PREVENTION OF POSTOPERATIVE PAIN

– A series of randomized clinical trials -

Thesis for the degree Ph.D.

Cand. med.

Ulrich Johannes Spreng

Department of Anaesthesiology
and Intensive Care

Bærum Hospital

Vestre Viken HF

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Ulrich Johannes Spreng

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CONTENTS

1. ACKNOWLEDGEMENTS

This thesis is based upon clinical trials that were conducted at my former workplace, the Bærum Hospital. I would like to express gratitude to all the patients who willingly participated in the trials.

I am grateful to my main supervisor, dr. med. Vegard Dahl, for sharing his knowledge, methodological and analysing skills, and fantastic optimism and humour with me. Vegard's ideas initiated the work leading to this thesis. I am proud to be his first candidate for the Ph.D.

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Finally, I would like to express my gratitude to Knut Magne Kolstadbråten for his understanding and patience and reminding me what life is really about.

2. LIST OF PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I Spreng UJ, Dahl V, Raeder J. Effects of perioperative S (+) ketamine infusion added to multimodal analgesia in patients undergoing ambulatory haemorrhoidectomy. Scandinavian Journal of Pain 2010 (1): 100-5.

II Spreng UJ, Dahl V, Raeder J. Effect of a single dose pregabalin on preoperative anxiety and postoperative pain in patients undergoing discectomy. Acta Anaesthesiol Scand 2011; 55:571-576.

III Spreng UJ, Dahl V, Hjall A, Fagerland MW, Ræder J. High-volume local infiltration analgesia combined with intravenous or local ketorolac + morphine compared with epidural analgesia after total knee arthroplasty. Br J Anaesth 2010; 105(5): 675-82.

3. ABBREVIATIONS

ASA:	American Society of Anesthesiologists
ATP:	Adenosine Triphosphate
AUC:	Areal Under the Curve
BIS:	Bispectral Index
C:	Cervical
CB:	Cannabinoid
CGRP:	Calcitonin-Gene-Related Peptide
CI:	Confidence Interval
CNS:	Central Nervous System
COX:	Cyclooxygenase
DNIC:	Diffuse Noxious Inhibitory Control
DRG:	Dorsal Root Ganglion
EDA:	Epidural Analgesia
FDA:	Food and Drug Administration
GABA:	Gamma Amino Butyric Acid
IASP:	International Association for the Study of Pain
L:	Lumbar
LA:	Local Anaesthetic
LIA:	Local Infiltration Analgesia
LIAiv:	Local Infiltration Analgesia with IV injections
NGF:	Nerve Groth Factor
NMDA:	N-Methyl-D-Aspartate
NNT:	Number Needed to Treat

NOP: Nociceptin Orphanin FQ Peptide Receptor

NRS: Numeric Rating Scale

NSAID: Non-Steroidal Anti-Inflammatory Drug

OIH: Opioid Induced Hyperalgesia

PACU: Post-Anaesthetic Care Unit

PCA: Patient Controlled Analgesia

PCEA: Patient Controlled Epidural Analgesia

PCP: Phencyclidine

PONV: Postoperative Nausea and Vomiting

RCT: Randomized Controlled Trial

S: Sacral

T: Thoracic

TENS: Transcutaneous Electrical Nerve Stimulation

THA: Total Hip Arthroplasty

TIVA: Total Intravenous Anaesthesia

TKA: Total Knee Arthroplasty

TRPV1: Transient Receptor Potential Vanilloid 1

VAS: Visual Analogue Scale

VRS: Verbal Rating Scale

4. SYNOPIS

Surgical procedures are associated with tissue injury and the majority of operated patients will experience some degree of pain after surgery. Many patients will suffer from moderate or even severe pain after the operation. Research has shown that poorly managed pain treatment may have both acute and chronic negative effects. Recovery after surgery may be prolonged by postoperative pain and complications may occur more frequently.

This thesis contains three studies, which were conducted during 2006 and 2009 at the Bærum Hospital, which is a tertiary teaching hospital near Oslo in Norway. All studies address research questions of improved postoperative pain control from a clinical point of view and were designed in a randomized controlled manner with a double blind design when possible.

The first study showed that the analgesic drug S (+) ketamine, given during haemorrhoidectomy, had no beneficial effect regarding postoperative pain, when used on top of a multimodal pain regimen.

The second study demonstrated that a single dose of the drug pregabalin, given one hour before surgery of the back, could reduce both preoperative anxiety, but also postoperative pain and the consumption of morphine after surgery.

The last study evaluated the effect of a new analgesic concept, known as local infiltration analgesia (LIA), and was compared with epidural analgesia in patients undergoing total knee replacement. LIA resulted in reduced opioid consumption, faster mobilisation and earlier readiness for hospital discharge. The study also demonstrated that the analgesic drugs ketorolac and morphine were more efficient when given locally than systemically.

The study results have been implemented into everyday clinical practice at the Bærum Hospital and may improve patient treatment and patient satisfaction.

5. SYNOPIS (Norwegian)

Operasjoner er forbundet med vevsskade og nesten alle pasienter som opereres vil oppleve en viss grad av smerte etterpå. Mange pasienter lider av moderate til sterke smerter etter en operasjon. Forskningen har vist at smerteomfang og utilstrekkelig smertelindring i forbindelse med operasjoner kan ha negative effekter både på kort og lang sikt. Det kan også ta lengre tid til å bli frisk.

Denne avhandlingen omfatter tre studier som ble gjennomført i årene 2006 til 2009 ved Bærum Sykehus, et lokalsykehus i nærheten av Oslo. Alle studiene er basert på klinisk forskning og har fokus på forbedret smertelindring etter operasjoner. Studiene har vært randomiserte og kontrollerte, med dobbel blinding der det var mulig.

Den første studien viste at pasienter som ble behandlet med det smertestillende medikamentet S (+) ketamin under operasjonen ikke hadde mindre vondt etter en hemorroide operasjon.

Den andre studien demonstrerte at en tablett pregabalin, gitt en time før en ryggoperasjon, ikke bare reduserte preoperativ angst, men også smerter og bruk av morfin etter operasjonen.

Den siste studien undersøkte effekten av et nytt smertekonsept som heter lokal infiltrasjonsanalgesi (LIA). LIA ble sammenlignet med epiduralanalgesi hos pasienter som fikk operert inn total kneprotese. Vi viste at LIA medførte mindre opioidforbruk, raskere mobilisering og at pasientene ble tidligere utskrivningsklare fra sykehuset. Studien demonstrerte i tillegg at de to smertestillende medikamentene ketorolak og morfin virker bedre når man gir de lokalt i kneet enn når man gir de intravenøst (systemisk).

Resultatene fra disse studiene har blitt innført i den daglige kliniske praksisen ved Bærum Sykehus og forhåpentligvis fører det til bedre pasientbehandling.

6. INTRODUCTION

The intensity of postoperative pain, the consumption of analgesics, the functional outcome and the incidence of adverse effects for some new analgesic treatment modalities after standard surgical interventions are the topics of this thesis.

Surgery is always associated with tissue injury and almost all patients will experience some degree of postoperative pain after surgical interventions, in spite of conventional pain treatment. This is the reason for my research interest in this topic.

To my knowledge, no data have been published regarding the incidence of postoperative pain or the efficacy of postoperative pain treatment in Norway. However, recent data suggest that at least 30-40% of all surgical patients do experience moderate or severe postoperative pain[1]. Further, there are studies in Norwegian cancer patients showing that many patients are suffering from moderate to severe pain without getting adequate pain relief[2,3]. International investigations on postoperative pain epidemiology confirm this. Fletcher et al. conducted a survey on postoperative pain management in France and found that nearly 90 percent of all patients reported postoperative pain after surgery. More than one quarter of the patients suffered from severe postoperative pain on movement and about four percent reported severe postoperative pain at rest[4]. Sommer et al. showed in a prevalence study of postoperative pain in the Netherlands that more than 40 percent of all patients suffered from moderate or severe pain at rest on the day of surgery[5]. Based on these studies, as well as on own clinical experience, one may assume that a significant proportion of

patients that undergo surgery in Norway still experience moderate to severe postoperative pain.

The ultimate vision is to improve postoperative pain handling to the point that pain after surgery can be prevented and surgery becomes 'pain free'.

The three studies in this thesis were conducted during 2006 and 2009 at the Bærum Hospital, which is a tertiary teaching hospital near Oslo in Norway. All research studies were designed in a randomized controlled manner with a double blind design when possible.

All studies address research questions from a clinical point of view. As a consequence the study results may hopefully be implemented into everyday clinical practice and improve patient treatment and patient satisfaction.

The layout of the present synopsis is made as suggested by a guideline for theses in Norway[6].

6.1 The pathophysiology of pain

The International Association for the Study of Pain (IASP) defines pain as:

"*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*"[7].

A surgical procedure causes nerve stimulation, tissue injury and damage of small nerve fibres. As a consequence histamine and inflammatory mediators are released. These inflammatory mediators include peptides (e.g., bradykinin), neurotransmitters (e.g., serotonin and ATP), lipids (e.g., prostaglandins), and neurotrophins (e.g., nerve groth factor)[8,9]. This "inflammatory soup" interacts with receptors or ion channels on sensory nerve endings (peripheral nociceptors) (Figure 1)[8,10]. Nociceptors may release peptides and neurotransmitters (e.g., substance P, calcitonin-gene-related peptide (CGRP) and ATP) locally when they are activated by noxious stimuli. This process is called neurogenic inflammation and induces vasodilatation and plasma extravasation (Figure 1)[8].

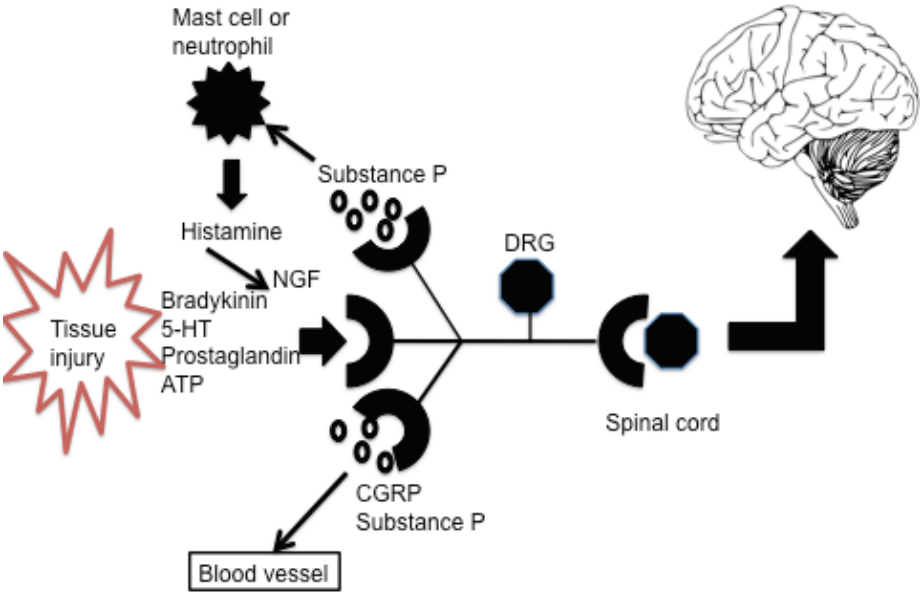

Figure 1: The 'inflammatory soup':

Peptides (bradykinin), lipids (prostaglandins), neurotransmitters (serotonin (5-HT) and ATP) and neurotrophins (NGF) are activated by tissue injury and lower the threshold (i.e., sensitization) or excite the terminals of the nociceptor by interacting with cell-surface receptors. Nociceptor activation transmits afferent messages to the dorsal horn of the spinal cord and further to the brain. Moreover the process of neurogenic inflammation may be initiated.

Release of neurotransmitters, e.g., substance P and calcitonin gene related peptide (CGRP), form peripheral nerve terminals may induce vasodilatation, extravasation of plasma as well as activation of non-neuronal cells (e.g., mast cells and neutrophils). DRG = Dorsal Root Ganglion.

Modified from Julius D. and Basbaum AL. Nature. 2001;413:203-210 (with permission)[8].

The activation of peripheral nociceptors by noxious stimuli is termed transduction. Further delivery of noxious stimuli as an action potential from peripheral somatic and visceral sites to the dorsal horn of the spinal cord via Aδ and C nerve fibres is called conduction, whereas the synaptic transfer of noxious impulses to secondary-order cells in the dorsal horn is termed transmission (Figure 2)[9,10]. Transmission of nociceptive information undergoes complex modulation in the spinal cord.

Pain-suppressive mechanisms take place locally within the dorsal horn and are mediated from higher levels of the brainstem and midbrain. Endogenous analgesic compounds, including enkephalin, norepinephrine, serotonin and gamma amino butyric acid (GABA), are released from spinal interneurons and terminal endings of inhibitory axons from supraspinal sites. Spinal modulation is mediated by the inhibitory actions of these endogenous analgesics[9,10].

Descending pathways in endogenous pain modulation may play an important role in the inhibition or promotion of noxious information. The term diffuse noxious inhibitory control (DNIC) describes the phenomenon that spinal neurons may be inhibited, often by spatially distant nociceptive stimulation[11,12].

