PIA PUOLAKKA

Some Challenges of Postoperative Pain Treatment

ACADEMIC DISSERTATION
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for public discussion in the Small Auditorium of Building M,
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ACADEMIC DISSERTATION
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To my family

Abstract

Multimodal analgesia is recommended after surgery to reduce the consumption of opioids. The efficacy of nonsteroidal anti-inflammatory drugs (NSAID) has been demonstrated, but they have certain adverse effects on haemostasis of gastric mucosa and platelet function. These adverse effects could be avoided by replacing NSAIDs with cyclo-oxygenase (COX)-2 inhibitors. In any case, the renal adverse effects of COX-2 inhibitors are thought to be equal to those of NSAIDs, but this is only poorly documented.
High prevalence of persistent pain has been documented after various operations. Numbers from orthopaedic surgery have varied between ten and 60%. Pain is mostly the main indication for knee replacement surgery. The evaluation of the prevalence of persistent pain among these patients is important, even as an outcome of the surgery itself. Underlying risk factors should be known to be affected.

The aim of this thesis was to study the efficacy and safety of coxibs in perioperative use and the prevalence and risk factors of persistent pain after total knee replacement. The efficacy studies (I-II) were prospective, randomized, double-blinded and placebo controlled. All the patients were undergoing laparoscopic cholecystectomy. Parecoxib 40mg or 80mg was given intravenously at the end of the procedure (I). Etoricoxib 120mg was given alone or in combination with paracetamol 1000mg as a part of premedication (II). The primary endpoint was to compare opioid consumption between the groups. The total number of patients was 148. Renal adverse effects of parecoxib were studied in patients undergoing laparoscopic surgery as a physiological stressful model with sensitive markers (III). The patients (15) enrolled were undergoing laparoscopic hysterectomy and received parecoxib 80mg intravenously at the beginning of anaesthesia. This prospective study was also double-blinded and placebo controlled.

Persistent pain after total knee replacement was studied by a questionnaire sent to all patients operated on the period from September 2002 to February 2004. Multivariate logistic regression analysis was performed to test assumed risk factors. The type of operation (primary, bilateral or revision) was assumed to influence the prevalence of persistent pain.The total number of patients recruited was 855.

Opioid sparing effect was evident with etoricoxib, but adding paracetamol to etoricoxib or giving parecoxib at the end of surgery did not show any opioid sparing effect. In any case, the worst pain score on the ward was significantly lower in the parecoxib 80mg treated group than in the placebo group. Parecoxib

80mg was also well tolerated in Study III. The sensitive markers of both glomerular and tubular damage did not differ significantly between the groups.

The response rate of the questionnaire was 65.7%. Prevalence of persistent pain after knee replacement surgery was 21.5% at rest and 29.8% during exercise. The risk factors for persistent pain were female gender, adjusted age, duration of pain (more than twelve months) prior to surgery and intensity of pain (more than mild) during the first postoperative week. The type of surgery did not influence the prevalence of persistent pain.

Tiivistelmä

Leikkauksen jälkeiseen kivunhoitoon suositellaan ns. multimodaalisuuden periaatetta. Perinteiset tulehduskipulääkkeet ovat tehokkaita vähentämään opioidien tarvetta, mutta niillä on omat haittavaikutuksensa kuten mahaärsytys ja vuotovaaran lisääntyminen. COX-2 selektiivisiltä tulehduskipulääkkeiltä nämä haittavaikutukset puuttuvat. Sen sijaan perinteisten ja COX-2 selektiivisten tulehduskipulääkkeiden oletetaan olevan samankaltaisia munuaisvaikutuksiltaan vaikkakin tutkimusnäyttö asiasta on vähäistä. Leikkauksen jälkeisen kivun pitkittyminen on yleistä. Sen esiintyvyys on ortopedisten leikkausten jälkeen vaihdellut kymmenestä kuuteenkymmeneen prosenttiin. Kipu on tärkein polven tekonivelleikkauksen syy ja yhtälailla leikkauksen tärkein tavoite on kivun lievittyminen. Pitkittyneen kivun yleisyyden ja mahdollisten riskitekijöiden selvittäminen auttavat hoidon suunnittelussa.

Väitöstutkimuksen tarkoituksena oli selvittää ensinnäkin COX-2 selektiivisten tulehduskipulääkkeiden tehoa ja turvallisuutta leikkauksen jälkeisen kivun hoidossa ja toisaalta pitkittyneen kivun esiintymistä ja riskitekijöitä polven tekonivelkirurgiassa. COX-2 selektiivisten tulehduskipulääkkeiden tehoa tutkittiin kahdessa prospektiivisessa, satunnaistetussa, kaksoissokkoutetussa ja lumelääke kontrolloidussa työssä. Leikkaustyyppinä oli molemmissa osatöissä sappirakonpoisto tähystämällä. Ensimmäisessä osatyössä potilaat saivat joko 40mg tai 80mg parakoksibia suonen sisäisesti leikkauksen lopussa ja toisessa osatyössä annettiin tutkimuslääke, etorikoksibi 120mg esilääkkeen yhteydessä joko yksin tai yhdessä parasetamoli 1g kanssa. Tärkein päätetapahtuma oli potilaiden itsensä annostelema opioidin määrä. Potilasmäärä ko. tutkimuksissa oli 148. COX-2 selektiivisten tulehduskipulääkkeiden munuaisturvallisuutta tutkittiin antamalla parekoksibi 80mg suonen sisäisesti ja mittaamalla herkkiä munuaismarkkereita potilailta, joille tehtiin tähystämällä kohdunpoisto. Osatyö oli satunnaistettu, kaksoisokkoutettu ja lumelääke kontrolloitu. Potilaita otettiin tutkimukseen yhteensä 30. Pitkittyneen kivun esiintyvyyttä selvitettiin lähettämällä kaikille tietyllä aikavälillä polvitekonivelleikatuille potilaille postitse kysely. Tutkimukseen osallistui 855 potilasta. Pitkittyneen kivun riskitekijät testattiin monimuuttujaisella riskianalyysillä. Leikkaustyypin oletettiin vaikuttavan pitkittyneen kivun esiintymiseen.

Etorikoksibi 120mg vähensi merkitsevästi leikkauksen jälkeistä opioidikulutusta. Sen sijaan parasetamolin lisääminen etorikoksibiin ei tuonut lisätehoa kivun lievitykseen. Myöskään parekoksibin tutkitut annokset eivät vähentäneet leikkauksen jälkeistä opioidikulutusta, vaikkakin parekoksibi 80mg vähensi merkitsevästi vuodeosastolla koettua pahinta mahdollista kipua.

Kolmannessa osatyössä vastaava annos parekoksibia ei aiheuttanut merkitseviä munuaismarkkereiden nousuja muutoin suhteellisen terveillä (ASAI-II, alla 60-vuotias) potilailla eli oli hyvin siedetty munuaisten osalta

Polvitekonivelpotilailla toteutetussa kyselytutkimuksessa oli vastausprosentti 65,7. Pitkittynyt kipu oli yleistä: 21.5% tutkituista kärsi kivusta levossa ja 29.8% rasituksessa. Riskitekijöitä kivun pitkittymiselle olivat naissukupuoli, mukautettu ikä, leikkausta edeltävän kivuliaisuuden kesto (yli 12 kuukautta) ja leikkauksen jälkeisen (ensimmäisen viikon) kivun voimakkuus (enemmän kuin lievä). Leikkaustyypillä ei ollut vaikutusta pitkittyneen kivun esiintymiseen. Riskitekijöihin vaikuttamalla pystytään myös pitkittyneen kivun esiintyvyyttä vähentämään. Näin ollen tekonivelleikkaus tulisi pyrkiä tekemään riittävän ajoissa ja toisaalta leikkauksen jälkeinen kipu tulee hoitaa tehokkaasti.

Contents

Abbreviations

APC	Adenoma prevention with Celecoxib
APPROV	Adenomatous Polyp Prevention on Vioxx
ARF	Acute renal failure
ASA	Anaesthetic risk groups according to the American Society of Anesthesiologists
ATP	Adenosintriphosphate
BMI	Body Mass Index
CI	Confidence intervals
CLASS	Celecoxib in Long-term Arthritis Safety Study
COMT	Catechol-O-methyltransferase
COX	Cyclo-oxygenase
CT	Computer tomography
$etCO_2$	End-tidal carbon dioxide
fMRI	Functional magnetic resonance imaging
GABA	Gamma-amino-butury-acid
GI	Gastrointestinal
GST	Glutathione-S-transferases
GTP	Guanosine Triphosphate
IASP	International Association for the Study of Pain
IC_{50}	Half maximal inhibitory concentration
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
LSD	Least significant difference
MEDAL	Multinational Etoricoxib and Diclofenac Arthritis Long-Term Programme
MEG	Magnetoencephalography
NaCl	Sodium Chloride
NMDA	N-methyl-D-aspartate
NRS	Numeral Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
ORL	Opioid Receptor Like
P	p-value
PCA	Patient controlled analgesia
PET	Positron emission tomography
PGE_2	Prostaglandin E_2
PGI_2	Prostacyclin
POD	Postoperative day

PONV	Postoperative nausea and vomiting
RCT	Randomized Controlled Trial
RR	Risk Ratio
S-Crea	Serum Creatinine
S-CysC	Serum Cystatin C
S-K	Serum Potassium
S-Na	Serum Sodium
SPECT	Single-photon emission computerized tomography
S-Urea	Serum Urea
TOF	Train-of-four
TXA_2	Thromboxane A_2
U-Crea	Urinary Creatinine
U-α-1-miglo	Urinary α-1-microglobulin
U-α-GST	Urinary α-glutathione-S-transferase
U-π-GST	Urinary π-glutathione-S-transferase
VAS	Visual Analogue Scale
VIGOR	Vioxx GI Outcomes Research
VRS	Verbal Rating Scale
WDR	Wide dynamic range
WHO	World Health Organization

List of original publications

I Puolakka PA, Puura AI, Pirhonen RA, Ranta AU, Autio V, Lindgren L, Rorarius MG. Lack of analgesic effect of parecoxib following laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2006; 50:1027-32.

II Puura A, Puolakka P, Rorarius M, Salmelin R, Lindgren L. Etoricoxib pre-medication for post-operative pain after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2006; 50:688-93.

III Puolakka P, Rintala S, Yli-Hankala A, Luukkaala T, Harmoinen A, Lindgren L, Rorarius M. The effect of parecoxib on kidney function at laproscopic hysterectomy. Renal Failure 2009; 31:284-9.

IV Puolakka P, Rorarius M, Roviola M, Puolakka T, Nordhausen K, Lindgren L. Persistent pain following knee arthroplasty. Eur J Anaesthesiol 2010; 27:455-60.

The original articles are referred to in the text by the above Roman numerals.

Introduction

Although pain is predictable after surgery, all efforts should be made firstly to minimize acute pain and secondly to prevent persistent pain. The most common concern among patients is experiencing the pain after surgery (Apfelbaum et al. 2003)

Opioids are most commonly used for postoperative pain relief although their adverse effects, especially nausea, are well documented. Combination of NSAIDs or COX-2 inhibitors with opioids as a multimodal analgesia is valuable because they reduce the use of opioids by about 20-50 percent (Gilron et al. 2003; Brune and Hinz 2004; Rømsing and Møiniche 2004). The COX-2 inhibitors have lost popularity because of documented risk of adverse cardiovascular events in long term use (Solomon et al. 2002; Solomon et al. 2004). However their perioperative use can be safe, especially when coxibs, unlike conventional NSAIDs, do not enhance surgical bleeding (Hegi et al. 2004) and peptic irritation can be reduced by a half compared to NSAIDs (Silverstein et al. 2000).

The renal adverse effects of COX-2 inhibitors are supposed to be equal to those of NSAIDs, because COX-2 is also expressed in the kidneys (Breyer and Harris 2001; Gambaro and Perazella 2003; Gilron et al. 2003; Brune and Hinz 2004; Rømsing and Møiniche 2004; Harris 2006; Winkelmayer et al. 2008). However, there are only few studies investigating (Koppert et al. 2006) or even reporting renal effect of coxibs in perioperative use (Malan et al. 2003; Ott et al. 2003; Reynolds et al. 2003).

The prevalence of persistent pain varies across operations and studies. (Wallace et al. 1996; Middelfart et al. 1998; Perttunen et al. 1999; Eisenberg et al. 2001; Kalso et al. 2001; Nikolajsen and Jensen 2001; Poobalan et al. 2003; Nikolajsen et al. 2004; Aasvang and Kehlet 2005; Lahtinen et al. 2006; Kalliomäki et al. 2008; King et al. 2008) In spite of variation, persistent postsurgical pain is common and has a significant effect on quality of life. This, in turn, means that persistent pain also has great economic significance.

Persistent pain after joint replacement surgery is of special interest, because pain is mostly the main indication for surgery and also the main outcome variable. The prevalence of persistent pain has been the subject of some studies (Johnsson and Thorngren 1989; Burkart et al. 1993; Brander et al. 2003; Garcia et al. 2003;Harden et al. 2003; Nikolajsen et al. 2006; Elson and Brenkel 2007; Martinez et al. 2007; Lundblad et al. 2008) but the risk factors for persistent pain have been evaluated more rarely (Johnsson and Thorngren 1989; Brander et al. 2003; Harden et al. 2003; Nikolajsen et al. 2006; Lundblad et al. 2008).

Our first two studies joined the clinical studies evaluating the efficacy of treatment methods in acute postsurgical pain. The third study was intended to investigate renal adverse effects of COX-2 inhibitor, parecoxib. The fourth study revealed the prevalence and the risk factors of persistent pain in patients after total knee replacement.

Review of the literature

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey and Bogduk 1994). Although pain is a psychological sensory experience, the biomedical model of pain is well documented.

