe APOP vs mild to no APOP.

^cHigher catastrophizing in global symptoms group compared to adaptive and sensitive group.

[†] $p \leq 0.05$.

^{††} $p \leq 0.01$.

^{†††} $p \leq 0.001$.

3.2.2. Self-Evaluation. Self-expected extent of pain after surgery has been found to predict moderate-to-severe acute pain after thoracoscopic surgery [37]. Furthermore, the individual ability to forecast postoperative pain and disability has been found to correlate with actual levels [28], and with more acute pain after mixed surgery [20], and breast cancer surgery [47]. Self-evaluation has also been linked to levels of PPOP [40, 48] (Table 1).

3.2.3. Evaluation of Pain Sensitivity. Scores obtained with the *Pain Sensitivity Questionnaire* (PSQ) have been reported to correlate with acute and persistent pain after cardiac surgery [49] and APOP within 24 h [50], whereas this correlation was not seen for persistent pain [33, 48].

The *Pain Self-Efficacy Questionnaire* (PSEQ) has been reported to independently predict acute pain after various kinds of surgery [51], whereas no correlation was found after joint arthroplasty [42].

The *Central Sensitization Inventory* (CSI) was developed to assess central sensitization [52]. In patients who underwent revision hip surgery, CSI was associated with persistent pain up until 2 years [53]. This result is consistent with those found in larger cohorts undergoing large joint arthroplasty and breast cancer surgery [35, 41, 42] (Table 1).

3.2.4. Evaluation of Anxiety and Stress. Feeling anxious has been associated with severe APOP, as has feeling helpless because of pain [54]. Furthermore, preoperative emotional state predicts negative expectations and acts as a mediator of acute pain in patients undergoing knee arthroplasty [55].

The *State-Trait Anxiety Inventory* (STAI) has recently been studied in breast cancer surgery and cesarean section, but the results are contradictory [29, 48, 56]. However, one study showed a correlation between the STAI and acute pain after cardiac surgery ($r = 0.48$, $p < 0.01$) [27].

The *Brief Measure of Emotional Preoperative Stress* (B-MEPS) is a prediction tool shown to predict acute pain after hysterectomy [57].

Fear of pain, according to the *Fear of Pain Questionnaire* (FOP-9), correlates to acute pain after thoracoscopic surgery [58, 59].

Psychological distress related to oncological surgery is a metric validated by the *National Comprehensive Cancer Network (NCCN) Distress Thermometer* and has been found to be an independent risk factor for acute pain in patients undergoing breast cancer surgery [60].

Psychological stress has been associated with acute and persistent pain after foot surgery [61] but not after orthopedic trauma [41].

One study used a machine learning algorithm on psychometric questionnaires in a large cohort of patients who underwent breast cancer surgery. This approach identified seven items in the BDI and STAI that could exclude PPOP with approximately 95% certainty [62] (Table 1).

3.2.5. Evaluation of Sleep Quality. Low sleep quality has been found to predict acute pain after cesarean section as

well as acute pain and longer hospital stay after breast cancer surgery [63, 64]. Additionally, low sleep quality is associated with persistent pain and opioid consumption at 6 months after hip arthroplasty [65]. In contrast, another recent study failed to repeat this association [66]. Lastly, obstructive sleep apnea syndrome (OSAS), a surrogate for poor sleep, has been found not to be associated with postoperative pain [67] (Table 1).

3.3. Quantitative Sensory Testing

3.3.1. Evaluation of Sensitivity to Temperature-Induced Pain.

Acute pain after video-assisted thoracoscopy was reported more frequently in patients with more pain on *supra-threshold cold stimulation*, whereas the *cold pain threshold* (CPT) was not predictive [37]. However, another study reported positive and negative results for CPT and supra-threshold cold stimulation, respectively, whereas heat-related QST was not associated with either APOP or PPOP [68]. On the same note, women with greater tolerance to pain induced by immersion of the hand in cold water were reported to be less likely to report persistent pain after breast cancer surgery [69]. Furthermore, no association was found between pain sensitivity to cold stimulation and pain outcomes after total knee arthroplasty [32, 70] or persistent pain after breast cancer surgery or thoracic surgery [35, 44].

Pain intensity elicited by a hot water bath has also been reported to be a predictor of APOP [50] (Table 2).

3.3.2. Evaluation of Sensitivity to Pressure-Induced Pain.

The *pain pressure threshold* (PPT) is the minimum applied force required to induce pain, and *pressure pain tolerance* is the maximum level of pressure tolerated. The PPT has been reported to predict acute pain after total knee arthroplasty [70], and moderate to severe APOP after pancreatic surgery, major proctological surgery, orthopedic surgery, or gynecological surgery [71, 72]. In contrast, PPT failed to predict acute pain, opioid use, or hospital length of stay after total hip or knee arthroplasty, anorectal surgery, or breast cancer surgery [73–75] and persistent pain after robot-assisted laparoscopic hysterectomy [76] (Table 2).

3.3.3. Evaluation of Sensitivity to Electrically Induced Pain.

Electrical pain threshold (EPT) was not associated with acute pain intensity after various kinds of major surgery or total knee arthroplasty [18, 70]. Similarly, no association could be established between acute pain and EPT after breast surgery [48] (Table 2). Conversely, in patients subjected to laparoscopic cholecystectomy, EPT was found to correlate with acute pain in women [77].

3.3.4. Dynamic Evaluation of Pain. Temporal summation of pain (TSP), a surrogate endpoint for central sensitization,

can predict acute pain early after total knee replacement [36]. However, in breast cancer surgery, the results are conflicting [75, 78]. *Conditioned pain modulus* (CPM) reflects endogenous descending analgesic ability. The CPM

TABLE 2: Summary of studies covering techniques for quantitative sensory testing to predict postoperative pain and published between 2016 and 2022.

Method of testing	Kind of surgery	Number of patients	Outcome	Statistics	Outcome measure and result (95% confidence interval)	Reference
Cold	VATS/thorotomy	107	PPOP	Dichotomous groups ^a	ns	Bayman 2017
	Thoracoscopic surgery	82	APOP	Dichotomous groups ^b	NRS > 3 vs NRS ≤ 3 [†]	Bayman 2019
	Breast cancer surgery	763	PPOP	Dichotomous groups ^a	Time to max NRS [†]	Lösch 2017
					Time to NRS 10 ^{††}	
					Sum of NRS [†]	
	Breast cancer surgery	166	PPOP	Dichotomous groups ^a	Max NRS during test ^{††}	Dams 2022
					If NRS 10 was reached [†]	
	Knee arthroplasty	248	PPOP	Dichotomous groups ^a	Detection cold, ns	Edwards 2022
	Thoracic surgery	111	PPOP	Dichotomous groups ^a	Pain sensitivity cold, ns	Wang 2022
					Cold pain tolerance, ns	
Heat	Breast cancer surgery	198	APOP	Dichotomous groups ^b	Cold pain after sensation, ns	Luna 2017
					Cold pain threshold ^{††}	
	Breast cancer surgery	166	PPOP	Dichotomous groups ^a	Cold detection threshold, ns	Rehberg 2017
					Cold pressure test, ns	
	Breast cancer surgery	139	PPOP	Dichotomous groups ^a	Heat pain intensity ^{††}	Dams 2022
					Detection heat, ns	
	Breast cancer surgery	74	APOP	Multiple linear regression	Pain sensitivity heat, ns	Dereu 2018
					Pain intensity heat, ns	
	Thoracic surgery	111	PPOP	Dichotomous groups ^a	ns	Ruscheweyh 2017
					Warm detection threshold, ns	
					Hot pain threshold, ns	Wang 2022

TABLE 2: Continued.

Method of testing	Kind of surgery	Number of patients	Outcome	Statistics	Outcome measure and result (95% confidence interval)	Reference
Pressure	General surgery	1002	APOP	Multiple regression	Pressure pain tolerance ^{†††}	Duan 2017
	Major urological, gynecological, proctological, or orthopedic surgery	150	APOP	Correlation	Pressure pain threshold ^{†††}	Wolmeister 2020
	Knee arthroplasty	60	APOP	Dichotomous groups ^b	Pressure pain tolerance, ns	Luna 2017
	Knee arthroplasty	41	APOP	Dichotomous groups ^b	Pressure pain threshold ^{††}	Hagverdian 2016
	Laparoscopic hysterectomy	160	PPOP	Dichotomous groups ^a	Pressure pain threshold, ns	Lunde 2020
	Knee arthroplasty	220	PPOP	Dichotomous groups ^a	Pressure pain detection, ns	Chen 2021
	Breast cancer surgery	166	PPOP	Correlation	Pressure pain threshold, ns Local mechanical detection, ns Pain sensitivity mechanical, $r = -0.26^{††}$	Dams 2022
	Knee arthroplasty	50	PPOP	Dichotomous groups ^a	Pain sensitivity pressure, ns	Kurien 2018
	Knee arthroplasty	248	PPOP	Dichotomous groups ^a	Pressure pain threshold, ns	Edwards 2022
	Anorectal surgery	128	APOP	Correlation	Pressure pain threshold, $r = -0.33^{†††}$	Luedi 2021
Electrical	Breast cancer surgery	74	APOP	Multiple linear regression	ns	Ruschewey 2017
	Knee arthroplasty	126	APOP	Multiple linear regression	Pressure pain threshold, ns	Abrecht 2019
	Breast surgery	234	APOP	Dichotomous groups ^b	Pressure pain tolerance, ns	Schreiber 2019
	Knee surgery	109	APOP	Multivariate analysis	Pressure pain threshold, ns	Thomazeau 2016
	Knee arthroplasty	60	APOP	Dichotomous groups ^b	Electrical pain sensitivity, ns	Luna 2017
	Laparoscopic cholecystectomy	153	APOP	Correlation	Electric pain threshold, ns	Persson 2017
	Breast surgery	139	APOP	Dichotomous groups ^b	Electrical pain threshold, $r = -0.27^{††}$	Dereu 2018
	Knee arthroplasty	129	APOP	Multiple linear regression	Electric pain threshold, ns	Abrecht 2019
	Breast surgery	234	APOP	Dichotomous groups ^b	Electric pain threshold, ns	Schreiber 2019
	Laparoscopic hysterectomy	160	PPOP	Dichotomous groups ^a	$\beta = 0.027^{††}$ APOP vs no APOP [†]	Lunde 2020
Temporal summation of pain	Knee arthroplasty	220	PPOP	Dichotomous groups ^a	ns	Chen 2021
	Knee arthroplasty	50	PPOP	Dichotomous groups ^a	ns	Kurien 2018
	Knee arthroplasty	248	PPOP	Dichotomous groups ^a	ns	Edwards 2022
	Breast cancer surgery	74	APOP	Dichotomous groups ^b	ns	Ruscheweyh 2017

TABLE 2: Continued.

Method of testing	Kind of surgery	Number of patients	Outcome	Statistics	Outcome measure and result (95% confidence interval)	Reference
Conditioned pain modulus	Knee arthroplasty	131	PPOP	Correlation	$r = -0.18^{\dagger}$	Larsen 2021
	Laparoscopic hysterectomy	160	PPOP	Dichotomous groups ^a	ns	Lunde 2020
	Breast cancer surgery	166	PPOP	Correlation	$r = 0.021$, ns	Dams 2022
	Breast surgery	95	PPOP	Dichotomous groups ^a	ns	Dereu 2018
	Knee arthroplasty	146	PPOP	Dichotomous groups ^a	PPOP vs no PPOP ^f	Dürsteler 2021
	Knee arthroplasty	248	PPOP	Dichotomous groups ^a	ns	Edwards 2022
	Knee arthroplasty	50	PPOP	Dichotomous groups ^a	ns	Kurien 2018
	Knee arthroplasty	126	APOP	Multiple linear regression	$r = 0.015$, ns	Abrecht 2019

Abbreviations: APOP, acute postoperative pain; NRS, numeric rating scale; PPOP, persistent postoperative pain; VATS, video-assisted thoracoscopic surgery.

^aPPOP vs no PPOP.

^bModerate to severe APOP vs mild to no APOP.

[†] $p \leq 0.05$.

^{††} $p \leq 0.01$.

^{†††} $p \leq 0.001$.

was found to predict PPOP after total knee arthroplasty [79]. However, there are several negative studies on TSP and CPM in regard to PPOP [29, 40, 48, 76, 80] (Table 2).

3.3.5. Combined Techniques of Testing. In combination, high levels of preoperative pain and expected pain after surgery together with proposed extensive surgery are strong predictors for moderate to severe acute pain after day surgery [81]. Low PPT combined with high PCS can find patients who will experience APOP, with 71% sensitivity and 62% specificity [70]. In a similar manner, the combination of preoperative pain, CPM, and PCS can predict PPOP at 12 months after total knee arthroplasty [82].

The *Risk Index for Chronic Pain* (RICP) is based on assessments of preoperative pain within the proposed field of surgery, movement-evoked acute pain 5 days after surgery, other preoperative chronic pain, and female sex [83]. The RICP has been reported to predict PPOP with 75% sensitivity and 73% specificity [84]. Another study combined risk factors for PPOP, preexisting pain, depression, the expectation of pain, and age under 50 years and found that the combination of risk factors could predict PPOP [48].

Predicting persistent pain after breast cancer surgery, using a combination of risk factors was evaluated in both Danish (AUC 0.739) and Scottish (AUC 0.740) patient cohorts [85]. Machine learning has also been used to predict postoperative opioid consumption using various preoperative data. The model was shown to predict postoperative opioid requirements with approximately 70% accuracy [86] (Table 3).

3.4. Other Techniques of Testing

3.4.1. Evaluation of Painful Routine Procedures. Using everyday procedures that cause noxious stimuli is a simple and pragmatic approach to differentiate patients with respect to pain sensitivity. Recently, pain during *subcutaneous infiltration of local anesthetic* (LA) before spinal anesthesia correlated with APOP and opioid consumption [87].

Similarly, *venous cannulation pain* (VCP) has been found to be associated with moderate to severe acute pain after various kinds of surgery, laparoscopic cholecystectomy, and laparoscopic nephrectomy; the latter two also reported on the association with postoperative opioid consumption (Table 4) [88–90].

3.4.2. Evaluation With Commercial Techniques. Several new nociceptive monitoring techniques have been proposed as potential perioperative predictors of APOP (Table 4).

The *Surgical Pleth Index* (SPI) score is based on photoplethysmographic analysis of the pulse contour wave and the heartbeat interval. The maximal SPI recorded during surgical incision was found to associate with APOP and postoperative opioid consumption [91]. Conversely, more modest results have been obtained in other studies. Recently, SPI was not associated with continuous APOP scores; however, higher levels were found in patients with moderate

to severe APOP. When applying an SPI cutoff of 30, a negative predictive value of 50% and a positive predictive value of 90% for APOP were found [92]. In a recent follow-up study by the same group, the overall performance of this test was poor [93]. Conversely, during liver resection, SPI correlated with acute pain in the postanesthesia care unit (PACU) ($r = 0.63$, $p < 0.001$). Furthermore, SPI was able to predict and distinguish between moderate and severe acute pain (AUC = 0.84), with sensitivity and specificity of 72% and 88%, respectively [94].

The *Pain Threshold Index* (PTI) is a neurophysiologic method used to evaluate the risk of pain in real-time. The PTI and the SPI have been reported to correlate well, and the PTI at the end of surgery can predict moderate to severe acute pain with 62% sensitivity and 91% specificity [95]. Specifically, a preoperative spectral power in the beta and gamma frequency spectrum has been reported to be associated with moderate to severe acute pain after thoracoscopic surgery [96].

Other EEG-derived indices, such as the *quantified noxious index score* (qNOX), were not found to predict acute pain in various kinds of surgical procedures [97].

The *Nociception Level Index* (NOL) is based on electrical skin conductance, heart rate variability, accelerometer, and skin temperature data provided by a finger electrode. Scores obtained immediately after skin incision at the start of surgery seem to have the highest predictive value, and scores above 20 at skin incision have been reported to predict moderate to severe APOP with 73% sensitivity and 53% specificity [98]. Notably, the NOL obtained later during surgery did not correlate with acute pain outcomes [98]. Recently, NOL levels recorded during both endotracheal intubation and surgical skin incisions were unable to predict APOP in a follow-up randomized controlled trial. However, higher time-weighted average NOL values during surgery and longer relative durations of surgery with NOL values above 25 were reported in patients with moderate to severe acute pain [99] (Table 4).

3.5. Genetic Testing. Data regarding genetic mapping and pain outcomes remain scarce and diverging. Single nucleotide polymorphism (SNP) in the ATP binding cassette subfamily B member 1 (ABCB1) gene is associated with acute pain after abdominal surgery [100]. Other studies have focused on genotyping and testing for alleles in catechol-O-methyl-transferase (COMT) and their association with pain after surgery [18, 101–103]. A potential association was reported between SNPs in COMT and persistent pain at six months after knee arthroplasty [103] and between SNP rs1799971 in COMT and opioid consumption after cesarean section [102].

The SNP rs11818426 in neuron navigator 3 (NAV3) has been correlated with persistent pain after hysterectomy and after total knee arthroplasty, but not in a meta-analysis of both study cohorts [104]. In another study, the SNPs rs6265 and rs1491850 in the brain-derived neurotrophic factor (BDNF) gene were both associated with persistent pain after ambulatory surgery [105].

TABLE 3: Summary of studies covering techniques for combined risk factor evaluation to predict postoperative pain and published between 2016 and 2022.

Method of testing	Kind of surgery	Number of patients	Outcome measure	Statistics	Outcome measure and result (95% confidence interval)	Reference
1. Preoperative pain	Mixed day surgery	1118	APOP	Multivariable logistic regression	Model distinction: AUC 0.82, insufficient model according to authors	Stessel 2017
2. Self-anticipated APOP						
3. Proposed extensive surgery						
1. Pressure pain threshold ^{††}	Total knee arthroplasty	60	APOP	Multivariate logistic regression	Model distinction: AUC 0.77 (0.65–0.89)	Luna 2017
2. Pain Catastrophizing Scale [†]						
1. Preoperative pain ^{††}	Total knee arthroplasty	131	PPOP	Multiple linear regression	$R^2 = 0.205$	Larsen 2021
2. Conditioned pain modulus						
3. Pain Catastrophizing Scale [†]						
1. Preoperative pain ^{††}	Orthopedic, neuro-, general or abdominal surgery	167	PPOP	Multiple logistic regression	Model distinction: AUC 0.81 (0.74–0.89)	Mathes 2017
2. Movement-evoked APOP at 5 days ^{†††}						
3. Other preoperative chronic pain [†]						
4. Female gender						
5. Marital status						
1. Preoperative pain ^{†††}	Breast cancer surgery	860	PPOP	Binary logistic regression	Model distinction: AUC 0.74 (0.67–0.81)-Danish cohort Model distinction: AUC 0.74 (0.65–0.83)-Scottish cohort	Meretoja 2017
2. High body mass index [†]						
3. Axillary node dissection ^{††}						
4. Severe APOP [†]						
1. Type of surgery	Mixed ambulatory surgery	13,700	APOP	Multinomial logistic regression	Model predicts opioids by accuracy 70%	Nair 2020
2. Medical history						
3. Duration of surgery						
1. Age	Sternotomy	174	PPOP	Multivariate logistic regression	Model distinction: AUC 0.91 (0.86–0.94)	Harrogate 2021
2. Highest APOP						
3. Duration of surgery						
4. Remifentanyl use						
5. Gender						
6. Left internal mammary artery harvest						
1. Preoperative pain ^{†††}	Breast cancer surgery	141	PPOP	Multivariable logistic regression	Model distinction: AUC 0.82 (0.73–0.91)	Dereu 2018
2. History of depression [†]						
3. Self-anticipated APOP ^{††}						
4. Age < 50 years ^{††}						

Note: Significance level for regression models and AUC are shown within confidence intervals.

Abbreviations: APOP, acute postoperative pain; OR, odds ratio; PPOP, persistent postoperative pain.

[†] $p \leq 0.05$.

^{††} $p \leq 0.01$.

^{†††} $p \leq 0.001$.

TABLE 4: Summary of studies covering other techniques to predict postoperative pain and published between 2016 and 2022.

Method of testing	Kind of surgery	Number of patients	Outcome	Statistics	Outcome measure and results (95% confidence interval)	Reference
Venous cannulation pain	Laparoscopic cholecystectomy	180	APOP	Multivariate logistic regression	OR 3.4 (1.6–7.3)	Persson 2016
	Mixed scheduled surgery	505	APOP	Multivariate logistic regression	OR 1.5 (1.0–2.3)	Persson 2019
	Laparoscopic nephrectomy	106	APOP	Multivariate logistic regression	OR 3.5 (1.3–9.3)	Peng 2020
Local anesthesia infiltration	Cesarean section	216	APOP	Correlation	$r = 0.56^{+++}$	Nimmaanrat 2021
Surgical Pleth Index	Laparotomy	50	APOP	Dichotomous groups ^a	AUC 0.67 (0.51–0.83)	Jung 2020
	Mixed scheduled surgery	60	APOP	Dichotomous groups ^a	AUC 0.71 ^{††}	Ledowski 2016
	Mixed scheduled surgery	196	APOP	Dichotomous groups ^a	AUC 0.59 [†]	Ledowski 2019
	Liver resection	49	APOP	Correlation	$r = 0.63^{+++}$	Park 2020
Pain Threshold Index	Laparoscopic urological surgery	76	APOP	Dichotomous groups ^a	AUC 0.77 (0.66–0.86), 62% sensitivity and 91% specificity	Wang 2020
qNOX score	Mixed scheduled surgery	144	APOP	Dichotomous groups ^a	AUC 0.50 (0.41–0.60), ns	Ledowski 2020
Nociceptive Level Index	Mixed scheduled surgery	74	APOP	Dichotomous groups ^a	NOL post incision AUC 0.68 (0.55–0.80)	Ledowski 2021
	Gynecological laparoscopic surgery	66	APOP	Dichotomous groups ^a	AUC 0.65 (0.51–0.79)	Morisson 2022
Full-EEG	Thoracic surgery	870	APOP	Correlation	$r = 0.84^{+++}$	Han 2021

Note: Significance level for regression models is shown within confidence intervals.
Abbreviations: APOP, acute postoperative pain; AUC, area under the curve; EEG, electroencephalography; OR, odds ratio; PPOP, persistent postoperative pain; qNOX, quantified noxious index.
†Moderate to severe APOP vs mild to no APOP.
†‡ $p \leq 0.05$.
††† $p \leq 0.01$.
+++ $p \leq 0.001$.

A multivariate regression analysis of a variety of genes revealed that the inflammatory acute phase reactants (IL6, rs2069840), tumor necrosis factor (TNF, rs1800610), and C-X-C motif chemokine ligand 8 (CXCL8, rs4073) were found to be associated with 79%, 63%, and 60% lower probabilities of risk of moderate to severe acute pain, respectively, after breast surgery [106] (Table 5).

3.6. Biochemical Testing. *Circulating mRNA* has been reported to correlate with pain relief and to explain 30% of postoperative pain intensity in a prediction model in total knee arthroplasty [107]. Blood neutrophil/lymphocyte ratio and acute pain were associated after shoulder repair surgery [108]. Higher serum levels of μ -opioid receptor activity were associated with less acute pain and need for rescue analgesics after septoplasty [109]. Furthermore, measuring *angiotensin II* receptor activity in blood correlated with persistent pain after knee surgery [40]. Analysis of cerebrospinal fluid for *Substance P* and *endorphins* has also been associated with APOP [110].

Ultraviolet B (UVB)-induced inflammation, measured as inflammation index, was studied in patients who underwent total knee arthroplasty [111]. In this study, the authors constructed an inflammation index using the expression of six UVB-inducible genes associated with pain and concluded that preoperative inflammation correlated negatively with APOP.

4. Discussion

This review summarizes the current knowledge on how to predict individual risks for postoperative pain by assessing different potential factors in an effort to identify clinically valuable methods. The ability to predict postoperative pain has practical implications in making clinicians aware of, and better prepared for, pain after surgery.

4.1. Psychometric Testing and Evaluation of Sleep. Psychometric tools for predicting postoperative pain have been associated with both APOP and PPOP (Table 1). Although different questionnaires have been reported to enable the prediction of postoperative pain, their relevance can be questioned partly since they are all reliant on patient self-assessment [112] but also because of the heterogeneity in results as mentioned in this review. The PCS has historically shown promising results regarding its ability to predict postoperative pain [70, 113] and is still being used in research. Nevertheless, the most recent studies have obtained conflicting results on the correlation with postoperative pain and opioid use. Frankly, we see no convincing results at all, despite 18 efforts included in the review, to justify its continued use for this purpose. We believe that the unpredictability shown with the PCS demands either its refutation or usage in a different context. Recently, the ability of the HADS to predict PPOP has been investigated but not statistically confirmed, except for one study in which both the HADS anxiety and HADS depression were reported to strongly correlate with persistent pain at 3 months after

hysterectomy [17]. On the other hand, the HADS score has been reported to be associated with acute pain intensity after various kinds of surgery [18–21]; thus, HADS perhaps merits more investigations regarding its use in an emergent setting. The six-item APAIS [114] was reported in the beginning of this millennium [7] to improve the prediction of APOP when combined with other tools, but more recent data are missing.

In contrast to many other psychometric tools, the Distress Thermometer is promising and not time consuming. Pak et al. evaluated psychological distress before breast cancer surgery in 956 women using the NCCN Distress Thermometer and showed that a cutoff ≥ 4 predicted APOP [60]. When used together with seven other known risk factors for APOP, the nomogram had an AUC of 0.735. Although intriguing findings have been reported in a fairly large cohort, these findings have yet to be reproduced in a prospective cohort.

Asking patients about their individual pain expectations seems promising, particularly considering the simplicity [28, 37], as do some questionnaires (PSQ and PSEQ) designed for this purpose [49, 50, 63].

Low sleep quality has been suggested to be associated with greater pain sensitivity [64]. Sleep quality based on the PSQI shows promise for preoperative screening, as the compiled study data reported in this review indicate that low-quality sleep may considerably worsen individuals' experience of postoperative pain. We anticipate a study to investigate if improved sleep quality can improve pain outcomes.

4.2. Quantitative Sensory Testing. Tests of experimental pain have historically been frequently linked to postoperative pain [115, 116]. Various methods for estimating pain thresholds induced by electricity, heat, cold, or pressure have all been reported to correlate with postoperative pain sensitivity. More complex dynamic methods, such as the TSP and CPM, are believed to evaluate pain processing pathways [117] and diffuse noxious inhibitory control [118]. Many recent studies on the use of QST for pain prediction have focused mainly on CPM, TSP, and pressure-induced pain (Table 2). Despite the massive amount of research performed, the results are not convincing enough to justify usage in clinical practice especially considering that its use is time-consuming and demands specific equipment and prepared surroundings.

4.3. Combined Techniques. Since no single preoperative test or method has been found to reliably predict postoperative pain, recent research has combined different techniques (Table 3). Several studies have come up with models that more or less associate with pain outcomes, some with fairly good results [11, 48, 119, 120]. Many, however, combine a multitude of risk factors making the clinical use complex. We are also concerned regarding publication bias since many combinations of risk factors probably were not associated with postoperative pain and thus were not elaborated on further. Despite the rationale of combining various

TABLE 5: Summary of studies covering techniques of genetic mapping to predict postoperative pain and published between 2016 and 2022.

Method of testing	Kind of surgery	Number of patients	Outcome	Statistics	Outcome measure and result (95% confidence interval)	Reference
C3435T (ABCB1)	Colorectal surgery	99	APOP	Post hoc analysis bonferroni	Homozygous CC vs homozygous TT ^{†††}	Dzambazovska-Trajkowska 2016
rs1799971 (OPRM1)	Knee arthroplasty	109	PPOP	Multivariate logistic regression	OPRM1 vs no OPRM1, ns	Thomazeau 2016
rs4680 (COMT)					COMT vs no COMT, ns	
rs4680 (COMT)	Knee arthroplasty	291	PPOP	Multivariate logistic regression	COMT vs no COMT, ns	Rice 2018
rs1799971 (OPRM1)					OPRM1 vs no OPRM1, ns	
rs1799971 (OPRM1)	Cesarean section	266	PPOP	Multivariate logistic regression	COMT vs no COMT, ns	Wang 2019
rs4680 (COMT)					OPRM1 vs no OPRM1, ns	
rs11818426 (NAV3)	Hysterectomy orthopedic surgery	330	PPOP	Logistic regression	No genome-wide significance	RRI van Reij 2020
rs6265 (BDNF)	Ambulatory surgery	246	PPOP	Multivariable logistic regression	G allele vs A allele OR 0.57 (0.39-0.85)	Tian 2018
rs2069840 (IL6)	Oncologic breast surgery	228	PPOP	Multiple logistic regression	OR 0.21 (0.07-0.63)	Stephens 2017
rs1800610 (TNF)					OR 0.40 (0.18-0.87)	
rs4073 (CXCL8)					OR 0.37 (0.15-0.89)	

Note: Significance level for regression models are shown within confidence intervals.
Abbreviations: ABCB1, ATP binding cassette subfamily B member; APOP, acute postoperative pain; BDNF, brain derived neurotrophic factor; COMT, catechol-O-methyl-transferase; CXCL8, C-X-C motif chemokine ligand 8; IL-6, interleukin 6; NAV3, neuron navigator 3; OPRM1, opioid receptor Mu 1; OR, odds ratio; PPOP, persistent postoperative pain; TNF, tumor necrosis factor.
[†] $p \leq 0.05$.
^{††} $p \leq 0.01$.
^{†††} $p \leq 0.001$.

individual risk factors to predict postoperative pain, the challenge is to achieve high enough predictive ability with as few clinically applicable factors as possible and to find the intersection between risk factors and maximum test performance. This is perhaps where machine learning and artificial intelligence come into play in the near future, since their potential reaches beyond current methodologies. However, a cautionary note must be said regarding the risk of overfitting models if too many risk factors are required to achieve high performance.

4.4. Other Techniques. Assessments of pain associated with standard procedures during routine preparation for surgery such as pain induced by tourniquet inflation, peripheral venous cannulation, and subcutaneous infiltration of LA have been used to evaluate pain sensitivity and predict postoperative pain intensity with promising results [88, 90, 121–123]. These techniques are simple, do not demand extra equipment, and are time-accessible, but more quality research is needed regarding its practical use.

Other new techniques, such as the SPI, the PTI, the qNOX index, the NOL index, or EEG-based techniques—all designed to quantify intraoperative nociception—have recently been proposed to predict APOP. However, it should be emphasized that results obtained with any technique based on real-time intraoperative recordings of nociception are necessarily influenced not only by individual pain sensitivity but also by the extent of surgery and potential interactions with the effects from analgesic and hypnotic drugs. The modest results obtained thus far do not currently merit investment in new intraoperative equipment for this specific purpose [91, 92, 97, 99, 124]. However, the SPI and PTI merit further investigation in clinical trials.

4.5. Genetics and Biomarkers. Genetic mapping is an interesting field of research since this method speaks to the very core of individualized perioperative medicine. However, current data do not suggest that this field of research is ready for clinical implementation since no genes of real interest have been identified so far. Additionally, for clinical application, sample analysis needs to be more accessible for the technique to be feasible, which is currently not achieved and argues against its use.

On the other hand, using serologic biomarkers is more accessible but brings an inherent complexity, which needs to be accounted for in order to reach its full potential in pain prediction. In the current review, none of the included studies were designed to assess the performance of a serologic biomarker as a primary outcome. At its best, association was established using group-based comparison with numeric cutoffs or correlation analyses with continuous pain outcomes. One review looked at neuroimaging-based biomarkers in pain and proposed a classification of these biomarkers based on the nature of their target variables. Here, categorization was made according to within-individual perception, between-individual sensitivity, and discriminability as well as the assessment of biomarkers for

persistent pain and prospective biomarkers for persistent pain [125]. Whether this classification can be extrapolated to serologic biomarkers remains to be seen. However, it seems assessing and analyzing serologic biomarkers in a multidimensional, instead of unidimensional, manner might result in findings with higher resolution. In light of this, we anticipate future clinical trials, with a multidimensional methodology, using serological biomarkers to perhaps make it accessible for clinical practice.

4.6. Limitations. The risk of bias within individual original reports was not assessed, despite the original plan presented in PROSPERO. We consider this to be the biggest limitation in this systematic review. We chose to address the primary research question and include a large number of studies rather than narrowing down in preference to detailed bias analyses and presentations. To minimize the risk of selection bias, we have written, published, and followed a study protocol for literature retrieval to avoid missing relevant studies. The risk of publication bias, i.e., risk of not identifying all available data on a topic, has been addressed as seen in a total of 16 articles found and added when doing a reference screen. We still have to be open to the fact that our search strategy was potentially not as broad and inclusive as initially planned. In this review, we deliberately included a large number of studies in order to find also negative results not highlighted in a study where the main result involves a different method in order to find methods tested but with a negative result.

Although completely without the possibility of economic gain, the main author has published an original study based on a new technique reported in this review potentially leading to bias due to competing interests. However, we do not consider this to have influenced the results and conclusions of this review.

5. Conclusions

In conclusion, although progress is being made in the quest to find better methods for predicting pain after surgery, we still have to rely on individual risk assessments based on multiple factors added together. Most important, and readily available, are sex, age, and preoperative pain intensity. Asking patients about their believed pain sensitivity and evaluating painful events (e.g., peripheral venous cannulation) at the bedside during preparation for surgery both seem promising, as do SPI and PTI. However, other new medicotechnical devices developed for this purpose still seem to have fundamental issues to address, and psychometrics and QST have yet to show sufficient clinical value. Genetics and biomarkers are interesting but have yet to present convincing results.

For future studies, there is an urgent need for consensus regarding which parameters to use for evaluation of postoperative pain to enable comparison between studies, and ideally also consensus regarding choice of statistical methods in predictive studies.

Nomenclature

APOP	Acute postoperative pain
PPOP	Persistent postoperative pain
QST	Quantitative sensory thresholds
PRISMA	Preferred Reporting Items for Systematic Reviews
HADS	The Hospital Anxiety and Depression Scale
CES-D	Center for Epidemiological Study of Depression
PCS	Pain Catastrophizing Scale
PSQ	Pain Sensitivity Questionnaire
PSEQ	Pain Self-Efficacy Questionnaire
CSI	Central Sensitization Inventory
STAI	State-Trait Anxiety Inventory
B-MEPS	Brief Measure of Emotional Preoperative Stress
FOP-9	Fear of Pain Questionnaire
NCCN	National Comprehensive Cancer Network
PSQI	Pittsburgh Sleep Quality Index
OSAS	Obstructive sleep apnea syndrome
CPT	Cold pain threshold
PPT	Pressure pain threshold
EPT	Electrical pain threshold
TSP	Temporal summation of pain
CPM	Conditioned pain modulus
RICP	Risk Index for Chronic Pain
VCP	Venous cannulation pain
SPI	Surgical Pleth Index
PACU	Postanesthesia care unit
NRS	Numeric rating scale
PTI	Pain threshold index
qNOX	Quantified noxious index score
NOL	Nociceptive Level Index
SNP	Single nucleotide polymorphism
COMT	Catechol-O-methyl-transferase
NAV3	Neuron navigator 3

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

The authors confirm the contribution as follows: Study conception and design: A.K.M.P. and J.Å. Data collection: A.K.M.P.. Data analysis and interpretation of results: K.M. and A.K.M.P.. Draft manuscript preparation: K.M. and A.K.M.P. Revision of the manuscript and preparation of the

final version: K.M., J.Å., and A.K.M.P.. All authors reviewed the results and approved the final version of the manuscript.

Funding

This study was funded by the grants from the Scientific Council of Southern Sweden, Sparbanken, Research and Educational Fund in Halland County and Region Halland.

Acknowledgments

The authors have nothing to report.

