Perioperative management of patients undergoing major reconstructive head and neck surgery

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on the 21st of November 2025 at 09:00 in Belfragesalen, Biomedical Centre (BMC), Lund, Sweden

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Abstract: For patients with locally advanced head and neck tumours or other defects, the preferred curative treatment is extensive reconstructive surgery using free microvascular flap(s), oftentimes followed by postoperative radiotherapy. The procedure offers superior functional and aesthetic advantages, but the treatment course is long and complex and burdened with a significant risk of complications. The aim of this thesis is to address certain key perioperative aspects, with the extended objective of reducing complications and improving the quality of care for head and neck reconstructive surgery patients.

Paper I evaluated the use of a continuous popliteal nerve block for patients undergoing head and neck surgery with reconstruction using a fibular graft. This prospective, double-blind trial included 24 patients randomised to receive an infusion of local anaesthetic or placebo during the first postoperative week. Results showed that patients in the local anaesthetic group had significantly fewer episodes of severe pain and a nearly halved opioid consumption during the study period, compared to patients in the placebo group. These results have led to the incorporation of popliteal nerve blocks into the local treatment protocol for this patient group.

In paper II focus was on preoperative risk prediction of perioperative complications. A retrospective review of medical records was conducted, including 388 patients. Uni- and multivariable regression analyses were performed to establish associations between biochemical and physiological parameters and serious medical and flap-related complications. In addition, several risk prediction instruments were evaluated. Results showed that longer duration of surgery and perioperative red blood cell transfusion were factors associated with flap compromise. For medical complications, several of the risk prediction instruments showed a strong association, as did lower preoperative albumin levels.

Paper III was a prospective observational study of haemostasis during surgery and the first postoperative week in 39 patients undergoing head and neck reconstructive surgery. Conventional routine coagulation tests, such as prothrombin time (PT-INR), activated partial thromboplastin time (APTT), and platelet count, showed tendencies toward impaired haemostasis, while more advanced tests, such as rotational thromboelastometry (ROTEM) and anticoagulant factor activity, indicated an enhanced haemostatic capacity. From these inconsistent results, the conclusion was drawn that conventional analyses are insufficient to monitor haemostasis during the complex perioperative course for this patient group.

In paper IV the same patient cohort was studied as in paper III, but with focus on vitamin K, which, in addition to haemostasis, is involved in several other physiological processes. Vitamin K-dependent proteins (VKDPs), formed as a result of vitamin K deficiency, are implicated in, among others, vascular calcification, inflammation and carcinogenesis. However, very little is known about the profile and functions of VKDPs in head and neck cancer patients and free flap surgery. The results from this prospective, descriptive study showed increased protein induced by vitamin K absence/antagonist-II (PIVKA-II), as a sign of subclinical vitamin K deficiency, and a rise in growth-arrest specific gene 6 (Gas6), potentially as an acute-phase reaction to the surgical trauma.

Limitations of the studies in the thesis include a limited number of patients, and an, in some respects, heterogeneous study population. The retrospective design in paper II also limits the ability to establish causal relationships. However, the results contribute to a broader knowledge in several key areas of perioperative management of patients undergoing major reconstructive head and neck surgery. Paper I establishes safety and efficacy of popliteal blocks for fibular graft harvest, and paper II highlights important aspects of preoperative risk assessment. The exploratory nature of papers III and IV can aid further studies on haemostasis and vitamin K physiology.

Key words: Head and neck cancer, free tissue transfer, microvascular surgery, preoperative risk assessment, perioperative management, pain management, haemostasis, vitamin K, vitamin K-dependent proteins

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Till min familj, med oändlig kärlek

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Preface

Being diagnosed with a condition that will potentially have a huge impact on your ability to eat and speak, change your appearance and even threaten your existence is a life-altering occurrence. To have the chance of cure you will have to go through extensive surgery, a long postoperative rehabilitation, and in most cases also radiotherapy. On top of it all, oftentimes the fast-growing nature of the tumour causing the eruption of your life requires decisions to be made with minimal time for contemplation or deliberation with family and friends. This is the reality for most patients included in the studies in my thesis.

As an anaesthesiologist I often come into my patients' lives sideways. Most people know of surgeons, nurses and physiotherapists, and in the efficient system of standardised treatment protocols the patients get to meet them all within a few hours after entering the doors of the otorhinolaryngology department. But few have met an anaesthesiologist before - or at least they don't remember it. Our speciality is usually one of quiet existence in the background interspersed with short contributions in critical situations. However, during the course of treatment for patients with advanced head and neck tumours or defects we can come to play a central role and have numerous opportunities to make a difference in both short- and long-term perspectives.

Perioperative medicine is a vast and continuously expanding clinical and scientific field. In its true form it covers the whole process from preoperative evaluation and optimisation through anaesthesia for the surgical procedure(s) itself, the immediate postoperative period (including intensive care if needed), and postoperative recovery of varying length. It's a science requiring expertise in several areas of medicine, as well as manual and technical skills, not to mention competence in teamwork and logistics.

But perioperative management for advanced surgical procedures is not only a science, it is also an art. It is the art of being an integral part of the team piloting the patient and their family (and sometimes the surgeon) through a crucial period in their lives. It is to be performed with ambition and commitment, flexibility and imagination, and great compassion. This thesis originates from the desire to perform both the science and the art of perioperative medicine as well as possible, in the service of the courageous patients we meet every day.

List of original papers

Paper I:
Pain management with popliteal block for fibular graft harvesting in head and neck reconstruction; a randomised double-blind placebo-controlled study
Karolina Persson, Johanna Sjövall, Thomas Kander, Louise Walther Sturesson
Oral Oncology, 128:105833 2022, DOI:
doi.org/10.1016/j.oraloncology.2022.105833

Paper II:
Perioperative risk prediction in head and neck free flap reconstructive surgery
Karolina Persson, Madeleine Torén, Louise Walther Sturesson, Thomas Kander, Caroline Nilsson, Johanna Sjövall
Acta Anaesthesiologica Scandinavica, epub ahead of print August 31 2025, DOI:
doi.org/10.1111/aas.70115

Paper III:
Perioperative coagulation in head and neck free flap surgery: a prospective observational study
Karolina Persson, Thomas Kander, Emily Batarseh, Johanna Sjövall, Louise Walther Sturesson, Karin Strandberg, Caroline Ulfsdotter Nilsson
Submitted

Paper IV:
Vitamin K-dependent proteins in patients undergoing head and neck free flap surgery – a prospective observational study
Karolina Persson, Caroline Ulfsdotter Nilsson, Johanna Sjövall, Louise Walther Sturesson, Leon Schurgers, Thomas Kander
Submitted

Abstract

For patients with locally advanced head and neck tumours or other defects, the preferred curative treatment is extensive reconstructive surgery using free microvascular flap(s), oftentimes followed by postoperative radiotherapy. The procedure offers superior functional and aesthetic advantages, but the treatment course is long and complex and burdened with a significant risk of complications. The aim of this thesis is to address certain key perioperative aspects, with the extended objective of reducing complications and improving the quality of care for head and neck reconstructive surgery patients.

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Populärvetenskaplig sammanfattning

Föreställ dig att du får tandvärk och bokar tid hos din tandläkare. Men det du trodde var ett vanligt hål visar sig vara en elakartad tumör i käken. För att bli botad krävs en stor operation och därefter strålbehandling. Ditt liv vänds upp och ner och många frågor snurrar runt i huvudet. Vad kommer att hända nu? Kommer jag att ha mycket ont? Vilka komplikationer kan uppstå under operationen, och hur stor är risken att just jag drabbas av dem?

För patienter som diagnostiseras med lokalt avancerade tumörer i munhåla eller käke är den rekommenderade botande behandlingen en operation där tumören tas bort med goda marginaler. Den defekt som uppstår behöver i vissa fall ersättas med vävnadstransplantat från någon annan del av kroppen, till exempel underarm eller -ben, en så kallad mikrovaskulär lambå. Blodkärl från den transplanterade vävnaden måste då kopplas ihop med blodkärl i huvud-/halsområdet för att lambån ska överleva, vilket är ett mycket känsligt moment. När operationsområdet läkt behöver de flesta patienter också strålbehandling för att säkerställa att alla tumörceller är borta. Operationsförloppet är dock långt och påfrestande, och komplikationer, både kirurgiska och medicinska, är vanliga och kan innebära ökad smärta och obehag, behov av fler operationer, och längre tid på sjukhus. Syftet med den här avhandlingen är att studera några av de områden som har betydelse för ett framgångsrikt operationsförlopp för de patienter som genomgår mikrovaskulär lambåkirurgi i huvud-/halsområdet.

I delarbete I studerades smärtlindring med kontinuerlig tillförsel av lokalbedövningsmedel i en kateter inlagd intill underbensnerven för patienter där operationsområdet i huvud-/halsområdet lagas med en lambå från vadbenet. Denna smärtbehandlingsmetod är väletablerad vid brott på vadbenet orsakade av olyckor, men hade inte tidigare utvärderats för den här specifika patientgruppen. Resultaten visade att nervblockad med lokalbedövningsmedel minskade tillfällena med svår smärta och behovet av smärtlindring med morfinliknande läkemedel avsevärt under den första veckan efter operationen.

I delarbete II undersöktes riskfaktorer för medicinska och kirurgiska komplikationer efter mikrovaskulär lambåkirurgi i syfte att hitta faktorer kopplade till ökad komplikationsrisk. I studien framkom att flera olika så kallade riskskattningsinstrument, strukturerade formulär med patientuppgifter som fylls i innan operationen, kan användas för att förutse medicinska komplikationer (till exempel hjärtinfarkt eller allvarliga infektioner) efter operationen. Även nivåerna av äggviteämne (albumin) i blodet innan operationen kan ha betydelse, där ett lägre albuminvärde var kopplat till ökad risk för medicinska komplikationer. När det gällde komplikationer i den mikrovaskulära lambån (till exempel att den transplanterade vävnaden drabbas av syrebrist och helt eller delvis dör) var längre

operationstid och att ha fått blodtransfusion under operationsdygnet faktorer associerade med ökade risker.

I samband med större operationer kan blodförlust, vätskebehandling och olika läkemedel påverka blodets levringsförmåga, och trots att de flesta patienter får proppförebyggande läkemedel finns en risk att drabbas av både större och mindre blodproppar. Vid mikrovaskulär lambåkirurgi kan även små blodproppar, och likaså blödningar i lambån, leda till att den transplanterade vävnaden dör. I delarbete III studerades hur vissa ämnen kopplade till blodets levringsförmåga förändras under operationsperioden. Studien visade att "vanliga" blodprover, som till exempel antalet blodplättar, visar tecken på en ökad blödningsbenägenhet, medan andra mer avancerade prover tvärtom antyder en ökad tendens till proppbildning. Vår tolkning av resultaten är att fler studier behövs, men att ökad användning av de avancerade proverna och individualiserad proppförebyggande behandling möjligen kan bidra till ännu bättre operationsresultat.

Vitamin K är ett fettlösligt vitamin som är nödvändigt för blodets levringsförmåga, men som också har visat sig ha betydelse för flera sjukdomsprocesser i kroppen, bland annat förkalkning av blodkärl och uppkomst av cancer. I delarbete IV undersöktes utvecklingen av några så kallade K-vitaminberoende proteiner under operationsförloppet hos patienter som opereras med mikrovaskulär lambå i huvud/-halsområdet. Väldigt lite är känt om hur dessa proteiner fungerar i samband med den här typen av operationer och arbetet syftade därför till att ge grundläggande kunskaper inför vidare studier. En av de slutsatser som dock kunde dras var att patienterna i studien visade tecken på K-vitaminbrist efter operationen, något som skulle kunna ha betydelse för läkning och återhämtning.

Sammantaget uppmärksammar avhandlingen flera centrala områden av betydelse för operationsförloppet för patienter som genomgår mikrovaskulär lambåkirurgi i huvud/-halsområdet, såsom vikten av riskbedömning inför operation och noggrann övervakning av blodets levringsförmåga. Dessutom påvisas säkerhet och effektivitet för en, i sammanhanget, ny metod för smärtlindring vid operationer med vadbenslambå.

Abbreviations

ACS-NSQIP	American College of Surgeons' National Surgical Quality Indicator Program
ADP	Adenosine diphosphate
AI	Artificial intelligence
ALT	Anterolateral thigh
ALAT	Alanine transferase
APC	Activated protein C
APTT	Activated partial thromboplastin time
ASA-PS	American College of Anesthesiologists' Physical Status
AT	Antithrombin
CCI	Charlson Comorbidity Index
CRP	C-reactive protein
CT	Clotting time
DOAC	Direct-acting oral anticoagulant
dp-uc-MGP	Dephosphorylated-uncarboxylated matrix Gla protein
ECG	Electrocardiogram
ERAS	Enhanced recovery after surgery
EXTEM	Extrinsic rotational thromboelastometry
Gas6	Growth-arrest gene 6
Gp	Glycoprotein
HNC	Head and neck cancer
HN-CCI	Head Neck Charlson Comorbidity Index
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
ICU	Intensive care unit
INTEM	Intrinsic rotational thromboelastometry
IQR	Interquartile range
LA	Local anaesthetic
LMWH	Low molecular weight heparin
LOS	Length of stay
MCF	Maximum clotting firmness
MDT	Multidisciplinary tumour board
Mg	Magnesium
ML	Machine learning
NaCl	Sodium chloride
NO	Nitrogen monoxide
NRS	Numerated rating scale
PAI	Plasmin activator inhibitor
PAP	Plasmin-antiplasmin complex
PIVKA-II	Protein induced by vitamin K absence/antagonist for fII(/prothrombin)

POD	Postoperative day
PT-INR	Prothrombin time international normalised ratio
RBC	Red blood cell
ROTEM	Rotational thromboelastometry
sAxl	Soluble Axl receptor
SCC	Squamous cell carcinoma
SCP	Standardised care pathway
SVF	*Standardiserat vårdförlopp*
TF	Tissue factor
TGA	Thrombin generation
t-PA	Tissue plasminogen activator
VHA	Viscoelastic haemostatic assays
VKDP	Vitamin K-dependent protein
VKOR	Vitamin K epoxide reductase
VTE	Venous thromboembolism
vWF	von Willebrand factor
UFH	Unfractionated heparin

Introduction

"*Primum noce apte.*"[1]

Joseph Bernstein

Microvascular reconstructive surgery in the head and neck area is one of the most complex surgical procedures imaginable. The purpose of the procedure is to cure the patient from a serious – potentially life-threatening – condition, while at the same time salvaging or restoring several critical functions such as the abilities to breathe, eat and speak. Hereby, the result also has important implications for social interactions, mental health and quality of life [1-3]. When successful it is a triumph of modern health care, but the stakes are high as complications are frequent and can have a detrimental impact on both morbidity and mortality.