Although some impulses pass to the ventral and ventrolateral horns and initiate segmental (spinal) reflex responses, it is assumed that most impulses are propagated to higher neuronal centres. This transmission is mediated via the spinothalamic and spinoreticular tracts and induces suprasegmental and cortical responses. This will finally lead to the perception of pain[9].

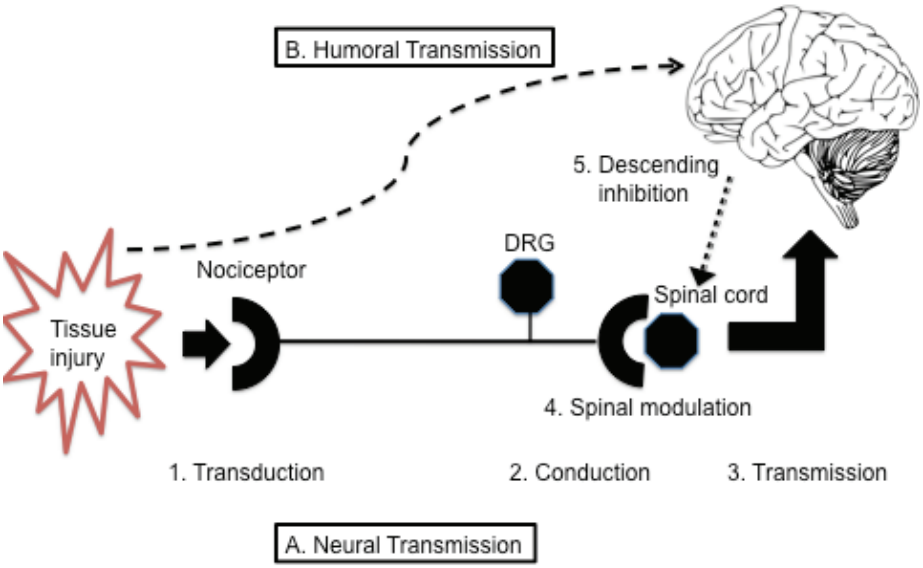

Figure 2: Overview over pain perception

A. Neural Transmission: Tissue trauma causes the release of noxious mediators, which activate the terminals of the nociceptor (1. Transduction). Noxious impulses are delivered to the dorsal horn of the spinal cord (2. Conduction) and via synaptic transfer to the central nervous system (3. Transmission). Spinal interneurons facilitate this noxious transmission (4. Modulation). CNS structures suppress pain transmission (5. Descending inhibition).

B. Humoral transmission: Tissue injury results in humoral transmission of noxious mediators to the CNS.

DRG = Dorsal Root Ganglion

Repeated or prolonged release of inflammatory mediators in the periphery may sensitize functional nociceptors. This sensitization is characterized by decreased activation threshold, increased discharge rate, and increased basal discharge. Furthermore, continuous nociceptive activity may activate dormant nociceptors and subsequently shift the dorsal horn to sensitised modes[9,13,14]. The phenomenon of neurohumeral alterations at the site of injury is called peripheral sensitization and may be responsible for primary hyperalgesia[10,15]. Hyperalgesia is defined as "*an altered state of sensibility in which the intensity of discomfort associated with repetitive noxious stimulation is markedly increased*"[10]. Intensive noxious stimulus from the periphery may also result in exaggerated dorsal horn responses to Aβ-fibre input[14]. This process is called central sensitization and will cause secondary hyperalgesia, which refers to an alteration in noxious sensitivity in nontraumatized regions[10,15].

6.2 Postoperative pain

Most surgical procedures are associated with tissue damage and the majority of operated patients will experience some degree of postoperative pain. After major surgery (e.g., hysterectomy), pain at rest is usually moderate during the initial two to three postoperative days and, in general, pain at rest reliefs within one week after the surgical procedure. In contrast to this, pain during activity (e.g., walking or coughing) is severe in many patients during the first 72 hours after surgery and pain intensity during activity will often remain moderate to severe for days and even longer[16,17].

Poorly managed postoperative pain may have both acute and chronic negative effects and may influence morbidity and mortality[18-20].

Transmission of painful stimuli from the periphery to the CNS causes neuroendocrine stress responses, which are characterized by an increased secretion of catabolic hormones including cortisol, catecholamines, adrenocorticotropic hormone, antidiuretic hormone, glucagon, aldosterone, renin and angiotensin II. Furthermore, anabolic mediators such as insulin and testosterone are inhibited[9,10].

Postoperative pain may activate the sympathetic nerve system. This sympathoadrenal stress response may increase myocardial oxygen consumption and decrease myocardial oxygen supply due to coronary vasoconstriction. In addition gastrointestinal activity may be decreased[19].

Acute postoperative pain may be followed by persistent, chronic postsurgical pain in 10 – 50 % of individuals after common surgical procedures, with 2-10 % of patients experiencing severe chronic postsurgical pain (Table 1)[21]. Chronic

post-surgical pain is defined as painful discomfort lasting for more than 2-6 months after surgery, corresponding to pain persisting beyond the normal process of complete wound healing[21,22]. Postsurgical chronic pain may be either a result of ongoing inflammation or, probably frequently, an expression of neuropathic pain, which may be a result from peripheral nerve injury during surgery[21]. The risk of developing chronic pain may be associated with the intensity of acute postoperative pain[22-24]. Buvanendran et al. have recently shown that the administration of pregabalin, an antihyperalgesic drug, may reduce both epidural drug consumption after total knee arthroplasty, but also the incidence of neuropathic pain at three and six month[25]. Furthermore, it has been shown that preoperatively initiated epidural analgesia is associated with a lower incidence of chronic post-thoracotomy pain[26].

The intensity of postoperative pain may, to a certain degree, be predicted prior to surgery[27-29] and various risk factors seem to influence the development of postoperative pain, e.g., age, gender, race, genetic polymorphism, as well as the intensity of preoperative pain and psycho-social aspects including anxiety and need for informaion[30-35].

Table 1: Estimated incidence of chronic postoperative pain and disability after selected surgical procedures

Type of surgery	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	US surgical volumes*
Amputation	30-50 %	5-10 %	159000 (lower limb only)
Breast surgery (lumpectomy and mastectomy)	20-30 %	5-10 %	479000
Thoracotomy	30-40 %	10 %	unknown
Inguinal hernia repair	10 %	2-4 %	609000
Coronary artery bypass surgery	30-50 %	5-10 %	598000
Caesarean section	10 %	4 %	220000

*National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

Modified form Kehlet H. et al. Lancet. 2006;367:1618-25 (with permission).

6.3 Principles of postoperative pain treatment

There are many options available for treating pain after surgery, including systemic analgesia (i.e., opioid and non-opioid drugs), regional analgesic techniques (i.e., neuraxial and peripheral), local anaesthetic wound infiltration and a combination of these. It is important to assess the risks and benefits of each treatment modality. The goal is an optimized postoperative analgesic regimen for each individual patient. Furthermore, patients' preferences have to be considered.

Beside pharmacological interventions, non-pharmacological approaches (e.g., acupuncture, transcutaneous electrical nerve stimulation and psychological interventions) may be part of postoperative pain management (Figure 3).

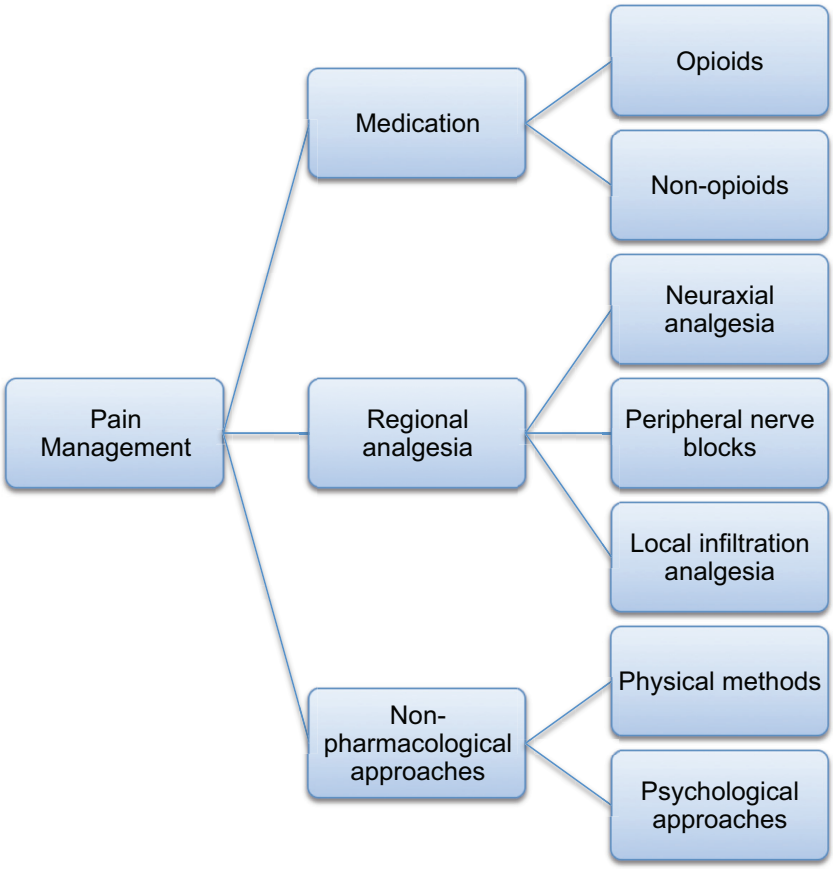

Figure 3: The different options for postoperative pain management

6.3.1 Systemic analgesia

Analgesic drugs may be divided into opioid and non-opioid drugs. The opioid drug class includes substances which bind to specific opioid receptors located throughout the central nervous system and other tissues[36,37]. The non-opioid drugs can be subclassified into specific and non-specific analgesics[38]. The specific drugs include paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) which act as cyclooxygenase inhibitors (two isoenzymes COX-1 and COX-2). The non-specific drug group consists of drugs with analgesic properties that are commonly used for other purposes, e.g., treatment of depression or epilepsy.

6.3.1.1 Opioids

Traditionally opioid analgesics are one of the cornerstones in the treatment of moderate or strong postoperative pain. Opioids can be classified as naturally occurring, e.g., morphine, or as synthetic substances, e.g., fentanyl, pentazocine and methadone[9]. The opioids bind to several types of opioid receptors in the body, all belonging to a family of G-protein-coupled receptors[39]. Three major types of opioid receptor have been identified: μ (mu), κ (kappa) and δ (delta) [40,41]. In addition a further opioid-like receptor has been identified, which was first named ORL1-receptor[42] and later termed nociceptin orphanin FQ peptide receptor (NOP)[43].

As a general rule, most opioids exert their analgesic effects through μ-receptor binding in the central nervous system. However, opioids may also bind to opioid receptors in the periphery, when they are present [37,44]. Their binding to the

different opioid receptors causes the different opioid drug effects. Morphine acts as an μ-agonist, whereas naloxone and naltrexone act as μ-, κ- and δ-opioid receptor antagonists. Pentazocine stimulates the κ-receptor. Buprenorphine is a partial μ-agonist (mixed agonist-antagonist)[9]. In general, clinical available pure μ-agonist opioids have a linear dose-response curve without ceiling of effect. They are therefore well suited for the management of postoperative pain, because opioids can be titrated intravenously until sufficient pain relief is obtained. The analgesic efficacy of opioids is typically limited by the occurrence of opioid-related side effects such as postoperative nausea and vomiting (PONV), constipation, sedation and respiratory depression[9]. One of the most common additional side effects of intrathecal and epidural administration of opioids is pruritus[45], whereas urinary retention may also occur.

Opioids are most commonly administered orally or intravenously. However, they may also be administered by the subcutaneous, transcutanous, intramuscular and transmucosal route[9,46]. In addition, opioids may be administered at specific anatomical sites e.g. neuraxial or intraarticular[37,44,47-49].

6.3.1.2 Non-opioids

6.3.1.2.1 Paracetamol (acetaminophen)

Paracetamol is a well-established analgesic drug for the postoperative period and is associated with few adverse effects in routine dosing and practice[50]. The drug can be administered by the oral, the intravenous and the rectal route[51,52]. Paracetamol crosses the blood-brain barrier rapidly and is concentrated in the cerebrospinal fluid[53]. The onset of clinical action after IV infusion has been shown after 5-10 minutes, with a peak analgesic effect at about 1-2 hours[54].

In clinical practice, paracetamol is often the baseline drug of multimodal postoperative pain management (see later) as there is good evidence for its analgesic efficiency[50,55,56]. Although the analgesic potency is limited, studies have shown that paracetamol may reduce postoperative morphine consumption[57]. The mechanism of paracetamol analgesia is not completely understood, but it seems to act by inhibition of the prostaglandin synthesis in the central nervous system (figure 4)[58]. Therefore, paracetamol is claimed to be part of the non-steroidal anti-inflammatory drug class by some authors,[9]. Paracetamol seems to have effects both via peripheral and central mechanisms[59]. Paracetamol, given as a single dose of 1000 mg, has a number needed to treat (NNT) of 3.8 (CI 3.4 – 4.4) for at least 50 % pain relief in patients with moderate to severe pain[60]. The NNT is used to assess the effectiveness of a health-care intervention versus placebo, and the lower the NNT, the more effective is the treatment[61].