References

- [1] E. K. Aasvang, T. H. Lunn, T. B. Hansen, P. W. Kristensen, S. Solgaard, and H. Kehlet, "Chronic Pre-Operative Opioid Use and Acute Pain After Fast-Track Total Knee Arthroplasty," *Acta Anaesthesiologica Scandinavica* 60 (2016): 529–536.
- [2] S. Kampe, B. Geismann, G. Weinreich, G. Stamatis, U. Ebmeier, and H. J. Gerbershagen, "The Influence of Type of Anesthesia, Perioperative Pain, and Preoperative Health Status on Chronic Pain Six Months After Thoracotomy-A Prospective Cohort Study," *Pain Medicine* 18 (2017): 2208–2213.
- [3] H. Khalil, A. Shajrawi, and R. Henker, "Predictors of Severe Postoperative Pain After Orthopedic Surgery in the Immediate Postoperative Period," *International Journal of Orthopaedic and Trauma Nursing* 43 (2021): 100864.
- [4] C. Strik, B. van den Beukel, D. van Rijckevorsel, M. W. J. Stommel, R. P. G. Ten Broek, and H. van Goor, "Risk of Pain and Gastrointestinal Complaints at 6 Months After Elective Abdominal Surgery," *The Journal of Pain* 20 (2019): 38–46.
- [5] K. Uyama, M. Ida, X. Wang, Y. Naito, and M. Kawaguchi, "Association of Preoperative Functional Disability With Chronic Postsurgical Pain: A Prospective Observational Study," *European Journal of Pain* 26 (2022): 902–910.
- [6] H. Kehlet, T. S. Jensen, and C. J. Woolf, "Persistent Postsurgical Pain: Risk Factors and Prevention," *Lancet* 367 (2006): 1618–1625.
- [7] C. J. Kalkman, K. Visser, J. Moen, G. J. Bonsel, D. E. Grobbee, and K. G. Moons, "Preoperative Prediction of Severe Postoperative Pain," *Pain* 105 (2003): 415–423.
- [8] H. Y. Ip, A. Abrishami, P. W. Peng, J. Wong, and F. Chung, "Predictors of Postoperative Pain and Analgesic Consumption: A Qualitative Systematic Review," *Anesthesiology* 111 (2009): 657–677.
- [9] B. C. Arends, L. Timmerman, L. M. Vernooij, et al., "Van Oud-Alblas HJB: Preoperative Frailty and Chronic Pain After Cardiac Surgery: A Prospective Observational Study," *BMC Anesthesiology* 22 (2022): 201.
- [10] C. R. Chapman and C. J. Vierck, "The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms," *The Journal of Pain* 18 (2017).
- [11] E. K. Aasvang, E. Gmaehle, J. B. Hansen, et al., "Predictive Risk Factors for Persistent Postherniotomy Pain," *Anesthesiology* 112 (2010): 957–969.
- [12] M. U. Werner, H. N. Mjoberg, P. R. Nielsen, and A. Rudin, "Prediction of Postoperative Pain: A Systematic Review of Predictive Experimental Pain Studies," *Anesthesiology* 112 (2010): 1494–1502.

- [13] R. Chou, D. B. Gordon, O. A. de Leon-Casasola, et al., "Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council," *The Journal of Pain* 17 (2016): 131–157.
- [14] A. Althaus, O. Arranz Becker, and E. Neugebauer, "Distinguishing Between Pain Intensity and Pain Resolution: Using Acute Post-Surgical Pain Trajectories to Predict Chronic Post-Surgical Pain," *European Journal of Pain* 18 (2014): 513–521.
- [15] M. Sommer, J. M. de Rijke, M. van Kleef, et al., "The Prevalence of Postoperative Pain in a Sample of 1490 Surgical Inpatients," *European Journal of Anaesthesiology* 25 (2008): 267–274.
- [16] Y. Liu, S. Xiao, H. Yang, et al., "Postoperative Pain-Related Outcomes and Perioperative Pain Management in China: A Population-Based Study," *The Lancet Regional Health—Western Pacific* 39 (2023): 100822.
- [17] C. Han, Z. Ge, W. Jiang, H. Zhao, and T. Ma, "Incidence and Risk Factors of Chronic Pain Following Hysterectomy Among Southern Jiangsu Chinese Women," *BMC Anesthesiology* 17 (2017): 103.
- [18] J. Thomazeau, A. Rouquette, V. Martinez, et al., "Acute Pain Factors Predictive of Post-Operative Pain and Opioid Requirement in Multimodal Analgesia Following Knee Replacement," *European Journal of Pain* 20 (2016): 822–832.
- [19] N. C. Borges, L. V. Pereira, L. A. de Moura, T. C. Silva, and C. F. Pedrosa, "Predictors for Moderate to Severe Acute Postoperative Pain After Cesarean Section," *Pain Research and Management* 2016 (2016): 5783817.
- [20] P. Bradshaw, S. Hariharan, and D. Chen, "Does Preoperative Psychological Status of Patients Affect Postoperative Pain? A Prospective Study From the Caribbean," *British Journal of Pain* 10 (2016): 108–115.
- [21] Q. R. Liu, Y. C. Dai, M. H. Ji, et al., "Predictors and Predictive Effects of Acute Pain Trajectories After Gastrointestinal Surgery," *Scientific Reports* 12 (2022): 6530.
- [22] D. Nishimura, S. Kosugi, Y. Onishi, et al., "Psychological and Endocrine Factors and Pain After Mastectomy," *European Journal of Pain* 21 (2017): 1144–1153.
- [23] M. F. Lindberg, C. Miaskowski, T. Rustoen, et al., "The Impact of Demographic, Clinical, Symptom and Psychological Characteristics on the Trajectories of Acute Postoperative Pain After Total Knee Arthroplasty," *Pain Medicine* 18 (2017): 124–139.
- [24] J. Gohari, L. Grosman-Rimon, M. Arazi, et al., "Clinical Factors and Pre-Surgical Depression Scores Predict Pain Intensity in Cardiac Surgery Patients," *BMC Anesthesiology* 22 (2022): 204.
- [25] J. M. Hah, E. Cramer, H. Hilmoe, et al., "Factors Associated With Acute Pain Estimation, Postoperative Pain Resolution, Opioid Cessation, and Recovery: Secondary Analysis of a Randomized Clinical Trial," *JAMA Network Open* 2 (2019): e190168.
- [26] M. J. L. Sullivan, S. R. Bishop, and J. Pivik, "The Pain Catastrophizing Scale: Development and Validation," *Psychological Assessment* 7 (1995): 524–532.
- [27] A. L. Tai, H. F. Hsieh, P. L. Chou, H. M. Chen, and Y. Liu, "The Influence of Preoperative Anxiety, Optimism, and Pain Catastrophizing on Acute Postoperative Pain in Patients Undergoing Cardiac Surgery: A Cross-Sectional Study," *Journal of Cardiovascular Nursing* 36 (2021): 454–460.
- [28] A. Alokozai, S. L. Eppler, L. Y. Lu, N. Sheikholeslami, and R. N. Kamal, "Can Patients Forecast Their Postoperative Disability and Pain?" *Clinical Orthopaedics and Related Research* 477 (2019): 635–643.
- [29] A. S. Habib, M. D. Kertai, M. Cooter, R. A. Greenup, and S. Hwang, "Risk Factors for Severe Acute Pain and Persistent Pain After Surgery for Breast Cancer: A Prospective Observational Study," *Regional Anesthesia and Pain Medicine* 44 (2019): 192–199.
- [30] J. M. Wilson, C. A. Colebaugh, K. M. Flowers, et al., "Applying the Rapid OPPERA Algorithm to Predict Persistent Pain Outcomes Among a Cohort of Women Undergoing Breast Cancer Surgery," *The Journal of Pain* (2022).
- [31] T. Vasilopoulos, R. Wardhan, P. Rashidi, et al., "Patient and Procedural Determinants of Postoperative Pain Trajectories," *Anesthesiology* 134 (2021): 421–434.
- [32] R. R. Edwards, C. Campbell, K. L. Schreiber, et al., "Multimodal Prediction of Pain and Functional Outcomes 6 Months Following Total Knee Replacement: A Prospective Cohort Study," *BMC Musculoskeletal Disorders* 23 (2022): 302.
- [33] S. Benlolo, J. G. Hanlon, L. Shirreff, G. Lefebvre, H. Husslein, and E. M. Shore, "Predictors of Persistent Postsurgical Pain After Hysterectomy—A Prospective Cohort Study," *Journal of Minimally Invasive Gynecology* 28 (2021): 2036–2046.e1.
- [34] X. Mi, B. Zou, P. Rashidi, et al., "Effects of Patient and Surgery Characteristics on Persistent Postoperative Pain: A Mediation Analysis," *The Clinical Journal of Pain* 37 (2021): 803–811.
- [35] L. Dams, E. Van der Gucht, V. Haenen, et al., "Biopsychosocial Risk Factors for Pain and Pain-Related Disability 1 Year After Surgery for Breast Cancer," *Supportive Care in Cancer* 30 (2022): 4465–4475.
- [36] C. R. Abrecht, M. Cornelius, A. Wu, et al., "Prediction of Pain and Opioid Utilization in the Perioperative Period in Patients Undergoing Primary Knee Arthroplasty: Psychological and Psychosocial Factors," *Pain Medicine* 20 (2019): 161–171.
- [37] E. O. Bayman, K. R. Parekh, J. Keech, N. Larson, M. Vander Weg, and T. J. Brennan, "Preoperative Patient Expectations of Postoperative Pain Are Associated With Moderate to Severe Acute Pain After VATS," *Pain Medicine* 20 (2019): 543–554.
- [38] J. Scheel, R. Sittl, N. Griessinger, et al., "Psychological Predictors of Acute Postoperative Pain After Hysterectomy for Benign Causes," *The Clinical Journal of Pain* 33 (2017): 595–603.
- [39] C. Horn-Hofmann, J. Scheel, V. Dimova, et al., "Prediction of Persistent Post-Operative Pain: Pain-Specific Psychological Variables Compared With Acute Post-Operative Pain and General Psychological Variables," *European Journal of Pain* 22 (2018): 191–202.
- [40] F. Chen, W. Gao, J. Hu, X. Yang, X. Chai, and D. Wang, "Preoperative Angiotensin II Type 2 Receptor Is a Predictor for Developing Chronic Post-Surgical Pain After Total Knee Arthroplasty Surgery," *Life Sciences* 278 (2021): 119654.
- [41] C. Edgley, M. Hogg, A. De Silva, S. Braat, A. Bucknill, and K. Leslie, "Severe Acute Pain and Persistent Post-Surgical Pain in Orthopaedic Trauma Patients: A Cohort Study," *British Journal of Anaesthesia* 123 (2019): 350–359.
- [42] E. M. Giusti, M. Lacerenza, S. Gabrielli, et al., "Psychological Factors and Trajectories of Post-Surgical Pain: A Longitudinal Prospective Study," *Pain Practice* 22 (2022): 159–170.

- [43] L. H. Høvik, S. B. Winther, O. A. Foss, and K. H. Gjeilo, "Preoperative Pain Catastrophizing and Postoperative Pain After Total Knee Arthroplasty: A Prospective Cohort Study With One Year Follow-Up," *BMC Musculoskeletal Disorders* 17 (2016): 214.
- [44] E. O. Bayman, K. R. Parekh, J. Keech, A. Selte, and T. J. Brennan, "A Prospective Study of Chronic Pain After Thoracic Surgery," *Anesthesiology* 126 (2017): 938–951.
- [45] K. Groesen, A. M. Drewes, H. K. Pilegaard, M. Pfeiffer-Jensen, B. Brock, and L. Vase, "Situational But Not Dispositional Pain Catastrophizing Correlates With Early Postoperative Pain in Pain-Free Patients Before Surgery," *The Journal of Pain* 17 (2016): 549–560.
- [46] P. Aceto, C. Lai, V. Perilli, et al., "Factors Affecting Acute Pain Perception and Analgesics Consumption in Patients Undergoing Bariatric Surgery," *Physiology and Behavior* 163 (2016): 1–6.
- [47] R. M. Sipilä, L. Haasio, T. J. Meretoja, S. Ripatti, A. M. Estlander, and E. A. Kalso, "Does Expecting More Pain Make it More Intense? Factors Associated With the First Week Pain Trajectories After Breast Cancer Surgery," *Pain* 158 (2017): 922–930.
- [48] D. Dereu, G. L. Savoldelli, C. Combescure, S. Mathivon, and B. Rehberg, "Development of a Simple Preoperative Risk Score for Persistent Pain After Breast Cancer Surgery: A Prospective Observational Cohort Study," *The Clinical Journal of Pain* 34 (2018): 559–565.
- [49] A. K. Bjørnnes, I. Lie, M. Parry, et al., "Association Between Self-Perceived Pain Sensitivity and Pain Intensity After Cardiac Surgery," *Journal of Pain Research* 11 (2018): 1425–1432.
- [50] B. Rehberg, S. Mathivon, C. Combescure, Y. Mercier, and G. L. Savoldelli, "Prediction of Acute Postoperative Pain Following Breast Cancer Surgery Using the Pain Sensitivity Questionnaire: A Cohort Study," *The Clinical Journal of Pain* 33 (2017): 57–66.
- [51] Y. Wang, Z. Liu, S. Chen, et al., "Identifying At-Risk Subgroups for Acute Postsurgical Pain: A Classification Tree Analysis," *Pain Medicine* 19 (2018): 2283–2295.
- [52] R. Neblett, H. Cohen, Y. Choi, et al., "The Central Sensitization Inventory (CSI): Establishing Clinically Significant Values for Identifying Central Sensitivity Syndromes in an Outpatient Chronic Pain Sample," *The Journal of Pain* 14 (2013): 438–445.
- [53] M. S. Kim, I. J. Koh, S. Sohn, B. M. Kang, D. H. Kwak, and Y. In, "Central Sensitization Is a Risk Factor for Persistent Postoperative Pain and Dissatisfaction in Patients Undergoing Revision Total Knee Arthroplasty," *The Journal of Arthroplasty* 34 (2019): 1740–1748.
- [54] A. Schnabel, M. Yahiaoui-Doktor, W. Weissner, P. K. Zahn, and E. M. Pogatzki-Zahn, "Predicting Poor Postoperative Acute Pain Outcome in Adults: An International, Multi-centre Database Analysis of Risk Factors in 50,005 Patients," *Pain Reports* 5 (2020): e831.
- [55] J. Stuhlfreyer and R. Klinger, "The Influence of Preoperative Mood and Treatment Expectations on Early Postsurgical Acute Pain After a Total Knee Replacement," *Frontiers in Psychiatry* 13 (2022): 840270.
- [56] J. Jin, L. Peng, Q. Chen, et al., "Prevalence and Risk Factors for Chronic Pain Following Cesarean Section: A Prospective Study," *BMC Anesthesiology* 16 (2016): 99.
- [57] W. Caumo, M. Nazare Furtado da Cunha, S. Camey, S. Maris de Jezus Castro, I. L. Torres, and L. Cadore Stefani, "Development, Psychometric Evaluation and Validation of a Brief Measure of Emotional Preoperative Stress (B-MEPS) to Predict Moderate to Intense Postoperative Acute Pain," *British Journal of Anaesthesia* 117 (2016): 642–649.
- [58] D. W. McNeil, S. G. Kennedy, C. L. Randall, et al., "Fear of Pain Questionnaire-9: Brief Assessment of Pain-Related Fear and Anxiety," *European Journal of Pain* 22 (2018): 39–48.
- [59] Y. Luo, J. He, L. Bao, H. Meng, C. Hu, and Q. Chen, "Fear of Pain as a Predictor for Postoperative Pain Intensity Among the Patients Undergoing Thoracoscopic Surgery," *Pain Research and Management* 2022 (2022): 2201501.
- [60] L. M. Pak, K. R. Pawloski, V. Sevilimedu, et al., "How Much Pain Will I Have after Surgery? A Preoperative Nomogram to Predict Acute Pain Following Mastectomy," *Annals of Surgical Oncology* (2022): 1–8.
- [61] L. Guichard, A. Vanhaesebrouck, D. Fletcher, Y. Stiglitz, A. Rouquette, and V. Martinez, "Pain Trajectory After Ankle Surgeries for Osteoarthritis," *Foot and Ankle International* 40 (2019): 367–373.
- [62] J. Lötsch, R. Sipilä, V. Dimova, and E. Kalso, "Machine-Learned Selection of Psychological Questionnaire Items Relevant to the Development of Persistent Pain After Breast Cancer Surgery," *British Journal of Anaesthesia* 121 (2018): 1123–1132.
- [63] J. P. Wang, S. F. Lu, L. N. Guo, C. G. Ren, and Z. W. Zhang, "Poor Preoperative Sleep Quality Is a Risk Factor for Severe Postoperative Pain After Breast Cancer Surgery: A Prospective Cohort Study," *Medicine (Baltimore)* 98 (2019): e17708.
- [64] S. Orbach-Zinger, S. Fireman, A. Ben-Haroush, et al., "Preoperative Sleep Quality Predicts Postoperative Pain After Planned Caesarean Delivery," *European Journal of Pain* 21 (2017): 787–794.
- [65] M. F. Bjurström, M. R. Irwin, M. Bodellson, M. T. Smith, and N. Mattsson-Carlgen, "Preoperative Sleep Quality and Adverse Pain Outcomes After Total Hip Arthroplasty," *European Journal of Pain* 25 (2021): 1482–1492.
- [66] D. Boye Larsen, M. Laursen, O. Simonsen, L. Arendt-Nielsen, and K. K. Petersen, "The Association Between Sleep Quality, Preoperative Risk Factors for Chronic Postoperative Pain and Postoperative Pain Intensity 12 Months After Knee and Hip Arthroplasty," *British Journal of Pain* 15 (2021): 486–496.
- [67] P. K. Strutz, V. Kronzer, W. Tzeng, et al., "The Relationship Between Obstructive Sleep Apnoea and Postoperative Delirium and Pain: An Observational Study of a Surgical Cohort," *Anaesthesia* 74 (2019): 1542–1550.
- [68] G. Wang, M. He, X. L. Ji, X. L. Wang, and Y. Feng, "Identifying Patients at High Risk of Chronic Pain After Video-Assisted Thoracoscopic Surgery Using Thermal Quantitative Sensory Testing," *Journal of Cardiothoracic and Vascular Anesthesia* 36 (2022): 2406–2411.
- [69] J. Lötsch, A. Utsch, and E. Kalso, "Prediction of Persistent Post-Surgery Pain by Preoperative Cold Pain Sensitivity: Biomarker Development With Machine-Learning-Derived Analysis," *British Journal of Anaesthesia* 119 (2017): 821–829.
- [70] I. E. Luna, H. Kehlet, M. A. Petersen, and E. K. Aasvang, "Clinical, Nociceptive and Psychological Profiling to Predict Acute Pain After Total Knee Arthroplasty," *Acta Anaesthesiologica Scandinavica* (2017).
- [71] G. Duan, S. Guo, Y. Zhang, et al., "Effects of Epidemiological Factors and Pressure Pain Measurements in Predicting Postoperative Pain: A Prospective Survey of 1,002 Chinese Patients," *Pain Physician* 20 (2017): E903–e914.

- [72] A. S. Wolmeister, C. L. Schiavo, K. C. K. Nazário, et al., "The Brief Measure of Emotional Preoperative Stress (B-MEPS) as a New Predictive Tool for Postoperative Pain: A Prospective Observational Cohort Study," *PLoS One* 15 (2020): e0227441.
- [73] B. A. Haghighi, D. J. Wright, and R. Schwarzkopf, "Pressure Pain Threshold as a Predictor of Acute Postoperative Pain Following Total Joint Arthroplasty," *Surgical Technology International* 29 (2016): 320–327.
- [74] M. M. Luedi, P. Schober, B. Hammoud, L. Anderegg, C. Hoenemann, and D. Doll, "Preoperative Pressure Pain Threshold Is Associated With Postoperative Pain in Short-Stay Anorectal Surgery: A Prospective Observational Study," *Anesthesia and Analgesia* 132 (2021): 656–662.
- [75] R. Ruscheweyh, A. Viehoff, J. Tio, and E. M. Pogatzki-Zahn, "Psychophysical and Psychological Predictors of Acute Pain After Breast Surgery Differ in Patients With and Without Pre-Existing Chronic Pain," *Pain* 158 (2017): 1030–1038.
- [76] L. Lunde, K. K. Petersen, E. Søgaard-Andersen, and L. Arendt-Nielsen, "Preoperative Quantitative Sensory Testing and Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer: Can Chronic Postoperative Pain Be Predicted?" *Scandinavian Journal of Pain* 20 (2020): 693–705.
- [77] A. K. Persson, L. E. Dyrehag, and J. Åkeson, "Prediction of Postoperative Pain From Electrical Pain Thresholds After Laparoscopic Cholecystectomy," *The Clinical Journal of Pain* 33 (2017): 126–131.
- [78] K. L. Schreiber, N. Zinboonyahoon, X. Xu, et al., "Preoperative Psychosocial and Psychophysical Phenotypes as Predictors of Acute Pain Outcomes After Breast Surgery," *The Journal of Pain* 20 (2019): 540–556.
- [79] C. Dürsteler, Y. Salazar, U. Rodriguez, X. Pelfort, and L. P. Verdié, "Conditioned Pain Modulation Predicts Persistent Pain After Knee Replacement Surgery," *PAIN Reports* 6 (2021): e910.
- [80] T. Kurien, L. Arendt-Nielsen, K. K. Petersen, T. Graven-Nielsen, and B. E. Scammell, "Preoperative Neuropathic Pain-Like Symptoms and Central Pain Mechanisms in Knee Osteoarthritis Predicts Poor Outcome 6 Months After Total Knee Replacement Surgery," *The Journal of Pain* 19 (2018): 1329–1341.
- [81] B. Stessel, A. A. Fiddlers, M. A. Marcus, et al., "External Validation and Modification of a Predictive Model for Acute Postsurgical Pain at Home After Day Surgery," *The Clinical Journal of Pain* 33 (2017): 405–413.
- [82] D. B. Larsen, M. Laursen, R. R. Edwards, O. Simonsen, L. Arendt-Nielsen, and K. K. Petersen, "The Combination of Preoperative Pain, Conditioned Pain Modulation, and Pain Catastrophizing Predicts Postoperative Pain 12 Months After Total Knee Arthroplasty," *Pain Medicine* (2021).
- [83] A. Althaus, A. Hinrichs-Rocker, R. Chapman, et al., "Development of a Risk Index for the Prediction of Chronic Post-Surgical Pain," *European Journal of Pain* 16 (2012): 901–910.
- [84] T. Mathes, C. Pape-Kohler, L. Moerders, E. Lux, and E. A. M. Neugebauer, "External Validation and Update of the RICP-A Multivariate Model to Predict Chronic Postoperative Pain," *Pain Medicine* (2017).
- [85] T. J. Meretoja, K. G. Andersen, J. Bruce, et al., "Clinical Prediction Model and Tool for Assessing Risk of Persistent Pain After Breast Cancer Surgery," *Journal of Clinical Oncology* 35 (2017): 1660–1667.
- [86] A. A. Nair, M. A. Velagapudi, J. A. Lang, et al., "Machine Learning Approach to Predict Postoperative Opioid Requirements in Ambulatory Surgery Patients," *PLoS One* 15 (2020): e0236833.
- [87] S. Nimmaanrat, W. Wongwiwattananon, S. Siripreukpong, V. Chongsuvivatwong, and M. P. Jensen, "A Prospective Observational Study to Investigate the Relationship Between Local Anesthetic Infiltration Pain Before Spinal Anesthesia and Acute and Chronic Postsurgical Pain in Women Undergoing Elective Cesarean Delivery," *International Journal of Obstetric Anesthesia* 45 (2021): 56–60.
- [88] A. K. Persson, F. D. Pettersson, L. E. Dyrehag, and J. Åkeson, "Prediction of Postoperative Pain From Assessment of Pain Induced by Venous Cannulation and Propofol Infusion," *Acta Anaesthesiologica Scandinavica* 60 (2016): 166–176.
- [89] A. K. M. Persson and J. Åkeson, "Prediction of Acute Postoperative Pain From Assessment of Pain Associated With Venous Cannulation," *Pain Practice* 19 (2019): 158–167.
- [90] F. Peng, Y. Li, Y. Ai, J. Yang, and Y. Wang, "Application of Preoperative Assessment of Pain Induced by Venous Cannulation in Predicting Postoperative Pain in Patients Under Laparoscopic Nephrectomy: A Prospective Observational Study," *BMC Anesthesiology* 20 (2020): 86.
- [91] K. Jung, M. H. Park, D. K. Kim, and B. J. Kim, "Prediction of Postoperative Pain and Opioid Consumption Using Intraoperative Surgical Pleth Index After Surgical Incision: An Observational Study," *Journal of Pain Research* 13 (2020): 2815–2824.
- [92] T. Ledowski, J. Burke, and J. Hruby, "Surgical Pleth Index: Prediction of Postoperative Pain and Influence of Arousal," *British Journal of Anaesthesia* 117 (2016): 371–374.
- [93] T. Ledowski, M. Schneider, M. Gruenewald, R. K. Goyal, S. R. Teo, and J. Hruby, "Surgical Pleth Index: Prospective Validation of the Score to Predict Moderate-To-Severe Postoperative Pain," *British Journal of Anaesthesia* 123 (2019): e328–e332.
- [94] M. Park, B. J. Kim, and G. S. Kim, "Prediction of Postoperative Pain and Analgesic Requirements Using Surgical Pleth Index: A Observational Study," *Journal of Clinical Monitoring and Computing* 34 (2020): 583–587.
- [95] R. Wang, Y. Deng, S. Zhou, and J. Zhang, "EEG-Derived Pain Threshold Index for Prediction of Postoperative Pain in Patients Undergoing Laparoscopic Urological Surgery: A Comparison with Surgical Pleth Index," *Journal of Clinical Monitoring and Computing* (2020).
- [96] Q. Han, L. Yue, F. Gao, L. Zhang, L. Hu, and Y. Feng, "The Prediction of Acute Postoperative Pain Based on Neural Oscillations Measured before the Surgery," *Neural Plasticity* 2021 (2021): 5543974.
- [97] T. Ledowski and I. Schmitz-Rode, "Predicting Acute Postoperative Pain by the Qnox Score at the End of Surgery: A Prospective Observational Study," *British Journal of Anaesthesia* 124 (2020): 222–226.
- [98] T. Ledowski, P. Schluter, and N. Hall, "Nociception Level Index: Do Intra-Operative Values Allow the Prediction of Acute Postoperative Pain?" *Journal of Clinical Monitoring and Computing* (2021).
- [99] L. Morisson, M. Nadeau-Vallée, F. Espitalier, et al., "Prediction of Acute Postoperative Pain Based on Intraoperative Nociception Level (NOL) Index Values: The Impact of Machine Learning-Based Analysis," *Journal of Clinical Monitoring and Computing* (2022).
- [100] V. Dzambazovska-Trajkovska, J. Nojkov, A. Kartalov, et al., "Association of Single-Nucleotide Polymorphism C3435T in the ABCB1 Gene With Opioid Sensitivity in Treatment of

- Postoperative Pain," *Pril (Makedon Akad Nauk Umet Odd Med Nauki)* 37 (2016): 73–80.
- [101] D. A. Rice, M. T. Kluger, P. J. McNair, et al., "Persistent Postoperative Pain After Total Knee Arthroplasty: A Prospective Cohort Study of Potential Risk Factors," *British Journal of Anaesthesia* 121 (2018): 804–812.
 - [102] L. Wang, C. Wei, F. Xiao, X. Chang, and Y. Zhang, "Influences of COMT Rs4680 and OPRM1 Rs179971 Polymorphisms on Chronic Postsurgical Pain, Acute Pain, and Analgesic Consumption After Elective Cesarean Delivery," *The Clinical Journal of Pain* 35 (2019): 31–36.
 - [103] J. Thomazeau, A. Rouquette, V. Martinez, et al., "Predictive Factors of Chronic Post-Surgical Pain at 6 Months Following Knee Replacement: Influence of Postoperative Pain Trajectory and Genetics," *Pain Physician* 19 (2016): E729–E741.
 - [104] R. R. I. van Reij, D. M. N. Hoofwijk, B. P. F. Rutten, et al., "The Association Between Genome-Wide Polymorphisms and Chronic Postoperative Pain: A Prospective Observational Study," *Anaesthesia* 75, no. Suppl 1 (2020): e111–e120.
 - [105] Y. Tian, X. Liu, M. Jia, et al., "Targeted Genotyping Identifies Susceptibility Locus in Brain-Derived Neurotrophic Factor Gene for Chronic Postsurgical Pain," *Anesthesiology* 128 (2018): 587–597.
 - [106] K. E. Stephens, J. D. Levine, B. E. Aouizerat, et al., "Associations Between Genetic and Epigenetic Variations in Cytokine Genes and Mild Persistent Breast Pain in Women Following Breast Cancer Surgery," *Cytokine* 99 (2017): 203–213.
 - [107] R. Giordano, K. K. Petersen, H. H. Andersen, et al., "Preoperative Serum Circulating microRNAs as Potential Biomarkers for Chronic Postoperative Pain After Total Knee Replacement," *Molecular Pain* 16 (2020).
 - [108] K. Öner, A. E. Okutan, M. S. Ayas, A. E. Paksoy, and F. Polat, "Predicting Postoperative Pain With Neutrophil/Lymphocyte Ratio After Arthroscopic Rotator Cuff Repair," *Asia-Pacific Journal of Sports Medicine, Arthroscopy, Rehabilitation and Technology* 20 (2020): 24–27.
 - [109] M. Gencer and A. Y. Göçmen, "The Relationship Between the Level of μ -Opioid Receptor (μ ORs) and Postoperative Analgesic Use in Patients Undergoing Septoplasty: A Prospective Randomized Controlled Trial," *BMC Anesthesiology* 20 (2020): 230.
 - [110] F. Wang, H. Li, Q. Mu, et al., "Association of Acute Postoperative Pain and Cigarette Smoking With Cerebrospinal Fluid Levels of Beta-Endorphin and Substance P," *Frontiers in Molecular Neuroscience* 14 (2021): 755799.
 - [111] T. H. Lunn, J. M. Dawes, F. Denk, et al., "Preoperative Ultraviolet B Inflammation in Skin: Modelling Individual Differences in Acute Postoperative Pain and Neuro-Immune Interactions," *European Journal of Pain* 22 (2018): 170–180.
 - [112] S. C. Karpen, "The Social Psychology of Biased Self-Assessment," *American Journal of Pharmaceutical Education* 82 (2018): 6299.
 - [113] M. Theunissen, M. L. Peters, J. Bruce, H. F. Gramke, and M. A. Marcus, "Preoperative Anxiety and Catastrophizing: A Systematic Review and Meta-Analysis of the Association With Chronic Postsurgical Pain," *The Clinical Journal of Pain* 28 (2012): 819–841.
 - [114] N. Moerman, F. S. van Dam, M. J. Muller, and H. Oosting, "The Amsterdam Preoperative Anxiety and Information Scale (APAIS)," *Anesthesia and Analgesia* 82 (1996): 445–451.
 - [115] K. K. Petersen, H. B. Vaegter, A. Stubhaug, et al., "The Predictive Value of Quantitative Sensory Testing: A Systematic Review on Chronic Postoperative Pain and the Analgesic Effect of Pharmacological Therapies in Patients With Chronic Pain," *Pain* 162 (2021): 31–44.
 - [116] M. U. Werner, "Prediction of Postoperative Pain: A Systematic Review of Predictive Experimental Pain Studies," *Anesthesiology* 112 (June 2010): 1494–1502.
 - [117] J. C. Cheng, N. Erpelding, A. Kucyi, D. D. DeSouza, and K. D. Davis, "Individual Differences in Temporal Summation of Pain Reflect Pronociceptive and Antinociceptive Brain Structure and Function," *Journal of Neuroscience* 35 (2015): 9689–9700.
 - [118] D. L. Kennedy, H. I. Kemp, D. Ridout, D. Yarnitsky, and A. S. C. Rice, "Reliability of Conditioned Pain Modulation: A Systematic Review," *Pain* 157 (2016): 2410–2419.
 - [119] K. J. Janssen, C. J. Kalkman, D. E. Grobbee, G. J. Bonsel, K. G. Moons, and Y. Vergouwe, "The Risk of Severe Postoperative Pain: Modification and Validation of a Clinical Prediction Rule," *Anesthesia and Analgesia* 107 (2008): 1330–1339.
 - [120] C. Kalkman, "Preoperative Prediction of Severe Postoperative Pain," *Pain* 105 (2003): 415–423.
 - [121] B. Carvalho, M. Zheng, and L. Aiono-Le Tagaloa, "Evaluation of Experimental Pain Tests to Predict Labour Pain and Epidural Analgesic Consumption," *British Journal of Anaesthesia* 110 (2013): 600–606.
 - [122] R. Rago, F. Forfori, G. Materazzi, et al., "Evaluation of a Preoperative Pain Score in Response to Pressure as a Marker of Postoperative Pain and Drugs Consumption in Surgical Thyroidectomy," *The Clinical Journal of Pain* 28 (2012): 382–386.
 - [123] S. Orbach-Zinger, A. Aviram, S. Fireman, et al., "Severe Pain During Local Infiltration for Spinal Anaesthesia Predicts Post-Caesarean Pain," *European Journal of Pain* (2015).
 - [124] R. Wang, Y. Deng, S. Zhou, and J. Zhang, "EEG-Derived Pain Threshold Index for Prediction of Postoperative Pain in Patients Undergoing Laparoscopic Urological Surgery: A Comparison With Surgical Pleth Index," *Journal of Clinical Monitoring and Computing* 35 (2021): 1395–1402.
 - [125] L. B. Zhang, Y. X. Chen, Z. J. Li, et al., "Advances and Challenges in Neuroimaging-Based Pain Biomarkers," *Cell Reports Medicine* 5 (2024): 101784.

Paper II



Effect of individualized anesthesia and analgesia on postoperative pain in patients stratified for pain sensitivity: A study protocol for the PeriOPERative individualization trial randomized controlled trial

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Email: krister.mogianos@med.lu.se**Abstract**

Background: Despite advancements in surgical and anesthesia techniques, acute and persistent postoperative pain are still a common challenge. Postoperative pain has direct effects on individual patient care and outcome, as well as putting strain on limited health care resources. Several prediction methods for postoperative pain have been described. One such method is the assessment of pain during peripheral venous cannulation (VCP). It is not known if different approaches to anesthesia and analgesia, depending on the evaluation of risk for postoperative pain, can improve outcome. The aim of this study is to evaluate if individualized anesthesia and analgesia can affect postoperative pain and recovery after surgery, in patients stratified by VCP.

Methods: Adult patients scheduled for laparoscopic surgery undergo pain-sensitivity stratification using VCP on the day of surgery. Patients scoring VCP ≥ 2.0 on the visual analogue scale (pain-sensitive) are randomized to multimodal anaesthesia and analgesia with opioids or standard of care. Patients scoring VCP ≤ 1.9 (pain-tolerant) are randomized to opioid-free anaesthesia or standard of care. The primary outcome is acute postoperative pain measured with numeric rating scale in the postoperative care unit. Secondary outcomes include analysis of pain after 24 h, persistent postoperative pain and quality of recovery.

Discussion: Individualized perioperative pain management has the potential to improve patient care. This study will examine the impact of different anesthesia and analgesia regimes, in patients with differing pain sensitivity, on postoperative pain.

Trial Registration: Prospectively posted at [ClinicalTrials.gov](https://clinicaltrials.gov), identifier NCT04751812.