Head and neck pathology and treatment

Head and neck cancer

Head and neck cancer (HNC) is a group of malignancies anatomically located at nine different sites above the clavicle, below the skull base, and anterior to the vertebral column. It is the seventh most common cancer type worldwide, and the incidence is increasing, entailing a vast global disease burden on patients, families and societies [4]. It is also largely a disease of social inequality as it disproportionately affects low and middle-income countries, as well as socio-economically disadvantaged population groups [5,6]. In Sweden over 1800 people, of whom a majority are men, are diagnosed with HNC annually, and the incidence rate is increasing by 3% per year [7]. While most patients are older, the median age at diagnosis is around 65-70 years [8], younger people are also affected. Although slowly decreasing, observed 5-year mortality is still nearly 40% in Swedish HNC patients, with large differences between different tumour sites. Despite the fact that treatment

[1] *First, do harm appropriately.*

options are improving, morbidity, mortality and societal costs are still significant [9-11].

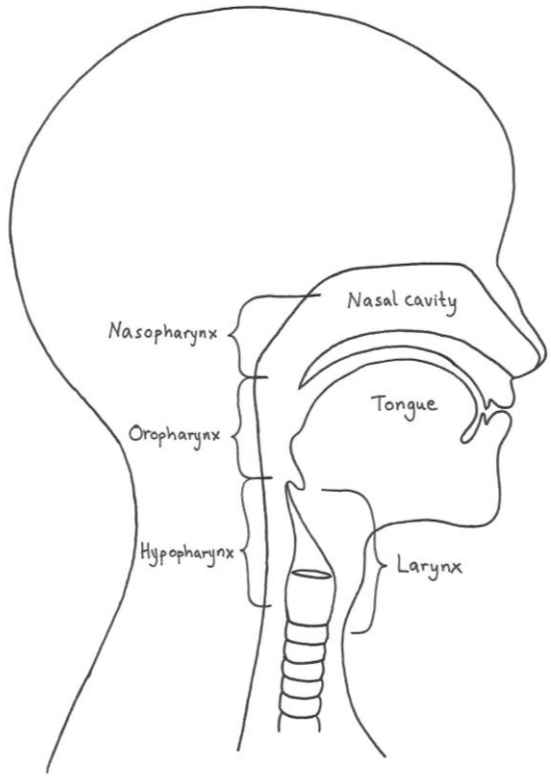

Figure 1. Normal head and neck anatomy.

Although HNC includes several histology types [12], the predominant is squamous cell carcinoma (SCC), constituting around 90% of all cases [8]. Major risk factors for SCC are smoking and alcohol consumption, when combined with synergistically negative effects, together causing a vast majority of all cases. Less significant risks, especially in Scandinavia, are exposure to environmental factors such as asbestos and smokeless tobacco [13,14]. In recent years human papillomavirus (HPV) has, as an independent risk factor, emerged as an increasing cause of HNC. In fact, HPV-related oropharyngeal malignancies is one of the most rapidly increasing cancer types in high-income countries. HPV positive (HPV+) oropharyngeal tumours differ from HPV negative (HPV-) in several aspects, including molecular characteristics and patterns of proliferation and spreading. The prognosis is far better for HPV-positive oropharyngeal tumours, some of which may also be susceptible to immunotherapy (although this treatment modality is still very limited in its

application) [15,16]. Because of these differences, HPV+ and HPV- oropharyngeal tumours are now being staged as separate entities [17]. Introduction of vaccination programmes against HPV has already led to decreased incidences of HPV-related cervical cancer [18], and hopefully similar effects will eventually be seen for HPV+ HNC.

Head and neck cancer symptoms and treatment

Symptoms of HNC vary depending on type and location, but commonly include lumps, wounds not healing as expected, discomfort and pain in the mouth, nose, ears or neck, as well as hoarseness and difficulties swallowing.

Patients with suspected HNC in Sweden are enrolled in a standardised fast-track protocol for diagnosis, including histopathology and radiology, and treatment. The so-called standardised care pathway (SCP) (*standardiserat vårdförlopp*, SVF), outlines strict time limits within which diagnostic examinations should be performed and chosen treatments commenced [19]. As head and neck tumours often are fast-growing [20], the time from diagnosis to treatment is shorter than for many other malignancies, and the SCP states that surgery should be performed within 12 days from treatment decision. This is a logistical and clinical challenge for the health care apparatus, and mentally stressful for many patients. General recommendations regarding preoperative cessation of smoking [21] and alcohol consumption can rarely be met, and there is seldom enough time to properly handle poorly treated comorbidities such as hypertension, ischemic heart disease or diabetes.

After diagnosis, patients at Skåne University Hospital (SUS) are discussed in a multidisciplinary tumour board (MDT), and recommendations are made regarding treatment modalities.

Treatment for HNC includes surgery, radiotherapy, chemotherapy and immunotherapy, alone or in combination, depending on tumour type, site, stage, treatment intent, and partially on national or local guidelines [22-25]. For curative treatment of many advanced tumours, surgical resection and postoperative (chemo)radiotherapy is the preferred option [26]. For locally advanced tumours, the extensive resection also requires simultaneous reconstruction using one or more free tissue flaps to achieve a satisfactory functional and aesthetic result. The subgroup of patients being subjected to this specific procedure is the focus of this thesis.

However, all treatment modalities have side effects causing morbidity and potentially even mortality, especially when several treatments in combination increase the physiological burden [27]. With smoking and alcohol as major risk factors for head and neck squamous cell carcinoma (HNSCC) comes a high prevalence of, among others, cardiovascular and pulmonary comorbidities, further increasing the physical strain on the patients.

Other causes of locally advanced head and neck defects

Apart from malignant tumours, there are several other indications for microvascular reconstructive surgery in the head and neck area, although altogether constituting a small minority. Benign tumours, while not life-threatening, can cause unacceptable functional and aesthetic inconveniences. Congenital malformations and trauma-related defects are other indications for free flap surgery, as well as osteoradionecrosis most commonly secondary to radiotherapy for previous localised HNC. These patients constitute a heterogeneous group but collectively differ from the cancer patients in several aspects. While benign defects can hinder eating and speaking and cause malnutrition and pain to some extent, most of these patients are not suffering from the many systemic effects of malignant disease, such as inflammatory response and potential coagulation disturbances. The resection part of the surgical procedures is also often less extensive, as there is no need to achieve wide margins to prevent cancer spread. In addition, surgery for malignant tumours almost always includes neck dissection of lymph nodes, which further prolongs the duration of operation and anaesthesia, and adds to the surgical trauma in cancer patients.

Major reconstructive head and neck surgery

At our institution, patients who are recommended for extensive resection, or secondary reconstruction, with free flap reconstruction attend another multidisciplinary appointment outlining surgical details. In this consultation head and neck, plastic and maxillofacial surgeons, anaesthesiologists, counsellors, and nurses participate, as well as the patient, preferably accompanied by a close relative or friend. One important topic of the meeting is deciding the preferred free flap, taking into account the location and extent of the defect to be resected, as well as patient factors such as anatomical and vascular status and comorbidities. Although many factors influence the choice of free flap, a basic principle is that soft tissue defects are reconstructed using soft tissue flaps (usually radial forearm or anterolateral thigh (ALT)), while osseocutaneous flaps (commonly fibula or scapula) are preferred for bony defects. Multidisciplinary preoperative conferences have, in a recent study, been shown to reduce the duration of surgery, the number of reoperations, and intensive care unit (ICU) length of stay (LOS) [28].

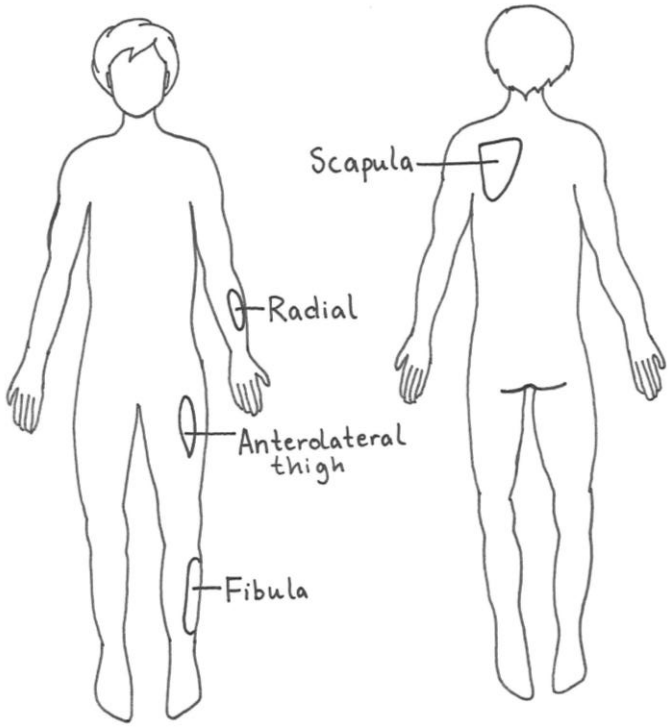

Figure 2. Common types of free flaps used for head and neck reconstruction.

If needed for surgical access, or peri- or postoperative airway protection, the surgical procedure is commenced with a tracheostomy. This is followed by neck dissection (in malignant conditions the extent is adapted to the tumour stage, while for benign conditions it is purely technical to gain adequate access for the reconstruction), and lastly resection of the tumour or pathological tissue. In Sweden, these parts of the operation are performed by head and neck surgeons. If needed, maxillofacial surgeons join to remove teeth, perform a mandibular swing, segmental or marginal mandibulotomies, or corresponding procedures in the maxilla. Parallelly, the flap is harvested by plastic surgeons and inserted when the tumour is completely removed, and access is supplied to the appropriate vessels for anastomosis. Finally, all tissue layers are sutured, drains inserted, and dressings applied. For postoperative monitoring of the blood flow to the flap, an implantable Doppler probe can also be inserted.

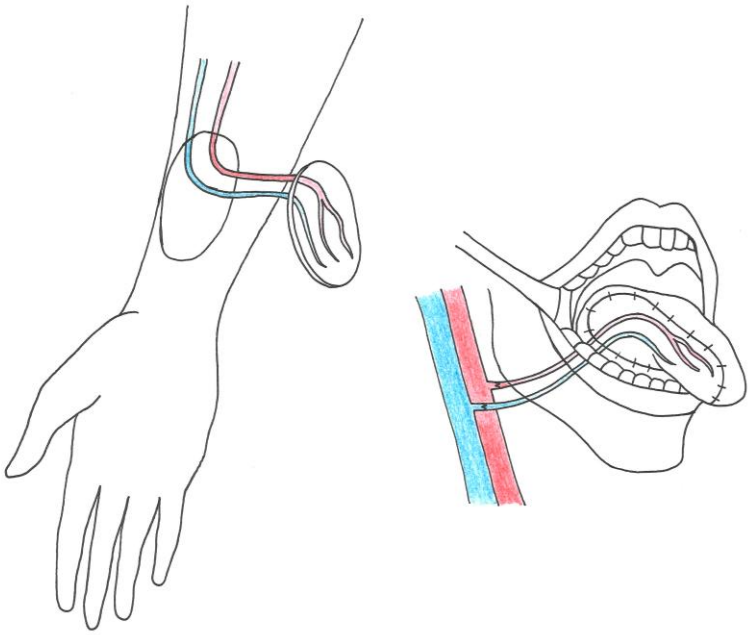

Figure 3. Radial free flap during harvest (left) and after insertion and vessel anastomosis (right).

Surgical complications

Since the early dawn of surgery, complications have been unwanted companions. Although enormous improvements have been made through crucial discoveries such as asepticism, antibiotics and blood transfusion - not to mention tremendous developments in education and training of surgeons - ancient complications such as infections and bleeding remain problematic even in modern medicine. Microvascular surgery is no exception; on the contrary, its complexity poses great challenges, and the risks of complications are high [29-32]. This section outlines the aspects of surgical complications, while systemic/medical complications are further discussed in the coming sections.

As a functioning free flap – well healed with adequate function and aesthetics – is the definition of successful reconstructive surgery, flap-related complications are at the centre of attention. The definitions of flap compromise and failure are not universal and vary between studies, but general definitions can be described as follows:

Flap compromise = thrombosis, bleeding, infection or other issues (including partial flap necrosis), risking the survival of the flap and/or requiring intervention(s)

Flap failure = necrosis of a majority of, or the entire, flap, impeding the desired functional and aesthetic results, and requiring intervention(s)

While the occurrence of flap compromise has been reported as high as 25 % (depending on definition) [33], flap failure is generally < 5% in larger centres [34,35]. However, both problems, and particularly flap failure, cause significant suffering for the patients who often need (multiple) reoperations and a prolonged hospital stay, and risk delay of the vital postoperative radiotherapy. In addition, the health care system and society in general are burdened with increased costs, both directly through increased health care spending and indirectly through productivity loss and sick leave costs [11]. Due to the importance of flap-related complications, flap compromise is a primary outcome in paper II, and the main topic of discussion in paper III (and partly paper IV).

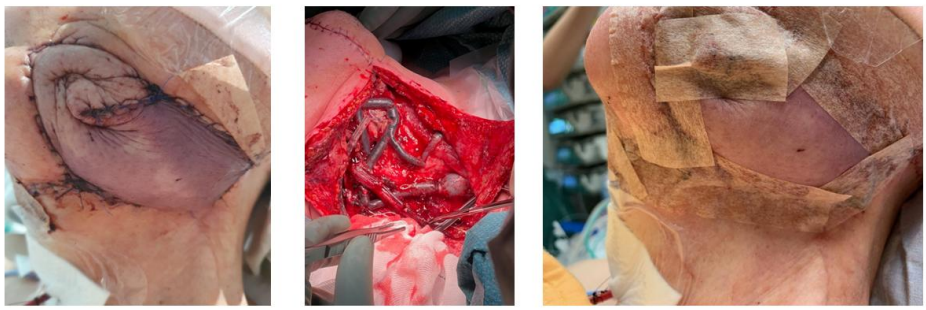

Figure 4. Photo series of a fibular flap with skin island showing early signs of venous stasis (left), congested veins during emergency surgical exploration (middle), and postoperative status after blood flow has been restored (right). Photo: Johanna Sjövall. With kind permission from the patient.