In clinical practice paracetamol may be used as premedication, e.g., 1000 – 2000 mg paracetamol (according to bodyweight), orally about 1 hour prior to

surgery[10,62]. Intravenous paracetamol is well-suited for the perioperative period, e.g., 1000 mg[63]. In the postoperative period the medication with paracetamol is continued, e.g., 1000 mg every 6 hours[64-66]. In paediatric patients a preoperative dose of 20 - 40 mg/kg may be followed by 20 mg/kg four times a day postoperatively[67]. The combination of paracetamol with the opioid codeine has shown to reduce moderate to severe postoperative pain[68]. These two drugs have additive analgesic effect and reduce the NNT to 2.2 (CI 1.7 – 2.9)[60].

6.3.1.2.2 Nonsteroidal anti-inflammatory agents

The arachidonic acid cascade system (figure 4) plays a key regulatory role in cell physiology. Oxidation of arachidonic acid by the cyclooxygenase (COX) mediated pathway results in several prostaglandins and thromboxanes, many which influence the perception of pain[69]. Prostaglandins play an important role as mediators in peripheral sensitization and hyperalgesia. Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their analgesic effect through inhibition of cyclooxygenase and synthesis of prostaglandins[9].

At least two isoforms of the COX enzyme have been discovered: COX-1 and COX-2. COX-1 is expressed constitutively in many cell types and contributes to the natural homeostasis, whereas COX-2 is mostly induced at the site of inflammation, in the periphery and centrally[70]. COX-1 mediated prostaglandins facilitate in platelet aggregation, haemostasis and gastric mucosal protection[71,72]. COX-2 is involved in pain, inflammation, and fever[73,74]. A COX-2 selective inhibitor would therefore, theoretically, reduce pain with little side effects. As a consequence selective COX-2 inhibitors have been developed[75]. However, the COX-2 isoenzyme is constitutive in some tissue such as kidney and lung and has a role in the complex mechanisms of cardiovascular disease. Thus, the possible benefit of COX-2 specificity is more limited than initially thought. Still, COX-2 inhibitors are associated with no bleeding tendency as well as less gastrictric mucosa side-effects compared to traditional, non-selective NSAIDs[76-78]. The analgesic efficacy of selective COX-2 inhibitors and non-selective NSAIDs seems to be equivalent[79-83].

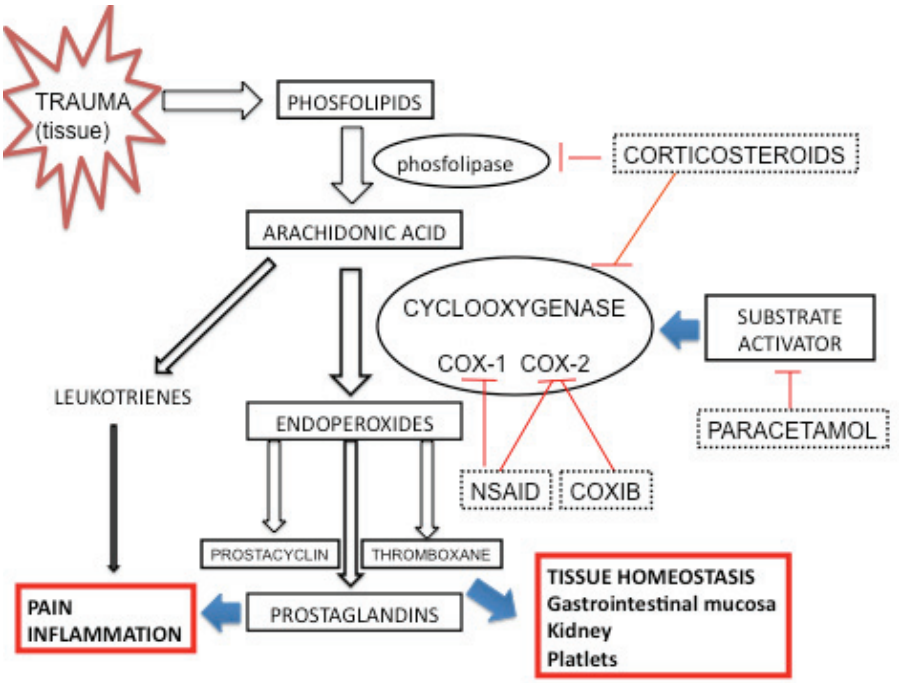

Figure 4: Surgical trauma leads to initiation of a biochemical cascade:

Cell membrane phospholipids are converted to arachidonic acid and oxygenation of arachidonic acid via the cyclooxygenase (COX) pathway generates a series of prostaglandins, thromboxanes and prostacyclines. Furthermore, arachidonic acid is converted to leucotrienes by lipooxygenase. NSAIDs and COX-2 inhibitors are thought to reduce pain by suppressing COX-mediated prostaglandin E_2. Corticosteroids suppress the action of phospholipase A_2 and paracetamol suppresses substrate activation of COX. Modified from Dahl V. Doctoral thesis 2000 (with permission)[69].

NSAIDs provide effective analgesia for mild to moderate pain when used as a sole agent[84]. Moreover, NSAIDs are considered to be a useful adjunct to opioids in the treatment of moderate to severe pain[85,86]. Several studies have demonstrated that NSAIDs may contribute to a reduction of opioid consumption after surgery[87,88]. However, it is debated if NSAIDs consistently reduce opioid-related adverse effects in postoperative pain management[88,89].

NSAIDs may be administered orally or parenterally and are especially useful as components of a multimodal analgesic regimen[9].

The perioperative use of NSAIDs may also be associated with other side effects, including negative effects on osteogenesis and bone healing. NSAIDs are contraindicated in patients with known renal failure and should be used with caution in hypovolemic patients. However, a recent Cochrane review revealed that NSAIDs were not associated with a clinically relevant reduction in renal function in patients with normal preoperative function[90]. Regarding bone healing, animal studies have demonstrated that NSAIDs may inhibit the healing process of fractures in a special clinical.[91-94]. A recently published study showed that short-term use of moderate doses of ketorolac (< 120 mg/d) had no significant effects on the ultimate fusion rates in patients undergoing spinal fusion procedures[95], whereas high-dose ketorolac (> 120 mg/d) increased the risk of non-union in this patient population[96].

The long-term use of COX-2 inhibitors has been associated with increased cardiovascular toxicity and as a consequence rofecoxib was withdrawn from the market in the year 2004. However, the cardiovascular risks of the different COX-2 inhibitors are variable and influenced by several factors such as specific

medication, dosage, and patient characteristics[97,98]. Also, often there is no clearcut and strict distinction between traditional NSAIDs and COX-2 inhibitors, as many classical NSAIDs also have a significant degree of COX- 2inhibition.

Interestingly, the traditional NSAID diclofenac may be associated with a higher cardiovascular risk than the modern COX-2 inhibitor celecoxib, whereas the cardiovascular risk for other traditional NSAIDs, like naproxen and piroxicam, may not be increased[98]. This may be due to the different COX-1/COX-2 ratio of these drugs[99].

It is important to notice that bronchospasm may be induced by traditional NSAIDs (including aspirin), and there is a risk for cross-sensitivity with paracetamol in aspirin-sensitive asthmatic patients[100]. The use of COX-2 inhibitors in asthma patients seems to be associated with less risk of bronchospasm[101,102].

Finally, it has to be mentioned that a part of the evidence concerning COX-2 inhibitors was based on the publications of Scott Reuben[103,104]. In the year 2009 more than 20 publications of this author were retracted due to research falsification and fabrication of data[105-107]. Therefore, further studies are needed to strengthen the evidence for the analgesic efficacy and safety of selective COX-2 inhibitors compared with non-selective NSAIDs.

6.3.1.2.3 Ketamine

In the early sixties a phencyclidine (PCP) derivate was synthesized named 2 (O-chlorophenyl)-2-methylamino-cyclohexanone or CI-581, "*a powerful analgesic and anaesthetic with an unusual spectrum of pharmacologic effectiveness*"[108]. This substance was subsequently known as ketamine, a racemic mixture of S (+) – and R (-) ketamine. The optical stereoisomer S (+) – ketamine has four times the affinity for the N-methyl-D-aspartate (NMDA) receptor than R (-) – ketamine and is clinically twice as analgesic potent as the racemic[109,110].

Ketamine interacts with several receptors and ion channels but is mainly an uncompetitive NMDA receptor antagonist[111,112]. NMDA receptor block prevents acute pain, and NMDA receptor mediated plasticity seems to play an important role in the development of central sensitization[111,113-115].

Traditionally, ketamine is known as a perioperative anaesthetic agent; lately, increasing interest in the use of low-dose ketamine for postoperative pain management has evolved. The NMDA-antagonistic properties of ketamine may attenuate opioid induced hyperalgesia (OIH) and opioid tolerance[116,117]. Various recently published studies have confirmed the antihyperalgesic effect of low-dose ketamine after major orthopedic or abdominal surgery[118-120].

Several systematic reviews have shown that subanaesthetic doses of ketamine can reduce the intensity of postoperative pain and the consumption of opioids[121-125]. Low doses of ketamine are defined as an intravenous bolus of less than 1 $mg \cdot kg^{-1}$ and/or continuous intravenous infusion at rates below 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [124]. McCartney and co-workers concluded recently in a qualitative

systemic review that administration of NMDA receptor antagonists before and/or during surgery was able to reduce postoperative pain[123].

NMDA receptor activity is important for normal function of the central nerve system, and NMDA receptor antagonists like ketamine have psychotomimetic side effects which may limit its use[111,126,127]. Recently published studies have demonstrated that S (+) –ketamine may have less psychotomimetic side effects than racemic ketamine in non-surgical patients[127,128], whereas surgical patients are not much studied in this context yet.

In general, ketamine is administered intravenously or intramuscularly. Also, ketamine can be given epidurally, intrathecally, intraarticularly, as well as orally and topically[129-136].

6.3.1.2.4 Gabapentin and Pregabalin (Gabapentinoids)

Gabapentin was licensed for the treatment of epilepsy in Europe in 1993, based on its anti-spastic effects and efficacy in experimental seizure models[137]. The antinociceptive properties of gabapentin were discovered at a later stage[138].

Pregabalin is structurally related to gabapentin and has been marketed for the treatment of seizures and neuropathic pain in the UK since 2004. This drug has analgesic, antihyperalgesic, anticonvulsant and anxiolytic properties[139-143].

Originally, pregabalin was designed to be an analogue of GABA[144]. However, despite the name gabapentinoids, pregabalin neither interacts with the GABA receptor nor mimics GABA action[139,145]. In common with gabapentin, pregabalin binds to the α_2-δ subunit of voltage-gated calcium channels localized particularly at synapses. Gabapentinoids may act by reducing the calcium influx via these presynaptic voltage-gated calcium channels. As a consequence, this may result in a decreased release of synaptic neurotransmitters (e.g., glutamate, norepinephrine, GABA, substance P). Gabapentinoids act as membrane stabilizers[145-147].

These drugs are only available for oral administration and the absorption of gabapentin is slow and limited by active transport in the gastrointestinal tract[148]. Plasma concentrations of gabapentin do not increase proportionally with increasing dose (non-linear absorption). In contrast, pregabalin absorption is more rapid and without a ceiling of amount absorbed. According to a first order kinetic, pregabalin absorption increases proportionally with increasing dose (linear absorption)[149]. In healthy volunteers peak plasma concentrations are achieved within one hour after the administration of pregabalin, whereas

maximum plasma concentrations for gabapentin are attained after 3-4 hours[141,149]. The bioavailability of pregabalin is high and exceeds 90 percent irrespective of the dosage, whereas the bioavailability of gabapentin drops from 60 percent to 33 percent as the dosage increases from 900 mg to 3600 mg daily[149]. For this reasons pregabalin has a favourable pharmacokinetic profile compared with gabapentin[141,149].

Gabapentin and pregabalin have proven efficacy in chronic neuropathic pain, e.g., diabetic neuropathy[150-153], postherpetic neuralgia[154,155], spinal cord injury[156] and phantom limb pain[157]. Furthermore, these two drugs may be helpful in the treatment of fibromyalgia[158,159].

Regarding acute pain, pregabalin and gabapentin act as antihyperalgesics and differ therefore from traditional antinociceptive drugs. Antinociceptive drugs, e.g., local anaesthetics, reduce the afferent input from intact and traumatized tissues, whereas antihyperalgesic drugs reduce the hyperexcitability of neurons located in the dorsal horn, which is caused by tissue injury[160]. Postoperative pain is commonly regarded as nociceptive (transient) pain. However, neurogenic, inflammatory and visceral mechanisms may contribute. Dahl et al. therefore define postoperative pain as "… *a transient, or reversible, type of 'neuropathic' pain*"[160].

Several systematic reviews have consistently shown beneficial effects of gabapentin and pregabalin in reducing postoperative pain and/or postoperative opioid consumption[161-164].

In the systematic review by Ho et al., the gabapentin dosage given preoperatively varied between 300 mg and 1200 mg, and both low-dose and

high-dose regimens effectively reduced pain intensity and opioid consumption for the first 24 hours after surgery. In addition the incidence of PONV was reduced; but the level of sedation was higher in patients who were treated with gabapentin compared with placebo[161].