KEYWORDS

acute postoperative pain, individualized anesthesia and analgesia in surgery, opioid-free anesthesia, opioid-included anesthesia, pain during peripheral venous cannulation, persistent postoperative pain, quality of recovery

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1 | BACKGROUND

Despite advances in surgical techniques and pharmacological treatment of postoperative pain, the prevention and treatment of acute and persistent postoperative pain remains a challenge in the anesthesia community. Worldwide, there are more than 230 million surgical procedures performed every year and it is estimated that 20%–80% of patients undergoing these procedures will suffer acute postoperative pain (APOP).^{1–3} Known surgical risk factors for APOP are large incisions and a type of procedure.^{4,5} Acute postoperative pain is associated with the development of postoperative respiratory complications, prolonged recovery and persistent postoperative pain (PPOP).^{6–8} These adverse events lead to a high degree of morbidity and societal cost.^{9,10} Furthermore, the development of PPOP has been identified as a main contributor to the current opioid epidemic, responsible for over 80,000 deaths in the United States alone.^{11,12}

Considering these aspects, it seems desirable to develop a more optimal and strategic use of perioperative analgesia. Focus has therefore shifted from procedure-specific to a more individualized approach when dealing with APOP, with increasing evidence addressing individual aspects of pain modulation. Current evidence has suggested several, both non-modifiable and modifiable, risk factors for APOP and PPOP on the individual level, such as female gender, younger age, pre-existing pain and opioid use, poor sleep quality, self-anticipated pain, and psychosocial strain.^{5,13–16} Individualized pain prediction may aid in the management of these patients. However, only a few promising prediction methods have satisfactory performance without being clinically laborious or time consuming. One such test involves assessing pain when cannulating for peripheral venous access (VCP). Patients grading their VCP above 2.0 VAS units had 3.4 times higher odds for moderate or severe postoperative pain after laparoscopic cholecystectomy¹⁷ and 1.7 times higher odds in a mixed group of patients and surgeries.¹⁸ These results have recently been confirmed in an independent study on patients undergoing laparoscopic nephrectomy. In this study, VCP correlated with APOP at both rest and cough ($r = .64, r = .65, p < .001$).¹⁹

In order for a pain prediction method to be clinically useful, it should be linked with an appropriate treatment option. We refer to this concept as Individualized Anesthesia and Analgesia in Surgery (IAAS). In IAAS, focus is on the individual patient, with their inherent risk-factors, while clinicians also consider other factors such as type of surgery, degree of urgency, contraindications for specific anesthetic techniques or drug, and goals for postoperative recovery. More specifically, there is a demand for a multimodal and targeted approach, which challenges the clinicians' adaptability and pharmacologic toolbox.

Even though VCP can predict patients at risk for APOP, it is unknown how this test performs in guiding anesthetic and analgesic treatment to the individuals' own need. More importantly, it is not known if tailored anesthesia and analgesia can affect APOP in patients with differing pain sensitivity.

The primary objective of this trial is therefore to examine if an individualized anesthesia and analgesia regime can affect postoperative pain in patients stratified for pain sensitivity.

2 | MATERIALS AND METHODS

2.1 | Aim

The aim of this study is to evaluate if individualized anesthesia and analgesia can affect postoperative pain and recovery after surgery, in patients stratified for pain-sensitivity using VCP.

2.2 | General design

The Peri-Operative Pain Individualization Trial (POPIT) is a randomized, controlled, patient and assessor-blinded, single-center, parallel group, clinical trial. Randomization will be performed as block randomization with a 1:1 allocation.

2.3 | Study setting

Patients scheduled for laparoscopic surgery in Halmstad County Hospital are considered for inclusion. This hospital is a non-tertiary center with approximately 7000 anesthesia procedures from different specialties, both ambulatory and elective, except for cardiothoracic and neurosurgery. Halmstad county hospital is situated in the city of Halmstad, with a catchment area of 150,000 inhabitants.

2.4 | Eligibility criteria

Inclusion criteria are; elective laparoscopic surgery, age > 18 years, American Society of Anesthesiology (ASA) class < III, and ability to understand and accommodate study information. Exclusion criteria are refusal to participate, pregnancy, allergy towards NSAID, and conversion to open abdominal surgery.

2.5 | Patient information and consent

Patients will be informed in writing a few days before and in person upon arrival at the hospital. Written and oral consent will be mandatory.

2.6 | Study timeline

The timeline for the POPIT protocol is depicted in Figure 1. All patients scheduled for elective laparoscopic surgery are assessed by an anesthesiologist in the pre-operative clinic. If inclusion criteria are met and no exclusion criteria are present, the patient is highlighted for potential inclusion in their chart. A text-message, containing study information and the consent form, is sent to the patients 1–7 days before surgery. If consent is given, patients are asked to fill in a baseline data form (age, gender, preoperative pain, pain catastrophizing scale (PCS), and treatment for depression). The PCS consists of

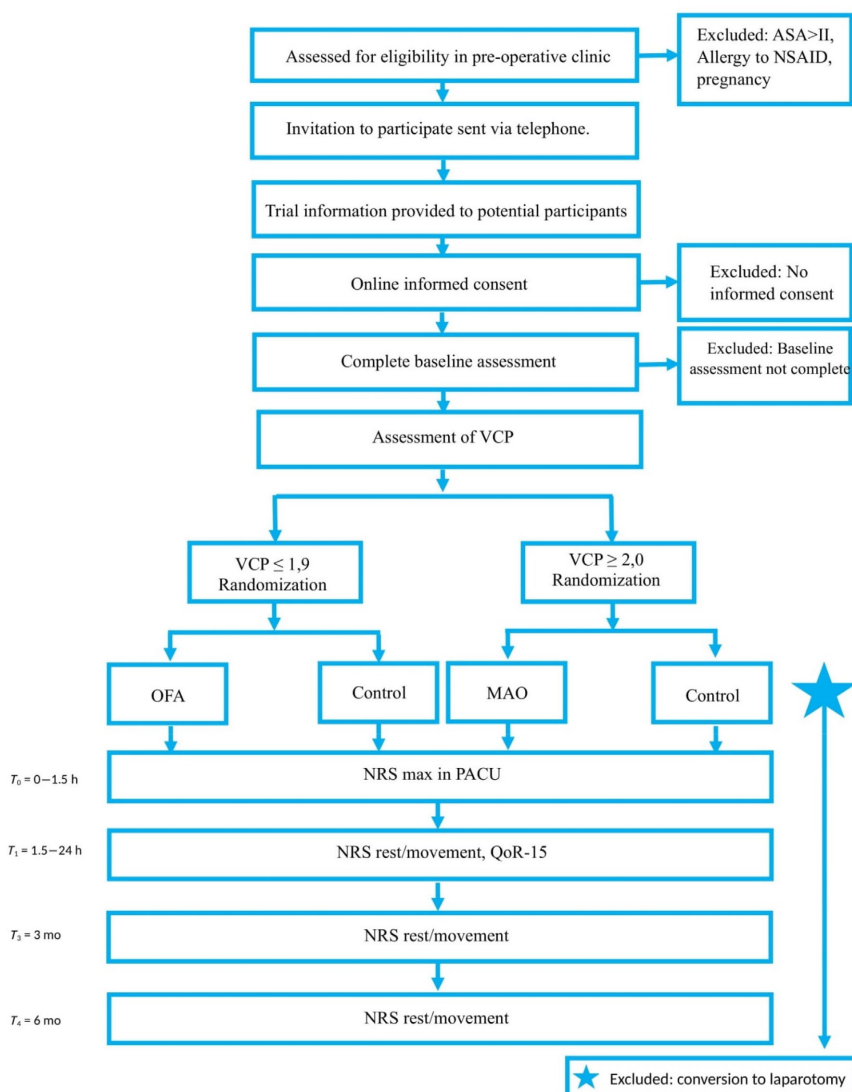


FIGURE 1 Flow diagram depicting the inclusion, allocation, randomization and follow-up process in PeriOperative Individualization Trial (POPIT).

13 statements regarding the subjective emotional aspects towards having pain, where participants rate the statements on a scale of 0 (not at all) to 4 (all the time), with a maximum score of 52.²⁰

On the day of surgery, patients are stratified into pain-sensitivity groups using VCP when vascular access is established. After pain-sensitivity stratification is complete, patients undergo a random

allocation to the study interventions. If open surgery is necessary, patients are excluded. In the post anesthesia care unit (PACU), patients are assessed for APOP as soon as possible and several times until discharge from the PACU. Twenty-four hours after surgery, patients are sent a text-message with follow-up regarding APOP and Quality of recovery (QoR). QoR is a 15-item questionnaire where the

patients are asked to rate their recovery in different dimensions from 0–10. The total amount of points is summed up to a total score ranging from 0 to 150, where 150 represents excellent health status.²¹ Following this, text-messages containing follow-up questions are sent to patients 3 and 6 months postoperatively.

2.7 | Peripheral venous cannulation

Before anesthesia, in the preoperative care area, a specialized nurse will perform the peripheral venous cannulation at a non-specified site. After venous cannulation, the pain associated with venous cannulation will be assessed using a visual analogue scale (VAS) with 0.0 representing no pain and 10.0 maximum pain imaginable.²²

2.8 | Stratification method

After venous cannulation, the pain associated with the procedure will be assessed. Patients will be divided into pain-tolerant ($VCP \leq 1.9$) and pain-sensitive ($VCP \geq 2.0$) groups, after which they get randomized into interventions described in the next section. The allocating cut-off is set to 2.0 VAS-units since this value has shown good performance in regard to prediction of postoperative pain.^{17,19} There will be two sets of instructions for perioperative treatment, one for pain-tolerant and pain-sensitive patients respectively.

2.9 | Randomization method

Randomization for treatment within each pain sensitivity group will be performed by blinded selection of color stratified by center with a 1:1 allocation (sequence generation), creating four arms with inherent independence. The randomization process will be performed in another room from the patient, where the nurse in charge for peripheral venous cannulation blindfolded will draw a colored ball from one of two opaque jars ($VCP \geq 2.0$ and $VCP \leq 1.9$ respectively). In each jar there are balls with two different colors, randomly allocating the patient to either intervention or control group. After randomization the nurses are instructed to throw away the ball drawn. Depending on selection of color, the patient's anesthesia chart, seen only by the anesthesia care team, will be highlighted for the specific protocol for anesthesia and analgesia.

2.10 | Blinding

All health care providers and staff around the patient are instructed not to talk to the patient about the study. If patients ask staff about the potential intervention, they are instructed not to give any details. Since the interventions include potent anesthetic agents, it is considered unsafe to blind the anesthesia providers to the intervention. Therefore, the anesthesia nurses, the anesthesiologist, and the

PACU-nurse will not be blinded to the intervention. The assistant nurse performing the postoperative pain assessments will be blinded to allocation group. Once the assistant nurse has performed the assessment, the PACU-nurse will decide on treatment depending on allocation and specific instructions. No-one in the surgical team is given any information about which intervention the patient is allocated to.

Reasons for unblinding are only accepted if a clear indication for exclusion is reached (eligibility section).

2.11 | Interventions

Patients in the pain-sensitive group can be subjected to either multimodal anesthesia with opioids or standard of care. Patients allocated to pain-tolerant group are subjected to either opioid-free anesthesia or standard of care.

2.11.1 | Opioid-free anesthesia (OFA)

Patients will receive pre-emptive etoricoxib 120 mg, paracetamol 1500 mg, and ondansetron 8 mg orally before surgery. As soon as vascular access is established and the patient arrives in the operating theatre, an infusion of dexmedetomidine will be started at 0.2 $\mu\text{g}/\text{kg}/\text{h}$, without bolus. The infusion-rate of dexmedetomidine remains constant throughout the perioperative process until the patient leaves the PACU. General anesthesia (GA) will be induced using propofol 2.0–2.5 mg/kg and esketamine 0.1 mg/kg bolus, with 8 mg of betamethasone. Anesthesia will be maintained with sevoflurane (MAC 0.6–1.0) together with an infusion of esketamine 0.1–0.3 mg/kg/h and dexmedetomidine 0.2 $\mu\text{g}/\text{kg}/\text{h}$. Perioperative analgesia will be standardized using lidocaine 1 mg/kg bolus 30 min before the end of surgery. Paracetamol is given at a dose of 1000 mg every 6 h. If patients experience APOP corresponding to NRS ≥ 4 , rescue intravenous analgesia with esketamine bolus 0.1 mg/kg and lidocaine 0.5 mg/kg will be administered.

2.11.2 | Multimodal anesthesia with opioids (MAO)

Patients will receive pre-emptive etoricoxib 120 mg, paracetamol 1500 mg, oxycodone 10 mg (5 mg if age > 75), and ondansetron 8 mg orally before surgery. Induction of GA will be conducted using propofol and remifentanyl, with anesthesia maintained with either total intravenous anesthesia (TIVA) with propofol according to the Marsh target control infusion (TCI) protocol, or sevoflurane, both together with remifentanyl using the TCI-protocol.²³ Betamethasone, 4 mg, will be given intravenously at induction. Directly after induction and airway establishment, patients will be administered i.v. esketamine 0.25 mg/kg. One hour before the end of surgery, clonidine 1 $\mu\text{g}/\text{kg}$ will be administered. Postoperative analgesia will be standardized using i.v. oxycodone 0.1 mg/kg and clonidine 1 $\mu\text{g}/\text{kg}$ before

terminating GA, and paracetamol 1000 mg every 6 h. Rescue analgesia, with oxycodone i.v., will be provided in the PACU if NRS ≥ 4 .

2.11.3 | Standard of care (SOC)

This perioperative strategy represents the usual clinical care of these patients and aligns well with typical international and national recommendations.²⁴ Patients will receive pre-emptive etoricoxib 120 mg, paracetamol 1500 mg, oxycodone 10 mg (5 mg if age > 75), and ondansetron 8 mg orally before surgery. Induction of GA will be conducted using propofol and remifentanyl, with anesthesia maintained with either TIVA with propofol, according to the Marsh TCI-protocol, or sevoflurane, both together with remifentanyl using the TCI-protocol.²³ Betamethasone 4 mg will be given i.v. at induction. Postoperative analgesia will be standardized using i.v. oxycodone 0.1 mg/kg, before terminating GA, and paracetamol 1000 mg every 6th hour. Rescue analgesia, with oxycodone i.v. will be provided in the PACU if NRS ≥ 4 .

2.11.4 | Modifications

Since all anesthetic agents used in this study are considered safe and only relatively healthy patients (ASA I-II) are eligible, no modifications are deemed needed. If serious surgical or anesthetic complications occur advanced life support or specific hospital protocol will be applied on the affected patients, as is the policy for this study center.

2.11.5 | Protocol adherence

To guarantee adherence to the study protocol, the treating anesthesiologic team, including pre-operative nurses, nurse anesthetists and PACU-nurses will receive regular educational sessions concerning the study protocol. After random allocation, a copy of intervention protocol is attached to the patient's chart. For the duration of the study, random adherence monitoring will be made by the investigators. Regarding the outcome measures in the PACU, all nurses are well-trained in performing pain assessment using the verbal numeric rating scale (NRS), as this tool is used in everyday clinical practice in the study site.

2.11.6 | Concomitant care

In the PACU, nurses are advised to use protocolized analgesic treatment if patients experience APOP equal to NRS ≥ 4 . If pain is not controlled within 30 min, further rescue analgesia is up to the discretion of the responsible anesthesiologist.

2.12 | Measurement and definition of pain

Preoperative pain is evaluated via a questionnaire sent to the patient asking them if they have pain lasting more than 3 months (yes/no), pain during the last 2 weeks (yes/no). They are also asked about depression (yes/no) and fill out the PCS.²⁰

Acute postoperative pain is evaluated in the PACU where pain is measured repeatedly using NRS (0–10). The worst pain measured during the first 1.5 h is used for analyses. For secondary outcomes a cut-off for moderate- to severe APOP is set to 4.0.

Twenty-four hours after surgery, pain is evaluated with a questionnaire where the patient is asked to evaluate the worst pain experienced since they left the PACU (NRS 0–10) at rest and during movement. Quality of recovery is also assessed using QoR-15.²¹

Persistent postoperative pain is evaluated at 3 and 6 months post-surgery with another questionnaire where patients are asked to evaluate their present pain with NRS (0–10) at rest and during movement. (Figure 1). In POPIT PPOP is defined as NRS ≥ 1.0 at 3 or 6 months after surgery.

2.13 | Study outcomes

The primary outcome is defined as the mean difference in APOP_{PACU}, during the first 1.5 h after admission to the PACU, using NRS between groups (OFA vs. SOC, MAO vs. SOC) (Table 1).

2.13.1 | Secondary outcomes

Several pre-defined secondary outcomes will be analyzed:

1. Difference in mean APOP (APOP_{PACU}, APOP_{24h}) between pain-sensitive and pain-tolerant groups (SOC_{VCP ≥ 2.0} vs. SOC_{VCP ≤ 1.9}).
2. Difference in proportion of patients experiencing moderate to severe APOP (NRS ≥ 4.0) between pain-sensitive and pain-tolerant groups (SOC_{VCP ≥ 2.0} vs. SOC_{VCP ≤ 1.9}).
3. Difference in proportion of patients experiencing moderate to severe APOP in pain-tolerant group (VCP ≤ 1.9) (OFA vs. SOC).
4. Difference in proportion of patients experiencing moderate to severe APOP in pain sensitive group (VCP ≥ 2.0) (MAO vs. SOC).
5. Quality of recovery (QoR) after 24 h between groups (OFA vs. SOC, MAO vs. SOC, SOC_{VCP ≥ 2.0} vs. SOC_{VCP ≤ 1.9}).
6. Difference in mean PPOP (PPOP_{3mo}, PPOP_{6mo}) between groups (OFA vs. SOC, MAO vs. SOC).
7. Difference in proportion of patients experiencing post-operative nausea and vomiting (PONV) between OFA and SOC groups.
8. Correlation between VCP and PPOP_{3mo} and PPOP_{6mo}.
9. Correlation between PCS score and VCP or APOP.
10. Predictive value of pre-operative patient-centered risk factors (age, gender, preexisting pain, preexisting depression, VCP) for APOP/PPOP.

TABLE 1 Description of study outcomes coupled with associated hypotheses, outcome measure and plan for data analysis.

Outcome	Hypothesis	Outcome measure	Method for analysis
APOP PACU ^a	• Pain-sensitive patients experiences more APOP compared to pain-tolerant patients • It is possible to treat pain-sensitive patients more aggressively with MAO to improve APOP • It is possible to omit opioids in the preoperative setting for pain-tolerant patients and still achieve comparable APOP as SOC (non-inferiority)	• Mean difference NRS_{max} • Relative risk NRS	• Independent-samples T-test • Chi-square test
APOP 24 H ^b	• As for APOP_{PACU}	• Mean difference NRS (rest) • Mean difference NRS (movement) • Relative risk NRS (movement)	• Independent-samples T-Test • Chi-square test
PPOP 3 MO	• Pain-sensitive patients experiences more APOP compared to pain-tolerant patients. • It is possible to treat pain-sensitive patients more aggressively with MAO to improve APOP • It is possible to omit opioids in the preoperative setting for pain-tolerant patients and still achieve comparable APOP as SOC (non-inferiority)	• Mean difference NRS (rest) • Mean difference NRS (movement) • Relative risk NRS (movement)	• Independent-samples T-Test • Chi-square test
PPOP 6 MO	• As for PPOP_{3mo}	• Mean difference NRS (rest) • Mean difference NRS (movement) • Relative risk NRS (movement)	• Independent-samples T-Test • Chi-square test
PONV PACU ^a	• Patients randomized to OFA has less PONV compared to SOC	• Yes/No	• Chi-square test
PONV 24 H ^b	• Patients randomized to OFA has less PONV compared to SOC	• Mean difference NRS	• Independent-samples T-Test
PAIN CATASTROPHISING SCALE	• There is an association between PCS and APOP • There is an association between PCS and VCP	• Totalt scale points	• Pearson correlation coefficient
PAIN PREDICTION	• Pre-existing pain, pre-operative treatment for depression, age, gender, PCS score and VCP ≥2.0 are associated with more APOP/PPOP at every data time-point.	• Yes/no • Years • Female gender	• Multivariate logistic regression

^aOutcome timeframe is set between arrival at and discharge from the PACU.
^bOutcome timeframe is set between discharge from the PACU and the remaining hours of the first postoperative day.

11. Proportion of patients still on opioid analgesia 3 months after surgery, between groups (OFA vs. SOC, MAO vs. SOC, $\text{SOC}_{\text{VCP} \geq 2.0}$ vs. $\text{SOC}_{\text{VCP} \leq 1.9}$).

Secondary outcomes will, when appropriate, be reported as mean difference in NRS with confidence interval (CI), relative risk (RR) with CI, odds ratio (OR) with CI and Pearson correlation coefficient (r) with CI.

2.14 | Sample size

We consider a difference between groups of at least 1.5 NRS to be a clinically important difference. This change is also reasonable to use as superiority and non-inferiority limits.

For the pain-sensitive group ($\text{VCP} \geq 2.0$), we have a superiority design where we want to show an improvement in pain levels in the group getting extra treatment (MAO). In a previous study, the acute postoperative pain in the pain-sensitive group was normally distributed with a mean value of 5.8 VAS-units and standard deviation 2.8.¹⁷ With a probability of type-I error (α) of 0.05 and a power (1- β) of 80%, 56 experimental subjects and 56 control subjects will be needed to detect a difference of 1.5 NRS between groups.

In the pain tolerant group ($\text{VCP} < 2.0$), we will have a non-inferiority set-up where we accept a result with a difference in pain intensity of less than NRS units 1.5 to consider the OFA-arm a success. We thereby choose the non-inferiority limit, d , to be the largest difference that is clinically acceptable, so that a difference bigger than this would matter in practice. This difference should also not be greater than the smallest effect size that the standard treatment would be reliably expected to have compared with control. In a previous study, the acute postoperative pain in the pain-tolerant group was normally distributed with a mean value of 3.7 VAS-units and standard deviation 2.7.¹⁷ With d set to 1.5 and standard deviation 2.7, power 0.8, and probability of type-I error 0.05 we need 56 subjects in each group.

With four groups with 56 subjects in each we will need to include a total of 224 patients. To allow 20% dropout we will include 280 patients.

2.15 | Data management

Regarding retention we use the data management software Entermedic (Entergate®, Halmstad Sweden) where patient data and contact information are stored. An electronic chart will be kept for each included patient in the platform Entermedic. Information regarding drugs used during anesthesia will be registered by the PI in Entermedic as well as APOP_{PACU}. Acute postoperative pain between 1.5 and 24 h and PPOP after 3 and 6 months will be registered by the patient in Entermedic. We have programmed the software to send out reminder text messages with short enough intervals that data will not be inaccurate (i.e. 3 months follow up after 4 months etc.). When all data points are complete, the system stops sending out text reminders. As a back-up, investigators check for potential incomplete data once a day.

Entermedic is specifically designed for simplicity and security regarding data management. Ethical approval from the Swedish Ethical Review Authority is mandatory for using the service. Entergate® has their servers in Sweden and does not outsource data for any reason. Entermedic is also certified with the international standard regarding security standard (ISO 27000:1) and completely adapted to the European Union's demands on General Data Protection Regulation (GDPR). The service is also adapted to fit Swedish law for patient data reporting, holding and management (Department of social affairs number 2008:335, 2010:659 and 1985:562). Furthermore, Entermedic is also approved by the Swedish Medical Products Agency.

2.16 | Statistical methods

We assume that data are normally distributed and hence plan parametric testing. A test of normality will be performed in order to guarantee analysis with the correct test. The planned statistical tests, coupled with hypotheses, and outcomes are summarized in Table 1. Since outcome related to APOP and PPOP is continuous, and outcome is different in mean NRS-values between two groups, independent-sample T-Test will be used. Quality of recovery is measured on a continuous scale of 0 to 150 and will also be analyzed using the Independent T-test. Quality of recovery is also validated for ordinal and categorical groups (poor, moderate, good, and excellent). For this, a non-parametric test will be used (Mann-Whitney).²¹

Data regarding the secondary outcome of APOP/PPOP, where the patients are dichotomized into no/mild pain and moderate/severe pain, result in a 4×4 contingency table and analysis with the chi-square test.

We also want to establish if there is a correlation between PCS and APOP and PCS and VCP, respectively using the Pearson correlation coefficient. Lastly, in order to parse out risk-factors for moderate to severe APOP and PPOP, we will perform a multivariable logistic regression using APOP/PPOP as a dependent variable and pre-existing pain, PCS, and VCP as independent variables.

There will be no planned interim analysis or any other additional analyses.

2.16.1 | Analysis and missing data

To prevent attrition bias, and preserve the benefits of randomization, outcome data obtained from all participants are included in the data analysis, regardless of protocol adherence. Analysis of primary and secondary outcomes will be performed according to intention-to-treat principles.

2.17 | Monitoring

There is no appointed Data Monitoring Committee (DMC) since no interim analysis is planned and the risks of the study interventions are considered not higher than for the SOC-group. Furthermore, the

patients in POPIT are continuously monitored regarding pulseoximetry, blood pressure, heart rate, and rhythm, ensuring patient safety. It is also hospital policy that patients will not leave the PACU until certain safety criteria are fulfilled.

3 | ETHICS AND DISSEMINATION

3.1 | Research ethics approval

This RCT is designed according to the principles of the Consolidated Standards of Reporting Trials (CONSORT) statement. Ethical approval has been obtained from the Swedish Ethics Review Authority with identification number: Dnr 2020-06178. The research protocol has also been registered in clinical trials under the record 2020-06178.

3.2 | Protocol amendments

New approval will be sought out for amendments (eligibility criteria, allocation, and intervention protocol).

3.3 | Consent or assent

Participation will be voluntary, and consent can be rejected at any time. Informed consent from each participating patient will be registered in Entermedic. The nurses in the pre-operative preparation clinic are instructed to check for consent before proceeding with the pain-sensitivity stratification phase. If patients have not replied with their consent, the same nurses will give them enough time to read the study information before consent decisions.

3.4 | Declaration of interests

One of the primary investigators (PI) in POPIT (AP) was also PI in the study investigating VCP as a predictive tool for APOP.¹⁷ We have no other conflicts of interest to declare.

3.5 | Ancillary and post-trial care

The POPIT trial is a study focused on individualized patient care in anesthesia and analgesia. Drug adverse effects may occur in the short term and are well recognized by staff in the PACU, as all drugs are familiar to the staff. As described under "monitoring", it is hospital policy to treat and document all complications related to surgery. With this in mind, we have no further monitoring or planned ancillary care of the participants in the study population.

3.6 | Dissemination policy

The trial results will be communicated to participants, healthcare professionals, and the public via publication in medical journals. There are no planned publication restrictions.

Authorship is predefined after consensus agreement between authors (KM, JU, and AP) and demands equal contribution regarding managing POPIT and writing associated manuscripts. Authorship in POPIT uses the same criteria as recommended by the International Committee of Medical Journal Editors (ICMJE): 1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. 2. Drafting the work or reviewing it critically for important intellectual content. 3. Final approval of the version to be published. 4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Access to the full study protocol and masked data sets may be provided through personal communication with the authors.

4 | DISCUSSION

The PeriOperative Individualization Trial has as sole purpose to explore if individualizing anesthesia and analgesia depending on risk of pain can have an impact on pain outcome. Regarding potential practical and operational issues, there are several that we need to address. The large number of staff that work around the patients during their hospital stay needs to be constantly informed and reminded about the study protocol in order to guarantee optimal adherence. Since this study will run over a period of several years, we also need to take into account the migration of health care personnel, which challenges us as investigators to be consistent with the awareness of the ongoing study.

As seen with the COVID-19 pandemic, periods when the hospitals' capacity is challenged may arise, to a degree that might affect the inclusion rate, i.e. fewer hospital beds lead to a decreased surgical capacity. Since the patients eligible for POPIT are elective, this might affect inclusion rate further. We are, however, confident that the structure of the study protocol is solid enough to ensure consecutive patients to be included no matter the inclusion rate.

Opioid-free anesthesia is one of the interventions in POPIT. This is a relatively new technique in the anesthesia community as well as for our study center. In order to limit the risk for observer bias when using OFA, we implemented this technique and our protocol into clinical practice at least 6 months before study commencement. We evaluated the implementation process of OFA by letting all anaesthesia nurses and anesthesiologists fill out a survey where they anonymously could report their experience with the implementation process. The results indicated that the implementation process was conducted in sufficient time before starting the study.

Lastly, we would like to address the issue of venous cannulation site, as well as operator experience and their impact on VCP. Previous research has shown that the location site for venous cannulation can affect how

much pain patients experience under the procedure.²⁵ In our study we wanted to emphasize the clinical applicability of VCP, and we believe that limiting cannulation sites will affect external validity negatively. Regarding operator experience, each nurse in the pre-operative preparations clinic has at least five years working experience, which we believe is enough to keep inter-operator variability at a minimum.

AUTHOR CONTRIBUTIONS

Study conception and design: AP. Grant Holders: AP, KM. Data collection: KM, AP. Data analysis and interpretation of results: KM, AP, and JU. Draft manuscript preparation: KM, AP, and JU. Revision of manuscript and preparation of final version: KM, AP, and JU. All authors approved the final version of this manuscript.

ACKNOWLEDGEMENTS

We would like to acknowledge the staff at the preoperative clinic, surgical & anesthesia department as well as in the PACU, in Halmstad county Hospital, for their humility, preservation, and adherence in this study.

FUNDING INFORMATION

This study has been funded with grants from The Scientific council of Southern Sweden, Sparbanken, Research and Educational fund in Halmstad County and Region Halland.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during this study.

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REFERENCES

- Buvanendran A, Fiala J, Patel KA, Golden AD, Moric M, Kroin JS. The incidence and severity of postoperative pain following inpatient surgery. *Pain Med*. 2015;16(12):2277-2283.
- Pogatzki-Zahn EM, Segelcke D, Schug SA. Postoperative pain-from mechanisms to treatment. *Pain Rep*. 2017;2(2):e588.
- Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet*. 2008;372(9633):139-144.
- Gerbershagen HJ, Pogatzki-Zahn E, Aduckathil S, et al. Procedure-specific risk factor analysis for the development of severe postoperative pain. *Anesthesiology*. 2014;120(5):1237-1245.
- Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618-1625.
- Coley KC, Williams BA, DaPos SV, Chen C, Smith RB. Retrospective evaluation of unanticipated admissions and readmissions after same day surgery and associated costs. *J Clin Anesth*. 2002;14(5):349-353.
- Morrison SR, Magaziner J, McLaughlin MA, et al. The impact of postoperative pain on outcomes following hip fracture. *Pain*. 2003;103(3):303-311.
- Thomas MA. Pain management – the challenge. *Ochsner J*. 2003;5(2):15-21.
- Cousins MJ, Power I, Smith G. 1996 Labat lecture: pain – a persistent problem. *Reg Anesth Pain Med*. 2000;25(1):6-21.
- Joshi GP, Ogunnaik BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. *Anesthesiol Clin N Am*. 2005;23(1):21-36.
- Bonnie RJ, Kesselheim AS, Clark DJ. Both urgency and balance needed in addressing opioid epidemic: a report from the National Academies of Sciences, Engineering, and Medicine. *JAMA*. 2017;318(5):423-424.
- Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E. Chronic opioid use after surgery: implications for perioperative management in the face of the opioid epidemic. *Anesth Analg*. 2017;125(5):1733-1740.
- Bayman EO, Parekh KR, Keech J, Larson N, Vander Weg M, Brennan TJ. Preoperative patient expectations of postoperative pain are associated with moderate to severe acute pain after VATS. *Pain Med*. 2019;20(3):543-554.
- Björström MF, Irwin MR, Bodelsson M, Smith MT, Mattsson-Carlgen N. Preoperative sleep quality and adverse pain outcomes after total hip arthroplasty. *Eur J Pain*. 2021;25(7):1482-1492.
- Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology*. 2009;111(3):657-677.
- Kalkman CJ, Visser K, Moen J, Bonsel GJ, Grobbee DE, Moons KG. Preoperative prediction of severe postoperative pain. *Pain*. 2003;105(3):415-423.
- Persson AK, Pettersson FD, Dyrehag LE, Åkeson J. Prediction of postoperative pain from assessment of pain induced by venous cannulation and propofol infusion. *Acta Anaesthesiol Scand*. 2016;60(2):166-176.
- Persson AKM, Åkeson J. Prediction of acute postoperative pain from assessment of pain associated with venous cannulation. *Pain Pract*. 2019;19(2):158-167.
- Peng F, Li Y, Ai Y, Yang J, Wang Y. Application of preoperative assessment of pain induced by venous cannulation in predicting postoperative pain in patients under laparoscopic nephrectomy: a prospective observational study. *BMC Anesthesiol*. 2020;20(1):86.
- Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess*. 1995;7(4):524-532.
- Lyckner S, Boregard IL, Zetterlund EL, Chew MS. Validation of the Swedish version of Quality of Recovery score -15: a multicentre, cohort study. *Acta Anaesthesiol Scand*. 2018;62(7):893-902.
- Delgado DA, Lambert BS, Boutris N, et al. Validation of digital visual analog scale pain scoring with a traditional paper-based visual analog scale in adults. *J Am Acad Orthop Surg Glob Res Rev*. 2018;2(3):e088.
- Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth*. 1991;67(1):41-48.
- Gelb AW, Morriss WW, Johnson W, Merry AF, International Standards for a Safe Practice of Anesthesia Workgroup. World Health Organization-World Federation of Societies of Anaesthesiologists (WHO-WFSA) International Standards for a Safe Practice of Anesthesia. *Can J Anaesth*. 2018;65(6):698-708.
- Goudra BG, Galvin E, Singh PM, Lions J. Effect of site selection on pain of intravenous cannula insertion: a prospective randomised study. *Indian J Anaesth*. 2014;58(6):732-735.

How to cite this article: Mogianos K, Undén J, Persson A. Effect of individualized anesthesia and analgesia on postoperative pain in patients stratified for pain sensitivity: A study protocol for the PeriOperative individualization trial randomized controlled trial. *Acta Anaesthesiol Scand*. 2024; 68(10):1532-1540. doi:[10.1111/aas.14487](https://doi.org/10.1111/aas.14487)

Paper III





Original Contribution



The additive effect of esketamine and clonidine in patients at high risk for acute postoperative pain undergoing laparoscopic surgery: A randomised controlled trial

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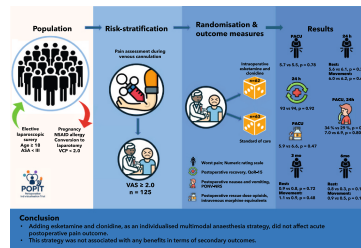
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HIGHLIGHTS

- Adding esketamine and clonidine did not improve APOP in patients predicted as high-risk for postoperative pain.
- Adding esketamine and clonidine did not improve recovery or PONV in patients predicted as high-risk for postoperative pain.
- The pursuit for individualised anaesthesia and analgesia needs further refinement.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:

NMDA-antagonism
Alpha-2-agonism
Pain sensitivity
Postoperative pain

ABSTRACT

Objective: To evaluate if adding esketamine and clonidine has positive effects on postoperative pain, postoperative nausea and vomiting, and quality of recovery in patients who are at high risk for postoperative pain.

Design: Patient- and assessor-blinded, superiority, randomised controlled trial.

Setting: Single centre between 2022 and 2024.

Patients: 125 adult patients, ASA I–II, planned for elective laparoscopic surgery and risk-classified as high risk of pain, based on perceived pain associated with venous cannulation.

Intervention: Patients were randomised to either an anaesthesia protocol, including an intravenous bolus of esketamine (0.25 mg.kg⁻¹) after induction and clonidine (1 µg.kg⁻¹) during maintenance phase (EC), or standard of care (SOC) no esketamine or clonidine included.

Measurements: Primary outcome: worst pain intensity in the PACU. Secondary outcomes: worst pain, and proportion having NRS ≥ 4, at 24 h (during rest and movement), worst pain and proportion having NRS ≥ 1, at 3- and 6-months (during rest and movement), postoperative recovery at 24 h, PONV in the PACU and at 24 h. Rescue dose opioids in the PACU was an exploratory outcome.

Results: Worst pain scores in the PACU were 5.7 in the EC group and 5.5 in SOC group (P = 0.78). After 24 h, no difference in postoperative pain (rest; 5.8 vs 6.1, P = 0.35, movement; 6.1 vs 6.2, P = 0.68), postoperative

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<https://doi.org/10.1016/j.jclinane.2025.112059>

Received 13 May 2025; Received in revised form 19 October 2025; Accepted 26 October 2025

Available online 4 November 2025

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recovery ($P = 0.92$) or PONV ($P = 0.80$) was found. Proportion of patients with NRS ≥ 4 in the PACU was 50 % vs 48 % ($P = 0.55$) and at 24 h 73 % vs 81 % at rest ($P = 0.27$) and 76 % vs 81 % during movement ($P = 0.50$). Rescue opioids in the PACU were similar (5.9 mg vs 6.6 mg, $P = 0.47$). There were no differences in persistent pain at 3 or 6 months at rest ($P = 0.72$, $P = 0.12$) or movement ($P = 0.48$, $P = 0.18$).

