Postoperative pain management after total hip arthroplasty. A focus on evidence, clinical practice and the individual patient's pain response.

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Postoperative pain management after total hip arthroplasty

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Anja Geisler

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle: Postoperative pain management after total hip arthroplasty -a focus on evidence, clinical practice and the individual patient's pain response

Abstract

Background: Patients experiencing high levels of pain after surgery remains a considerable clinical problem. Often, no consensus about the best analgesic treatment is present. The majority of clinical trials regarding postoperative pain, generally, target the average analgesic efficacy. In terms to step forward, a focus on the individual patients´ pain levels is needed and an identification of the patients in risk of developing higher postoperative pain levels.

Aim: The overall aim was to explore the pain management for total hip arthroplasty (THA) patients by investigating the evidence in the literature, and the manifestation in clinical practice, including a focus on the individual patient and possible predictive tools.

Methods: A systematic review was conducted investigating the different analgesic treatments in randomised clinical trials (RCT) regarding THA patients (Study I). To investigate the analgesic efficacy at the individual patient level, in terms of obtaining, 'no worse than mild pain / VAS ≤30, a re-analysis was performed which included individual patient data of previous RCTs (Study II). The effect of multimodal analgesic treatment in THA patients in clinical practice was mapped in a large multicenter cohort study at five different hospitals (Study III). Finally, we investigated if four different and simple approaches were able to predict high levels of pain postoperatively: pain during peripheral venous cannulation (PVC), highest pain levels at the Post Anaesthesia Care Unit (PACU), PACU nurses prediction, and patient's forecast. (Study IV).

Results: In the systematic review, we found that the literature regarding the analgesic treatment for THA was heterogeneous and with no "gold standard". The re-analysis demonstrated, based on the success criteria 80% should obtain VAS-pain ≤30, at 6 and 24hr postoperatively, half of the patients succeeded reaching the goal at rest. During mobilisation only 14-15% obtained the goal. The multicenter study demonstrated large differences in the analgesic treatment between hospitals. Surprisingly, did the patients´ pain levels not differ much, no matter which kind of analgesic treatment they had received, neither at a hospital-level nor at an individual patient level. None of the four predictive tools showed efficacy in predicting high pain responders at 24hr postoperatively during mobilisation.

Conclusions: The literature regarding analgesic treatment for THA is heterogenic with no "gold standard." When re-analysing 16 previous RCTs we found insufficient pain treatment at the individual patient level, especially during mobilisation. The pain treatment for THA at five different hospitals differed a lot. No matter how complex the multimodal pain was, patients´ outcomes were very similar according to pain and side effects. PVC-pain preoperatively could not be used as a predictive tool for patients with high pain levels after 24hr during mobilisation postoperatively. That was also the findings with PACU nurses prediction, highest pain levels at the PACU and patients forecast

Key words: Postoperative pain, total hip arthroplasty, prediction, multimodal non-opioid analgesics, individual patient

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MADE IN SWEDEN

“A Picture of Pain”

I tried to paint a picture,
Of how I really feel.
But I could not find the colors,
To make it all seem real.
Not one color was hot enough,
To show the burning pain.
Not one color bright enough,
To make me wince again.
Not one was dark enough,
To show the isolation.
In the end saw one thin line,
Worn, frayed and almost broke,
To my mind that one thin line,
Is a single thread of hope.

By Bear Peterson

Table of Contents

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Original studies

This thesis for the doctoral degree is based on the following papers referred to by Roman numerals I-IV. The studies have been reprinted with permission from the publishers.

I. Højer APK., Geisler A., Petersen PL., Mathiesen O., Dahl JB.
Postoperative pain treatment after total hip arthroplasty: a systematic review
PAIN 2015; 156: 8-30

II. Geisler A., Dahl JB., Karlsen APH., Persson E., Mathiesen O.
Low degree of satisfactory individual pain relief in postoperative pain trials
Acta Anaesthesiol Scand 2017; 61: 83-90

III. Geisler A., Dahl JB., Thybo KH., Pedersen TH., Jørgensen ML., Hansen D., Schulze LK., Persson E., Mathiesen O.
Pain management after total hip arthroplasty at five different Danish hospitals: A prospective, observational cohort study of 501 patients
Acta Anaesthesiol Scand 2019; 63:923-930

IV. Geisler A, Zachodnik J, Laigaard J, Kruuse L, Sørensen CV, Sandberg M, Persson E, Mathiesen O
Does preoperative pain levels by venous cannulation predict postoperative pain levels? – A prospective cohort study of total hip arthroplasty patients
Submitted to BMC Anesthesiology

Abbreviations

ASA	American Society of Anesthesiologists
CRF	Case Report Form
EQV.	Equivalents
GA	General Anaesthesia
GABA	Gabapentin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital Anxiety and Depression Score
IASP	International Association for the Study of Pain
IV	Intra Venously
IQR	Interquartile range
LIA	Local Infiltration Analgesia
MIREDIF	Minimal relevant difference
NMDA	N-methyl-D-aspartate receptor
NNT	Numbers Needed to Treat
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PVC	Peripheral Venous Catheter
PCM	Paracetamol
PCS	Pain Catastrophizing Scale
PACU	Post Anaesthesia Care Unit
PCA	patient controlled analgesia
PONV	Postoperative nausea and vomiting
PROM	Patient Reported Outcome Measure
RCT	Randomised Clinical Trial
ROC	Receiver Operating Characteristic curves
SA	Spinal anaesthesia
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
STROBE	Strengthening The Reporting of Observational Studies in Epidemiology
THA	Total Hip Arthroplasty
TSA	Trial sequential analysis
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
WHO	World Health Organization
ZUHK	Zealand University Hospital Køge

Preface

As a newly educated nurse, I first got acquainted with patients´ in pain working at an acute neurological ward. Patients with e.g. Guillain Barrés disease suffered terribly from neuropathic pain, resulting in a great challenge for the nursing staff. Especially when it came to mobilising these patients. At that time, it was common knowledge that little could be done to ease the patients´ pain sufficiently. The trick was not touching the patients unless having a good reason for it. Merely trying to avoid causing pain to the patients, which sometimes could continue for hours afterwards, resulting in a feeling of failure and helplessness as a nurse. In the next step in my career, at an intensive care unit for neurological and neuro-surgical patients, we also had to work shifts in the post anaesthetic care unit (PACU). At the PACU, we took care of surgical patients, among others, patients after major spine surgery. The patients often woke up after surgery, crying in severe pain or even screaming. The issue was very much the same as at the neurological ward, very little could be done to ease their pain. The patients were offered analgesic treatment but often it did not have a sufficient effect. These shifts at the PACU seemed endless. It was a great satisfaction many years later when I participated in the design and implementation of a multimodal analgesic combination for that particular patient population as a part of the Section of Acute Pain Management at Rigshospitalet in Copenhagen. The treatment resulted in mostly calm, satisfied patients and relatives, in the PACU, and also at the ward. I realised then that it is indeed possible to support most patients, by reducing or preventing severe pain which delays or eliminates most of the goals set in order to achieve a satisfying patient course.

Introduction

Pain management is an essential aspect of patient care (1). The International Association for the study of pain (IASP) declared in 2010 with the declaration of Montreal, that pain management is a fundamental human right (2). This is supported by a statement from the world health organization (WHO) made in June 2019. *"WHO remains fully committed to ensuring that people suffering severe pain have access to effective pain relief medication, including opioids. WHO is concerned that there is very low access to medication for moderate and severe pain, particularly in low and middle-income countries"*. The American Pain Society published guidelines to improve the management of acute and cancer pain for the first time back in 1995. These were revised in 2005(3) where a panel of experts recommended an increased focus on the following five issues: 1. Prompt recognition and treatment of pain. 2. The involvement of patients in the pain management plan. 3. Improvement of treatment patterns. 4. Reassessment and adjustment of the pain management plan as needed. 5. Monitoring processes and outcomes of pain management. Likewise, a number of guidelines for the management of pain has been published, including the recent recommendations in 2016 by The American Pain Society (4). Why is it, despite decades with guidelines, focus from the utmost important societies regarding pain, and statements from the WHO that postoperative pain still is insufficiently treated (5–9)?

According to the Statistics Denmark, 565.000 in-hospital and 1.4 million outpatient surgical procedures were performed in 2018 in Denmark (10). Worldwide, surgical procedures annually exceeds 300 million (11). These numbers underpin the need for effective and optimal postoperative pain management. A search on PubMed using the search terms: 'pain' and 'pain treatment' results in >61.000 randomised trials and >4.300 meta-analyses regarding this subject.

In spite of all these efforts in pain research, recent studies have shown that approximately 80% of patients suffer from pain after surgery (1,9) and that the experience of moderate to severe pain after both minor and major surgery remains a significant clinical problem, experienced by approximately 30% of the patients (1,6,9).

Pain is a subjective experience influenced by both biological, psychological and social factors (12) and is accordingly very complex to manage. The patients do not only suffer from pain itself, but pain also influences mood (13), quality of sleep

(14,15), and quality of life (16). Furthermore, pain hinders an effective postoperative rehabilitation, which is a cornerstone for optimal patient courses after surgery. Multimodal pain treatment is generally accepted as the leading principle in postoperative pain treatment, using combinations of non-opioids and analgesic techniques, resulting in a limited need of opioids (17). In spite of that, opioids still remain the first choice in treatment, when the subject is acute pain (7).

A typical side effect to opioid treatment is postoperative nausea and vomiting (PONV) which is experienced by 25%-50% of patients (18–20). Insufficiently relived pain is also strongly associated with persistent postoperative pain (21–24). The prevalence of persistent postoperative pain is highly dependent on the type of surgery and is reported to vary from 5% to 85% (25,26). Long lasting persistent pain does not only affect the patient and next of kin, but can also be a major socioeconomic burden, and lead to continued or chronic postoperative opioid use (27,28).

Therefore, there is an urgent need to focus on ways to improve clinical pain treatment. Investigating the best evidence-based analgesic treatment is essential, but equally important is investigating how effective such treatment is when applied in a clinical setting. Research on efficacy typically have a focus on the average effect in groups of patients and renders little knowledge about how individual patients respond to the treatment. Accordingly, initiatives to identify or predict individuals with increased risk of excessive postoperative pain are warranted. This may lead to sufficient knowledge to prevent patients from enduring high levels of pain in the future, by planning and optimising the individual pain treatment.

The focus of this Ph.D. thesis, using total hip arthroplasty (THA) as the scientific model, is to investigate the current evidence for postoperative analgesic treatment, and how postoperative analgesic treatment works in clinical practice. Furthermore, the focus is to identify ways to predict higher levels of postoperative pain in this group of patients. Additionally, based on previous randomised trials, we will investigate how effective the typical analgesic treatments are, for the individual patients, in different RCTs and different types of surgery, aiming to reach the goal “no worse than mild pain”.

Background

Acute pain

Pain is defined in 1979 by The International Association for the Study of Pain (IASP) as: “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”(29) This addresses how complex pain is. It has not only a sensory dimension but also includes cognitive and emotional components.

What is the purpose of pain? The body uses pain as a warning sign to secure survival, likewise for humans and animals. The purpose is not only to acknowledge the potential damage but also to protect the damaged part in order to allow the healing process to take place. At the same time, we learn from the painful experience, resulting in avoidance of a future similar painful situation.

Acute pain is the result of internal or external nociceptive stimuli caused by thermal, mechanical or chemical character. When tissue is damaged, e.g. during a surgical procedure, a specialised group of nerve cells is activated (30,31). These nerve fibers are activated by nociceptors and are to be found in tissue such as skin, muscles, periostea, connective tissue, cornea, ligaments, and teeth. The impulse from the nerve is immediately transmitted from the damaged tissue to the dorsal horn of the spinal cord (first neuron). Here it connects to long ascending nerves, wide dynamic range neurons (second neuron). In this way, the signal is passed to different areas in the brain: the brainstem, thalamus, and the cortical and more profound areas of the brain (third neuron). Activity in those parts of the medulla and brain are both responsible for the evaluation of information about intensity and locality as well as the emotional (amygdala) and cognitive components, which are a part of the complex pain experience (30,31). (See Figure 1)

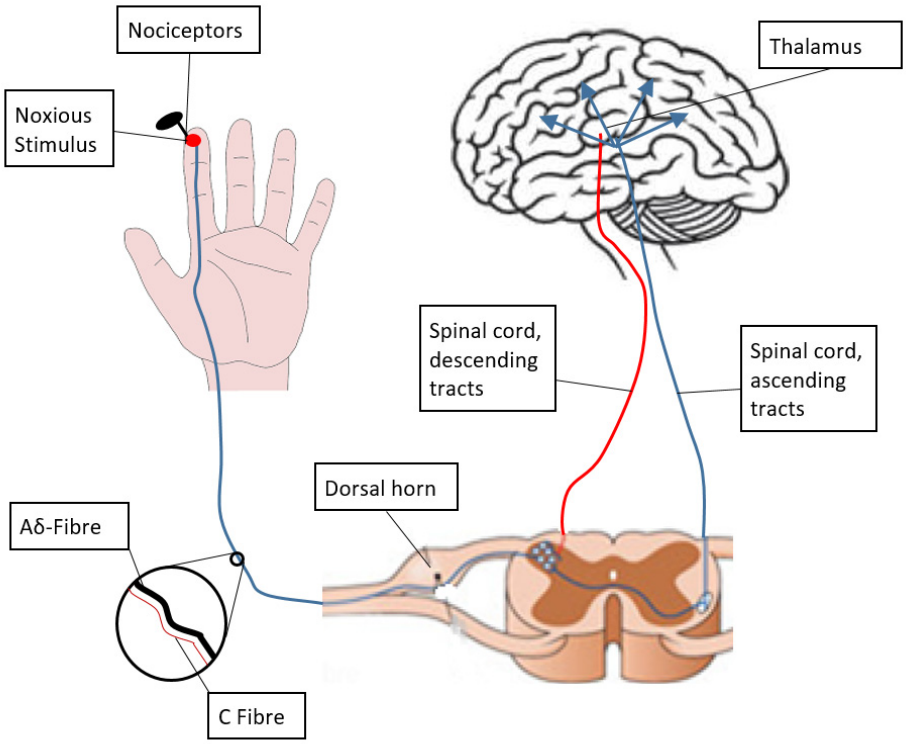

Figure 1.
The pain pathways

Impulses from the nociceptors are transmitted through fibres such as; Aδ fibres, which are covered with myelin and give the feeling of a fast and sharp pain and C fibres which give a more pounding, diffuse, and slow signal of deep pain. (Figure 1)

The nociceptive system has integrated plasticity, which ensures a system modulation depending on e.g. the strength and duration of the incoming pain signal. Brief pain is normally self-limiting and does not change the pain threshold or intensity. Several conditions can reduce the pain threshold (allodynia) and increase the intensity (hyperalgesia) e.g. persistent nociceptive stimuli or inflammation caused by tissue damage. The neuroplasticity changes in the peripheral nerve system are many and involve a cascade of both inflammatory and neurogenic mechanisms. The result is an increased sensitisation of the peripheral nerve-roots, also seen when the nerve is damaged, which leads to a persistent sensitisation of the afferent nociceptive fibres, spontaneously activity (feels like pain), and reduced pain threshold. Altogether, these triggering mechanisms are called peripheral

sensitisation, also known as primary hyperalgesia, and are active in acute pain (32). One of the contributing factors is the inflammation which is induced by a cocktail of cytokines which are released from the wounded tissue (31,33). Central sensitisation is the result of a powerful increased pain signal from the sensitised peripheral nociceptive afferent neurons. As a result of that, pain threshold can be decreased, leading to an increased pain response, and an increased area which feels pain (30,31). This clinical state is termed secondary hyperalgesia. When defining postoperative pain, it is a sum of the different pain mechanisms: nociceptive pain (described in the paragraph above), neuropathic and visceral pain. All the mechanisms can have an additional inflammation acting as an amplifying mechanism (31). Following is a description of inflammatory pain, visceral pain, and neuropathic pain.