Apart from flap compromise and failure, a number of other surgical complications, such as infections and bleeding, can arise in the donor site, neck dissection or tracheostomy area. Inadequate healing causing fistulas and suboptimal functions of speech, eating or swallowing also occurs. However important for the patients, these complications are not the focus of this thesis, except for coagulation-related complications, which are further discussed in the coming sections.

Postoperative convalescence and Enhanced Recovery After Surgery (ERAS) programmes

Surgical convalescence is naturally focused on wound healing and restoration of key physiological functions such as eating and speaking. To enable this, a large apparatus is initiated, starting already preoperatively with dieticians calculating nutritional plans, and physiotherapists, occupational and speech and language therapists introducing exercises. The purpose of these efforts is to achieve, among

other things, early mobilisation, return to oral intake and weaning from tracheostomy, factors shown to be associated with fewer complications and improved recovery [36]. These goals of early return of preoperative abilities, with subsequent expected reductions in hospital LOS and health care costs, are part of the Enhanced Recovery After Surgery (ERAS) concept. Formalised ERAS protocols have been applied with success worldwide for a number of major surgical procedures, such as colorectal surgery and knee and hip replacement [37,38], and for head and neck reconstructive surgery several studies have shown the benefits of bundles of perioperative actions [39-41]. A standardised protocol was presented by the ERAS© Society in 2017 [42], but this has not yet been universally adopted. Several central elements, such as early mobilisation and intraoperative goal-directed fluid therapy, have been implemented at SUS Lund, although not in a formalised protocol.

Perioperative medicine and anaesthesiologic aspects

The physiological trauma of surgery

Surgery, even when performed optimally, causes trauma to the body and affects many physiological processes [43]. Sympathetic nervous system stimulation increases levels of circulating catecholamines and activates the renin-angiotensin (RAAS) system with subsequent rises in pulse and blood pressure. Activation of the hypothalamus-pituitary axis, with cortisol release, can potentially worsen preexisting cardiovascular and endocrine comorbidities. Exposure of sterile tissues and organs to foreign materials and pathogens causes inflammatory and immunological responses aiming to protect the body from threatening invaders, but, through cytokine release, further increasing circulating stress hormone levels. Furthermore, hypermetabolism increases blood glucose levels and protein catabolism. The acute-phase response causes release of a number of proteins, such as C-reactive protein (CRP) and fibrinogen, as well as Growth-arrest gene 6 (Gas6), which is a vitamin K-dependent protein studied in paper IV and covered in more detail in upcoming sections. Postoperative pain, especially when inadequately treated, can lead to sensitisation and contribute to fear, anxiety and the development of chronic pain conditions [44].

Anaesthesia and intensive care versus perioperative medicine

Anaesthesia and intensive care is a young speciality. For the predominant part of the history of surgery, anaesthesia largely consisted of alcohol and herbal potions, and towels to bite down on, with the first “modern” (inhalation) anaesthesia

provided in the 1840s [45]. Intensive care is even younger, with the introduction of artificial ventilation during the great polio epidemic in Denmark in the 1950s [46]. However, no part of modern surgery would be possible without advanced anaesthesia and intensive care, performed by skilled anaesthesiologists. In recent years the specialty has begun broadening into perioperative medicine, covering the entire perioperative process. The aim is to identify and address patients and situations with increased risk of complications early, optimise conditions when possible, and perhaps refrain from surgery altogether when too precarious [47]. In many countries, anaesthesia and intensive care are carried out by separate specialities, while in Scandinavia a model of one cohesive specialty covering both areas has been adopted. This gives us unique opportunities to create continuity throughout the entire treatment process and thereby improve the quality of care. The desire to contribute to this objective is a fundamental aim of this thesis.

Preoperative anaesthetic evaluation

When both patient and surgeon express the desire to proceed with extensive reconstructive surgery, the assessment by the anaesthesiologist becomes another piece of the preoperative puzzle. Medical history, including previous surgeries and experience of anaesthesia, is carefully considered, as well as physical status, allergies and current medications, all put in relation to the desired plan for the procedure as outlined by the surgeon. Depending on the information obtained, further tests, including laboratory workup, electrocardiogram (ECG), echocardiogram or other examinations, are conducted. The overall picture formed from the results lays the foundation for choices of everything from airway management strategies and anaesthetic drugs to postoperative pain management. Ideally this is all done in close cooperation between all parts of the multidisciplinary team, as compromises often have to be made based on the individual patient's condition and situation. In rare cases, for patients with exceptionally high estimated surgical or anaesthesiologic risks, the preoperative evaluation can result in the patient being advised against surgery, and a change of treatment plan.

Preoperative risk assessment

A specific part of the preoperative evaluation is the assessment of the risk of peri- and postoperative complications. While looming threats are always at the back of the anaesthetist's mind, formal risk estimation has gained increasing attention over the past decades. A multitude of risk scoring instruments have been developed, by different specialties and with different patient populations and outcomes in mind. The American College of Surgeons' Physical Status (ASA-PS) class was introduced as early as in the 1940s [48], and today it is one of the most widely adopted scoring instruments worldwide. Although originally designed for statistical calculations

rather than clinical decision making, and with substantial interrater variability, it still stands strong with only minor adjustments after nearly a century [49]. It has repeatedly proven useable to predict perioperative complications for a number of procedures, including head and neck reconstructive surgery [50,51].

After the introduction of ASA-PS a number of other risk prediction instruments have been presented [52], some of them specific for HNC, and even further specified to include the free flap surgery patients [53,54]. However, none have made a convincing impact. One of the models widely used in surgery and oncology is the Charlson Comorbidity Index, CCI [55]. It was introduced in the 1980s to predict mortality in hospitalised patients, but has also shown good predictive properties in perioperative settings, including for head and neck free flap surgery [56,57]. However, CCI is extensive with many included variables, and several modified/simplified versions have been developed. One of them is the Head Neck CCI (HN-CCI), presented by Böje and colleagues in 2014, to predict survival in HNSCC patients undergoing radiotherapy [58]. Since then, it has been evaluated in general head and neck surgical patients [59], but, at the commencement of our project, not specifically for reconstructive surgery.

While most risk prediction instruments present risk estimates on a group level, the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) risk calculator was developed in the 21st century, claiming to be able to deliver individualised risk scores based on an extensive form [60]. However, its predictive properties in head and neck surgery have been questionable [61], with several studies showing significantly underestimated complication risks [62].

As prediction instruments vary widely in model design and included variables and outcomes, as well as target patient populations, comparison between instruments, and extrapolation to other patient groups, is challenging. Broader models with fewer and more general parameters included (such as ASA-PS) have the advantage of being easy to apply, but also risk being less accurate and detailed in their predictions. More detailed instruments have the potential of being more precise in their estimates, but are often also lengthier and more complex, impeding clinical implementation [63] and extrapolation.

Anaesthesia

Anaesthesia originates from the Greek word *an* meaning *without* or *not*, and the root *aisthesis* (αἴσθησις) meaning *sensation*. In modern medicine (much as in ancient Greece, actually) it is the speciality focused on establishing controlled unconsciousness and pain alleviation, while maintaining stability of vital organ systems before, during and after surgical procedures. It is an intricate task, especially for advanced surgery.

For head and neck reconstructive surgery the patient needs to be fully anaesthetised during the entire procedure. The airway needs to be secured, which can be a challenge due to the nature and location of the tumour/defect – many HNC patients have difficult airways [64]. During surgery, ventilation and circulation (and in the extension organ oxygen supply) need to be stably maintained for the patient as a whole, as well as for the vulnerable free flap. Postoperatively, this stability of vital functions must be maintained, and adequate management of pain, nausea and other discomforts must be established. While there is no specific protocol for anaesthesia administration for free flap surgery at SUS Lund, treatment adheres to general local and national guidelines stating standard of care.

Several intraoperative factors, usually in the hands of the anaesthetist, including intraoperative blood pressure [65] and goal-directed fluid therapy [66,67], have been associated with flap survival, while the long-prevailing theory that vasopressors cause flap failure has simultaneously been disproven in repeated studies [68,69].

Postoperative pain management and recovery

While pain is an important signal intended to protect the body from harm, prolonged and inadequately managed pain is, in itself, harmful. It is a central part of the trauma of surgery described previously and can lead to impaired healing, anxiety, and chronic pain conditions. For HNC patients, the latter has been shown to negatively affect quality of life [70], and can contribute to chronic opioid use, something that has even been associated with poorer survival [71]. Preoperative pain in the tumour area is also common among HNC patients [72], contributing to central sensitisation processes and potentially to chronic post-surgical pain [73]. This further complicates – but also highlights the importance of – zealous pain management.

Treating postoperative pain after head and neck reconstructive surgery requires a multimodal approach, especially as the pain may be localised to several parts of the body (donor and recipient sites, neck dissection, and tracheostomy areas) and accompanied by general soreness following long immobilisation in the operating room. This is also the recommendation in modern pain management [74], including guidelines from international societies [42,75]. An important part of this approach is using local anaesthetics and peripheral nerve blocks when possible [76]. This has been an indisputable part of orthopaedic surgery for many years [77,78], but only recently added to the head and neck reconstructive surgery arsenal [79]. At the commencement of the work with paper I, no publications specifically showing the efficacy of continuous popliteal blocks for fibular graft harvesting could be found.

The recovery period for head and neck reconstructive surgery is long - the time to return to baseline function level (if possible) is, in clinical experience, estimated to be around one year. A number of bodily functions must be regained in the early phase, including nutritional intake (most patients receive a nasogastric tube for

postoperative nutrition), mobilisation and speech. These are processes where the anaesthesiologist, with expertise in, for instance, venous access, fluid and electrolyte balance, and coagulation, can contribute to a favourable course. While challenging to prove in studies, it is my conviction that the advantages of multidisciplinary cooperation continue throughout the entire hospital stay, and even beyond.

Perioperative systemic (medical) complications

In addition to the potential surgical complications previously discussed, medical complications are common during the complex perioperative period. Reported risks of medical complications vary widely depending on definitions, time periods and patient subgroups, but range from 3-35% [31,80]. Commonly reported medical complications are pneumonia [81], pulmonary embolism and cardiovascular events [82]. Mortality, likewise, varies depending on study design (in particular the time period covered), but has been reported as high as 5% in-hospital in patients with ischemic heart disease [83], and 12% over 90 days for octogenarians [57]. Another factor often studied, and of obvious interest, is hospital LOS. However, since SUS Lund is a tertiary referral centre, with a catchment area of approximately 1.9 million, many patients are discharged to local hospitals to continue treatment and rehabilitation there, making our LOS data unreliable and therefore not included as an outcome in our studies.

Haemostasis in health and disease

Haemostasis is the process of stopping bleeding, a vital function to ensure survival after trauma or surgery. It involves several steps beginning the very second a blood vessel wall is injured. The goal of a well-functioning haemostatic system is to stop the bleeding while ensuring continued blood flow to the organs and avoiding pathological blood clotting.

Primary haemostasis

As an effect of vascular injury, subendothelial substances stimulate vascular contraction and the formation of a platelet plug through a series of interacting steps that can concisely be summarised as follows [84]:

1. Adhesion: Exposure of subendothelial structures to von Willebrand factor (vWF) and other proteins causes platelets to adhere to the vascular wall.

2. Activation: Metabolic activation of the platelets causes them to change shape and receptor expression, and release granules with, among others, adenosine diphosphate (ADP), serotonin and thromboxane A2.
3. Aggregation: The released substances activate additional nearby platelets that, through binding with Glycoprotein (Gp) IIb/IIIa and fibrinogen, form the platelet plug.

When reaching undamaged endothelium containing nitrogen monoxide (NO) and heparan sulphate, the platelet activation and aggregation is discontinued, naturally inhibiting the formation of pathological thrombi.

Secondary haemostasis/coagulation

While very important, the platelet plug alone cannot stop the bleeding; a fibrin network stabilising the clot is also needed. This stable structure is achieved through the effects of a series of liver enzymes included in what is termed the coagulation cascade, or secondary haemostasis. Just like the primary haemostasis, it is an intricate process, here described in a few summarised steps [85]:

1. Initiation: After enzymatic cleavage activating coagulation factors, tissue factor (TF) released from the subendothelium of the injured vessel wall binds to Factor VII (FVII), forming an active TF/FVIIa complex. This, in turn, causes activation of a number of further coagulation factors, with the final stage being the FXa/FVa complex converting a small amount of prothrombin into free thrombin (FIIa).
2. Amplification: The small amount of free thrombin further activates other coagulation factors and platelets, enabling further reactions.
3. Propagation: The conversion of prothrombin to thrombin accelerates to create a large amount of thrombin, the thrombin pulse, which converts substantial quantities of fibrinogen into fibrin. The fibrin, in interaction with other substances, establishes the network that stabilises the platelet plug and forms the blood clot.

Anticoagulation and fibrinolysis

Despite the vital importance of blood clot formation, the ability to halt the process is equally important, as unlimited clot formation is as lethal as bleeding. The process by which the body limits clot formation (anticoagulation) and stimulates breakdown (fibrinolysis) [86] is described in brief here:

1. Anticoagulation: Several substances and reactions are involved in limiting exaggerated blood clot formation. Among these is the binding of thrombin

to thrombomodulin, activating protein C, which, together with protein S, inhibits several coagulation factors. Protein C and S are both vitamin K-dependent and produced in the liver. Antithrombin (AT) is another important protein that inhibits thrombin and FXa, and anticoagulant drugs such as unfractionated heparin (UFH) and low-molecular weight heparin (LMWH) both exert their effects by inhibition of thrombin and FXa through an AT-dependent mechanism.

2. Fibrinolysis: Tissue Plasminogen Activator (t-PA) converts plasminogen into plasmin, breaking down the fibrin network. This reaction is limited to the surface of blood clots, ensuring that the effect is local and does not cause generalised bleeding tendencies. A number of factors, including Plasmin Activator Inhibitor (PAI) 1 and antiplasmin, contribute to the regulation of fibrinolysis to achieve a balanced process.