Conclusion: Adding esketamine and clonidine, as an individualised multimodal anaesthesia strategy, did not influence acute or persistent postoperative pain, early recovery, need of rescue opioids or PONV in patients, who were assessed as high risk for APOP.

1. Introduction

Preventing and treating acute postoperative pain (APOP) is still a major challenge despite extensive research. If neglected, APOP can cause complications for patients and lead to strain on the healthcare system. Some of these complications are well-known, such as pulmonary complications, delayed ambulation, and delayed recovery [1–4].

Despite advancements in surgical techniques and recovery protocols, around 80 % of patients still experience APOP, with 50 % facing moderate to severe pain [5–7]. Research suggest that individual risk factors significantly influence the development of both APOP and persistent postoperative pain (PPOP). Some of these independent risk factors include young age, female gender, smoking history, anxiety, depression, preoperative pain and opioid use [8–12]. As a result, there has been a shift from procedure-specific to personalised treatment protocols to manage APOP and reduce PPOP [13,14]. Predicting a patient's specific risk, and thereby providing an individualised approach, may facilitate management of these patients.

Multimodal anaesthesia and analgesia involve using different drugs to target various pain pathways, helping to prevent neuroplastic changes that cause APOP and PPOP [15]. Esketamine is the S-enantiomere to ketamine that binds more strongly to NMDA receptors and has been shown to improve postoperative pain outcomes [16]. Similarly, clonidine, an α_2 -agonist, also enhances pain relief for patients under general anaesthesia [17,18]. Combining these two drugs is now common practice for managing severe postoperative pain, as evidence suggests they work well together to enhance pain relief [6] and are recommended as part of a multimodal strategy [6,19].

Pain associated with peripheral venous cannulation (VCP) can predict risk of APOP. Patients who rate their VCP at 2.0 or higher on the Visual Analog Scale (VAS) have 3.4 times higher odds of experiencing moderate to severe postoperative pain after laparoscopic cholecystectomy [20] and 3.5 times higher odds after laparoscopic nephrectomy [21]. In a mixed group of patients and surgeries, these odds were 1.7 times higher [22]. In individualised perioperative medicine, it is appealing to use a simple clinical tool to classify patients for their individual risk for postoperative pain but also be able to intervene and attempt to ameliorate this pain.

In the pragmatic PeriOperative Individualisation Trial (POPIT) [23] we have used VCP to classify patients as high or low risk for APOP. The primary objective of this trial was to examine if an individualised anaesthesia and analgesia regime can affect postoperative pain in patients stratified for pain sensitivity. The trial includes two different RCTs. The main goal of this study was to determine if adding esketamine and clonidine to the anaesthetic and analgesic regimen as a multimodal approach is superior to standard of care, in terms of pain and pain-related outcomes, in patients identified as high risk for APOP. As secondary outcomes, we also investigated other benefits like nausea, quality of recovery and persistent pain.

2. Methods

2.1. Study design and ethics

This single-centre clinical trial employed a randomised, controlled, parallel-group design with blinding of both participants and objective

outcome assessors. Ethical approval was granted by the Swedish Ethical Review Authority (approval ID: 2020–06178). To ensure transparency, the study protocol and methodology were made publicly available prior to trial commencement [24]. The trial was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) under the identifier NCT04751812, with the registration dated February 9, 2021.

The protocol adheres to the ethical principles of the declaration of Helsinki and follow CONSORT guidelines.

2.2. Patient recruitment

Inclusion criteria: elective laparoscopic surgery, age > 18 years, ASA class $< III$, ability to understand information in Swedish. Exclusion criteria: refusal to participate, withdrawal of consent, pregnancy, NSAID allergy, and conversion to open abdominal surgery.

Patients meeting eligibility requirements received a text message containing study information approximately one week prior to their procedure. After providing written informed consent, participants submitted baseline data, which included sociodemographic information, history of preoperative pain lasting longer than three months, current use of analgesic medications, and any diagnosis or treatment for depression.

Participants also completed the Pain Catastrophizing Scale (PCS), which consists of 13 items assessing emotional responses to pain. Each item is rated on a scale from 0 (not at all) to 4 (all the time), yielding a total score ranging from 0 to 52 [25]. On the day of surgery, current pain intensity was measured using a Numeric Rating Scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain).

2.3. Measurement of pain sensitivity

On the day of surgery, patients were differentiated into pain-sensitivity cohorts using VCP during peripheral venous cannula placement. A cannula size 0.9–1.1 mm was placed at a non-specific site on the upper limb. All insertions were carried out by nurses with a minimum of three years of clinical experience. Procedural pain was assessed using a visual analogue scale from 0.0 (no pain) to 10.0 (worst pain imaginable) [26]. Based on their VCP scores, patients were assigned to one of two cohorts: those scoring ≥ 2.0 were classified as high-risk, while those scoring < 2.0 were placed in the low-risk group. The threshold of 2.0 was determined in advance, informed by findings from previous studies [20–22].

2.4. Randomisation method and blinding

This study was part of the POPIT [24], in which two independent randomised controlled pathways were established based on pain sensitivity, as determined by the VCP assessment. This stratification resulted in two distinct cohorts: high-risk and low-risk for postoperative pain. Randomisation was then performed separately within each cohort. The present article reports findings exclusively from the high-risk cohort.

Participants were randomly assigned in a 1:1 ratio to receive either EC or SOC, using a sequentially generated allocation process (see Fig. 1). The randomisation procedure is described in detail in the prepublished study protocol [24]. Patients were blinded to their group assignment. Randomisation sequences were generated by nurses in the preoperative

clinic, who also enrolled participants and allocated them to their respective interventions. Anaesthesiologists, anaesthesia nurses and post anaesthesia care nurses, responsible for administering anaesthetic and analgesic drugs, were not blinded to the interventions for safety reasons. Primary (APOP_{PACU}) and secondary outcome (PONV) assessments were conducted by blinded assessors (face-to-face) in the post anaesthesia care unit (PACU) while later outcomes were self-reported by participants themselves.

2.5. Study interventions

2.5.1. Standard of care augmented by the addition of esketamine and clonidine (EC)

Etoricoxib 120 mg, paracetamol 1500 mg, oxycodone 10 mg (5 mg if age > 75) and ondansetron 8 mg was given orally in the preparations before surgery. Induction of anaesthesia was conducted using propofol and remifentanyl, with anaesthesia maintained with either propofol according to a target controlled infusion protocol (Marsh model), or sevoflurane, both together with remifentanyl using target control infusion (Minto model). Betamethasone 4 mg was given intravenously after induction. After airway establishment, patients were given an i.v. bolus of esketamine 0.25 mg.kg⁻¹. At the start of surgery, the surgeon administered 20 ml of Ropivacaine (7.5 mg/ml) into the entrance holes of the laparoscopy for all patients. Postoperative analgesia was standardised

using i.v. oxycodone 0.1 mg.kg⁻¹ and clonidine 1 µg.kg⁻¹ before terminating general anaesthesia. Paracetamol 1000 mg was given every 6 h. Rescue analgesia, with oxycodone i.v. was provided in the PACU if NRS ≥ 4.

2.5.2. Standard of care

This perioperative strategy aligns with typical international and national recommendations [27]. Etoricoxib 120 mg, paracetamol 1500 mg, oxycodone 10 mg (5 mg if age > 75) and ondansetron 8 mg were given orally before surgery. General anaesthesia was induced with propofol and remifentanyl, maintained with either propofol (TCI, Marsh model), or sevoflurane, both with remifentanyl (TCI, Minto protocol). The choice between sevoflurane and propofol as the GABA_A-agonist was determined entirely by technical intraoperative considerations. Specifically, robotic-assisted laparoscopies were performed using sevoflurane, as intravenous access is less readily available during these procedures. In contrast, non-robotic laparoscopies allowed for the use of propofol via TCI. At the start of surgery, the surgeon administered 20 ml of Ropivacaine (7.5 mg/ml) into the entrance holes of the laparoscopy for all patients. Betamethasone 4 mg was given i.v. at induction. Postoperative analgesia included i.v. oxycodone 0.1 mg.kg⁻¹, before terminating general anaesthesia, and paracetamol 1000 mg every 6th hour. Rescue analgesia, with oxycodone i.v. was provided in the PACU if NRS ≥ 4.

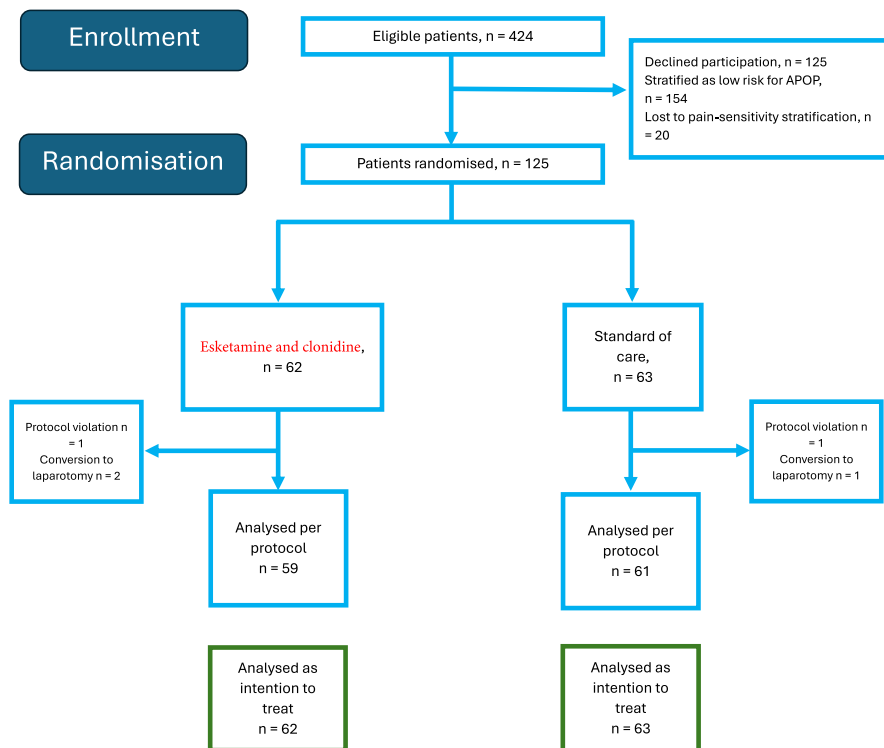


Fig. 1. Flow-chart depicting the consecutive flow to which the participating patients were subjected to both as intention-to-treat and as per protocol. APOP, acute postoperative pain; PACU, Post anaesthesia care unit; PONV, postoperative nausea and vomiting; POD1, postoperative day one; PPOP, persistent postoperative pain; QoR, quality of recovery.

2.6. Postoperative outcome assessment and data collection

In the PACU patients were asked to grade their pain according to the verbal NRS for pain. The 11-point numeric scale pain-assessment tool is commonly used and allow participants to rate their subjective pain level; a score of 0 represents no pain, a score of 1–3 mild pain, a score of 4–6 moderate pain and a score of 7–10 represents severe pain [28]. Acute postoperative pain in the PACU (APOP_{PACU}) was defined as the worst pain score during the first 90 min from arrival to the PACU. Moderate- to severe APOP was defined as NRS ≥ 4 in the PACU and after 24 h.

On the first postoperative day (POD1) the participating patients received a text message containing follow-up questions regarding worst pain score in NRS after 24 h (APOP_{POD1}) during both rest and movement, thus making this outcome self-reported. Movement as this time-point was defined as ambulation to the edge of the bed.

As patient centred functional outcome, we used the 15-item Quality of recovery (QoR-15) evaluated at POD1 [29]. The QoR-15 contains 15-items, where participants are asked to rate their recovery on a 11-point scale ranging from 0 to 10 for each item representing an evaluation of both physical and mental health status [30]. The total amount of points was summed up to a total score ranging from 0 to 150, where 150 represents excellent health status. The QoR-15 has been validated in the Swedish population [31].

Postoperative nausea and vomiting were assessed, after 24 h (PONV_{POD1}), using the 13th item in the QoR-15; "Have you been feeling nauseous or vomited during the last twenty-four hours? On a scale from 0 to 10, where 10 = not at any time (excellent) and 0 = during the whole time (bad)" (PONV_{POD1}). Dichotomous data, e.g. if the patient had PONV or not, was also gathered and registered in the PACU (PONV_{PACU}).

Postoperative opioid requirements were defined as the rescue dose of opioid, calculated to morphine milligram equivalents (MME), that the patient was given after awakening from general anaesthesia until discharge from the PACU. The intraoperative dose, given as post-operative analgesia (oxycodone 0.1 mg.kg⁻¹) was not included in this outcome. MME was calculated using an opioid converting tool, to convert all opioids given into intravenous oxycodone. Subsequently, this number was multiplied by the factor 1.5 to obtain the amount of intravenous morphine milligram equivalents [32].

Persistent postoperative pain (PPOP) was evaluated with NRS during rest and movement (walking) at 3 and 6 months after surgery (PPOP_{3mo}, PPOP_{6mo}). PPOP was defined as present if having a NRS ≥ 1 at 3 and 6 months, either during movement or rest.

2.7. Study outcomes

Primary outcome was difference in worst APOP_{PACU} score between groups. Predefined secondary outcomes were proportion of patients experiencing moderate- to severe APOP_{PACU} (NRS ≥ 4), difference in worst APOP_{POD1} score at rest and during movement, difference in postoperative recovery, QoR-15 total score, after 24 h (QoR_{POD1}), difference in worst PPOP score at rest and during movement after 3- and 6-months respectively (PPOP_{3mo}, PPOP_{6mo}), difference in proportion of patients experiencing NRS ≥ 1 after 3 and 6 months, difference in proportion of patients experiencing PONV in the PACU (PONV_{PACU}) and difference in worst PONV-NRS score after 24 h (PONV_{POD1}). As a non-predefined exploratory outcome, difference in total dose rescue opioids in the PACU was evaluated.

2.8. Sample size and statistical analysis

A difference of at least 1.5 units on the Numeric Rating Scale (NRS) between groups was considered clinically meaningful and served as the predefined threshold for superiority. We wanted the effect to matter clinically. Although no firm evidence exists in the perioperative population, data from non-operative research suggest that a pain reduction of 30 % is meaningful to patients on a population level [33,34].

Based on prior research, the average APOP score was normally distributed with a mean of 5.8 NRS-units and SD 2.8 [20]. Using these parameters, and assuming an alpha level of 0.05 and a beta level of 0.2 (corresponding to 80 % power), the required sample size was calculated to be 56 participants per group (EC and SOC), resulting in a total of 112 subjects. To account for an anticipated 20 % dropout rate, the final target sample size was set at 140 patients.

A *Shapiro-Wilks* test was performed, which concluded that the continuous data for primary outcome was normally distributed. Furthermore, a *Levene's test* showed that there was no variance between groups in primary outcome. As the primary aim was to detect a difference in APOP_{PACU} for EC compared to SOC group, a two-sided *Independent t-test* was used for hypothesis testing. For secondary outcomes, continuous data for PONV_{POD1}, QoR_{POD1} and opioid consumption were analysed using two-sided *Independent t-test*. Dichotomous outcomes were analysed using a *Chi-Square test*.

Group comparisons are presented as P – values, with margin for type 1 error set to 0.05, in conjunction with the 95 %CI. Standard deviation is used as statistical dispersion for all mean values.

An intention-to-treat (ITT) analysis was conducted for primary, secondary and explanatory outcomes, with per protocol results in supplementary materials.

3. Results

3.1. Descriptive data and population

Patients were recruited from March 2022 to February 2024. Out of 424 eligible patients, 125 declined, leaving 299 patients for risk assessment (Fig. 1). Twenty patients who fulfilled inclusion criteria and had given informed consent, did not undergo pain assessment during venous cannulation and were not included. 154 patients were classified as low risk (VCP < 2.0) and of 125 patients were classified as high risk (VCP ≥ 2.0). These 125 patients were randomised to EC (n = 62) or SOC (n = 63) groups. In accordance with the data-analysis plan, data was analysed as intention to treat (Fig. 1). All 125 patients were analysed for primary (APOP_{PACU}), secondary (PONV_{PACU}), and non-predefined exploratory (opioid consumption) outcomes. Seven patients had missing data at POD1, leaving 118 for secondary/exploratory outcomes analysis (QoR_{POD1}, PONV_{POD1}, APOP_{POD1}, opioid consumption). Three of these 7 provided data for PPOP (n = 121).

Demographic data, including factors that may influence pain (age, BMI, gender, preoperative pain condition and levels, depression, PCS), are presented in Table 1 (Table 1).

3.2. Types of surgery

Patients underwent various laparoscopic procedures, primarily colorectal and gynaecologic (Table 1).

3.3. Acute postoperative pain PACU

APOP_{PACU} was 5.7 (± 2.7) and 5.5 (± 2.8) NRS units for EC and SOC groups, respectively. This resulted in a non-significant difference of 0.2 (95 %CI – 0.8 to 1.1, $P = 0.78$) (Table 2) (Fig. 2). There was no difference between groups in proportion of patients who experienced NRS ≥ 4 in the PACU ($P = 0.55$) (Table 2).

3.4. Acute postoperative pain at 24 h

APOP_{POD1} was similar between EC and SOC groups, both at rest (5.6, ± 2.5 and 6.1 ± 2.6 respectively) and during movement (6.0 ± 2.5 and 6.2 ± 2.4 respectively) (Fig. 2), which resulted in a difference of 0.5 (95 % CI – 1.4 to 0.5, $P = 0.35$) and 0.2 (95 % CI – 1.1 to 0.7, $P = 0.68$) respectively (Table 2). There was no difference in proportion of patients who experienced moderate to severe APOP_{POD1}, neither at rest (73 % vs

Table 1
Baseline characteristics of both intervention groups. Values are mean (SD) or proportion [%].

	Esketamine and clonidine n = 62	Standard of care n = 63
Age	53 (± 16)	53 (± 16)
Female gender; n	52 [84]	56 [89]
Body mass index; kg/m ²	26.7 (± 5.4)	27.1 (± 5.3)
ASA; n		
I	27 [44]	24 [38]
II	35 [56]	39 [62]
Preoperative pain; n	32 [52]	35 [56]
Current pain at day of surgery; NRS	1.6 (± 2.3)	1.9 (± 2.4)
Preoperative depression; n	9 [15]	8 [13]
PCS; points	16 (± 11)	15 (± 10)
VCP; NRS	3.7 (± 1.5)	3.8 (± 1.9)
Type of surgery; n		
Rectum resection	1 [1.6]	6 [9.5]
Hemicolectomy	5 [8.1]	3 [4.8]
Sigmoidectomy	8 [12.9]	6 [9.5]
Cholecystectomy	12 [19.4]	16 [25.4]
Hernia repair	2 [3.2]	1 [1.6]
Adrenal resection	0 [0.0]	1 [1.6]
Ovarian cyst enucleation	4 [6.5]	5 [7.9]
Uni-/bilateral salphingo-oophorectomy	11 [17.7]	11 [17.5]
Hysterectomy	19 [30.6]	14 [22.2]

ASA; American society of anaesthesiologists' physical status classification system, NRS; Numeric rating scale, PCS; Pain catastrophizing scale, VCP; Venous cannulation pain.

81 %, $P = 0.27$) or during movement (76 % vs 81 %, $P = 0.50$).

3.5. Postoperative nausea and vomiting in the PACU and at 24 h

Thirty-four percent and 29 % of patients experienced PONV in EC and SOC groups respectively ($P = 0.53$). At POD1n EC group reported a PONV-NRS of 7.0 (± 3.3) compared to patients in SOC who had a PONV-NRS of 6.9 (± 3.3), corresponding to a difference of 0.1 (95 % CI -1.1 to 1.4, $P = 0.80$) (Table 2).

3.6. Postoperative recovery

QoR_{POD1} was 93 (± 23) and 94 (± 23) for EC and SOC, respectively, with a mean difference of 1.0 (95 %CI -9.0 to 8.0, $P = 0.92$) (Table 2). For both groups, these values equate to moderate recovery in the validated group-based version of QoR-15 [31].

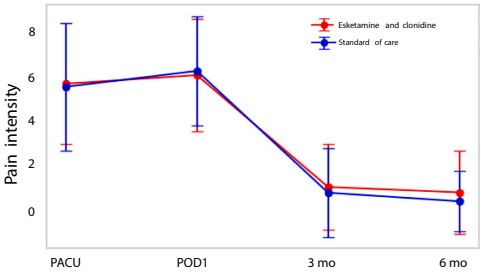


Fig. 2. Pain trajectory showing pain (NRS) at different time-points during movement (POD1, 3mo, 6mo). Whiskers for each time-pint measure represent the standard deviation for each group. PACU, post anaesthesia care unit; POD1, postoperative day 1.

Table 2
Primary and secondary outcome data from intraoperative and postoperative variables of both intervention groups, as *intention-to-treat*, in patients categorised as high risk for postoperative pain. Values are mean (SD) or proportion [%].

	Esketamine and clonidine n = 62	Standard of care n = 63	Difference	95 % CI	P-value
APOP _{PACU} ; NRS	5.7 (± 2.7)	5.5 (± 2.8)	0.2	-0.8 - 1.1	0.78
APOP _{PACU} ; NRS ≥ 4; n	50 [81]	48 [76]	2 [5]		0.55
PONV _{POD1} ; PONV-NRS	7.0 (± 3.3)	6.9 (± 3.3)	0.1	-1.1 - 1.4	0.80
PONV _{PACU} ; n	21 [34]	18 [29]	3 [5]		0.53
QoR _{POD1} ; points	93 (± 23)	94 (± 23)	1	-9-8	0.92
PPOP _{3mo} ; NRS					
Rest	0.9 (± 1.7)	0.8 (± 1.8)	0.1	-0.5 - 0.7	0.72
Movement	1.1 (± 1.9)	0.9 (± 2.0)	0.2	-0.4 - 0.9	0.48
PPOP _{3mo} ; NRS ≥ 1.0; n					
Rest	20 [34]	18 [30]	2 [4]		0.61
Movement	23 [39]	17 [28]	6 [11]		0.20
PPOP _{6mo} ; NRS					
Rest	0.8 (± 1.8)	0.3 (± 1.0)	0.5	-0.1 - 1.0	0.12
Movement	0.9 (± 1.8)	0.5 (± 1.3)	0.4	-0.2 - 1.0	0.18
PPOP _{6mo} ; NRS ≥ 1.0; n					
Rest	11 [18]	8 [13]	3 [5]		0.43
Movement	16 [26]	12 [20]	4 [6]		0.36

APOP; Acute postoperative pain, NRS; numeric rating scale, PACU; post-anaesthesia care unit, PONV; postoperative nausea and vomiting, POD1; postoperative day 1, PPOP; Persistent postoperative pain, QoR; Quality of recovery.

3.7. Postoperative rescue dose opioids

The amount of rescue opioids in the PACU was 5.9 mg (± 4.9) for EC and 6.6 mg (± 5.6) for SOC group, which resulted in a difference of 0.7 mg (95 %CI -2.5 to 1.2, $P = 0.47$).

4. Discussion

In this study, adding esketamine and clonidine to standard anaesthesia failed to improve pain outcomes in patients assessed as high risk for APOP undergoing laparoscopic surgery. In light of current clinical practice, with high demands on fast recovery, it is desirable to identify patients in need of extra analgesia. High-risk patients, who are more resource-demanding, would in theory benefit from a multimodal anaesthesia strategy. In everyday practice, it may be difficult to decide who and how to treat and, equally important, not to overtreat. As a reaction to this, evidence related to perioperative pain prediction is increasing [35–38]. Instinctively, one would treat those in greatest need, i.e. those with higher risks of post-operative pain. The secondary and explorative outcomes in this study reflect various aspects of post-operative pain, both direct and indirect. While these outcomes could indicate potential benefits, our findings did not show a positive association.

Multimodal anaesthesia and analgesia, specifically adding clonidine and esketamine, has previously been shown to improve pain outcomes and to reduce the need for rescue opioids [16,17,39,40]. Our intervention strategy for high-risk patients was chosen based on pharmacodynamic properties and drug-synergy, with esketamine and clonidine working well together [6,41]. Furthermore, in the multidisciplinary consensus statement from the Association of Anaesthetists and the British Pain Society they recommend using multimodal analgesia including paracetamol, NSAIDs, α -2 adrenergic agonists, NMDA-antagonists and corticosteroids [19]. Considering the concept of multimodal anaesthesia, several other well-known drugs could have been considered. Lidocaine, with its sodium-channel interference and anti-inflammatory properties, has been used in anaesthesia for many years [42]. The use of Lidocaine is still not common practice in many hospitals in Sweden and it is not recommended in the British guidelines mentioned previously [19]. Dexmedetomidine, a pharmacologic relative of clonidine, has also gained significant interest in perioperative medicine. Interestingly, some studies suggest that dexmedetomidine may be superior to remifentanyl and potentially more advantageous than clonidine in terms of postoperative pain management [17,43]. Magnesium, sometimes seen as a more pure NMDA-antagonist when compared to esketamine, has been shown to be efficacious in terms of APOP [44]. In our study, we cannot rule out that magnesium, dexmedetomidine or lidocaine could have been viable alternatives, or adjuncts, to esketamine or clonidine to improve pain outcomes for these high-risk patients.

There are many pharmacological options for individualising anaesthesia and analgesia, but challenges remain with dosing, drug synergism, and administration methods. Modulating the NMDA receptor has well-documented effects on postoperative pain [39]. Despite recent discussions suggesting that continuous infusion of ketamine is advantageous to intermittent boluses, a meta-analysis of 39 clinical trials failed to conclude this superiority [45]. Alpha-2 agonism has opioid sparing and analgesic effects [17]. In a recent meta-analysis, both clonidine and dexmedetomidine were shown to be efficacious regarding pain outcomes, with dexmedetomidine seemingly more advantageous [17].

4.1. Strengths and limitations

This study has several strengths, with the randomised design being the most significant. All patients received similar management, except for the interventions they were randomised to. A superiority margin of 1.5 NRS units was selected to represent a difference considered clinically

relevant, rather than merely statistically significant. While smaller variations might reach statistical significance, they are unlikely to reflect changes that are noticeable to patients or that would influence clinical decision-making. Selection bias is considered low and follow-up rates were above 90 %. Our sample size calculations included a minimum of 112 patients but our goal was to include 140 patients to account for 20 % drop-out. However, we only included 125 patients but we had complete data for primary outcome; hence the study was adequately powered.

The limitations in this study are several. The study-population was limited to laparoscopic surgery; hence the potential impact of the intervention may differ in other types of surgery. Besides individual risk factors, earlier studies have identified procedure-related risk factors such as large skin incisions, nerve damage, time in theatre and extensive transfusions as having impact on postoperative pain [46]. The advances in procedure technique and safety have diverged from the magnitude of acute pain outcomes, the latter still being high and frequent. This might suggest that procedure-specific factors in APOP play a lesser role than previously thought. Subsequently, laparoscopic surgery is a good surgical model when striving to standardise the surgical-specific factors and it is a surgical procedure associated with high pain outcomes [47,48]. In addition, limiting the population to ASA I – II would also affect external validity negatively. Furthermore, APOP score might have been different in both groups if a broader patient selection were applied as ASA $\geq$ III is associated with more APOP [49].

We recognise that the levels of APOP, both in the PACU and during the first 24 h, are high. As shown by Gerbershagen et al with data from the QUIPS registry, even after laparoscopic surgery, worst pain levels tend to be remarkably high [50]. In the present cohort, possible explanations for the high APOP may be the relatively young age, the predominance of female patients and an unexpected high number of patients with preoperative pain, factors that should make them at high risk for postoperative pain. Secondary outcomes were self-reported (regarding previous 24 h of symptoms) by patients which may involve recall bias.

Venous cannulation, as a method for pain sensitivity classification, is both scientifically proven and clinically applicable to patients scheduled to undergo general anaesthesia [20–22]. Despite these aspects, it is unknown whether other methods may have yielded different results. One example is the cut-off value ($VAS \geq 2.0$ / $VAS < 2.0$), which may have underperformed in the POPIT cohort. Patients in this study appeared to be at an overall higher risk compared to the general population, i.e. female gender and preoperative pain were over-represented. In practical terms, the $VCP \geq 2.0$ threshold may have failed to accurately identify high-risk individuals, mistakenly classifying some as low-risk. The implication in this study is not as relevant compared to that of the low-risk cohort, since patients in this study were more likely to be truly at high-risk of APOP.

To enhance generalizability, we allowed cannulation at any site on the upper extremity. This may have influenced risk allocation, as venous cannulation on the dorsal hand is typically more painful than in the antecubital fossa. Additionally, we did not collect data on the number of attempts required for successful cannulation, which could have impacted cohort allocation (high-risk vs low-risk). However, the use of highly skilled specialist nurses likely mitigated this issue by minimizing the number of attempts and ensuring a consistently high level of procedural success.

A systematic review of preoperative bedside methods for predicting postoperative pain concluded that clinically derived approaches, those thought to reflect individual pain sensitivity, currently appear most promising [51]. In contrast, other testing modalities, such as quantitative sensory testing, genetic mapping, and serologic biomarkers, have yielded inconclusive results and are each associated with specific limitations. There is growing interest in real-time intraoperative monitoring of nociception as a potential tool to individualise pain management. However, these technologies are not yet ready for widespread clinical

implementation.

Concerning doses and modalities of administration in the intervention, we cannot rule out that infusion of esketamine, and using dexmedetomidine instead of clonidine, would have rendered a different outcome as discussed previously.

Lastly, the primary outcome (APOP_{PACU}) may not be optimal, and was selected based on previous research on VCP. However, we present results regarding self-evaluated pain at several time-points plus other surrogates for pain and functional outcome (postoperative recovery, pain during movement, opioid consumption, PACU length of stay) which together present a solid evaluation of the patients' postoperative pain experiences. Furthermore, there is no consensus regarding which timepoints to use for evaluation in research. We used several different timepoints in this study; immediate postoperative, 24 h, 3 months and 6 months. To further improve validity, we used QoR-15 for evaluation of health status at 24 h [30]. Ideally, patient-centred outcomes, such as patient satisfaction, should be more extensively evaluated, including in studies such as this [52,53].

5. Conclusion

Adding esketamine and clonidine, as an individualised multimodal anaesthesia strategy, did not affect acute or persistent postoperative pain, early recovery, need of rescue opioids or PONV in patients, who were assessed as high risk for APOP.

CRedit authorship contribution statement

Krister Mogianos: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Josefine Holgersson:** Writing – review & editing, Investigation, Formal analysis. **Johan Undén:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization. **Anna K.M. Persson:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Funding sources

This work was supported by the Research Council, Halmstad Halland County; and the Southern Healthcare Region Sweden.

Declaration of competing interest

None of the authors have any conflict of interest to declare.

Acknowledgement

We want to direct a special thanks to the nurses, in the preoperative preparations clinic, whose engagement in the recruitment process never failed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jclinane.2025.112059>.

References

- [1] Coley KC, Williams BA, DaPos SV, Chen C, Smith RB. Retrospective evaluation of unanticipated admissions and readmissions after same day surgery and associated costs. *J Clin Anesth* 2002;14:349–53.
- [2] Morrison SR. The impact of post-operative pain on outcomes following hip fracture. *Pain* 2003;303–11.
- [3] Ding X, Zhang H, Liu H. Early ambulation and postoperative recovery of patients with lung cancer under thoracoscopic surgery—an observational study. *J Cardiothorac Surg* 2023;18:136.
- [4] Odor PM, Bampoe S, Gilhooly D, Creagh-Brown B, Moonesinghe SR. Perioperative interventions for prevention of postoperative pulmonary complications: systematic review and meta-analysis. *BMJ* 2020;368:m540.
- [5] Buvanendran A, Fiala J, Patel KA, Golden AD, Moric M, Kroin JS. The incidence and severity of postoperative pain following inpatient surgery. *Pain Med* 2015;16:2277–83.
- [6] Pogatzki-Zahn EM, Segelcke D, Schug SA. Postoperative pain—from mechanisms to treatment. *Pain Rep* 2017;2:e588.
- [7] Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008;372:139–44.
- [8] Kalkman JC, Visser K, Moen J, Bonsel JG, Grobbee ED, Moons MKG. Preoperative prediction of severe postoperative pain. *Pain* 2003;105:415–23.
- [9] Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology* 2009;111:657–77.
- [10] Khalil H, Shajrawi A, Henker R. Predictors of severe postoperative pain after orthopedic surgery in the immediate postoperative period. *Int J Orthop Trauma Nurs* 2021;43:100864.
- [11] Aasvang EK, Lunn TH, Hansen TB, Kristensen PW, Solgaard S, Kehlet H. Chronic pre-operative opioid use and acute pain after fast-track total knee arthroplasty. *Acta Anaesthesiol Scand* 2016;60:529–36.
- [12] Kampe S, Geismann B, Weinreich G, Stamatis G, Ebmeyer U, Gerbershagen HJ. The influence of type of Anesthesia, perioperative pain, and preoperative health status on chronic pain six months after thoracotomy—a prospective cohort study. *Pain Med* 2017;18:2208–13.
- [13] Aasvang EK, Gmaehle E, Hansen JB, Gmaehle B, Forman JL, Schwarz J, et al. Predictive risk factors for persistent postthoriotomy pain. *Anesthesiology* 2010;112:957–69.
- [14] Chapman CR, Vierck CJ. The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. *J Pain* 2017;18:359, e1–e38.
- [15] Brown EN, Pavone KJ, Naranjo M. Multimodal general Anesthesia: theory and practice. *Anesth Analg* 2018;127:1246–58.
- [16] Hung KC, Kao CL, Ho CN, Hsing CH, Chang YJ, Wang LK, et al. The impact of perioperative ketamine or esketamine on the subjective quality of recovery after surgery: a meta-analysis of randomised controlled trials. *Br J Anaesth* 2024;132:1293–303.
- [17] Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic $\alpha 2$ agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* 2012;116:1312–22.
- [18] Tonner PH. Additives used to reduce perioperative opioid consumption 1: Alpha2-agonists. *Best Pract Res Clin* 2017;31:505–12.
- [19] El-Boghdady K, Levy NA, Fawcett WJ, Knaggs RD, Laycock H, Baird E, et al. Perioperative pain management in adults: a multidisciplinary consensus statement from the Association of Anaesthetists and the British pain society. *Anaesthesia* 2024;79:1220–36.
- [20] Persson AK, Pettersson FD, Dyrehag LE, Åkeson J. Prediction of postoperative pain from assessment of pain induced by venous cannulation and propofol infusion. *Acta Anaesthesiol Scand* 2016;60:166–76.
- [21] Peng F, Li Y, Ai Y, Yang J, Wang Y. Application of preoperative assessment of pain induced by venous cannulation in predicting postoperative pain in patients under laparoscopic nephrectomy: a prospective observational study. *BMC Anesthesiol* 2020;20:86.
- [22] Persson AKM, Åkeson J. Prediction of acute postoperative pain from assessment of pain associated with venous cannulation. *Pain Pract* 2019;19:158–67.
- [23] Mogianos K, Undén J, Persson A. Effect of individualized anesthesia and analgesia on postoperative pain in patients stratified for pain sensitivity: a study protocol for the PeriOperative individualization trial randomized controlled trial. *Acta Anaesthesiol Scand* 2024;68:1532–40.
- [24] Mogianos K, Undén J, Persson A. Effect of individualized anesthesia and analgesia on postoperative pain in patients stratified for pain sensitivity: a study protocol for the PeriOperative individualization trial randomized controlled trial. *Acta Anaesthesiol Scand* 2024;68(10):1532–40.
- [25] Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess* 1995;7:524–32.
- [26] Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, et al. Validation of digital visual Analog scale pain scoring with a traditional paper-based visual Analog scale in adults. *J Am Acad Orthop Surg Glob Res Rev* 2018;2:e088.
- [27] Gelb AW, Morris WW, Johnson W, Merry AF, Abayadeera A, Belli N, et al. World Health Organization-world Federation of Societies of anesthesiologists (WHO-WFSA) international standards for a safe practice of Anesthesia. *Anesth Analg* 2018;126:2047–55.
- [28] Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs* 2005;14:798–804.
- [29] Kleif J, Waage J, Christensen KB, Gogenur I. Systematic review of the QoR-15 score, a patient-reported outcome measure measuring quality of recovery after surgery and anaesthesia. *Br J Anaesth* 2018;120:28–36.
- [30] Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118:1332–40.