Different doses of preoperative pregabalin from 75 mg to 300 mg have been used in the literature [163-165]. Although the majority have used a single dose of pregabalin given about one hour before surgery, there is some evidence that a repeated dose of pregabalin about 12 hours after surgery may be beneficial[164].

The administration of pregabalin is associated with side effects, especially when used in higher doses. Common adverse effects are dizziness, sedation, and visual disturbance[164,166-168]. However, pregabalin may reduce opioid-related adverse effects such as postoperative vomiting[164].

Gabapentinoids have anxiolytic properties[142] and some studies have shown reduced preoperative anxiety with these drugs [169,170]. Reduction in preoperative anxiety is good for the patient's preoperative well-being and has been reported to be associated with decreased levels of postoperative pain[29].

6.3.1.2.5 Glucocorticoids

Glucocorticoids are naturally occurring hormones. Their secretion follow a diurnal rhythm and circulating levels are increased during trauma and stress[10]. They act by binding to nuclear corticosteroid receptors and genetic activation, which is associated with a significant latency to effect[10,171]. Systemic glucocorticoids have potent anti-inflammatory effects. Furthermore, this group of drugs has both analgesic and antiemetic properties[172-175] with subsequent accelerated recovery after surgery [173,176,177]. A recently conducted meta-analysis demonstrated that a single perioperative dose of dexamethasone during adenotonsillectomy in paediatric patients resulted in a significant reduction in post-tonsillectomy pain[178]. The analgesic effect of glucocorticoids may be comparable to NSAIDs[179,180], and a combination of glucocorticoids and NSAIDs seems to have an additive effect[181-183]. With a multimodal approach and baseline paracetamol medication, combining dexamethasone and rofecoxib (COX-2 antagonist) resulted in prolonged postoperative analgesia when compared to rofecoxib alone[183].

Romundstad et al. have recently shown that intravenous glucocorticoids may reduce the risk for chronic pain after breast surgery[184].

A systematic review of data from 1900 patients who underwent major surgery concluded that a single dose of methylprednisolon (up to 30 mg/kg) was not associated with any adverse effects[185]. Still, glucocorticoids interfere with the metabolism of glucose, with reports of somewhat increased blood glucose in the postoperative period[186].

6.3.1.2.6 α_2- Adrenergic receptor agonists

The α_2-receptor agonists have sedative, analgesic, anxiolytic and hemodynamic properties[38]. At least three different subtypes of the α_2- adrenergic receptor have been identified, which may mediate sedation and antinociception separately[187]. Traditionally the α_2-receptor agonists are mainly used to treat hypertension[188] and opioid drug addiction[189], but in later years the use of this class of drugs has expanded into the field of anaesthesia and analgesia[190]. This includes the use of α_2-receptor agonists for peri- and postoperative pain relief, anxiolysis, sedation as well as treatment of chronic pain syndromes[38,190]. The analgesic effect of α_2-receptor agonists is mediated by both peripheral and central mechanisms[190].

The α_2-receptor agonists clonidine, dexmedetomidine and epinephrine are used in clinical anaesthesiologic practice. The receptor selectivity ratio for α_2:α_1 is 1600:1 for dexmedetomidine, 200:1 for clonidine and 1:1 for epinephrine[10,191]. Clonidine may be administered intravenously, orally, intraarticularly intrathecally and epidurally[47,192-194]. Systemic administration of clonidine during surgery reduces both postoperative pain and opioid consumption[195]. A review regarding clonidine as an adjunct to local anaesthesia for peripheral nerve blockade showed improved analgesia duration[196]. Intrathecally administrated clonidine seems to have analgesic effect[197], whereas the effects of epidural clonidine are inconclusive[190]. The injection of clonidine in joints has shown promising results regarding postoperative pain management[198].

The effect of dexmedetomidine on postoperative pain has not been much investigated compared with clonidine and most of the dexmedetomidine studies

address the sedative effect of this drug. However, a opioid-sparing effect of dexmedetomidine has been demonstrated[190].

Epinephrine is widely used as an adjunct for postoperative epidural analgesia and the synergistic pain relief with minor incidence of hemodynamic instability and motor block is well-documented[10,199,200]. Furthermore, epinephrine is used as an adjuvant to local anaesthetics in local infiltration analgesia (LIA)[48,201-203].

6.3.1.2.7 Other analgesic adjuvants

Neostigmine

Endogenous acetylcholine levels can be increased by the inhibition of the acetylcholinesterase[204]. Neostigmine acts as a parasympathomimetic agent inhibiting cholinesterase in the synaptic area. Several studies have explored the use of neostigmine in anaesthesia and analgesia. Neostigmine may be administered intrathecally, epidurally, caudally and intraarticularly. In addition the drug may be used as adjuvant to local anaesthetics in peripheral nerve blocks[10,205]. Unfortunately, neostigmine affects the emesis centre in the brain stem and this results in a high incidence of nausea. The practical use of neostigmine as an adjunct is therefore limited. Nausea occurs more frequently after intrathecal neostigmine compared to the other routes of administration[205]. Intraarticular neostigmine may have a beneficial effect regarding postoperative pain in patients undergoing arthroscopic knee surgery[192,206].

Nicotine

Pain may be inhibited by acetylcholine action and the alkaloid nicotine interacts with ion channels of the nAChR family[10,207]. Smokers may have more postoperative pain than non-smokers, when they discontinue smoking due to hospitalisation[208]. Several studies have investigated if systemic nicotine could provide postoperative analgesia[207], but there are also negative studies published[209,210]. Non-smoking patients undergoing uterine surgery received at

the end of surgery either 3 mg of nicotine by a nasal spray or placebo. Patients getting nicotine reported less pain during 24 hours as well as reduced morphine consumption[211]. Furthermore, transdermal nicotine patches applied before surgery in non-smoking patients resulted in improved analgesia after general surgery; although the opioid consumption was not reduced by nicotine in this study[212]. However, in smokers, transdermal nicotine patches failed to reduce postoperative pain[209].

Despite of these promising results more studies on nicotine analgesia in the clinical setting are needed.

Magnesium

Magnesium has antinociceptive properties due to its non-competitive blockade of the NMDA receptor. Moreover, magnesium is a physiological calcium antagonist at different voltage-gated channels[213]. Several clinical investigations have demonstrated that intravenous magnesium infusion during surgery can reduce postoperative pain[214,215]. Furthermore, magnesium may be an effective adjuvant to both intrathecal and epidural anaesthesia due to its potential analgesic effect[216,217].

Magnesium has also been used as an adjuvant to intraarticularly administered local anaesthetics and showed analgesic effect comparable to intraarticular morphine[218].

However, a recently published systematic review investigating the analgesic effect of intravenous magnesium did not find convincing evidence that magnesium is beneficial in the management of postoperative pain[213].

Cannabinoids

Two cannabinoid receptors have been cloned (CB1 and CB2) and various proposed endocannabinoid ligands have been identified[219,220]. This has resulted in an extensive research and the development of cannabinoid agonists and antagonists[10]. Cannabinoids have been applied in clinical practice as a potent antiemetic in cancer chemotherapy patients[221,222].

Cannabinoids have antinociceptive properties in acute pain models in animals[220]. The analgesia produced by cannabinoids is generally modest. A recently conducted review of randomized controlled trials in humans concluded that the role of cannabinoids in the management of pain is questionable. Cannabinoids induce CNS depression and several adverse effects as drowsiness, dizziness, memory impairment and confusion are related to this class of drugs[221].

Capsaicin and the TRPV1-receptor

The capsaicin receptor TRPV1 (transient receptor potential vanilloid 1) on C-fibers is an emerging peripheral target for the treatment of pain. Capsaicin is the pungent chemical found in chilli peppers, and may elicit strong sensations of noxious heat and pain[223]. However, when the initial pain is vanishing, capsaicin may inactivate the TRPV1 fibers for days to weeks, and thereby producing selective C-fibre analgesia. Recently the FDA approved a dermal patch containing capsaicin to be applied after pretreatment with lidocaine. The

application of topical capsaicin may be beneficial in the treatment of pain, including neuropathic pain, and itch. Furthermore, perineural capsaicin injections may be useful in cancer patients with intractable pain[224].

6.3.2 Regional Analgesia

6.3.2.1 Neuraxial nerve blocks

Neuraxial nerve blocks include spinal (subarachnoid), epidural and caudal nerve blocks. Depending on the dose, concentration and volume of local anaesthetic, this results in sympathetic blockade, sensory analgesia, or anaesthesia and block of the motor activity[9].

A systematic review has demonstrated that neuraxial nerve blocks may be associated with a lower incidence of complications (e.g., deep vein thrombosis, pulmonary embolism, pneumonia, myocardial infarction and renal failure). In addition, the overall mortality may be reduced[225].

However, neuraxial nerve blocks are also associated with rare complications caused either by the neuraxial procedure (e.g., needle and catheter placement and removal), or by the medication used for the blockade[36,226,227]. Permanent neurological complications after central neuraxial blockades can have severe consequences for the patient in question, although the general incidence is very low[226-228].

Local anaesthetics used for neuraxial nerve blocks include lidocaine, mepivacaine, ropivacaine and bupivacaine[9]. Vasoconstrictors, such as epinephrine and phenylephrine, may be added to prolong the action of the neuraxial blockade[9,199] but may also have a specific analgesic action mediated by the alfa-2 agonist effect[33,199,200]. Moreover, adjuvants to local anaesthetics, e.g., opioids are frequently used in clinical practice[47,229].

6.3.2.1.1 Spinal anaesthesia

The spinal cord extends from the brainstem to the conus medullaris (L1 in adults, L3 in children); the subarachnoid space continues to S2/S3[9,36]. Spinal anaesthesia acts by blocking nerve roots as they pass through the subarachnoid space and requires a small amount of local anaesthetic to provide complete sensory analgesia. A spinal nerve block should only be performed at the lumbar level in order to avoid trauma to the spinal cord[230]. Spinal anaesthesia is a common regional technique for surgical procedures below the umbilicus.

6.3.2.1.2 Epidural anaesthesia and analgesia

In contrast to spinal anaesthesia, epidural nerve blocks can be carried out at the sacral, lumbar, thoracic, or cervical levels. An epidural nerve block performed at the sacral level is called caudal nerve block and caudal epidural anaesthesia is a common regional procedure in paediatric patients[36]. Compared to spinal anaesthesia, larger amounts of local anaesthesics are necessary in epidural nerve blocks to provide profound analgesia[9].

There are many indications for epidural nerve blocks and the duration of analgesia can be prolonged by the insertion of an indwelling catheter. Analgesic effect can be obtained by the use of intermittent bolus doses, either controlled by the medical staff or by the patient himself (PCEA), and/or by a continuous infusion[58]. Epidural analgesia is very efficient for postoperative pain relief in patients undergoing major lower joint replacement[231] major abdominal surgery[232-234] or thoracotomy[235-237]. Moreover, perioperative epidural analgesia

may reduce adverse physiological responses to surgery[238] and modulate immune function during surgery[239]. Some studies show that epidural nerve blocks may be beneficial regarding postoperative cardiovascular and pulmonary complications[225,238,240], although the benefit seems to be limited to high-risk patients and high-risk procedures[20,241,242]. Thoracic epidural analgesia differentiates from lumbar epidural analgesia due to more profound sympathetic block, which promotes coronary perfusion and gastrointestinal motility[243,244]. Beattie et al. have shown, that postoperative thoracic epidural analgesia may reduce the incidence of postoperative myocardial infarctions to a greater extend than lumbar epidural analgesia[245]. This may be caused by improved balance of oxygen supply and demand in the ischemic heart[243]. Furthermore, thoracic epidural analgesia may be superior to lumbar epidural analgesia regarding the incidence of postoperative pneumonia[225]. This is probably due to the beneficial effect of thoracic analgesia on postoperative breathing and coughing[243]. Lumbar epidural analgesia may more frequently be associated with motor block of the lower extremities and urinary retention than thoracic epidural analgesia[246,247].

6.3.2.2 Peripheral nerve blocks

Blocks of peripheral nerves may be used for anaesthesia during surgery, either alone or in conjunction with general anaesthesia, or central neuraxial blocks. Furthermore, peripheral nerve blocks are commonly used for postoperative pain control, and for acute and chronic pain management[36].

Electric nerve stimulation and/or the use of ultrasound facilitate the identification of peripheral nerves[248-251].

Peripheral nerve blocks include blocks of the head, neck and trunk. Surgical anaesthesia of the shoulder and the upper extremity can be achieved by neural blockade of the brachial plexus (C5-T1) or its cords and terminal branches[36,249]. Lower limb nerve blockades are practised less frequently than upper limb blocks. The reasons for this are that it is impossible to block the whole lower limb with one injection and that neuraxial techniques may prove simpler[58].

Different approaches and techniques are used to carry out lower limb blocks in clinical practice[252]. Especially in major lower joint surgery, e.g., total knee arthroplasty (TKA), peripheral nerve blocks are frequently used. The femoral nerve block with or without a sciatic nerve block is suitable for postoperative pain treatment after TKA, either as a single shot injection, or as a continuous infusion[253]. Both single shot injections and continuous peripheral nerve blocks can be used for the management of peri- and postoperative pain and are associated with accelerated patient recovery and reduced length of hospital stay[254].