Inflammatory pain: Inflammatory pain refers to increased sensitivity due to the inflammatory response associated with tissue damage. Inflammatory pain is a type of nociceptive pain derived from activation and sensitisation of nociceptors by inflammatory mediators' such as prostaglandin, bradykinin, cytokines, histamine, glutamate, etc. A way to reduce the inflammatory response is by using e.g. Non-Steroidal Anti-Inflammatory Drugs NSAIDs or glucocorticoids (31).

Visceral pain: Visceral pain emanates from the internal thoracic, pelvic, or abdominal organs. Unlike nociceptive pain, visceral pain is generally vague, poorly localised (referred pain), and characterised by a hypersensitivity to a stimulus such as an organ distension. The most effective treatment is a removal of the problem, which causes the distension e.g. experienced with constipation (34). Regarding the analgesic treatment for visceral pain, the knowledge is sparse but epidural infusion tends to have an effect (35).

Neuropathic pain: Neuropathic pain is developed as a result of lesions or diseases affecting the peripheral and/or central somatosensory nervous system. Clinical characteristics depend on the type and the progression of the disease but include burning pain, dysesthesias, pain to light stroking of the skin, sensory deficits, and widespread pain. The analgesic treatment often used for neuropathic pain are gabapentinoids or tricyclic antidepressants (36).

The Bio-psycho-social model

A great variation in patients' experience of postoperative pain exists, even though they have undergone the same surgical procedure (9). One of the reasons is, as explained by Engel, that pain is not only a one-dimensional physical part but is combined with a mental/cognitive and a social part (37). This is illustrated in the bio-psycho-social model introduced in 1977 (38). (Figure 2)

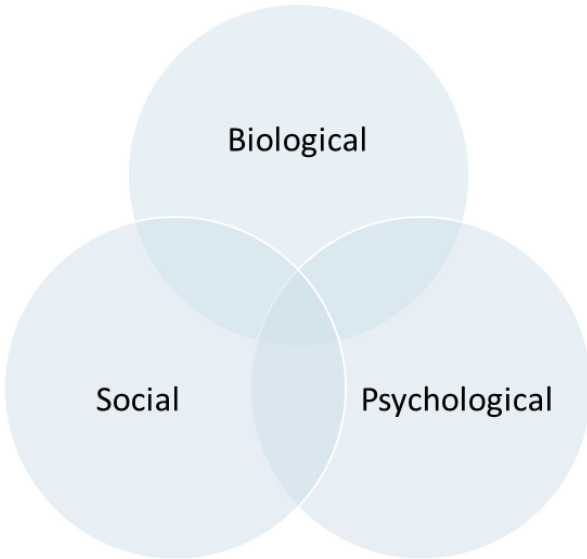

Figure 2.
The Bio-Psycho-Social Model

The bio-medical modal which explains all illnesses as a measurable biological and somatic variable, separating the psycho-social from the somatic part (37) has been the most common way to consider pain in hospitals for many years (37,39). However, Engels model from 1977 argued that a model which include both the patient and the illness would be preferable (38).The elements in the model are as follows: Biological, which includes: age, gender, diseases, and genetic factors. Psychological, which include the patient's self-understanding, mood, psychological vulnerability, level of anxiety and catastrophizing. Social, which is defined as marital status, social life, leisure activities, religion, occupation and family life (31).

It is more or less accepted today that illness and health are the results of an interaction between biological, psychological, and social factors (12).Nevertheless, is the model mainly used in chronic pain patients

The model by Engel has later been criticised for lacking some parts. Therefore, a newer model has been developed which include an existential part as well (31). see Table 1.

Table 1.
Pain explained according to the physical, psychological, social, and existential parts

Physical part	• Lesions • Nerves • Pain-receptors • Analgesics
Psychological part	• Pain-experience • Fear • Coping with pain • Fight-flight reactions
Social part	• Loss of work • Loss of identity • Family-dynamics • Social limitations • Economically consequences
Existential part	• Powerlessness • Hopelessness • Loss of meaning • Robustness • Fighting capability • Hope

These factors need to be taken into considerations when planning the patients´ pain treatment (40). Knowing that e.g. the psychological robustness has a major effect on how patients experience pain (41). The bio-psycho-social model is mainly used for patients with persistent pain disorders but needs to be considered when trying to optimise the acute pain management. It is important to pay attention to all parts, bio, psycho, social and existential (31). These areas can be discussed during e.g. the nurse interview when the patient is admitted. The nurse can ask the patient about former experiences with surgery and pain, identifying anxiety, depression and catastrophizing, e.g. by using the validated questionnaires Pain Catastrophizing Scale (PCS) (42) and Hospital Anxiety and Depression Score (HADS) (43) and ask about the patient´s social life as well.

Multimodal analgesia

Multimodal or balanced analgesia is the leading principle in managing postoperative pain to enhance pain relief (44). The concept was introduced several decades ago when an understanding of how complex the multiple nociceptive mechanisms was developed, often appearing as a combination of visceral, neuropathic, and inflammatory pain (45). Therefore, to attenuate the different pain pathways, a treatment with combinations of different analgesics was suggested. (Figure 3)

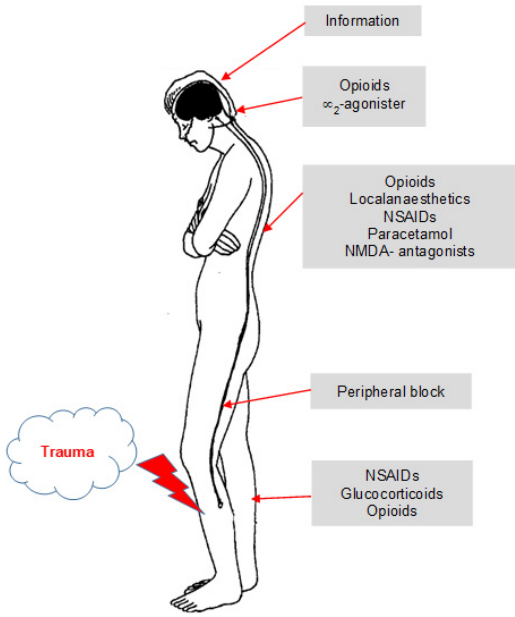

Figure 3.
Mechanisms of analgesics.
NSAID: Non-Steroidal Anti-Inflammatory Drug. NMDA-antagonits= N-methyl-D-aspartate receptor

The principle for multimodal analgesia is as follows: when patients are treated with different combinations of non-opioid analgesics after surgical procedures it is possible to obtain an additive or synergistic effect and consequently, less need for individual analgesics and especially opioids (17,46,47).

Hereby, a reduction in the well-known adverse effects, such as PONV, sedation, dizziness, respiratory depression, pruritus, constipation, ileus, and urinary retention is often achieved (22). According to the principle, the pain treatment ought to be planned already during admittance (48). The patient should both pre- and postoperatively receive combinations of different non-opioid analgesics. Most analgesics used in clinical practice have proven to be effective when administrated as monotherapy (49). A diversity of non-opioid analgesic combinations have been employed in clinical practice over the years (50) but the knowledge about benefits and harms of such combinations is however, still sparse (51).

The following is a short description of some of the analgesics, which are usually used and combined, in the multimodal approach, followed by a description of non-pharmacological ways to treat pain.

Pharmacological treatments

Paracetamol:

One of the most used antipyretic and analgesic drug worldwide. Recommended dosage for adults: 1000mg, 3-4 times a day.

Paracetamol has proved effective in treating postoperative pain (49). A review reports that numbers needed to treat (NNT) for paracetamol is 3─4, meaning that half of the participants treated with paracetamol at standard doses achieved at least 50% pain relief over the next four to six hours (52). It reduces postoperative morphine (eqv) consumption with 6─8 mg/24h (53), and the risk of opioid related side effects such as nausea is reduced (52). Paracetamol is cheap, generally safe when used within recommended doses, and is considered as a basic non-opioid analgesic recommended for most surgeries (54).

Non-Steroidal Anti-Inflammatory Drug (NSAID):

Commonly used drug with antipyretic and anti-inflammatory properties. The recommended dosage for acute pain for the frequently used NSAID, Ibuprofen: 400 mg, 3-4 times a day.

NSAIDs are generally effective for the treatment of post-operative pain with NNT ≥ 2 and < 4.3, depending on drug and dosage (49). It reduces postoperative morphine consumption with about 10 mg/24hr. A recently published RCT investigates PCM and NSAIDs and its combination for THA patients´, found that PCM plus ibuprofen significantly reduced morphine consumption compared with PCM or ibuprofen alone, during the first 24hr postoperatively (55). Opioid-related adverse effects, as PONV has been found reduced with NSAIDs (56).

Gabapentinoids:

Gabapentin: Antiepileptic drug, used for neuropathic and acute pain. Anti-hyperalgesic. Typical doses used for acute pain: 300 - 600mg. (off label) (48).
A recent systematic review found significantly reduced postoperative pain and opioid usage throughout the first 24hr regardless of the dose of gabapentin given before surgery (57). Concomitant reduced risk of opioid-related side effects as PONV was also reported, but with increased risk of sedation or dizziness (57).

Pregabalin: Antiepileptic drug, used in the treatment for neuropathic and acute pain. Anti-hyperalgesic.

Typical doses used for acute pain: 75─150 mg x 2, maximum 300 mg x 2
A recent review investigates pregabalin for postoperative pain treatment, found a significant reduction in pain levels at rest and during mobilisation as well as opioid consumption (0-24hr), compared with placebo (58). A reduction in opioid-related adverse events as PONV and pruritus were also found, but with increased risk of

sedation, dizziness, and visual disturbance in the groups treated with pregabalin compared to placebo (58).

Two recently performed reviews question the results based on the included RCTs regarding gabapentin and pregabalin. The risk of bias in these trials is most often uncertain or high, and therefore, the results concluded on that background can be questionable (59,60).

Dexamethason:

Glucocorticoid. Administrated one-time pre- or per-operatively.

A review has reported effectiveness of dexamethasone in multimodal strategies to reduce postoperative pain and opioid consumption when using dosages up to 0.2 mg/kg (61). In this review, most of the included trials used lower dosages. Therefore, as indicated in the study from Lunn and colleagues (62), using a higher dose, as methylprednisolone 125 mg IV for total knee arthroplasty could possibly be more effective.

Peripheral nerve block:

Nerves that transmit pain from a specific organ or body region can be blocked with the injection of local anaesthetic. Various types of peripheral nerve blocks with a local anaesthetic and with a varying duration for different surgical procedures have been demonstrated (63).

Non-pharmacological treatments

Information:

Anxiety (43), expectations of suffering from high levels of pain (40) and surgical fear (64), increases patients' pain threshold. A way for caregivers to counteract this is to provide the patients with information about what to be expected before and after the surgical procedure, to establish a dialogue where the patient can express fear and tell about former experiences with pain as well as expectations regarding the pain treatment.

Others:

Both emotional and attentional modulation of pain can be used as non-pharmacological interventions such as yoga, massage, acupuncture, meditation, distraction, deep breaths, music therapy, and cold or warm coverings. There are considerably differences in level of evidence regarding the effect of the different types of non-pharmacological treatments (65–71). The uses of these treatments in managing acute pain is not a part of this thesis.

Measuring pain

From systematic reviews investigating single analgesics based on RCTs we have evidence of efficacy. However, we only have little information about how well the different analgesics works when combined. Furthermore, there may be a large difference in the RCTs with in- and exclusion criteria, compared to patients treated in the daily practice at Zealand University hospital, Køge (ZUHK), since the external validity is unknown. Therefore, we need to establish best evidence from the literature, but also to investigate how well the principle of multimodal analgesia works at the hospitals. Especially, focusing on the effect for individual patients.

Pain evaluation

Pain assessment and management is an important part of nursing care (72). It is not possible to, objectively, measure patients´ pain. Pain will always be a subjective and individual experience. When nurses and doctors try to measure the patients´ pain objectively on behalf of patients, we fail, mostly by underestimating the levels of pain (73,74). A recent review found that healthcare providers´ underestimation tended to increase with pain severity in the majority of the included studies (75-91%) (75). Therefore, the only way to evaluate and report pain is to ask the patients. In this regard, we need validated tools, which give the patients the opportunity, to report accurately (76). By measuring pain with e.g. a number or verbally statements, we can monitor the individual patient´s pain. This provides us with knowledge of whether the pain management is adequate or not, and if analgesic dose and type need to be changed (77,78). It is of great importance that the pain estimation not only takes place when the patients are resting but also during mobilisation since it is crucial for rehabilitation that the pain levels not obstructs that purpose (6,73).

The following three types of validated tools, to measure pain, are the most commonly used, worldwide, at hospitals today (79). They all require that the patients can express themselves verbally and are somewhat cognitively intact. (Figure 4)

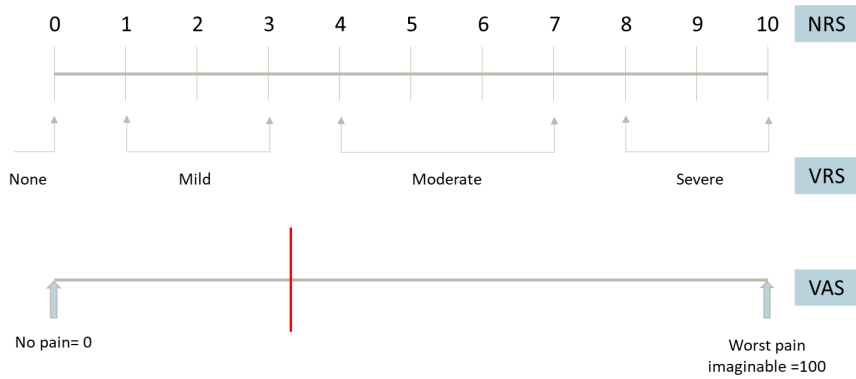

Figure 4.
Three different pain rating scales; numeric rating scale (NRS), verbal rating scale (VRS) and visual analogue scale (VAS

Visual analogue Scale (VAS)

The VAS was implemented at the hospitals during the 1930s for research purposes (80). The VAS measures pain by using a ruler. The ruler is marked with a 10 cm horizontal line. In one end of the line, is marked: "no pain at all" and in the other end is marked: "worst pain imaginable." The patient then places a moveable marker, on the line, at the ruler that corresponds to the amount of experienced pain. On the backside of the ruler, is either numbers from zero to 10 or 0 to 100, indicating the pain intensity. Zero indicates no pain at all and 10 or 100 indicates worst imaginable pain (80). (Figure 4)

Numeric rating scale (NRS)

NRS is the most commonly used validated tool for pain measurement (81). It is a simple method to use in a clinical setting since no ruler or other object are needed. The method is to simply ask the patient: "How much pain do you feel from zero to 10. Zero is no pain at all and 10 is the worst pain imaginable you can ever think of?" The patient then indicates a number corresponding to the experienced level of pain (80). (Figure 4)

Verbal rating scale (VRS)

Several studies indicated that using the VRS where pain can be stated verbally is the easiest tool for patients to understand and to use including those with cognitive impairments (82). The patients rate their pain by adjectives that, what they feel, best indicate how much pain they endure. Mostly four levels of verbally statements are used starting with "no pain" and then stepwise higher to "mild pain" "moderate pain" and at last "severe pain" (78,83), indicating the worst imaginable pain. (Figure 4).

Pain history

The validated tools described in the paragraph above only monitor the levels of pain in one dimension. To find out what might cause, ease, or provoke pain, it is important to ask the patients to supplement the number or verbally statement chosen from the pain tool, with a pain history (31,83).