- [31] Lyckner S, Böregård IL, Zetterlund EL, Chew MS. Validation of the Swedish version of quality of recovery score –15: a multicentre, cohort study. *Acta Anaesthesiol Scand* 2018;62:893–902.
- [32] (CMS) CMMS. Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors Table for Prescription Drug Coverage. 2020.
- [33] Olsen MF, Bjerre E, Hansen MD, Hilden J, Landler NE, Tendal B, et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med* 2017;15:35.
- [34] Bahreini M, Safaie A, Mirfazaelian H, Jalili M. How much change in pain score does really matter to patients? *Am J Emerg Med* 2020;38:1641–6.
- [35] Werner MU, Mjöbo HN, Nielsen PR, Rudin A. Prediction of postoperative pain: a systematic review of predictive experimental pain studies. *Anesthesiology* 2010; 112:1494–502.
- [36] Liu R, Gutiérrez R, Mather RV, Stone TAD, Santa Cruz Mercado LA, Bharadwaj K, et al. Development and prospective validation of postoperative pain prediction from preoperative EHR data using attention-based set embeddings. *NPJ Digit Med* 2023;6:209.
- [37] Lee S, Xue Y, Petricca J, Kremic L, Xiao MZX, Pivetta B, et al. The impact of pre-operative depression on pain outcomes after major surgery: a systematic review and meta-analysis. *Anaesthesia* 2024;79:423–34.
- [38] Yang MMH, Hartley RL, Leung AA, Ronskley PE, Jetté N, Casha S, et al. Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. *BMJ Open* 2019;9:e025091.
- [39] McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand* 2014;58:1199–213.
- [40] Zakine J, Samarq D, Lorne E, Moulbarak M, Montravers P, Beloucif S, et al. Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. *Anesth Analg* 2008;106:1856–61.
- [41] Sollazzi L, Modesti C, Vitale F, Sacco T, Ciocchetti P, Idras AS, et al. Preinductive use of clonidine and ketamine improves recovery and reduces postoperative pain after bariatric surgery. *Surg Obes Relat Dis* 2009;5:67–71.
- [42] Foo I, Macfarlane AJR, Srivastava D, Bhaskar A, Barker H, Knaggs R, et al. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. *Anaesthesia* 2021;76:238–50.
- [43] Grape S, Kirkham KR, Frauenknecht J, Albrecht E. Intra-operative analgesia with remifentanyl vs. dexmedetomidine: a systematic review and meta-analysis with trial sequential analysis. *Anaesthesia* 2019;74:793–800.
- [44] Peng YN, Sung FC, Huang ML, Lin CL, Kao CH. The use of intravenous magnesium sulfate on postoperative analgesia in orthopedic surgery: a systematic review of randomized controlled trials. *Medicine (Baltimore)* 2018;97:e13583.
- [45] Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. *Pain Med* 2015;16:383–403.
- [46] Othow CO, Ferde YA, Tawuye HY, Aytolign HA. The magnitude and associated factors of post-operative pain among adult patients. *Ann Med Surg (Lond)* 2022;81: 104406.
- [47] Ekstein P, Szold A, Sagie B, Werbin N, Klausner JM, Weinbroum AA. Laparoscopic surgery may be associated with severe pain and high analgesia requirements in the immediate postoperative period. *Ann Surg* 2006;243:41–6.
- [48] Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain* 2001;90:261–9.
- [49] Tai Y-H, Wu H-L, Lin S-P, Tsou M-Y, Chang K-Y. Influential factors of postoperative pain trajectories in patients receiving intravenous patient-controlled analgesia: a single-Centre cohort study in Taiwan. *BMJ Open* 2019;9:e031936.
- [50] Gerbershagen HJ, Aduckathil S, van Wijck AJM, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after SurgeryA prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013;118:934–44.
- [51] Mogianos K, Åkeson J, Persson AKM. Systematic review of methods for individual prediction of postoperative pain. *Pain Res Manag* 2025;2025:1331412.
- [52] Schwenkgleks M, Gerbershagen HJ, Taylor RS, Pogatzki-Zahn E, Komann M, Rothaug J, et al. Correlates of satisfaction with pain treatment in the acute postoperative period: results from the international PAIN OUT registry. *Pain* 2014; 155:1401–11.
- [53] Kaiser U, Liedgens H, Meissner W, Weinmann C, Zahn P, Pogatzki-Zahn E. Developing consensus on core outcome domains and measurement instruments for assessing effectiveness in perioperative pain management after sternotomy, breast cancer surgery, total knee arthroplasty, and surgery related to endometriosis: the IMI-PainCare PROMPT protocol for achieving a consensus on core outcome domains. *Trials* 2020;21:773.

Paper IV





Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

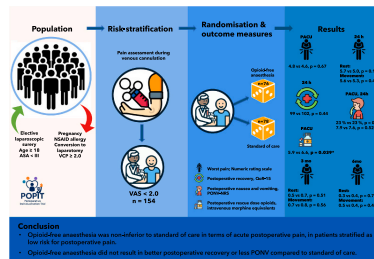
Opioid-free versus opioid-based anaesthesia and analgesia for patients at low risk for acute postoperative pain undergoing laparoscopic surgery: A randomised controlled trial

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HIGHLIGHTS

- Opioid-free anaesthesia, including esketamine, dexmedetomidine and lidocaine is non-inferior to opioid-based anaesthesia in terms of acute postoperative pain, for adult patients, predicted as at low-risk for postoperative pain.
- Opioid-free anaesthesia, including esketamine, dexmedetomidine and lidocaine did not improve postoperative recovery, postoperative nausea and vomiting or persistent pain when comparing with a traditional opioid-based anaesthesia strategy.
- Opioid-free anaesthesia can be considered in adult ASA I – II patients, predicted as low risk for acute postoperative pain, planned for laparoscopic surgery.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:

Individualised anaesthesia
Opioid-free anaesthesia
Postoperative pain and recovery

ABSTRACT

Objective: To evaluate if opioid-free anaesthesia (OFA), is non-inferior to standard of care (SOC), in patients at low risk for acute postoperative pain (APOP).

Design: Patient- and assessor-blinded, non-inferiority, randomised, controlled trial.

Setting: Single centre between March 2022 to February 2024.

Patients: 154 adult patients, ASA I – II, planned for elective laparoscopic surgery and risk-classified as low risk for APOP based on perceived pain during venous cannulation (VAS < 2.0).

Intervention: Patients were randomised to receiving OFA, including sevoflurane, dexmedetomidine, esketamine and lidocaine, or standard of care (SOC), a traditional GABA_A and opioid-based strategy. Patients were subjected to the intervention from time to arrival at the day of surgery until discharge from the PACU.

Measurements: Primary outcome: worst pain intensity in the PACU. Secondary outcomes: worst pain, and proportion having NRS ≥ 4, at 24 h (during rest and movement), worst pain and proportion having NRS ≥ 1, at 3-

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<https://doi.org/10.1016/j.jclinane.2025.112058>

Received 7 September 2025; Received in revised form 19 October 2025; Accepted 26 October 2025

Available online 31 October 2025

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and 6-months (during rest and movement), postoperative recovery at 24 h, PONV in the PACU and at 24 h. Rescue dose opioids in the PACU was an exploratory outcome.

Results: Pain scores were 4.8 in the OFA group and 4.6 in SOC group ($P = 0.67$). At 24 h, worst pain at rest was 5.7 vs 5.0 ($P = 0.11$), and during movement 5.6 vs 5.3 ($P = 0.43$). Proportion of patients with NRS ≥ 4 in the PACU was 66 % vs 69 % ($P = 0.65$) and at 24 h 76 % vs 60 % at rest ($P = 0.042$) and 73 % vs 69 % during movement ($P = 0.65$). There was no significant difference in PPOP at 3 or 6 months, either at rest ($P = 0.51$, $P = 0.56$) or movement ($P = 0.72$, $P = 0.48$), PONV (PACU: $P = 0.93$), at 24 h: ($P = 0.52$) or postoperative recovery at 24 h (99 vs 102, $P = 0.44$). OFA group required less rescue opioids in the PACU (3.4 mg vs 5.1 mg, $P = 0.039$). **Conclusion:** When individualising anaesthesia based on predicted risk for APOP, OFA is non-inferior to a traditional GABA_A and opioid-based anaesthesia strategy, for patients with a low risk for APOP undergoing laparoscopic surgery. No secondary advantages, i.e. lower PONV, less PPOP, better quality of recovery, was associated with OFA.

1. Introduction

Acute postoperative pain (APOP) can lead to significant consequences like pulmonary complications, delayed ambulation and prolonged recovery [1–3]. Furthermore, APOP is a well-established risk factor for persistent postoperative pain (PPOP), a feared complication contributing to significant morbidity and societal cost [4–7]. Despite advancements in surgical techniques and enhanced recovery protocols, it is estimated that 80 % of patients will experience APOP, with approximately 50 % reporting moderate to severe pain [8–10]. A vast amount of research regarding pain prediction has identified several independent risk factors for postoperative pain. The most important are young age, female gender, history of smoking, anxiety and depression, preoperative pain and opioid consumption [11–13]. In anaesthesia, focus has shifted from procedure-specific management to an individualised strategic approach to better address APOP and PPOP. Predicting a patient's specific risk and individualising anaesthesia to accommodate this risk are crucial aspects of this strategy.

Pain associated with peripheral venous cannulation (VCP) can be used to predict the risk of APOP. Patients grading their VCP ≥ 2.0 VAS units have an OR of 3.4 for moderate or severe postoperative pain after laparoscopic cholecystectomy and an OR of 1.7 in a mixed group of patients and surgeries [14,15]. These results have recently been replicated by an independent study on patients undergoing laparoscopic nephrectomy, where patients who experienced VCP ≥ 2.0 had an OR of 3.5 for APOP [16]. The rationale of using a risk classification method, such as VCP, is to identify individuals with an upregulated pain-signalling physiology and hence higher risks of pain following surgical procedures.

Postoperative recovery and resource consumption are clearly influenced by pain [17]. Healthcare systems face challenges due to supply and demand mismatches, necessitating more efficient perioperative management. This includes shorter hospital stays with fewer complications, without compromising patient safety. Opioids in the perioperative setting are linked to postoperative complications [18]. Opioid-free anaesthesia (OFA) is currently a well-recognised concept with some evidence supporting its use [19,20]. However, its effectiveness compared to opioid-based methods is unclear, and it remains uncertain who benefits most from OFA [21,22]. An intriguing idea is to use OFA as an individualised perioperative strategy for suitable patients [23,24].

In the pragmatic PeriOperative Individualisation Trial (POPIT) [25], VCP was used to classify patients as high or low risk for APOP. The primary objective of this trial was to examine if an individualised anaesthesia and analgesia regime can affect postoperative pain in patients stratified for pain sensitivity. The trial includes two different RCTs. The aim of this study was to determine if OFA, with dexmedetomidine, esketamine and lidocaine, was non-inferior to standard of care (SOC), a traditional GABA_A/opioid-based anaesthesia strategy, in patients identified as low risk of APOP. Our hypothesis was that OFA has comparable acute pain outcomes, with standard of care but with secondary advantages in PONV, early recovery and PPOP.

2. Methods

2.1. Study design and ethics

This randomised, controlled, patient and assessor-blinded, single-centre, parallel group, clinical trial was approved by the Swedish Ethical Review Authority (approval number 2020–06178). For transparency, the study protocol and methods have been pre-published [25] and complies to the ethical principles of the declaration of Helsinki. The study was also registered in clinicaltrials.gov (NCT04751812) on 9th of February 2021. This study is reported in accordance with the CONSORT guidelines.

2.2. Patient recruitment

Inclusion criteria: elective laparoscopic surgery, age > 18 years, ASA class $< III$, ability to understand information in Swedish. Exclusion criteria: refusal to participate, withdrawal of consent, pregnancy, NSAID allergy, and conversion to open abdominal surgery.

Eligible patients received a text message with study information one week before surgery. Upon giving written consent, participants provided baseline data including sociodemographic details, presence of preoperative pain > 3 months, use of analgesics, diagnosis/treatment for depression. They also completed the Pain Catastrophizing Scale (PCS), rating 13 statements about emotional aspects of pain from 0 (not at all) to 4 (all the time), with a maximum score of 52 [26]. Current pain was evaluated at the day of surgery using a numeric rating scale (NRS) with 0 representing no pain and 10 the worst pain imaginable.

2.3. Measurement of pain sensitivity

On the day of surgery, patients were differentiated into pain-sensitivity cohorts using pain assessment during peripheral venous cannula placement (VCP). A cannula size 0.9–1.1 mm was used at a non-specific site on the upper extremity. The operators were nurses trained in peri-operative management with a minimum of three years working experience. Procedural pain was assessed using a visual analogue scale from 0.0 (no pain) to 10.0 (worst pain imaginable) [27]. Patients with VCP < 2.0 were allocated to the low-risk cohort and included in this study.

2.4. Randomisation method and blinding

The participating patients were randomised to either OFA or SOC in a 1:1 sequenced generated fashion (Fig. 1). The randomisation process is described in further detail in the prepublished protocol [25]. Nurses in the preoperative clinic generated the random allocation sequence, enrolled participants, and assigned interventions.

Patients were blinded to the intervention. Primary (APOP_{PACU}) and secondary outcome (PONV_{PACU}) assessments were conducted face-to-face by blinded assessors in the post anaesthesia care unit (PACU) while later outcomes were self-reported by participants.

Anaesthesiologists, anaesthesia nurses and post anaesthesia care nurses, responsible for administering anaesthetic and analgesic drugs, were not blinded to the interventions for safety reasons since intervention protocols differed substantially.

2.5. Study interventions

All patients received general anaesthesia following standardised protocols and underwent various laparoscopic procedures (Table 2). At the start of surgery, the surgeon administered 20 ml of ropivacaine 7.5 mg/ml around the laparoscopy entrance holes.

2.5.1. Opioid-free anaesthesia

Pre-emptive etoricoxib 120 mg, paracetamol 1500 mg and ondansetron 8 mg were given orally. Upon arrival to the operating theatre, a dexmedetomidine infusion was started at $0.2 \mu\text{g.kg}^{-1}.\text{hr}^{-1}$ and maintained until discharged from the PACU. General anaesthesia was induced with propofol $2.0\text{--}2.5 \text{ mg.kg}^{-1}$ and an esketamine 0.1 mg.kg^{-1} i.v bolus. Betamethasone 8 mg i.v was administered after induction. Anaesthesia was maintained with sevoflurane (age adjusted MAC $0.6\text{--}1.0$) along with esketamine $0.1\text{--}0.3 \text{ mg.kg}^{-1}.\text{hr}^{-1}$ and dexmedetomidine $0.2 \mu\text{g.kg}^{-1}.\text{hr}^{-1}$. Anaesthesia providers adjusted antinociceptive treatment using the esketamine infusion. Lidocaine 1 mg kg^{-1} bolus was given 30 min before the end of surgery. Paracetamol

1000 mg was given every 6 h. For APOP (NRS ≥ 4), rescue i.v analgesia included esketamine 0.1 mg.kg^{-1} and lidocaine 0.5 mg.kg^{-1} boluses. If adequate analgesia was not achieved within 30 min, opioid-based analgesia was allowed.

2.5.2. Standard of care

This perioperative strategy represents the usual clinical care of these patients and aligns well with typical international and national recommendations [28]. Etoricoxib 120 mg, paracetamol 1500 mg, oxycodone 10 mg (5 mg if age > 75) and ondansetron 8 mg were given orally before surgery. General anaesthesia was induced with propofol and remifentanyl, maintained with either propofol (TCI, Marsh model), or sevoflurane, both with remifentanyl (TCI, Minto protocol). The choice between sevoflurane and propofol as the GABA_A-agonist was determined entirely by technical intraoperative considerations. Specifically, robotic-assisted laparoscopies were performed using sevoflurane, as intravenous access is less readily available during these procedures. In contrast, non-robotic laparoscopies allowed for the use of propofol via TCI. Betamethasone 4 mg was given i.v. at induction. Postoperative analgesia included i.v. oxycodone 0.1 mg.kg^{-1} , before terminating general anaesthesia, and paracetamol 1000 mg every 6th hour. Rescue analgesia, with oxycodone i.v. was provided in the PACU if NRS ≥ 4 .

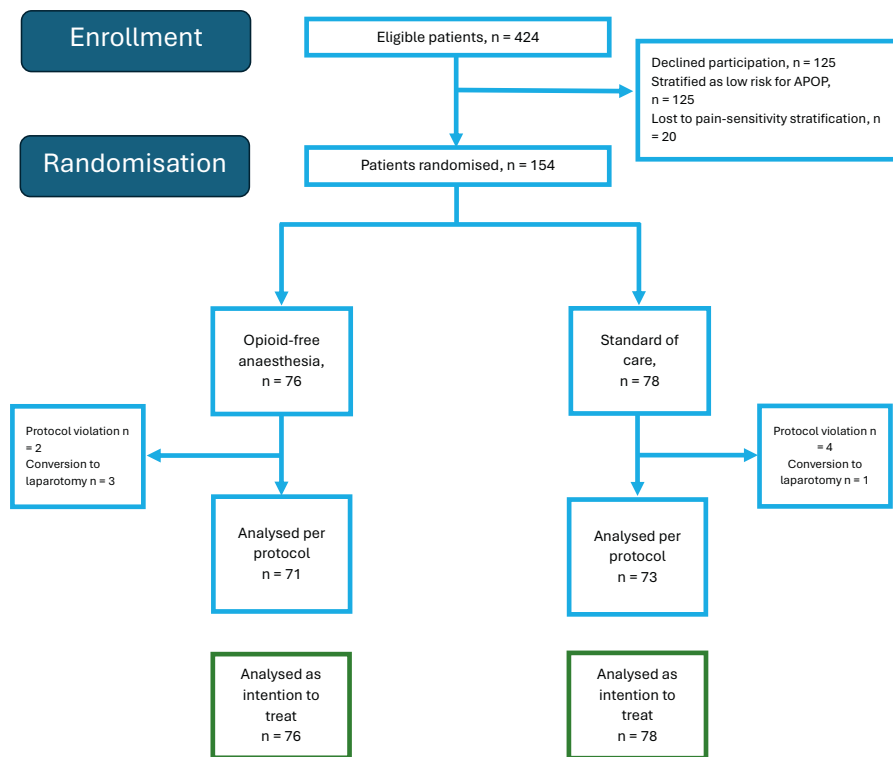


Fig. 1. Flow-chart depicting the consecutive flow to which the participating patients were subjected to both as intention-to-treat and as per protocol. APOP, acute postoperative pain; PACU, Post anaesthesia care unit; PONV, postoperative nausea and vomiting; POD1, postoperative day one; PPOP, persistent postoperative pain; QoR, quality of recovery.

2.6. Postoperative outcome assessment and data collection

In the PACU, patients were asked to grade their pain according to the verbal NRS. The 11-point numeric scale pain-assessment tool is commonly used and allow participants to rate their subjective pain level; a score of 0 represents no pain, a score of 1–3 mild pain, a score of 4–6 moderate pain whereas a score of 7–10 represents severe pain [29]. Acute postoperative pain in the PACU (APOP_{PACU}) was defined as the worst pain score during the first 90 min from arrival to the PACU. Moderate- to severe APOP was defined as NRS ≥ 4 for both time-points (PACU, POD1).

On the first postoperative day (POD1), patients received a text message containing follow-up questions regarding worst pain at 24 h (APOP_{POD1}), measured in NRS. Data for both pain at rest and during movement was patient self-reported. Movement at this time-point was defined as ambulation to the edge of the bed.

We measured patient-centred functional outcomes and recovery using the 15-item Quality of Recovery (QoR-15) questionnaire. This was sent to patients 24 h after surgery (POD1). In the questionnaire, patients rated their recovery on an 11-point scale (0 to 10) for 15 different items, assessing both physical and mental well-being [30]. The total amount of points was summed up to a total score ranging from 0 to 150, where 150 represents excellent health status. The QoR-15 has been validated in the Swedish population [31].

Postoperative nausea and vomiting was assessed, after 24 h (PONV_{POD1}) using the 13th item in the QoR-15; "Have you been feeling nauseous or vomiting during the last twenty-four hours? On a scale from 0 to 10, where 10 = not at any time (excellent) and 0 = during the whole time (bad)". Dichotomous data, e.g. present or non-present, about PONV was also gathered and registered in the PACU.

Postoperative opioid requirements were defined as the rescue dose of opioid, calculated to intravenous morphine milligram equivalents (MME), that the patient was given after emerging from general anaesthesia until discharge from the PACU. The intraoperative dose, given as postoperative analgesia (oxycodone 0.1 mg.kg⁻¹) was not included in this outcome. The outcome was calculated using an opioid converting tool, to convert all opioids given into intravenous oxycodone. Subsequently, this number was multiplied by the factor 1.5 to obtain intravenous morphine milligram equivalents [32].

Persistent postoperative pain was defined as maximal pain intensity during rest and movement, the latter defined as walking, after 3 and 6 months (PPOP_{3mo}, PPOP_{6mo}). Also, having PPOP was defined as NRS ≥ 1 at 3 and 6 months in both movement and rest.

2.7. Study outcomes

Primary outcome was the difference in worst APOP_{PACU} score between groups. Predefined secondary outcomes included the proportion of patients experiencing NRS ≥ 4 in the PACU, differences in worst APOP_{POD1} score at rest and during movement, difference in post-operative recovery, QoR-15 total score, after 24 h (QoR_{POD1}), differences in PPOP score at rest and during movement after 3 and 6 months (PPOP_{3mo}, PPOP_{6mo}), difference in proportion of patients experiencing NRS ≥ 1 after 3 and 6 months, difference in proportion of patients experiencing PONV in the PACU (PONV_{PACU}) and differences in worst PONV-NRS score after 24 h (PONV_{POD1}). The difference in total dose rescue opioids in the PACU was evaluated as a non-predefined exploratory outcome.

2.8. Sample size and statistical analysis

A non-inferiority design aimed to show OFA could be maintained without increasing APOP_{PACU}, potentially reducing PONV, improving early recovery and reduced PPOP. Our aim was for the observed effect to be clinically meaningful. While there is currently no firm evidence supporting specific thresholds in the perioperative population, data

from non-perioperative research suggest that a 30 % reduction in pain is considered meaningful for patients at the population level [33,34]. In the context of the non-inferiority design, OFA was then considered non-inferior if the difference in APOP_{PACU}, including the confidence interval, did not exceed 1.5 NRS units. A difference of 1.5 NRS units was therefore chosen as the non-inferiority limit.

Previous studies showed APOP with a mean value of 3.7 NRS units and SD of 2.7 [14]. With d set to 1.5, alpha of 0.05, and beta of 0.2, the sample size needed was 56 per group, totalling 112 participants for statistical power. Allowing for 20 % dropout, the total study sample size was set to 140 patients.

An intention-to-treat (ITT) analysis was conducted for primary, secondary and explanatory outcomes, with per protocol results in supplementary materials.

A Shapiro-Wilks test confirmed normal distribution of primary outcome data, and a Levene's test showed no variance between groups. For primary outcome (APOP_{PACU}), a one-sided Independent *t*-test was used for non-inferiority design. Continuous secondary and exploratory outcomes (PONV_{POD1}, QoR_{POD1} and rescue opioid requirements) were analysed using two-sided Independent *t*-test. Dichotomous outcomes (PONV_{PACU}, APOP_{PACU}) were analysed using a Chi-Square test.

Group comparisons are presented as *P* – values, with type 1 error margin set to 0.05, and 95 % CI. Standard deviation is used as statistical dispersion for all mean values.

3. Results

3.1. Descriptive data and population

The recruitment period was from March 2022 to February 2024. Out of 424 eligible patients, 125 declined participation, leaving 299 for risk classification with VCP (Fig. 1). After inclusion and informed consent, 20 patients did not undergo pain-sensitivity classification and were not included. 154 patients were classified as low risk for APOP (VCP < 2.0) (mean VCP 0.8 $\pm$ 0.6). In POPIT, there were two independent enrolments and randomisation logistical flows, one for the high-risk cohort (VCP ≥ 2.0) and one for the low-risk cohort (VCP < 2.0). The enrolment for the high-risk cohort closed first, which mandated us to continue recruiting until the sample in the low-risk cohort was complete. This resulted in a total sample size of 154 patients in this cohort, 14 more than originally intended. These patients were randomised to receive either OFA (*n* = 76) or SOC (*n* = 78). In the OFA group, there were two protocol violations and three conversions to laparotomy (Fig. 1). In the SOC group, four patients did not receive the study drug as per protocol and one was converted to laparotomy (Fig. 1). Data was analysed as ITT (*n* = 154). All 154 patients were analysed for predefined primary (APOP_{PACU}), secondary (PONV_{PACU}), and non-predefined explorative outcome (rescue opioid consumption). Twelve patients had missing data at POD1, leaving 142 for secondary/exploratory outcomes analysis (QoR_{POD1}, PONV_{POD1}, APOP_{POD1}). Six of these 12 provided data for PPOP (*n* = 148).

Demographic data, including factors that may influence pain (age, BMI, gender, preoperative pain condition and levels, depression, PCS), are presented in Table 1 (Table 1).

3.2. Types of surgery

Patients underwent various laparoscopic procedures, primarily colorectal and gynaecologic (Table 1).

3.3. Acute postoperative pain PACU

APOP_{PACU} was 4.8 ($\pm$ 3.2) for OFA and 4.6 ($\pm$ 3.1) for SOC, resulting in a non-inferior difference of 0.2 (95 %CI –0.8 to 1.2, *P* = 0.67) (Table 2) (Fig. 2). There was no difference in proportion of patients with moderate to severe APOP (NRS ≥ 4) in the PACU (66 % vs 69 %, *P* =

Table 1
Baseline characteristics for the cohort, categorised as low risk for postoperative pain using pain assessment during venous cannulation. Values are mean (SD) or proportion [%].

	Opioid-free anaesthesia n = 76	Standard of care n = 78
Age	56 (± 16)	57 (± 15)
Female gender; n	51 [67]	58 [74]
Body mass index; kg/m ²	27.5 (± 5.0)	25.8 (± 4.2)
ASA; n		
I	28 [37]	33 [42]
II	48 [63]	45 [58]
Preoperative pain; n	35 [46]	30 [38]
Current pain at day of surgery; NRS	0.9 (± 1.5)	0.8 (± 1.2)
Preoperative depression; n	9 [12]	6 [8]
PCS; points	12 (± 9)	13 (± 9)
VCP; NRS	0.8 (± 0.6)	0.7 (± 0.6)
Type of surgery; n		
Rectum resection	9 [11.8]	9 [11.5]
Hemicolectomy	4 [5.3]	10 [12.8]
Colectomy	1 [1.3]	1 [1.3]
Sigmoidectomy	2 [2.6]	2 [2.6]
Cholecystectomy	23 [30.3]	21 [26.9]
Hernia repair	8 [10.5]	5 [6.4]
Adrenal resection	1 [1.3]	0 [0.0]
Ovarian cyst enucleation	3 [3.9]	2 [2.6]
Uni-/bilateral salpingo- ophorectomy	11 [14.5]	13 [16.7]
Hysterectomy	14 [18.4]	15 [19.2]

ASA; American society of anaesthesiologists' physical status classification system, NRS; Numeric rating scale, PCS; Pain catastrophizing scale, VCP; Venous cannulation pain.

Table 2
Primary and secondary outcome data from intraoperative and postoperative variables of both intervention groups, as *intention-to-treat*. Values are mean (SD) or proportion [%].

	Opioid-free anaesthesia n = 76	Standard of care n = 78	Difference	95 % CI	P-value
APOP _{PACU} ; NRS	4.8 (± 3.2)	4.6 (± 3.1)	0.2	-0.8 - 1.2	0.67
APOP _{PACU} ; NRS ≥ 4; n	50 [66]	54 [69]	4 [3]		0.65
PONV _{POD1} ; PONV-NRS	7.9 (± 3.0)	7.6 (± 3.0)	0.3	-0.7 - 1.3	0.52
PONV _{PACU} ; n	18 [23]	18 [23]	0 [0]		0.93
QoR _{POD1} ; points	99 (± 26)	102 (± 24)	3	-11-5	0.44
PPOP _{3mo} ; NRS					
Rest	0.5 (± 1.3)	0.7 (± 1.5)	0.2	-0.6-0.3	0.51
Movement	0.7 (± 1.5)	0.8 (± 1.8)	0.1	-0.7-0.4	0.56
PPOP _{3mo} ; NRS ≥ 1.0; n					
Rest	15 [21]	19 [25]	4 [4]		0.52
Movement	17 [24]	21 [28]	4 [4]		0.54
PPOP _{6mo} ; NRS					
Rest	0.3 (± 1.0)	0.4 (± 1.1)	0.1	-0.4-0.3	0.72
Movement	0.5 (± 1.5)	0.4 (± 1.1)	0.1	-0.3-0.6	0.48
PPOP _{6mo} ; NRS ≥ 1.0; n					
Rest	9 [13]	11 [15]	2 [2]		0.73
Movement	13 [18]	14 [20]	1 [2]		0.80

APOP; Acute postoperative pain, NRS; numeric rating scale, PACU; post-anaesthesia care unit, PONV; postoperative nausea and vomiting, POD1; post-operative day 1, PPOP; persistent postoperative pain, QoR; Quality of recovery.

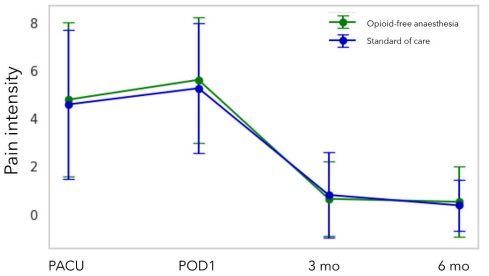


Fig. 2. Pain trajectory depicting worst pain (NRS) at different time-points during movement (POD1, 3 mo, 6 mo). Opioid-free anaesthesia was a non-opioid based anaesthesia strategy consisting of mainly dexmedetomidine, esketamine and lidocaine. Standard of care was a traditional GABA_A and opioid-based anaesthesia strategy. Whiskers for each time-point measure represent the standard deviation for each group. PACU, post anaesthesia care unit; POD1, postoperative day 1.

0.65) (Table 2).

3.4. Acute postoperative pain at 24 h

APOP_{POD1} was similar between groups at rest (5.7, ± 2.7 for OFA and 5.0 ± 2.8 for SOC) and during movement (5.6 ± 2.6 for OFA and 5.3 ± 2.7 for SOC). The differences were 0.7 (95 % CI - 0.2 to 1.7, *P* = 0.11) at rest and 0.3 (95 % CI - 0.5 to 1.2, *P* = 0.43) during movement (Fig. 2). The proportion of patients experiencing moderate to severe pain (NRS ≥ 4) after 24 h at rest was higher in OFA group (76 %) compared to SOC (60 %) (*P* = 0.042). For APOP_{POD1} during movement there was no difference in proportions experiencing NRS ≥ 4 after 24 h (73 % vs 69 % respectively, *P* = 0.65).

3.5. Postoperative nausea and vomiting in the PACU and at 24 h

Twenty-three percent of patients in both groups experienced PONV_{PACU} (*P* = 0.93). PONV_{POD1} were 7.9 (± 3.0) for OFA and 7.6 (± 3.0) for SOC (*P* = 0.52) (Table 2).

3.6. Postoperative recovery

QoR_{POD1} were 99 (± 26) for OFA and 102 (± 24) for SOC (*P* = 0.44) (Table 2). For both groups, these values suggest moderate postoperative recovery after 24 h in the validated version of QoR-15 [31].

3.7. Postoperative rescue dose opioids

The amount of rescue opioids in the PACU was 3.4 mg (± 5.1) for OFA and 5.1 mg (± 5.3) for SOC (*P* = 0.039).

4. Discussion

In this randomised controlled study, we show that opioid-free anaesthesia has similar outcomes in terms of acute and persistent pain, PONV and early recovery, when compared to routine anaesthesia in patients with low risk of APOP undergoing laparoscopic surgery. Most low-risk patients met pain-relief goals (NRS < 4) without opioids, which might have safety implications, as opioids are well-known to cause postoperative respiratory depression, independent if opioid naïve or tolerant [35]. We speculated that low-risk patients in the long run would be subjected to fewer interventions and have shorter lead times during their hospital stay. However, PACU stay was even longer for OFA compared to SOC. A more detailed investigation revealed that this was

not related to APOP, PONV, or uncertain surgical outcomes, but rather due to logistical confounders affecting admission to the ward. Importantly, we do not believe that this finding was associated with the use of dexmedetomidine or esketamine. Therefore, no definitive conclusions can be drawn from this observation. Furthermore, this study was not designed to elaborate on implicit impact on health-care strain or any other patient-related outcomes. The only difference found here was a larger proportion of patients in the OFA cohort experiencing moderate to severe APOP at POD1 (76 % vs 60 %, $P = 0.042$). As no difference was observed in continuous outcomes for the same measure and time-point during movement, it is plausible that this observation is due to insufficient power, possibly representing a type II error. Furthermore, in per protocol analyses, the difference was no longer present regarding this secondary outcome. There was a difference in dose of rescue opioids (lower in OFA) in the PACU, but the difference was small and applicable to the fact that the OFA group was, per protocol, treated with esketamine and lidocaine before opioids.

OFA has previously been shown to be a feasible option for general anaesthesia [19,20,23], although the optimal patient selection for this strategy is unknown. Evidence related to perioperative pain prediction is increasing [36–38]. If an individualised perioperative approach to general anaesthesia is desirable, over a one-size fits all approach, classifying patients based on risk of APOP is adamant. Ideally, the method used is high performing (reliable and valid), easy to use and clinically feasible. The logical first step would be to remove opioids for those with least risk for postoperative pain. To our knowledge, this is the first study to consider OFA in a subset of patients with lower risks of post-operative pain, hence exploring a strategy of individualising anaesthesia.

In terms of acute pain, OFA has not been clearly shown to be advantageous compared to conventional opioid based anaesthesia methods [23], although some studies report it to be non-inferior [39,40]. A recent randomised controlled trial showed improved recovery in the OFA arm, although this improvement was only modest, with questionable clinical relevance [24]. One surprising result in our study, that deviated from current literature, was PONV being low but similar between groups. In fact, current evidence and guidelines have highlighted PONV as a potential outcome that could be alleviated by OFA [21,40]. However, a recent RCT demonstrated no difference in PONV in patients undergoing thoracoscopic surgery [41]. Given the ongoing opioid epidemic, it's clear that OFA is a competitive method in terms of the risk for tolerance development. In the light of this, our results suggest that OFA could be preferable for patients with a low risk of APOP, as well as for those with chronic substance disorders and obesity [42,43].

4.1. Strengths and limitations

The randomised study design is considered the greatest strength of this study, due to its ability to control known and unknown confounding factors and thus better prove causal effect. The effect size of 1.5 NRS-units was predefined to reflect a clinically meaningful difference, rather than a purely statistical one. Smaller differences, while potentially statistically significant, may not translate into perceptible or actionable improvements in patient care. Furthermore, selection bias was held at a minimum, since few protocol violations occurred, and follow-up rates were high.

Being a pragmatic trial, the primary outcome was chosen as one we normally measure (APOP_{PACU}). There were no extra follow-up visits, and data collection from POD1 onwards were performed via electronic surveys. There is no consensus regarding how, when or how often to evaluate postoperative pain, especially in clinical trials. A strength with this study is that we measure pain at several time-points, at rest and during movement, and we also present data on surrogates of pain, i.e. quality of recovery and need of rescue opioids. The most common method to measure postoperative pain is still using unidimensional scales, that are not without flaws [44]. However, evaluating pain both at rest and during movement may improve clinical significance. Another

potential outcome measure is pain trajectories, where slopes and intercepts are compared between groups [45]. To further improve validity, we used QoR-15 for evaluation of health status at 24 h [31]. This is a comprehensive analysis of postoperative pain, especially since the results are consistent in all measured modalities. Adding other patient-centred outcomes, such as satisfaction [46] or other health values [47] could increase validity and should also be considered in future efforts.