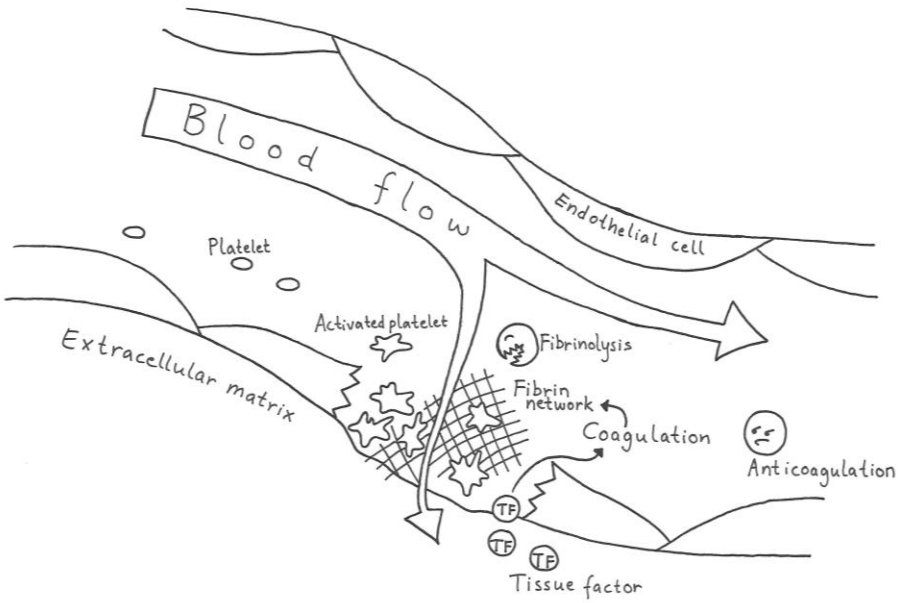

Figure 5. Normal haemostasis. The picture illustrates damage to a blood vessel with bleeding. Several processes are activated to form a clot as well as to regulate excessive clot formation.

Disturbances of haemostasis

Many conditions, congenital as well as acquired, interventions, and drugs affect the coagulation system, and extensive surgery and the perioperative process cause significant haemostatic disturbances through different mechanisms. To start with, the indication for surgery itself could entail inherent coagulation disorders. It is

well-known that cancer causes procoagulant changes and is a risk factor for venous thromboembolism [87]. In addition, many patients with HNC have, as previously mentioned, cardiovascular comorbidities treated with anticoagulant drugs. Even in young, previously completely healthy, patients, extensive surgery entailing tissue trauma, bleeding, immobilisation, and exposure to multiple drugs (including routine thromboprophylaxis) will cause both pro- and anticoagulant disturbances throughout the treatment period [88,89].

Thromboprophylaxis and implications for this thesis

Patients included in all papers in this thesis have routinely received the following antithrombotic treatment:

- Low-molecular-weight heparin (enoxaparin) 40 mg SC on the evening before surgery, followed by 40 mg twice a day starting on the evening of the day of surgery. This prophylaxis is continued until the patients are well mobilised and fairly well-functioning in their activities of daily life, which usually means discharge from the hospital.
- Unfractionated heparin 2500 International Units (IU) IV bolus intraoperatively at the time of vessel anastomosis.
- Acetylsalicylic acid 75 mg PO if/when the platelet count exceeds 500 x 10^9/L, in which case the LMWH prophylaxis is simultaneously reduced to 40 mg once daily.

In addition to pharmacological thromboprophylaxis, all patients without contraindications are fitted for intermittent pneumatic compression stockings that are applied until patients are adequately mobilised postoperatively. (Pneumatic stocking is not applied to the donor site leg if fibular or other lower leg graft is used.)

Naturally, exceptions from this routine have been made, but it still constitutes the foundation on which interpretations of the results of this thesis can be made. No patients were under treatment with vitamin K antagonists or direct-acting oral anticoagulants (DOAC) at the time of surgery. None of the patients received non-steroidal anti-inflammatory drugs (NSAIDs) in the immediate perioperative period. For patients receiving popliteal blocks, the timing of enoxaparin administration was adjusted relative to the catheter insertion according to national guidelines for central blocks, for added safety [90].

Perioperative routines at SUS Lund previously included dextran 60 (Macrodex®) IV to optimise rheology and fluid balance intraoperatively, but with the termination of production of Macrodex® and similar fluids (around the year 2015), the current thromboprophylactic routine was implemented. However, this means that the thromboprophylaxis for patients included in paper II varies, which should be

considered when interpreting the results. It is worth noting that there is no national or international consensus on perioperative thromboprophylaxis for head and neck reconstructive surgery, and regimes vary widely between institutions [91-93].

Haemostasis-related surgical complications

Haemostasis-related complications are the major causes of severe flap compromise and failure, without any specific factor yet identified as the root origin. They are reported to occur in 5-15%, although figures vary, and even though thrombosis is the more common issue, bleeding(/hematoma) also constitutes a significant problem [94,95]. Although uncommon, repeated flap thrombosis in the same patient occasionally occurs, presenting a source of huge frustration. Hence, clotting and thrombosis are areas of great interest for anyone aiming to improve free flap surgery, and perioperative haemostasis-related complications are therefore the focus of paper III (and to some extent paper IV).

Most complications related to clotting arise in the early postoperative phase, within the first 48 hours [96], which is one of the main arguments for postoperative monitoring in the ICU, and for the meticulous monitoring of flap blood flow. Arterial flow surveillance, with implantable Doppler probes attached to the recipient end, is often used to rapidly detect reduced flow. The same technique can be used for venous monitoring, but the interpretation is more difficult, which is problematic as venous stasis or thrombosis constitutes a majority of the complications [96]. If identified and addressed immediately, chances of salvage of a compromised flap are reported to vary between 22% and 67%, with favourable factors being venous congestion, absence of hyper-coagulability, and short time to take-back [97].

Many factors have been associated with flap thrombosis in different studies, including surgical techniques [98,99], previous history of venous thromboembolism (VTE) [100], and (sometimes undiagnosed) coagulopathies such as activated protein C (APC) resistance and increased levels of procoagulant factors [101-103]. However, in many cases no specific cause can be found, which is not only frustrating for everyone involved but also makes preventive interventions in the case of attempting a new reconstruction difficult. Reasonably, most cases of flap failure can be said to have multifactorial causes, which again strengthens our conviction as to the importance of multidisciplinary teamwork to cover as many areas of competence as possible.

Assessing haemostatic function

To detect and manage disturbances of haemostasis and associated clinical complications, adequate methods for biochemical monitoring are needed. Ideally, these should be easily accessible, available around the clock, and give clear answers

to the questions crucial for clinical decision-making. However, needless to say, this is not the case. Indeed, many questions cannot be answered directly, but rather through surrogate methods. Despite the potentially detrimental consequences of haemostasis-related complications, there is no gold standard for haemostasis monitoring in head and neck reconstructive surgery, and several theoretically useful analyses are currently unavailable in clinical practice.

The definition of "routine coagulation tests", repeatedly referred to in this thesis, is not universal. However, in the daily clinical context (in health care facilities in the developed world), they often include measurements of prothrombin time/international normalised ratio (PT-INR), activated partial thromboplastin time (APTT), and platelet count. While the first two test parts of the coagulation factor cascade, the third is simply a count of the number of platelets, saying nothing about their function. Functional platelet tests exist but are currently mainly used in highly specialised settings to assess pharmacological effects. Other easily available tests routinely used (in centres performing advanced reconstructive surgery) are analyses of fibrinogen and antithrombin, as well as anti-factor Xa activity, sometimes used for monitoring of LMWH treatment or prophylaxis. However, no easily available analysis yet exists to monitor fibrinolysis.

While in many situations useful, the tests covered in the previous paragraph can at best answer questions about specific details, rather than the entirety – a little like looking at a soccer match through a straw: you get a close-up look at specific parts, but no overall picture of how the game is actually played. To solve this problem, viscoelastic haemostatic assays (VHAs) have been developed as global tests of haemostasis. Rotational thromboelastometry (ROTEM) is the VHA most commonly used in Sweden. The exact techniques vary to some extent, but all ROTEM tests use whole blood in a cup, in which a small pin rotates, resulting in real-time measurements of several parameters, such as time to start of clot formation, clot strength and breakdown. Various reagents can be added to test, or eliminate, effects of specific substances (for instance heparin) or parts of the clotting process. However, there are pitfalls in interpreting VHAs, for instance therapeutic effects of several anticoagulant and antiplatelet drugs cannot always be ruled out [104]. One must also remember that even though ROTEM measures whole blood in a more comprehensive way, many differences still exist between the analysis apparatus and in vivo conditions. Still, ROTEM has proven useful in guiding transfusion and coagulation factor substitution in trauma [105], and cardiac [106] and obstetric surgery [107]. Its applicability in reconstructive surgery, where hypercoagulability (for which the value of ROTEM is still debated) is a more common problem than massive bleeding, is not fully established. However, some studies indicate usefulness in predicting free flap thrombosis [108], and in a recent review of ROTEM for miscellaneous otolaryngology surgery the authors claimed that the scarce evidence may simply be due to lack of familiarity with the analyses among head and neck surgeons [109].

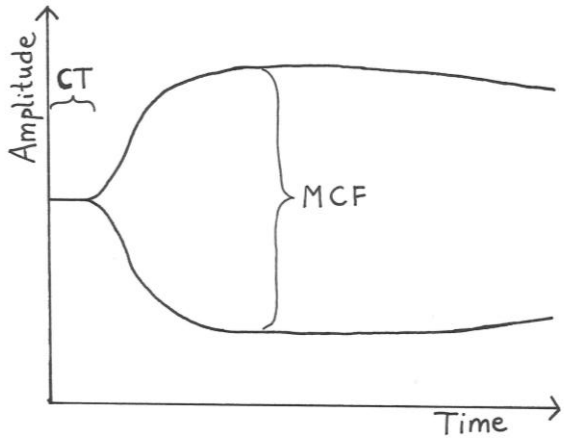

Figure 6. Classic rotational thromboelastometry (ROTEM) curve.

For anticoagulant factors other than antithrombin, no daily clinically available tests exist in regular clinical practice. Activity of protein C and free protein S can be measured on a weekly basis in many centres and are included in thrombophilia investigations. Furthermore, genetic tests for mutations affecting coagulation factors (for instance factor V von Leiden mutations causing APC resistance, which are reported to affect 5-10% of European Caucasians [110]) are also available from specialised laboratories. However, no such test is currently used in the preoperative screening of head and neck reconstructive surgery patients at SUS Lund, nor were they included in the studies in this thesis.

Vitamin K and vitamin K-dependent proteins (VKDPs)

Physiological functions of vitamin K

Vitamin K was discovered in the 1920s by Danish biochemist Henrik Dam when studying chickens with bleeding disorders. The vitamin was subsequently given the letter K for *koagulering*, and Professor Dam's discovery rendered him (and American colleague Edward A Doisy) the 1943 Nobel Prize in Physiology or Medicine. Although vitamin K has since then been implicated in several biological processes, its main established role remains in haemostasis, where it has several crucial functions.

In nature, vitamin K exists in two forms: phylloquinone (K1), of which the main dietary source is leafy vegetables, and menaquinone, which is produced by bacteria and therefore primarily found in meat, liver and fermented foods, including

fermented Baltic herring (*surströmming*) and the Japanese dish natto. While some endogenous production occurs in the colon, vitamin K is considered an essential micronutrient [111].

Vitamin K has a central role in post-translational carboxylation of coagulation factors II, VII, IX and X, along with protein C, S and Z, all synthesised in the liver. The carboxylation is achieved through a series of enzymatic modifications called the vitamin K cycle [112], where one of the steps is the regeneration of vitamin K by the enzyme Vitamin K Epoxide Reductase (VKOR). This is of interest to physicians as it is by inhibiting VKOR that warfarin and similar substances exert their effects. Although vitamin K metabolism is highly complex, the result of clinical deficiency is simple: a lack of multiple substances vital to the haemostatic process, and subsequent increased bleeding tendencies.

Vitamin K-dependent proteins and their implications for this thesis

In addition to the essential role of vitamin K in haemostasis, a number of other functions have been presented over the past decades, involving proteins synthesised extrahepatically, but with the same need for carboxylation of γ-glutamate to γ-carboxyglutamate to function adequately. Some of the processes where vitamin K-dependent proteins (VKDPs) are implicated are vascular calcification [113,114], carcinogenesis [115] and inflammation [116].

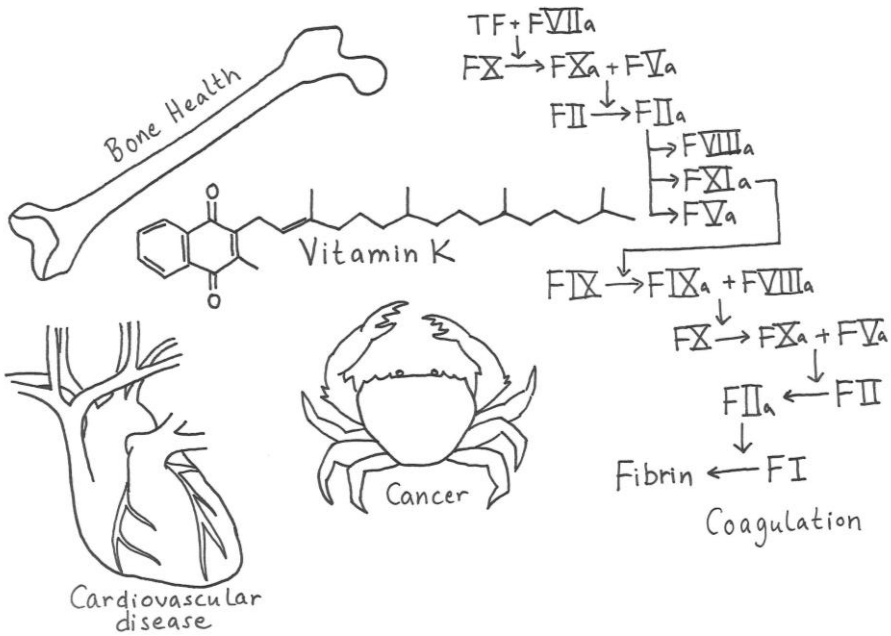

Figure 7. Physiological functions of vitamin K-dependent proteins, VKDPs.