Localisation of the pain

Patients can suffer from a variety of pain not necessarily located to the surgical wound. It can be back pain from lying in the hospital bed, or a headache. It can be referred pain where the location can be elsewhere than the effected organ (84). Sometimes the pain is covering whole areas of the body or can be located to one side. Sometimes pain changes location during the day. To understand the spread of the pain, a chart can be used for the patient to mark areas of pain illustrated by a drawing of a human body (85,86).

The nature of pain

In order to help and support the patients, in the best way, it is necessary, if possible, to determine which kind of pain the patient is experiencing e.g. inflammation, visceral or neuropathic pain (31,32,34,36). By understanding how the pain is experienced it is easier to find a suitable treatment. Is it nociceptive pain where the pain is easily located? Does the pain occur during movements (e.g inflammatory). Is it diffuse as in referred pain experienced with visceral pain (e.g. pain in the left arm when the heart is affected)? Is it burning, aching, or feels as electric shock as in neuropathic pain (31)?

Progression over time

Some types of pain like e.g. diabetic polyneuropathy (69) can be worse at night and e.g. arthritis can be worse in the morning. This may also be the case with acute pain. Therefore, it is important to ask the patients about progression or fluctuations over time. Break through pain can be a major problem for most patients postoperatively (87). It disturbs sleep, and affects mood, functionality, and mental health. Often it can be explained by an “end of dose” issue. Not seldom is it a fact in clinical practice that the patients receive their latest dose of analgesics at 10 PM and will not receive their next dose until 8 AM. Consequently, patients have a lack of analgesics for about 10 hours resulting in break through pain early in the morning.

Other factors that can affect pain

Psychological factors such as depression, anxiety and catastrophizing can increase the risk of suffering from high levels of postoperative pain (13,41). Different tools are developed to measure catastrophizing, anxiety and depression, e.g. HADS (43,88) and PCS (89). This kind of information can be collected from the patients preoperatively, and additively it is informative to know how the patients cope with pain at home. Hereby, the health care providers can use that knowledge actively when planning the patients´ pain treatment. If the patient has good prior experiences easing stress and anxiety with e.g. music, the nurse can encourage the patient to bring music and headphones. The coping strategies patients use are many. As examples: meditation, talking with relatives or friends, reading, television, praying or exercising (90,91).

No worse than mild pain

Patients respond very differently after surgery when it concern acute pain. Some patients experience high levels of pain, whereas one in 20 patients is not bothered with pain at all (92). Pain relief is not normally distributed but usually binary Either the pain is at an acceptable level or it is not (93). Which goals should be aimed at during these circumstances? Moore et al. stated, when patients are asked regarding pain and satisfaction they prefer either a large reduction in pain levels or experiencing “no worse than mild pain” (94). Previous studies have established that mild/low pain corresponds to NRS <3 and VAS< 30 (95). Moore et al. also found that there are great confusion about how to use the pain scoring systems and how we as health care providers should act upon the results. Consequently, they suggested keeping a simple outcome aiming for “no worse than mild pain” at all times (94). Hereby, achieving patient satisfaction and minimising side effects such as fatigue, distress, and loss in quality of life.

The trials used in pain research (efficacy trials) typically report their results as averages (mean or median) when comparing the groups. This provides sparse information about treatment success from the individual patient´s point of view e.g. how many experiences moderate or severe pain? Therefore, in terms of succeeding in providing a better individual focus, it is suggested, that the focus regarding pain treatment and pain research trials should not only be according to the average result, but in particular focusing on the individual response to treatment, aiming for “no worse than mild pain”, and herby greater patient satisfaction (93,94).

Which factors can predict pain?

Despite considerable efforts in optimising postoperative pain, it still remains a challenge in clinical practice (9). Bisgaard et al demonstrated in their article from 2001 (96), 150 patients having same standard analgesic regimen, same kind of surgery, and had their average pain levels lowered to an acceptable level (up to 7 days postoperatively). The results showed that individual patient´s pain levels differed enormously and that a considerable number of patients continued to have moderate or even severe pain (96). Therefore, preoperative identification of individuals who have enhanced pain sensitivity and, therefore, are at risk for developing persistent postoperative pain, is important. Thus, we can plan and provide those patients with a more sufficient pain treatment.

One-third of patients undergoing common surgical procedures report persistent or intermittent pain of varying severity after one year postoperatively (25) Some studies found patients that suffer from high pain levels in a longer period (10% of patients), leading to chronic pain (25,97). The main areas investigated according to the prediction of pain are visualised in Figure 5.

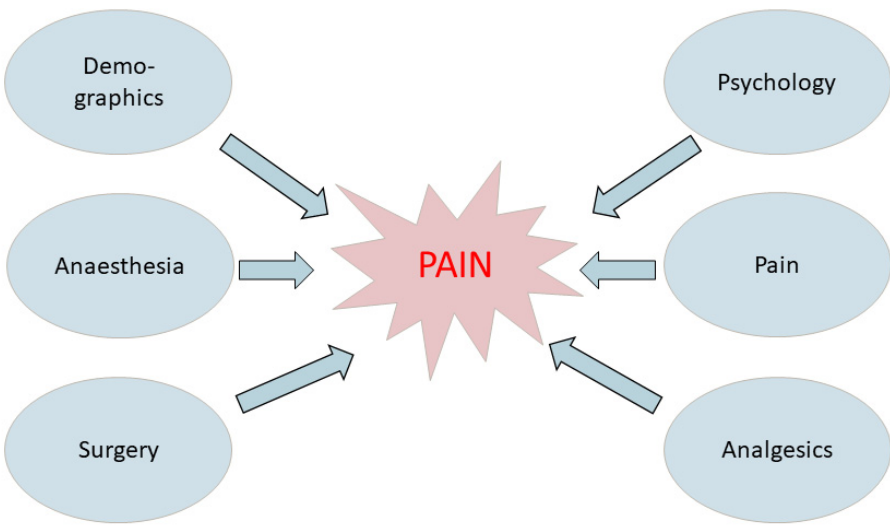

Figure 5.
Research areas important for the prediction of high pain responders

Demographics

Studies indicated that there are gender-related differences in the perception of pain (98,99). Aubrun et al (100) found that women experienced more frequent severe postoperative pain and required a greater dose (average 11%) of morphine than men in the immediate postoperative period. Differences in pain levels and opioid consumption have also been detected when it comes to age. Patients with younger age tend to suffer from more pain and require larger doses of opioids (40,98,101,102). Opposite, older people tend to require lower doses. Thomazeau and colleagues demonstrate that in a study where they found that opioid consumption decreased in total by 0.9 mg for each additional year (103).

Anaesthesia

When comparing spinal anaesthesia (SA) with general anaesthesia (GA) a study indicated that VAS scores at admission to PACU were less with SA than with GA, and the need for analgesics for postoperative pain was also significantly less for the SA group. Patients in the GA group had a reduced length of stay at the PACU compared to the SA group (104). Another study found that regional anaesthetic technique compared with GA decreased the risk of acute postoperative pain, but only on the day of the surgery (40).

Surgery

Persistent postoperative pain is a well-known risk after a number of surgical procedures (25). After e.g. thoracotomy and mastectomy, the number of patients with persistent pain may be as high as 50% of patients (102,105). Some of the reasons are the intraoperative nerve handling which results in patients enduring high levels of pain for a longer time. It is not possible to use epidural analgesia after this kind of surgery and therefore it can be difficult to ease the patients´ pain sufficiently (106).

Psychology

Different psychological factors can affect patients´ pain experience postoperatively. Some of the well-documented factors are pain catastrophizing (101,107,108) and anxiety and depression (43,109). Several other factors have proven to affect the pain experience as well. For example if the patients expect to endure a lot of pain after the surgical procedure (40,110), suffer from surgical fear (110,111), lacks optimism (111), or have a reduced quality of life (111). It seems as these factors all have an influence on patients´ postoperative pain levels. In contrary, patients with a higher

preoperative and postoperative quality of life, as well as a generally higher optimism, are better protected against a reduced global recovery (111).

Pain

A recent systematic review by Werner et al. demonstrated that the use of preoperative sensory testing to predict the patients nociceptive status, could only predict 4 - 54% of the variance of postoperative pain in individual patients (112). Several studies found that one of the most important predictors for postoperative pain was the presence of preoperative pain (40,64,106,111,113). It is very common that certain patient populations suffer from pain for a long time preoperatively, that is the fact for e.g. total hip arthroplasty (114), total knee arthroplasty (115), and shoulder surgery (23). Studies have found moderate to severe postoperative pain to be a predictor of persistent pain (101,113), therefore, these conditions need to be avoided. One study found that especially pain levels during mobilisation were important to pay attention to (102).

Analgesics

There are indications that opioids can increase sensitivity to noxious stimuli and cause opioid-induced hyperalgesia (116). This is underpinned by several studies, which found that patients with a pre-operative opioid use have an increased risk of high levels of postoperative pain, and additively, an increased opioid consumption (116–118).

Since no single factor, yet, has shown solely to have the ability to predict postoperative pain, researchers have tried to combine a variety of factors to design predictive rules. For example, Kalkman and colleagues (119) combined 11 different factors such as age, gender, type of surgery, the expected size of incision, preoperative pain scores etc., to predict patients with severe pain shortly after awakening from GA (119). Also Aasvang et al (120) found four predisposing factors in their study regarding persistent post-herniotomy pain. Preoperative activity assessment score, preoperative pain to tonic heat stimulation, 30-day postoperative pain intensity, and sensory dysfunction in the groin at 6 months. Unfortunately, there is not enough time in clinical practice to test for all these combinations including many different factors that can predict pain. Simple, easy-to-use methods useful in a clinical setting are needed, not methods resulting in a lot of pressure to the already fragile patients adding several questionnaires or different kinds of additional sensory testing. Persson and colleagues (121) found that pain induced by PVC preoperatively could be used as a simple predictor for pain at rest in the PACU postoperatively. PVC is used in most surgical procedures already. Further research is needed to investigate if PVC also can be used for predicting pain levels after discharge from the PACU during mobilisation.

Surgical stress response

After major surgery, it is common that patients have several complications, not only due to the surgical or anaesthetic techniques but because of the surgical stress response (122). The response causes hormonal and metabolic changes as a part of the systemic reaction, which encompasses a wide range of endocrinological, immunological and hematological effects (123). This is also reinforced by pain because of the increased release of inflammatory mediators and hereby cytokine release (122). The intensity of the stress response correlates with size of the surgical procedure thus increases the response when it comes to thoracic, abdominal and orthopedic surgery (31,122). Afferent blockade by regional anaesthesia has been reported to reduce the classical endocrine metabolic stress response as well as minimal invasive surgery (22).

Total hip arthroplasty

THA was introduced at Danish hospitals in the 1960s. In the 1970s most of the orthopedic wards was able to perform the operation (124). The procedure has increased over the last 15 years (125). and is now one of the most frequent elective operation performed in Denmark. According to the Danish Hip Arthroplasty Register (126), 10.435 THAs were performed in 2017 in Denmark (126). Worldwide the number was 950.000 in 2010 (127). The main reason for having a THA performed is arthritis. The median age is 70 and THA is performed more frequently in females (125). Some of the preoperative symptoms patients primarily suffer from are pain, mobility disability, and loss of quality of life (124). The surgical procedure is performed via an incision along the side of the hip continuing to move the muscles connected to the top of the thighbone exposing the hip joint. There are three common used surgical approaches, the posterior, the lateral, and

Picture 1 X-ray image of total hip arthroplasty

more rarely the anterior approach (128). After the incision, the ball portion of the joint is removed by cutting the thighbone with a saw. Then an artificial joint is attached to the thighbone using either cement or a special material that allows the remaining bone to attach to the new joint. Then the surface of the hipbone is prepared, removing any damaged cartilage and attaches the replacement socket part to the hipbone. The new ball part of the thighbone is then inserted into the socket part of the hip (picture 1). Regardless of the approach the patients suffer from moderate to severe pain shortly after the operation (9). Some of the complications after THA are wound infections, loosening and wear, and dislocation (129). THA is performed in either general or spinal analgesia and the surgery is normally performed in less than two hours (130). A patient satisfaction questionnaire study reports that 89% of the patients were satisfied after THA. The major reason for those who were not satisfied was persistent pain (131). The multimodal analgesic approach is the standard of care for THA (132).

NN is 65 years old and she shares her story when I am including her in my study.

> "In the past I ran 2 or 3 marathons per year. I retired early and found a good companionship in the local running club. My troubles started out with an aching pain on the side of the hip when I ran the long distances. I just thought I needed new running shoes. The pain disappeared when I wasn´t running so I just tried to recover for a longer time. After 3 months I couldn´t run at all without having pain and often I had pain at night disturbing my sleep. My mood was affected and I felt powerless. I missed my running trips and the companionship with the others in the club. At home, I found myself sitting in my chair most of the days since it was the only way to be painless. Finally, my husband told me to go and see the doctor. I went and after x-rays and many examinations she told me, I had arthritis. A long the way she gave me many different painkillers but nothing really helped. In the end they offered me a hip replacement and told me that I possibly can run again someday which I hope for with all of my heart."

Aims

With this PhD study, we aimed to investigate different aspects of multimodal postoperative pain management including a special focus on the efficacy of pain treatment and the individual patients. We, therefore, conducted the following studies:

Study I: A systematic review investigating the evidence for analgesic effects of procedure-specific medication-based interventions after THA surgery.

Study II: A recalculation of pain outcomes based on data from individual patients using 16 previously published RCT´s, and "no worse than mild pain" (VAS ≤30) as a criterion for individual treatment success. Additionally, to perform a re-analysis with data from a systematic review to obtain the same goal.

Study III: A clinical prospective cohort study investigating postoperative pain treatment in 501 THA patients at five different Danish hospitals with a focus on the efficacy of multimodal analgesia both on a hospital and on individual patient level.

Study IV: A prospective clinical cohort of 100 THA patients investigating if pain by PVC preoperatively could predict high pain responders at 24hr postoperatively during mobilisation. Furthermore, to explore if moderate/severe pain at the PACU, or the PACU nurse´s expectations, or patients´ own forecast was associated with increased pain at 24hr during mobilisation.

Methods and outcomes

Study I

In this procedure-specific systematic review with meta-analyses, the effect of analgesic interventions for postoperative pain relief after THA in adults >18 years, was assessed. The review was structured according to the PRISMA statement (133) and the Cochrane guidelines (134).

The literature search was conducted with a wide search string in PubMed, Embase and the Cochrane Library. The final search was performed in august 2014. All of the studies, which appeared according to the search-string, were extracted according to abstracts and headlines individually by the primary author (AK) and the co-author (AG). The trials that was suitable for full text screenings were then divided between the two co-authors (PLP and AG). The primary author (AK) extracted all studies. All included trials were evaluated and discussed between the primary author and the co-authors.

To assess the risk of systematically errors, a risk of bias assessment was carried out regarding all included trials according to the Cochrane Handbook of Systematic Reviews (134). The risk of bias was evaluated individually using the structure and bias-evaluation as described in the data extraction form in Table 2.