For surgical anaesthesia the choice of local anaesthetic (e.g., lidocaine, mepivacaine, ropivacaine, bupivacaine) for a peripheral nerve block depends

on the duration of the surgical procedure and need of strong postoperative analgesia. For prolonged nerve blockade, including postoperative pain management, long-acting agents such as bupivacaine, levo-bupivacaine or ropivacaine are often preferred[9]. Vasoconstrictors, usually epinephrine, are frequently added to the chosen local anaesthetic to fasten the onset of action and decrease systemic toxicity of local anaesthetics. Various adjuvants have been reported to improve duration and quality of the nerve blockade, e.g., opioids, clonidine, ketamine and neostigmine[9,255]. However, the effects of adjuvants in peripheral nerve blocks are controversial in the literature[47].

6.3.2.3 Local anaesthetic infiltration

Infiltration of local anaesthetics (LAs) into surgical wounds is a simple method to provide postoperative analgesia. The basic concept of this technique is to block pain at the origin due to local application of anaesthetics. LAs block voltage-gated sodium channels and as a consequence the transmission of pain from the surgical wound is reduced or abolished. In addition the inflammatory response to the injury is suppressed[222].

In minor surgical procedures, e.g., herniotomy, the efficacy of incisional local anaesthetics regarding postoperative pain has been demonstrated several years ago[256]. Moreover, the use of local anaesthetics injected intraarticularly for pain relief has shown beneficial effect in orthopaedic surgery[49,257-259]. However, a single injection of LAs into the surgical wound is unlikely to have long-lasting effects. This is why new techniques for wound infiltration have been developed during the last decade[260].

The insertion of indwelling catheters at the end of surgical procedures has established new properties for the use of LAs, and facilitates the use of this technique in more extensive surgical procedures. These catheters can be placed into the incision, around a fascia, intraabdominally and intraarticularly. In clinical practice a bolus injection via the catheter at the end of surgery is often followed by either intermittent injections or a continuous infusion of local anaesthetics[261-263].

Dahl and Møiniche (2009) have recently published a review regarding the efficacy of topical local anaesthetic infiltration on pain relief in patients undergoing major abdominal surgery, e.g., abdominal hysterectomy and open

colonic surgery. They concluded that about half of the studies regarding hysterectomy and only one study about colonic surgery showed a beneficial analgesic effect[261]. Furthermore, Kim et al. recently published data where they have compared intraperitoneal lidocaine with intravenous lidocaine in patients undergoing laparoscopic appendectomy. They concluded that both treatment modalities were equally effective regarding postoperative pain and opioid consumption[264].

Another technique that is called local infiltration analgesia (LIA) has recently been introduced in major orthopaedic joint surgery[261]. The infiltration analgesia techniques for total knee and total hip arthroplasty (TKA and THA) were developed by Bianconi et al.[265] and Kerr and Kohan[201] in the beginning of this millennium. This approach involves the administration of large volumes of dilute local anaesthetics, e.g., ropivacaine, with or without adjuvants into different tissue structures during orthopaedic surgery.

At the end of surgery the orthopaedic surgeon can place an indwelling catheter into the artificial joint, which makes it possible to prolong the analgesic effect by refilling local anaesthetics through this catheter in the postoperative period (top-up dose)[202,203,266].

Various adjuvants can be added to the LIA mixture, e.g., epinephrine, ketorolac and morphine[48,267].

6.3.3 Non-pharmacological approaches

With the goal to provide the best postoperative pain regimen with the least number of associated adverse effects, all analgesic approaches have to be considered. Many non-pharmacologic analgesic techniques have their origin from eastern medicine practices. Acupuncture may be best known and has been used for more than 2500 years[268]. Acupuncture is based on a theory of interconnectedness where one energy source is spread throughout the universe and all things within it. The energy flow, which is called qi, remains balanced between the forces of yin and yang. The pathways for this energy flow are termed meridians. The human body is composed of several traditional meridians with more than 360 specific acupuncture points. The stimulation of these acupuncture points with needles may relieve obstructed flow of qi[10,268]. Regarding the use of acupuncture in the management of postoperative pain, Sun et al. recently have conducted a systematic review and concluded that perioperative acupuncture may be a useful adjunct. They demonstrated reduced opioid consumption, decreased postoperative pain intensity and a lower incidence of opioid-related adverse effects in patients who were treated with acupuncture[269]. However, it may be difficult to interpret the results of most of the studies, because of blinding issues and heterogeneity of the reviewed studies[270]. Moreover, several studies have been published with negative results of acupuncture [271-274].

Transcutaneous electrical nerve stimulation (TENS) was developed about 40 years ago and uses either low- (acupuncture-like) or high-frequency electric pulses. These pulses are applied by plaster electrodes, which are placed

transdermal near painful areas, the site of surgery, or peripheral nerves. The mechanism of action is thought to be a reduction of anterograde nociceptive transmission caused by an activation of GABA and opioid receptors on the spinal level[270]. Overall, there is more evidence for the efficacy of TENS on postoperative pain compared to acupuncture. DeSantana and co-workers recently have demonstrated in a prospective, double-blinded, randomized trial that high-frequency TENS reduced both postoperative pain and postoperative analgesic requirements in patients undergoing inguinal herniorrhaphy[275]. Furthermore, analgesic efficacy of TENS has been shown after laparoscopic and cardiac surgery[276,277].

Psychological interventions may be useful in the management of postoperative pain. Devine has shown in a quantitative review that psychological interventions, like health care relevant information, skills teaching and psychosocial support, may have a beneficial effect on pain intensity, psychological distress and recovery[278]. Adequate patient information plays an important role in pain management. Kalkman et al. have recently shown that a strong information seeking behaviour before surgery may reduce the incidence of severe postoperative pain[29]. However, some patients may habitually cope by avoiding detailed information[279]. Psychosocial support includes the identification of patient concerns before and after surgery, the encouragement of the patient to ask questions throughout the hospital stay and the provision of appropriate reassurances[278].

Another non-pharmacological approach in postoperative pain management is attentional control. Distraction from an acute pain stimulus by conversation or

music may help to reduce pain intensity[279]. Good et al. demonstrated that relaxation and music therapy reduced pain intensity after major abdominal surgery[280]. Hypnosis may be defined as an altered state of awareness[10]. By suggestion through a hypnotist, the patient may experience various changes in sensation, perception, cognition or control over motor behavior[281]. Montgomery et al. have conducted a meta-analysis and concluded that hypnosis may be useful for surgical patients[282].

6.4 Pre-emptive and preventive analgesia

The term pre-emptive analgesia describes an "*antinociceptive treatment that prevents establishment of altered processing of afferent input, which amplifies postoperative pain*"[283]. Various studies have been conducted comparing pre-incisional analgesic treatment with post-incisional pain management. Meta-analyses have shown conflicting results regarding the efficacy of pre-emptive analgesia[284,285]. While Ong and colleagues have demonstrated a beneficial effect of pre-emptive epidural analgesia, local anaesthetic wound infiltration and the administration of NSAIDs[285], Moiniche et al. failed to find evidence for the pre-emptive effect of both local anaesthetic wound infiltration and NSAIDs[284].

A few years ago, the term preventive analgesia was introduced[286,287]. In contrast to a typical pre vs. post design (pre-emptive analgesia), in preventive analgesia the analgesic treatment is compared to another treatment given after the nociceptive stimulation is initiated. A preventive analgesic effect is present, when the observed effect (e.g., postoperative pain or reduced rescue analgesic consumption) exceeds the expected traditional duration of the analgesic agent[288]. It has been proposed that not the timing, but the duration of pain management may play an important role for the prevention of central sensitization and hyperalgesia[286,287]. Loco-regional techniques and different classes of drugs, e.g., NMDA receptor antagonists and gabapentin may have antihyperalgesic properties and may therefore be useful in a preventive analgesic strategy in the peri- and postoperative period[123,161,289].

6.5 Multimodal analgesia

Pain is caused by various mechanisms at various levels in the nervous system. In theory, the combination of different analgesic drugs and techniques should improve the efficacy of pain management by acting on different mechanisms and levels of action. Moreover, patient safety may be improved because, in general, reduced drug doses of each drug when combined are accompanied with a reduction of dose-dependant adverse effects. This type of pain management strategy is called multimodal or balanced analgesia[64,290,291]. However, despite all evidence for the efficacy of multimodal analgesic approaches[292,293], these techniques seem underused in clinical practice[294]. In order to identify the most suitable multimodal analgesic strategy, a procedure-specific approach is recommended[291]. The reason for this is that one analgesic technique, e.g., continuous epidural analgesia, may be beneficial in a specific type of major abdominal surgery (e.g., open colonic surgery), while being inappropriate in other types of abdominal surgery (e.g., nephrectomy). Moreover, different surgical procedures are associated with various complications (e.g., postoperative bleeding) and therefore the multimodal pain management has to be tailored according to this[291].

7. HYPOTHESES

1. Multimodal analgesia in the perioperative period leads to a reduction of postoperative pain (papers I + II) or decreased postoperative opioid consumption or both. (Paper II)

2. Preoperative anxiety is associated with postoperative pain and preoperatively administered pregabalin can reduce anxiety before surgery. (Paper II)

3. Multimodal antinociceptive treatment with S (+) ketamine or pregabalin is not associated with an increased frequency of adverse effects. (Papers I-II)

4. Local infiltration analgesia (LIA) for total knee replacement can reduce post-operative pain and opioid consumption compared to epidural analgesia. Furthermore mobilisation can be fastened and the hospital stay can be shortened. (Paper III)

5. Local infiltration of ketorolac and morphine during total knee arthroplasty is more effective than systemic administration of these drugs. (Paper III)

6. Local infiltration analgesia compared to epidural analgesia is not associated with an increased frequency of adverse effects. (Paper III)

8. METHODS

8.1 Study design

Research studies might either have a prospective or a retrospective design. A prospective study looks forward in time, and the study is designed before data is collected. In contrast, retrospective studies look backwards and the data collection is already finished at the start of the study. A prospective study design allows the researcher to include a control group (e.g., alternative or placebo treatment) and this may eliminate many confounding variables. Study participants can be followed throughout the whole study period to measure the outcome in question. The strength of evidence, which is derived from prospective studies, is higher than from retrospective studies. However, in prospective study design, data collection is more time-consuming and expensive. Furthermore, if the outcome is uncommon, the size of prospective investigation that is required to draw conclusions is often too large to be feasible and a retrospective design may be more suitable in these cases.

When choosing study design in this thesis, the prospective approach for all three studies was regarded to be most suitable, because different treatment modalities were compared. Important data may often be non-available in a retrospective design. Furthermore, it is also difficult to control bias and confounders.

Randomization of the study population is used to eliminate selection bias and to assure similar treatment groups. The purpose of randomization is to ensure that only one, controlled variable is different between two or more treatment groups. As a result of the randomization causalities can be attributed. Different

randomization techniques are in use: simple randomization (flipping a coin), block randomization (insure that the numbers of participants allocated to each treatment is not far out of balance) and stratified randomization (additional factors, e.g., gender or age, are balanced between the groups).

RCTs are considered to be the most reliable form of scientific evidence[295]. Non-randomization is afflicted with bias and this weakens the scientific evidence of the study.

Randomization of the study participants was regarded to be important when planning this thesis and all three studies are randomized controlled trials (RCT). Permuted block randomization was carried out by the hospital pharmacy of the Asker and Bærum Hospital for all three studies.

Blinding of the study participants and the observers (double blinding) is an attempt to eliminate subjective bias and results in more reliable data and strengthens the scientific evidence. Two clinical trials of this thesis (papers I and II) have been conducted in a double-blinded manner. For the knee study, which is described in paper III, the study design was double-blinded for the two groups that were treated with local infiltration analgesia. Participants who were randomized to the epidural group were regarded as not fully blinded, as study participants and/or investigators might have realized if they got an epidural puncture or not.

All studies included in this thesis were conducted in accordance to the Declaration of Helsinki and conformed to the CONSORT guidelines[296,297] with written informed consent of all study participants.

8.2 Study approval and registration

The National Committee for Medical and Health Research Ethics in Norway and the Norwegian Medicines Agency have approved all studies in this thesis before study start.

All three studies were registered at http://clinicaltrials.gov before patient enrollment (paper I: NCT00354029, paper II: NCT00353704, paper III: NCT00562627). ClinicalTrial.gov is a worldwide registry of clinical trials hosted from the U.S. National Institutes of Health[298].

Collection of data and data analysis of the knee study (paper III) have been externally monitored (Section for Good Clinical Practice, Oslo University Hospital, Ullevaal).

8.3 Participants

Adult persons (≥ 18 years), ASA grade I+II (paper I) and ASA grade I-III (papers II + III) were enrolled with written informed consent. Exclusion criteria for all three studies were moderate or severe heart, liver, kidney, or psychiatric disease, pregnancy and breast-feeding. Participants with regular use of opioids and participants not understanding Norwegian were also excluded from participation. Patients with a history of gastric ulcer disease (all papers) or glaucoma (only paper I) were not included into the studies.

8.4 Surgical procedures, anaesthesia and analgesia

Participants in paper I were scheduled for day-care haemorrhoidectomy. Patients in paper II were undergoing elective lumbar single-level discectomy and the participants in paper III were operated with unilateral total knee replacement.