Matrix gla protein (MGP) is a small VKDP that requires both carboxylation and phosphorylation for complete function as a vascular calcification inhibitor. Various inactive forms have been shown to work differently, but it's completely inactive form, dephosphorylated-uncarboxylated matrix gla protein (dp-uc-MGP), is a strong indicator of vitamin K deficiency and has been tightly associated with vascular calcification [114]. MGP expression in tumour cells has also been associated with tumour progression for several different cancer types [117].

Growth-arrest gene 6 is another VKDP, and the primary ligand of the receptor tyrosine kinase Axl (membrane-bound or soluble as sAxl). Both proteins have been linked to cancer progression, increased disease severity and poorer prognosis in HNC, and have been proposed as potential prognostic markers and future targets for immunotherapy [118-120].

Protein induced by vitamin K absence/antagonist for fII(/prothrombin) (PIVKA-II) is yet another VKDP, and perhaps the one most introduced into clinical medicine. It is a well-established, sensitive, and early marker of vitamin K deficiency [121], and emerging as a prognostic marker in hepatocellular carcinoma [122]. In surgical patients, postoperative elevations have been reported [123], however without association with increased bleeding [124].

It should be noted that most studies on Axl and Gas6 have been conducted in vitro or in animal models, and protein levels discussed are expressed on tumour cells rather than measured in blood samples. Apart from studies of Axl and Gas6, published research on VKDPs in head and neck free flap surgery, and surgery in general, is scarce. For all VKDPs (PIVKA-II perhaps being the exception), clear and universally accepted reference intervals are lacking, and interpretation is complicated by varying analysis methods. Currently, analyses of most VKDPs are restricted to specialised/research laboratories, further limiting their clinical use.

Aim

"*Anaesthesia is the art of balancing pain and awareness, risk and benefit, science and compassion...*"

Jannike Mellin-Olsen

This thesis attempts to address certain critical areas of the perioperative course for patients undergoing extensive head and neck surgery with simultaneous reconstruction using free flap(s). The questions and aims of each paper originate in practical questions posed by the multiprofessional team in everyday clinical work. How can we preoperatively identify patients at increased risk of perioperative complications and, ultimately, prevent these adverse events? How can we optimise haemostasis monitoring, thromboprophylaxis and pain management throughout the perioperative course? While the overarching questions are asked with a broad perspective in mind, they are formulated to be answered from the anaesthetist's view, with the objective that our speciality will be able to provide the best possible contribution to the whole process. The specific aims of each paper are presented below.

Paper I

To evaluate the efficacy of continuous popliteal blocks on postoperative pain and pain management in patients undergoing extensive head and neck surgery including reconstruction using a free fibular flap.

Paper II

To identify factors, amenable to preoperative intervention, associated with perioperative complications in major reconstructive head and neck surgery by evaluating well-known preoperative risk prediction instruments and readily available clinical parameters.

Paper III

To prospectively describe perioperative haemostasis in patients undergoing major reconstructive head and neck surgery, focusing on evaluating easily available routine analyses as well as specialised coagulation tests, with the long-term goal of identifying the most useful analyses for prevention, early identification and management of haemostasis-related complications.

Paper IV

To characterise the profile of vitamin K-dependent proteins (VKDPs) in patients undergoing major reconstructive head and neck surgery, and evaluate possible implications for postoperative complications.

Ethical considerations

"*So in everything, do to others what you would have them do to you…*"

Matthew 7:12

All studies in this thesis were subject to assessment and approval by the Swedish national ethical review authorities. For the prospective studies, written consent forms were signed by all participating patients prior to inclusion, and exclusion criteria included any conditions rendering patients unable to comprehend information given and consent to interventions. For the retrospective review of medical records (paper II), signed consent was waived by the ethical review authority and replaced by an opt-out possibility. Information about the study was published on the university website as well as in the membership magazine of the Swedish head and neck cancer patient organisation, and no patient actively chose to be excluded.

Research involving patients with serious, potentially life-threatening diseases always entails enormous responsibility. In projects such as ours, where the staff involved has double roles as both treating physicians and researchers, this responsibility is even greater, although studies have indicated that patients are more willing to participate in trials that are presented and conducted by their own doctors [125]. For many patients with HNC, the fast-growing nature of the tumour leads to a short time frame from diagnosis to treatment, a period often characterised by shock and emotional turmoil. Making informed decisions regarding research procedures in the midst of this can be difficult, and this could potentially influence patients' inclination to participate in studies. Additionally, paper I involved an invasive procedure, possibly causing discomfort and pain, potentially without any personal gain for the individual patient.

Despite the above-mentioned challenges, our projects had very low exclusion rates, with basically none due to patient unwillingness to participate. On the contrary, many patients were almost eager to contribute to our studies. When spontaneously stating their reasons to accept participation, "helping other patients" and "contributing to better health care" were two recurring arguments, something that is also in line with studies on patients' attitudes towards medical research [126]. We believe that this high acceptance rate is attributable to multidisciplinary teamwork throughout the whole treatment process, making patients feel safe and a part of the treatment team.

Blood sampling for papers III and IV was coordinated with already planned sampling according to clinical guidelines, to avoid unnecessary pain and discomfort for the patients, as part of the requirements in the ethical review authority approval. This turned out to pose occasional ethical dilemmas when sampling was difficult (for instance because of poor venous access). In some of these cases the responsible physician chose to omit the clinical blood sampling to spare the patient, and therefore the study sampling was also inhibited. However, some patients were so keen to contribute to the study that they asked to have blood drawn despite this (even when several attempts were needed), again highlighting both patients' willingness to aid research and the responsibility of scientists to conduct studies with great care.

Methods

"To ask the right question is to know a lot."

Old proverb

This thesis aims to cover several aspects of the perioperative course for patients undergoing extensive head and neck surgery with simultaneous reconstruction using one or more free microvascular flaps. The focus on various questions concerning a specific patient population, rather than any more clearly demarcated phenomenon, is reflected in the varied choice of methodology for the different studies.

A common challenge in studies of head and neck free flap surgery patients is the limited number of study subjects. Even though overall HNC incidence is rising, and SUS Lund has a relatively large catchment area, the number of individuals eligible for this very highly specialised procedure remains low (around 50 patients per year). While most patients undergo surgery due to malignant tumours, a small number have other indications for surgery, such as osteoradionecrosis or trauma-related defects. In our studies we have included all patients regardless of surgical indication, but this can be questioned. The studied population is also heterogeneous in several other important aspects, such as age, smoking status, and comorbidities. Another difficulty is that the outcomes of interest in this thesis, flap compromise (and failure) and serious medical complications, luckily, are rare. The combination of a heterogeneous patient population and rare outcomes makes sub-group analyses, however interesting, almost impossible for many variables.

For all studies in the thesis, the condition applies that all treatment, except for the specific interventions described in the study protocols, followed local routines and national guidelines. Some parts, for instance specific surgical decisions such as the extent of dissection of primary tumour and neck lymph nodes, and indication for postoperative radiotherapy, are relatively strictly regulated by treatment protocols [19]. However, decisions regarding many perioperative aspects are left to the discretion of the anaesthesiologist or surgeon in charge, leaving room for individual preferences. Furthermore, for paper II the study period covered more than a decade, during which several potentially influential changes in the care protocols were made, regarding, for instance, transfusion thresholds, perioperative fluid strategy, and use of vasopressors.

The challenges mentioned above give rise to important questions regarding study design. Is it preferable to conduct, as we have, single-centre studies where it is possible to oversee all aspects of the treatment course at the price of a lower number of participants, or would multicentre studies involving a larger number of patients, but with the risk of introducing more confounding factors, be superior? While prospective clinical multicentre studies allow for larger and more generalisable patient cohorts, they also require substantial organisational, logistical and financial resources. Our methodological choices of single-centre design and manageable laboratory-based and clinical outcomes enabled the studies to be conducted with realistically achievable resources, while still ensuring a high degree of methodological control. The small and consistent team involved in both research and clinical care will hopefully ensure relatively high internal validity, as treatment and research conditions are tightly controlled. The external validity that is achieved through broader generalisability in multicentre projects is, however, more limited in our studies, given that many factors regarding patient populations and care practices are known to vary across centres.

The problem with limited possibilities for extrapolation of conclusions was discussed particularly in the work with paper II, as extended application of different risk prediction instruments developed for, or tested in, specific conditions can be questioned.

The number of studied patients in this thesis may be limited, but we believe that even small studies, especially randomised controlled trials, if well-conducted, can contribute to important insights further used in, for instance, reviews and metanalyses. This has also been the case for paper I, which was recently included in a metanalysis evaluating nerve blocks for head and neck reconstructive surgery with lower extremity flaps [127], where it was deemed to be one of few studies with low risk of systematic errors.

All clinical parameters in all papers were assumed not to be normally distributed, and the choices of statistical analyses were made based on that assumption. Statistical analysis methods were chosen prior to the conduction of the studies and approved by all authors. If nothing else is mentioned, statistical significance was defined as a p-value of < 0.05. Data is presented with median and range or interquartile range (IQR) in brackets for continuous variables. Numbers are presented as n with percent (%) in brackets.

Paper I

Paper I was a single-centre, prospective, randomised, double-blind, placebo-controlled study including 24 patients consecutively scheduled for head and neck surgery with reconstruction using a free fibular flap at SUS Lund, Sweden. All

patients over 18 years of age were eligible for inclusion, with exclusion criteria comprising cognitive impairment preventing informed consent, allergy to local anaesthetics, and/or coagulopathy rendering the patient unsuitable for nerve blocks according to national guidelines [90]. Patients with significant lower extremity motor or sensory defects were also excluded, as they were disqualified from fibular harvesting by the plastic surgeons.

Included patients received popliteal blocks with an indwelling catheter and were randomised in a 1:1 ratio to receive either levobupivacaine 0.375% (perioperative bolus injection) and 0.2% ropivacaine (postoperative infusion), or placebo. All handling of randomisation and preparation and management of study substances and block catheters was performed by separate staff at the pain management department, to ensure blinding for all staff involved in patient care.

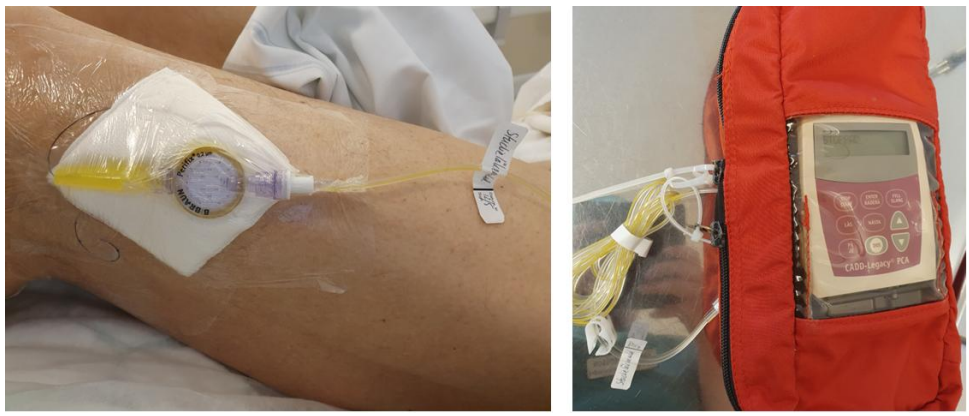

Figure 8. Popliteal block with infusion of study substance (left) and blinded substance infusion bag (right). Photo: Karolina Persson. With kind permission from the patient.

The primary outcome was donor site (extremity) pain according to the numerated rating scale, NRS, where a supposed two-point reduction constituted the basis for calculating the sample size, accordingly set at 24 individuals. Secondary outcomes were opioid consumption, nausea, motor and sensory function (assessed using a simplified three-step Bromage scale where 0 = normal function, 1 = mild impairment, 2 = significant impairment), time to mobilisation, and consumption of other analgesics, all during the first postoperative week. Long-term follow-up interviews were conducted six to twelve months postoperatively, assessing all included outcomes.

Differences between the intervention groups were analysed using Mann-Whitney U test, and for dichotomous variables Chi-squared and Fisher's exact tests were used. All results were analysed on an intention-to-treat basis.

The study was approved by the regional ethical board, Lund, Sweden (dnr 2018/362, May 8, 2018) and prospectively registered in the Clinical Trials database (NCT03607227).

Paper II

Paper II was a retrospective registry-based study of 388 patients undergoing major head and neck reconstructive surgery at SUS Lund, from 2009 to 2022. The study was approved by the Swedish Ethical Review Authority (dnr 2019-02011, June 12th, 2019). The need for written consent was waived by the authority and replaced by an opt-out possibility. No patient sought to be excluded; however, one patient had all medical records blocked for privacy reasons and was therefore excluded. The study was conducted and reported in accordance with the STROBE guidelines [128]. Primary outcomes were flap compromise (defined as flap necrosis (total or partial), return to the operating room due to flap insufficiency and deep surgical site infection) and systemic complications comprising sepsis, pulmonary embolism, deep vein thrombosis, arrhythmia (atrial fibrillation, atrioventricular blockage or need for rhythm conversion), myocardial infarction, pneumonia, heart failure, return to the ICU and transfer to internal medicine high dependency unit or cardiac intensive care unit.

One of the key origins for this thesis was frustration over the lack of practically applicable instruments to predict peri- and postoperative complications for patients undergoing free flap surgery [129], and hence limited possibilities to predict these complications. Paper II therefore focused on readily available parameters, potentially amenable to preoperative interventions. Univariate regression analyses were used to establish associations between the chosen variables and the two outcomes, flap compromise and systemic complications, and multivariable regression analyses were thereafter run to ascertain parameters remaining significant as potential predictors of complications.

Paper III

Paper III was a prospective observational study describing the coagulation profile of 39 patients undergoing major reconstructive head and neck surgery at SUS Lund, Sweden, from September 2020 to November 2021. The study was approved by the Swedish Ethical Review Authority (dnr 2020-00718, June 6th, 2020) and registered in the Clinical Trials database (NCT04517461). Patients were included consecutively, and written consent was obtained prior to inclusion. The study was conducted and reported according to the STROBE guidelines [128].

Blood sampling was conducted at predefined times on the day of surgery (D0) and postoperative days (POD) 1, 2 and 6. Analyses were performed of coagulation tests available around the clock at SUS Lund, such as PT-INR (Owren method), APTT and platelet count, as well as ROTEM, in line with the thesis focus on clinical applicability. These tests were run at the accredited laboratory at SUS Lund, Sweden, without delay. Furthermore, extended tests of haemostasis such as thrombin generation (TGA), protein C and free protein S were analysed (following centrifugation and storage at -80°C) at the accredited Clinical Chemistry Coagulation laboratory, SUS Malmö, Sweden. While these analyses are not immediately available, and therefore less useful in emergency situations, they could potentially play a role in coagulopathy screening, something currently not included in preoperative evaluations at SUS Lund. While convincing support for preoperative screening has not been presented [130], undiagnosed protein C deficiencies have, in some studies, been associated with increased risk of flap failure [102], an experience confirmed by anecdotal cases in our department.