1. Mechanisms of postsurgical pain

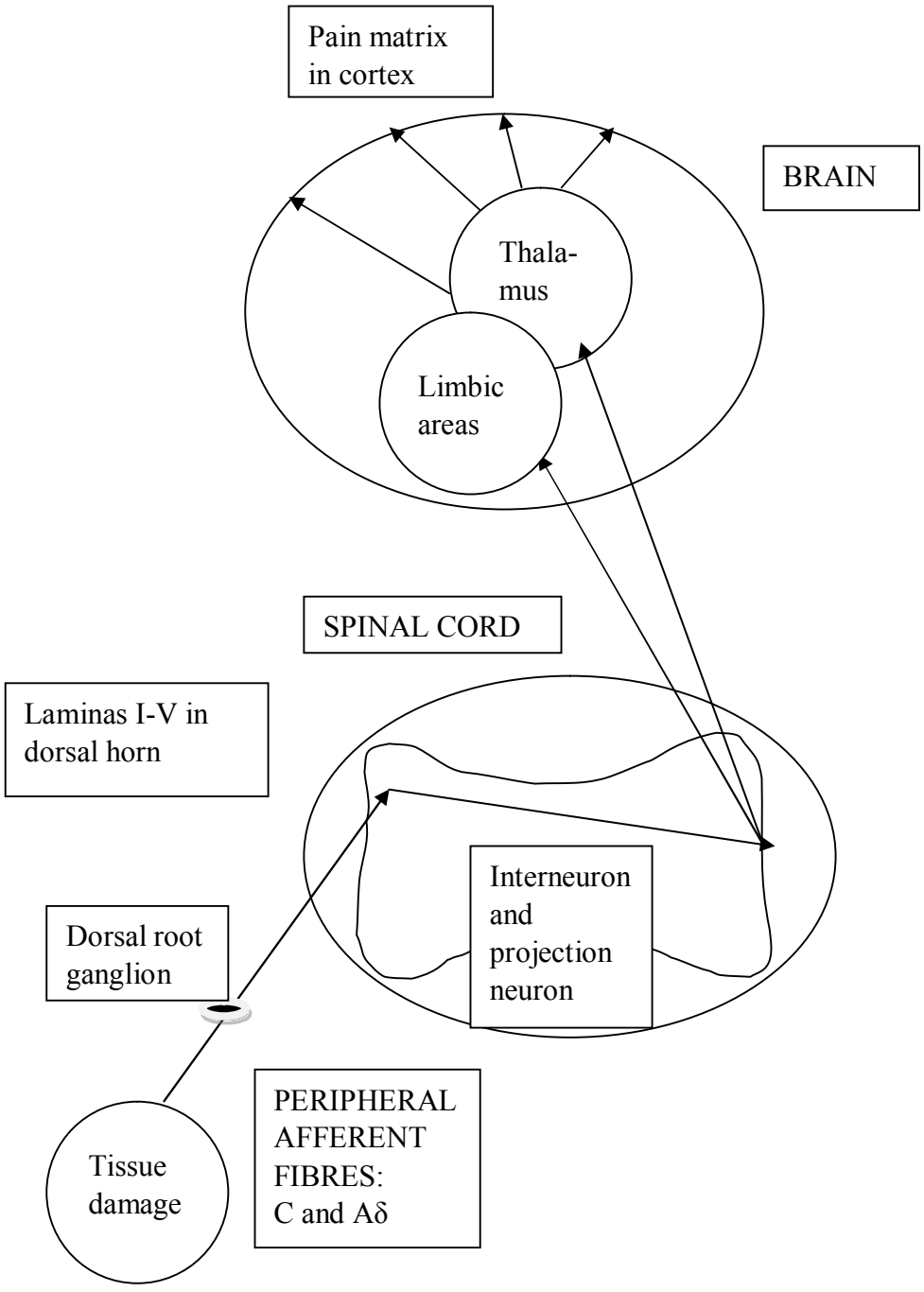
The cascade from tissue damage to the sensation of pain can be divided into four steps: transduction, transmission, modulation and perception (Kalso et al. 2009). Transduction refers to the action potential of nociceptors, which is caused by tissue damage. Transmission, in turn, refers to the signal transporting system from periphery to brain and modulation refers to all the inhibitory and excitatory events along that pathway. Perception is the end stage cascade, the sensation of pain (Kalso et al. 2009).

In the peripheral nervous system there are four main types of sensory afferent fibres: Aα, Aß, Aδ and c. Aα-fibres and Aß-fibres are both large in diameter, myelinated and responsible in propriosepting (Aα, Aß) or heavy touch (Aß). Aδ-fibres are thinly myelinated and c-fibres nonmyelinated, but both can be termed nociceptors or pain fibres. The diameter is small, the conductance is slow and the response threshold to stimulus - mechanical, chemical or thermal - is high. In a clinical situation they can be differentiated by temperature- Aδ-fibres are responsible in cold and c-fibres in hot temperature sensation (D'Mello and Dickenson 2008; Kalso et al. 2009).

These afferent pain fibres transmit impulses from the periphery through the dorsal root ganglion to the dorsal horn of the spinal cord, where they synapse with projection neurons and interneurons. The spinal cord is divided into laminas according to anatomical features. C-fibres synapse with projection neurons, which are located in lamina I-II and V and Aδ-fibres synapse with neurons in lamina I and V (Kalso et al. 2009). These projection neurons are called nociceptive specific cells or wide dynamic range (WDR) neurons depending on which afferent fibres they synapse with (D'Mello and Dickenson 2008). WDRs are located in lamina V and synapse with a wider variety of fibres (Aß, Aδ, c) (D'Mello and Dickenson 2008). These WDRs are able to increase the responses evoked after repeated stimuli (so-called wind-up) (D'Mello and Dickenson 2008; Kalso et al. 2009). Projection neurons from lamina I innervate areas such as the

parabrachial area and periaqueductal grey, which are affected by limbic areas. Lamina V neurons mainly project to the thalamus via the spinothalamic tract. From the thalamus, the primary sensory pathway projects to the various cortical regions (D'Mello and Dickenson 2008). Other ascending sensory tracts projecting pain are spinoreticular, spinomesencephalic, spinotectal and spinohypothalamic (Soinila et al. 2006). These all use the anterolateral column of the spinal cord on the contralateral side. Some spinocerebellar tracts include pain fibres in addition to proprioseptic ones (Soinila et al. 2006).

Figure 1. Simplified pathway from tissue damage to pain sensation



The function of interneurons in the spinal cord may be either excitatory or inhibitory. The major excitatory neurotransmitter is glutamate and the major inhibitory one is GABA (D'Mello and Dickenson 2008). In addition, peptides like endogenous opioids, substance P and somatostatin are documented neurotransmitters of interneurons (Kalso et al. 2009). These interneurons, in turn, are controlled by descending pathways from the brainstem and the hypothalamus. They are all responsible for modulation. Melzack and Wall published this gate-control theory of pain as early as 1965 (Melzack and Wall 1965).

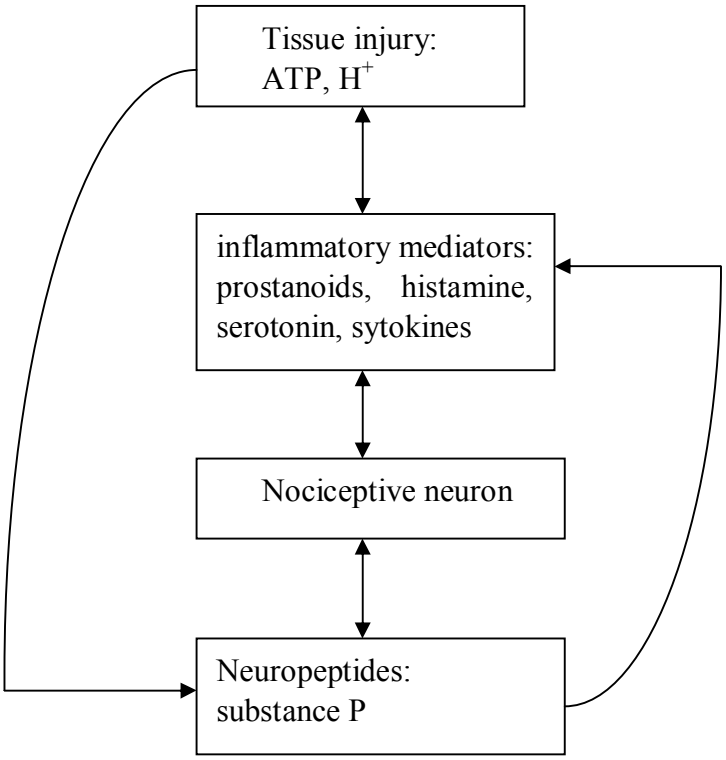
The perception of pain is a cortical process, in which various cortical regions take part. Imaging facilities (CT, PET, SPECT, fMRI, MEG) have been able to show that at least primary and secondary somatosensory cortex, insular cortex, anterior cingulated cortex and prefrontal cortex are involved in pain perception. These areas together are called the pain matrix (D'Mello and Dickenson 2008).

Visceral pain sensation, perception is different, from somatic perception. The visceral organs have only few nociceptors (Aδ and c). In addition Aß responsive to pressure sensation projects pain from the visceral system. Because of these, visceral pain is poorly localized and different in nature-more dull or vague than somatic pain. Interaction with projection neurons in the dorsal horn of the spinal cord causes pain to be referred to different parts of the body confounding patients and clinicians (Kalso et al. 2009).

1.1 Pathophysiology of acute postsurgical pain

A surgical procedure always damages the operated and surrounding tissues. This damage releases chemical mediators like protons, ATP, serotonin, histamine, bradykinin and arachidonic acid from injured and inflammatory cells (Kalso et al. 2009). Arachidonic acid is converted via the cyclo-oxygenase pathway into prostanoids and leukotrienes. All these mediators in turn directly or indirectly stimulate peripheral sensory neurons and cause so-called peripheral sensitisation, primary hyperalgesia, by reducing the threshold of nociceptive receptors and increasing the excitability of the neurons (Kehlet et al. 2006a). The excessive stimulation of the nociceptive neurons also results in the release of stored neuropeptides like substance P, which is a potent activator of inflammatory response in surrounding tissue (Kalso et al. 2009). A vicious circle has been created. This is illustrated schematically in Figure 2.

Figure 2. Schematic presentation of transmitters in tissue injury



Central sensitisation, secondary hyperalgesia, is the next step, where continuing stimulus from the periphery causes increased and altered excitability of the sensory neurons in the dorsal horn of the spinal cord (Kehlet et al. 2006a). One primary mechanism in the spinal cord is so-called wind-up, which is mediated by glutamate via NMDA receptors (D'Mello and Dickenson 2008; Kalso et al. 2009). Central sensitisation is also mediated by the central nervous system with descending pathways to the dorsal horn of the spinal cord (D'Mello and Dickenson 2008; Kalso et al. 2009).

Fortunately, these processes are reversible and the inflammatory mediators gradually disappear once the wound has healed (Kehlet et al. 2006a). Primary hyperalgesia can be evoked by a stimulus to the injured area, but secondary hyperalgesia can also be provoked from the surrounding area (Kalso et al. 2009).

1.2 Pathophysiology of persistent postsurgical pain

The pathophysiology of persistent pain is similar to that of acute variety if the reason for persistent pain is a complication such as infection, incorrect fracture correction etc. (Kehlet et al. 2006a). The pain should then abate if the peripheral driving force is removed.

The situation is totally different, if the reason for persistent postsurgical pain is surgical injury to any part of the sensory pathway system. Although the primary events of nerve injury are quite similar to any tissue damage, causing peripheral and central sensitization in time, the main difference arises from nerve injury itself. If an injured axon is not restored to its target, this specific neuron dies. Gradually, apoptosis also destroys the neurons in the dorsal horn of the spinal cord and in the grey matter of the cortex. During the process, chemicals from dying cells aggravate the inflammation and sensitization. The consequence, the combination of sensory loss with paradoxical hypersensitivity, is a key feature of neuropathic pain (Kehlet et al. 2006a). Welch et al. reported a prevalence of only 0.03% in nerve injuries after surgery (Welch et al. 2009). The data were retrospectively collected from different databases including the bias that not all cases were reported to these data sources. The true prevalence of nerve injuries after surgery is not known, but it exceeds these numbers (Prielipp and Warner 2009).

Although biomedical models of pain are useful, they are not always able to explain persistent pain. Persistent pain can develop without preexisting nerve damage (Prielipp and Warner 2009). By contrast, nerve damage does not necessarily cause pain. The careful technique for identifying and sparing intercostobrachial nerve in axillary node dissection did not reduce the incidence of pain although skin sensation was better preserved than in standard dissection (Abdullah et al. 1998). The biomedical model needs to be expanded to a biopsychosocial model, where cultural differences, past experiences, personality variables, hormonal state etc. are taken into account (Gatchel et al. 2007).In addition, there are increasing amount of data about genetic predisposition to persistent pain (Belfer et al. 2004;Diatchenko et al. 2005;Stamer and Stuber 2007a;Stamer and Stuber 2007b;George et al. 2008;Reimann et al. 2010).

2. Pharmacological treatment of acute postsurgical pain

The WHO has developed a recommendation, a three-step ladder, for cancer pain (http://www.who.int/cancer/palliative/painladder/en/). This recommendation has been adapted to all kinds of acute pain. The idea is to start immediate administration of drugs in the following order: nonopioids (NSAID, paracetamol), mild opioids (codeine, tramadol) and strong opioids (morphine, oxycodone) until the patient is free from pain. To maintain this state, drugs should be given regularly rather than “on demand”. Antidepressants, sedatives and surgical interventions are mentioned as adjuvants. The following review of pharmacological treatment of acute pain is written in the order of the WHO ladder. The adjuvants, except regional anaesthesia as anaesthesiological technique, have been omitted.

2.1 Paracetamol

Paracetamol, also called acetaminophen, was first synthesized by Harmon Northrop Morse in 1877 (Morse 1878), but it was not until the early fifties that paracetamol came into wider clinical use. However, the mechanisms of the action of paracetamol are still not fully understood. It is usually mentioned to be a weak inhibitor of prostaglandin production although the molecular mechanism is uncertain.