Table 2.
Bias domains

Type of bias	Domains	How to select grade Low, High or Unclear
Selection bias	Allocation sequence	**Low** • Referring to a random number table • Using a computer random number generator • Tossing coin, shuffling cards or envelopes, throwing dice, drawing lots **High** • Sequence generated by odd or even date of birth • Sequence generated by some rule based on date (or day) of admission • Sequence generated by some rule based on hospital or clinic record number • Allocation by judgement of the clinician, preference of the participant or availability of the intervention **Unclear** • Insufficient information about the sequence generation process to permit judgement of ‘yes’ or ‘no’

Type of bias	Domains	How to select grade Low, High or Unclear
Selection bias	Concealment of allocation	**Low** • Central allocation (including telephone, web-based and pharmacy-controlled randomisation) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes **High** • Using an open random allocation schedule (e.g. a list of random numbers) • Assignment envelops were used without appropriate safeguards (e.g. if envelops were unsealed or non-opaque or not sequentially numbered • Alternation or rotation, date of birth, case record number • Any other explicitly unconcealed procedure **Unclear** • Insufficient information to permit judgement of 'yes' or 'no'. If the method of concealment is not described in sufficient detail to allow a definite judgement.
Performance bias	Blinding of participants and personnel.	**Low** • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. **High** • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. **Unclear** • Insufficient information to permit judgement of 'Low risk' or 'High risk', or the study did not address this outcome.
Detection bias	Blinding of outcome assessment.	**Low** • If specified that participants and personnel were blinded **High** • If stated that participants or the personnel were familiar to which group they were randomised to **Unclear** • Nothing was state
Attrition bias.	Incomplete outcome data	**Low** • If the numbers and reasons for dropouts and withdrawals in the intervention groups were described or if it was specified that there were no dropouts or withdrawals **High** • If the number or reasons for dropouts and withdrawals were not described **Unclear** • If the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated

Type of bias	Domains	How to select grade Low, High or Unclear
Reporting bias.	Selective outcome reporting	**Low** • If predefined or clinically relevant and reasonably expected outcomes are reported on **High** • If one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded **Unclear** • If not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not
Other bias	Other sources of bias	**Low** • No risk of other bias, the trial appears to be free of other components that could put it at risk of bias e.g. funding is stated **High** • There are other factors in the trial that could put it at risk of bias, e.g. 'for profit' involvement or authors have conducted trials on the same topic **Unclear** • The trial may or may not be free of other components that could put it at risk of bias

Each trial had a summarised risk of bias; low when all domains were low, unclear if at least one domain was unclear, and high if at least one domain was high.
To grade the quality of evidence and strength of recommendations The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was summarised by the primary author (AK) using GRADEpro 3.6 by the GRADE working group (135). As stated by Guyatt and collagues (135) evidence may be decreased for several reasons: study limitations, inconsistency of results, and indirectness of evidence, imprecision and reporting bias. Therefor GRADE gives the opportunity to provide transparency by rating the studies as: High quality if further research is very unlikely to change the confidence in the estimate of effect. Moderate quality if further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate. Low quality if further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality means any estimate of effect is very uncertain (135,136).

Thereafter, continuous data for pain and opioid consumption for subgroups of three or more trials were analysed by the primary author (AK) with the use of Review manager (137). Inclusion criteria were RCTs, adults´ ≥18 years having THA surgery where an analgesic intervention took place versus placebo or no treatment at all. Studies were excluded if they concerned hip fractures, children, or were of any observational or explorative kind. If data were missing during the data extraction or bias evaluation they were classified as unclear in one or more domains, the corresponding author was contacted by email to confirm or obtain data. Trial sample

size bias was evaluated according to Dechartres et al (138), <50 participants as high risk of bias, 50-199 participants as a moderate risk of bias, 200-499 participants as low risk of bias. Data were entered into an Excel file by two independent authors and compared. The different pain scales used in the RCTs were all converted to VAS 0-100 (139).

Trial sequential analysis (TSA) was performed only for opioid consumption and pain scores that demonstrated a statistically significant difference and consisted at least three RCTs.

The primary outcome was opioid-sparing effect of the active interventions 0─24hr postoperatively. Secondary outcomes were levels of pain during rest and mobilisation at 6±2hr and 24±4hr postoperatively as well as opioid-related adverse effects, and length of stay (LOS).

Study II

In this paper, data from previously published RCTs were re-analysed using individual patients´ pain levels NRS (0─10) or VAS (0─100). The data were delivered from trials performed by members of the same research group, which all investigated postoperative pain treatment. The pain scores from the individual patient at 6 or 24hr postoperatively, during rest and if possible mobilisation, were extracted from the RCTs and subsequently entered into an Excel file.

To validate the data and the findings data was used from trials included in a systematic review (140) (Study I). Since the data from the individual patient were not available in the systematic review, mean and standard deviations were used instead. The proportions of patients achieving VAS pain ≤ 30 at rest and during mobilisation were afterward calculated, using the probability methodology described by Altman (141).

The primary outcome was to explore how many studies that achieved the defined goal, at least 80% of patients in trial groups, should obtain VAS ≤ 30 at 6 and 24hr postoperatively.

Study III

This prospective, multicentre, observational cohort study was performed at five different hospitals in two different Regions in Denmark. Data was collected from April 2014 to April 2016.

Inclusion criteria were adult patients (≥ 18 years) scheduled for primary THA, speaking Danish and/or English. Exclusion criteria were not able to cooperate, drug or alcohol abuse assessed by the local investigator, and patients using opioids on a daily basis.

At each hospital, the local investigator (doctor/nurse) enrolled consecutive patients until 100 evaluable patients were obtained. The manuscript followed the

Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines (142).

The following data were registered from the patients´ electronic records. Preoperatively: height, weight, sex, American Society of anesthesiology (ASA) physical score, the use of daily analgesics, and if any analgesic intake before surgery (premedication). Perioperative: type of anaesthesia, analgesic and anti-emetic treatment, duration of surgery, and surgical approach. Postoperative: the pain levels at rest and during mobilisation as well as side effects at 6±2hr and 24±2hr postoperatively, recorded by asking patients directly. All pain levels were recorded using NRS 0─10. (Zero= no pain at all and 10= the worst imaginable pain). Side effects as nausea, dizziness and sedation were monitored by using VRS (none, mild, moderate, severe), vomiting was reported as either "Yes" or "No." Opioid consumption 0─24hr was reported and converted into IV morphine equivalents (eqv.). LOS reported in numbers of nights the patient stayed at the hospital. Data were entered directly into the patient´s case report form (CRF) by the local investigator.

This study had two primary outcomes: Pain levels according to NRS, during mobilisation at 6±2hr postoperatively and morphine consumption 0─24hr postoperatively. Data were compared at a hospital level, and at an individual patient level, based on the non-opioid analgesic treatment of the individual patient.

Study IV

Consecutive adult patients (≥18 years) speaking Danish and/or English, scheduled for primary THA at Zealand University Hospital in Køge, were enrolled in this prospective observational cohort study. The manuscript followed STROBE (142). Patients were enrolled during the pre-surgery information meeting two weeks before surgery. After written and verbally informed consent patients filled out the PCS questionnaire (42) and additively answered questions regarding their socio-economic status and forecast of pain threshold meaning they stated if they considered themselves as someone who could endure a lot of pain (forecast low) or managed pain badly (forecast high). Shortly before surgery, a PVC was placed on the back of the dominant hand and the anaesthetic nurse rated the patient´s pain using NRS from 0─10. The patients were later, for the comparisons, divided in two groups, those patients with NRS≤2 (group low) by PVC and those with NRS>2 (group high). Postoperatively in the PACU patients highest NRS score was reported and the PACU nurse then predicted if the patient was a high (NRS>3) or a normal (NRS≤3) pain responder according to her point of view. The background for her choice was stated in the case report form (CRF). At the ward, postoperatively pain levels after 24±2hr were recorded with NRS from 0─10 during rest and mobilisation. (Table 3)

Table 3.
Explanation of the four prediction groups

Prediction groups	Defined in the study as	Explanation of group categorisation
PVC	PVC Low and PVC High	Patients divided in two groups according to NRS pain levels by PVC. Group Low= PVC≤2 and group High=PVC>2
PACU nurse	Nurse Low and Nurse High	Patients divided in two groups according to PACU nurses prediction. Nurse Low= PACU nurse predicting patients pain to be NRS ≤ 3 at 24hr postoperatively Nurse High= PACU nurse predicting patients pain to be NRS > 3 at 24hr postoperatively
PACU	PACU NRS≤3 and PACU NRS>3	Patients divided in two groups according to highest NRS at the PACU. PACU NRS ≤ 3 and NRS > 3
Forecast	Forecast Low and Forecast High	Patients divided in two groups according to how the patients forecast their pain threshold preoperatively. Forecast Low=Normal pain threshold and Forecast High= Easily enduring high levels of pain

Preoperative, per-operative and postoperative information was recorded from the electronic patient records. Preoperatively: height, weight, sex, ASA, usual preoperative analgesic consumption, and analgesics used before surgery. Perioperative data: the amount of analgesic and antiemetic treatment, and duration of surgery. Postoperative data: analgesics used from 0─24hr postoperatively, and LOS.

The primary outcome was differences between groups, based on levels of NRS pain by preoperative PVC dichotomised to NRS ≤ 2 (PVC low) or > 2 (PVC high), compared to levels of NRS pain during mobilisation at 24±2hr postoperatively.

Statistical analyses

Study I:

All analyses, including the meta- analyses were conducted by the primary author (AK) using Review Manager 5 (RevMan, Version 5.1.6; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) (137). Forest plots were used to assess intervention effects for outcomes reported in three or more trials considering comparable interventions, with 95% CI. P values of 0.05 or less was considered statistically significant. A random-effects model was used for higher degrees of heterogeneity and fixed-effects model for lower degrees (143). The heterogeneity was assessed by I^2, which quantifies the observed differences. An I^2 =50% has been recommended as a moderate degree of heterogeneity (144). TSA was used to evaluate the risk of type 1 and type 2 errors, The TSA (145) was carried out using the program version 0.9 beta (www.ctu.dk/tsa). TSA were performed for opioid-sparing effects and pain scores (145). Sensitivity to detect a minimal relevant difference (MIREDIF) was set to 10 mg morphine IV pr 24hr and as 15 mm on the VAS scale for pain scores.

Study II:

To conduct the re-analyses data from 16 RCTs, Statistical Package for the Social Science (SPSS) were used (version 22 and 25, SPSS Inc. Chicago, IL). The proportions (in percentages) were calculated for the patients who achieved VAS pain ≤ 30 at rest and during mobilisation from treatment and control groups. VAS was measured from 0─100 (zero=no pain and 100= worst imaginable pain). A 95% confidence interval was estimated using the statistical calculator "Causa Scientia" (146). To validate the findings mean and standard deviations were compared from the trials included in a systematic review (140). Since the review had no individual patient data we presented data as normal distributed by using the method for calculation of proportions described by Altman (141).

Study III:

In this prospective observational cohort study, the statistical analysis was performed using SPSS (v.22 and 25, SPSS Inc, Chicago, IL). Normal distribution was tested by using the One-sample Kolmogorov-Smirnov test. Data were expressed as mean and standard deviation (SD) if normally distributed, or as median and interquartile range (IQR), also as numbers and percentages as appropriate. The non-parametric

Kruskal-Wallis test was used to compare groups, and if significant, the Mann-Whitney U test was used to group-wise comparisons. Chi^2 was used to test for differences between two groups. The p-values of <0.01 were considered statistically significant for the primary outcomes. Bonferroni correction was used to counteract for mass-significance when considered relevant.

A sample size estimation was conducted for the primary outcome, NRS-pain during mobilisation at 6hr postoperatively. Using an SD of 1.7, $\alpha = 0.01$and a power of 0.90. This resulted in 88 patients needed for inclusion from each hospital in order to detect a minimal relevant difference of 1.0. We also estimated sample size for the second primary outcome, morphine consumption (IV eqv.), at 24hr postoperatively with an SD of 17 and $\alpha= 0.01$, a power = 0.90. This resulting in 88 patients were needed to detect a minimal relevant difference of 10 mg (IV eqv.). To compensate for missing data and dropouts 100 patients from each hospital were included.

To identify associations between outcomes either multiple linear regressions or logistic regressions (binary outcomes) were performed. All regression analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC). Model fit was tested by residual spread and distribution, Cook´s distance and tests for linearity. The logistic regression was tested for statistical overspreading, goodness-of-fit and residual spread.

Study IV:

In this predictive prospective, observational cohort study, all statistical calculations were performed using SPSS (version 22 and 25, SPSS Inc, Chicago, IL). Normal distribution was tested visually in histograms and Q-Q plots and quantitatively with One-sample Kolmogorov-Smirnov test. Data were expressed as a mean and a SD if normally distributed, or as a median and an IQR, or as numbers and percentages if appropriate. The non-parametric Kruskal-Wallis test was used to compare groups if significant the Mann-Whitney U test was used to group-wise comparisons. Chi^2 was used to test for differences between two groups. P-values for the primary outcome of <0.01 was considered statistically significant. Bonferroni correction was used to counteract for mass-significance when considered relevant.

A sample size estimation was performed for NRS pain during mobilisation based on results from study III. With a SD of 2.5, $\alpha = 0.01$, a power of 0.90, we found that 93 patients were needed to detect a minimal clinically important difference (MCID) of NRS-pain at 1.0. To compensate for the uncertainty of SD we aimed to include 100 consecutive patients undergoing THA.

For the exploratory part, multiple linear regressions were performed using SPSS (v.22 and 25, SPSS Inc. Chicago, IL), adjusted an unadjusted. SPSS was also used for evaluating and comparing predictive models in the Receiver Operating Characteristic curves (ROC).

Ethical considerations

The studies included in this thesis follow the ethical principles for medical research involving humans according to The Helsinki Declaration (147). In addition, they follow the principles of health care ethics in the matter of respect for autonomy, non-maleficence, beneficence, and justice (148).

Study I was a systematic review, therefore, no ethical approval was needed.

Study II was a re-analyse, all data were anonymised of the included individual, and no ethical approval was needed.

Study III. The Danish Ethical Committee was contacted before the study began. No approval was needed since the study was exploratory and did not have a direct effect on, or change of patients´ treatment (H-1-2014-FSP-027). Since the author changed workplace to another Danish Region whilst the study was conducted, both acceptance from The Danish data Protection Company in the Capital Region (03145/301323) and in the Zealand Region (REG-02-2015) was necessary. At the time where the study was designed and performed informed consent from the patients was not mandatory but acceptance from the departmental head was granted by each included site.

Study IV. The Danish Ethical Committee was contacted before the study began. No approval was needed since the study did not have any change of patients´ treatment (J.nr. 17-000048). The Danish Data Protection Company in the Zealand Region (REG-158-2017) accepted the study. Patients were explained about the content of the study verbally by the investigator and they additively read a written declaration in easily understandable Danish, two weeks before surgery. One can consider if it is ethical acceptable to ask patients, after a long day with lots of information, x-rays, and blood tests, to participate in a study, fill out questionnaires, and answering many different questions. The optimal way is having the opportunity to consider the participation for at least 24hr and have time to fill out questionnaires in a calm place. Unfortunately, this was not possible due to the logistics. Furthermore, the legal terms were explained and handed out in a written paper. Especially the paragraph included stating that the patient at any time could withdraw from the study without consequences, was underpinned. Afterwards, the patient decided if he/she wanted to participate and filled out the written informed consent. If the patients felt, it would be all right to be contacted by phone after the study has ended, for a one-year follow up, they could additively write their phone number on the informed consent note.

Results

Study I

In this systematic review, 8.483 trials were screened, and 58 RCTs were included for further data extraction. Nineteen different analgesic interventions was found. The risk of bias was high or unclear in 155 of 406 domains. The summarised bias was unclear or high in 48 out of 58 trials for the exact distribution please look at figure 6.