Sample size calculation for paper III was based on a previous study of coagulation in major surgery [131], with the intent of demonstrating a difference in ROTEM EXTEM (extrinsic rotational thromboelastometry) maximum clotting firmness (MCF) from baseline to POD2, and the study population was set to 38 patients. To allow for dropout and missing analyses, the aim was to include 40 patients.

Changes in the haemostasis parameters over the study period were analysed using the Kruskal-Wallis test with a post-hoc Dunn's test with correction for multiple comparisons. For anti-Xa, which was only analysed as trough levels on POD2 and 6 (to ensure steady-state of enoxaparin), the Mann-Whitney test was used. To address the potential problem of multiple testing, a modified Bonferroni correction was applied, and the level of statistical significance was set at < 0.01.

Paper IV

Paper IV was a substudy originating in paper III, but with focus on more experimental analyses of vitamin K-dependent proteins (VKDPs) with potential effects on coagulation as well as other physiological processes. The study population consisted of the same 39 patients as in paper III, wherefore the same ethical approval, Clinical Trials registration, and informed consent applied. STROBE guidelines were followed as for the previous studies.

Blood sampling was performed simultaneously with sampling for paper III. Analyses included were PIVKA-II, Gas6, dephospho-uncarboxylated MGP (dp-uc-MGP), and sAxl. Blood for analyses of PIVKA-II, Gas6 and sAxl was centrifuged and plasma stored at -80°C and transported to the accredited Clinical Chemistry's Coagulation laboratory at SUS Malmö, Sweden, for analysis. Plasma for dp-uc-

MGP was prepared similarly and analysed at the Coagulation Profile Laboratory, Maastricht University, The Netherlands. Exact details regarding analysis methods are presented in the method sections of papers III and IV.

As the study was a substudy of paper III and exploratory in nature, no sample size calculation was made. Differences between preoperative values and POD1, 2 and 6 were analysed with the same Kruskal-Wallis test and Dunn's post hoc multiple comparisons test. The level of statistical significance was set at <0.05.

Results

"*A disease known is half cured.*"

Old proverb

Paper I

All 24 included patients completed the intervention period without adverse events attributable to the blocks; however, seven patients (four in the local anaesthetic (LA) group and three in the placebo group) had their catheters removed in less than six days from surgery. Of these, three had accidental catheter dislocation, three catheters were removed due to lack of need for analgesics, and the final patient was transferred to a high dependency unit because of atrial fibrillation, and the administration of the study substance was terminated. The primary outcome, postoperative extremity pain, was reduced in the group receiving local anaesthetics (LA) as shown by lower overall NRS pain scores POD1-6; median NRS 2 (IQR 0–3) compared to the placebo group, median 2 (IQR 1–4), p=0.008. Furthermore, the LA group had significantly fewer episodes of breakthrough pain, defined as NRS ≥ 4; 17% of observations compared to 33% of observations in the placebo group, p=0.009, during the same time period.

Opioid consumption, measured as intravenous oxycodone equivalents, was significantly lower during the first postoperative week in the LA group compared to patients receiving placebo; median 109 mg (IQR 74–134) versus 202 mg (IQR 135–241), p=0.01.

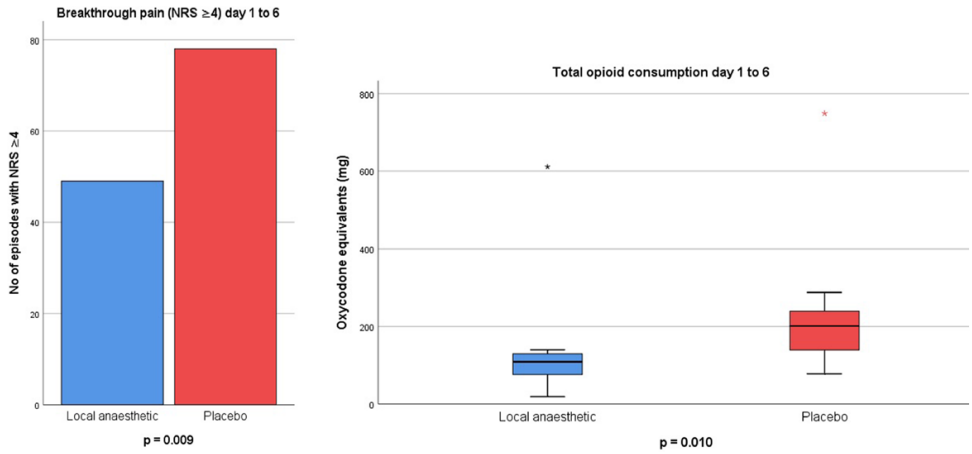

Figure 9. Left: Episodes of breakthrough pain (NRS ≥4) during the first postoperative week in the local anaesthetic (blue) and placebo (red) groups. Right: Total opioid consumption in the first postoperative week in the local anaesthetic (blue) and placebo (red) groups. Reprinted with permission.

Paper II

For paper II two main outcomes were chosen: flap compromise and systemic (serious medical) complications. Flap compromise occurred in 53 cases (14%) and flap failure in 25 cases (6%). Forty-eight patients (12%) experienced at least one systemic complication during their primary in-hospital stay. The median age at surgery was 66 years (IQR 56-71), and the ratio of male to female patients was 61% to 39%. Indication for surgery was mainly malignant tumour (95%), with the remaining cases comprising benign tumours, trauma or osteoradionecrosis.

Factors associated with flap compromise in univariate logistical regression analysis were use of any flap type other than the radial ($p=0.003$), longer duration of surgery ($p<0.001$), intraoperative blood loss ($p=0.017$), and red blood cell (RBC) transfusion within the first 48 h ($p<0.001$). In addition, lower preoperative alanine transferase (ALAT) was seen in patients with flap compromise ($p=0.04$). No association was shown between preoperative radiotherapy, tumour stage, smoking or alcohol consumption and flap-related complications.

For systemic complications age ($p=0.021$), lower preoperative albumin levels ($p=0.026$) and perioperative magnesium (Mg) substitution ($p=0.031$) showed significant association. Furthermore, all tested risk prediction instruments displayed association with systemic complications: ASA-PS ($p=0.002$), CCI ($p=0.005$), HN-CCI ($p=0.006$) and ACS-NSQIP ($p=0.006$). None of the included isolated comorbidities were associated with complications, neither systemic nor flap-related.

In the multivariable analyses we included variables with statistically significant association in univariate analyses and likely clinical relevance. Collinearity testing resulted in the omission of age in some models, and, despite lack of collinearity between risk prediction instruments, no model included more than one such instrument. For flap compromise, surgery time (p=0.005) and RBC transfusion (p=0.001) remained significant. For systemic complications, the associations with age and ACS-NSQIP score were eliminated, while preoperative albumin levels, perioperative Mg substitution (p-values for both varying depending on model), and the risk prediction instruments ASA-PS (p=0.012), CCI (p=0.021) and HN-CCI (p=0.024) showed continued significance.

TABLE 3 | Multivariable analyses of factors associated with flap compromise and systemic complications respectively.[a]

Independent variables	OR	95% CI of OR	*p-value*
Flap compromise[b]			
Surgery time (h)	1.192	1.054–1.347	**0.005**
Red blood cell transfusion <48 h	2.835	1.493–5.384	**0.001**
Systemic complications[c]			
ASA-PS	2.059	1.175–3.609	**0.012**
Albumin preop (g/L)	0.935	0.871–1.004	0.066
Mg substitution (mmol)	1.022	1.001–1.043	**0.036**
Systemic complications[d]			
CCI	1.285	1.038–1.590	**0.021**
Albumin preop (g/L)	0.928	0.863–0.997	**0.041**
Mg substitution (mmol)	1.019	0.999–1.040	0.064
Systemic complications[e]			
HN-CCI (≥ 1)	2.169	1.109–4.242	**0.024**
Albumin preop (g/L)	0.927	0.863–0.996	**0.038**
Mg substitution (mmol)	1.021	1.000–1.042	**0.047**
Systemic complications[f]			
NSQIP serious complications	1.069	0.993–1.151	0.074
Albumin preop (g/L)	0.933	0.868–1.003	0.062
Mg substitution (mmol)	1.021	1.001–1.042	**0.042**

[a]Only the final step of the backward Wald method is presented.
[b]Variables included: surgery time (h), red blood cell transfusion within 48 h, blood loss, previous radiotherapy, flap type.
[c]Variables included: ASA, age, preoperative albumin (g/L), Mg substitution (mmol).
[d]Variables included: CCI, preoperative albumin (g/L), Mg substitution (mmol).
[e]Variables included: HN-CCI, age, preoperative albumin (g/L), Mg substitution (mmol).
[f]Variables included: NSQIP serious complications, age, preoperative albumin (g/L), Mg substitution (mmol).

Table 1. Factors associated with flap compromise and systemic complications in multivariable analyses. Reprinted with permission.

Paper III

In this study of 39 patients, the median age was 66 years (range 21-81), with 21 (54%) male and 18 (46%) female patients. Flap compromise (according to the same definition as in paper II) occurred in seven (18%) of cases, but with no complete flap failure during primary hospitalisation. One patient experienced what was classified as a thrombotic flap complication, while three suffered from bleeding complications requiring medical or surgical intervention.

Routine coagulation tests showed signs of hypocoagulation, with a decrease in platelet count from baseline to POD1 ($p=0.005$) and POD2 ($p=0.004$) and increases in PT-INR from baseline to POD1 and POD2 (both $p<0.001$) and in APTT from baseline to POD2 ($p=0.001$). PT-INR, APTT and platelet count all returned to preoperative levels on POD6.

For ROTEM analyses no significant changes were seen in clotting time (CT), neither for intrinsic nor extrinsic rotational thromboelastometry (INTEM and EXTEM, respectively). All analyses, however, showed increasing maximum clotting firmness (MCF), for INTEM and EXTEM to POD6 ($p<0.001$), for FIBTEM to both POD2 and POD6 ($p<0.001$).

As opposed to the routine tests, extended analyses displayed a tendency towards hypercoagulation with decreased levels of protein C and free protein S from baseline to POD1 and 2 (all $p<0.001$), with return to preoperative levels on POD6. Plasmin-antiplasmin complex (PAP) similarly decreased from baseline to POD1 ($p=0.004$) but with an increase to supra-baseline, and above reference, values on POD6 ($p<0.001$).

Anti-Xa trough levels (sampling performed shortly before administration of enoxaparin) were unchanged between POD2 and 6, and no changes were seen between specific days for thrombin generation (TGA), neither in peak concentrations nor endogenous thrombin potential (ETP).

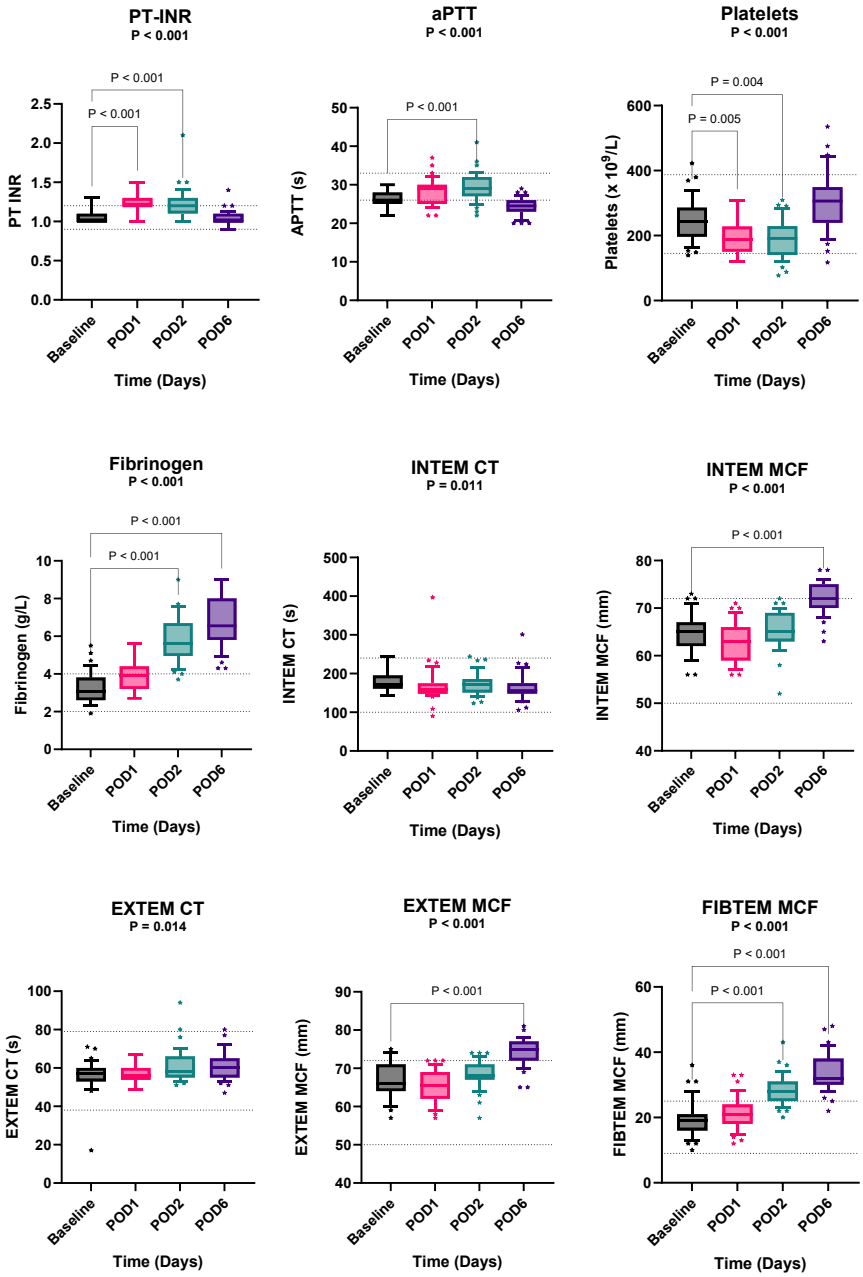

Figure 10. Box plots of routine haemostasis and ROTEM analyses. Whiskers include 10th to 90th percentiles, outliers marked with *. Overreaching p-values are presented beneath graph titles; statistically significant differences between specific days are illustrated by lines with p-values above. Dotted lines in figures indicate reference intervals for analyses as given by instrument manufacturers or accredited laboratories (if different for sexes, the widest range for both sexes is given).