In 2002 Chandrasekharan et al. were able to introduce a variant of COX-1, which was depressed by paracetamol and called for COX-3 (Chandrasekharan et al. 2002). This enzyme was detectable in dog (Chandrasekharan et al. 2002) and rat brain (Kis et al. 2003). This was believed to solve the question of the mechanism of paracetamol. Later it became evident that the enzyme could not be found in human brain and the action of the enzyme was not strong enough to explain the analgesic and antipyretic effect of paracetamol (Schwab et al. 2003a;Schwab et al. 2003b;Graham and Scott 2005).

Paracetamol is today believed to act more like COX-2 inhibitors. COX-2 inhibition is chosen if the concentration of arachidonic acid is low and COX-1 inhibition if the concentration of arachidonic acid is high (Graham and Scott 2005). This is line with the fact that paracetamol works rather in the central nervous system than on the periphery, where the concentration of arachidonic acid must be high because of ongoing trauma or inflammation. In addition, paracetamol is known to act in the spinal cord by stimulating the descending serotonergic pathways and thus inhibiting the nociceptic pathways from the periphery (Bonnefont et al. 2003; Graham and Scott 2005).

The pharmacodynamic and pharmacokinetic profiles of paracetamol are summarized in Table 1.

Table 1 Pharmacodynamic and pharmacokinetic profiles of paracetamol 1g po

Peak plasma concentration	12.3µg/l
Time to peak plasma concentration	1h
IC_{50} (COX-2/COX-1)*	44/94µg/l
Mean oral availability	80-88%
Route of elimination	hepatic 95%, renal 5%
Elimination half-life	2.8h

* IC_{50} is indicated by lipopolysaccaharide-induced prostaglandin synthesis (COX-2) and thromboxane B2 generation (COX-1) in human blood cells (Sciulli et al. 2003).

The analgesic efficacy of paracetamol in acute pain is known to be superior to placebo, but in most studies it has been shown to be inferior to NSAIDs. The combination of paracetamol with NSAIDs has been believed to increase the efficacy of both. The evidence to support this is still rather poor (Rømsing et al.

2002), but the lack of adverse effect supports the combination treatment (Hyllested et al. 2002).

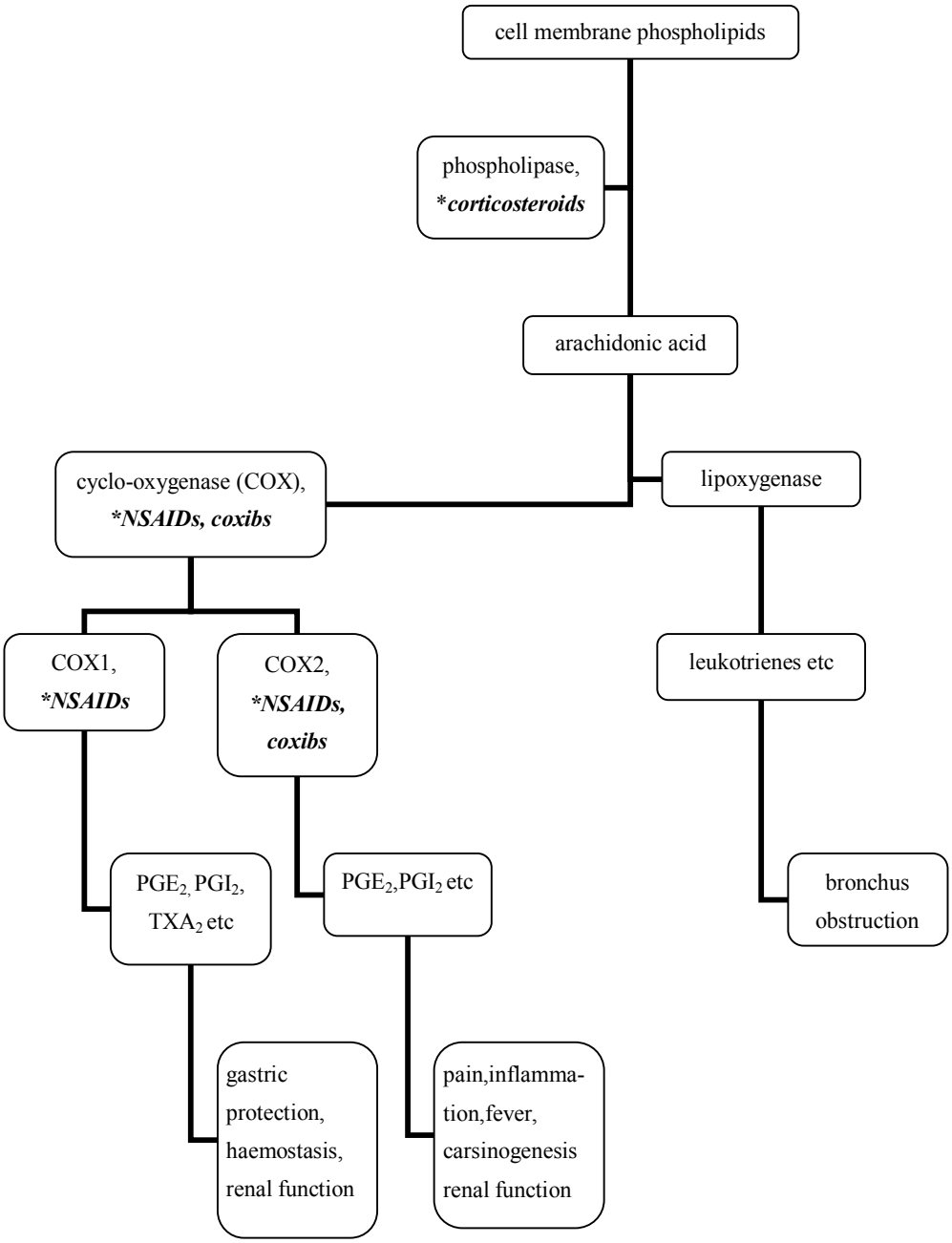
Adverse effects of paracetamol are rare, < 1/10000 (Duggan and Scott 2009). The most serious one is hepatotoxicity. An overdose of paracetamol can lead to irreversible liver necrosis which may be lethal. The necrosis is due to the toxic metabolite of paracetamol. The single adult dose to cause severe liver damage is 150-250mg/kg, which is ten times the recommended one (Prescott et al. 1971). However, among chronic alcoholics even therapeutic doses of paracetamol have been reported to be harmful (Seeff et al. 1986) although the underlying mechanism is not clear (Prescott 2000a; Prescott 2000b). Paracetamol is believed to act by COX-2 inhibition, but doubling the recommended single dose to 2000mg seems to inhibit platelet function (Munsterhjelm et al. 2005).

Paracetamol can be administered enterally and parenterally. Bioavailability is almost 100% if orally administered. The analgesic effect begins within 30 minutes and the maximum effect is achieved in one hour if orally administered. The elimination half-life of paracetamol is only 2 hours, necessitating administration three to four times a day. The onset of analgesia occurs within 5-10 ten minutes of the intravenous administration of paracetamol but the pharmacodynamic profile is otherwise similar to that of enteral administration. The recommended single doses are 1g for adults and 15mg/kg for children (Duggan and Scott 2009). These doses are the same for enteral and parenteral route, although the bioavailability of suppositories is known to be variable and only 80% of that of tablets. Therefore, the single dose of paracetamol suppositories needed for pain relief after surgery has to be as high as 40-60mg/kg (Korpela et al. 1999). The rate of absorption is also slower and maximum plasma concentration is achieved about 2-3 hours after rectal administration (Korpela et al. 1999). The recommended doses for antipyretic effect are half of that needed for analgesic effect (Plaisance and Mackowiak 2000), confusing patients, parents and partly clinicians, too.

2.2 Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs are known to act by inhibition of the cyclo-oxygenase enzyme, which catalyzes the synthesis of prostaglandins from arachidonic acid (Vane 1971). The COX gene was cloned in 1988 and since then two isoforms have been identified: COX-1 and COX-2 (Gajraj 2003). COX-1 is expressed more constitutively throughout the body. COX-2 is expressed predominantly in reaction to inflammation by the inflammatory cells. COX-1 is essential in homeostatic processes (gastrointestinal protection, platelet aggregation, renal function), but later studies have revealed that COX-2 also has certain role in homeostasis although its main role is pathologic processes such as pain, fever and carcinogenesis (McCrory and Lindahl 2002). The simplified cyclo-oxygenase pathway with differential expression of COX-1 and COX-2 is illustrated in Figure 3. Pharmacological treatment with action sites is represented by *.

Figure 3. Cyclo-oxygenase pathway



The efficacy of NSAIDs in acute pain has been demonstrated in a vast number of studies and summarized in meta-analyses showing numbers needed to treat around 2-3 (http://www.thecochranelibrary.com). The opioid-sparing effect is approximately 35% (Rorarius et al. 1993) and they seem to work even better than opioids in movement-evoked pain (Pavy et al. 1995) .

The principle behind the adverse events is based on the mechanism of NSAIDs. Inhibition of cyclo-oxygenase enzyme results in the shunting of arachidonic acid to the lipoxygenase pathways, resulting in increased leukotriene synthesis. This in turn increases the probability of broncospasm. Inhibition of COX-1 causes adverse effects by disrupting the gastric mucosa and platelet aggregation. The adverse effect in platelet aggregation is beneficial in the prophylaxis of thrombotic events (myocardial, cerebrovascular etc.) and the absence of that adverse effect may even be harmful with selective COX-2 inhibitors, coxibs (Solomon et al. 2002; Solomon et al. 2004). Renal adverse effects of NSAIDs will be discussed together with COX-2 inhibitors (see text in Chapter 3). Fracture healing may also be disturbed by NSAIDs but on the other hand, they have a beneficial effect on ectopic bone formation (Beck et al. 2005; Vuolteenaho et al. 2008; Boursinos et al. 2009). NSAIDs have also been studied in the primary prevention of cancer and efficacy has been reported in a meta-analysis of colorectal (Rostom et al. 2007) and lung cancer (Khuder et al. 2005).

2.3 COX-2 inhibitors

COX-2 selective NSAIDs, so called COX-2 inhibitors or coxibs, were widely introduced in 1999, one hundred years after the first NSAID, acetylsalicylic acid (Aspirin). Celecoxib, rofecoxib, valdecoxib, parecoxib and etoricoxib were those introduced, although nimesulide and meloxicam were marketed in Europe long before the discovery of COX-2 offering precursor molecules for these newer COX-2 inhibitors (Gilron et al. 2003).

The COX-2 inhibitors were reported to be equally effective in pain relief in acute postoperative pain model, which was underlined in several reviews (http://www.biomedcentral.com). Only celecoxib failed to prove its efficacy when compared to NSAIDs (Rømsing and Møiniche 2004). Parallel to these efficacy studies were studies demonstrating a positive profile in gastrointestinal adverse effects (Bombardier et al. 2000; Silverstein et al. 2000) because of the absence of COX-1 inhibition.

Only some years after launching, the results of the so-called VIGOR trial were published, showing increased risk for cardiovascular events in rofecoxib compared to naproxen (Mukherjee et al. 2001). To confuse the audience, the CLASS trial was unable to show similar risk with celecoxib (Silverstein et al. 2000). Finally, rofexocib together with valdecoxib were withdrawn from the market in 2004 after the so-called APPROVe trial (Bresalier et al. 2005). This was in line with the APC study (Solomon et al. 2005). In both trials, the coxib treated patients with colorectal neoplasia showed an increased risk for cardiovascular events (Bresalier et al. 2005; Solomon et al. 2005). Later the MEDAL Programme failed to show any difference in thrombotic cardiovascular events between etoricoxib and diclofenac (Cannon et al. 2006).

The story of the latest and most selective COX-2 inhibitor, lumiracoxib, was even shorter than that of rofecoxib and valdecoxib. It was introduced in 2005 and only two years later it was withdrawn from the market

(http://www.tga.gov.au/recalls/2007/lumiracoxib.htm) in most countries because of several serious liver adverse events.

The only COX-2 inhibitors still available for clinical use are celecoxib, parecoxib and etoricoxib. Celecoxib is less selective than the others and after failing in acute pain models (Rømsing and Møiniche 2004), it is mostly only used long term. Parecoxib is a COX-2 inhibitor, which can be administered parenterally. It is a pro-drug metabolized by the liver to valdecoxib. The analgesic effect of valdecoxib starts within 10 minutes and the maximum effect is reached within half an hour. The elimination half-life of valdecoxib is 8 hours. Administered 40mg twice a day, steady-state plasma concentration is achieved in 4 days (Cheer and Goa 2001). Etoricoxib is orally administered and its bioavailability is almost 100 %. The analgesic effect of etoricoxib begins within 30 minutes and the maximum effect is achieved within one hour. The elimination half-life of etoricoxib is 22 hours allowing administration once a day. Steady-state plasma concentration is reached with 120mg in 7 days (Cochrane et al. 2002). After steady-state achievement both drugs are recommended to be administered in reduced amounts. The pharmacodynamic and pharmacokinetic parameters of investigational COX-2 inhibitors are summarized in Table 2.

Table 2. Pharmacodynamic and pharmacokinetic profiles of parecoxib and etoricoxib

	Parecoxib 40mg iv	Etoricoxib 120mg po
Peak plasma concentration	1.02mg/l	3.6mg/l
Time to peak plasma concentration	0.6h	1h
IC_{50} (COX-2/COX-1)*	0.005/140 µg/l	1.1/ 116 µg/l
Mean oral availability	-	100%
Route of elimination	renal	hepatic
Elimination half-life (parecoxib/valdecoxib)	0.69/7.88h	22h

* IC_{50} is indicated by lipopolysaccaharide-induced prostaglandin synthesis (COX-2) and thromboxane B2 generation (COX-1) in human blood cells (Tacconelli et al. 2002).

The renal adverse effects of COX-2 inhibitors will be discussed later in Chapter 3. In addition to these renal adverse effects and cardiovascular adverse effects mentioned above, COX-2 inhibitors share the effects on bone formation and remodelling with traditional NSAIDs. In any case, the data from human studies are sparse (Beck et al. 2005; Vuolteenaho et al. 2008; Boursinos et al. 2009). Similarily, COX-2 inhibitors have been suggested to be beneficial in cancer prophylaxis (Rostom et al. 2007).