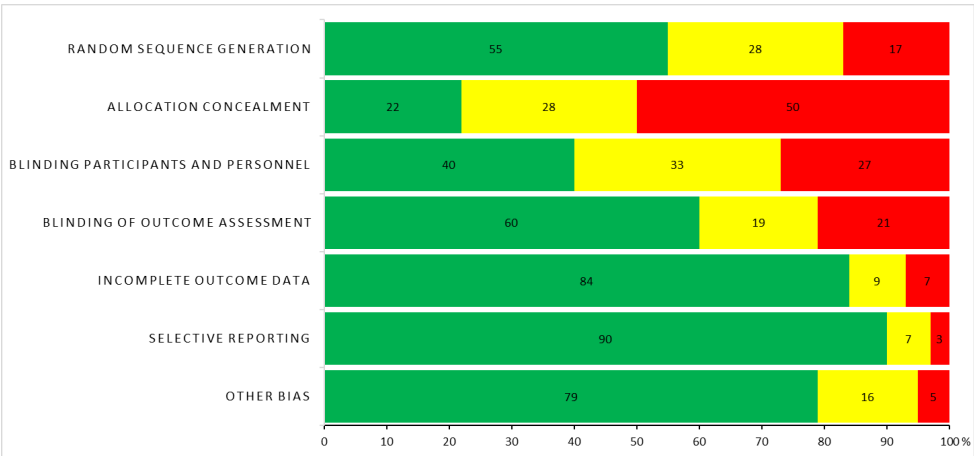

Figure 6.
The distribution of bias for the 58 studies according to the seven bias domains
Green: Low risk of bias. Yellow: Unclear risk of bias. Red: high risk of bias

The Meta-analyses were performed for NSAIDS, local infiltration analgesia (LIA), intrathecal opioid and lumbar plexus block. The results regarding the opioid sparing effects demonstrated statistically significance for all four interventions, ranging from 7.5 mg─19.8mg (Table 4).

The evidence according to GRADE was low to very low (Table 4). When exploring the pain levels in the four different interventions there were a decrease in VAS (0-100) of 9─15 mm. Here the quality of evidence was low to very low (Table 4).

In general, we found the analgesic treatment for THA to be very heterogeneous, and that the combined literature was not able to present any “gold” analgesic standard.

Table 4.
Reduction of morphine consumption, and levels of pain at 6 and 24hr according to interventions

Intervention	Numbers of RCT´s included	IV morphine con-sumption (24hr) reduced in mg. Effect of the interven-tion vs. placebo	*GRADE level	Pain reduction Effect of the inter-vention vs. placebo (VAS 0–100), 6hr at rest	*GRADE level	Pain reduction Effect of the inter-vention vs. placebo (VAS 0–100), 24hr at rest	*GRADE level
Non-steroidal anti-inflammatory drugs/COX-2-inhibitor	10	14.1	Low	14	Low	9	Very low
Local infiltration Analgesia (LIA)	11	7.5	Low	8	Low	3	Low
Intrathecal opioids	7	19.8	Very low	13	Very low	1	Very low
Lumbar plexus block	4	11.9	Very low	31	Very low	11	Very low

*Quality of evidence expressed with GRADE are divided in, High levels (highest quality), Moderate levels, Low levels and very low levels (worst quality of evidence)

Study II

Six-teen RCTs were included for re-analysis with a total of 1122 patients, 694 patients in the active treatment groups and 428 in the control groups. Both major and minor surgical procedures were included in the re-analysis, including orthopaedic surgery, gynaecological surgery, abdominal surgery, ear-nose-throat surgery and urologic surgery. The goal we aimed for was 80% of the individual patients in the trials should obtain no more than VAS $\leq$ 30. We found that, for patients allocated to active treatments for pain at rest at 6hr that 50% (95% CI: 31–69), reached the goal (Figure 7). During mobilisation at 6hr we found 14% (95% CI: 5–34) reached the goal (Figure 8). At 24hr at rest, 60% (95% CI: 38–78) reached the goal (Figure 9) and during mobilisation at 24hr, 15 % (95% CI: 5–36) reached the goal (Figure 10).

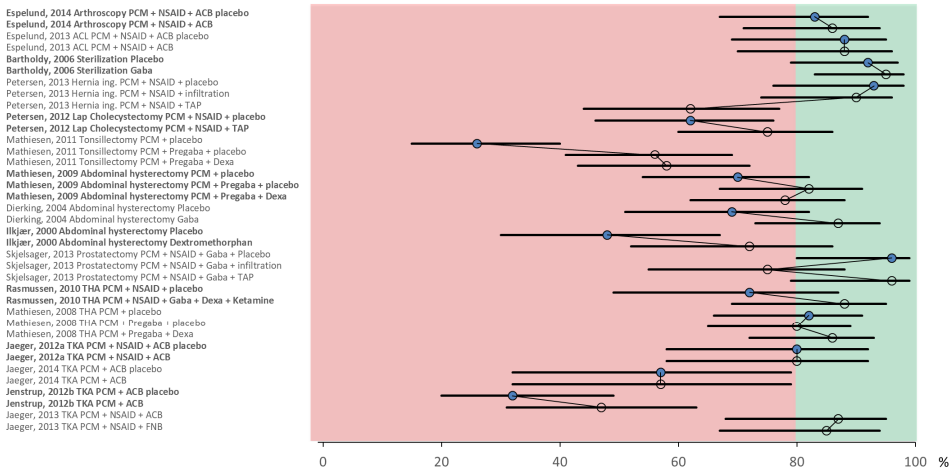

Figure 7.
Pain 6hr at rest.
Legend for figure 7, 8, 9 and 10. The trials in the green area reach the goal of 80% of patients obtaining VAS ≤ 30; the trials not obtaining the goal are in the red area.
The dots connected by strings symbolise one trial. The blue dot is the placebo treatment and the clear dot is the active intervention. Some trials have more than one active intervention, and some trials have no placebo group.

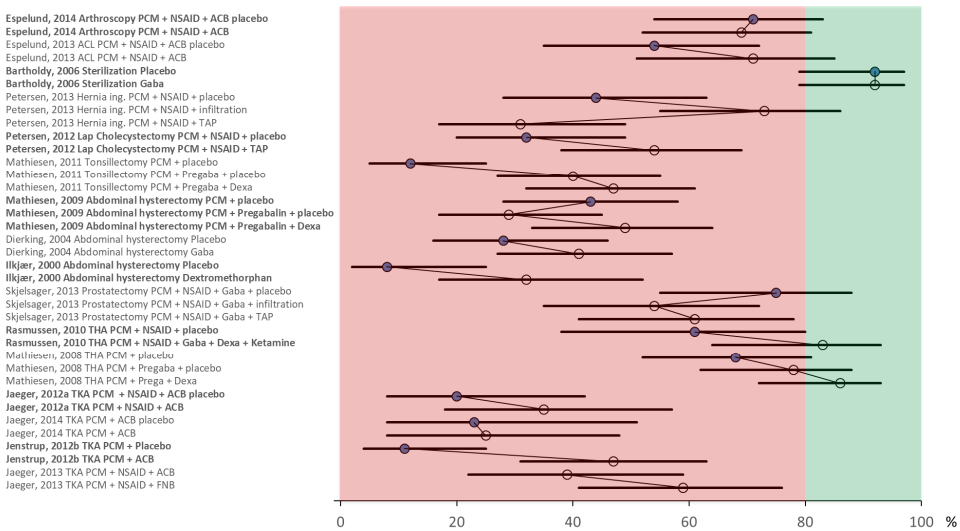

Figure 8.
Pain 6hr during mobilisation
Legend: See Figure 7

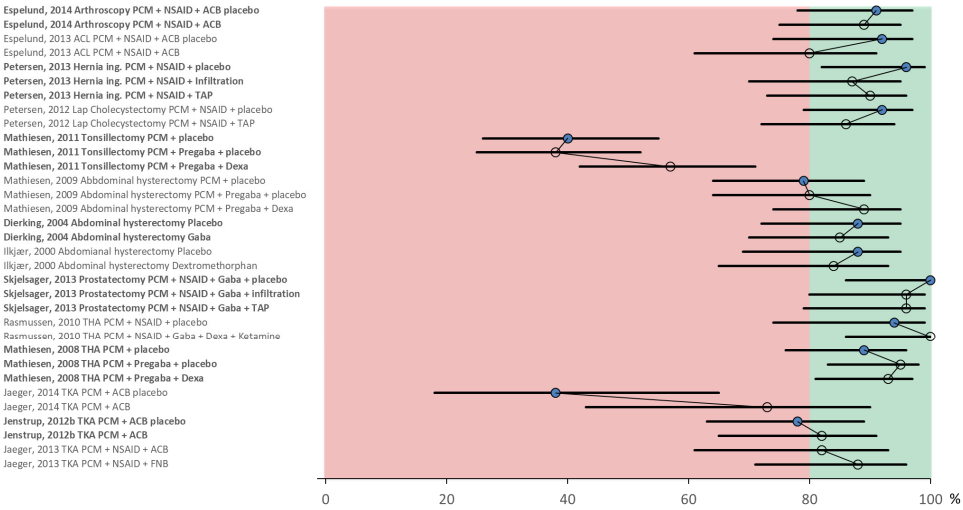

Figure 9.
Pain 24hr at rest
Legend: See Figure 7

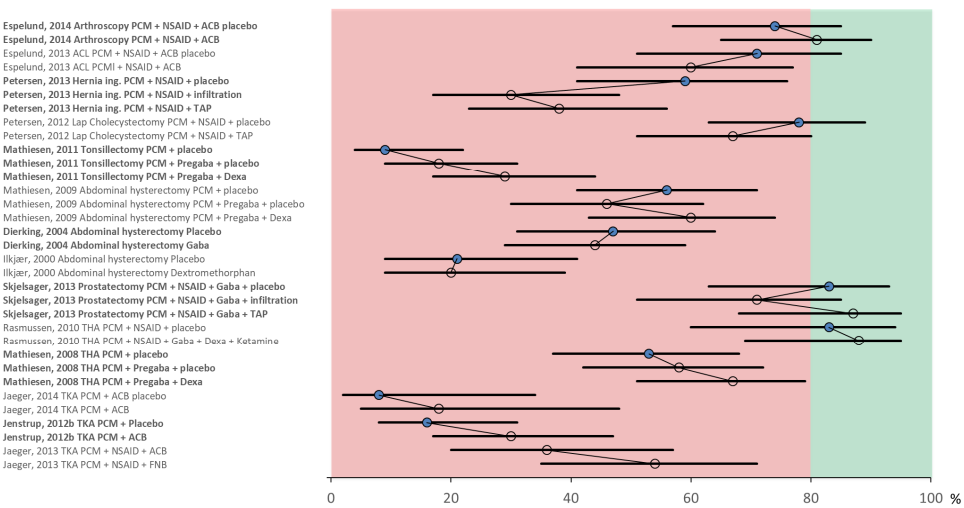

Figure 10.
Pain 24hr during mobilisation
Legend: See Figure 7

We also identified trials where the active group had worse outcomes than the control group. This was the issue for pain during rest at 6hr (3 trials) and during mobilisation (4 trials). For 24hr, this was observed in eight trials at rest and seven trials during mobilisation.

The review included for comparison (140) only comprised data for pain at rest. The following analgesic interventions for THA were investigated in the review: NSAIDs, local infiltration, LIA, intrathecal opioids and lumbar plexus blockade. A total of 58 RCTs having a total of 4310 patients, respectively 2518 in the active treatment groups and 1792 in the control groups. Here, the findings were very similar. For pain at rest at 6hr 56% (95% CI, 37─73) reached, the goal postoperatively and at 24hr at rest, 45% (95% CI, 27─66) of the active treatment reached the goal of 80% success.

Study III

In this study, 635 patients who had THA surgery, at five different hospitals, were assessed for inclusion. After exclusions, 501 patients were included for the data collection. In total, 262 male and 239 female THA patients were included consecutively. Patient characteristics were comparable between hospitals. For further details, please look at table 5

Table 5.
Patient characteristics

Hospitals		A (n=95)	B (n=100)	C (n=100)	D (n=101)	E (n=105)
Age, year	**mean (SD)**	71 (10)	66 (10)	69 (9)	70 (9)	71 (9)
Height, cm	**mean (SD)**	169 (8)	169 (8)	170 (9)	170 (8)	170 (9)
Weight, kg	**mean (SD)**	76 (16)	80 (16)	77 (15)	77 (16)	81 (17)
Sex m/f, %		32/68	43/57	34/66	41/59	47/53
ASA (I/II/III/IV/missing), n		No data	27/64/8/0/1	22/58/14/0/7	42/52/4/0/2	14/59/28/1/3

Pain treatment

Almost half (43%) of the patients used analgesics at home before admission, most frequently non-opioids. In regard of anaesthesia during surgery, the most preferable was SA, except at hospital E, which used GA.

The pain treatment varied greatly between hospitals (Table 6) and no hospitals used the same perioperative analgesic treatment.

Table 6.
Analgesic used for perioperative pain treatment at the five different hospitals A to E.

Hospitals	A (N=95) (%)	B (N=100) (%)	C (N=100) (%)	D (N=101) (%)	E (N=105) (%)
Analgesic premedication					
PCM+extended release morphine	95				
Extended release oxycodone			78		
PCM + GABA + tramadol				94	
During anaesthesia					
Methylprednisolone*			93		
Local infiltration analgesia	20				
Analgesic postoperatively					
PCM*	98	100	98	96	93
NSAID*		90	91	27	9
Gabapentin*		30		63	
Chlorzoxazone*		7		3	
LFCN block*		29			
Morphine IV (mg) (0-24 h) usage (median (IQR))	20 (13-30)	18 (8-26)	28 (20-41)	27 (22-34)	31 (19-49)

PCM=paracetamol. NSAID= non-steroidal anti-inflammatory drug. GABA= gabapentin, LCFN=Lateral Femoral Cutaneous Nerve.

*Dosages administered (0-24h): PCM (1-5 gram) Ibuprofen (400 – 2400mg) Keterolac 30mg, Etodolac (600 -900mg), Gabapentin (300 – 2700mg), Chlorzoxazone (250 -500mg), Methylprednisolone (125 mg), LFCN block (8 ml ropivacaine 0.75%)

Opioid usage

The 24hr morphine consumption (IV. morphine (eqv.)) for all hospitals, which were the primary outcome was 25 mg (18-35) (median (IQR)). Two hospitals (A and B) used significantly less morphine compared to the other hospitals. (See Table 6)

Analgesic league table

The patients were divided according to the combinations of non-opioid analgesics they have received, recorded pain levels and morphine usage. With the use of an analgesic league table, which divides patients into different groups according to the analgesics they have received, we tried to find an analgesic combination superior to the others. Only a marginally difference was detected comparing pain levels at 6hr and 24hr during rest and mobilisation. No non-opioid analgesic treatment was superior to the others.

An exploratory regression analyses was performed according to the analgesic league division of patients, adjusted for anaesthesia, sex and non-opioid analgesics. Here the findings demonstrated that the combination of PCM + NSAID and PCM + NSAID + GABA was associated with a significant reduction in 24hr morphine (eqv) consumption compared to PCM alone, (-6 mg (95% CI -10;─1)) and (-11 mg (95% CI -17;─4)). That was also the case with PCM + NSAID + Glucocorticoid which could demonstrate a significantly reduction in pain during mobilisation at 6h postoperatively (0.7 in NRS (95% CI 0.05─1.35). For the other analgesic combinations, no statistically significant differences were found. (Table 7)

Table 7.
Regression models for anaesthesia, sex and non-opioid analgesics, correlated to morphine (eqv.), pain and adverse-effects. All patients at all hospitals

Co-variates	**Morphine usage (eqv) 0-24h** Multiple linear regression Estimate mg (95% CI)	p-value	**Pain (NRS) 6h mobilisation** Multiple linear regression Estimate NRS (95% CI)	p-value	**Adverse-effects 24h** Logistic regression Estimate OR (95% CI)	p-value
PCM+NSAID	-5.54 (-10.25;-0.83)	0.021	0.38 (-0.27;1.03)	0.26	0.92 (0.52;1.61)	0.63
PCM+NSAID+GCC	3.34 (-1.37;8.06)	0.17	0.7 (0.05;1.35)	0.035	1.37 (0.79;2.37)	0.09
PCM+NSAID+GABA	-10.54 (-17.34;-3.75)	0.0024	0.18 (-0.73;1.09)	0.71	1.31 (0.57;2.99)	0.29
PCM+GABA	-1.30 (-6.92;4.32)	0.65	0.40 (-0.43;1.25)	0.34	0.75 (0.38;1.49)	0.77

PCM= paracetamol. NSAID= non-steroidal anti-inflammatory drug. GCC= glucocorticoid. GABA= gabapentin. In this table, patients receiving PCM only was the reference. For type of anaesthesia the reference is spinal. For gender reference is male. Side-effects are based on total summed incidences of dizziness, nausea, vomiting and sedation.