This study has several limitations. As a single-centre study, external validity may be limited. Furthermore, the study-population was limited to laparoscopic surgery, and the results may not be applicable to other surgical techniques. However, concerning individualised anaesthesia as a concept, we want to stress the importance of individual risk-factors for post-operative pain, rather than only procedure specific risk-factors. Earlier studies have identified independent procedure-related risk factors such as large skin incisions, nerve damage, time in theatre as well as extensive transfusion as having some impact on post-operative pain [48]. Thus, laparoscopic surgery is a valid surgical model when striving to fixate the surgical-specific factors. Furthermore, this type of surgery is proven to be painful even though minimally invasive [10].

We recognize that the levels of APOP in this study, both in the PACU and during the first 24 h, are high. As shown by Gerbershagen et al with data from the QUIPS registry, even after laparoscopic surgery, worst pain levels tend to be remarkably high [10]. In the present cohort, possible explanations for the high APOP may be the relatively young age, the predominance of female patients and an unexpected high number of patients with preoperative pain, factors that should make them at high risk for postoperative pain. Additionally, restricting the study population to ASA I–II would have negatively impacted external validity. A broader inclusion of patients, particularly those with ASA ≥ III, could have influenced the APOP scores, as higher ASA classifications are associated with increased postoperative pain [49]. Therefore, the observed outcomes might have differed between groups had a wider patient selection been applied.

We did not collect data on opioid consumption after PACU stay, which may have influenced outcome measure after PACU discharge. Secondary outcomes were self-reported (regarding previous 24 h of symptoms) by patients which may involve recall bias. Even though venous cannulation, as a method for pain sensitivity classification, has been found to have predictive potential [14–16], it is unknown whether other predictive methods would have yielded different results. Venous cannulation pain as a method used for pain sensitivity classification deserves recognition since it has scientific merits and has a pragmatic clinical bearing [14–16], the latter in contrast to other time-consuming and labour-intensive quantitative sensory testing methods. A systematic review on preoperative bedside methods for predicting postoperative pain concluded that clinically derived approaches, those believed to reflect individual pain sensitivity, currently show the most promise [38]. Other methods of testing, such as quantitative sensory testing, genetic mapping and serologic biomarkers, have so far yielded inconclusive results and are each associated with their own limitations. There are some hopes that real-time intraoperative monitoring of nociception will refine our thinking in how to treat patients on an individual level. However, these monitoring devices are not yet ready for broad clinical use. Additionally, it is adamant that clinicians and researchers recognize that VCP, and other pragmatic clinically derived prediction methods, is a mere surrogate test for an up-regulated pain signalling on an individual level and not a detailed test for pain physiology. Thus, we are open to the fact that the results in this study might have been skewed due to inherent differences between patients in terms of individual pain physiology.

One limitation of VCP in the context of this study was its pragmatic application. We wanted to maximize the generalizability of the method, e.g. allowing for cannulation on any site on the upper extremity. This might also have affected the allocation since venous cannulation on the dorsal aspect of the hand is more painful than in the antecubital fossa. Furthermore, we did not control for number of attempts until successful cannulation, since we didn't collect this data, which might have affected

cohort allocation (high-risk vs low-risk) in some aspect. However, only highly skilled specialist nurses were used as operators, which likely reduced the risk of multiple attempts by ensuring a consistently high level of procedural success.

Lastly, the primary outcome may not be optimal and was selected based on previous research on VCP. However, we also present self-evaluated pain at several time-points and other surrogates for pain and functional outcomes which together present a solid evaluation of the patients' postoperative pain experiences.

5. Conclusion

In patients with a low risk for APOP undergoing laparoscopic surgery, OFA was comparable with a standard opioid-based anaesthesia strategy in terms of APOP, quality of recovery, PONV and persistent pain. Thus, for patients with a low-risk for APOP, an OFA-strategy is a viable clinical option.

CRedit authorship contribution statement

Krister Mogianos: Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Josefine Holgersson:** Writing – review & editing, Project administration, Investigation, Formal analysis. **Johan Undén:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Conceptualization. **Anna K.M. Persson:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Funding

This work was supported by the Research Council, Halmstad Halland County; and the Southern Healthcare Region Sweden.

Declaration of competing interest

None of the authors have any conflict of interest to declare.

Acknowledgement

We want to direct a special thanks to the nurses, in the preoperative preparations clinic, whose engagement in the recruitment process never failed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jclinane.2025.112058>.

References

- Morrison SR. The impact of post-operative pain on outcomes following hip fracture. *Pain* 2003;303–11.
- Ding X, Zhang H, Liu H. Early ambulation and postoperative recovery of patients with lung cancer under thoracoscopic surgery—an observational study. *J Cardiothorac Surg* 2023;18:136.
- Odor PM, Bampoe S, Gilhooly D, Creagh-Brown B, Moonesinghe SR. Perioperative interventions for prevention of postoperative pulmonary complications: systematic review and meta-analysis. *BMJ* 2020;368:m540.
- Aasvang EK, Gmaehle E, Hansen JB, Gmaehle B, Forman JL, Schwarz J, et al. Predictive risk factors for persistent postherniotomy pain. *Anesthesiology* 2010; 112:957–69.
- Chapman CR, Vierck CJ. The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. *J Pain* 2017;18:359.e1–e38.
- Cousins MJ, Power I, Smith G. Labat lecture: pain—a persistent problem. *Reg Anesth Pain Med* 1996;25:6–21.
- Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. *Anesthesiol Clin North Am* 2005;23:21–36.
- Buvanendran A, Fiala J, Patel KA, Golden AD, Moric M, Kroin JS. The incidence and severity of postoperative pain following inpatient surgery. *Pain Med* 2015;16: 2277–83.
- Pogatzki-Zahn EM, Segelcke D, Schug SA. Postoperative pain—from mechanisms to treatment. *Pain Rep* 2017;2:e588.
- Gerbershagen HJ, Aduckathil S, van Wijck AJM, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after Surgery A prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013;118:934–44.
- Kalkman JC, Visser K, Moen J, Bonsel JG, Grobbee ED, Moons MKG. Preoperative prediction of severe postoperative pain. *Pain* 2003;105:415–23.
- Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology* 2009; 111:657–77.
- Aasvang EK, Lunn TH, Hansen TB, Kristensen PW, Solgaard S, Kehlet H. Chronic pre-operative opioid use and acute pain after fast-track total knee arthroplasty. *Acta Anaesthesiol Scand* 2016;60:529–36.
- Persson AK, Pettersson FD, Dyrehag LE, Åkeson J. Prediction of postoperative pain from assessment of pain induced by venous cannulation and propofol infusion. *Acta Anaesthesiol Scand* 2016;60:166–76.
- Persson AKM, Åkeson J. Prediction of acute postoperative pain from assessment of pain associated with venous cannulation. *Pain Pract* 2019;19:158–67.
- Peng F, Li Y, Ai Y, Yang J, Wang Y. Application of preoperative assessment of pain induced by venous cannulation in predicting postoperative pain in patients under laparoscopic nephrectomy: a prospective observational study. *BMC Anesthesiol* 2020;20:86.
- Bowyer AJ, Royce CF. Postoperative recovery and outcomes—what are we measuring and for whom? *Anaesthesia* 2016;71(Suppl. 1):72–7.
- Wheeler M, Oederda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *J Pain* 2002;3:159–80.
- Olaussen A, Svensson CJ, Andrell P, Jildenstal P, Thorn SE, Wolf A. Total opioid-free general anaesthesia can improve postoperative outcomes after surgery, without evidence of adverse effects on patient safety and pain management: a systematic review and meta-analysis. *Acta Anaesthesiol Scand* 2022;66:170–85.
- Olaussen A, Jildenstal P, Andrell P, Angelini E, Stenberg E, Wallenius V, et al. Effects of an opioid-free care pathway vs. opioid-based standard care on postoperative pain and postoperative quality of recovery after laparoscopic bariatric surgery: a multicentre randomised controlled trial. *Eur J Anaesthesiol* 2025;42:714–26.
- Salome A, Harkouk H, Fletcher D, Martinez V. Opioid-free anesthesia benefit-risk balance: a systematic review and meta-analysis of randomized controlled trials. *J Clin Med* 2021;10.
- Shanthanna H, Joshi GP. Opioid-free general anesthesia: considerations, techniques, and limitations. *Curr Opin Anaesthesiol* 2024;37:384–90.
- Feenstra ML, Jansen S, Eshuis WJ, van Berge Henegouwen MI, Hollmann MW, Hermanides J. Opioid-free anesthesia: a systematic review and meta-analysis. *J Clin Anesth* 2023;90:111215.
- Léger M, Perrault T, Pessiot-Royer S, Parot-Schinkel E, Costerousse F, Rineau E, et al. Opioid-free anesthesia protocol on the early quality of recovery after major surgery (SOFA trial): a randomized clinical trial. *Anesthesiology* 2024;140:679–89.
- Mogianos K, Undén J, Persson A. Effect of individualized anesthesia and analgesia on postoperative pain in patients stratified for pain sensitivity: a study protocol for the PeriOperative Individualization trial randomized controlled trial. *Acta Anaesthesiol Scand* 2024;68:1532–40.
- Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess* 1995;7:524–32.
- Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, et al. Validation of digital visual analog scale pain scoring with a traditional paper-based visual analog scale in adults. *J Am Acad Orthop Surg Glob Res Rev* 2018;2:e088.
- Gelb AW, Morris WW, Johnson W, Merry AF, Abayadeera A, Belli N, et al. World Health Organization-world Federation of Societies of Anesthesiologists (WHO-WFSA) international standards for a safe practice of anesthesia. *Anesth Analg* 2018; 126:2047–55.
- Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs* 2005;14:798–804.
- Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118: 1332–40.
- Lyckner S, Børegård IL, Zetterlund EL, Chew MS. Validation of the Swedish version of quality of recovery score –15: a multicentre, cohort study. *Acta Anaesthesiol Scand* 2018;62:893–902.
- (CMS) CMMMS. Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors Table for Prescription Drug Coverage. 2020.
- Bahreini M, Safaei A, Mirfazaieian H, Jalili M. How much change in pain score does really matter to patients? *Am J Emerg Med* 2020;38:1641–6.
- Olsen MF, Bjerre E, Hansen MD, Hilden J, Landler NE, Tendal B, et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med* 2017;15:35.
- Ayad S, Khanna AK, Iqbal SU, Singla N. Characterisation and monitoring of postoperative respiratory depression: current approaches and future considerations. *Br J Anaesth* 2019;123:378–91.
- Werner MU, Mjöbo HN, Nielsen PR, Rudin A. Prediction of postoperative pain: a systematic review of predictive experimental pain studies. *Anesthesiology* 2010; 112:1494–502.
- Yang MMH, Hartley RL, Leung AA, Ronksley PE, Jetté N, Casha S, et al. Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. *BMJ Open* 2019;9:e025091.

- [38] Mogianos K, Åkeson J, Persson AKM. Systematic review of methods for individual prediction of postoperative pain. *Pain Res Manag* 2025;2025:1331412.
- [39] Wang D, Liao C, Tian Y, Zheng T, Ye H, Yu Z, et al. Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial. *EClinicalMedicine* 2023;63:102188.
- [40] Zhang Z, Li C, Xu L, Sun X, Lin X, Wei P, et al. Effect of opioid-free anesthesia on postoperative nausea and vomiting after gynecological surgery: a systematic review and meta-analysis. *Front Pharmacol* 2023;14:1330250.
- [41] Yan X, Liang C, Jiang J, Ji Y, Wu A, Wei C. Effects of opioid-free anaesthesia on postoperative nausea and vomiting in patients undergoing Video-assisted thoracoscopic surgery (OFA-PONV trial): study protocol for a randomised controlled trial. *Trials* 2023;24:819.
- [42] Berlier J, Caraballona JF, Teie H, Bouffard Y, Le-Goff MC, Cerro V, et al. Effects of opioid-free anesthesia on postoperative morphine consumption after bariatric surgery. *J Clin Anesth* 2022;81:110906.
- [43] Sultana A, Torres D, Schumann R. Special indications for opioid free anaesthesia and analgesia, patient and procedure related: including obesity, sleep apnoea, chronic obstructive pulmonary disease, complex regional pain syndromes, opioid addiction and cancer surgery. *Best Pract Res Clin Anaesthesiol* 2017;31:547–60.
- [44] Baamer RM, Iqbal A, Lobo DN, Knaggs RD, Levy NA, Toh LS. Utility of unidimensional and functional pain assessment tools in adult postoperative patients: a systematic review. *Br J Anaesth* 2022;128:874–88.
- [45] Vasilopoulos T, Wardhan R, Rashidi P, Fillingim RB, Wallace MR, Crispen PL, et al. Patient and procedural determinants of postoperative pain trajectories. *Anesthesiology* 2021;134:421–34.
- [46] Schwenkglenks M, Gerbershagen HJ, Taylor RS, Pogatzki-Zahn E, Komann M, Rothaug J, et al. Correlates of satisfaction with pain treatment in the acute postoperative period: results from the international PAIN OUT registry. *Pain* 2014;155:1401–11.
- [47] Kaiser U, Liedgens H, Meissner W, Weinmann C, Zahn P, Pogatzki-Zahn E. Developing consensus on core outcome domains and measurement instruments for assessing effectiveness in perioperative pain management after sternotomy, breast cancer surgery, total knee arthroplasty, and surgery related to endometriosis : the IMI-PainCare PROMPT protocol for achieving a consensus on core outcome domains. *Trials* 2020;21:773.
- [48] Othow CO, Ferede YA, Tawuye HY, Aytolign HA. The magnitude and associated factors of post-operative pain among adult patients. *Ann Med Surg (Lond)* 2022;81:104406.
- [49] Tai Y-H, Wu H-L, Lin S-P, Tsou M-Y, Chang K-Y. Influential factors of postoperative pain trajectories in patients receiving intravenous patient-controlled analgesia: a single-centre cohort study in Taiwan. *BMJ Open* 2019;9:e031936.

Paper V



RESEARCH

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Anesthesia depth monitoring during opioid free anesthesia – a prospective observational study

Krister Mogianos^{1,2*} and Anna KM Persson^{1,2}

Abstract

Background Patients undergoing general anesthesia are more frequently monitored for depth of anesthesia using processed electroencephalography. Opioid-free anesthesia is nowadays an accepted modality for general anesthesia, however it is unclear how to interpret data from processed electroencephalography when using a mixture of non-opioid anesthetic drugs. Our objective was to describe density spectral array patterns and compare processed encephalographic data indices between opioid-free and routine opioid based anesthesia.

Methods This prospective observational cohort study was conducted on 30 adult patients undergoing laparoscopic surgery in a non-tertiary regional hospital. The patients underwent general anesthesia with three different methods and were monitored for anesthesia depth using processed encephalography and density spectral array. Primary outcome is a group-derived mean difference in patient state index and spectral edge frequency. As a secondary outcome a descriptive comparison of the spectral power, derived from the density spectral array, was done between groups.

Results The opioid-free anesthesia group had significantly higher patient state index and spectral edge frequency compared to routine anesthesia. Density spectral array patterns were also different, most notably lacking the high power in alpha frequency spectrum seen in the other routine anesthesia methods.

Conclusions Processed electroencephalography monitoring can be used in opioid-free anesthesia, however clinicians should expect higher values in monitoring indices. The density spectral array pattern using a common protocol for opioid-free anesthesia, with mainly sevoflurane combined with low doses of dexmedetomidine and esketamine, differs from well described opioid and GABA-ergic anesthesia methods. These findings should be further validated using other protocols for opioid-free anesthesia in order to safely monitor anesthesia depth.

Trial registration Clinicaltrials.gov registration number NCT06227143, registration date; 26th of January 2024.

Keywords Processed electroencephalography, Opioid-free anesthesia, Opioid-based anesthesia, Density spectral array, Spectral edge frequency, Patient state index

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Background

Providing opioid free anesthesia (OFA) for major surgery has during the past decade proven to be both feasible and safe and has shown good results on postoperative pain outcome, without the side effects of opioids [1, 2]. The key concept in this anesthesia method is combining well-known anesthetic agents, which act synergistically in low doses to produce the desired effect, i.e. hypnosis, antinociception, amnesia, immobilization and neuromuscular blockade without compromising the hemodynamic physiology [3]. However, for anesthesia providers trained mainly in opioid-based anesthesia this is a challenging task. Some clinical signs, usually used for determining adequate level of anesthesia, are lacking, making assessment challenging.

Processed electroencephalography (pEEG) is one adjunct available to anesthesia providers when assessing brain function during anesthesia. Typically, pEEG contains unprocessed raw-EEG and an algorithm-based index-value between 0 and 100 for example the patient state index (PSI) (Massimo™) [4] and the spectral edge frequency under 95% (SEF95), a point in the frequency spectrum below which 95% of the total spectral power is contained [5]. Processed EEG is a way of monitoring brain function to determine anesthesia depth in patients under general anesthesia [6, 7]. Since its discovery this monitoring method has been refined into commercially available devices. By using pEEG in clinical practice, anesthesia providers have developed empirical knowledge of how to use this technology when assessing brain function to determine anesthesia depth. However, this is only true for routine anesthesia protocols using volatile agents or propofol together with opioids.

Since real-time assessment of unprocessed raw-EEG patterns requires profound knowledge and experience in order to identify disturbances in brain function during anesthesia, simplifying methods have been implemented in monitoring devices. Density spectral array (DSA) is a color-coded spectrogram, containing the power of exhibited frequencies over time [8, 9] enabling easy interpretation of where the patient's current oscillating frequencies are focused for the cortical area monitored [6].

Density spectral array is useful as an adjunct in clinical practice. However, it requires knowledge on how specific anesthetic regimens look at different brain states during general anesthesia. Current evidence fails to present a guide on how to interpret pEEG in new types of anesthesia methods where anesthetic drugs are combined, like in OFA. Therefore, the aim of this prospective cohort-study was to evaluate pEEG, specifically PSI, SEF95 and DSA, during OFA and compare the values to those seen during routine anesthesia with either volatile anesthetic or total intravenous anesthesia (TIVA) in conjunction with opioids. We hypothesized that PSI and SEF95 for OFA

will be higher, for the same anesthesia depth, compared to routine anesthesia methods and that DSA-pattern differed between the anesthetic regimens.

Methods

Patient recruitment and ethics

The patients in this prospective observational cohort study were consecutively recruited from an ongoing randomized control trial (RCT), carried out at a regional hospital in Halmstad, Sweden [10]. Patients in the TIVA and volatile anesthesia groups in this study were recruited from standard of care groups in this ongoing RCT. In short, patients were recruited from the pain-tolerant arm, where they subsequently got randomized to either OFA or one of two protocolized routine anesthesia methods used as controls.

The project plan was published on Clinical Trials, (NCT06227143, date; 24th of January 2024), before data were accessed. Recruitment process was conducted between 1st of August 2023 and 1st of February 2024. All participants in this study gave both oral and written informed consent. The protocol was approved by the Swedish Ethical Review Authority on 2023-01-18 with Dnr 2022-07156-02. We have followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines when writing and reporting this study.

Inclusion criteria were elective laparoscopic surgery, age > 18 years, American Society of Anesthesiologist (ASA) class < III and ability to understand and accommodate information. Exclusion criteria were refusal to participate, pregnancy and allergy towards non-steroidal anti-inflammatory drugs (NSAIDs), as the latter was part of the multimodal concept in OFA.

Group allocation

We included 30 patients where anesthesia was maintained with either sevoflurane and remifentanyl (*volatile group*), propofol and remifentanyl by target control infusion (TCI) (*TIVA group*) or OFA. The patients were consecutively recruited from an ongoing trial where patients were risk-stratified regarding risk of acute postoperative pain using pain during venous cannulation (VCP). This risk-stratifying method has shown promise when it comes to differentiating patients into either pain-sensitive or pain-tolerant [11–13]. In order to match the OFA group with control groups, subjected to routine anesthesia methods, the patients in this study were recruited from the pain-tolerant groups since the pain-sensitive group included non GABA-ergic and non-opioid anesthetic agents that potentially would bias the pEEG regarding outcomes in this study. If patients were allocated to the pain-tolerant group they could either be randomized into receiving OFA or routine anesthesia

(TIVA or Volatile), creating the three groups [10]. The anesthesia nurse and the anesthesiologist in charge were instructed to perform induction and maintenance of anesthesia using conservative measures, i.e. everything but the pEEG monitor device like blood pressure, heart rate, anesthetic drug dosage, pupillary size and skin appearance.

Anesthesia protocol

Total intravenous anesthesia; Induction and maintenance of anesthesia was conducted using a TCI protocol (Marsh model) with propofol and remifentanyl in conjunction with betamethasone 4 mg i.v [14]. Anesthesia was further maintained with propofol and remifentanyl at the discretion of the anesthesia-provider in charge.

Anesthesia with volatile agent; Induction of anesthesia was conducted using propofol and remifentanyl in conjunction with betamethasone 4 mg i.v. Anesthesia was maintained with sevoflurane and remifentanyl at the discretion of the anesthesia-provider in charge. Remifentanyl was administered using TCI-protocol [14].

Opioid-free anesthesia; As soon as vascular access was established, and the patient arrived in the operating theatre, an infusion of dexmedetomidine was started at 0.2 µg/kg/hour and maintained throughout the perioperative process until the patient left the PACU. General anesthesia was induced using propofol and esketamine 0.1 mg/kg bolus in conjunction with betamethasone 8 mg i.v. Anesthesia was maintained with sevoflurane (MAC 0.6–1.0) together with infusion of esketamine 0.1–0.3 mg/kg/hour and dexmedetomidine 0.2 µg/kg/hour.

Monitoring of brain function during anesthesia and data description

We used the Root® and SedLine® (Masimo Corporation, Irvine, CA, USA) monitor for brain function during general anesthesia. The monitor displays four channels of unprocessed EEG (two per side of the brain), PSI, left and right SEF95, suppression ratio (SR), electromyography (EMG) and DSA (Fig. 1). Patient state index is a number calculated by a Sedline algorithm reflecting the level of unconsciousness and should be between 25 and 50 for routine opioid based general anesthesia [4]. Spectral edge frequency 95 is the frequency, measured in Hz, below which 95% of the frequency-power is represented [15]. Suppression ratio (SR) is the percentage of time by which the oscillating activity is isoelectric ($\pm 0.5 \mu V$), during a one-minute epoch, in the frontal and pre-frontal cortex. A high contrast-enhancement (Multitaper) was used on all patients and DSA trends were set to -5 dB (upper limit) and -30 dB (lower limit) as standard. Frequency limit were set between 0 and 30 Hz. As the research question regarded a descriptive comparison between anesthesia methods, rather than individual patients, it

was allowed to change contrast enhancement with the purpose of achieving the best and most representative illustrations for each individual patient at the time of data collection.

Data collection and outcome measures

Data regarding the included patients was collected from standard hemodynamic monitoring (heart rate, non-invasive blood pressure), drug dose from infusion-pumps and the ventilator (calculated age adjusted minimal alveolar concentration).

Data regarding the brain state during general anesthesia was collected from the Sedline monitor (Fig. 1) when anesthetic steady state, after surgical incision, had been achieved for at least 20 min. The attending anesthesiologist and anesthesia nurse were blinded to the pEEG monitor. When the clinicians confirmed adequate level of unconsciousness and anesthetic steady-state, after skin incision, has been maintained for at least 20 min, quantitative data and DSA-pattern was extracted. All patients were followed up with an interview regarding potential intraoperative awareness and postoperative hallucinations.

Primary outcome was the difference in mean PSI between the three anesthesia groups (TIVA vs. Volatile vs. OFA). We defined the null hypothesis as; There is no difference in mean PSI between groups.

The secondary outcome was the difference in mean SEF95 between the three anesthesia groups. The mean SEF95 used in data analysis was calculated from the right and left prefrontal cortex area (SEF95R and SEF95L) on the monitor. Finally, we used the DSA-graphs for a case derived comparison of DSA-pattern between OFA and the two other routine anesthesia groups (TIVA, Volatile).

Statistical analysis

In a study comparing the bispectral index (BIS) with PSI during TIVA with propofol and remifentanyl the mean standard deviation (SD) for PSI values at different time points was 9.1 [16]. We assumed our group means for PSI to be 30, 35 and 45 for TIVA, volatile and OFA groups respectively. Calculating power analysis for *one-way ANOVA* comparing three groups with the power of 0.8 and alpha-value of 0.05, the calculated sample size in each group was 8. We decided to include 10 patients for each group to be able to detect a difference in primary outcome.

The data was concluded to be normally distributed with a *Shapiro-Wilk test*. A *Levene's test* was done and resulted in no significant variance between groups. As data for primary, secondary outcomes and age were of continuous origin, and groups were independent, the null hypothesis was tested using *one-way-ANOVA*.

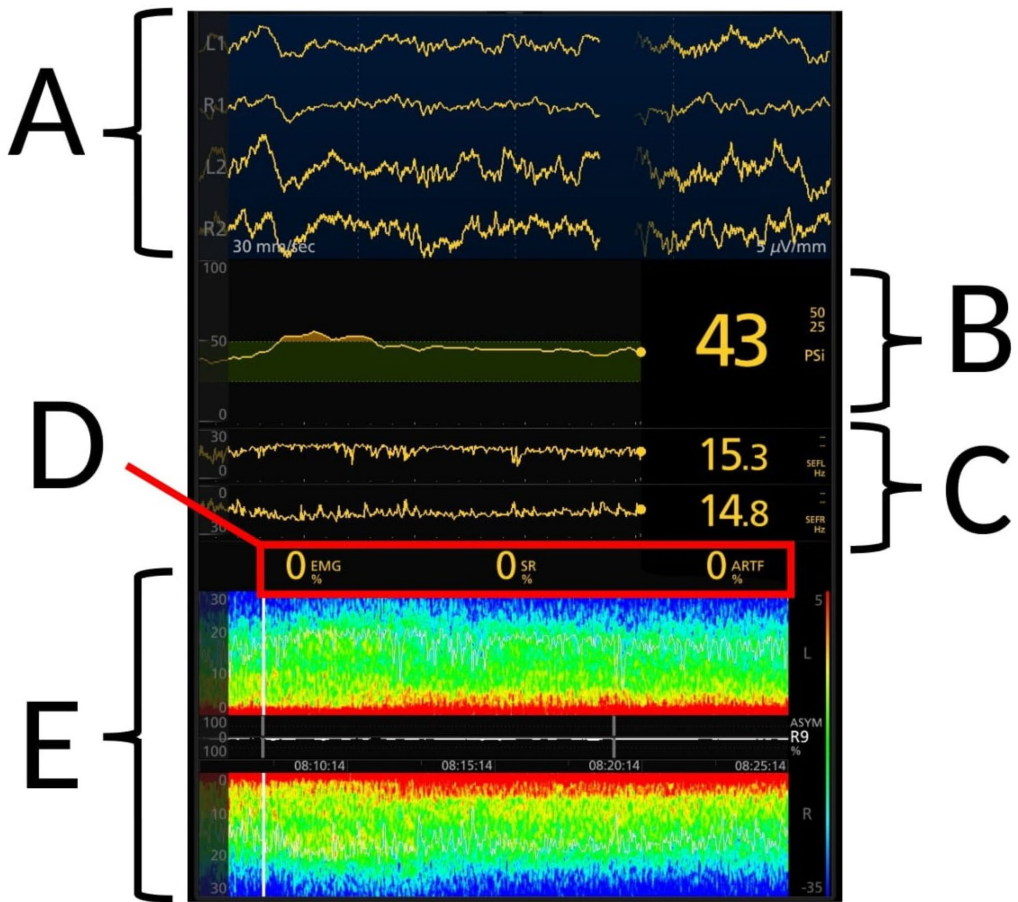


Fig. 1 Description of Sedline Monitor indices. **(A)** The four channels of electroencephalography (EEG) representing two locations on right and left frontal lobes respectively. **(B)** Patient state index (PSI), algorithm-based quantitative index for monitoring of brain function to determine anesthesia depth during general anesthesia. **(C)** Spectral edge frequency (SEF95) containing 95% of the electric activity, also separated for left and right side. **(D)** Electromyography (EMG), which is an index over temporal muscle relaxation. Suppression ratio (SR) represents percentage of isoelectric electrical activity ($\pm 0.5 \mu V$) per minute in prefrontal and frontal cortex. Artefacts (ARTF) reflect environmental noise as artifacts, conveyed as vertical white lines in DSA. **(E)** Density spectral array (DSA) showing the power of frequencies over time as a color-scale. The upper and lower part reflects left and right frontal lobes

Data is presented as mean values and standard deviation as dispersion measure. Statistical significance was set at a p -value of less than 0.05.

The data was analyzed using the IBM SPSS 29.0 (IBM Inc., Armonk, NY, USA) software.

Results

Patient characteristics

A total of 30 patients were included in the data analysis. Ten patients were allocated to each group (volatile, TIVA, OFA). There was a numeric difference in age

between the groups, however, this difference was not statistically significant ($p = 0.142$) (Table 1). Statistical analysis concluded that there was no significant difference in hemodynamic parameters, during anesthetic steady state after skin incision. There was a predominance of female gender in all groups, with no difference between groups (Table 1).

Primary quantitative outcome

At the drug doses used in this study, and when anesthetic steady state after skin incision was achieved, there

Table 1 Descriptive data of enrolled patients

	Volatile	TIVA	OFA	<i>p</i> -value
Number of patients	10	10	10	
Age, years	55 (± 18.4)	49 (± 16.4)	65 (± 18.2)	0.142
Female gender	8/10	7/10	7/10	
Heart rate	63 (± 12.7)	62 (± 10.1)	71 (± 10.3)	0.176
Systolic blood pressure, mmHg	109 (± 18.5)	100 (± 37.7)	100 (± 17.9)	0.661
Diastolic blood pressure, mmHg	67 (± 10.0)	63 (± 11.6)	68 (± 6.4)	0.510
Patient state index	31 (± 3.9)	28 (± 3.7)	40 (± 8.5)	< 0.001*
Spectral edge frequency, Hz	12.5 (± 1.8)	11.1 (± 1.3)	16.4 (± 3.1)	< 0.001*

Oneway ANOVA comparison between groups in regard to study outcome and clinical parameters. A single asterisk (*) indicates a significant difference between study groups. The standard deviation is reported within the brackets

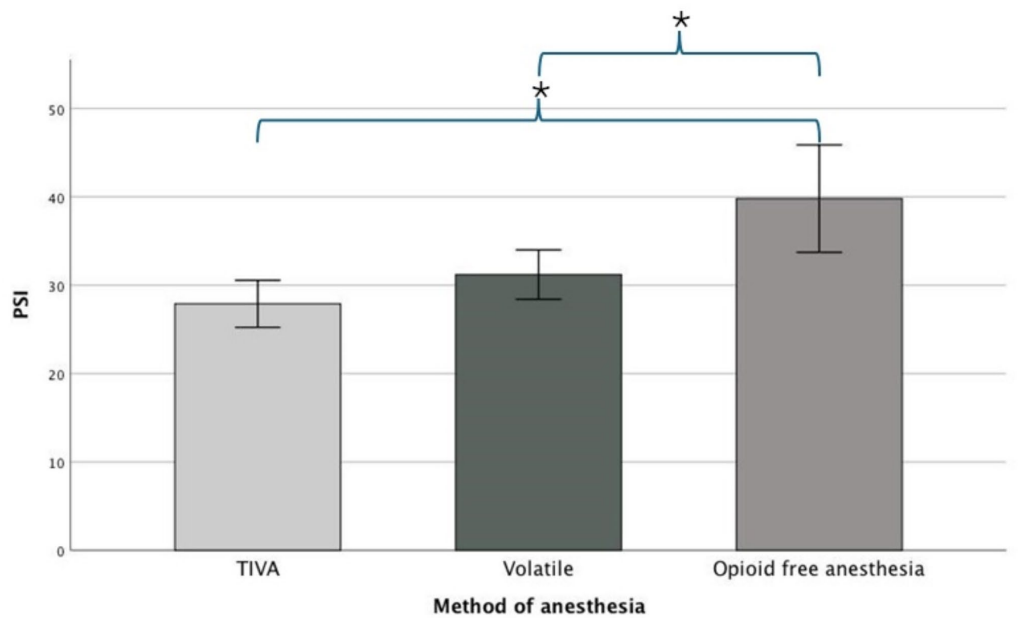


Fig. 2 Primary outcome. Bar chart illustrating difference in mean patient state index (PSI) between total intravenous anesthesia (TIVA), volatile and opioid-free anesthesia (OFA) groups. The whiskers represent the 95% confidence interval. A single asterisk (*) indicates a statistically significant difference between groups

was a statistically significant difference in mean PSI between groups as determined by one-way ANOVA ($F(2,27) = 11.173, p < 0.001$). A Tukey post hoc test revealed that the mean PSI was significantly lower in TIVA group at 27.9 ($SD = \pm 3.7, p < 0.001$) and volatile group at 31.2 ($SD = \pm 3.9, p = 0.007$) compared to OFA group which had a mean value of 39.8 ($SD = \pm 8.5$) (Table 1). There was no statistically significant difference in mean PSI between TIVA and volatile groups ($p = 0.424$) (Fig. 2).

Secondary quantitative outcome

At the drug doses used in this study, and when anesthetic steady state after skin incision was achieved, there

was a statistically significant difference in mean SEF95 between groups as determined by one-way ANOVA ($F(2,27) = 15.207, p < 0.001$). A Tukey post hoc test revealed that the mean SEF95 was significantly lower in TIVA group at 11.1 ($SD = \pm 1.3, p < 0.001$) and volatile group at 12.5 ($SD = \pm 1.8, p = 0.001$) compared to OFA group (16.4 ± 3.1) (Fig. 3). There was no statistically significant difference between TIVA and volatile groups ($p = 0.387$) (Table 1).

None of the patients in this study had potential interference from EMG. Three patients had a SR of 4%, 6% and 6% respectively, two of which being in the TIVA-group and one in OFA-group.

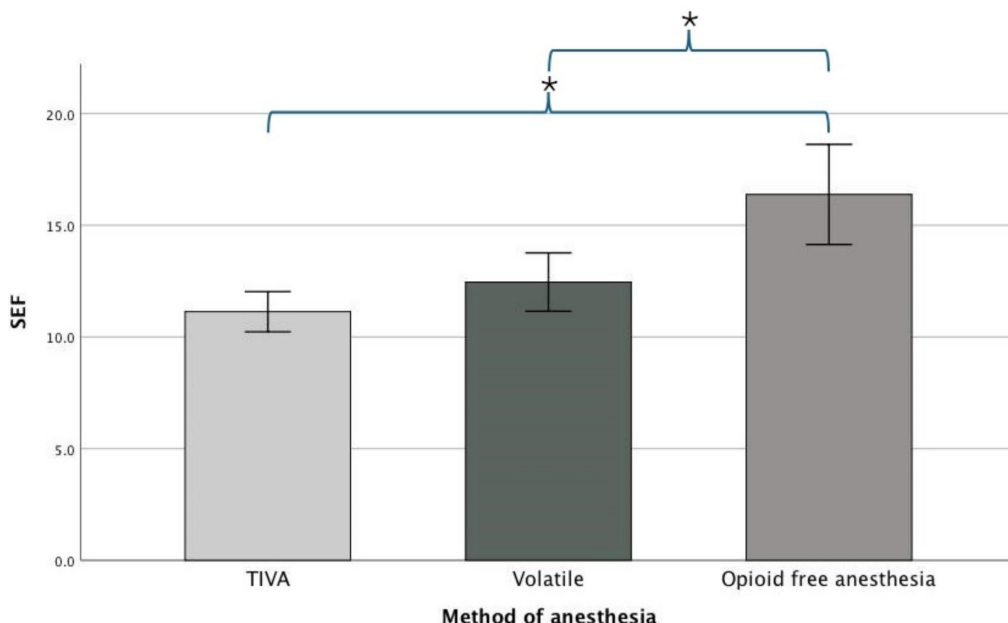


Fig. 3 Secondary quantitative outcome. Bar chart illustrating difference in mean spectral edge frequency (SEF) between total intravenous anesthesia (TIVA), volatile and opioid-free anesthesia (OFA) groups. The whiskers represent the 95% confidence interval. A single asterisk (*) indicates a statistically significant difference between groups

Secondary descriptive outcome

Opioid-free anesthesia

There was typically a different DSA-pattern compared to the routine anesthesia groups with generally a predominance of power (red) in the theta-spectrum whilst a low-powered spectrum (green) was seen in the delta to beta spectrum (Fig. 4). This was seen in most patients except for patients (g_1), (i_1) and (j_1), who all exhibited a typical -alpha/delta- pattern recognized in established routine anesthesia techniques. For one patient (b_1) there was mostly a high-power pattern in the low beta-spectrum, resembling patterns of N-Methyl-D-aspartate (NMDA)-antagonists, with a SEF95 of 19.0 and PSI of 46. For (d_1) a similar pattern was seen as for the other patients (a_1 , c_1 , e_1 - h_1), however there was a more widespread absence of the low-power pattern seen in the other examples.