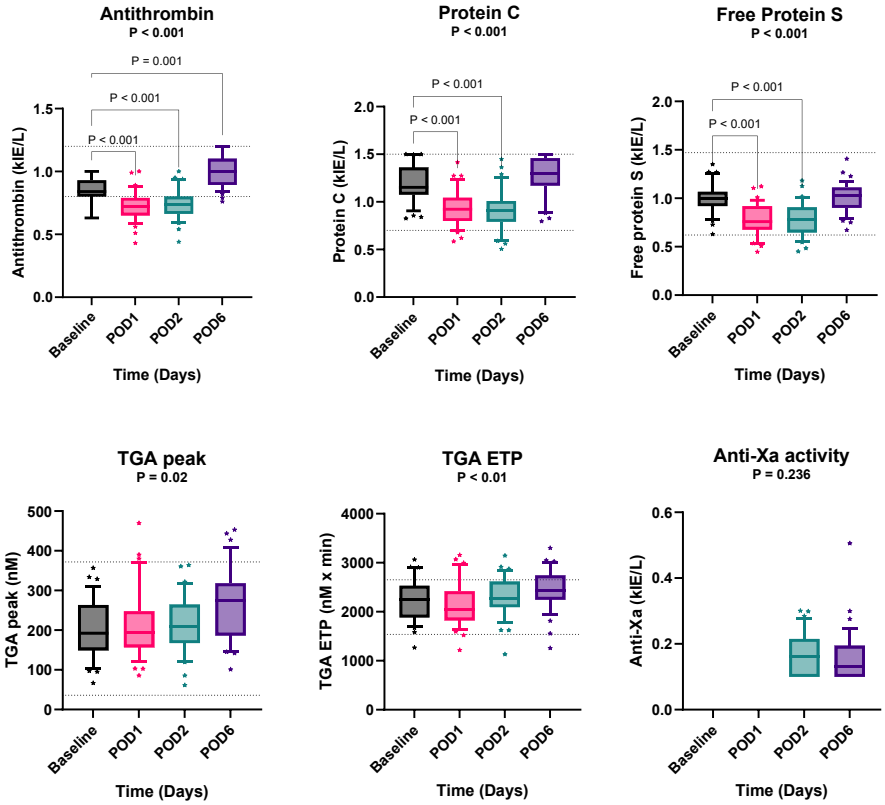

Figure 11. Box plots of extended analyses of haemostasis. Whiskers include 10th to 90th percentiles, outliers marked with *. Overreaching p-values are presented beneath graph titles; statistically significant differences between specific days are illustrated by lines with p-values above. Dotted lines in figures indicate reference intervals for analyses as given by instrument manufacturers or accredited laboratories (if different for sexes, the widest range for both sexes is given).

Paper IV

As this study was conducted parallelly with paper III, it included the same cohort of patients, with their baseline data, and the same time points for sampling.

Analyses of PIVKA-II showed a continuous increase during the study period with statistical significance between preoperative values and POD2 and 6 ($p<0.001$ for both days), while Gas6 showed a significant increase between baseline levels and POD1 ($p<0.001$), POD2 ($p<0.001$) and POD6 ($p=0.002$). No statistically significant changes were seen between specific days for dp-uc-MGP or sAxl.

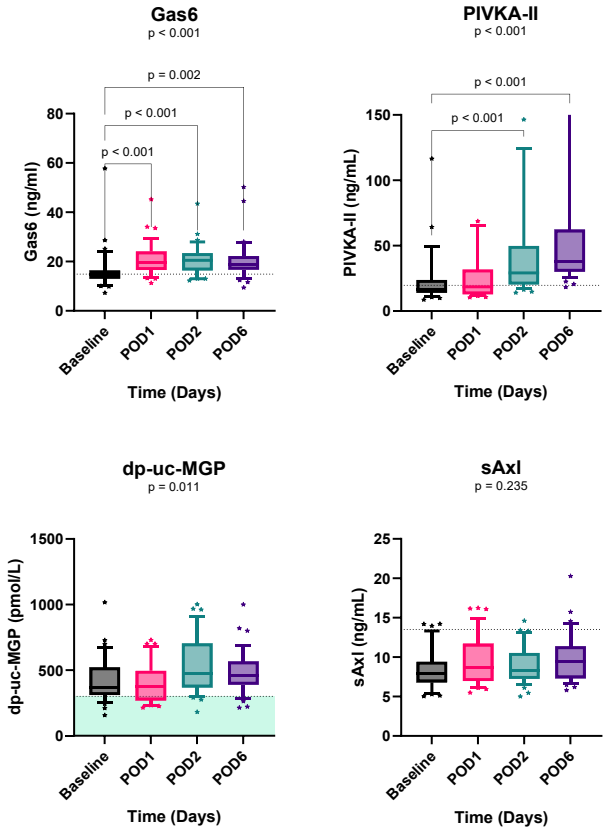

Figure 12. Box plots of analyses of vitamin K-dependent proteins (VKDPs). Whiskers include 10th to 90th percentiles, outliers marked with *. Overreaching p-values are presented beneath graph titles; statistically significant differences between specific days are illustrated by lines with p-values above. Horizontal dotted lines represent mean values, and light green shading for dp-uc-MGP represents the reference interval, as presented in the methods section.

Discussion

"*Problems worthy of attack prove their worth by hitting back.*"

Piet Hein

Perioperative management of patients undergoing major reconstructive head and neck surgery is multifaceted and challenging. From the first preoperative visit to discharge from the hospital postoperatively, any number of foreseeable or unforeseeable situations may arise. Still, sometimes even the frailest patients sail through the whole process, seemingly unaffected by its challenges, demonstrating that immense burdens can be overcome. While some aspects of this long treatment course are difficult to influence, several parameters can be affected, in both positive and negative directions, by actions taken by the medical team, in which the anaesthesiologist has a leading role. What we do matters.

Preoperative considerations

As mentioned in the introduction, the anaesthesiologist's work begins at the first preoperative consultation, where one of the most important tasks is risk assessment. Paper II aimed to answer one of the main questions of this thesis: how can we predict which patients will suffer from complications during the perioperative period, and can these predictions help us prevent complications? This question is important for several reasons. First, of course, being able to predict difficulties and potentially avoid them is of enormous value to the individual patient who can evade the suffering of added surgeries, medications, pain, and discomfort, and an extended hospital stay. Second, the same benefits apply to the health care system, for which vast resources can be saved for every serious complication avoided. Third, in cases where multiple or serious complications can be anticipated, reliable risk prediction can be used as a basis for discussions regarding treatment options with patients and families. While extensive reconstructive surgery may be the only curative option, suffering through a seemingly endless stretch of misery to be given an uncertain chance of cure might not be a price all patients are willing to pay. These potentially life-decisive discussions deserve to be well-founded.

With an ageing population and increasing incidence of HNC, more elderly, potentially frailer, patients with multiple comorbidities are likely to come into question for major reconstructive surgery in the coming years. While frailty is a challenge for all parts of the health care system, not least those involved in perioperative medicine, the results from paper II showed no association in multivariable analysis between chronological age or any isolated comorbidity and the outcomes studied. The lack of effect of older age is in line with several previous studies and is important since age (although rephrased to avoid formal discrimination) is often invoked as a reason for denying patients surgery. However, all evaluated risk prediction instruments, aside from ACS-NSQIP, were significantly correlated with systemic complications, indicating that the cumulative burden of comorbidities, as well as the frailty likely intrinsic to most anaesthesiologists' ASA-PS scoring, has a substantial effect on recovery from surgery.

The lack of association between ACS-NSQIP surgical risk calculator scores and complications is interesting. When introduced, ACS-NSQIP was presented as an instrument predicting individual risks for specific complications, a very appealing idea for anyone attempting to anticipate perioperative difficulties [60]. The algorithm is elaborate (although somewhat elusive for those not involved in its development), and the database currently contains data from over five million procedures [132]. But results have been mixed, with several studies showing poor risk discrimination for most complications [133], and a recent review of its predictive properties in head and neck surgery (including but not limited to reconstructive procedures) concluded that ACS-NSQIP underestimates almost all included complications except for mortality [62]. One possible explanation for ACS-NSQIP not being the success many of us had hoped for might be what should have been its strength: the complexity. With a long list of procedures, sometimes difficult to distinguish between, and an extensive form to fill out, the risk of poor in-data quality is not negligible. Vernooij and colleagues conducted an extensive evaluation of ten risk prediction models with respect to both risk discrimination and user-friendliness and found that ACS-NSQIP had among the highest burden for data collection [63], which is disadvantageous in a high-paced preoperative setting.

With the rapid development of artificial intelligence (AI) and machine learning (ML), a paradigm shift is likely to soon be seen for several aspects of anaesthesiology and intensive care [134]. A number of AI and ML risk prediction models already exist and have shown promising results, being able to incorporate a multitude of variables [63,135]. However, all models require some form of integration with digital medical records to be applicable in clinical practice. These interfaces are still largely lacking for many systems, and consolidation of different medical data systems also raises important integrity issues [136]. Furthermore, increasing the number of variables entered into a model, or the advanced calculations conducted, still will not (at least not entirely) solve the problem of poor data quality: any model

based on unreliable or incorrect data will still give an unreliable result. While the exploration of the AI universe will undoubtedly continue, we believe that the current evidence, including the conclusions from paper II, supports the use of basic models based on a limited number of variables [137], such as ASA-PS and HN-CCI. The results of any one risk prediction instrument must also – still – be interpreted by a human doctor and integrated into the clinical assessment, once again highlighting the importance of skilled medical practitioners in cooperation.

During the time passing from the first anaesthetic consultation to the day of surgery, there is an, albeit small for the HNC population, window of opportunity to improve all patient conditions possible. Such improvements, collectively referred to as prehabilitation, have gained increasing interest for many patient populations and procedures, but for the head and neck reconstructive surgery group the subject is still in the bud. While there is increasing evidence that HNC patients undergoing chemo-/radiotherapy benefit from pre- and peri-treatment interventions such as physical exercise and enhanced nutritional support, studies investigating patients undergoing surgery are still limited [138,139]. However, prehabilitation has shown significant positive effects for other extensive procedures [140], and physiologically it would be reasonable to assume that these benefits could be extrapolated to the head and neck reconstructive surgery population.

One of the parameters potentially amenable to optimisation in the short preoperative period is malnutrition. In paper IV we demonstrated that our cohort experienced vitamin K deficiency consistent with malnutrition, and in paper II an association was seen between lower albumin levels and postoperative systemic complications. This is in line with other studies of this patient group where albumin and similar indicators of malnutrition, such as sarcopenia, have been shown to correlate with a number of both medical and surgical complications [141]. In addition, ALAT, a potential marker of frailty and biological ageing [142], was in univariate analysis in paper II associated with flap compromise. Prospective interventional studies are unfortunately still rare, but in a study by Xu and colleagues head and neck free flap patients receiving perioperative albumin substitution suffered significantly fewer surgical complications [143]. This, and other modes of time-effective prehabilitation, would be of great interest for further research.

A significant inherent weakness in retrospective studies, such as paper II, is the risk of unreliable and low-quality data, especially for more qualitative parameters, such as socioeconomic factors and alcohol consumption. Several such factors have been shown to have important effects on postoperative complications and recovery [144,145], but reliable and consistent information is often difficult to obtain. The database created for paper II will hopefully contribute with high-quality data for some of these parameters for future studies, especially as it will be possible to prospectively add variables with proven predictive properties, such as a frailty scale [146], and a clearly defined assessment of physical performance status.

Perioperative management

When the day of surgery has arrived, the window of opportunity for pre-emptive measures is closing, but optimal intraoperative management is of just as great importance to ensure a continued successful course. How can we foresee haemostasis-related flap compromise and failure? Can we detect early intraoperative haemostatic changes prognosticating difficulties, and what actions are then to be taken? And, the pivotal question, the cry of frustration: what do we do in the middle of the night when the third anastomosis has been sutured but the blood to the flap still won't flow? While the limited settings of paper III could not possibly answer these questions fully, the deep desire to better understand the haemostatic aspects of flap complications was the spark that ignited paper III (and to some extent also paper IV).

Since the first free tissue transfers in the 1960s, patency of vessel anastomoses has been a central issue, as it is the cornerstone of a surviving free flap [147]. The potential reasons for insufficient blood flow and flap necrosis are many, with surgical techniques being a major topic for debate. Factors such as surgeon experience [148] and mechanical anastomotic coupling devices [149] have been implicated as causes of flap failure, but divergent study protocols and conflicting conclusions have resulted in a lack of compelling evidence for any specific technical factor as the root cause.

Although many issues can result in flap failure, thrombosis and bleeding are the major causes. With surgical techniques not providing clear solutions for these problems, haemostatic disturbances would be the other obvious field of interest. Unfortunately, despite numerous studies with varied research questions, definitive conclusions in this area are still just as rare. But in order to know, we need to test. This is true in managing haemostasis, as well as in science in general. However, just as the perfect study setting answering all questions is yet to be developed, the optimal tests for haemostatic monitoring in reconstructive surgery are not established. Basic tests such as PT-INR, APTT and platelet count are often used as preoperative screening tools, even though their predictive properties are poor: serious risks of bleeding or systemic thrombosis are better caught through thorough review of a patient's medical history [150]. The findings of paper III further support this conclusion, as none of the above-mentioned routine coagulation tests showed any preoperative deviations that would have prompted intervention in case of complications, according to current practice. The postoperative changes followed the expected course for patients subjected to major surgery: bleeding, with coagulation factor and platelet consumption, haemodilution and laboratory dilutional coagulopathy [89].

With routine coagulation tests not revolutionising treatment directions, other means of intra- and postoperative haemostatic monitoring are needed, and more global functional tests would be appealing. ROTEM is one such test, nowadays readily

available in real time in many larger centres. In paper III the ROTEM analyses rather indicated a hypercoagulable state in the early postoperative phase, further supported by the transient decreases in PAP and protein C and S. TGA, which has been of great interest as a global haemostatic test, remained unchanged perioperatively. As the haemostasis-related events in the cohort studied in paper III were few, causal relationships cannot be established, but the contradicting results from the different analyses – unfortunately – strengthen the view that the optimal monitoring methods for major reconstructive surgery are still uncertain.