Pain levels

When looking at all patients at all five hospitals, the results for the co-primary outcome NRS-pain at 6hr during mobilisation, was 5 (3─6) (median (IQR)). At rest NRS-pain was 3 (2─5) (median (IQR)). After 24hr during mobilisation 5 (3─6) (median (IQR)) and at rest 2 (1─4). The individual hospitals pain levels demonstrated a very similar result. The only significant finding was pain at 24h postoperatively at rest, where hospital B (2 (0─3) (median (IQR)) demonstrated lower pain levels compared to hospital E (3 (2─5) (median (IQR)) (p=0.01).
The percentage of individual patients achieving a maximum pain of NRS < 3 ("No worse than mild pain") were calculated as suggested by Moore (94). Illustrated in Figure 11 for all five hospitals, 23─ 47% achieved that goal at 6hr during mobilisation and 44─ 63% at rest. At 24hr, this was 24─37% during mobilisation and 65─80% at rest. No significant differences were found between the hospitals, but as figure 11 illustrates, less patients achieved NRS < 3 during mobilisation at 6 and 24hr compared to at rest.

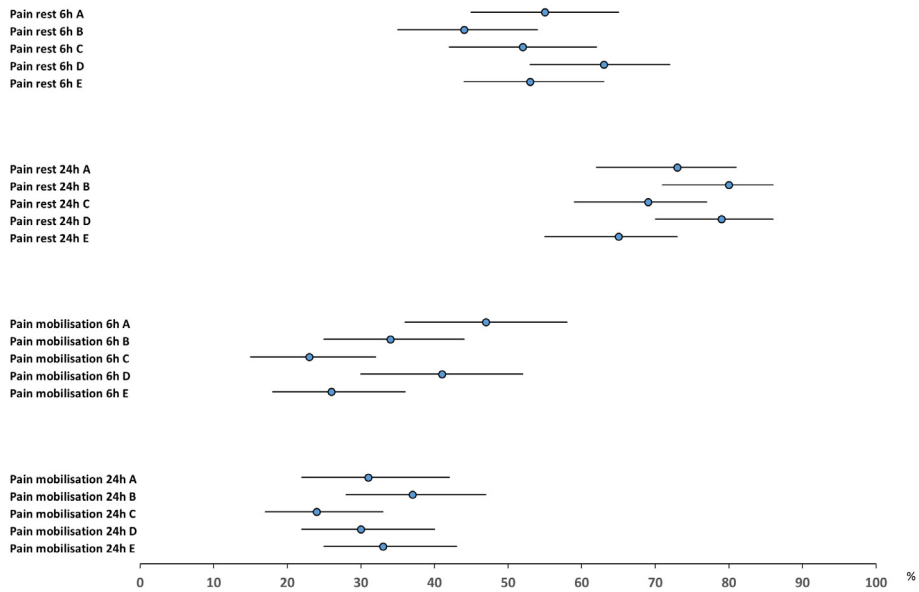

Figure 11.
Percentage of patients achieving NRS ≤ 3 for pain at rest during mobilisation at 6h and 24h postoperatively at hospital A to E
Data are presented as percentage (95% CI)

Adverse effects

There was a marginally difference between hospitals regarding nausea, vomiting, sedation and dizziness between the five hospitals.

We found that the total amount of opioid in mg patients used for 24hr was significantly reduced in the group who had SA 23mg (16─32) (median (IQR)) compared to GA 32mg (21─47), $p<0.0001$. This finding was supported by the multiple regression analysis.

Study IV

In this observational study, 150 consecutive patients scheduled for THA were assessed for eligibility. After exclusions, 102 patients were enrolled, 35 males and 67 females. For baseline and demographic data, please see table 8.

Table 8.
Demographics and baseline data

	Total population n=102	Missing data (n)	PVC-Low (n=67)	Missing data (n)	PVC-High (n= 35)	Missing data (n)	PVC-Low vs High p-value
Sex m/f, (n)	35/67	0	26/41	0	9/26	0	0.18
Age, yr, mean (SD)	69 (19)	0	71 (8)	0	66 (10)	0	0.02
Height, cm, mean (SD)	169 (8)	15	168 (8)	11	169 (8)	4	0.58
Weight, kg, median (IQR)	75 (65-85)	15	75 (64-83)	11	75 (66-98)	4	0.41
ASA 1/2/3 (n)	21/62/16	3	15/40/10	2	6/22/6	1	0.57
Education after high school (no/ yes), (n)	24/71	7	16/46	5	8/25	2	0.98
Civil status (married/living alone) (n)**	73/ 29	0	48/19	0	25/10	0	0.06
Employed (no/yes), (n)	72/30	0	51/16	0	21/14	0	0.72
Patients forecast (high pain responder/ normal responder) (n)	21/79	2	16/49	2	5/30	0	0.70
Daily use of any analgesics (no/yes), (n)	47/52	3	28/37	2	19/15	1	0.67
PCS (0-52) median (IQR)	14 (7-21)	0	13 (6-18)	0	17 (12-28)	0	0.91
PCS ≤30 / >30 (n)	87/15	0	58/9	0	29/6	0	

PVC = Peripheral venous cannulation, ASA = American Society of Anesthesiologist classification, PCS = Pain Catastrophizing Scale, **Living alone: Divorced, single, widowed, or not in a relationship.

In this study, four predictive parameters were used trying to predict high pain responders postoperatively. Pain by PVC, highest pain levels at the PACU, PACU nurses prediction and the patients forecast (Table 9).

For the primary outcome the groups PVC-high (NRS>2) and PVC-low (NRS≤2) were compared according to NRS pain during mobilisation at 24hr, median (IQR). For group PVC-Low 6 (4-8) and group PVC-High 7 (5-8) we found no significance difference (p=0.10) (Table 9). For the comparison of group PVC and pain at rest and morphine consumption, no significance was found (Table 9).

None of the groups Nurse high and low, PACU ≤NRS 3 and NRS>3, and Forecast low and high were able to predict pain at rest or during mobilisation after 24hr as well as morphine consumption (See Table 9 for further results).

Table 9.
Comparisons between predictive groups

	PVC-Low (n=67)	PVC-High (n=35)	p-value	Nurse-Low (n=49)	Nurse-High (n=32)	p-value	PACU-NRS≤3 (n=90)	PACU-NRS>3 (n=12)	p-value	Forecast-Low (n=79)	Forecast-High (n=21)	p-value
Pain (mobilisation) 24hr postop.	6 (4-8)	7 (5-8)	0.10	5 (4-8)	6 (4-7)	0.78	5 (4-8)	7 (6-8)	0.74	6 (4-8)	6 (4-8)	0.79
Pain (at rest) 24hr postop.	2 (0-3)	3 (2-5)	*0.12	2 (0-4)	2 (0-4)	0.65	2 (0-4)	3 (2-5)	0.22	2 (1-4)	2 (0-3)	0.19
Morphine consumption (eqv.), IV, mg, (0-24hr)	20 (15-24)	23 (15-28)	0.20	19 (15-23)	22 (15-29)	0.16	20 (15-25)	26 (18-33)	*0.12	20 (15-28)	20 (15-23)	0.35

* Bonferroni correction. PVC= Peripheral Venous Cannulation. PACU= Post Anaesthesia Care Unit. NRS=Numerical Rating Scale. Data are median and interquartile range (IQR), pain are numerical rang scale (NRS). Nurse-Low means patients that the PACU nurse evaluates to be an ordinary pain responder and Nurse-High was evaluated to be a high pain responder. Forecast-Low means ordinary pain responder and Forecast-High means high pain responder, according to evaluation by patients themselves before surgery.

Methodological considerations

Study I:

A comprehensive search strategy is fundamental when designing a systematic review. A wide search-string was conducted in order to include all suitable studies. All studies were included, regardless of the language. The literature search was conducted solely by the primary investigator. To strengthen the study, a professional e.g. a librarian, educated in performing large literature searches may have designed and conducted the literature search in a more professional matter. Unfortunately, we did not have that kind of resources. To avoid duplicate, and increase transparency, the study was registered at PROSPERO the data base of systematic reviews. The trial methodology was evaluated using The Cochrane method for assessing risk of bias (risk of systematic errors)(table 1). This is a well-proven tool that provides rigorous guidelines and the seven bias domains are easily followed. Nevertheless, when different investigators perform the bias extraction they perceive differently and consequently a risk of extracting the data differently appears. To minimise this, the data extraction was kept on few hands. The primary author extracted all studies and two co-authors extracted one half each. One senior researcher with expertise in the field solved all discrepancies. To strengthen the bias assessment the authors were contacted by email if unclear issues appeared. The stringency in Cochranes methodology can be very harsh for studies performed in the older days. The researchers in past times had their ways to perform, in their point of view, excellent RCT´s. The methodology has changed and improved over the years and the Cochrane approach reflecting this, therefore favors the newer studies. Systematic reviews, and our study as well, are fundamentally limited by the quality of the underlying studies, the so-called "garbage in, garbage out" principles. Even though a meta-analysis of high quality randomised clinical trials is considered the best available evidence in health care management and the basis for clinical practice guidelines, it is difficult to make any conclusions if the trials included are mostly high risk of bias with small populations included. The GRADE tool was used to strengthen the quality of evidence by rating the quality for each outcome by five separate factors. Clinical heterogeneity can be defined as differences in clinically related trial characteristics which may lead to variations in the pooled treatment effect estimates across trials not covered by the bias assessment of the included trials. Therefore, TSA was performed to avoid false positive (type I errors) and false negative results (type II errors) which can appear in studies with few patients included and repeated significance testing in the meta-analyses. Some of the

recalculations that was made could limit the study. For example, the results expressed in median and IQR (non-parametric) were converted to mean and SD (parametric) data. If no SD was present it was calculated from the p-value. All pain scores, VAS 0─10, NRS 0─10, and categorical scale were converted to VAS 0─100mm. Reducing and converting all pain tools to one is a limitation of the study as well. The sensitivity to detect a minimal relevant clinical difference was chosen to be 10mg morphine IV and for pain, 15mm on a VAS scale from 0─100. One can discuss if these numbers are clinically relevant for the patients. Especially regarding the pain scores. The clinical relevant difference between groups, regarding pain management, is debatable and small differences in VAS are probably not something that affect patients satisfaction a lot (149).

Study II:

This re-analysis study was conducted by using secondary data from RCT´s. The patients had not given their consent to participate in the study but since the individual data was handed over anonymised, one can consider it to be acceptable to do so. On the other hand, the data regulation states that using patient data for other purposes than the patients originally signed for, can be problematic. Should another study have been conducted, in order to solve the problem, even though the data was already there? This is an issue that needs to be addressed. The consideration was only contemplated after attending the ethical course and the article submitted. Furthermore, ICMJE and journals now require that de-identified data are shared in order to increase transparency and avoid fraud.

(http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html#two)

Another limitation was that no power calculation was made before the study began. All data which the authors were kind to hand over were used for the analyses. Since the aim was to underpin the difference between the average patient´s pain and the individual patient´s pain, using the same RCTs, a power calculation being performed or not was not of importance.

A strength of the study was that individual pain data were available for all patients. Some limitations were detected that possibly can have affected the results. The RCTs was not designed to create the best treatment for the patients. Therefore, the surgical procedure was used only as a model for testing an analgesic effect of a specific intervention. Accordingly, the studies were not powered for investigating the individual patients´ pain levels. Consequently, some of the included studies had a small number of participants, not representative for the surgical approach. This might have caused imprecision, and no “gold” standard was found. A limitation could be that both minor and major surgery was included. Since we wanted to present the individual patients´ pain levels we did not take that into consideration.

The goal set for this study, that 80% of patients in the active group should obtain VAS≤30, is questionable. Actually, we should have aimed for 100% as suggested by Moore and colleagues (94). However, knowing that probably very few studies would obtain the goal, we lowered the bar. We wanted to underpin the difference between conducting an RCT aiming for the average intervention effect, and investigating the individual patients´ pain levels, using the same trials. This could highlight the importance of clinical studies supplementing the RCT´s to present a greater picture.
The probability calculations performed by using the method by Altman (141) might also have affected the results. The calculations were performed on the assumptions that the true distribution is normal which pain data seldom are.

In some of the appearing results, the active treatment actually worsened the patients' pain. Maybe that specific result reflects the rebound pain after peripheral nerve block or reflects an actual ethical matter that needs to be taken into consideration.

Study III:

In this observational cohort study, 501 THA patients were included. To create a wider perspective five hospitals, were chosen from two different Regions, some with a small amount of THA surgeries annually and some with many. If other hospitals had been chosen, the results might have been different. Patients did not give their written or orally informed consent to use their data, as this was not mandatory in Denmark at that time the study began. Only acceptance from the leading nurse and doctor at the wards was necessary. Therefore, collecting data regarding mortality and readmission was not possible, since it was only allowed to go through hospitalised patients´ journals. Today a permission is needed from all the patients, both written and orally, if the study is not based on quality assurance. This study was explorative in its design and does not allow us to conclude how the analgesic treatment was performed on Danish hospitals. It provides us with a hint. What is very useful, however, is the knowledge about how much pain patients suffer from after THA, since we have individual pain data from 501 patients. A point which is often criticised in observational studies is the way data has been "fished". To avoid data "fishing" the protocol was submitted and pre-registered before the study began to ClinicalTrials.gov.

Even though the study was explorative, a power calculation was performed to secure enough participants to perform e.g. a T-test . Consecutive inclusion of patients was aimed for but not always possible e.g. due to the daily bustle at the ward or summer holidays. Clinical studies can be affected by many different factors which can affect data and results. For example, five different local investigators participated in the data collection, one from each hospital. Even though the investigators were briefed about the same things and in the same way, their way of approaching patients and collecting data were different from each other. Some investigators did not like to wake up sleeping patients when it was time for data collection. Instead, they stated

"asleep" or "%" in the CRF resulting in missing data. Some investigators did not like to encourage patients to be mobilised if they suffered from pain at rest, which resulted in a statement of "mobilisation is not possible" in the CRF. As a consequence, the lack of data could result in an underestimation of pain levels during mobilisation. Of course, ethical considerations should be taken about how much one should push the patients to be mobilised if they are in a lot of pain, and if and when it is meaningful to wake patients up from their sleep. Sometimes it may be necessary to collect enough data to understand clinical practice, but discussions addressing this important issue must be held. The first primary endpoint, pain during mobilisation at 6hr, was difficult to obtain since especially the patients who had surgery late in the afternoon did not have the opportunity to be mobilised during the evening shift because of the lack of nurses. In order to get data, we therefore agreed, that mobilisation could be lifting the leg from the bed, not necessarily getting out of bed. This could have provided us with a false impression of how much pain patients endure during an out of bed mobilisation. The second primary outcome, morphine consumption after 24hr, also has its limitations. Since the patients received all kinds of opioids a conversion had to be done. It was calculated using an application which could convert all kinds of opioids into IV morphine eqv. When converting numbers errors can occur and in the process the numbers are rounded up not giving the exact result. Several factors can affect the picture we are getting of patients´ morphine intake. For example, did the patient hold back not asking for analgesics because they were afraid of addiction or not wanted to bother the busy nurse? Did they ask, but the nurse forgot to deliver it? Was it administrated and dispensed in the patient´s medical journal without the patient taking the tablets? In order to control all factors, the study has to be conducted as an RCT and the patients should have escape analgesic immediately available, as e.g. being equipped with a patient controlled analgesic (PCA) pump. The results from the regression analyses could indicate that local differences matter, not only the analgesic treatment. To determine which factors a hospital benefits from in terms of e.g. staff knowledge, the surgeons´ expertise, empathic behavior from the staff, is almost impossible. If the study was supplemented with e.g. qualitative methods such as patients´ interviews some of these factor could have been uncovered. The data collection took place in a total period of two years. Many changes might have been done along the way affecting the results. In terms of strengthen the study, a data collection beyond 24hr could have been of great interest just as a qualitative part where the participant supplemented pain levels with pain history or PROMs.