2.4 Opioid analgesics

Acute pain, which is moderate or severe in intensity, generally cannot be solved without opioids. Opioids act through specific receptors (μ, δ, κ, ORL_1) on injured tissue, in the dorsal horn of the spinal cord and in the brain (Kalso et.al. 2009).

The efficacy of opioids is well documented, but so are the adverse effects. Some of the adverse effects are more harmful than others, but all of them cause patients severe discomfort. The most potent adverse effect, mediated centrally by μ-opioid receptors, (Dahan et al. 2010) is respiratory depression. The incidence of respiratory depression is low, 0.5% (Dahan et al. 2010), but significant, because this adverse effect can be fatal. Fortunately, the respiratory drive of a patient with marked postoperative pain is increased, making opioid treatment safe in general. By contrast, nausea and vomiting are very common adverse effects and consequences from direct central stimulation of the Chemoreceptor Trigger Zone (Kalso et al. 2009). Opioid-related PONV may jeopardize early recovery after surgery. Therefore, opioid-sparing regimens are welcome in clinical acute pain treatment. Opioid related ileus and constipation are in turn due to decreased smooth muscle contractility. Pruritus is the most common adverse effect of spinal administration (Dahan et al. 2010). In an animal study, the existence of a specific spinothalamic pathway for itch has been demonstrated (Andrew and Craig 2001). Opioids reduce the inhibition of this pathway allowing the spontaneous activity of central itching neurons to increase (Schmelz 2001). Another issue recently addressed is opioid-induced hyperalgesia, which is documented even after short-term administration of short-acting opioids like remifentanil (Guignard et al. 2000). This phenomenon is also called acute opioid tolerance and may apply other opioids, too (Angst and Clark 2006). Both analgesic and adverse effects differ between genders and individuals. Females are more sensitive to the effects of opioids, although the onset of analgesia is faster in males (Dahan et al. 2008).

Opioid analgesics can be administered in several ways. Oral, intramuscular, intravenous, sublingual, intranasal, intra-articular, transcutaneous and intraspinal administrations all have their advantages.

2.5 Regional anaesthesia

Regional anaesthesia, i.e. central and peripheral blocks and wound infiltration can be regarded as pharmacological treatment of acute pain (Bonica 1984). It is most commonly used as a regimen of postoperative care, but regional anaesthesia could also be utilised in palliative and trauma care. Properly designed and performed, regional anaesthesia has proved to be beneficial to patients suffering from acute pain. A recently published review on central neuraxial blocks showed a clear correlation between blocks and improved comfort but also between blocks and reduced morbidity and mortality after surgical procedure (Breivik et al. 2010).

Despite the convincing evidence on the benefits of regional anaesthesia, there are some disadvantages, too. Neuraxial blocks are invasive in nature and there is always a risk of infection and needle or catheter-induced nerve injury. Pain and paraesthesia have been shown to be important predictors of nerve damage underlying the importance of performing blocks in the awake state (Faccenda and Finucane 2002). Ultra-sound guided regional anaesthesia has been believed to increase the safety of patients but a meta-analysis of 22 RCTs failed to prove any increased safety regarding peripheral neural injury when compared to standard nerve localisation tools (Neal 2010). Fortunately, the rate of complications was low in both groups. Liu et al. have reported the greatest number of symptomatic nerve injuries after interscalene blocks at 1 week: 8% in an ultra-sound guided group, and 11% in a nerve stimulation group (Liu et al. 2009). Accidental vascular puncture with increased systemic toxicity of local anaesthetic was more common with patients whose regional anaesthesia was performed with standard nerve localisation than with ultra-sound guided technique (Neal 2010). This systemic toxicity (central nervous system toxicity, cardiotoxicity) of local anaesthetic can be further reduced by reducing the volume of anaesthetic which goes in line with ultra-sound guided blocks. Newer agents, ropivacaine and levobupivacaine have enhanced the safety profile when compared to bupivacaine (Veering 2003). Local anaesthetic also has local neurotoxicity, which is most obvious with spinally used 5% lidocaine (Rigler et al. 1991). The contact myotoxicity of local anaesthetic is known to cause necrosis of the skeletal muscles. Fortunately, this necrosis is followed by rapid regeneration of the muscle cells (Hogan et al. 1994).

Complications associated with central neuraxial blocks are rare but serious. One study covering all complications after central neuraxial blocks in Sweden during the 1990s, reported an incidence of 1:52000 in spinal haematomas after central neuraxial blocks (1:18 000 after epidural technique and 1:160000 after spinal technique) (Moen et al. 2004). Seventy-two percent occurred during the second half of the decade (Moen et al. 2004), which is in line with the increasing use of antihaemostatic drugs. Other risk factors for spinal bleeding are haemostatic disorders, anatomical abnormalities of the spine and spinal blood vessels, elderly patients, renal and hepatic impairments (Breivik et al. 2010). To minimize the risk of this serious complication, recommendations for safe clinical practice with neuraxial blocks have recently been published (Breivik et al. 2010). Several studies have tried to confirm that regional anaesthesia could reduce postsurgical persistent pain (Senturk et al. 2002; Tiippana et al. 2003; Nikolajsen et al. 2004), but the evidence is not convincing (Macrae 2008; Breivik et al. 2010).

3. Cyclo-oxygenase inhibitors and renal function

Although COX-2 is induced at the sites of inflammation, both COX-1 and COX-2 are highly expressed in the kidneys. The localization of COX-1 and COX-2 is illustrated in Figure 4. COX-1 is expressed in the medullar collecting ducts and in interstitial cells. COX-2 in turn has been detected in cortical thick ascending limbs including macula densa and the renal vascular components, podocytes and arteriolar smooth muscle cells (Breyer et al. 2001). In addition, COX-2 expression can be upregulated in conditions where the production of prostaglandins has become crucial, such as renal artery stenosis (Mann et al. 2001) and heart failure (Abassi et al. 2001).

COX-1 and COX-2 derived prostaglandins have several roles in the kidney. In euvolemic, unstressed state these roles are meaningless, but in pathophysiological states they become critical. For instance, sympathetic activation following several perioperative situations like volume depletion, pain and nausea, constricts afferent arterioles of the glomerulus reducing the glomerular filtration rate (GFR). Both PGI_2 and PGE_2 can counteract and produce vasodilatation of renal arterioles maintaining GFR. PGI_2 production in turn increases renin release, which in turn activates the renin-angiotensin-aldosterone-system. Prostaglandins also inhibit active absorption of sodium in thick ascending limbs and collecting ducts (Breyer et al. 2001; Gambaro and Perazella 2003; Harris 2008).

3.1 Clinical implications of COX inhibitors for renal function

The inhibition of the synthesis of these prostaglandins by NSAIDs and COX-2 inhibitors causes a variety of clinical renal syndromes. The cyclo-oxygenase inhibitors can decrease the renal blood flow in the afferent arteriole. This in turn decreases intraglomerular pressure and GFR will be reduced. Acute renal failure (ARF) will manifest. If the stressed state persists, acute renal ischaemia turns to acute tubular necrosis. The use of cyclo-oxygenase inhibitors also results in a decreased release of renin. The lowered production of renin in turn decreases aldosterone secretion, which can lead to hyponatremia and hyperkalemia. The use of both NSAIDs and COX-2 inhibitors may also result in sodium and water retention with oedema, hypertension and congestive heart failure formation (Breyer et al. 2001; Gambaro and Perazella 2003; Barkin and Buvanendran 2004).

The prolonged use of cyclo-oxygenase inhibitors has also led rarely to syndromes like analgesic nephropathy, interstitial nephritis, nephrotic syndrome, papillary necrosis and cancer (Gambaro and Perazella 2003; Markowitz and Perazella 2005).

Acute renal failures associated with conventional NSAIDs are well documented (Fong and Cohen 1982; Feldman et al. 1997; Whelton 1999; Kallanagowdar et al. 2006). The overall incidence of ARF was around one

percent and the risk of ARF was doubled with more than five days prolonged therapy with ketorolac (Feldman et al. 1997) In addition, sodium retention and oedema are found in five percent of the population taking NSAIDs (Whelton 2000)

The renovascular effect of COX-2 inhibitors may be even more evident with them than with traditional NSAIDs (Cannon et al. 2006; Chan et al. 2009). These results are in line with the MEDAL Programme, where discontinuations because of hypertension were more frequent in the etoricoxib-treated group (incidence 2.3 %) versus the diclofenac-treated group (incidence 0.7%) (Cannon et al. 2006). In addition, congestive heart failure and oedema were more common causes of discontinuation in the etoricoxib group with incidences of 0.7 and 1.9% respectively (Cannon et al. 2006). There are also some case reports of ARF associated with the use of COX-2 inhibitors in patients with predisposing factors (Perazella and Eras 2000; Braden et al. 2004).

3.2 Novel biomarkers of renal function

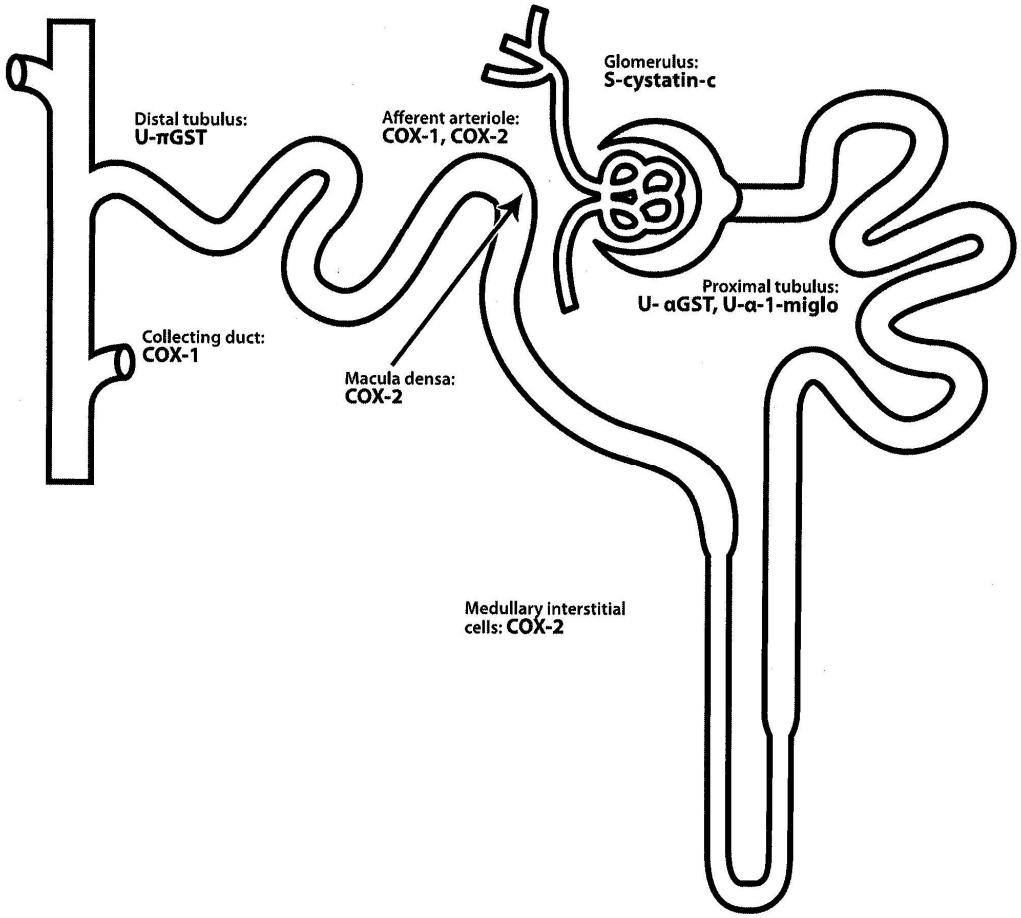
Novel sensitive biomarkers of renal function are cystatin C, α-1-microglobulin and glutathione-s-transferases α and π. The sites of biomarkers in the nephron are presented in Figure 4. Cystatin C and α-1-microglobulin are in clinical use but glutathione-s-transferases are used only in research.

Cystatin C is the plasma protein, which is produced regularly by all nucleated cells. The production of cystatin C is less dependent on age, gender, diet and muscle mass than the production of creatinine. Cystatin C works as a cysteine protease inhibitor. It is freely filtrated by the glomerulus. The serum level of cystatin C increases if the glomerular filtration rate decreases. The upper limit of the normal value is 1.4mg/l for those under 50 years and 1.5mg/l for those over 50 years (Harmoinen et al. 2003; Shlipak et al. 2006). A meta-analysis comparing serum cystatin C to creatinine as markers for GFR showed the superiority of cystatin C (Dharnidharka et al. 2002).

α-1-microglobulin is the plasma protein which is synthesized by hepatocytes. It is filtrated relatively freely by the glomerulus and reabsorbed and catabolised by the proximal tubular cells. The urinary level of α-1-microglobulin is used to measure proximal tubular dysfunction. The upper limit of normal value is 8mg/l. α-1-microglobulin is responsible for immunomodulation. (Akerström et al. 2000)

Glutathione-s-transferases (GST) are cytosolic enzymes and involved in the detoxification of endogenous and exogenous substances. α-GST is localized in the proximal and π-GST in the distal tubular cells of the kidney. Damage to these cells is associated with an increase in urinary levels of specific GST (Svendsen et al. 2000). The normal values corrected for urinary creatinine are 0.10-1.93 µg/mmol with α-GST and 0.25-7.41 µg/mmol with π-GST.

Figure 4. Localizations of COX-1, COX-2 and biomarkers in the nephron.



4. Persistent postsurgical pain

Despite our ability to treat acute pain pharmacologically during and immediately after surgery, a remarkable part of that pain persists and causes a major problem for patients recovering from surgery. The definition of persistent or chronic postsurgical pain varies, but the most referred to definition was proposed by Macrae W.A. (Macrae 2008). The pain should have developed after a surgical procedure, other causes of pain must be excluded and the pain should be of least two months duration (Macrae 2008). On the other hand, most trials studying chronic pain assume that the minimum duration of the pain is three months (Merskey and Bogduk 1994) and this definition is sometimes also used in the postsurgical literature (Kehlet et al. 2006b). The recommendation for RCTs of chronic pain made by the IMMPACT consensus meeting is also in line with the IASP definition, but encourages the use of a minimum duration of six months to increase the specificity of trials (Dworkin et al. 2010).