Total intravenous anaesthesia (TIVA) with propofol and remifentanil was used in two of the studies (paper I+II), whereas patients undergoing total knee arthroplasty (paper III) received spinal anaesthesia.

Paracetamol was administered to all patients as premedication and every six hours postoperatively. All patients were observed in the post-anaesthestic care unit (PACU) after completed surgery. Participants undergoing discectomy (paper II) were treated with diclofenac 50 mg three times daily during the hospital stay.

Patients scheduled for day surgery (paper I) were given an envelope containing analgesics and an information letter on how the medication should be taken. In-hospital patients (paper II+III) were equipped with an IV patient-controlled morphine pump (PCA) for the first 24 hours (paper II) or 48 hours (paper III). Postoperative nausea and vomiting (PONV) was treated with IV odansetron 4 mg and IV metoclopramide 10 mg.

8.5 Treatment comparisons

Paper I:

Participants in this study were randomized to either perioperative IV S (+) ketamine or placebo.

After insertion of the laryngeal mask, but before start of surgery, patients in the S (+) ketamine group received an intravenous bolus dose of 0.35 mg· kg^{-1} S (+) ketamine (Pfizer, 2.5 mg·ml^{-1}) followed by continuous infusion of 5 μg·kg^{-1}·min^{-1} S (+) ketamine. Patients in the placebo group received an equivalent volume of isotonic saline (bolus and infusion). Continuous infusion was stopped two minutes after end of surgery. Following the concept of multimodal analgesia, all patients received intravenous 8 mg dexamethasone and 30 mg ketorolac perioperatively. After completion of surgery the surgeon injected local anaesthesia (10-20 ml bupivacaine 2.5 mg·ml^{-1} + epinephrine 5 μg·ml^{-1}) in the surgical field.

Paper II:

Participants in this study were randomized to receive either oral pregabalin 150 mg, or an identically looking placebo capsule about one hour before surgery.

Paper III:

Patients were randomized to receive either postoperative epidural analgesia for a 48-hour period or to receive local infiltration analgesia. Patients getting local infiltration analgesia were further randomized in two groups and got, in addition to standard local infiltration analgesia, both ketorolac 30 mg and morphine 5 mg

injected either into the knee or intravenously. The standard local infiltration mixture (150 ml) contained 150 mg ropivacaine and 0.5 mg epinephrine added to isotonic saline. This mixture was injected peri- and intraarticularly by the orthopedic surgeon during total knee arthroplasty. In addition a catheter was placed into the knee joint at the end of operation. An intraarticular re-injection via this catheter with ropivacaine 142.5 mg and either intraarticular or IV ketorolac 30 mg was given 22-24 hours after surgery. The knee catheter was removed immediately after injection.

Patients randomized to epidural analgesia got epidural infusion with 2 $\mu g \cdot ml^{-1}$ fentanyl, 1 $\mu g \cdot ml^{-1}$ epinephrine, 1 $mg \cdot ml^{-1}$ bupivacaine started as soon as the spinal anaesthesia started to wear off. The infusion rate was programmed according to body height.

8.6 Outcome measures

The outcome measures used in this thesis are preoperative anxiety, postoperative pain, opioid consumption, time to mobilization and hospital discharge, as well as the occurrence of adverse effects.

The scientific measurement of anxiety and pain is challenging, since both anxiety and pain are subjective experiences. Nevertheless, several methods for the assessment of acute pain have been developed and are used in both clinical and research practice.

The visual analogue scale (VAS) uses a straight, non-graded line with the extremes of intensity on either end. The VAS can be used for the assessment of the intensity of both anxiety and pain. Typically a 100 mm ruler is used to

determine VAS. One end is defined as “not at all”, while the other end is defined as “worst imaginable”. The participants are asked to indicate the point on this line, which describes the intensity that they are currently experiencing. Thereafter the investigator measures the distance between the marked place by the participant and the zero-point in millimeters or centimeters. Some VAS-rulers use words or faces along the scale to help the participant to better assess the intensity[228].

The numeric rating scale (NRS), where intensity is ranged from 0-10 and 0 refers to “not at all” and 10 indicates “worst imaginable”, can also be used to assess pain and anxiety. The NRS may be more practical than the VAS because it can be used to assess the intensity of pain also during telephone interview[228].

Verbal rating scales (VRS) assess intensity using a list of words describing the intensity. Traditionally this kind of scales contains three to five categories. A 5-point rating scale may consist of adjectives like none, mild, moderate, severe and very severe. The participant chooses the most appropriate word for the present experience. When comparing VAS, NRS and VRS, Breivik et al have shown that the power to detect a difference in pain intensity was higher with the NRS and the VAS data when compared with the VRS data[299]. However, especially in the elderly, the VRS is a well applicable tool for the registration of pain intensity[300].

Regarding the measurement of pain it is important to measure pain both at rest and also during movement and/or function as shown in a recently published systematic review[301]. Minimization of pain during movement is an important

clinical issue in terms of getting the patient mobilized and accessible for physiotherapy as well as resumption of normal level of activity. Pain assessment should be procedure specific and pain registrations during well-defined and relevant function are essential[302].

8.6.1 Measurement of anxiety

Preoperative anxiety was determined in participants undergoing lumbar discectomy (paper II) before induction of anaesthesia using an 11-point (0-10) visual analogue scale (VAS) ranging from “not at all anxious” to “extremely anxious”. Alternative instruments to measure anxiety are the Amsterdam Preoperative Anxiety or Information Scale (APAIS) and the state component of the State-Trait Anxiety Inventory (STAI). The APAIS consists of six questions asking about patients’ worries regarding anaesthesia and surgery as well as asking about patients’ requires for information[303,304]. The STAI presents 20 statements describing anxiety states and the participant gives a score ranging from 1-4 for each statement[305].

8.6.2 Measurement of pain

Pain intensity was assessed during the stay in the PACU and either during the stay on the surgical ward (paper II+III) and/or by telephone interviews (paper I+II). During the hospital stay the visual analogue scale (VAS) was used in all patients. In addition the numeric rating scale (NRS) was used in paper I and II, whereas a verbal rating scale was used in paper II and III. Postoperative pain

was assessed at rest in all study participants. Pain during movement was assessed differently in the conducted studies:

In patients who underwent haemorrhoidectomy (paper I), NRS was used to assess pain during sitting and defecation at seven days after surgery. In participants who were operated with lumbar discectomy (paper II), VRS was determined during mobilization one week after surgery. Patients undergoing total knee replacement were asked about pain intensity (VAS and VRS) during active 45-degree knee flexion at several time points during their hospital stay.

8.6.3 Measurement of the consumption of analgesics

In paper I, study participants were treated with rescue pain medication when pain excided VAS > 30, NRS > 3 or upon patient request. Rescue analgesics were fentanyl 0.05-0.1 mg IV during the first 30 minutes after surgery and a combination of oral paracetamol 500 mg and codeine 30 mg later on. Consumption of rescue pain medication was recorded for the PACU period and after hospital discharge.

In papers II and III all patients were equipped with an IV patient-controlled morphine pump (PCA) for either 24 hours (paper II) or 48 hours (paper III). The PCA was programmed to deliver 2 mg morphine on demand with 10 minutes lockout time. Total PCA morphine consumption was recorded. Patients undergoing TKA (paper III) received 10 mg oral slow release oxycodone twice a day and 5 mg standard oxycodone on request (rescue analgesic medication) from the third postoperative day. Cumulated oxycodone consumption was registered. Furthermore, cumulated opioid consumption during the first 72 hours

after surgery was calculated adding total PCA morphine consumption and total oxycodone consumption. A 1:1 ratio in analgesic potency between IV morphine and oxycodone was presumed as shown by Silvasti et al[306].

8.6.4 Measurement of function:

Functional outcome was measured in patients who were scheduled for total knee arthroplasty (paper III). The physiotherapist assessed the active and passive range of motion of the knee joint after surgery. Furthermore the achieved walking distance on day first and second postoperative day was recorded. Each postoperative day discharge readiness was assessed by an orthopaedic surgeon, a pain nurse, a ward nurse and a physiotherapist according to the following criteria: no evidence for surgical complications, VAS pain at rest ≤ 30, which is controlled by oral analgesics, ability to eat and drink and ability to walk with elbow crutches and to climb ≥ 8 stairs.

8.6.5 Measurement of adverse effects:

Postoperative nausea and vomiting (PONV) was assessed in all patients postoperatively. Furthermore hypotension (systolic blood pressure <80 mmHg), dizziness and respiration depression were registered in all patients who were equipped with a PCA (paper II+III). Patients scheduled for haemorrhoidectomy (paper I) were postoperatively asked if they experienced abnormal colour vision, double vision or hallucinations to detect potential adverse effects related to S (+) ketamine. In patients undergoing lumbar discectomy (paper II), known side effects of pregabalin as sedation, pruritus, urinary retention and headache

were recorded in the postoperative period. In patients who were operated with total knee arthroplasty (paper III), muscle weakness during mobilization was registered.

8.7 Statistical analysis

Power calculations were carried out for all three studies of this thesis and the intensity of postoperative pain was defined as the primary endpoint in each of the studies. Two of the papers (I and II) compared two groups, whereas paper III examined three different treatment modalities.

The primary end point for the S (+) ketamine study (paper I) was the NRS pain intensity during the first postoperative day. In paper II, the pregabalin study, the VAS score for pain at rest 120 minutes after surgery was defined as the primary endpoint. In the knee study, paper III, mean VAS (at rest or at knee flexion) about 48 hours after total knee arthroplasty represented the primary endpoint of the study.

The distribution of data was assessed with frequency histograms in all three studies. For comparisons of normally distributed data among two treatment groups (papers I+II), student t-test was used. Mann-Whitney U test was used for non-normally distributed data. Non-parametric variables were analysed with Kruskal-Wallis test, Chi-square test and Fisher's exact test (papers I+II). Mean area under the curve (AUC) comparisons and Pearson's correlations were used in paper II.

For tests of differences in continuous variables between three groups (paper III), one-way ANOVA tests were used. Pairwise comparisons were done with Bonferroni correction. The distributions of all dependent variables were examined to assess the appropriateness of using parametric tests.

Categorical data were analyzed with chi-squared tests and Kruskal-Wallis tests adjusted for ties. Analyses for mean effects over repeated measurements (longitudinal data) were performed with linear mixed models.

For data analysis SPSS® (version 16.0 – 18.0), StatXact 8 (Cytel inc., 2007) and CIA (www.som.soton.ac.uk/cia) were used.

9. RESULTS

The results from the three studies in this thesis are presented according to the hypotheses. All studies have been conducted at the Bærum Hospital (Vestre Viken HF, Norway) in the time period between 2006 and 2009. Demographic data were comparable for the different groups in the respective papers.

1st Hypothesis: Multimodal analgesia in the perioperative period leads to a reduction of postoperative pain (papers I + II) or decreased postoperative opioid consumption or both. (Paper II)

In paper I, seventy-seven participants scheduled for haemorrhoidectomy were enrolled in this randomized, double-blind, controlled study and received either perioperative IV S (+) ketamine or placebo.

Pain scores (NRS and VAS) did not differ significantly between the groups at any time points. Less than 10% of the patients had VAS ≥ 30 or NRS ≥ 3 during the PACU period. The pain scores (worst NRS during the sixth postoperative day) reported by telephone interview seven days after hospital discharge did not differ significantly between the groups but were markedly higher than reported in the previous interviews. This was mainly due to reports of pain during defecation. The majority of all study patients reported “no pain” during the interview after three months.

In paper II, 50 participants undergoing lumbar discectomy were enrolled in this randomized, double-blind, controlled study and received either preoperative oral pregabalin 150 mg or placebo.

The pain scores at rest (VAS) were significantly lower in the pregabalin group at 120 min after surgery. There was a 34.5 percent reduction in the mean area under the curve (AUC) for VAS pain at rest in the pregabalin group during the PACU period (p = 0.011) and morphine consumption was higher in the placebo group. Pain scores and morphine consumption did not differ significantly at 24 hours after surgery. Verbal pain scores were similar one week after surgery.

2nd Hypothesis: Preoperative anxiety is associated with postoperative pain and preoperatively administered pregabalin can reduce anxiety before surgery. (Paper II)

There was a statistical significant positive correlation (p=0.002) between preoperative anxiety and postoperative pain at 120 min. When analyzing each group separately, the difference was only evident in the pregabalin group (p=0.02), whereas in the placebo group no correlation was found (p=0.26). However, these were explorative findings as correlation analysis between preoperative anxiety and postoperative pain was not planned in the study protocol.

Participants in paper II, who received 150 mg pregabalin about one hour prior to surgery reported significantly lower grade of anxiety (VAS) before induction of anaesthesia (2.23 ± 1.11 vs. 4.17 ± 2.37, 95%CI: 0.82 to 3.05, p=0.001).

3rd Hypothesis: Multimodal antinociceptive treatment with S (+) ketamine or pregabalin is not associated with an increased frequency of adverse effects (Papers I-II)

Adverse effects were more frequent in patients who were treated with S (+) ketamine (paper I). The most frequent reported side effect was diplopia (6 patients vs. 1 patient; p=0.052). None of the study participants experienced hallucinations. The incidence of PONV was equal in both study groups. Furthermore, emergence from anaesthesia was significantly longer in the group of patients, which was randomized to S (+) ketamine (13.1 min vs. 9.3 min; p<0.001). Finally, BIS values were significantly influenced by S (+) ketamine.