One patient (g_1) had a SR of 6% during anesthetic steady state after skin incision. This was a 30-year-old female undergoing robotic gynecologic surgery receiving Sevoflurane at MAC 1.0, dexmedetomidine 0.2 $\mu\text{g/kg/hr}$ and esketamine 0.2 mg/kg/hr . This patient had lower than average SEF95 and PSI of 10 and 23 respectively. Another two patients (i_1 , j_1) exhibited a more classic -alpha/delta-pattern, however with a high SEF95, 17.1 Hz and 18.1 Hz respectively, and PSI, 38 and 48 respectively.

None of these patients received interfering EMG signals, that otherwise could potentially increase SEF95-values. Mean MAC for sevoflurane was 0.9 with a range of 0.8 to 1.2. No patients in this group described an experience of awareness during the intraoperative phase.

Total intravenous anesthesia

All but one patient exhibited a well-described alpha/delta-frequency pattern on DSA (Fig. 5) [6]. Patient (a_2) had no visual frequency pattern in the alpha spectrum, but rather almost exclusively in the theta spectrum. However, when looking at the raw-EEG there is clearly a presence of alpha-waves at approximately 10–12 Hz. This patient was a 66-year-old male undergoing laparoscopic colorectal surgery with calculated serum-levels of 4.7 ng/ml (remifentanyl) and 2.5 $\mu\text{g/ml}$ (propofol). One patient (c_3) had isoelectric EEG-pattern with an SR of 4%. This was a 63-year-old female undergoing robotic gynecologic surgery with an on average low calculated serum concentration of remifentanyl (2.5 ng/ml) and propofol (2.5 $\mu\text{g/ml}$). Patient g_2 had a clear theta (Hz 5–7) fill in effect although PSI and SEF95 values were not dramatically different from the other patients. This patient was 60 years old and needed a bit higher dose of Remifentanyl (6.0 ng/ml) and propofol (3.0 $\mu\text{g/ml}$) for clinically reaching an

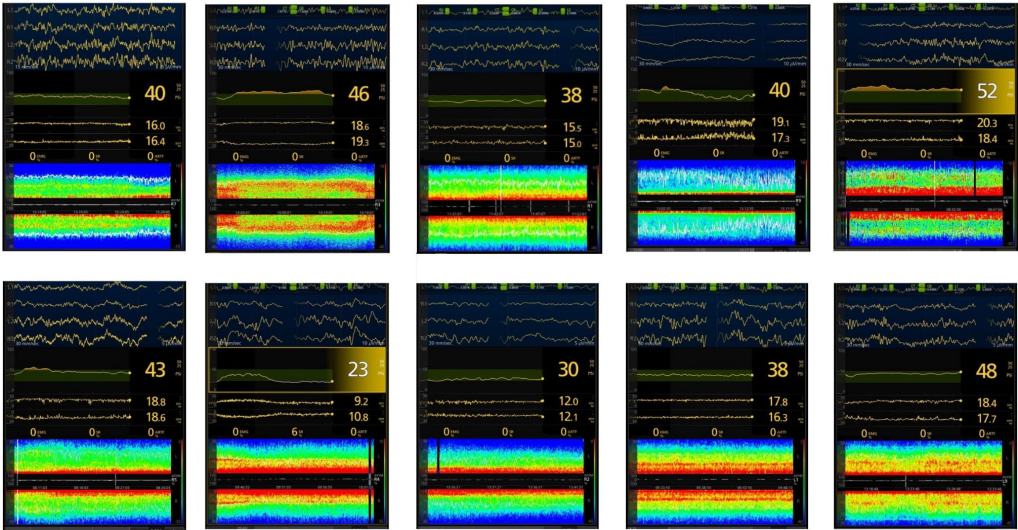


Fig. 4 Secondary quantitative outcome. Data from processed electroencephalography and density spectral array (DSA) for all ten patients in opioid-free anesthesia (OFA) group. Patients in this figure were labeled $a_1 - j_1$ starting on top left to bottom right. All patients were considered to be in anesthetic steady state after skin incision

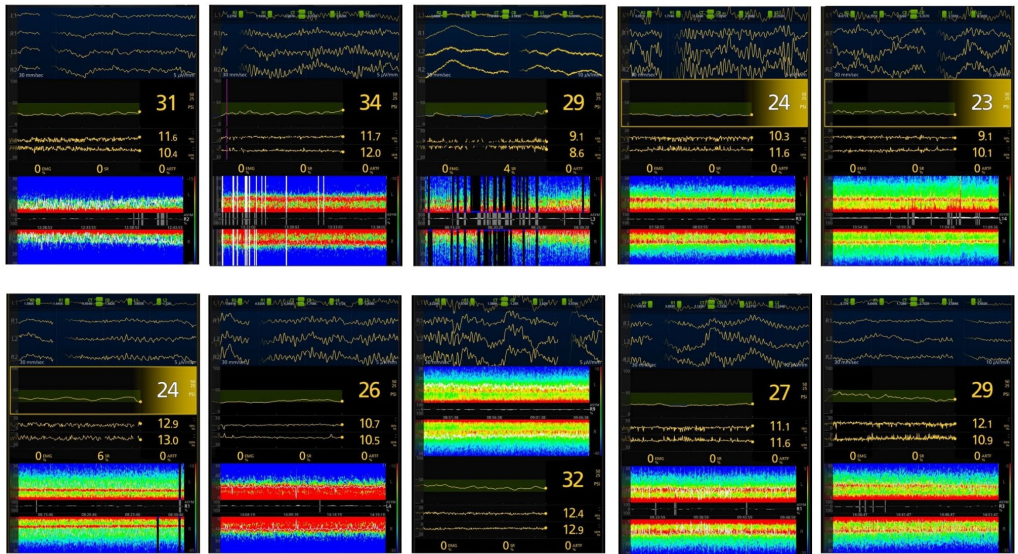


Fig. 5 Secondary quantitative outcome. Data from processed electroencephalography of anesthesia and density spectral array for all ten patients in total intravenous anesthesia (TIVA) group. Patients in this figure were labeled $a_2 - j_2$ starting on top left to bottom right. All patients were considered to be in anesthetic steady state after skin incision

adequate level of anesthesia with preserved vital parameters, blood pressure 120/70 and heart rate 75. The fill in effect could be due to higher doses of remifentanyl but also partly due to a change of contrast enhancement. No patients in this group described an experience of awareness during the intraoperative phase.

Volatile anesthesia

All patients showed a similar DSA-pattern, more precisely high power in the alpha/delta-frequency spectrum (Fig. 6). No patient in this group had interfering EMG-activity or isoelectric EEG-activity. Mean MAC was 0.8 with a range of 0.7 to 0.9. Mean calculated serum level remifentanyl was 4.7 ng/ml, ranging between 3.0 and 6.0 ng/ml. No patients in this group described an experience of awareness during the intraoperative phase.

Discussion

In this observational cohort study, we have used DSA, SEF95 and PSI from pEEG monitoring to compare OFA with two types of routine anesthesia. Findings confirm that pEEG can be used for OFA that is mainly based on volatile anesthetic agents in combination with other non-opioid intravenous agents, all affecting the EEG-pattern [6]. We believe that it is important to validate OFA towards monitoring techniques in order to guarantee patient safety and equity when using this anesthetic modality.

In this study both PSI and SEF95 were significantly higher compared to routine anesthesia groups when using pEEG to determine brain function during general anesthesia. The OFA-protocol utilized is roughly based on modulating peripheral sensitization (Etoricoxib, paracetamol, betamethasone), NMDA-receptors (esketamine) in the spinal cord and α_2 -receptors (dexmedetomidine) affecting the descending anti-nociceptive pathways [17]. One key issue in this study is to evaluate the effect of combinations of several anesthetic agents on neurophysiologic signaling and pEEG-pattern. Earlier studies have shown that dexmedetomidine and ketamine, used separately, affect EEG-pattern and DSA in a manner that is different from volatile agents and propofol [6, 18, 19]. Also, volatile agents as main anesthetic are described to show similar EEG-patterns, but with a dose-dependent difference from propofol. To our knowledge, there are currently no published data on what to expect, regarding neurophysiologic signaling and pEEG-pattern, when combining GABA-ergic, NMDA-antagonists and α_2 -agonists as well as non-sedating agents such as NSAID, betamethasone and paracetamol. We believe that it is reasonable that the combination of these agents effect neurophysiologic transmission in a different manner than each for itself.

In the OFA group the mean age was 66 compared to 55 and 49 in Volatile and TIVA group respectively. Since patients in this study were included from a larger RCT, we cannot fully explain why this difference was seen if

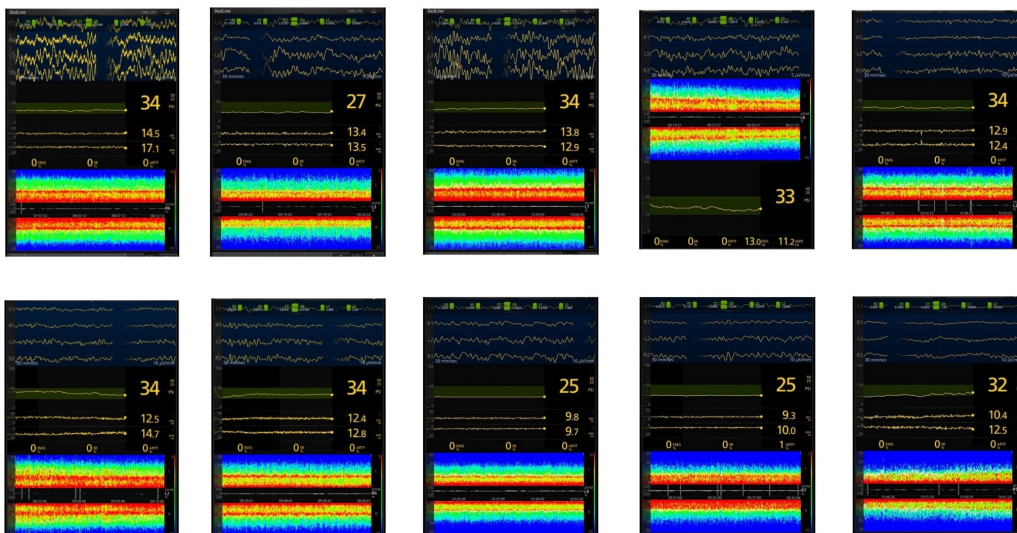


Fig. 6 Secondary quantitative outcome. Data from processed electroencephalography of anesthesia and density spectral array for all ten patients in volatile group. Patients in this figure were labeled $a_3 - j_3$ starting on top left to bottom right. All patients were in anesthetic steady state after skin incision

not by chance. However, statistical analysis did not result in the observed difference being statistically significant. It is well-known that age influence EEG-patterns and therefore the results in this study demand a more nuanced discussion [20, 21]. In a secondary analysis, Obert et al. sought out to evaluate the influence of patients' age on PSI [22]. In this study anesthesia was maintained either by propofol, sevoflurane or desflurane and a linear regression model showed that PSI increased with approximately 2 points per decade and SEF increased with 0.5 Hz per decade. If using their model ($PSI = 0.23 * \text{age} + 22.69$) for sevoflurane a resulting mean PSI would be 33 in the volatile group and 35 in the OFA group in the current study. The delta PSI values (current study minus calculated PSI from model; 35 – 33 and 40 – 35) are 2 and 5 respectively, arguing that there is a factor other than age influencing the higher PSI values seen in OFA. Since no adjunct anesthetic was reported in the aforementioned study we hypothesize, but cannot state, that OFA rather than age is the driver of our findings. Regarding SEF95, one study demonstrated that values differed between age groups receiving general anesthesia with Sevoflurane as single agent. The highest value (16 Hz) was found in the middle age group 55 to 63 years old [23]. The younger and older patient groups who received sevoflurane had lower values, 14 and 15 Hz respectively. In the OFA group the mean SEF95 was 16.4 Hz. In this group there was one outlier with mean SEF95 of 10 Hz, which if removed from analysis raised clustered mean SEF95 for OFA-group further ($17.1, SD \pm 2.3$). With only two patients in the aforementioned age group (55–63), reported by Kanazawa et al., we doubt, but cannot exclude, that age interfered with the higher SEF95 values reported in our study. This indicates that anesthesia providers could expect higher SEF95 values in achieving adequate anesthesia depth in OFA.

Even though maintenance of anesthesia in our OFA-protocol was conducted mainly by sevoflurane and the doses of both esketamine and dexmedetomidine were very low, we saw a different DSA-pattern and quantitative data. Most notably, frequencies in the alpha spectrum were generally missing in conjunction with a high SEF95, at a level more associated with light sedation [5]. We hypothesized that the impact of NMDA-antagonism and α_2 -agonism play an intricate role in this finding. However, it would be reasonable if DSA-pattern were to be more similar with that of volatile group since sevoflurane used in our OFA-protocol is arguably the most dominant in keeping the patient unconscious. If this hypothesis was to be true, there is a low predictability from dexmedetomidine and esketamine on their effect on pEEG since doses used in this study generally were low. We believe that earlier findings, regarding the antinociceptive synergism between esketamine and dexmedetomidine, carry

great influence on our findings [24]. Furthermore, the high SEF95 in the OFA-group indicates that even at a low dose, NMDA-antagonism affects the overall picture.

In the descriptive outcome we saw a DSA-pattern predominately in the theta spectrum for the OFA group. As this might be a signature for OFA it is also possible that this is a consequence of the averagely high dose sevoflurane seen (0.9 compared to 0.8) in the OFA group in comparison to the Volatile group. Earlier research have described that changes in EEG-pattern occur as the dose of isoflurane increases beyond that which cause alpha/delta-pattern [25]. More specifically, increasing the dose of isoflurane beyond that which cause alpha/delta-pattern will canalize the oscillating frequencies in the below 4 Hz range. Another study compared EEG-patterns between sevoflurane and propofol in patients undergoing general anesthesia and found that sevoflurane had larger theta and beta oscillation power, and similar slow and alpha oscillation power [26]. In the light of this we cannot exclude the fact that sevoflurane has influenced the descriptive outcome in a dose dependent manner even though the group-based difference in MAC of 0.1 is considered small. Future studies should standardize the dose of volatile anesthetic to be able to elucidate this further.

This study adds to the perspective of making OFA a safer anesthesia method as well as ensuring that it is up to date regarding newer monitoring adjuncts. Future studies should focus on reproducing findings in this study in larger cohorts. When validated, there is a potential for research in OFA where pEEG is used as a pain prediction adjunct, a research field that has potential but up till now has carried conflicting results.

Strengths and limitations

This study was of prospective design and enrolled consecutive patients who had been randomized to receive a certain type of anesthesia. These groups were not amended regarding this study, as seen when data analysis concluded the groups to be well matched, thus lowering the risk of selection bias. In regard to bias this design and enrollment is seen as this study's greatest strength. We also believe that having anesthesia protocols regarding drug doses, instead of leaving treatment to the discretion of the anesthesiologist, contributed to a decreased risk of attrition bias and confounding.

Previous studies have used 8–13 Hz as the optimal SEF to achieve general anesthesia [27]. With mean SEF-levels of 12.5 Hz for the volatile group and 11.3 Hz for the TIVA group we have kept within the higher span in our study. Despite that we see a clear difference in the OFA-group with SEF levels of 16.4 Hz. This might of course differ a bit depending on the combination of drugs used in the OFA protocol but one should expect a higher level of SEF.

The limitations in this study are several. The patients in the study were recruited as part of an ongoing RCT, including only elective laparoscopic surgery, affecting generalizability. This is also the case with the study-design being limited to one center with its own protocol for OFA. However, we believe that laparoscopic surgery is an excellent routine procedure with elements seen in many types of modern surgical procedures, which challenges the anesthesia team when determining anesthesia depth and nociception. The small sample size, calculated only for PSI, is probably insufficient to draw clear conclusions about DSA-pattern in OFA. We included patients who were risk-stratified as being pain-tolerant, which is a step towards a more differentiated cohort. This was one of the main purposes in the other clinical trial, from which patients in this study were recruited [10]. However, this could potentially affect the generalizability of the result as patients in this study might have a different neurophysiologic response to anesthetic agents.

Even though findings in this study are compelling, we advise readers to observe caution before implementing them into clinical practice as we believe more high-quality studies need to be conducted on this topic.

Conclusion

Findings in this study suggest that OFA affects both quantitative indices and DSA-pattern in pEEG. More specifically, SEF95 and PSI can be expected to be higher compared to other opioid based routine anesthesia methods. Furthermore, DSA-pattern for OFA showed a high power in the theta frequency spectrum, with low power in higher frequency spectrums. More studies are needed in order for these findings to have more robust implications.

Abbreviations

ARTF	Artefacts
ASA	American Society of Anesthesia
BIS	Bispectral index
EEG	Electroencephalography
EMG	Electromyography
MAC	Minimal Alveolar Concentration
NMDA	N-Methyl-D-Aspartate
NSAID	Non-steroidal anti-inflammatory
OFA	Opioid-free anesthesia
PACU	Post-anesthesia care unit
pEEG	Processed Electroencephalography
PSI	Patient State Index
RCT	Randomized Control Trial
SEF	Spectral Edge Frequency
SD	Standard Deviation
SR	Suppression Rate
TIVA	Total Intravenous Anesthesia
TCI	Target Control Infusion

Acknowledgements

We would like to thank the nurses in the preoperative preparations clinic for their dedication and help in the recruitment process.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by KM and AP. The first draft of the manuscript was written by KM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

Open access funding provided by Lund University. This study was given financial support from the research council, Halmstad Halland County and also the southern healthcare region Sweden.

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Oral and written informed consent was given from all participants in this study. Approval was granted by the Swedish Ethical Review Authority of Uppsala University lead by chairman Anna Onell (Date 2023-01-18/ Dnr 2022-07156-02).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 1 October 2024 / Accepted: 11 December 2024

Published online: 24 January 2025

References

- Olaussen A, Svensson CJ, Andrell P, Jildental P, Thorn SE, Wolf A. Total opioid-free general anaesthesia can improve postoperative outcomes after surgery, without evidence of adverse effects on patient safety and pain management: A systematic review and meta-analysis. *Acta Anaesthesiol Scand*. 2022;66(2):170–85.
- Frauenknecht J, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. *Anaesthesia*. 2019;74(5):651–62.
- Beloelil H. Opioid-free anaesthesia. *Best Pract Res Clin Anaesthesiol*. 2019;33(3):353–60.
- Drover DR, Lemmens HJ, Pierce ET, Plourde G, Loyd G, Ornstein E, Pritchep LS, Chabot RJ, Gugino L. Patient State Index: titration of delivery and recovery from propofol, alfentanil, and nitrous oxide anaesthesia. *Anesthesiology*. 2002;97(1):82–9.
- Schwender D, Dauberer M, Mulzer S, Klasing S, Finsterer U, Peter K. Spectral edge frequency of the electroencephalogram to monitor depth of anaesthesia with isoflurane or propofol. *Br J Anaesth*. 1996;77(2):179–84.
- Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical Electroencephalography for Anesthesiologists: Part I: Background and Basic Signatures. *Anesthesiology*. 2015;123(4):937–60.
- Roche D, Mahon P. Depth of Anesthesia Monitoring. *Anesthesiol Clin*. 2021;39(3):477–92.
- Bickford RG, Fleming N, Billinger T. Compression of EEG data. *Trans Am Neurol Assoc*. 1971;96:118–22.
- Fleming RA, Smith NT. An inexpensive device for analyzing and monitoring the electroencephalogram. *Anesthesiology*. 1979;50(5):456–60.
- Mogianos K, Undén J, Persson A. Effect of individualized anaesthesia and analgesia on postoperative pain in patients stratified for pain sensitivity: A study protocol for the PeriOperative individualization trial randomized controlled trial. *Acta Anaesthesiol Scand*. 2024.
- Persson AK, Pettersson FD, Dyrehag LE, Åkeson J. Prediction of postoperative pain from assessment of pain induced by venous cannulation and propofol infusion. *Acta Anaesthesiol Scand*. 2016;60(2):166–76.

12. Persson AKM, Åkeson J. Prediction of Acute Postoperative Pain from Assessment of Pain Associated With Venous Cannulation. *Pain Pract.* 2019;19(2):158–67.
13. Peng F, Li Y, Ai Y, Yang J, Wang Y. Application of preoperative assessment of pain induced by venous cannulation in predicting postoperative pain in patients under laparoscopic nephrectomy: a prospective observational study. *BMC Anesthesiol.* 2020;20(1):86.
14. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth.* 1991;67(1):41–8.
15. Drummond JC, Brann CA, Perkins DE, Wolfe DE. A comparison of median frequency, spectral edge frequency, a frequency band power ratio, total power, and dominance shift in the determination of depth of anesthesia. *Acta Anaesthesiol Scand.* 1991;35(8):693–9.
16. Kim D, Ahn JH, Heo G, Jeong JS. Comparison of Bispectral Index and Patient State Index values according to recovery from moderate neuromuscular block under steady-state total intravenous anesthesia. *Sci Rep.* 2021;11(1):5908.
17. Brown EN, Pavone KJ, Naranjo M. Multimodal General Anesthesia: Theory and Practice. *Anesth Analg.* 2018;127(5):1246–58.
18. Huupponen E, Maksimow A, Lapinlampi P, Sarkela M, Saastamoinen A, Snäpär A, Scheinin H, Scheinin M, Meriläinen P, Himanen SL, et al. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. *Acta Anaesthesiol Scand.* 2008;52(2):289–94.
19. Tsuda N, Hayashi K, Hagiwara S, Sawa T. Ketamine, an NMDA-antagonist, increases the oscillatory frequencies of alpha-peaks on the electroencephalographic power spectrum. *Acta Anaesthesiol Scand.* 2007;51(4):472–81.
20. Obert DP, Schweizer C, Zinn S, Kratzer S, Hight D, Sleight J, Schneider G, García PS, Kreuzer M. The influence of age on EEG-based anaesthesia indices. *J Clin Anesth.* 2021;73:110325.
21. Ni K, Cooter M, Gupta DK, Thomas J, Hopkins TJ, Miller TE, James ML, Kertai MD, Berger M. Paradox of age: older patients receive higher age-adjusted minimum alveolar concentration fractions of volatile anaesthetics yet display higher bispectral index values. *Br J Anaesth.* 2019;123(3):288–97.
22. Obert DP, Schneider F, Schneider G, von Dincklage F, Sepulveda P, García PS, Kratzer S, Kreuzer M. Performance of the SEDLine Monitor: Age Dependency and Time Delay. *Anesth Analg.* 2023;137(4):887–95.
23. Kanazawa S, Oda Y, Maeda C, Okutani R. Electroencephalographic effect of age-adjusted 1 MAC desflurane and sevoflurane in young, middle-aged, and elderly patients. *J Anesth.* 2017;31(5):744–50.
24. Riccardi A, Serra S, De Iaco F, Fabbri A, Shiffer D, Voza A, Study. Research Center of the Italian Society of Emergency M: Uncovering the Benefits of the Ketamine-Dexmedetomidine Combination for Procedural Sedation during the Italian COVID-19 Pandemic. *J Clin Med* 2023, 12(9).
25. Hagiwara S. Changes in the electroencephalogram during anaesthesia and their physiological basis. *Br J Anaesth.* 2015;115(Suppl 1):i27–31.
26. Akeju O, Westover MB, Pavone KJ, Sampson AL, Hartnack KE, Brown EN, Purdon PL. Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. *Anesthesiology.* 2014;121(5):990–8.
27. Jildenstal P, Backstrom A, Hedman K, Warren-Stomberg M. Spectral edge frequency during general anaesthesia: A narrative literature review. *J Int Med Res.* 2022;50(8):3000605221118682.

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Paper VI



Article

Venous Cannulation Pain as a Marker of Postoperative Pain Vulnerability: A Pre-Specified Secondary Analysis of a Randomized Controlled Trial

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Abstract

Background: Identification of patients at risk and prevention of acute postoperative pain (APOP) are central to individualized anesthesia and analgesia. Venous cannulation pain (VCP) has shown promise as a predictor of APOP. In the PeriOperative Individualization Trial (POPIT), VCP was evaluated as a pain-sensitivity stratification method to guide anesthesia and reduce postoperative pain. This report presents a predefined secondary analysis with the primary aim to evaluate VCP as a method for postoperative pain prediction. As a secondary aim, we sought to explore factors that influence VCP. **Methods:** 271 patients were stratified into two cohorts, high-risk ($VCP \geq 2.0$) and low-risk ($VCP < 2.0$), for APOP, based on their VCP. Within each group, patients were randomized to receive either: standard care or opioid-free anesthesia (low-risk cohort), and standard care or multimodal anesthesia with opioids (high-risk cohort). Differences in acute and persistent pain, quality of recovery, postoperative opioid consumption, and proportion of patients experiencing moderate to severe APOP depending on VCP levels were investigated. The predictive capacity of VCP was evaluated and adjusted for in terms of potential confounders. **Results:** High-risk patients, grading $VCP \geq 2.0$ (VAS units) experienced more APOP on the day of surgery (difference 0.9 NRS-units, 95% CI 0.2–1.6, $p = 0.009$) and after 24 h during movement (difference 0.6 NRS-units, 95% CI 0.0–1.3, $p = 0.048$). Patients grading $VCP < 2.0$ had better quality of recovery after 24 hr (difference 7, 95% CI 1–13, $p = 0.002$) and lower postoperative opioid consumption (difference 7.5 mg, 95% CI 5.7–9.3, $p < 0.001$). The OR for $VCP \geq 2.0$ to predict APOP in PACU was 1.76 (95% CI 1.02–3.04, $p = 0.043$), but in a multivariate model, adjusted for age, $VCP \geq 2$, gender, pain catastrophizing, preoperative pain, and pain on the day of surgery, female gender was the only independent predictor of APOP (OR 2.65 (95% CI 1.33–5.29), $p = 0.006$). **Conclusions:** Pain during venous cannulation as a predictor of acute pain after surgery was significant in univariate regression, but the results were lost when adjusting for confounders like gender and current pain. However, VCP continues to show potential in associated postoperative recovery outcomes such as opioid consumption. The level of pain associated with venous cannulation is influenced by gender, preoperative pain, and current pain on the day of surgery. Pain sensitivity stratification needs refinement before implementation in clinical practice.



Academic Editor: Cyrus Motamed

Received: 4 December 2025

Revised: 30 December 2025

Accepted: 19 January 2026

Published: 22 January 2026

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Keywords: venous cannulation; postoperative pain; pain prediction; individualization; pain sensitivity

1. Introduction

Prevention and treatment of acute postoperative pain (APOP) is, despite many years of scientific interest, an ongoing challenge. Traditionally, procedure-specific treatment protocols have been used, but the focus is shifting towards individualized therapeutic strategies to manage APOP, postoperative recovery, and persistent postoperative pain (PPOP) [1,2]. Risk factors for APOP include female gender, younger age, pre-operative pain, psychosocial factors (e.g., anxiety and depression), certain types of surgery, specifically surgery with nerve damage, and large skin incision [3–6]. Various preoperative screening methods have been proposed to help predict the risk of APOP. These include psychometric evaluations, quantitative sensory testing (QST), serologic biomarkers, genetic profiling, and real-time perioperative monitoring. Integrative models combining multiple risk factors are also being explored. However, none of these methods have yet demonstrated sufficient predictive accuracy and feasibility for routine clinical use [7–9].

Pragmatic approaches have been developed to assess pain sensitivity during routine preoperative procedures. These include tourniquet-induced pain and pain from subcutaneous local anesthetic injection before spinal anesthesia [10,11]. Similarly, pain associated with peripheral venous cannulation, “venous cannulation pain” (VCP), has been linked to earlier requests for epidural analgesia in obstetric patients [12] and has also been shown to predict acute pain in the perioperative setting. In a study on elective laparoscopic cholecystectomies, pain-sensitive patients grading their VCP above 2.0 VAS units had 3.4 times higher odds of moderate to severe APOP [13]. Similarly, in a mixed group of patients undergoing different surgical procedures, the OR for pain-sensitive patients ($VCP \geq 2.0$) was 1.7 [14]. These results were further confirmed in an independent cohort undergoing laparoscopic nephrectomy, showing that VCP predicted moderate to severe APOP with an OR of 3.5 and a strong correlation with APOP ($r_s = 0.64$) [15]. VCP is a quick, intuitive method and merits further investigation as a tool for individualized perioperative pain management.

This study was a pre-specified secondary analysis of the PeriOperative Individualization Trial (POPIT), which aimed to improve pain outcomes by individualizing anesthesia for patients in a randomized, controlled study based on a stratified risk for postoperative pain. Here we present data in terms of VCP as a stratification method and explore its use in individualized anesthesia. The primary aim of this pre-specified secondary analysis was to evaluate VCP as a method for postoperative pain prediction when accounting for potential confounders. Our secondary aim was to evaluate factors that may influence VCP. We present results on persistent pain for the first time and associations with other preoperative risk factors like gender, age, psychometric variables, and preoperative pain.

2. Methods

2.1. Study Design and Ethics

The POPIT is a randomized, controlled, patient- and assessor-blinded, single-center, parallel-group clinical trial. The protocol was approved by the Swedish Ethical Review Authority (approval number 2020-06178) and complies to the ethical principles of the declaration of Helsinki. This manuscript was written in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and was also pre-published in ClinicalTrials.gov (ID NCT04751812). In favor of total transparency, the study protocol and methods have been pre-published. As a pre-specified secondary outcome, the ability of VCP to predict APOP and PPOP and its relationship to other perioperative risk factors were the focus of this study.

2.2. Patient Recruitment

The recruitment and data gathering process was ongoing between March 2022 and February 2024.

Inclusion criteria were elective laparoscopic surgery, age > 18 years, American Society of Anesthesiologist (ASA) class < III, and the ability to understand and accommodate information in Swedish. Exclusion criteria were refusal to participate or withdrawal of consent, pregnancy, allergy towards NSAID, and conversion to open abdominal surgery.

2.3. Preoperative Evaluation

Self-reported information regarding age, gender, psychometric evaluation, and preoperative pain were collected preoperatively. For psychometric evaluation, we used the pain catastrophizing scale (PCS), a questionnaire with 13 questions measuring the negative orientation around the thought of pain [16]. Participants rate statements on a scale of 0 (not at all) to 4 (all the time), with a maximum score of 52. A few recent studies have correlated the PCS to the intensity of APOP [17,18] and PPOP [19,20]. Patients were also asked about depression or ongoing treatment for depression (yes/no).

Patients were asked to state the presence of preoperative pain lasting more than 3 months (yes/no), preoperative pain during the last 2 weeks (yes/no), as well as the usage of analgesics (yes/no). Upon arrival at the preoperative preparation unit, patients were asked to grade their current pain on the day of surgery (NRS units).

2.4. Venous Cannulation Pain

All patients received an intravenous cannula, either at the dorsal aspect of the hand or antecubital fossa on the upper extremity, by a nurse with at least 3 years of working experience. After venous cannulation, patients were asked to grade their pain associated with the successful procedure on a handheld visual analog scale (VAS) where far left was described as no pain and denoted 0.0, and far right was described as the worst pain imaginable corresponding to 10.0. Patients grading their VCP < 2.0 were stratified as “low-risk”, while patients grading their pain as VCP $\geq$ 2.0 were considered “high-risk”. Thus, low-risk and high-risk cohorts were created from the initial sample. The cut-off (VCP < 2.0/VCP $\geq$ 2.0) was derived from previous independent studies concluding this to have promising predictive performance [13–15].

2.5. Anesthesia Protocol

Patients’ risk stratified as “high-risk” (VCP $\geq$ 2.0) were randomized to receive anesthesia either as standard of care (SOC) or multimodal anesthesia (MAO). Patients’ risk-stratified as “low-risk” (VCP < 2.0) were randomized to either SOC or opioid-free anesthesia (OFA). Details in terms of anesthesia protocols can be found in the pre-published protocol article. The randomization process was conducted in a 1:1 fashion for each cohort. All were given premedication with paracetamol, etoricoxib, and ondansetron. All but the OFA group were also given preemptive oxycodone. Maintenance of anesthesia were facilitated with a combination of sevoflurane/remifentanyl or propofol/remifentanyl (SOC and MAO) or sevoflurane/esketamine/dexmedetomidine (OFA). Before terminating general anesthesia, postoperative analgesia was given at a dose of 0.1 mg/kg oxycodone iv for SOC and MAO groups. Perioperative anti-nociception with esketamine and clonidine iv was given in the MAO group. The OFA group was given dexmedetomidine, esketamine and lidocaine as intraoperative anti-nociception.

2.6. Outcomes

Outcomes in this study were pre-specified as secondary outcomes in the POPIT. The main outcomes were the differences in worst APOP in the PACU and after 24 h at rest and during movement ($APOP_{POD0}$, $APOP_{POD1rest}$, $APOP_{POD1movement}$), as well as the differences in PPOP after 3 and 6 months at rest and during movement ($PPOP_{POD90rest}$, $PPOP_{POD90movement}$, $PPOP_{POD180rest}$, $PPOP_{POD180movement}$), between “high-risk” and “low-risk” patients in both the full cohort and the SOC-only cohort. Furthermore, the proportions of patients experiencing moderate to severe pain ($NRS \geq 4$) in the PACU and after 24 h, the differences in postoperative opioid consumption, and the quality of recovery (QoR_{POD1}) between “high-risk” and “low-risk” patients in both the full cohort and the SOC-only cohort were compared. Postoperative opioid consumption was defined as the sum of intraoperatively given oxycodone, before terminating general anesthesia, and postoperative rescue opioids until discharge from the post anesthesia care unit (PACU). This was measured using intravenous morphine milligram equivalents (MME), calculated by multiplying the intravenous dose of oxycodone by 1.5. Since only short-acting opioids (remifentanyl) were used intraoperatively, this was not considered as postoperative opioid consumption.

2.7. Statistical Analysis

The full cohort from the POPIT was analyzed in this study. Since the main purpose was to assess VCP as a preoperative method to predict risk of APOP, patients in each cohort were clustered to obtain higher power and more robust data. As presented in the results of the POPIT, there was no difference in pain outcome between treatment arms in the two cohorts justifying the use of all patients in this study [21,22]. However, we have presented an evaluation of the differences in the two standard of care arms.

As POPIT was a pragmatic interventional trial meant to be able to show a clinically significant difference in APOP, a sample effect of 1.5 NRS units was chosen as this is in line with what is clinically meaningful for patients [23,24]. Previous studies in our institution have shown a SD of 2.8 and 2.7 in the high-risk cohort and low-risk cohort, respectively [13]. Collectively, 280 patients were needed to answer the primary research question in POPIT and account for a 20% dropout rate.

For all outcomes, the goal was to detect superiority between cohorts. Thus, in outcomes based on continuous data, hypothesis testing was conducted using the two-sided Independent T-test. For dichotomized pain outcomes, cohort comparison was performed using four-by-four contingency tables and the Chi-Square test.