Study IV:

The participants in this observational study gave their written and orally consent to participate. To strengthen the design and secure transparency the STROBE guidelines was used. A power calculation was performed before the study began using our experiences from study III. During the data management, the patients were, from the results, divided into the four prediction groups but in a skewed way.

Many patients in some groups, and few in others. This made it difficult to make a comparison and consequently, the results may be questionable. The cut-off point of NRS≤/> 2, for the division of groups, was based on the study by Persson et al. (121) which also investigated preoperatively pain by PVC. Perhaps a different cut-off point should have been considered in order to detect any differences. By lowering the cut-off point to e.g. NRS 1, the result would have been even more questionable. However, a strength of the study was that the fast-track approach made the patient courses very similar. Only two senior surgeons performed all the THAs and the PVCs were all placed on the back of the dominant hand by experienced anaesthetic nurses. Some patients rated their pain by PVC to zero, meaning no pain at all. This makes it questionable to whether the patients understood how to use the NRS properly. The patients who rated the PVC to zero were not excluded from the analysis. Since zero is no pain, it could have been a contributing factor for the skewness in the findings.

A Bonferroni correction was made in two different cases to avoid type I errors due to multiple comparisons. This could on the other hand have led to type II errors instead. Another limitation was the missing data. Especially the relatively large proportion of missing data regarding the nurses at the PACU´s prediction. This could have influenced our results. One predictor we know to be very powerful is patients suffering from preoperative pain (150). It could have been a strength for this study if patients have been asked about their pain levels before surgery and not only postoperatively. We did ask for preoperatively analgesic use which can provide us with some kind of clue if patients suffered from pain preoperatively. Furthermore, we asked for several different psychological and socio-economic information. Maybe it would have been more valuable as a predictor to ask the patients if they were afraid prior to the surgery or had former experiences with pain during surgery.

In order to identify the causality and confounders this study could have been strengthen with the use of a directed acyclic graphs diagram (151).

Discussion

Principal findings

In the first study, we found a significant effect of some analgesic interventions, but the RCTs regarding analgesic treatment for THA were very heterogeneous, and with the majority having uncertain/high risk of bias. This weakens the conclusions. Furthermore, the review showed that the literature did not provide a "gold standard" of treatment, because most trials did not seek the best treatment, but were rather efficacy trials, investigating a single intervention, which used the THA as a surgical model.

In the second study, individual patient data from 16 previous RCTs were investigated using the goal of, 80% of the patients in the active groups should obtain no worse than mild pain (VAS≤30), in order to meet patients' expectations of low levels of pain. Unfortunately, this was only achieved by 50% of the studies at rest after 6hr, and 60% after 24hr postoperatively. During mobilisation, the outcome was obtained for only 14% at 6hr and 15% at 24hr.

In the third study, we aimed to investigate how effective the analgesic treatment was in clinical practice. We found the analgesic treatment provided for THA for 501 patients at five hospitals, to be very heterogeneous. No analgesic treatment was found to be superior to others. Patients´ pain levels at the different hospitals were very similar even though the patients received different types and amounts of non-opioid and opioid analgesics.

In the fourth study, we investigated if four simple tools, such as pain by PVC, could be used as a predictor for pain during mobilisation in a cohort of THA patients, at 24hr postoperatively. We did not find that PVC or any of the other predictors could significantly predict pain.

The results from the studies conducted in this thesis indicate that the management of postoperative pain, still remains suboptimal. This will be illuminated by focusing on and discussing some of the key findings derived from this thesis in the following.

The multimodal approach

The principles of multimodal analgesics used for postoperative pain has been recommended for years (45).

Unfortunately, it is not clear, when searching the literature, which kind of combinations is preferable (152). The RCTs included in study I, were primarily designed to show an effect of analgesic interventions and uses the surgical procedure (THA) as a scientific model. Consequently, the trials are not designed to find the best pain treatment for a certain patient population. Therefore, it makes it difficult to adapt those results directly into clinical practice. The findings from study I, which searched the literature regarding pain treatment for THA, showed that many different treatments and combinations were used for THA. It was also the finding when looking into clinical practice. In study III, the multimodal concept is challenged since we found that all five hospitals used their own multimodal combination for THA and that no treatment was superior to the others. Two hospitals in study III provided the patients with slow-release opioids as premedication. This can have affected the results of pain levels and opioid consumption. Did all patients need opioids already before the surgery? Probably not. Knowing the side effects provided by opioids, the choice might not have been such a reasonable idea. If high pain responders could be detected before surgery, these patients could receive an expanded pain treatment, which e.g. could include opioids as premedication, and then other patients could avoid over-treatment.

It is still not clear which patients can benefit from which kinds of analgesic combinations after which type of surgery. The research regarding the kinds of non-opioids to combine in order to obtain the synergistic effect is not clear (152). The results from the regression analysis in study III (table 5) indicate that a combination of PCM and NSAID, as well as PCM+NSAID+GABA, may reduce morphine consumption significantly. To validate these findings, they should be supported by large pragmatic RCTs. This way, a new RCT that combine PCM and NSAID looks promising (55). Here, they found an opioid-sparing effect significantly higher for the combination than for each analgesic used alone (55). Little is known about how the addition of further analgesics will benefit or if it only increases the risk for side effects and complications (153). Looking at the analgesic league table (table 10), from study III, it is difficult to detect the big differences in pain levels going from two to three additive analgesics.

Table 10.
Analgesic league tables based on types of multimodal non-opioid analgesia

Analgesic combination	Pain At rest (6h)	Pain Mobilisation (6h)	Pain At rest (24h)	Pain Mobilisation (24h)	Morphine i.v. (eqv) (mg) (0-24h)
PCM (n = 205)	3 (2-5)	5 (3-6)	3 (1-4)	5 (3-6)	24 (16-36)
PCM + NSAID (n = 81)	4 (2-5)	5 (3-7)	2 (0-3)	4 (3-5)	21 (10-36)
PCM + NSAID + GCC (n=84)	3 (2-5)	5 (4-7)	2 (1-4)	5 (3-7)	24 (20-41)
PCM + NSAID + GABA (n=36)	3 (2-5)	4 (2-6)	2 (0-3)	4 (1-6)	21 (7-27)
PCM + GABA (n=49)	3 (2-4)	5 (3-6)	2 (0-3)	4 (3-6)	25 (20-32)

A large cohort study suggested that the way the principles for multimodal therapy is being performed is built upon nonmedical and institution-specific factors such as local hospital culture and individual physician preference (154). Our findings in study III support that. The analgesic treatment varied from hospital to hospital, but the pain levels did not. Therefore, the local hospital culture and maybe staff education might be an explanation for that.

A study showed, a significant reduction in opioid consumption and side effects and enhanced early mobilisation, when a combination of analgesics and PONV prevention for the surgical procedure, here spine surgery, combined with education and implementation is used (48).

Are NRS 3 the right cut off point?

Unrelieved pain has major consequences for the patients in the matter of not only suffering but also concerning increased surgical stress, and delayed rehabilitation (24). Persistent pain can lead to chronic pain causing the patients psychologically and sociologically problems (24). Patients' pain responses vary greatly (9). Moore and colleagues stated in their study that patients want at least 50% pain reduction or no worse than mild pain (94), not suffering from sleep disturbances or a reduced quality of life. The use of average measures for the comparison of study groups is not helpful when it comes to the individual patient´s pain since most patients experience pain in a dichotomised matter. Either the pain is acceptable or not. Average pain relief is something experienced by very few patients and, therefore, the measure is not suitable for clinical practice (93). The results from study II showed a very little achievement regarding the goal of 80% of patients in the active group in the study obtaining VAS≤30 (no worse than mild pain), especially during mobilisation. An explanation could be that the studies were designed to investigate the best effect of an analgesic and not the best treatment for the patient population. In clinical practice, the acceptable goal for pain during mobilisation is usually set to VAS 50/NRS 5, but is this cut-off point ideal for the patients? Is it only chosen

because NRS ≤3 is too hard to aim for? A study regarding chronical musculoskeletal patients shows that NRS scores ≤ 5 correspond to mild, scores of 6-7 to moderate and scores ≥8 to severe pain in pain-related interference with mobilisation (155). When dividing the population into subgroups, according to levels of catastrophizing, they find, interestingly, patients with low catastrophizing tendency, having NRS scores ≤ 3 corresponding to mild, scores of 4-6 to moderate and scores ≥7 to severe pain when it comes to mobilisation (155). In study IV, we did not find a correlation between high levels of catastrophizing and high levels of pain during mobilisation at 24hr postoperatively. When trying to create cut-off points on a VRS compared with VAS, another study found that dividing into three categories were the best solution with the classes 0.1 to 3.8 (mild pain), 3.9 to 5.7 (moderate pain), and 5.8 to 10 cm (severe pain) (156). The levels of uncertainty, regarding what we should aim for in clinical practice, calls for other parameters. The goals ought to be that the patients can return to daily living as quickly as possible, with a decent sleep quality, capability of mobility, and good quality of life (16). An understanding can be obtained about whether the pain management is sufficient or not by asking the patients if they feel capable to e.g. get out of bed or cough. It can provide the patients with a robustness if they are informed preoperatively about the different possibilities regarding their pain management, and what to look out for, in a shared decision-making. If the patients feel something is wrong with the pain treatment postoperatively it is much easier to discuss alternative solutions.

How is pain management conducted?

Nurses are first in line when it comes to managing the patient´s pain, since they work in close collaboration with the patients most of the time. Pain management is a multidisciplinary responsibility and requires collaboration between many different occupations. However, studies demonstrated that ward nurses and doctors are trained to a very low extent in managing adequate pain relief (157–159). Pain assessment ought to be conducted by the patients´ subjectively point of view. That is the fact when conducting research studies but not always in clinical practice. A review found an underestimation of pain levels by professionals in 78% of the included studies. The extent of underestimation increased with pain severity (75). Often pain-related behavioural signs, vital signs (160) or former experiences, are used by the nurses as indicators of pain. In study IV we wanted to test if that "gut feeling" could be useful as a predictor, for forecasting high pain responders, but our findings could not support that.

A well-known, predictor for increased levels of postoperative pain is anxiety (161). Nurses can identify the patients with high levels of anxiety prior to surgery, by e.g. using HADS (88) during the admission interview. Thereafter, strategies can be made in accordance with that, hindering patients from having a negative surgical experience (162). The admission interview has also proven useful in terms of having

a dialogue with the patient not only regarding the expected pain treatment but also other subjects important for the patients to discuss e.g. how the patient usually copes with pain. By minimising insecurity, postoperative pain levels can be affected in a positive way (163).

IASP has a focus-point called “the involvement of patients in the pain management plan” (3). For that purpose, patient-reported outcome measures (PROMs) are used in clinical practice. PROMs have shown effective to facilitate shared decision-making (114,164), which provide attention to patients´ feelings and subjective experiences when incorporating patients’ psycho-socio characteristics and background when measuring pain (165). In matching the results from PROMs and patient satisfaction, a mismatch appears. In a study with thoracic surgery patients, the authors reported that despite a large number of analgesics, and patients suffering from moderate levels of pain, 96% of patients were still satisfied with the pain management (166). These findings were also supported by the study from Apfelbaum et al. (1). They found almost 25% of patients who received pain medications experienced adverse effects; however, almost 90% of them were satisfied with their pain medications (1). On the other hand, another study that investigates patient dissatisfaction found that persistent pain and functional limitation were the two leading reasons for dissatisfaction (131). Results from the international PAIN OUT registry might explain why there is such a big difference between pain levels and patient satisfaction. The study indicated that satisfaction with postoperative pain management is associated with the patient's impression of improvement and that the staff are doing the best as they can, and even more strongly if they can be included in the decision about their pain treatment (167). Therefore, to optimise the pain management patients need to be included in shared decision making, which gives them enough information to choose the setting, which is most suitable for them (164). A study by Connor underpinned that (168). The results showed that patients wanted to feel that the nurses genuinely listened to what they had to tell about their pain treatment and e.g. trust when they tell that their epidural analgesia did not work sufficiently (168). Another way that has proven effective is patient education. Already back in 1964 Egberts et al. (169) reported improvements in patient outcomes after providing pain education to patients. They found a 50% decrease in patients´ opioid consumption and they were discharged sooner (169). Patient education is also a part of the guidelines from the American Pain Society (3). They recommend that patients and their families receive pain education preoperatively which include an explanation of the surgical procedure; the expected postoperative routine, the interventions, and options for pain relief, including available pain medication; and the necessity of progressive increased mobility (3).

Measuring pain

In clinical practice today a number on a scale is still used as a guideline for the treatment using a predefined tool often VAS or NRS. The tools are not chosen according to what is most suitable for the individual patient but what the local ward or hospital prefer. The way pain measurement is described in local guidelines is that the patient has to specify a number on a scale and then an analgesic treatment is provided if the number is too high. After 20 to 30 minutes, the nurse will ask the patient again about the level of pain to evaluate the treatment. If not sufficient, more analgesics will be provided. Pain scales can be used to guide the treatment decisions, but with this aggressive approach, several challenges can occur. As described in a study, the intensified opioid use resulted in a two-fold increase in related adverse events (170). It is difficult choice for patients whether they want pain treatment or opioid-related side effects. Another challenge is the elderly population who sometimes suffer from dementia and other cognitive dysfunctions. A study conducted on nursing home residents, which compares five different pain tools and levels of cognitive impairment demonstrated that the use of the VRS was most successful. Repeatedly explanations regarding how to use the tool raised the completion rate (171). Those with severe dementia found it extremely difficult using any of the pain tools (171). These findings indicate that more than one tool is needed in the toolbox to find the most suitable for the individual patient and it is crucial to take the time needed to instruct the patients properly in terms of using the tool in the best way. Sometimes only facial expressions, heart rate, respiratory rate, and blood pressure are used as indicators for pain as in e.g. intensive care patients or patients suffering from severe dementia. Pain measuring tools have been developed for these patient populations as well (172,173), we just have to use them.

When the most commonly used pain scales were compared in a study, VAS, NRS, and VRS, differences between how patients use NRS and VRS were found, just as great variances in how the patients understood the verbal statements in the VRS. The conclusion was that both VRS and NRS data must be used with caution (79).

In all four studies in this thesis, pain is measured with either VAS or NRS. In study I, included RCT´s use either VAS or NRS. To compare the studies all ratings were changed to VAS afterwards. In study II all of the 16 RCT´s used VAS. In study III, the patients were asked to rate their pain from 0-10 using the NRS and likewise for study IV. NRS was chosen for study III and IV since it common practice in the clinical practice. Even though the pain measurement tools used in the studies are all validated it is difficult to know how many patients who have used the pain measure tools properly. Although we create RCT´s, the pain ratings could be wrong. Many people do not know what worst experienced pain is which indicates the 10 or 100 and therefore, makes it difficult to use the tools properly. The patients do not know what the consequences are if they chose e.g. the number 67. They think, “is the number too low to receive help” or “is it too high and, therefore, morphine is

mandatory and addiction is unavoidable"? Another question is whether the cut-off points even matter? As addressed in a study, pain measurements are very sparse assessed (34%), and only documented in 44% cases in the patients´ chart (159). Even though, the patient has performed the pain measurement subjectively, another challenge is the doctors and nurses underestimation of the patient pain levels, of various reasons, they do not believe what the patient says (174).