Although monitoring may be important, so is action. Surgery and immobilisation are known risk factors of systemic VTE, with significantly further increased risk for cancer patients [87]. Hence, the use of perioperative thromboprophylaxis for extensive and/or malignant surgery is currently uncontroversial [151]. However, for head and neck reconstruction, as for many other procedures, no international consensus exists on the choice of drug(s), doses, or duration of treatment [92,93]. Besides the, for many procedures, well-established LMWH prophylaxis, a multitude of substitutes and additives have been tried. Current regimes worldwide include UFH in bolus doses or infusion, acetylsalicylic acid and dextran solutions, as well as different combinations of drugs [91]. However, several studies have shown increased risks of bleeding without reducing the frequency of flap thrombosis [152,153], emphasising that thromboprophylaxis is not harmless, and that its effects also need monitoring. In paper III, anti-Xa was mainly within the suggested reference ranges. This, in combination with lack of signs of impaired haemostasis in, for instance, TGA, indicates that the current thromboprophylaxis regime at SUS Lund seems to be safe for the general cohort.

With thromboprophylaxis regimes and coagulation test routines wildly varying between countries and centres, the current flap failure rate seems steady at around or just below 5%. Does this mean that it does not matter what we monitor or how we attempt to prevent haemostasis-related complications? Possibly. But my conviction is in fact the opposite. I believe that both haemostatic monitoring and thromboprophylaxis are essential but should be individualised and used with caution. Routine screening of all patients using tests with low predictive values is a waste of limited health care resources, and should be replaced, or at least accompanied, by a structured medical history evaluation [100,154], followed by directed testing of specific aspects of haemostatic physiology. Pharmacological thromboprophylaxis, while likely mandatory in some form during parts of the treatment course, should be continuously evaluated and adjusted according to changes in patient status. However, as we still lack the optimal test of global haemostasis, future research should be aimed at developing such easily available and effective tests. Furthermore, optimal haemostatic management also requires expansion of knowledge for both surgeons and anaesthesiologists, again aided by close multidisciplinary cooperation.

The major weakness of paper III is the failure to statistically demonstrate the stipulated change in ROTEM EXTEM MCF, a methodological limitation signalling potential underpowering of the study. However, as the study was descriptive in its nature, the results can hopefully contribute to a broadening of the basis of knowledge about haemostasis in head and neck free flap surgery, and to the design of future prospective studies.

As for the other studies included in this thesis, no exclusions of patients were made in paper III based on indication for surgery, comorbidities, ongoing medical treatment, or other factors. While many factors could potentially act as confounders or mediators in the complex perioperative course, we attempted not to introduce risks of type II errors by disqualifying certain patients from inclusion. However, this choice can be discussed as some factors (malignant versus benign surgical indications, previous venous thromboembolism, and treatment with certain drugs) could significantly affect haemostasis and thereby have unjustifiable effects on analysis results.

Another topic of interest, partly related to haemostasis, is blood transfusion. In paper II, a strong association was seen between perioperative RBC transfusion and flap compromise, even after adjusting for blood loss and other potential confounders. This is in line with several previous studies [155-157], some of which have even shown decreased overall survival for head and neck reconstructive surgery patients receiving perioperative RBC transfusions [158]. While the pathophysiologic causes of these associations, and optimal haemoglobin levels, are not fully elucidated, current evidence supports a restrictive transfusion policy.

Postoperative care and recovery

After the final dressing has been applied and the patient emerges from anaesthesia and is being transferred to the intensive care unit, the postoperative phase is entered. This period is perhaps the most varied in both length and potential hurdles arising, but this only emphasises the importance of excellent management to ensure optimal recovery. While haemostatic monitoring and vigilance of potential complications continue to be essential, pain management, patient comfort, and regaining impaired physical functions are added components.

In paper I, we demonstrated that a continuous popliteal block significantly reduces postoperative donor site pain and opioid consumption during the first postoperative week in head and neck reconstructive surgery patients undergoing fibular flap harvest. While long known in orthopaedic surgery, the evidence regarding the patient population in this thesis has been limited, and our study is one of the first to show prospective results. In a recent metanalysis, in which paper I was included, the authors concluded that although all studies had a limited number of participants,

preventing strong recommendations, blocks clearly contributed to lower opioid requirements for lower extremity flap patients [127]. This in itself is an important finding, knowing the many negative side effects of opioids [70,71,74]. It is also consistent with previous studies showing higher pain scores and increased risk of prolonged opioid use for patients reconstructed with bony flaps compared to soft tissue transfers [159].

A major weakness of paper I is that it failed to demonstrate the postulated significant change in the primary outcome, a two-point reduction in NRS ratings. However, in retrospect, this outcome could be said to be poorly defined, as the time interval for the change in pain perception was not specified. With a total observation time of one week, it is questionable how useful a two-point reduction of pain occurring at any point during such a long time period would be. In the analysis of the results, we therefore chose to put more emphasis on episodes of breakthrough pain, defined as NRS ≥ 4, during the observation period. While pain is a challenging phenomenon, NRS ≥ 4 is generally seen by both patients and health care professionals as an unacceptable level of pain that must be addressed and treated [160].

Some key aspects were not included in the outcome parameters of paper I. While pain was regularly evaluated, no assessments were made of other subjective values, such as patient satisfaction, which has been shown to be positively affected by nerve blocks in similar studies [161]. In addition, staff perception of the patients' recovery was not included. Although blinded, the nursing staff, numerous times during the study period, claimed to be able to tell between patients with active substance versus placebo based on the general ease of their recovery, and, when breaking the blinding after completion of the study, their assumptions turned out to be correct for a large majority of cases.

Other aspects of perioperative management

Performing perioperative medicine well doesn't only entail covering well-established aspects but also attempting to broaden our competence. Not long ago known vitamin K functions were limited to the coagulation system, but nowadays we recognise the involvement of vitamin K in a number of other processes. Several of these could be altered in patients with head and neck tumours, of which some could have valuable implications for the perioperative course. However, knowledge of the profile and effects of VKDPs in head and neck reconstructive surgery is extremely scarce, and reference values are virtually non-existent, especially as analysis methods are varied. Exploratory studies, such as paper IV, are therefore needed, and some interesting findings in the study can be highlighted for further investigation.

The most established VKDP in our study, PIVKA-II, showed a continuous increase during the first postoperative week, indicating subclinical vitamin K deficiency. Even though all patients in our study had individualised nutrition plans composed by the clinic dieticians, there are many potential obstacles to their implementation in the early postoperative course (for example non-functional nasogastric tubes and nausea). While over-nutrition has shown negative effects in critically ill patients, many of the patients in our study likely received less than even the low-calorie recommendations (less than 70% of normal intake or 6-8 kcal/kg/day) from large societies [162,163] during the first postoperative days. This underfeeding could potentially contribute to impaired wound healing and an increased number of postoperative infections [42]. With PIVKA-II being an early and sensitive marker of vitamin K deficiency, it could potentially be a useful addition to the arsenal when monitoring malnutrition, as well as haemostasis.

For dp-uc-MGP and sAxl no significant changes were seen over the study period in paper IV. Both these variables have longer reaction times (weeks or months), making them less suitable for studies of shorter time periods. But it is also worth noticing that a majority of patients were outside of the reference values (as they were set by the providers of analysis equipment) already on preoperative sampling. As cellular expression of dp-uc-MGP, Gas6 and sAxl is currently believed to reflect tumour progression and disease severity in several malignant conditions, a possible deviation of these markers in blood samples, in a study population containing mainly HNC patients, would be worth exploring in further studies.

We recognise that paper IV has several important limitations, with a major one being the exploratory design, limiting the possibility of drawing causal conclusions. However, as mentioned, the knowledge about VKDPs in this specific patient group is minimal. Descriptive studies are therefore needed to obtain basic information and establish reference values of these analyses, enabling interpretation and extrapolation. Again, as in the previous studies, all patients undergoing head and neck reconstructive surgery were included in paper IV, among whom a small number had a non-cancer indication for surgery (benign tumour, trauma, or osteoradionecrosis). With VKDPs, especially Gas6, which rose continuously throughout our study period, being involved in central processes of tumour biology [164], the fact that most study subjects had malignant tumours could potentially affect the analysis results. Further studies exploring physiological changes during the perioperative period, and comparing cancer and non-cancer patients in order to establish potentially different reference levels, would be of interest.

Conclusions

"*Do not quench the spirit. Do not treat prophecies with contempt but test them all; hold on to what is good, reject every kind of evil.*"

1 Thessalonians 5:19-22

Paper I

Continuous popliteal blocks are safe and significantly reduce postoperative pain and opioid consumption during the first postoperative week in patients undergoing fibular graft harvesting for head and neck reconstructive surgery.

Paper II

Surgery time and transfusion of red blood cells are factors strongly associated with flap compromise in patients undergoing major reconstructive head and neck surgery.

Preoperative albumin levels and the risk prediction instruments ASA-PS, CCI, and HN-CCI are independently associated with systemic complications in the same patient cohort.

This is the first study that, to our knowledge, demonstrates predictive properties of HN-CCI for this patient population.

Paper III

Routine coagulation tests (such as PT-INR, APPT and platelet count) show signs of impaired haemostasis during the first postoperative week in patients undergoing major reconstructive head and neck surgery.

Extended analyses of coagulation (including coagulation factor levels and thrombin generation), on the contrary, show a tendency towards enhanced haemostatic capacity in the same time frame.

Routine tests are insufficient to adequately monitor the complex haemostatic system in patients undergoing extensive surgery. Extended, preferably global and functional, tests need to be further evaluated and incorporated into perioperative management.

The current regime of perioperative thromboprophylaxis at SUS Lund seems to be safe for the patient cohort studied; however, individualised therapy and monitoring are topics of interest for future research.

Paper IV

Patients undergoing major reconstructive head and neck surgery show signs of vitamin K deficiency during the first postoperative week.

Further studies on the role of vitamin K-dependent proteins in HNC and perioperative settings are warranted.

Future aspects

"*Look and you will find it. What is unsought will go undetected*."

Sophocles

Staying curious, with the aspiration to expand your knowledge and improve the medical care you provide, is the hallmark of any accomplished physician. During the work on this thesis, I have come to realise to what a great extent this includes conducting and evaluating research. And the opportunities of conducting research involving patients undergoing reconstructive head and neck surgery are, unfortunately, ample. Despite advances made in many areas, enormous challenges remain, not least with the increasing incidence of HNC and an ageing population. As discussed in previous sections, prospective multi-centre randomised controlled trials are, in many cases, ideal, but they are difficult, sometimes even impossible to accomplish. A wise senior colleague often says (perhaps paraphrasing Voltaire) that "*The best must not become the enemy of the good*", and I believe this is worth keeping in mind for future studies. The perfect study might not always be feasible, but with our enthusiastic and dedicated multidisciplinary team, several areas of research are approachable, all with the possibility of making significant improvements in the treatment course of our patients.

In paper I, we demonstrated the benefits of local anaesthetics and peripheral nerve blocks in fibular graft harvesting, and popliteal blocks are now part of our treatment routine for these patients. This is, of course, not the only head and neck reconstructive procedure where regional anaesthesia can be useful, and evaluating a structured, multimodal, pain management plan, including local anaesthetics and other drugs such as ketamine and alpha2-agonists, would be very interesting. Related to this area is also the management of alcohol overconsumption and/or withdrawal, as well as sleep disturbances and anxiety, issues that all affect pain perception and recovery, but are often treated in a stepmotherly manner. Furthermore, the vasodilative effects of local anaesthetics are not yet well studied in head and neck reconstructive surgery, but could theoretically improve blood flow and oxygen delivery, and thereby potentially increase flap viability.

For paper II, digitalisation of an analogue register initiated by retired Associate Professor Peter Wahlberg, SUS Lund, was conducted, and this register was merged with data from several electronic systems (including electronic medical charts and surgical planning programs). This created a database containing extensive

information about all head and neck free flap surgery patients treated in Lund since the 1980s, which is continuously updated. As a broad perspective has been applied, a number of aspects are included apart from those with anaesthesiologic implications. The relatively large (and growing) cohort, together with a multitude of variables of interest for all surgical specialities involved, will enable further studies on numerous aspects of the entire treatment process. A parameter that is still missing in the database is a frailty index, even though some of these could be useful in predicting postoperative complications [146]. This would definitely be worth adding to the already included risk prediction instruments.

An emerging area in perioperative medicine, related to risk prediction and prevention, is prehabilitation. Although the time between diagnosis and surgery is often short for our patients, certain interventions might still be possible to improve nutrition and physical fitness, thereby potentially attenuating malnutrition and sarcopenia. Personally, I enjoyed the relative methodological simplicity of the randomised controlled trial in paper I, and to set up a similar study of, for instance, albumin substitution or preoperative carbohydrate loading would be very interesting. Similar evaluations of vitamin K substitution could also be of interest; however, they need to be preceded by studies establishing causal relationships between vitamin K deficiency and postoperative outcomes.

Although no definitive conclusions regarding optimal haemostatic monitoring for the prevention of flap complications could be drawn from paper III, the one patient experiencing flap thrombosis was also the only one in the cohort with a previous history of VTE. However anecdotal, it is in line with studies indicating increased risk of flap failure in patients with existing coagulopathies. Currently, no structured preoperative screening for thrombophilia is conducted at SUS Lund, and I believe that a study of a standardised screening protocol including, for instance, a questionnaire on previous VTE and genetic testing for APC resistance, would identify a significant number of patients for whom increased haemostatic monitoring and individualised thromboprophylaxis might be of value.

Finally, as multidisciplinary teamwork has been at the heart of this thesis, it would be my personal desire to extend the cooperation with my surgical colleagues even further. As mentioned, published studies on VKDPs in HNC patients are currently limited to tumour tissue expression, where they, however, seem to be increasingly convincing as predictors for disease severity and prognosis. It would be interesting to expand the collaboration with the head and neck surgeons to study potential correlations between VKDPs in tumour cells and blood, possibly being able to introduce blood levels of Gas6 or sAxl as prognostic markers for head and neck cancer.

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"*If I've seen further, it is by standing on the shoulders of giants.*"

Sir Isac Newton

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