Regarding paper II, there was no difference in sedation levels at arrival in the PACU. Furthermore, the occurrence of adverse effects in the postoperative period was equal in all patients.

4th Hypothesis: Local infiltration analgesia (LIA) for total knee replacement can reduce postoperative pain and morphine consumption compared to epidural analgesia. Furthermore mobilisation can be fastened and the hospital stay can be shortened. (Paper III)

In paper III, 102 participants undergoing unilateral total knee arthroplasty were enrolled in this randomized study and received either postoperative epidural analgesia (EDA) or peri- and postoperative local infiltrations with either local (LIA) or IV (LIAiv) ketorolac and morphine.

Verbal pain scores at discharge from PACU were significantly lower in the epidural group both at rest and during active knee flexion, but the time to discharge from the PACU was delayed (*EDA* 428 min vs. *LIA* 327 vs. *LIAiv* 360 min; p=0.007).

After discharge from the PACU the *LIA-group* had significantly lower pain scores (VAS) at rest compared to the *EDA-group* on day one, two and three after surgery. The mean reduction in VAS at rest for the *LIA-group* compared with the *EDA-group* from discharge PACU until 72 hours after surgery was 7.52, 95%CI: 2.49 to 12.5, p=0.004. VAS during active knee flexion was significantly higher in the *EDA-group* 72h after surgery compared with patients in the *LIA-group*.

Morphine consumption was lowest in the epidural group during the first day after surgery (ns), but thereafter morphine consumption was lowest in the *LIA-group*.

Patients in both the *LIA-group* and the *LIAiv-group* could be mobilized earlier after operation. The relative risk of not being able to walk more than 10 meters about 48 hours after surgery was 3.5 (95% CI: (1.6, 7.5) for patients randomized to the *EDA-group* compared to the *LIA-group* and the *LIAiv-group*. Mean time to readiness for hospital discharge was shorter in the *LIA-group* compared to the *LIAiv-group* and the *EDA-group* (3.5 ± 0.7 days vs. 4 ± 1.3 days vs. 5.5 ± 1.6 days; $p<0.001$).

5th Hypothesis: Local infiltration of ketorolac and morphine during total knee arthroplasty is more effective than systemic administration of these drugs. (Paper III)

There were no differences between the two local infiltration groups during the PACU stay. For the time period from the discharge from the postanaesthestic care unit until 72 hours after surgery, the mean reduction in VAS for the *LIA-group* compared to the *LIAiv-group* was at rest 5.26, 95%CI: 0.25 to 10.3, p=0.040 and during active knee flexion 7.11, 95%CI: -0.23 to 14.5, p=0.058. Cumulated morphine consumption during the first 48 hours was lower in the LIA-group compared to the LIAiv group (49 ± 36 mg vs. 77 ± 39 mg; p=0.004). Mobilisation after surgery and readiness for hospital discharge were similar between the two groups.

6th Hypothesis: Local infiltration analgesia compared to epidural analgesia is not associated with an increased frequency of adverse effects (Paper III)

In paper III, hypotension occurred only in the *EDA-group* (3 of 33 patients). There was no difference between the groups regarding PONV. In five patients, the epidural regimen had to be modified less than 4 hours after surgery due to insufficient effect. Delayed mobilisation for patients in the epidural group during the first postoperative day was mainly due to muscle weakness (6 patients), pain (6 patients), dizziness (2 patients) and nausea (4 patients).

One patient in the study (*EDA-group*) had to be re-operated after 16 days due to knee infection. None of the patients who were treated with local infiltration analgesia got knee infection.

10. DISCUSSION

10.1 Discussion of the main findings

The discussion in this thesis will be divided according to the objectives of the thesis with the following main findings:

- The addition of perioperative S (+) ketamine for postoperative analgesia after haemorrhoidectomy was not associated with a reduction of postoperative pain and low-dose S (+) ketamine on top of a multimodal peri- and postoperative pain regimen including dexamethasone and ketorolac cannot be recommended

- The administration of perioperative S (+) ketamine was associated with an increased frequency of adverse effects

- Preoperative oral administration of a single dose of pregabalin (150 mg) before lumbar discectomy showed a reduction in acute postoperative pain. Furthermore, morphine consumption during the PACU period was decreased without increased incidence of side-effects

- Preoperative anxiety was associated with postoperative pain and one capsule with 150 mg pregabalin about one hour prior to surgery resulted in a reduction of the grade of anxiety before induction of anaesthesia

- Local infiltration analgesia (LIA) with a mixture of ropivacaine, epinephrine, ketorolac and morphine reduces postoperative pain and opioid consumption after the initial 24 hours compared to epidural analgesia in patients undergoing total knee arthroplasty

- Treatment with local infiltration analgesia is not related with an increased frequency of adverse effects

- Participants getting local infiltration analgesia compared to epidural analgesia can be mobilized faster and are earlier ready for hospital discharge

- Local infiltration of ketorolac and morphine during total knee replacement is more effective than systemic administration of these drugs regarding postoperative pain and morphine consumption

Effect of perioperative IV S (+) ketamine on postoperative pain in patients scheduled for haemorrhoidectomy (Paper I)

The effect of subanaesthetic doses of racemic ketamine and S (+) ketamine on postoperative pain and opioid consumption has been shown in several systematic reviews[121-125]. However, in our study, when S (+) ketamine was added on top of a multimodal analgesic regimen including preoperative paracetamol, perioperative dexamethasone, ketorolac and local anaesthetics, there was no reduction in postoperative pain scores. Although haemorrhoidectomy is known as a painful procedure[307], our multimodal analgesic approach resulted in a low number of patients complaining about moderate to severe pain even in the control group. Kwok et al. showed recently that a single dose of racemic ketamine before incision for gynaecologic laparoscopy reduced pain scores significantly. However, patients in this study received neither paracetamol, steroids, NSAIDs nor local or epidural anaesthesia[308]. In contrast to this, patients undergoing uterine artery embolization and receiving adjunctive paracetamol and diclofenac, showed no additive effect of racemic ketamine[309].

Another explanation for the absence of an additional analgesic effect of S (+) ketamine in our study may be due to low dosage given. Our dosing of S (+) ketamine perioperatively was according to recently published recommendations[113]. Adverse effects were observed more frequently in our S (+) ketamine group, suggesting that the dose should not be increased further.

A possible reason for our negative findings may be that we stopped the S (+) ketamine infusion at the end of surgery and did not continue S (+) ketamine in

the postoperative period as proposed by Lahtinen et al[310]. However, continued S (+) ketamine infusion postoperatively is not practical in the day surgery setting with rapid discharge from recovery and rapid mobilization.

Adverse effects of the treatment with S (+) ketamine (Paper I)

In paper I we found negative clinical effects of S (+) ketamine regarding both time for emergence after the end of surgery and the length of stay in the PACU. This may be due to the sedative effects of ketamine. A potential confounder may be a slightly higher dose of propofol in the S (+) ketamine group, as dosage of propofol based on BIS values is more difficult to evaluate when S (+) ketamine is used. Several authors have demonstrated the influence of ketamine by increasing the BIS values in the past[311,312].

Delay of emergence from anaesthesia increases the need for resources in the operation theatre and during the postoperative stay, and this is especially unfavourable in day care surgery with a high patient turnover.

Diplopia shortly after emergence from anaesthesia was more frequent in our patient population, which was treated with S (+) ketamine. However, impairments of vision were reported as mild and short-lasting and none of the study participants reported hallucinations.

In contrast to our findings, Lahtinen et al observed a significantly increased occurrence of major psychotomimetic adverse responses in the patient group that was treated with S (+) ketamine[310]. However, the S (+) ketamine infusion was continued for 48 hours after surgery in their study, while S (+) ketamine infusion was stopped at the end of surgery in our study.

Effects of preoperative pregabalin on postoperative pain and opioid consumption in patients undergoing lumbar discectomy (Paper II)

Several systematic reviews have shown that antihyperalgesic drugs, such as gabapentin and pregabalin, can contribute to reduce postoperative pain and opioid consumption[161-163]. Our study results confirm the beneficial effects of pregabalin in lumbar disc surgery, as described recently[313]. Lumbar discectomy is usually associated with moderate levels of postoperative pain[314] and the use of NSAIDs may be controversial in patients undergoing spine surgery, due to their possible influence on postoperative bone repair and tissue healing[96]. Therefore the use of pregabalin in these patients may be an alternative to NSAIDs.

In general, postoperative pain is transient somatic pain. However, inflammatory, neurogenic and visceral mechanisms may contribute and postoperative pain may be defined as a transient type of ‘neuropathic‘ pain[160]. Surgical procedures are always associated with tissue damage. This may result in a local inflammatory response and a sensitization of the nociceptors in the periphery. As a consequence, transduction and conduction of nociceptive impulses towards the CNS may be altered. While traditional antinociceptive drugs reduce the afferent input, pregabalin (and gabapentin) may decrease the hyperexcitability of dorsal horn neurons, which may be induced by tissue injury [160]. Therefore, the difference in pain intensity between the groups in our study may represent an antihyperalgesic effect of pregabalin.

Adverse effects of the treatment with pregabalin (Paper II)

In paper II, we were not able to demonstrate increased sedation levels after surgery. In contrast do this, several investigators have described increased sedation postoperatively in patients treated with pregabalin[166,315]. One reason for the absence of increased sedation in our study may be the relatively low dose of pregabalin (i.e. 150 mg). Other explanations may be low sensitivity in our sedation score or the potential sedative effect of higher opioid use in the control group during the first postoperative hours, matching a potential sedative effect of pregabalin in the other group.

Dizziness is another side-effect of pregabalin [168,316]. However, the frequency of dizziness was equal between the patient groups in our study. Again, a possible explanation for this may be that the pregabalin dose in our study was only half the dose as used in the studies by Hill et al. and White et al., where patients got 300 mg of pregabalin[168,316].

The incidence of PONV was similar in the whole patient population in our study. This is in accordance with the findings of other authors[315,317,318].

Effects of preoperative pregabalin on preoperative anxiety in patients undergoing lumbar discectomy and association of preoperative anxiety on postoperative pain (Paper II)

Our study results determined that anxiety was lower in participants who were treated with pregabalin. The anxiolytic effect of pregabalin has been demonstrated earlier in a surgical population[169], and in a dental anxiety model[142]. However, White et al. recently have published data where pregabalin in doses between 75 mg and 300 mg failed to reduce preoperative state of anxiety[168]. The heterogeneity of surgical procedures in the above mentioned study and the fact that only patients undergoing short-stay surgery (< 24 hours) were included may be a possible explanation for the negative findings of White et al. Further studies are needed to confirm the anxiolytic effect of pregabalin.

Different authors have shown, that the grade of preoperative anxiety is associated with the level of postoperative pain[27,29]. Our results were in accordance to this and we found a positive correlation between preoperative anxiety and postoperative pain. However, we did not plan such correlation analyses when we designed the study protocol and therefore these results should be interpreted with caution. Jokela et al. have recently shown that pregabalin compared to diazepam is more effective in reducing the intensity of postoperative pain, while both drugs are equal when evaluating the level of anxiety before anaesthesia[319]. A possible explanation for these findings may be that pregabalin, on one hand, may reduce postoperative pain by lowering preoperative anxiety. On the other hand, pregabalin may also independently reduce postoperative pain due to its direct antihyperalgesic effects.

Effects of local infiltration analgesia (LIA) on postoperative pain and opioid consumption compared to epidural analgesia in patients undergoing total knee arthroplasty (Paper III)

Epidural analgesia or continuous peripheral nerve blocks have been traditionally recommended as the best postoperative pain treatment after total knee arthroplasty[231,320-322]. In our patient population, epidural analgesia was superior to local infiltration analgesia in the early hours after surgery. This may be due to the fact that an epidural bolus dose was given just before the spinal anaesthesia weared off. However, epidural setup had to be modified due to suboptimal analgesia in several patients. Our findings of superior analgesia with LIA for observations beyond the first hours are in accordance with Choi et al. They conducted a systematic review regarding epidural analgesia versus systemic analgesia in patients undergoing knee or hip replacement and concluded that the beneficial effect of epidural analgesia on pain relief was limited to the early postoperative period[231].

In our study, the pain scores at rest were lower from 24 hours after surgery until discharge from the hospital in patients getting LIA with intraarticular ketorolac and morphine. These findings are comparable to a recently published study where continuous epidural analgesia was compared to local infiltration analgesia in patients undergoing total hip arthroplasty[323]. The authors found significantly reduced narcotic consumption and reduced length of stay in patients treated with local infiltration analgesia. The same research group recently published results of a study were continuous epidural analgesia was compared with local infiltration analgesia in patients scheduled for total knee

replacement[324]. The authors concluded that LIA was associated with improved pain relief and reduced opioid consumption. In contrast to our study design, local infiltration analgesia was administered continuously for 48 hours after surgery. Essving and co-workers have recently published a study in TKA patients comparing LIA to no injections during surgery and consecutively LIA to saline for postoperative intraarticular re-injection[203]. The results of this study showed that LIA provided excellent postoperative pain relief for up to 48 hours after total knee replacement as well as lower opioid consumption in the same time period.