4.1 Epidemiology of persistent pain in different types of surgery

The prevalence of persistent pain after different types of surgery has been summarised in the following Table 3. The most common is persistent pain after amputation (Perkins and Kehlet 2000; Nikolajsen and Jensen 2001) and thoracotomy (Perttunen et al. 1999; Kalso et al. 2001). In both situations, as many as half of patients operated on suffer from persistent pain (Perttunen et al. 1999; Kalso et al. 2001; Nikolajsen and Jensen 2001) .The intensity of the persistent pain has in general been from mild to moderate (Kehlet et al. 2006b). Only a minority (5-10%) of patients operated on have suffered from severe, disabling pain (Kehlet et al. 2006b).

Table 3. Prevalence of persistent pain after surgical procedures

Surgical procedure	Prevalence of persistent pain (%)	References
Amputation	60-80	(Perkins and Kehlet 2000; Nikolajsen and Jensen 2001)
Thoracotomy	40-60	(Perttunen et al.1999; Kalso et al. 2001)
Sternotomy	20-50	(Eisenberg et al. 2001; Lahtinen et al. 2006; King et al. 2008)
Breast surgery	10-60	(Tasmuth et al. 1995; Wallace et al. 1996)
Inguinal hernia repair	5-30	(Poobalan et al. 2003; Aasvang and Kehlet 2005; Kalliomäki et al. 2008)
Cholecystectomy	10-50	(Middelfart et al. 1998)
Caesarean section	12	(Nikolajsen et al. 2004)
Orthopaedic surgery	10-60	(Johnsson and Thorngren 1989; Burkart et al. 1993; Brander et al. 2003; Garcia et al. 2003; Harden et al. 2003; Nikolajsen et al. 2006; Elson and Brenkel 2007; Martinez et al. 2007; Lundblad et al. 2008)

4.2 Risk factors of persistent postsurgical pain

The risk factors of persistent postsurgical pain can be divided into patient factors and medical factors. Awareness of these factors can be useful in the prevention of postsurgical persistent pain.

4.2.1 Medical risk factors for persistent postsurgical pain

One medical risk factor above all others is the surgical procedure itself. This should be kept in mind, especially when patients are operated on for other reasons than illnesses - cosmetic surgery, sterilization etc. The possibility of chronic pain should be realized before making the decision to operate. The situation is the same with all types of surgery. Inguinal hernia repair is a typical procedure which may provoke persistent pain for previously painfree patients (Page et al. 2002) and by contrast, watchful waiting has proven to be a safe method in this subgroup (Fitzgibbons et al. 2006). There are also studies showing that different surgical techniques used to treat the same illness offer a different safety profile concerning persistent pain (Macrae 2008). Laparoscopic herniorrhaphy, for instance, decreases the risk of nerve damage and pain compared to open surgery (Aasvang and Kehlet 2005). Yet, many new techniques have been taken into clinical practice without any long-term studies exploring the risk of persistent pain (Macrae 2001).

Other medical factors include anaesthesia, perioperative analgesia and various treatments given. The hypothesis behind this is to inhibit hypersensitization during acute trauma and thus reduce the incidence of persistent pain. The data around this topic are controversial: some studies have shown a beneficial effect (Senturk et al. 2002; Tiippana et al. 2003; Nikolajsen et al. 2004), and some have not (Ho et al. 2002; Jensen and Andersen 2004; McCartney et al. 2004; Kalliomäki et al. 2008). The explanation may be that even a brief period of pain before or during operation is enough to sensitize the neurons and cause persistent pain (Macrae 2008). The effect of pre-existing pain on pre-emptive analgesia was tested in one prospective study in orthopaedic surgery and the result was clear: pre-emptive epidural analgesia was ineffective in the presence of pre-surgical pain (Aida et al. 2000). However, the impact of pre-emptive analgesia is far from established (Møiniche et al. 2002).

4.2.2 Patient risk factors for persistent postsurgical pain

Patient-related risk factors for persistent postsurgical pain are genetic predisposition, pre-existing pain in the operated site or elsewhere, acute postsurgical pain, various psychosocial factors, young age, increased BMI or weight and female gender (Kehlet et al. 2006b; Macrae 2008).

A genetic variation in the development of persistent pain, in the baseline sensitivity to pain and in the different responses to pharmacological treatments, has recently been under vigorous investigation (Belfer et al. 2004; Diatchenko et al. 2005; Stamer and Stuber 2007a; Stamer and Stuber 2007b; George et al. 2008; Reimann et al. 2010). The genetic polymorphism behind the synthesis of catechol-O-methyltransferase (COMT) is known and low COMT activity in turn correlated with risk of persistent pain in the model of temporomandibular joint pain in healthy female volunteers (Diatchenko et al. 2005). By contrast, high COMT activity was associated with higher pain ratings among patients evaluated 3-5 months after shoulder surgery compared to those with low COMT activity (George et al. 2008). This disparity in the results shows one challenge of this kind of research: totally different populations. Healthy volunteers cannot be compared with patients with pre-existing pain. In 2006 Tegeder et al. demonstrated that a certain human haplotype responsible for the synthesis of GTP cyclohydrolase 1 (Dopa-responsive dystonia) was associated with reduced persistent pain after lumbar discectomy (Tegeder et al. 2006). GTP cyclohydrolase is known to be essential in the production of tetrahydrobiopterin, which in turn is a cofactor for the synthesis of catecholamines, serotonin and nitric oxide. This makes GTP cyclohydrolase an important enzyme in the development of peripheral neuropathic and inflammatory pain. This haplotype was found in 15.4 % of patients (Tegeder et al. 2006). The voltage-gated sodium channel type 9 α in peripheral neurons is responsible for the potential production and is encoded by the gene whose mutations cause different phenotypes in pain sensations - from total inability to feel pain to paroxysmal extreme pain disorder (Drenth and Waxman 2007; Reimann et al. 2010). Other candidate genes listed to be investigated are those responsible for the production of interleukin 6 and 1ß, neuronal nitric oxide synthase and tumor necrosis factor α (Belfer et al. 2004). The aim in the future is to find a correlation between the single nucleotide polymorphism and the risk of developing persistent pain after primary injury.

Pre-operative pain has in general increased the risk of persistent pain after surgery. This was clearly shown with phantom limb pain after amputation (Nikolajsen et al. 1997c). The more intense and enduring the preamputation pain, the more severe was phantom pain (Nikolajsen et al. 1997c). This led to several studies where preamputation pain was properly treated (Nikolajsen et al. 1997a; Nikolajsen et al. 1997b). Unfortunately, the incidence of phantom limb pain could not be reduced after the first positive study (Bach et al. 1988); the

hypersensitization had already occurred. Keller et al. showed that preoperative use of narcotics increased the risk of persistent pain after thoracotomy (Keller et al. 1994) and preoperative pain was also a risk factor for persistent pain in inguinal herniorraphy (O'Dwyer et al. 2005; Kalliomäki et al. 2008) and in total knee replacement (Brander et al. 2003;Lundblad et al. 2008). On the other hand, pre-existing pain was not a risk factor for persistent pain in cholecystectomy (Middelfart et al. 1998) or in hip replacement (Nikolajsen et al. 2006).

Acute postoperative pain is more evidently associated with persistent postsurgical pain than preoperative pain. The results from trials concur. The association was first published in patients recovering from thoracotomy (Kalso et al. 1992), but postoperative pain has also been found as a risk factor for persistent pain after coronary artery bypass grafting (Bruce et al. 2003), hernia repair (Aasvang and Kehlet 2005), breast cancer surgery (Poleshuck et al. 2006), orthopaedic surgery (Nikolajsen et al. 2006) and Caesarean section (Nikolajsen et al. 2004).

Certain pain conditions: fibromyalgia, irritable bowel syndrome, irritable bladder, Raynaud's syndrome, migraine and backache, are known to be related to elevated risk of persistent pain after injury (Courtney et al. 2002; Wright et al. 2002; Brandsborg et al. 2008). The explanation may be found when the genetic polymorphism behind all these conditions is identified (Macrae 2008).

Advanced age seems to reduce the risk of persistent pain after surgery. There are several studies in which younger patients were more prone to developing persistent pain after hernia repair (Poobalan et al. 2003; Aasvang and Kehlet 2005; Kalliomäki et al. 2008) or breast cancer surgery (Smith et al. 1999; Poleshuck et al. 2006). This contradicts the finding of age as a risk factor for postherpetic neuralgia after acute herpes virus infection (Jung et al. 2004). The baseline prevalence of chronic pain is also higher in older people, which was shown in a large population study (Saastamoinen et al. 2005). Age over 50 years increased the risk of persistent pain at one year after knee arthroscopic procedure (Rosseland et al. 2008). This can be explained by the higher overall prevalence of chronic pain in this population rather than by the arthroscopy itself.

Weight and BMI may be risk factors for persistent pain, at least in hip and knee arthroplastic surgery (Bagge et al. 1991). There is little evidence to support this hypothesis because BMI or weight has not been taken account in risk analysis. After revision total hip arthroplasty high BMI ($30kg/m^2$ or over) was associated with persistent pain (Singh and Lewallen 2009).

Female gender in turn is a well documented risk factor for persistent pain (Rosseland and Stubhaug 2004; Kehlet et al. 2006a; Bernardes et al. 2008; Macrae 2008; Singh and Lewallen 2009).

Psychiatric disorders assumed to be the risk factors for persistent postsurgical pain are depression and anxiety. This association is difficult to investigate because of the bidirectional causality of these states. Several large epidemiological studies have shown that depression and anxiety overall predict the onset of chronic pain syndromes (Gureje et al. 2001; Harkness et al. 2004) but on the other hand, chronic pain at baseline also predicts subsequent depression or anxiety (Gureje et al. 2001). The evidence from surgical patients is

scarce. Tasmuth et al. showed that patients who suffered from persistent pain one year after breast cancer operation were more likely to be depressive than those who were painfree (Tasmuth et al. 1996). Psychosocial risk factors for persistent pain have gradually been taken into account. In the 1990s studies were conducted where neuroticism (Jess et al. 1998) and introverted personality (Borly et al. 1999) were found to be risk factors for persistent pain after cholecystectomy. In the 2000s investigators took a greater interest in the psychosocial factors behind pain and rehabilitation. Preoperative depression and anxiety were both associated with persistent pain after both knee replacement (Brander et al. 2003; Harden et al. 2003) and hip replacement (Rolfson et al. 2009). Anxiety was not tested but preoperative depression was also a risk factor for persistent pain after revision total hip arthroplasty in a study by Singh et al. (Singh and Lewallen 2009). Fear of the long-term consequences of the operation was associated with persistent pain in a large prospective on the predictors of long-term unfavourable surgical outcomes (Peters et al. 2007).

By contrast, there are many studies which show that psychosocial factors have predicted subsequent acute postoperative pain (Taenzer et al. 1986; Tacconelli et al. 2002; Granot and Ferber 2005; Katz et al. 2005; Papaioannou et al. 2009). Severe acute postoperative pain in turn has consistently been found to be a risk factor for persistent pain (Kalso et al. 1992; Bruce et al. 2003; Nikolajsen et al. 2004; Aasvang and Kehlet 2005; Nikolajsen et al. 2006; Poleshuck et al. 2006). Therefore we can assume that associations between psychosocial factors and persistent pain are also waiting to be found.

Aims of the study

The aim of this thesis was to study therapy of postoperative pain and the prevalence and risk factors of persistent pain after surgery. The specific aims were:

1. To study whether parecoxib 80mg is a more appropriate dose than 40mg for postoperative pain relief in patients undergoing laparoscopic cholecystectomy (I).

2. To study whether etoricoxib 120mg either alone or in combination with paracetamol 1000mg given in premedication reduces additional postoperative pain treatment in patients undergoing laparoscopic cholecystectomy (II).

3. To ascertain the renal adverse effects of the COX-2 inhibitor, parecoxib 80mg, by measuring the sensitive markers of both tubular and glomerular damage in patients undergoing laparoscopic hysterectomy (III).

4. To study whether the type of operation (primary, bilateral, revision) affects the development of persistent pain after knee arthroplasty and to reveal the overall degree and risk factors of persistent pain after knee arthroplasty with a questionnaire in a large, register-based cross-sectional prevalence study (IV).

Patients and methods

The studies were approved by the ethic committees of the participating institutions (I-IV) and the National Agency for Medicines (I-III).

1. Patients

Written informed consent was obtained from each patient.
Studies I-III were prospective, randomized, blinded and placebo controlled. The randomization procedure was guaranteed by computer-generated random numbers. Double-blindness was in turn guaranteed by arranging the delivery of investigational medicine through a special nurse. The dose-response Studies, I and II were so-called one-centre studies, but Study III was conducted in two centres.
The inclusion criteria differed slightly between the prospective Studies, I-III. Congestive heart disease, angina pectoris and cerebrovascular circulatory symptoms were included in the exclusion criteria in the ongoing Study II after alarming reports about thrombotic events in other published trials. The inclusion and exclusion criteria of Studies I-III are collected in Table 4.

Study IV was a questionnaire-based, cross-sectional prevalence study. Patients who had undergone knee arthroplasty during the period from 1 September 2002 to 28 February 2004 were recruited from the arthroplasty registry of an arthroplasty specialized hospital. The total number of patients receiving the questionnaire was 855.