Lastly, the predictive capability of VCP was analyzed with a stepwise multivariate logistic regression model with moderate to severe APOP ($NRS \geq 4$) as a dependent variable. Candidate predictors were selected based on clinical relevance (preoperative pain, age, BMI, gender) and prior ambiguous evidence from the literature (PCS). In addition, variables showing a potential association with the outcome ($p < 0.1$ in univariate analysis) were retained for multivariate modeling. In the final step, a significance level of $p < 0.05$ was selected to mark the variable as an independent predictor. With a similar modus, we also conducted a multivariate logistic regression, with $VCP \geq 2.0$ as a dependent variable, to investigate which variables influenced its value. Since the focus in this study was to evaluate VCP, how it influences APOP, and in turn what influences this variable, the same candidate predictors were used as in the initial model for APOP. To address concerns about model overfitting, discrimination was assessed by the area under the ROC curve (AUC). The calibration was assessed by calibration-in-the-large (intercept), calibration slope (e.g., regressing the outcome on the model’s linear predictor), and the Hosmer–Lemeshow test. The coefficient stability was examined with BCa bootstrapping (1.000 resamples).

All statistical analyses were performed using IBM SPSS Statistics (version 29), with a significance level set at $p < 0.05$.

3. Results

In this pre-specified secondary analysis, a total of 271 patients were included. All of them were assessed for APOP and postoperative opioid consumption up to discharge from the PACU. On POD1, 12 patients were lost to follow-up, leaving 259 patients available for analysis of APOP_{POD1rest}, APOP_{POD1movement}, and QoR_{POD1}. Of the previous 12 patients who were initially lost to follow-up on POD1, 8 were later able to provide data for PPOP at 90 and 180 days. (Figure 1). Background characteristics of the study population are summarized in Table 1 (Table 1).

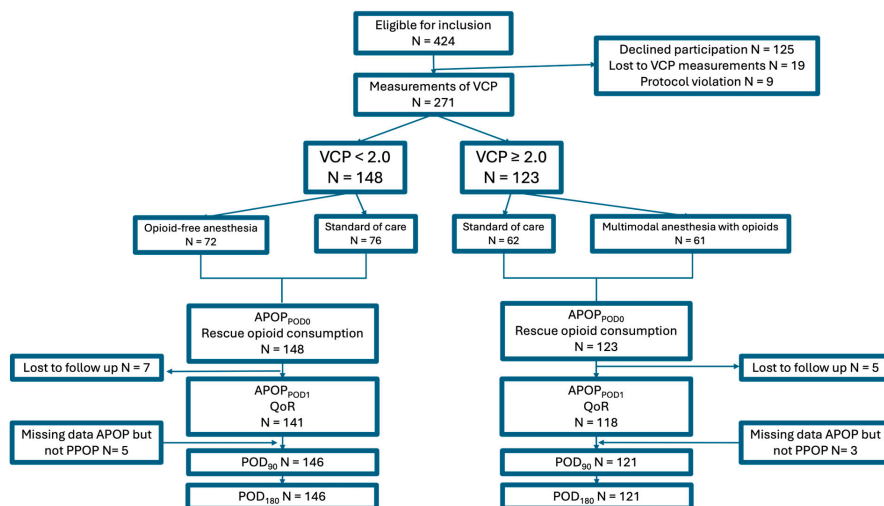


Figure 1. Inclusion flow-chart. Abbreviations: APOP; acute postoperative pain, POD; postoperative day, QoR; quality of recovery, VCP; venous cannulation pain, PPOP; Persistent Postoperative Pain.

Table 1. Preoperative data and group-based comparison between high-risk and low-risk groups in both the full cohort and standard of care only cohort, respectively.

	Full Cohort			SOC-Groups		
	High-Risk (VCP ≥ 2.0), n = 123	Low-Risk (VCP < 2.0), n = 148	p-Value	High-Risk (VCP ≥ 2.0), n = 62	Low-Risk (VCP < 2.0), n = 76	p-Value
Age, (SD)	53 (±16)	56 (±16)	0.099	53 (±16)	57 (±15)	0.146
Female gender, n (%)	105 (86.1)	107 (72.3)	0.006 **	55 (75.0)	57 (88.7)	0.040 *
Body mass index, kg/m ² (SD)	26.8 (±5.2)	26.5 (±4.6)	0.671	26.9 (±5.0)	28.6 (±24.2)	0.593
ASA, n (%)						
I	50 (42.6)	59 (40.1)	0.800	24 (38.7)	32 (42.7)	0.639
II	70 (57.4)	88 (59.9)		38 (61.3)	43 (57.3)	
Preoperative pain, n (%)	67 (54.5)	65 (43.9)	0.072	35 (56.5)	30 (39.5)	0.047 *
Current pain on day of surgery, NRS (SD)	1.8 (±2.4)	0.9 (±1.4)	<0.001 **	0.8 (±1.2)	1.9 (±2.5)	<0.001 **
Preoperative depression, n (%)	17 (13.8)	15 (10.1)	0.336	8 (12.9)	6 (7.9)	0.332
PCS, (SD)	15 (±10)	13 (±9)	0.046 *	15 (±10)	13 (±9)	0.321

Table 1. Cont.

	Full Cohort			SOC-Groups		
	High-Risk (VCP ≥ 2.0), <i>n</i> = 123	Low-Risk (VCP < 2.0), <i>n</i> = 148	<i>p</i> -Value	High-Risk (VCP ≥ 2.0), <i>n</i> = 62	Low-Risk (VCP < 2.0), <i>n</i> = 76	<i>p</i> -Value
VCP, VAS (SD)	3.7 (± 1.7)	0.8 (± 0.6)	<0.001 **	3.8 (± 1.9)	0.7 (± 0.6)	<0.001 **
Lap. rectum resection	7 (5.7)	16 (10.8)		6 (9.7)	9 (11.8)	
Lap. hemicolectomy	8 (6.6)	12 (8.1)		3 (4.8)	10 (13.2)	
Lap. colectomy	0 (0.0)	2 (1.4)		0 (0.0)	1 (1.3)	
Lap. sigmoideum resection	14 (11.5)	4 (2.8)		6 (9.7)	2 (2.6)	
Lap. cholecystectomy	28 (23.0)	42 (34.4)		16 (25.8)	19 (25.0)	
Lap. hernia repair	3 (2.5)	13 (8.8)		1 (1.6)	5 (6.6)	
Lap. adrenal resection	1 (0.8)	1 (0.7)		1 (1.6)	0 (0.0)	
Lap. ovarian cyst enucleation	9 (7.4)	5 (3.4)		4 (6.5)	2 (2.6)	
Lap. uni/bilateral salphingoophorectomy	21 (17.2)	24 (16.2)		11 (17.7)	13 (17.1)	
Lap. hysterectomy	31 (25.4)	29 (19.6)		14 (22.6)	15 (19.7)	

Abbreviations: SD; Standard deviation, ASA; American society of anesthesiologists' physical status classification system, NRS; Numeric rating scale, PCS; Pain catastrophizing scale, VCP; Venous cannulation pain, VAS; Visual analog scale. Statistically significant differences are marked by an asterisk (*) in conjunction with the absolute value. * Significance at 0.05 level. ** Significance at 0.01 level.

3.1. Postoperative Pain

3.1.1. Acute Postoperative Pain

High-risk patients (VCP ≥ 2.0) reported higher levels of APOP (in the PACU and at POD1) compared to low-risk patients (VCP < 2.0), in both cohorts. Group-based difference in worst APOP_{PACU} were 0.9 (95% CI 0.2–0.6, $p = 0.009$) and 1.1 (95% CI 0.0–2.0, $p = 0.047$) NRS-units for the full cohort and SOC-only cohort, respectively. Worst APOP_{POD1} was consistently higher in the high-risk group for the full cohort, but a statistically significant difference was only found during movement (group-based difference 0.6, 95% CI 0.0–1.2, $p = 0.048$) (Figure 2). This pattern was consistent between SOC-only groups and statistically significant both at rest (group-based difference 1.2, 95% CI 0.2–2.1, $p = 0.016$) and during movement (group-based difference 0.9, 95% CI 0.1–1.8, $p = 0.039$) (Table 2).

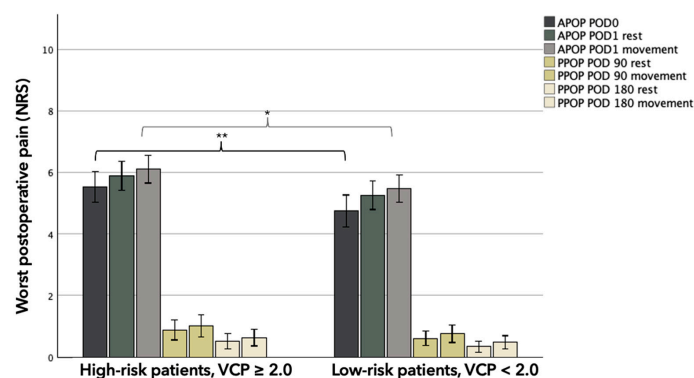


Figure 2. Bar chart depicting worst postoperative pain levels (NRS) grouped after levels of pain associated with venous cannulation. Whiskers represent 95% CI. Abbreviations: APOP; Acute Postoperative Pain, PPOP; Persistent Postoperative Pain, POD; postoperative day, NRS; numeric rating scale, VCP; venous cannulation pain. * Significance at 0.05 level. ** Significance at 0.01 level.

Table 2. Postoperative outcomes and group-based comparison between high-risk and low-risk groups as group-based mean values with standard deviation.

	All Patients				Standard of Care Groups Only			
	VCP < 2.0	VCP ≥ 2.0	p-Value	95% CI	VCP < 2.0	VCP ≥ 2.0	p-Value	95% CI
APOP _{POD0} NRS (± SD)	4.7 (3.1)	5.6 (2.7)	0.009 **	0.2–1.6	4.5 (3.1)	5.6 (2.8)	0.047 *	0.0–2.0
APOP _{POD1rest} NRS (± SD)	5.3 (2.8)	5.9 (2.5)	0.063	0.0–1.2	4.9 (2.8)	6.1 (2.6)	0.016 *	0.2–2.1
APOP _{POD1movement} NRS (± SD)	5.5 (2.7)	6.1 (2.4)	0.048 *	0.0–1.3	5.3 (2.7)	6.2 (2.4)	0.039 *	0.0–1.8
QoR _{POD1} mean (± SD)	100 (25)	93 (23)	0.018 *	1–13	102 (24)	94 (23)	0.048 *	0–17
PPOP _{POD90rest} NRS (± SD)	0.6 (1.4)	0.9 (1.7)	0.146	−0.1–0.7	0.7 (1.5)	0.8 (1.7)	0.593	−0.4–0.7
PPOP _{POD90movement} NRS (± SD)	0.7 (1.7)	1.0 (1.9)	0.267	−0.2–0.7	0.8 (1.8)	0.9 (2.0)	0.831	−0.6–0.7
PPOP _{POD180rest} NRS (± SD)	0.3 (1.1)	0.5 (1.4)	0.264	−0.1–0.5	0.4 (1.1)	0.3 (1.0)	0.990	−0.4–0.4
PPOP _{POD180movement} NRS (± SD)	0.5 (1.3)	0.6 (1.5)	0.335	−0.2–0.5	0.4 (1.1)	0.5 (1.3)	0.562	−0.3–0.5
Postoperative opioids MME Mg (± SD)	10.0 (8.3)	17.5 (5.9)	<0.001 **	5.8–9.2	15.2 (6.5)	17.5 (6.5)	0.048 *	0.1–4.5

Abbreviations: APOP; Acute postoperative pain, MME; Morphine milligram equivalents, NRS; Numeric rating scale, POD; Postoperative day, PPOP; Persistent postoperative pain, QoR; Quality of recovery, SD; Standard deviation. Statistically significant difference is marked by an asterisk (*) in conjunction with the absolute value. * Significance at 0.05 level. ** Significance at 0.01 level.

3.1.2. Persistent Postoperative Pain

PPOP at POD 90 and POD 180 did not differ significantly between the groups. The pain scores at rest and during movement were numerically higher in the high-risk group, but none of these comparisons reached statistical significance in either the full cohort or the SOC-only cohort (Table 2) (Figure 2).

3.1.3. Risk Factors for Acute Postoperative Pain

A stepwise multivariate logistic regression for the full cohort was performed to identify independent predictors for moderate to severe APOP_{PACU} (NRS ≥ 4). In the univariate model, six variables were significantly associated with the outcome (Table 3). Subsequently, in the multivariate model, female gender was the only independent risk factor for moderate to severe APOP_{PACU} (OR = 2.65, 95% CI 1.33–5.29, $p = 0.006$). This association was consistent for moderate to severe APOP_{POD1}, (female gender: OR = 2.20, 95% CI 1.05–4.56, $p = 0.036$). Additionally, at this timepoint, age reduced the odds for NRS ≥ 4 by 30% for each 10-year increase in age ($p = 0.002$), and PCS acted as independent risk factors for moderate to severe APOP_{POD1} (OR = 1.04, 95% CI 1.00–1.07, $p = 0.045$).

Table 3. Stepwise multivariate logistic regression for moderate to severe APOP in the PACU as dependent variable, with predefined variables in terms of clinical significance and earlier scientific merits (PCS).

Predictor	Univariate OR (95% CI)	p-Value	Multivariate OR (95% CI)	p-Value
VCP ≥ 2.0	1.76 (1.02–3.04)	0.043 *	1.31 (0.73–2.36)	0.361
Current pain	1.22 (1.03–1.45)	0.022 *	1.06 (0.88–1.27)	0.551
Female	3.21 (1.75–5.89)	<0.001 *	2.65 (1.33–5.29)	0.006 **
Age	0.98 (0.97–0.99)	0.039 *	1.00 (0.98–1.02)	0.699

Table 3. Cont.

Predictor	Univariate OR (95% CI)	p-Value	Multivariate OR (95% CI)	p-Value
PCS	1.04 (1.01–1.07)	0.019 *	1.03 (0.99–1.06)	0.133
BMI	1.01 (0.98–1.03)	0.675	-	-
Preoperative pain	2.29 (1.32–3.98)	0.003 *	1.76 (0.95–3.24)	0.071

Significance level for univariate logistic regression $p < 0.1$ are highlighted in bold with single asterisk (*). For the multivariate model, only female gender acted as an independent risk factor for moderate to severe APOP (NRS ≥ 4) in the PACU. Significance level of $p < 0.05$ are highlighted as bold and with double asterisk (**).

3.1.4. Multivariate Model Performance

Among 271 patients, 193 (71%) had NRS ≥ 4 . With six predictors, the events per variable was ~ 32 . Apparent discrimination was AUC = 0.691 (95% CI 0.628–0.754, $p < 0.001$) and 0.738 (95% CI 0.679–0.797, $p < 0.001$) for moderate to severe APOP_{PACU} and APOP_{POD1}. Calibration was acceptable for both time points: intercept ≈ 0.00 (95% CI -0.44 – 0.44) and calibration slope ≈ 1.00 (95% CI 0.60–1.40); Hosmer–Lemeshow $p = 0.213$ (APOP_{PACU}), $p = 0.459$ (APOP_{POD1}). In 1000 sample BCa bootstrapping, female gender remained a robust adjusted predictor, whereas age, pain- and PCS-related predictors were not robust after adjustment, which was consistent with collinearity among related constructs.

3.2. Venous Cannulation Pain

A multivariate logistic regression analysis was performed looking at factors potentially influencing the VCP level (Table 4). The model demonstrated acceptable calibration, as assessed by the Hosmer–Lemeshow goodness-of-fit test ($p = 0.801$). In the final model, preoperative current pain on the day of surgery (OR = 1.23, 95% CI 1.05–1.43, $p = 0.008$) and female gender (OR = 2.25, 95% CI 1.11–4.55, $p = 0.024$) were independent predictors for VCP ≥ 2.0 , as was the pre-specified cut-off. Other variables, including age, PCS, and preoperative pain, were not significantly associated with VCP ≥ 2.0 in the multivariate model.

Table 4. Stepwise multivariate logistic regression for VCP ≥ 2.0 as a dependent variable, with predefined variables in terms of clinical significance and earlier scientific merits (PCS).

Variable	Univariate OR (95% CI)	p-Value	Multivariate OR (95% CI)	p-Value
Current pain	1.28 (1.14–1.44)	<0.001 *	1.23 (1.05–1.43)	0.008 **
Female gender	2.65 (1.56–4.52)	0.003 *	2.25 (1.11–4.55)	0.024 **
Age	0.99 (0.97–0.99)	0.068 *	0.99 (0.98–1.02)	0.868
PCS	1.03 (1.00–1.05)	0.050 *	1.02 (0.99–1.04)	0.279
BMI	0.99 (0.97–1.01)	0.501	-	-
Preoperative pain	1.53 (1.02–2.29)	0.084 *	0.98 (0.58–1.72)	0.990

Significance level cut-off for univariate logistic regression $p < 0.1$ are highlighted in bold with a single asterisk (*). For the multivariate model, female gender, and preoperative current pain on the day of surgery influenced VCP ≥ 2.0 . Significance level of $p < 0.05$, highlighted as bold and with a double asterisk (**).

4. Discussion

In this study, VCP was associated with higher APOP and greater opioid consumption in unadjusted group comparisons. Patients with VCP ≥ 2.0 reported significantly more pain in the PACU and at POD1, and had better recovery scores, suggesting that nociceptive sensitivity, with VCP as a surrogate, may reflect a broader vulnerability to postoperative pain. However, when controlling for other variables in a multivariate regression, VCP did

not remain an independent predictor for APOP, indicating that while preoperative VCP may be associated with worse pain outcomes, its predictive value is likely confounded by other factors, mainly female gender. However, VCP may reflect a preoperative pain-sensitive phenotype and provides a practical way to add nuance to how we phenotype patients who otherwise arrive in the operating theater as an undifferentiated group. From a clinical perspective, this means VCP should not be viewed as a standalone predictor but as part of a broader risk profile. While the effect size for VCP was modest after adjustment, its ability to capture a dimension of vulnerability remains relevant for early identification and individualized perioperative strategies. Furthermore, VCP's ability to reflect individual pain sensitivity aligns with evidence supporting other preoperative pain prediction methods [7]. This suggests that VCP could complement existing strategies and help tailor perioperative pain management more effectively.

In regards to gender, since the cohort in this study consisted mainly of female patients (full cohort; 79%, SOC cohort; 82%) due to high proportion of gynecological procedures, the skewed sample does not exclude the possibility that gender in fact does not influence VCP. In this study, $VCP \geq 2.0$ was more common among women (50% vs. 28%), and women had higher APOP_{PACU} incidence (77% vs. 52%). However, the small sample size in the male subgroups ($n = 58$, $n = 16$ with $VCP \geq 2.0$) precludes us from drawing any certain conclusions about the interaction between gender and VCP. Other studies on VCP as a prediction tool did not find any gender-based influence on its outcome [13–15]. In the overall perioperative literature, female gender is widely accepted as an independent risk factor for postoperative pain [25–27]. For pain in general, 45% of women and 31% of men reported experiencing pain during their lifetime [28]. Before inferring casual inference, other factors such as biological (hormonal fluctuations), psychosocial factors (pain catastrophizing, cultural norms around pain expression), and measurement bias (differences in reporting behavior) must be further elucidated [29,30].

The differences in APOP depending on VCP levels presented in this study are smaller than in previous studies. Several factors may explain this. Earlier studies by Persson [13] and Peng [15] excluded patients with preoperative pain, whereas our cohort included many patients with significant pain before surgery. Since preoperative pain is one of the strongest predictors of postoperative pain, this likely influenced our results. Consequently, our cohort was heavily skewed toward high-risk patients for APOP.

The difference in APOP was smaller than what we have regarded as clinically meaningful, but we argue that the test's easy accessibility, such as not demanding equipment or procedures not otherwise used, still adds value in the assessment of pain sensitivity.

Despite the cohort being high-risk, 148 patients were classified as low-risk and 123 patients as high-risk based on VCP. This imbalance raises questions about the sensitivity and specificity of VCP in this context. Specifically, in a high-risk cohort, sensitivity may be reduced if VCP misclassifies high-risk patients as low-risk, while specificity may be distorted due to the rarity of true low-risk cases. Future studies may need to recalibrate VCP thresholds for imbalanced cohorts or apply propensity score adjustments to balance covariates.

Unlike regression modeling (models the outcome), which focuses on estimating the effect of predictors on the outcome, propensity score methods (models the exposure) ensure that patients classified as high- or low-risk for APOP are comparable in terms of baseline characteristics. This was not pre-specified in our statistical plan. However, when performing a post hoc propensity score adjustment for the same variables used in the multivariate logistic regression model, VCP still did not act as an independent predictor. The propensity score was highly significant ($p < 0.001$), indicating that baseline covariates explain most of the variation in APOP risk.

Another difference is that, in this study, the location for cannulation varied. In previous studies with higher predictive values, the anatomical location for cannulation was limited to the back of the hand, which is known to be more painful. In another cohort of 505 patients, the VCP intensity was scored significantly lower in the antecubital fossa than on the back of the hand (1.0 vs. 2.0 VAS units, $p < 0.001$), and when combining sites of cannulation found an OR of 1.7 (95% CI 1.2 to 2.6, $p = 0.005$) for $VCP \geq 2.0$ to render moderate to severe APOP [14]. Studies that measured VCP using cannulation at the back of the hand have reported the strongest associations, with odds ratios of 3.4 and 3.5, respectively [13,15]. One study failed to even show an association with VCP using only the back of hand (0.88, 95% CI -0.18 – 1.94 , $p = 0.10$) in a cohort of 102 patients undergoing knee arthroplasty in spinal anesthesia [31]. Both latter studies included patients with preoperative pain, whereas the study that failed to show an association only included patients receiving spinal anesthesia, which has previously been shown to influence results [14].

There are some limitations to this study. We included patients of both genders, but it turns out the cohorts were overrepresented by females. This is most likely related to the fact that we perform gynecological surgeries at our hospital but not urologic. However, there was no gender difference in other abdominal surgery types. The mean age was 55 years, which in this context is quite young. And no less than 47% answered yes to the question of having had preoperative pain lasting more than 3 months before surgery. At first glance, this might look like a typical cohort for major surgery, but in reality, it is relatively young, predominantly female, and characterized by high levels of preoperative pain. The small male subgroup ($n = 58$, only 16 with $VCP \geq 2.0$) limits power to detect gender-based interaction effects. Given these findings, VCP's unique predictive value appears limited once gender is accounted for. Modeling VCP as a continuous variable and evaluating incremental discrimination and calibration may clarify whether VCP adds meaningful predictive performance beyond established risk factors. Larger, gender-balanced studies are needed to confirm these observations.

Another limitation worth noting is the generally high levels of APOP observed in this study. In the PACU, 72% of patients experienced moderate to severe APOP, with mean pain scores of $5.0 (\pm 3.0)$ NRS units. On POD 1 at rest, 69% reported similar pain levels, averaging $5.4 (\pm 2.7)$. Persistent postoperative pain (PPOP) was present in 27% of patients at 3 months ($NRS \geq 1.0$) and 19% at 6 months. Even though it is minimally invasive, laparoscopy is known to be associated with high APOP [6,32]. The skewness of gender and the high presence of preoperative pain may explain this, as the cohort can be considered as high-risk for APOP. We were also surprised by the overall low doses of opioids administered in the PACU. This will surely be something for us to improve in the future.

Although 271 participants were included in the multivariate analysis, the sample size may still be insufficient to fully support complex modeling. This could limit robustness and generalizability because confidence intervals for several predictors were wide, and some associations that were significant in the univariate analysis (e.g., all but gender) lost significance after adjustment. Such instability suggests reduced power to detect smaller effects and a higher risk that estimates may vary in other populations.

Finally, the difference in anesthesia and analgesia strategy has the potential to influence APOP due to different pharmacodynamic properties. It lies within every anesthesiologist's belief that we can modulate outcomes with our pharmacological interventions. However, in the main study, which aimed to pharmacologically intervene upon APOP in different risk cohorts, there was no statistical difference between the groups [21,22]. Thus, we believe that the difference in pharmacological interventions in this sample did not contribute to significant bias in this study.

One of the main strengths of this study is its original randomized design, which provides strong internal validity by minimizing the risk of bias. Although this pre-specified analysis was secondary, the controlled nature of the trial reduces the likelihood of confounding factors, thereby strengthening the causal interpretation of the findings. In addition, the POPIT was designed as a pragmatic trial, enhancing its relevance and applicability to real-world clinical practice. Finally, the study protocol was published in advance and all outcomes in this study were pre-specified, reducing the risk of type I errors and increasing transparency.

5. Conclusions

In conclusion, VCP levels were able to predict risk for moderate to severe APOP with an OR of 1.8 in a univariate regression model, but, in this cohort, VCP's predictive performance did not withstand adjustment for known clinical confounders, mainly driven by gender. Moreover, VCP was not effective in predicting PPOP. Current pain on the day of surgery and female gender influenced the pain associated with venous cannulation.

Future studies should aim to replicate these findings with a more gender-balanced sample. Furthermore, such studies should also explore whether different cut-off values for VCP and combining VCP with other risk factors might improve predictive accuracy in order to acquire a more robust model.

Author Contributions: Conceptualization, A.K.M.P. and K.M.; methodology, A.K.M.P. and K.M.; software, A.K.M.P. and K.M.; validation, A.K.M.P. and K.M.; formal analysis, A.K.M.P. and K.M.; investigation, A.K.M.P. and K.M.; resources, A.K.M.P. and K.M.; data curation, A.K.M.P. and K.M.; writing—original draft preparation, A.K.M.P.; writing—review and editing, K.M.; visualization, A.K.M.P. and K.M.; supervision, A.K.M.P.; project administration, K.M.; funding acquisition, A.K.M.P. and K.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Research Council, Halmstad Halland County; and the Southern Healthcare Region Sweden and the APC was funded by Lund University.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Swedish Ethical Review Authority, Uppsala University hospital, department of Medicine Uppsala (approval number 2020-06178, approval date 16 December 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to institution policy.

Acknowledgments: We extend our heartfelt thanks to the nurses in the preoperative preparation clinic, whose unwavering commitment to the recruitment process was invaluable.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

APOP	Acute postoperative pain
MAO	Multimodal anesthesia with opioids
NRS	Numeric rating scale
OFA	Opioid free anesthesia
PCS	Pain catastrophizing scale
POPIT	Perioperative individualization trial
PPOP	Persistent postoperative pain
PACU	Post-anesthesia care unit

POD	Postoperative day
QST	Quantitative sensory testing
SOC	Standard of care
VCP	Venous cannulation pain
VAS	Visual analog scale

References

- Chapman, C.R.; Vierck, C.J. The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. *J. Pain* **2017**, *18*, 359.e1–359.e38. [\[CrossRef\]](#)
- Aasvang, E.K.; Gmaehle, E.; Hansen, J.B.; Gmaehle, B.; Forman, J.L.; Schwarz, J.; Bittner, R.; Kehlet, H. Predictive risk factors for persistent postherniotomy pain. *Anesthesiology* **2010**, *112*, 957–969. [\[CrossRef\]](#)
- Ip, H.Y.; Abrishami, A.; Peng, P.W.; Wong, J.; Chung, F. Predictors of postoperative pain and analgesic consumption: A qualitative systematic review. *Anesthesiology* **2009**, *111*, 657–677. [\[CrossRef\]](#)
- Kalkman, C.J.; Visser, K.; Moen, J.; Bonsel, G.J.; Grobbee, D.E.; Moons, K.G. Preoperative prediction of severe postoperative pain. *Pain* **2003**, *105*, 415–423. [\[CrossRef\]](#) [\[PubMed\]](#)
- Kehlet, H.; Jensen, T.S.; Woolf, C.J. Persistent postsurgical pain: Risk factors and prevention. *Lancet* **2006**, *367*, 1618–1625. [\[CrossRef\]](#)
- Gerbershagen, H.J.; Aduckathil, S.; van Wijck, A.J.M.; Peelen, L.M.; Kalkman, C.J.; Meissner, W. Pain Intensity on the First Day after Surgery A Prospective Cohort Study Comparing 179 Surgical Procedures. *Anesthesiology* **2013**, *118*, 934–944. [\[CrossRef\]](#)
- Mogianos, K.; Akeson, J.; Persson, A.K.M. Systematic Review of Methods for Individual Prediction of Postoperative Pain. *Pain Res. Manag.* **2025**, *2025*, 1331412. [\[CrossRef\]](#) [\[PubMed\]](#)
- Wu, F.; Liu, J.; Zheng, L.; Chen, C.; Basnet, D.; Zhang, J.; Shen, C.; Feng, X.; Sun, Y.; Du, X.; et al. Preoperative pain sensitivity and its correlation with postoperative acute and chronic pain: A systematic review and meta-analysis. *Br. J. Anaesth.* **2024**, *133*, 591–604. [\[CrossRef\]](#) [\[PubMed\]](#)
- Armstrong, R.A.; Fayaz, A.; Manning, G.L.P.; Moonesinghe, S.R.; Peri-Operative Quality Improvement Programme (PQIP) Delivery Team; Oliver, C.M.; PQIP Collaborative. Predicting severe pain after major surgery: A secondary analysis of the Peri-operative Quality Improvement Programme (PQIP) dataset. *Anaesthesia* **2023**, *78*, 840–852. [\[CrossRef\]](#)
- Rago, R.; Forfori, F.; Materazzi, G.; Abramo, A.; Collareta, M.; Miccoli, P.; Giunta, F. Evaluation of a preoperative pain score in response to pressure as a marker of postoperative pain and drugs consumption in surgical thyroidectomy. *Clin. J. Pain* **2012**, *28*, 382–386. [\[CrossRef\]](#)
- Orbach-Zinger, S.; Aviram, A.; Fireman, S.; Kadechenko, T.; Klein, Z.; Mazarib, N.; Artiuch, A.; Reuveni, A.; Iosovich, A.; Eidelman, L.A.; et al. Severe pain during local infiltration for spinal anaesthesia predicts post-caesarean pain. *Eur. J. Pain* **2015**, *19*, 1382–1388. [\[CrossRef\]](#)
- Carvalho, B.; Zheng, M.; Aiono-Le Tagaloa, L. Evaluation of experimental pain tests to predict labour pain and epidural analgesic consumption. *Br. J. Anaesth.* **2013**, *110*, 600–606. [\[CrossRef\]](#)
- Persson, A.K.; Pettersson, F.D.; Dyrehag, L.E.; Akeson, J. Prediction of postoperative pain from assessment of pain induced by venous cannulation and propofol infusion. *Acta Anaesthesiol. Scand.* **2016**, *60*, 166–176. [\[CrossRef\]](#)
- Persson, A.K.M.; Åkeson, J. Prediction of Acute Postoperative Pain from Assessment of Pain Associated with Venous Cannulation. *Pain Pract.* **2019**, *19*, 158–167. [\[CrossRef\]](#) [\[PubMed\]](#)
- Peng, F.; Li, Y.; Ai, Y.; Yang, J.; Wang, Y. Application of preoperative assessment of pain induced by venous cannulation in predicting postoperative pain in patients under laparoscopic nephrectomy: A prospective observational study. *BMC Anesth.* **2020**, *20*, 86. [\[CrossRef\]](#) [\[PubMed\]](#)
- Sullivan, M.J.L.; Bishop, S.R.; Pivik, J. The Pain Catastrophizing Scale: Development and validation. *Psychol. Assess.* **1995**, *7*, 524–532. [\[CrossRef\]](#)
- Alokozai, A.; Eppler, S.L.; Lu, L.Y.; Sheikholeslami, N.; Kamal, R.N. Can Patients Forecast Their Postoperative Disability and Pain? *Clin. Orthop. Relat. Res.* **2019**, *477*, 635–643. [\[CrossRef\]](#)
- Habib, A.S.; Kertai, M.D.; Cooter, M.; Greenup, R.A.; Hwang, S. Risk factors for severe acute pain and persistent pain after surgery for breast cancer: A prospective observational study. *Reg. Anesth. Pain Med.* **2019**, *44*, 192–199. [\[CrossRef\]](#)
- Benlolo, S.; Hanlon, J.G.; Shirreff, L.; Lefebvre, G.; Husslein, H.; Shore, E.M. Predictors of Persistent Postsurgical Pain After Hysterectomy-A Prospective Cohort Study. *J. Minim. Invasive Gynecol.* **2021**, *28*, 2036–2046.e2031. [\[CrossRef\]](#)
- Dams, L.; Van der Gucht, E.; Haenen, V.; Lauwers, M.; De Pauw, S.; Steurs, T.; Devoogdt, N.; Smeets, A.; Bernar, K.; De Vrieze, T.; et al. Dapsychosocial risk factors for pain and pain-related disability 1 year after surgery for breast cancer. *Support. Care Cancer* **2022**, *30*, 4465–4475. [\[CrossRef\]](#)

21. Mogianos, K.; Holgersson, J.; Undén, J.; Persson, A.K.M. Opioid-free versus opioid-based anaesthesia and analgesia for patients at low risk for acute postoperative pain undergoing laparoscopic surgery: A randomised controlled trial. *J. Clin. Anesth.* **2026**, *108*, 112058. [[CrossRef](#)]
22. Mogianos, K.; Holgersson, J.; Undén, J.; Persson, A.K.M. The additive effect of esketamine and clonidine in patients at high risk for acute postoperative pain undergoing laparoscopic surgery: A randomised controlled trial. *J. Clin. Anesth.* **2025**, *108*, 112059. [[CrossRef](#)]
23. Bahreini, M.; Safaie, A.; Mirfazaelian, H.; Jalili, M. How much change in pain score does really matter to patients? *Am. J. Emerg. Med.* **2020**, *38*, 1641–1646. [[CrossRef](#)]
24. Olsen, M.F.; Bjerre, E.; Hansen, M.D.; Hilden, J.; Landler, N.E.; Tendal, B.; Hróbjartsson, A. Pain relief that matters to patients: Systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med.* **2017**, *15*, 35. [[CrossRef](#)] [[PubMed](#)]
25. Pereira, M.P.; Pogatzki-Zahn, E. Gender aspects in postoperative pain. *Curr. Opin. Anaesthesiol.* **2015**, *28*, 546–558. [[CrossRef](#)]
26. Yang, M.M.H.; Hartley, R.L.; Leung, A.A.; Ronsley, P.E.; Jetté, N.; Casha, S.; Riva-Cambrin, J. Preoperative predictors of poor acute postoperative pain control: A systematic review and meta-analysis. *BMJ Open* **2019**, *9*, e025091. [[CrossRef](#)] [[PubMed](#)]
27. Schnabel, A.; Yahiaoui-Doktor, M.; Meissner, W.; Zahn, P.K.; Pogatzki-Zahn, E.M. Predicting poor postoperative acute pain outcome in adults: An international, multicentre database analysis of risk factors in 50,005 patients. *Pain Rep.* **2020**, *5*, e831. [[CrossRef](#)]
28. Tsang, A.; Von Korff, M.; Lee, S.; Alonso, J.; Karam, E.; Angermeyer, M.C.; Borges, G.L.; Bromet, E.J.; Demyttenaere, K.; de Girolamo, G.; et al. Common chronic pain conditions in developed and developing countries: Gender and age differences and comorbidity with depression-anxiety disorders. *J. Pain* **2008**, *9*, 883–891. [[CrossRef](#)]
29. Racine, M.; Tousignant-Lafamme, Y.; Kloda, L.A.; Dion, D.; Dupuis, G.; Choiniere, M. A systematic literature review of 10 years of research on sex/gender and experimental pain perception—Part 1: Are there really differences between women and men? *Pain* **2012**, *153*, 602–618. [[CrossRef](#)]
30. Racine, M.; Tousignant-Lafamme, Y.; Kloda, L.A.; Dion, D.; Dupuis, G.; Choiniere, M. A systematic literature review of 10 years of research on sex/gender and pain perception—Part 2: Do biopsychosocial factors alter pain sensitivity differently in women and men? *Pain* **2012**, *153*, 619–635. [[CrossRef](#)] [[PubMed](#)]
31. Geisler, A.; Zachodnik, J.; Laigaard, J.; Kruuse, L.S.; Sorensen, C.V.; Sandberg, M.; Persson, E.I.; Mathiesen, O. Using four different clinical tools as predictors for pain after total hip arthroplasty: A prospective cohort study. *BMC Anesth.* **2020**, *20*, 57. [[CrossRef](#)] [[PubMed](#)]
32. Bisgaard, T.; Klarskov, B.; Rosenberg, J.; Kehlet, H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain* **2001**, *90*, 261–269. [[CrossRef](#)] [[PubMed](#)]

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