Effects of local infiltration analgesia (LIA) on postoperative mobilization and readiness for hospital discharge compared to epidural analgesia in patients undergoing total knee arthroplasty (Paper III)

The patients in our study who received LIA, either with IV or local ketorolac and morphine, had superior knee function and were mobilized faster compared with participants who were treated with epidural analgesia. This is in accordance with a recently published study on knee arthroplasty patients, were the authors demonstrated improved knee flexion for the first 48 hours after surgery in patients treated with LIA[203]. Toftdahl et al. who studied LIA versus femoral nerve block in patients undergoing TKA showed that participants treated with LIA could walk more than three meters earlier on the first two postoperative days.[325]. Regarding treatment with LIA and readiness for discharge from the hospital after major knee surgery, specific discharge criteria are only defined in a few studies[203,266]. Essving et al., who used defined criteria for home

readiness, demonstrated that participants who were treated with LIA compared to epidural analgesia were significant earlier ready for hospital discharge (3 vs. 5 days)[203]. This is in accordance to our findings.

Effects of local infiltration of ketorolac and morphine compared to intravenous administration of the same drugs on postoperative pain and opioid consumption in patients undergoing TKA (Paper III)

Participants in our study receiving LIA with locally administrated ketorolac and morphine had lower pain scores at rest after discharge from the PACU and consumed less morphine during the first 48 hours after surgery compared with patients who were treated with intravenous ketorolac and morphine. Therefore, we may assume that ketorolac and morphine can have a specific local effect. However, some effect of systemic absorption cannot be ruled out with our study design. Moreover it is unclear if the analgesic result is based on the effect of either ketorolac or morphine or a combination of both drugs. We used only ketorolac, but not morphine, for the re-injection through the knee catheter about 22-24 hours after surgery. The fact that we observed a significant analgesic effect following the knee injection taken into consideration: we may speculate that ketorolac plays a key role in the LIA mixture.

Gupta et al. have conducted a study where they compared the effect of morphine or ketorolac with a combination of both drugs in patients scheduled for knee arthroscopy[326]. They found that morphine alone injected intraarticularly provided no pain relief, ketorolac alone offered some degree of pain relief and the authors concluded that the combination of morphine plus ketorolac provided

best analgesia and that the result could be a synergistic effect of these two drugs.

Regarding the local effect of ketorolac, Romsing et al. have conducted a systematic review where they investigated the evidence for a peripheral analgesic effect of the local infiltration with NSAIDs in postoperative pain[327]. They concluded that intraarticularly administrated NSAIDs might have a clinically relevant peripheral action. However, Scott Reuben conducted two of the reviewed studies[328,329] and one of these two articles was retracted[328], which may question the conclusion of the meta-analyses.

Several systematic reviews have been conducted to investigate the analgesic effects of intraarticular morphine alone and the results are controversial. While Kalso et al.[330] and Gupta et al.[331] concluded that intraarticular morphine may have some effect in reducing postoperative pain and analgesic consumption, Rosseland et al. drew the opposite conclusion, that there is no added analgesic effect of intraarticularly administrated morphine[332].

The pharmacological differences between IV morphine and IM morphine have been described by several authors[46,333,334]. However, only limited data is available regarding the plasma concentration of morphine after intraarticular administration, but some drug will diffuse into systemic circulation [335,336]. In conclusion, the combination of an NSAID (ketorolac) and morphine given locally seems to have better efficacy than the same drugs given systemically.

Adverse effects of the treatment with epidural analgesia or local infiltration analgesia (Paper III)

In our study (III), hypotension occurred only in patients who were treated with epidural analgesia. Choi et al. have conducted a Cochrane review comparing epidural analgesia with systemic analgesia and found an odds ratio of 2.78 for low blood pressure in the epidural group[231].

Regarding practical problems with epidural analgesia, the majority of all procedures to improve epidural analgesia were carried out within 240 minutes after end of surgery and in all these patients epidural analgesia became adequate after catheter manipulation. Also, spinal anaesthesia lasted longer than surgery, and the periods of inadequate epidural treatment was therefore relatively short and had probably minor influence on later pain course.

Suboptimal epidural analgesia due to catheter misplacement or suboptimal catheter position is a known problem among anaesthesiologists and is a part of the practical aspects of this method in everyday clinics. Literature supports the technique of partial catheter withdrawal for better efficacy[337].

Regarding the delayed mobilisation for patients in the epidural group during the first postoperative days, this was mainly caused by muscle weakness, dizziness and nausea. Muscle weakness of the lower extremities is a known side-effect in lumbar epidural analgesia. Dizziness and nausea may be associated with the rescue treatment of pain with morphine[9].

Local infiltration analgesia with the insertion of a catheter into the artificial knee joint after total knee replacement may theoretically be associated with an increased risk of postoperative knee infection. However, by now, none of the

published studies investigating the use of LIA in knee arthroplasty has shown an increased incidence of knee infections[48,202,203,266,324,325,338-345]. One patient in our study who was treated with epidural analgesia (i.e. no knee injections) was re-operated after 16 days due to knee infection. None of the patients who were treated with local infiltration analgesia got knee infection.

However, the overall number of data published on local infiltration analgesia is still small and large-scale studies are needed to address potential differences in the very low risk of knee infection. Also, the analysis of data from national knee arthroplasty registers may be used in the future to increase the knowledge about this potential risk.

10.2 Strengths and limitations of the studies

The three studies were conducted in a randomized controlled manner with a double blind design when possible. RCTs are considered to be the most reliable form of scientific evidence[295].

Furthermore, all studies address research questions from a clinical point of view and as a consequence they may be implemented into everyday clinical practice and improve patient treatment and patient satisfaction.

Therefore, preoperative pregabalin (150 mg) is now routinely added to the standard premedication for patients undergoing lumbar discectomy at the Bærum Hospital. Moreover, local infiltration analgesia with locally applied ketorolac and morphine has been established as standard treatment for all patients who are scheduled for total knee arthroplasty in our orthopaedic department. In contrast to this, perioperative S (+) ketamine is no longer added on top of multimodal pain prophylaxis for haemorrhoidectomy.

There are, however, several limitations to our studies.

Regarding the use of perioperative S (+) ketamine (paper I), all participants were treated with a multimodal analgesic regimen including ketorolac, dexamethasone and local anaesthetics in the surgical field. This resulted in a low number of patients who were complaining about moderate to severe postoperative pain in the control group and subsequent difficulties with showing any difference with any additional measure. The majority of the studies, showing a beneficial effect of subanaesthetic doses of racemic ketamine and S (+) ketamine on postoperative pain and opioid consumption, did not use a

multimodal postoperative pain management[121,123-125]. Therefore, the use of low-dose ketamine or S (+) ketamine may be an alternative in procedures where NSAIDs and/or glucocorticoids are contraindicated for some reason or controversial due to their possible influence on post-operative bone repair and tissue healing.

Regarding the use of premedication with pregabalin (paper II), it is important to notice that preoperative anxiety was assessed only by VAS and not by more extensive anxiety scales like the Amsterdam Preoperative Anxiety or Information Scale (APAIS) or the state component of the State-Trait Anxiety Inventory (STAI). However, there is a positive correlation between the VAS and the other two psychological tests (APAIS and STAI)[303,305]. Furthermore, when evaluating anxiety short time before the induction of anaesthesia, the use of time-consuming tests may be unpractical, whereas the VAS is fast and easy to use.

Another limitation of paper II is the fact that during the PACU period, pain was only analysed by VAS at rest and not during movement. The assessment of the intensity of acute pain during movement or provocation (dynamic pain) usually is a more sensitive tool for detecting differences in post-operative pain[228,301]. However, patient movement was discouraged during the PACU period in our patient population due to the believed importance of keeping a stable, resting position in the early hours after surgery.

In paper II, pregabalin was given as a single dose before surgery only and the beneficial effects regarding postoperative pain and opioid consumption were

only present in the early postoperative period. A prolongation of the analgesic effect might have been possible by re-administration of pregabalin about 12 hours after the initial dose, as recently shown in patients who underwent thyroidectomy[167]. The authors of that study reported reduced verbal pain scores at both 24 hours and 48 hours postoperatively following the administration of 150 mg pregabalin preoperatively and a repeated dose of 150 mg pregabalin about 12 hours later. However, sedation was more frequent and more profound in patients receiving pregabalin.

Regarding the use of LIA in total knee arthroplasty (paper III), it is important to notice that the technique of LIA is not standardized, and different approaches have been used in the published studies[48,201,265]. The amount of infiltrated ropivacaine in published studies varies from 200 mg - 400 mg[48,201,266]. Moreover, the addition of adjuvants such as NSAIDs, opioids and epinephrine differs in between the studies[48,202,325]. It is unclear which injection volumes should be used and where the injections should be placed (intraarticular vs. extraarticular)[339]. Timing, content and frequency of "top-up" doses through a knee catheter is also controversial in the litterature[202,203,266]. Some authors use continuous intraarticular infusions instead of bolus doses[267,324]. We cannot rule out that our results could have been different with different dosing and timing of drugs. Further good-quality studies are needed addressing one or a few specific items at a time, standardizing the others.

Another limitation of paper III is the absence of a placebo group. However, several double-blinded and randomized studies comparing local infiltration

analgesia to placebo in major knee and hip surgery have consistently shown that these methods are superior to placebo[202,203]. Therefore we decided that another placebo-controlled study was not needed, also as including placebo groups for pain studies of different efficient drugs may be ethically controversial.

Our study was conducted in a fully double-blind manner regarding patients' randomization to either local or intravenous administered ketorolac and morphine. Still, we consider the comparison between the LIA groups and the epidural group as potentially un-blinded from the patients' perspective. However, none of the patients were informed about what kind of treatment they were randomized to receive. Also, all patients got local skin infiltration analgesia before spinal puncture and in the epidural group before epidural puncture, too. Patients were informed that they would get spinal anaesthesia and that some patients would, in addition, get epidural analgesia. They were not informed in details on how many injections in the back they were supposed to feel. Postoperative nurse assessments at 240 minutes postoperatively, at discharge from PACU and in the whole post-PACU period were done by nurses who were not involved in patient treatment and who did not know the group allocation. Nevertheless, in spite of dummy catheters and syringe pumps, it is possible that some patients and/or researches found out whether true epidural analgesia was given or not.

A general problem with all clinical studies with a low number of standardized patients is to have enough statistical power to say anything about differences in in-frequent side-effects. This may also be a problem with our studies. According to a recently published review about high-volume, local infiltration in major joint

replacement, only 14 randomised studies have been conducted regarding total knee arthroplasty. All together about 500 patients have been treated with LIA in these studies[346]. Therefore, large-scale studies assessing the safety of this method are needed. Moreover, data from national knee arthroplasty and hip surgery registers may be of help to get further information regarding the safety of LIA.

11. SUGGESTIONS FOR FUTURE RESEARCH

Two of the studies in this thesis have demonstrated that postoperative pain management can be improved. However, the study participants still experienced pain after surgery and 'pain free' surgery remains the ultimate vision.

Only little data are available regarding the use of low-dose ketamine or S (+) ketamine in a multimodal postoperative pain management and additional studies in this field are needed. Clinical research with ketamine, which is focusing on surgical interventions that are usually associated with moderate to severe pain, and where the use of NSAIDs and/or glucocorticoids is controversial due to their possible influence on post-operative bone repair and tissue healing, should be encouraged.

Future research regarding the use of pregabalin should focus on the question whether repeated postoperative doses can reduce the intensity of postoperative pain for a longer time-period and if this can influence the establishment of chronic neuropathic pain states. The correlation between preoperative anxiety and postoperative pain, and pregabalins' effect on this should also be studied further.

In the field of local infiltration analgesia, good-quality studies addressing the different components in the LIA mixture are needed. There is a great need to define[289] the optimal LIA cocktail (e.g.,, which drugs and which injection

volumes should be used). The necessity of “top-up” doses through a knee catheter should be studied further with focus on frequency, timing and content of the re-injections.

Finally, the measurement of plasma concentrations of the locally injected agents in LIA versus systemic administration is needed to confirm a real local effect of these drugs.

12. CONCLUSIONS

- The addition of perioperative S (+) ketamine for postoperative analgesia after haemorrhoidectomy on top of a multimodal peri- and postoperative pain regimen does not seem to be warranted, due to delayed emergence from anaesthesia, more adverse effects and the absence of an additive analgesic effect.

- A single dose of pregabalin (150 mg) can reduce postoperative pain at rest as well as morphine consumption during the first hours after lumbar discectomy.

- A single dose of pregabalin (150 mg) about one hour prior to surgery can reduce anxiety before induction of anaesthesia.

- Local infiltration analgesia (LIA) with local adjuvants compared with epidural analgesia in total knee arthroplasty can result in reduced post-operative pain at rest, lower opioid consumption, faster mobilization and earlier readiness for hospital discharge.

- Local infiltration of ketorolac and morphine during total knee arthroplasty is more efficient than intravenous administration of these drugs regarding postoperative pain and morphine consumption.

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14. PAPERS I-III

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III