Table 4. Inclusion and exclusion criteria of Studies I-III

	Study I	Study II	Study III
Inclusion criteria	Laparoscopic cholecystectomy, ASA I-II, 30-60 years, 60-100kg	Laparoscopic cholecystectomy, ASA I-III, 16-70 years	Laparoscopic hysterectomy, ASA I-II, 30-60 years, 50-80kg
Exclusion criteria	allergy to aspirin-like drugs/ sulphonamide, bronchial asthma, liver or renal dysfunction, peptic ulcer, bleeding disorder, pregnancy, substance abuse, chronic pain	BMI>40kg/m^2, allergy to aspirin-like drugs, bronchial asthma, liver or renal dysfunction, peptic ulcer, bleeding disorder, pregnancy, substance abuse, chronic pain, congestive heart disease, angina pectoris and cerebrovascular circulatory symptoms	allergy to aspirin-like drugs/ sulphonamide, bronchial asthma, liver or renal dysfunction, peptic ulcer, bleeding disorder, pregnancy, substance abuse, chronic pain

2. Anaesthesia and fluid treatment

General anaesthesia was standardized in Studies I-III. Induction was with fentanyl 2µg/kg, propofol 2-3mg/kg and rocuronium 0,6mg/kg. An equal amount of fentanyl was given about 3 minutes before skin incision. A semi-closed breathing system with fresh gas flow of 2-3 l/min was used. Anaesthesia was maintained with sevoflurane in air/O_2 66/34% and adjusted to keep systolic blood pressure level between 85–130 mmHg (sevoflurane end-tidal concentration, about 2%). Muscle relaxation was maintained with rocuronium. $EtCO_2$ was kept between 5.0 and 5.5 % by adjusting the ventilation. Residual neuromuscular block was antagonized with neostigmine and glycopyrrolate. Regional anaesthesia, i.e. wound infiltration with 5 mg/ml bupivacaine with adrenaline, was used only in Study II.

Anaesthesia for patients in Study IV was produced mainly by spinal block but an epidural catheter was inserted to ensure anaesthesia in prolonged cases.

Fluid treatment was equal in the dose-response studies (I-II). Ringer's acetated solution was administered perioperatively and then followed by a liter of a mixture of 0.3% NaCl in 5% glucose in the next 12 hours. In Study III with renal markers, fluid treatment was designed to be more restricted than liberal to support the stress model for the kidneys. Ringer's acetated solution, bolus of 5ml/kg followed by 5ml/kg/h, was administered during surgery and followed directly with one liter of a mixture of 0.3% NaCl in 5% glucose in the next 12 hours. Five hundred ml of 4% gelatine solution was used only if surgical blood loss was over 400ml. Fluid administration was not evaluated in Study IV.

3. Pain assessment, pain treatment and premedication

The protocols for pain assessment and rescue pain treatment were quite similar in all the prospective studies, I-III. During the preanaesthetic round the patients were instructed in the use of a visual analogue scale (VAS, 0 - 10). Pain intensity at rest, during coughing, and during leg elevation were assessed using VAS in the preoperative round, on arrival in the operating theatre, at 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, and 20 h after the end of surgery. The patients were also asked to evaluate the worst pain score at rest encountered during the previous period at two hours and at 20 hours after the end of surgery. At the end of the observation period the patients were asked to express their opinion concerning the efficacy of the pain relief treatment (0 = excellent, 1 = good, 2 = unknown, 3 = fair, 4 = poor).

The patients were instructed preoperatively and assisted postoperatively in the use of the patient-controlled analgesia device (PCA), programmed to deliver 50 µg of fentanyl during two minutes. The lockout time was 5 min, and the maximum dose was 10 ml/h (= 500 µg) during the first 2 hours in the recovery room and 5 ml/h (= 250 µg) on the ward until 20 hours after the end of surgery.

During emergence from anaesthesia, the recovery room nurses were allowed to give additional fentanyl boluses via the PCA device at the patients' request. The time interval between the end of surgery and the first bolus of fentanyl delivered by the PCA device was recorded. Additional need for pain treatment was evaluated by the frequency and by the amount of PCA delivered in fentanyl boluses during the first 20 postoperative hours.

The medications studied were parecoxib 40mg (I) and 80mg (I, III), etoricoxib 120mg (II) and paracetamol 1000mg (II). Intravenously administered parecoxib was given at the end of anaesthesia in Study I, but before the induction of anaesthesia in Study III. Orally administered etoricoxib alone or combined with paracetamol was given as premedication. Premedication was otherwise similar in all prospective studies, oxazepam 15mg orally, but the placebo-group was given oxycodone 10mg orally in Study III to ensure efficient pain relief.

Pain assessment in Study IV was performed by the questionnaire, which is presented later. Acute pain relief until the first postoperative day was ensured by epidural analgesia combined with paracetamol and NDSAID if appropriate. Epidural analgesia was replaced with opioids.

4. Adverse events and laboratory samples

The patients in Studies I-II were asked about nausea using VAS during the preoperative round, on arrival in the operating theatre and at 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, and 20 h postoperatively. At the same time points, the patients were also asked about the type and degree (VAS) of other possible adverse effects of any kind. The antiemetics used were recorded at 2 h and 20 h postoperatively

Laboratory samples were taken in Study III. The samples for the analyses of serum and urine were collected during the induction of anaesthesia, 2 hours thereafter, 2 hours after anaesthesia and on the first postoperative day. The samples of serum creatinine, urea, sodium, potassium, α-1-microglobulin and cystatin C were analysed on the next working day. Samples for GST were conserved in a tube with stabilizer (containing mertiolate and azide) and stored at -20°C before analysis. All these samples were stored and analysed according to good laboratory practice by the laboratory of Tampere University Hospital.

5. Questionnaire

The questionnaire, used in Study IV, was mailed to all patients with a prepaid return envelope in July 2004. In case of no reply, one reminder was sent. The demographics were elicited. All the other questions concerned pre- and postoperative pain. The duration of preoperative pain and the intensity of postoperative pain during the first week (mild, moderate, severe, unbearable) were elicited. If the patient still had pain when receiving the questionnaire, pain

intensity at rest and during exercise was evaluated. The degree of disturbance of daily life and sleep due to pain (none, mild, moderate, severe) and the consumption of analgesics for persistent pain in the operated knee were elicited. The questionnaire is presented in the Appendix. The time interval between the surgery and the questionnaire was minimum 4 months and maximum 22 months.

6. Statistics

6.1 Sample size estimation

The sample size estimation in Study I was based on our hypothesis that parecoxib reduces the need for postoperative pain treatment during the first 20 postoperative hours to the same degree as traditional nonsteroidal anti-inflammatory drugs. We calculated that with 20 patients/group the sample size would be sufficient to detect a difference of 40 % in the overall number of fentanyl boluses during the first 20 postoperative hours between the group P80 and the control group ($\alpha = 0.05$, power = 80%). The sample size estimation in Study II was based on the assumption that etoricoxib reduces the need for opioids by 33%. Thus, with $\alpha = 0.05$ and power = 80%, the sample size was 23 patients in each group. In Study III we assumed that the novel renal markers would be more sensitive than earlier ones to show if any clinically significant renal damage had occurred. A sample size of thousands would have been needed to find differences in outcomes such as increased creatine level, because renal adverse events with COX-2 inhibitors have been reported to occur in less than 2% of the population. Study IV was not an intervention study. The questionnaire was sent to all patients operated on and the number of patients responding was sufficient for risk analysis.

6.2 Data analysis

The numerical variables were reported by means with standard deviations or by medians and quartiles depending on data distribution. The categorical variables were presented as absolute and relative frequencies. The significance tests used in Studies I-III are listed in Table 5. $P < 0.05$ was considered statistically significant.

Table 5. Significance testes and programmes used in Studies I-III

	Study I	Study II	Study III
Demographic data	ANOVA	ANOVA	t-test
Categorized data	Pearson's χ^2	Pearson's χ^2	Pearson's χ^2
Data of fentanyl consumption, VAS scores, laboratory samples (skewed distribution)	Kruskall-Wallis	Kruskall-Wallis	Mann-Whitney
Statistical programme	SPSS for Windows 11.5	SPSS for Windows 11.5	SPSS for Windows 14.02

The data from the returned questionnaires and from the hospital registry in Study IV were analysed using multiple logistic regression analysis. The dependent variable was pain at the time of the questionnaire. The explanatory variables were treatment, age (centred at age 70 and including a quadratic term), gender, body mass index, pain score and duration prior to surgery, pain score during the first week after surgery, type of prosthesis and diagnosis. The results of the univariate and multivariate logistic regression analyses are presented as odds ratios with 95% confidence intervals. Logistic regression was used instead of linear regression because the object of the study - persistent pain or not - was binominal. All these computations were done with R Development Core Team, 2008.

Results

1. Patient recruitment and baseline characteristics

Patients involved in the prospective Studies I-III are shown as a flow chart in Figure 5. Nine patients were excluded from Study I for the following reasons: laparoscopic operation turned into open cholecystectomy in four patients; local anaesthetics were used on one patient, one foreign patient was unable to answer the questions, two patients did not fit the protocol (weight >100kg) and one patient was rejected because of an extremely difficult and time consuming operation (>120min). Three patients were excluded from Study II for the following reasons: laparoscopic operation turned into open cholecystectomy in two patients and macroscopic hepatic cirrhosis, diagnosed at the beginning of the laparoscopy, also caused the cancellation of the operation. In addition to these three patients, VAS scores for postoperative pain and PONV were missing for 6 patients.

Baseline data from the prospective Studies I-III are shown in Table 6. The variables are expressed in percentiles, means with standard deviations (±SD) or medians and quartiles (Q_1,Q_3). Appropriate significance tests were applied, but the groups were statistically equal. The total population of Study IV is presented in Table 7.

Figure 5. Flow chart of patients in Studies I-III

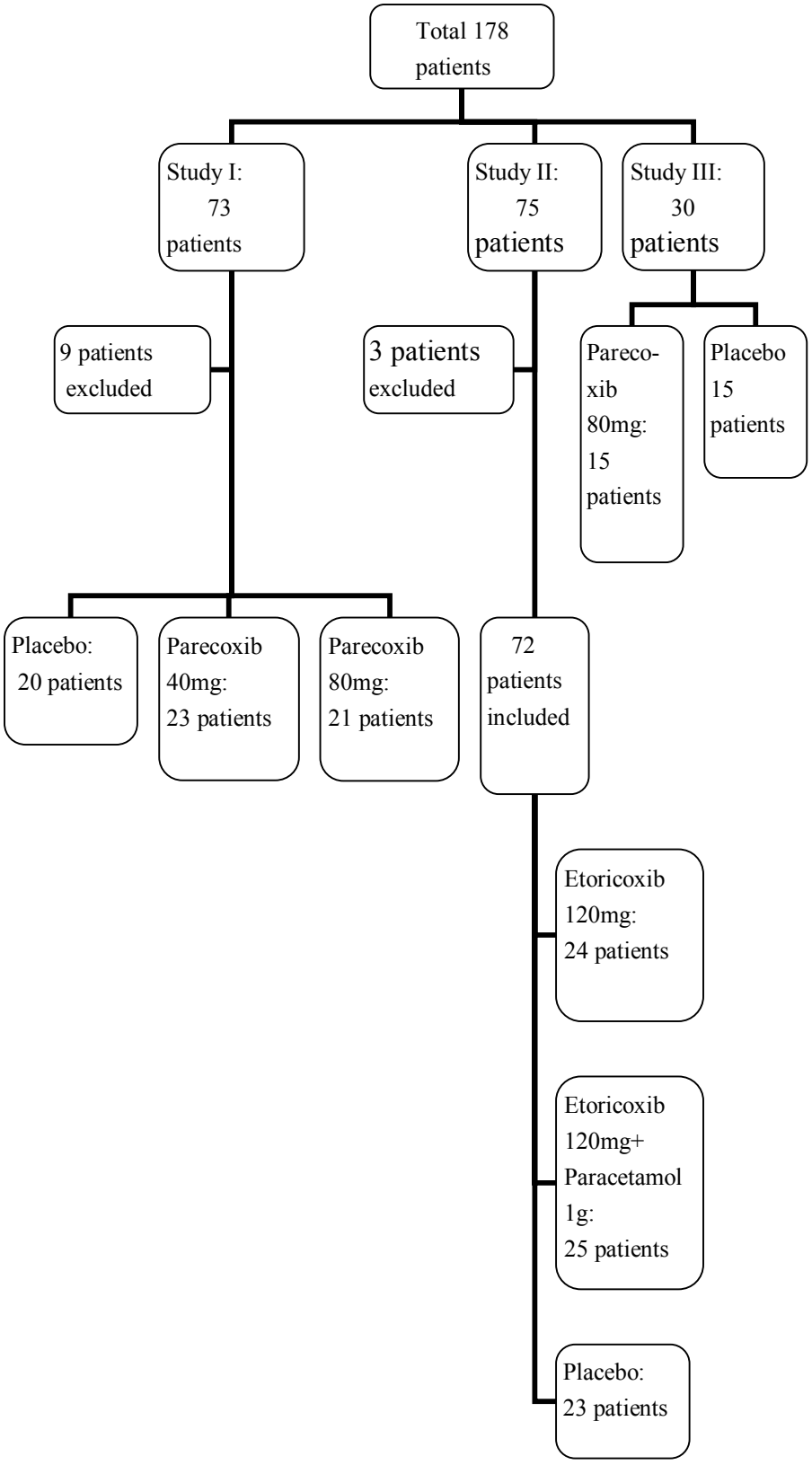


Table 6. Baseline data in Studies I-III

	Px40 (n=23)	Px80 (n=21)	PlaI (n=20)	E (n=24)	E+P (n=25)	PlaII (n=23)	Px (n=15)	PlaIII (n=15)
Age (year)	45±9	44±12	41±10	46±12	45±11	45±9	49±8	51±5
Gender (Female%)	74	81	70	79	80	70	100	100
Weight (kg)	77±14	77±12	75±11	79±14	84±12	78±15		
BMI (kg/m^2)							24.8±2.9	25.2±2.4
ASA I/II/III (%)	48/52/0	62/38/0	60/40/0	38/54/8	40/56/4	48/39/13	67/33/0	67/33/0
surgery duration (min)	63±37	56±24	54±25	55 (44,75)	63 (48,68)	72 (47,91)	103±28	103±34
Creatinine clearance (ml/min)	-	-	-	-	-	-	100.7± 20.4	105.9± 23.3

Study I: Px40= parecoxib 40mg, Px80=parecoxib80mg, PlaI=placebo
Study II: E=etoricoxib 120mg, E+P= etoricoxib 120mg+paracetamol 1g, PlaII=placebo
Study III: Px=Parecoxib80mg, PlaIII=placebo

Table 7. Baseline data in Study IV

	n (%)	mean ±SD
Total population	855	
Responders	562 (65.7)	
*Age (years)		69±9
*BMI (kg/m^2)		29.1±4.4
*Female gender	396 (70.5)	
*Diagnosis		
osteoarthritis	535 (95.2)	
rheumatoid arthritis	18 (3.2)	
unknown	9 (1.6)	
*Operation		
primary arthroplasty	433 (77.0)	
bilateral arthroplasty	95 (16.9)	
revision arthroplasty	34 (6.1)	
*Presurgical pain score		
no pain or mild	40 (7.1)	
moderate, occasional	271 (48.2)	
moderate continuous	200 (35.6)	
severe	44 (7.8)	
unknown	7 (1.3)	
*Presurgical duration of pain		
≤12months	51 (9.1)	
>12months	493 (87.7)	
unknown	18 (3.2)	
*Early postsurgical pain score		
mild	151 (26.9)	
moderate	244 (43.4)	
severe	135 (24.0)	
unbearable	24 (4.3)	
unknown	8 (1.4)	

*variables were assumed to be the risk factors for persistent pain

2. Analgesic efficacy

The analgesic efficacy of the investigational drugs was studied in Studies I and II by comparing data from cumulative fentanyl consumption delivered from the PCA-device. Pain scores expressed by VAS were evaluated. Global satisfaction in pain treatment was also analysed.