In most cases, patients know simply, if the pain is unbearable or not and if they want to receive analgesics or not. As health care providers, it is our duty to ease the patients´ pain and by including the patients in the decision-making they can feel confident that we will try and do the best we can, at all times. In addition, it is crucial to ensure that the patient´s pain does not hinder sufficient sleep, mobilisation, and coughing as well as nutrition intake. We must talk with the patients about what the consequences can be if they suffer from high levels of pain and e.g. fears addiction to morphine. Also trying to find a suitable tool to use for evaluating the pain treatment together with the patient, preferably, preoperatively.

Prediction of postoperative pain

An important focus for the improvement of postoperative pain is the ability to predict patients who will experience high levels of pain postoperatively. This could lead to an improvement in recovery and a potential reduction in the risk of persistent post-surgical pain. From the identification of persons at risk, it would be possible to design and tailor pain management strategy. However, this is difficult, as no clinical useful tool has yet been found that can be used as a valid prediction tool. Most likely, the prediction of patients at risk will rely on combinations of risk factors, of which some of the most promising are the female gender (100), younger age (40,101,102), increased pain catastrophizing (102), and the presence of preoperatively pain (113).

A newer study by Persson and colleagues (121) found that pain by PVC could be used as a predictor for pain immediately after surgery in the PACU at rest. Inspired by that study, we designed study IV. However, we aimed to investigate an association between pain by PVC preoperatively and pain during mobilisation 24hr postoperatively, as we regarded later pain levels to be more important for rehabilitation.

In study IV, we also collected several other possible co-risk factors such as gender, age, marital status, working life, educational level, pain catastrophizing, and daily use of analgesics. Apart from pain by PVC, we investigated three other prediction groups: NRS pain ≤ 3 or >3 at the PACU, PACU nurses prediction, and patients forecast, and not only looked for associations with pain during mobilisation at 24hr, but also with pain at rest, and morphine consumption at 24hr (table 9). We did not find any significant associations, but, interestingly, we saw a trend in most groups

towards higher pain in the groups we had used to predict higher pain. We used Bonferroni corrections due to repeated comparisons resulting in no significant differences, which may have been too harsh with our data, as the study was only hypothesis generating. Before the Bonferroni correction, a significant difference was found between the group, pain levels at the PACU, NRS≤3 and NRS>3 at the PACU and morphine consumption (p=0.03). A significant difference was also detected between group PVC≤2 and PVC>2 and pain at rest after 24hr (p=0.03). Seen in the light of a possible type II error, the results can be used as an indication for conducting further investigations, and maybe with another cut-off point than NRS≤ 2. It might be that the patients that suffer from NRS pain >3 at the PACU are those who are at risk of suffering from high levels of pain later in the postoperatively course. Our study does not disprove the study by Persson et al (121). The uncorrected findings of association, we found, between PVC and pain at rest after 24hr, can rather be considered as supportive and underpin that PVC probably can be used as a predictor for pain at rest.

Prediction of postoperative pain continues to be an important goal of research, but maybe this issue is so complex that new methods are more likely to be successful, like e.g. collection of big data that can enable discovery of predictors that are useful in the daily clinical bustle at the departments. A recent study on machine learning algorithms for identification of patients with increased risk of prolonged opioid consumption pointed towards new use of big data in this area (175).

Conclusions

In conclusion, this thesis overall contributes to an increased understanding of how the pain treatment for THA patients is performed, in literature, RCTs and clinical practice. The major conclusions that could be drawn from the papers in this thesis are the following:

- Study I: This systematic review regarding the analgesic treatment for THA patients found a number of analgesic methods with a significant impact on postoperative pain, but only a few studies had a low risk of bias, and the review was not able to designate a "gold standard" for analgesic treatment for THA.
- Study II: The results from the re-analysis of the selected previous RCTs indicated that the majority of patients did not obtain a satisfactory pain relief (VAS ≤ 30). The trial highlights the need for not only investigating average differences between groups of efficacy trials but to always supplement such trials with an investigation of individual patient´s pain.
- Study III: In this observational cohort study, we investigated pain treatment for THA at five different hospitals and found that no hospital used the same pain treatment regime. Despite that, the patient´s outcomes regarding pain were very similar, and we were not able to designate a superior non-opioid analgesic pain treatment, neither between hospitals nor when looking at individual patients multimodal pain treatment. In the exploratory regression analyses, we found that some combinations showed to be more promising than others (PCM+NSAID) and (PCM+NSAD+GABA), but further supplemental RCTs need to be conducted to support these findings.
- Study IV: This prospective cohort study including 102 THA patients did not find that pain by PVC preoperatively; using a cut-off point of NRS ≤2 could be used as a tool to predict patient´s postoperative pain levels after 24hr during mobilisation. That was also the fact for NRS pain at the PACU, PACU nurse's prediction and patients' forecast.

Further research

It is clear from the results coming from the systematic review (study I), that we need large, pragmatic, randomised trials that investigate the best analgesic treatment for pain after THA. The RCTs must have high external validity with exclusion criteria that enables the results to be implemented in clinical practice. An important focus should be that such trials must investigate the best combinations of analgesics taking into consideration both beneficial and harmful effects. Such trials should also include a focus of analgesic effect from the individual patient´s point of view.

We also need future studies to investigate a relevant cut-off point for postoperative pain. What is a relevant level for pain at rest, and during mobilisation? To be relevant for clinical practice, such studies should be conducted with real patients using combinations of pain levels and PROMs.

Does it affect patient´s pain levels in a positive way when patients are educated in pain treatment preoperatively and with shared decision-making included in their pain treatment? Studies show that this might have a positive effect, and it could be interesting to investigate the subject in a more controlled manner.

It might also be interesting to conduct a RCT in the future dividing groups according to e.g. social and psychological factors such as surgical fear and preoperatively pain, catastrophizers and so on. The patients we suspect would suffer from high levels of pain postoperatively could receive a nurse consultation with a focus on patients coping strategies, providing the patients with a possibility to express their anxiety and fear regarding the surgery. The outcome could be monitored with postoperative PCA opioid use.

The length of stay after surgery continues to decrease across many procedures, but little is known about how the patients perform when they are discharged from the hospital. Consequently, we need studies that follow patients after discharge aiming to identify those with an increased need for analgesic support. This could include patient diaries with questions on daily average and highest pain levels during rest and mobilisation, adverse events, analgesic usage, sleep quality, and quality of mood. Furthermore, to perform a one-year follow up after discharge asking the patients about similar questions as in the diary, but also supplemented with mobility capacity.

Summary in Danish / dansk resume

Trods øget fokus på smertebehandlingen igennem mange år og indførelsen af multimodal smertebehandling ved de fleste operative indgreb, er der stadigvæk mange patienter, der lider af moderat til svære smerter efter operationen. Endvidere kan der være mange bivirkninger postoperativt så som kvalme og opkast på grund af et øget opioid forbrug, men også en forsinket rehabilitering, og gældende for nogle, længerevarende persisterende smerter. En af årsagerne til at vi ikke er bedre til at smertedække patienterne kan være, at det blandt andet, er vanskeligt at gennemskue, hvilken smertebehandling der er den bedste. De fleste studier der undersøger smertebehandling er designet til at have fokus på at smertelindre den gennemsnitlige patient, og mangler fokus på, hvor mange smerter den enkelte patient kan have. Det er meget forskelligt fra person til person, hvor ondt man har efter den samme operation. Nogle årsager til dette kan blandt andet være, alder, køn, psykologiske faktorer og smerter før operationen, men andre faktorer vi endnu ikke er bekendt med, kan også tænkes at have en påvirkning. For at blive bedre til at smertedække patienterne i fremtiden, bliver vi nødt til at fokusere på den enkelte patients behov, og blandt andet forsøge at afdække nogle af de faktorer, der kan benyttes til at identificere de patienter, der kan tænkes at lide mere af smerte end andre efter deres operation, og gerne ved hjælp af metoder, der er simple at udføre i klinisk praksis.

Denne afhandlingen består af fire artikler (studie I, II, III, IV)

Afhandlingens titel er:

"Postoperativ smertebehandling efter total hofte alloplastik – med fokus på evidens, klinisk praksis og den individuelle patients smerte respons".

Det overordnede formål med denne afhandling er at undersøge hvordan evidensen ser ud i litteraturen der vedrøre smertebehandlingen til THA patienter. Endvidere hvilken multimodal smertebehandling der bliver givet på hospitalerne, og hvilken effekt den har for den enkelte patient både ved at undersøge tidligere publicerede RCTér men også den kliniske praksis. Tillige om det er muligt, ved hjælp af simple kliniske værktøjer, at forudsige hvilke patienter, der vil få mere ondt end andre efter operation for THA.

Artikel I: Behandlingen af postoperative smerter bør baseres på resultater fra randomiserede forsøg af høj kvalitet. Formålet med dette systematiske review er at

undersøge den procedure specifikke evidens der findes i litteraturen omhandlende smertebehandling til THA patienter. Særlig fokus er på det totale forbrug af opioider efter 24 timer, patienternes smerter i hvile og ved mobilisering, samt bivirkninger og længden af hospitalsindlæggelsen. Der blev identificeret 58 studier til dataekstraktion indeholdende 19 forskellige interventioner. Meta-analyserne viste en opioid besparende effekt af NSAID 14.1(95% CI 8-20.2) mg, lokal infiltration, 7.5 (95% CI 3.7-11.3) mg, intrathecale opioider 19.8 (95%CI 14.9-24.7) mg og lumbar plexus blok 11.9 (95% CI 6.4-17.3) mg. NSAID og lumbar plexus blok viste reduktion i patienternes smerte. Ud af disse meget heterogene studier var de fleste med høj risiko for bias og lav til meget lav grad af evidens. Derfor kunne man ikke ud fra resultaterne konkludere at én behandling havde bedre effekt end andre.

Artikel II: De fleste studier der handler om smertebehandling fokuserer på den gennemsnitlige effekt af et analgetika og ikke hvordan den individuelle patient har det. Et nyt succeskriterie for smertebehandling er blevet foreslået til at være VAS ≤30. Derfor var formålet med dette studie at undersøge patienternes individuelle smerteintensitet, ved at benytte tidligere publicerede randomiserede forsøg, alle omhandlende smertebehandling efter forskellige små og store operative indgreb. Målsætningen var at 80% af patienterne i studierne skulle opnå VAS≤30 som et kriterie for behandlings succes. Endvidere at lave en re-analyse af data fra et systematisk review ud fra samme målsætning.

Der blev udført re-analyser på individuelle patienters smerter målt med VAS i hvile og ved mobilisering efter 6 og 24 timer, i 16 randomiserede tidligere publicerede studier. Her blev udregnet, hvor mange studier der havde patienter inkluderet hvor 80% havde VAS≤ 30 både i den aktive og i kontrolgruppen. Som en kontrol benyttedes et systematisk review, men da disse studier ikke indeholdt den enkelte patients smerteniveauer udregnedes den procentvise fordeling ved hjælp af Altmans proportion formel.

Resultaterne viste at efter 6 timer postoperativt var der 50% (95% CI 31-69) af patienterne i de aktive grupper, der opnåede succes kriteriet, i hvile, under mobilisering var det 14% (95% CI 5-34). Efter 24 timer i hvile havde 60% (95% CI 38-78) af patienterne, i hvile, opfyldt succeskriteriet postoperativt. Ved mobilisering var det 15% (95% CI 5-36). Lignende resultater blev fundet for det systematiske review.

Få af patienterne opfyldte succeskriteriet på 80% med VAS≤30 da de randomiserede forsøg blev re-analyseret med det individuelle patientperspektiv for øje. Derfor bør fremtidige kliniske studier udføres således at der ikke kun tages udgangspunkt i den gennemsnitlige effekt af smertebehandlingen men også tages udgangspunkt i den individuelle patient.

Artikel III: Det er ikke muligt at påvise ud fra litteraturstudier hvilken smertebehandling til THA, der er den bedste. Derfor var formålet med dette studie

at undersøge smertebehandlingen til en stor gruppe af THA patienter på fem forskellige hospitaler i en klinisk kontekst.

I dette multicenter studie blev der inkluderet 501 fortløbende THA patienter i to regioner (Hovedstaden og Sjælland) fra april 2014 til april 2016, på fem forskellige hospitaler. I studiet var der primært fokus på patienternes smerteniveau ved mobilisering efter 6 timer postoperativt, målt ved NRS (0-10), og det totale morfinforbrug efter 24 timer målt i mg.

Der var stor forskel på smertebehandlingerne på de fem hospitaler, ingen hospitaler benyttede den samme behandling. Median (IQR) smerte udregnet for alle patienter på alle hospitaler var 5 (3-6) ved mobilisering 6 timer postoperativt, og morfinforbruget fra 0-24 timer var 25 mg (18-35). Selvom der var signifikant forskel på morfinforbruget på de fem hospitaler, var der ingen behandling, som man kunne sige var bedre end de andre. Generelt var patienternes smerter i hvile lave eller moderate og ved mobilisering et moderat niveau.

Trods den meget store variation i smertebehandlingen på de fem hospitaler var der ikke stor variation at spore i patienternes smerteintensitet, som generelt var lave i hvile og moderate ved mobilisering. Derfor kan man ikke sige at nogen behandling viste sig at være bedre end de andre til THA patienter.

Artikel IV: Behandlingen af postoperative smerter forbliver en klinisk udfordring. Derfor er det nødvendigt at kunne forudsige, hvilke patienter der vil udvikle mange smerter efter operationen. Det primære formål med dette studie var at undersøge om smerter ved anlæggelse af perifer venekanyle (PVK) før operationen, kunne forudsige smerteintensiteten efter 24 timer ved mobilisering hos THA patienter efter operationen.

I dette observationelle kohorte studie blev 102 THA patienter inkluderet på Sjællands Universitetshospital i Køge. Der blev i dette studie benyttet flere forskellige måder at forudsige smerter på i hvile og ved mobilisering.

1) Den smerte patienten oplevede ved anlæggelsen af PVK før operationen målt på NRS (0-10) delt op i to grupper. Gruppe lav, NRS smerter ≤2 og Gruppe høj, NRS>2.
2) Opvågningssygeplejerskens forudsigelse af om patientens smerteintensitet ville være normal eller høj efter 24 timer ved mobilisering. Delt op i 2 grupper
3) Patientens højeste NRS smerte på opvågningen inddelt i gruppe lav, NRS≤3 og gruppe høj>3.
4) Patientens egen forudsigelse af om de har en høj eller en lav smertetærskel inddelt i to grupper, gruppe høj og gruppe lav.

Der blev ikke fundet nogle signifikante forskelle mellem PVK smerter før operationen og patientens smerter 24 timer efter operation ved mobilisering. PVK lav median (IQR) 6 (4-8) versus PVK høj 7 (5-8). For de to PVK grupper sammenlignet med smerter i hvile efter 24 timer var smerterne på NRS median (IQR) gruppe lav 2 (0-3) og gruppe høj, 3 (2-5). Der blev heller ikke fundet nogle signifikante forskelle for de andre tre grupper. I studiet blev der ikke påvist at PVK med en cut-off på NRS≤2 kunne benyttes til at forudsige THA patienternes smerter ved mobilisering efter 24 timer. Heller ingen af de andre 3 metoder kunne benyttes til dette formål.

De vigtigste aspekter sammenfattet i denne afhandling er følgende. For at kunne vurdere om vi tilbyder den bedst mulige smertebehandling til patienterne, må den baseres på studier udført i klinisk praksis, da den tilgængelige litteratur på området, ikke har tilstrækkelig kvalitet til, at man kan regne den for evident. Hvis vi ønsker at gøre den fremtidige smertebehandling bedre, bør der designes smertebehandling procedure-specifikt og ikke udelukkende afprøves analgetisk effekt på patient grupper. Dog bør behandlingen også tage udgangspunkt i den enkelte patients behov, for at kunne være sufficient gerne med anvendelse af værktøjer der kan forudsige hvilke patienter der vil opleve høj smerteintensitet efter operationen.

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