2.1 Opioid sparing effect

Opioid sparing effect was evident with both etoricoxib treated groups, but adding paracetamol to premedication or giving parecoxib alone at the end of surgery did not show any opioid sparing effect.

Table 8. Cumulative postoperative fentanyl consumption, µg/kg (medians (Q_1,Q_3)) during the first 20 hours in Studies I and II

	1h	2h	4h	10h	20h
Px40	1.2(0.6,2.3)	1.9(1.3,3.1)	3.2(1.9,5.0)	3.9(3.2,8.3)	5.2(3.9,10.9)
Px80	0.6(0.6,1.2)	1.2(0.6,3.1)	2.6(1.2,3.7)	4.5(2.8,5.2)	5.8(3.6,7.6)
PlaI	1.3(0.7,2.0)	2.7(1.7,3.7)	3.3(2.7,7.3)	5.3(3.3,10.0)	6.7(4.0,14.7)
E	0.02(0.01,0.03)	0.03*(0.02,0.06)	2.3*(1.5,4.2)	4.2*(2.4,6.3)	6.8*(3.7,8.6)
E+P	0.02(0.01,0.04)	0.04*(0.03,0.06)	2.5*(2.0,5.0)	3.9*(2.5,7.4)	7.0*((4.3,9.7)
PlaII	0.04((0.01,0.07)	0.05(0.03,0.1)	5.3(2.5,6.6)	7.5(4.7,10.3)	8.8(7.2,15.1)

Px40= parecoxib 40mg, Px80=parecoxib80mg, PlaI=placebo
E=etoricoxib 120mg, E+P= etoricoxib 120mg+paracetamol 1g, PlaII=placebo
*$p<0.05$ when compared to placebo and tested by Kruskall-Wallis.

2.2 Pain scores

Pain scores were tested at rest, during coughing and leg elevations 1h, 2h, 4h, 6h, 8h 10h and 20h postoperatively. Especially at night, there were missing values disturbing the analysis. VAS scores could be analysed in 130 patients out of total 136 patients. The scores also remained low (VAS $\leq$ 6) in the placebo groups. There were no clinically or statistically significant differences between the groups when tested with nonparametric test.

The worst pain on the ward was also evaluated by VAS score. Patients treated with parecoxib 80mg at the end of surgery evaluated their worst pain on the ward significantly lower than did the placebo group ($p= 0.014$). Mean values with standard deviations for VAS scores were 3.9±1.9 and 5.8±3.0 respectively.

2.3 Global evaluation of analgesia

Almost all patients evaluated their analgesia as excellent or good when asked at the end of the study. Nevertheless, there was a clear tendency to lower values in evaluations in the placebo groups.

Table 9. Global evaluation of analgesia (n(%))

Groups	Excellent	Good	Unknown	Fair	Poor
Px40	17(73.9)	5 (21.7)	1 (4.4)	0	0
Px80	14 (66.7)	7 (33.3)	0	0	0
PlaI	9 (42.8)	6 (28.6)	4 (19.0)	1 (4.8)	1 (4.8)
E	16 (66.7)	6 (25.0)	2 (8.3)	0	0
E+P	19 (76.0)	3 (12.0)	3 (12.0)	0	0
PlaII	9 (39.1)	9 (39.1)	5 (21.8)	0	0

3. Adverse events

Adverse events were recorded in VAS parallel to pain scores in Studies I and II. Nausea and vomiting were equally distributed at each time point between the groups. The only clinically and statistically significant difference was found in the proportion of patients whose highest PONV score on the ward was more than three in VAS (p=0.033). This proportion was 5% with etorixocib and paracetamol treated patients, 18% with etoricoxib treated patients and 33% with placebo treated patients. Antiemetic doses did not differ between the groups.

Other adverse effects mentioned were headache, dizziness and blurred vision, but these were small in number and also equally distributed between the groups.

Study III concentrated on renal adverse events with parecoxib. The results are presented in Tables 10a and 10b. There were few statistically but no clinically significant differences between groups in any renal measurement during the study period. The values of U-π-GST/U-crea were increased two hours after the start of anaesthesia in both groups. The increase was also statistically significant (Mann-Whitney test): p= 0.013 in the parecoxib and p= 0.033 in the placebo group when compared to baseline levels. The number of patients is mentioned at each measurement in each group, because data was either missing or the outliers were omitted (seven measurements). One third of the measurements of urinary α-1-microglobulin was undetectable (<5.2mg/L) making statistical analysis impossible. However, there was no clinical difference between the groups in urinary α-1-microglobulins. The urinary output during the first four hours was small in volume but there was no difference between the groups.

Table 10a. Renal measurements (n, median (Q_1,Q_3)) with normal values

Measurement, group	Baseline	2h after induction	2h after end of anaesthesia	1. POD
S-crea <95 µmol/l				
parecoxib	14, 61(58,67)	14, 60(57,69)	14, 63(56,71)	13, 57(55,70)
placebo	14, 62(54,66)	14, 61(49,64)	14, 59(52,64)	12, 56(47,60)
S-urea 2.6-6.4 mmol/l				
parecoxib	15, 3.7(2.8,4.8)	15, 3.3(2.9,4.0)	15, 3.3(3.0,4.8)	13, 2.4(2.2,3.8)
placebo	14, 4.2(3.6,5.4)	15, 4.0(3.5,5.0)	15, 4.2(3.5,5.0)	12, 2.7(2.3,3.1)
S-CysC <1.4-1.5 mg/l				
parecoxib	15, 0.74(0.66,0.85)	15, 0.67(0.55,0.76)	15, 0.66(0.57,0.83)	13, 0.68(0.60,0.78)
placebo	15, 0.71(0.64,0.84)	15, 0.65(0.56-0.78)	15, 0.66(0.56,0.72)	12, 0.67(0.55,0.78)
S-K 3.5-4.5 mmol/l				
parecoxib	15, 4.1(4.0,4.3)	14, 4.1(4.0,4.4)	12, 4.1(4.0,4.6)	13, 4.0(3.8,4.2)
placebo	14, 4.2(4.0,4.2)	15, 4.2(4.0,4.4)	14, 4.0(3.9,4.2)	12, 3.6(3.4,3.8)
S-Na 137-145 mmol/l				
parecoxib	15, 140(139-142)	15, 139(138,141)	15, 140(137,141)	13, 139(136,142)
placebo	14, 139(138,141)	15, 140(138,141)	14, 139(138,141)	11, 137(136,139)

Table 10b. Urinary renal measurements (n, median (Q_1,Q_3)) with normal values

	Baseline	2h after induction	2h after end of anaesthesia	1.POD
U-αGST/u-crea 0.10-1.93 µg/mmol				
parecoxib	14, 2.07(0.33,2.46)	13, 0.42(0.05,0.77)	13, 0.15(0.05,0.67)	10, 0.50(0.01,0.98)
placebo	13, 0.62(0.17,1.75)	13, 0.15(0.02,0.93)	12, 0.13(0.04,0.98)	11, 0.58(0.15,0.99)
U-πGST/u-crea 0.25-7.41 µg/mmol				
parecoxib	14, 2.8(1.2,6.5)	13, 12.2(1.9,36.6)*	13, 3.1(0.3,7.1)*	10, 2.1(0.6,3.7)
placebo	13, 4.5(1.6,5.5)	13,17.3(11.8,22.9)*	12, 2.1(0.7,3.6)*	10, 1.7(0.9,4.0)

POD=postoperative day

* $p<0.05$ when compared to baseline measurement and tested by Mann-Whitney

4. Persistent pain

Persistent postsurgical pain was the research object of Study IV. The results are divided into two sections: prevalence and intensity of persistent pain and risk factors for persistent pain.

4.1 Prevalence and intensity of persistent pain

The prevalence of persistent pain after knee arthroplasty was 21.5% at rest and 29.8% during exercise. Of the patients, 35.1 % suffered from pain disturbing daily life while 24.3 % of the patients reported disturbances of sleep because of pain. The proportion of patients still using analgesics because of pain in the operated knee was 43.3%. The intensity of pain at rest and during exercise is shown in Figures 6 and 7. Effect on daily life and sleep are presented in Figures 8 and 9.

Figure 6. Pain at rest

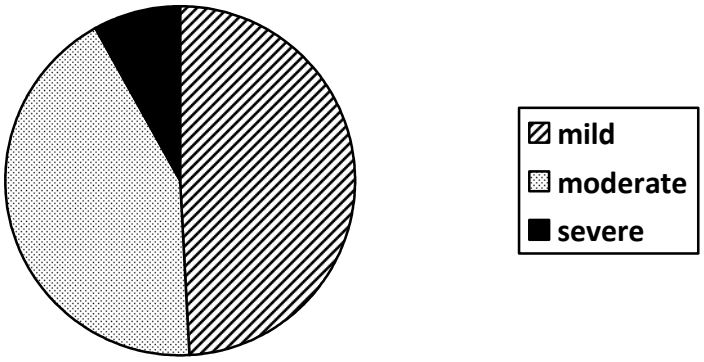


Figure 7. Pain during exercise

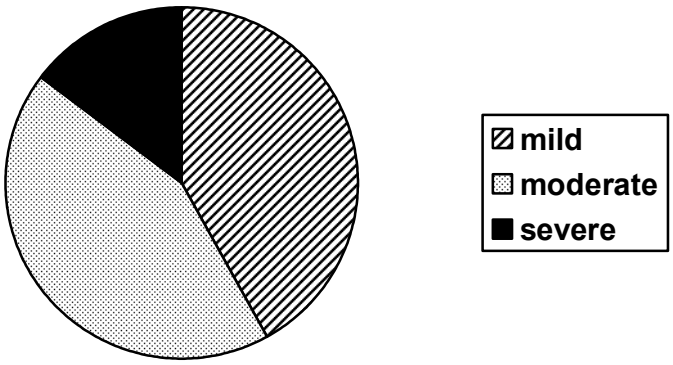


Figure 8. Disturbance of daily life

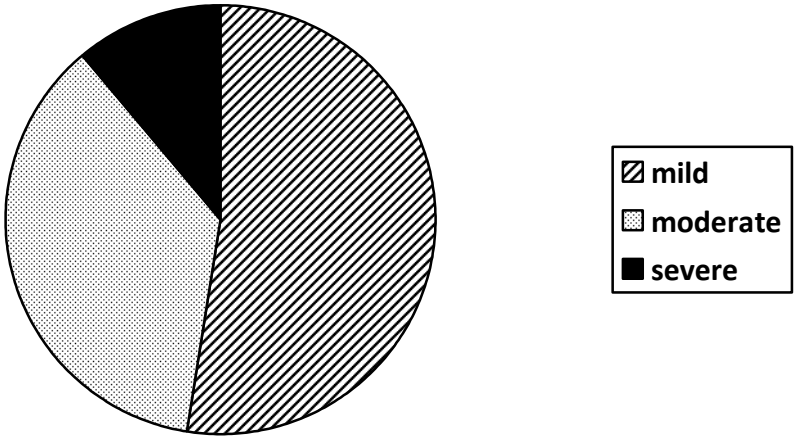
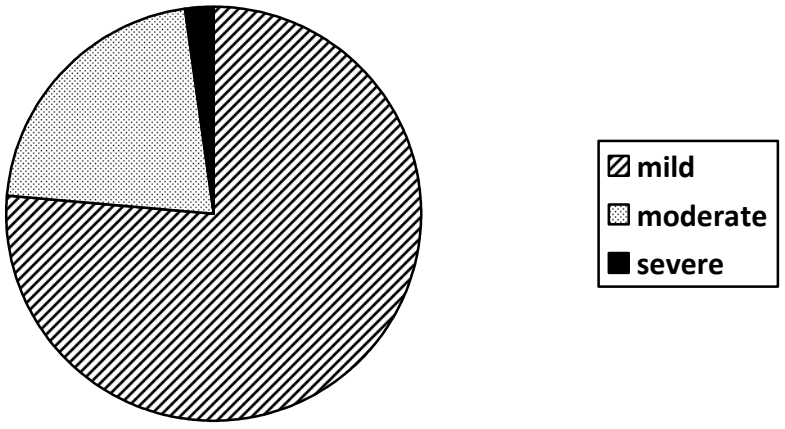


Figure 9. Disturbance of sleep



4.2 Risk factors for persistent pain

Table 11. Analysis of risk factors predicting persistent pain after knee arthroplasty

Variable	Pain Yes/No	Univariate analysis OR(95%CI)	Multivariate analysis OR(95%CI)
Operation:			
Primary	101/304		
Bilateral	22/70	0.95(0.55-1.58)	0.89(0.48-1.56)
Revision	7/22	0.96(0.37-2.20)	1.09(0.37-2.89)
Age		0.98(0.96-1.00)	1.01(0.99-1.04)
Age, squared and centred at 70 years		1.0027(1.0007-1.0048)	
BMI		1.01(0.97-1.06)	
Gender:			
Male	25/128		
Female	105/268	2.00(1.25-3.31)	1.90(1.14-3.28)
Diagnosis:			
Rheumatoid arthritis	6/18		
Osteoarthritis	124/378	0.98(0.40-2.76)	
Presurgical pain score:			
No pain or mild	7/31		
Moderate, occasional	59/196	1.33(0.59-3.43)	
Moderate, continuous	48/139	1.53(0.66-3.98)	
Severe	15/24	2.77(1.00-8.26)	
Presurgical duration of pain			
≤12 months	5/42		
>12 months	122/342	3.00(1.27-8.82)	2.84(1.14-8.65)
Early postsurgical pain score:			
Mild	11/128		
Moderate	50/179	3.25(1.69-6.80)	3.11(1.59-6.62)
Severe	56/74	8.81(4.50-18.70)	8.17(4.04-17.83)
Unbearable	13/11	13.75(5.09-39.10)	10.69(3.63-32.63)

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Severe presurgical pain seemed to be a risk factor for persistent pain according to the univariate analysis. Backward selection of multivariate logistic regression analysis left only age and its quadratic term, gender, the duration of pain prior to surgery and early postoperative pain for the final model. The type of operation was kept in the model to test our primary hypothesis - the degree of primary injury is associated with persistent pain. ORs for continuous variables (age, quadratic term of age, BMI) refer to one unit change.

Discussion

1. Analgesic efficacy of COX-2 inhibitors

Parecoxib failed to prove any significant opioid sparing effect in Study I. By contrast, the opioid sparing effect of etoricoxib was seen almost throughout Study II. According to other published studies parecoxib should have had some analgesic effect when compared to the placebo. Perioperatively administered parecoxib has spared opioid requirements after cholecystectomy (Gan et al. 2004), hysterectomy (Tang et al. 2002; Ng et al. 2003), total knee (Hubbard et al. 2003; Reynolds et al. 2003) or hip arthroplasty (Camu et al. 2002; Malan et al. 2003) and coronary artery bypass surgery (Ott et al. 2003). Statistical significance was reached by increasing the size of the study groups (Camu et al. 2002; Hubbard et al. 2003; Malan et al. 2003; Ott et al. 2003; Reynolds et al. 2003; Gan et al. 2004) or using parametric test although the normality of the data was questionable (Tang et al. 2002). Difference in opioid consumption was around 30 % in all these studies, which can be regarded as clinically significant (Merskey 1994). The situation is different when analgesic efficacy is compared with different pain scores. The statistical difference persists (Camu et al. 2002; Ott et al. 2003; Reynolds et al. 2003; Gan et al. 2004; Beaussier et al. 2005) but the clinical importance of the values is difficult to evaluate without absolute numbers (Camu et al. 2002; Ott et al. 2003; Reynolds et al. 2003; Beaussier et al. 2005). Our study showed the greatest decrease in opioid consumption (50%) during the first two postoperative hours, but nonparametric test did not give statistical significance to that difference between parecoxib 80mg and placebo treated groups. At four hours the difference was reduced to 20% and after ten hours to 15 %. This is in line with the pharmacodynamic profile of parecoxib. Administration twice a day would have offered a more stable analgesic concentration and probably also analgesic efficacy.

Etoricoxib showed an opioid sparing effect respectively of 50% to 20% from two to 20 postoperative hours in our study. This is in line with other published studies on the perioperative use of etoricoxib. Compared to placebo, etoricoxib has proved its efficacy in arthroscopic acromioplasty (Toivonen et al. 2007), thyroid surgery (Smirnov et al. 2008), knee or hip arthroplasty (Rasmussen et al. 2005) and in several dental impaction pain models (Malmstrom et al. 2003; Chang et al. 2004).

The overall evaluation of analgesia was favorable to coxibs, which has been demonstrated in other studies, too (Hubbard et al. 2003; Ott et al. 2003; Reynolds et al. 2003; Beaussier et al. 2005; Rasmussen et al. 2005). Beaussier et

al. were even able to show the superiority of parecoxib 40mg over propacetamol 2g twice during the first 12 hours after open herniorraphy (Beaussier et al. 2005)

Combining paracetamol 1g with etorixocib as premedication did not result in any further reduction in fentanyl consumption in our study. The action of paracetamol was limited to the first hours after surgery because of its short half-life. At the same time, opioids used and local anaesthesia infiltrated during the operation reduced the need for any additional pain treatment during those first postoperative hours hiding any analgesic effect of paracetamol. The loading dose of paracetamol of 2g might have been more efficacious, because at least after dental surgery it increased both the extent and the duration of analgesia of paracetamol (Juhl et al. 2006).

There are two systematic reviews with contradictory conclusions regarding the effect of paracetamol in clinical pain relief when combined with NSAIDs (Hyllested et al. 2002; Rømsing et al. 2002). Both reviewers found very limited data concerning the combination. Hyllested et al. opted to combine paracetamol with NSAIDs while Römsing et al. found no evidence to support such a practice. The only supportive study evaluated by analgesic sparing effect was in dental surgery, where paracetamol 1g added to diclofenac 100mg was more effective than diclofenac alone during the first eight hours (Breivik et al. 1999). In addition, there are animal studies (Miranda et al. 2006) and studies with healthy volunteers (Romundstad et al. 2006) showing a synergistic interaction between paracetamol and NSAIDs.

2. Safety of COX-2 inhibitors

The safety of COX-2 inhibitors has been under discussion for years. Both the beneficial gastrointestinal safety profile (Bombardier et al. 2000; Silverstein et al. 2000) and the negative cardiovascular profile have scrutinized (Bresalier et al. 2005; Nussmeier et al. 2005; Solomon et al. 2005). Our study was not designed to detect such effects.

The safety of the investigated drugs was evaluated in efficacy Studies I-II by regularly eliciting any adverse effects. The special interest was in nausea and vomiting, which were assumed to be reduced in the coxib treated groups. The only difference detected was in nausea score on the ward and in favour of etoricoxib. This concurs with the opioid sparing effect of etoricoxib. Surprisingly, there was no difference in the doses of antiemetics used. Römsing et al. also failed to produce clear evidence of a reduction in opioid related adverse events after reviewing studies on the opioid sparing effect of coxibs (Rømsing et al. 2005).The conclusion was also the same as the meta-analyses of all randomized trials comparing multimodal analgesia to morphine alone.(Elia et al. 2005)

Study III was designed to show any renal adverse events of parecoxib with sensitive markers. We were not able to find any clinical and only a few statistically significant differences between the placebo and the parecoxib group.

Oliguria was detected in both groups and could be explained by the laparoscopic surgery.

COX-2 is expressed in the distal tubular component, macula densa, which damage can be detected by U-πGST. The statistically and clinically significant increase in U-πGST/U-crea ratio in both groups was two hours after the start of anaesthesia. The values normalized during the study period. The increase can be explained by the operation itself and indicates some distal tubular damage. There was no significant difference between the groups. There was a tendency to higher values in the control group than in the parecoxib-treated group. This underlines the safety of parecoxib, but further studies are warranted.

The preoperative level of the U-αGST/U-crea was relatively high in both our groups. One explanation is preoperative fasting, which causes relative dehydration. The values were lowest two hours after anaesthesia. This differs from the study showing an increase at that time point when comparing ketorolac to normal saline in patients undergoing breast surgery (Laisalmi et al. 2001). This emphasizes the differences in the action sites of the kidneys between the traditional NSAIDs and coxibs (Breyer et al. 2001).

Cystatin C was employed as a sensitive marker of GFR (Harmoinen et al. 2003; Shlipak et al. 2006). It has also been gradually introduced into clinical use (Sear 2005; Shlipak et al. 2006). Parecoxib was unable to increase the level of cystatin C. This means that GFR was not affected by parecoxib in our study.

Efficacy studies on coxibs have reported sporadic renal adverse effects. Parecoxib 40mg administered every 12 hours for 36 hours after hip arthroplasty did not result in any significant increase in serum creatinine level (Malan et al. 2003). Six out of 311 patients (0.003%) treated with valdecoxib twice a day after coronary surgery had increased serum creatinine level (over 180µmol/L or 63µmol/L over baseline) (Ott et al. 2003). Reynolds et al. studied patients undergoing total knee replacement and reported one patient who developed acute renal failure after two doses of the study drug, valdecoxib 20mg. The patient's baseline serum creatinine was increased (over 180µmol/L) and she was already oligouric in the postanaesthesia care unit prior to drug administration (Reynolds et al. 2003). Based on these three studies with seven cases reported Elia et al. concluded in their meta-analysis that the odds ratio for renal failure after major surgery was 4.86 (95%CI 1.01-23.4) if patients were treated with COX-2 inhibitors and PCA morphine. The number needed to harm was 73 (95%CI 42-277) (Elia et al. 2005). These numbers should be viewed with caution because of the limited data behind them.

Koppert et al. were able to show a parecoxib-associated decrease in creatinine clearance postoperatively in elderly patients undergoing orthopaedic surgery. The decrease was clinically significant, 31.2%. Values were normalized after 4 hours although parecoxib treatment was continued for three days. Adequate recovery may be due to excessive fluid treatment. Mean central venous pressure was maintained over 13cmH_2O during the operation (Koppert et al. 2006). Another study on elderly persons receiving recommended doses of rofecoxib, indomethacin or placebo for six days showed a decrease in GFR if tested with the most sensitive test, inulin clearance. Creatinine clearance did not

change. The decrease in GFR was evident only if patients were on low salt diet but vanished on normal salt diet (Swan et al. 2000). This indicates that a low sodium diet increases the dependency of renal function on prostaglandins. Low sodium diet induced state mimics contracted intravascular volume states like cardiovascular shock, cirrhosis and hypovolaemia. By contrast, rofecoxib used for seven days on elderly patients with moderate chronic renal failure had no effect on the glomerular filtration rate (Horackova et al. 2005) The number of patients in this study was low, only ten, and the patients were also younger than in the studies by Koppert and Swan.

There is increasing evidence of heterogeneities in COX-2 inhibitors (Hermann et al. 2005). Celecoxib has even shown a renoprotective effect in both animal (Hermann et al. 2005) and human studies (Pamuk and Cakir 2006). Selective COX-2 inhibitor called SC58236 is commonly used in laboratory animals and renoprotection has been demonstrated in several studies (Wang et al. 2000; Cheng et al. 2002). Regularly administered rofecoxib reduced proteinuria in proteinuric patients (Vogt et al. 2009). Intrarenal administration of parecoxib in a porcine model was also able to attenuate an otherwise evident creatinine clearance decrease after cross-clamping of the suprarenal aorta (Hauser et al. 2005). All these preliminary studies are still far from clinical use.

The Cochrane Library has several times performed meta-analyses of the effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. The most recent version was edited in 2009 but the conclusion remained the same. NSAIDs caused only a clinically unimportant transient reduction in renal function and should not be withheld from adults with normal preoperative renal function (http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD002765/frame.html). Use on risk patients should be regarded with caution. Elderly patients should be under supervision. This conclusion also applies to COX-2 inhibitors.

3. Persistent postsurgical pain

Pain is the main indication for knee arthroplasty and pain relief is the most important postoperative outcome. However, there are only few studies with persistent pain as the outcome measure after knee arthroplasty (Johnsson and Thorngren 1989; Burkart et al. 1993; Brander et al. 2003; Garcia et al. 2003; Harden et al. 2003; Nikolajsen et al. 2006). Most studies focus on the survival of the prosthesis.

The prevalence of persistent pain in our study was significantly higher than in the majority of earlier studies. The study by Brander et al. reported 22.6% prevalence of significant pain (Visual Analog Scale>4) at three months, 18.4% at six months and 13.1% at one year (Brander et al. 2003). In another study the prevalence of moderate pain was ten percent (Garcia et al. 2003). Lundblad et al. reported prevalences close to those found in our study. The prevalence of

persistent pain was 24% at rest and 66% during movement at 18 months after surgery (Lundblad et al. 2008).

The differences between the studies may be explained by the study methods. The pain of our patients was not assessed by clinicians as in some earlier studies (Brander et al. 2003; Garcia et al. 2003). The patients were able to express their feelings confidentially using the questionnaire, which may have increased the reported prevalence of pain. The inclusion criteria of pain intensity varied across studies. Mostly the patients in our study suffered from mild to moderate pain, but patients suffering from mild pain were excluded from the study by Brander et al. lowering the prevalence in their study (Brander et al. 2003). There were also remarkable differences between the time points for evaluating existing pain. The shortest time to the first evaluation was one month (Brander et al. 2003) and the latest time point was at seven years (Garcia et al. 2003). The recommended definition of postsurgical persistent pain allows us to call pain persistent if it has lasted more than two months (Macrae 2008). This is not reasonable in patients recovering from knee replacement. Pain after knee replacement seems to abate gradually. The time point for studying postsurgical pain should be long enough.

Our strongest risk factor for persistent pain was the intensity of early (the first week) postoperative pain. Earlier studies on knee replacement have not included the intensity of early postoperative pain in their risk analyses, which has left the intensity of preoperative pain as a risk factor (Brander et al. 2003; Lundblad et al. 2008). Instead, the study on total hip arthroplasty revealed that persistent postoperative pain was related to the recalled intensity of early postoperative pain rather than to the intensity of preoperative pain (Nikolajsen et al. 2006).

Female gender was a risk factor for persistent pain in our study as in many others (Brander et al. 2003; Rosseland and Stubhaug 2004; Kalliomäki et al. 2008; Singh and Lewallen 2009). After hip arthroplasty the proportion of patients suffering from persistent pain was equal between women and men, but women were more likely to have daily or constant pain than men (Nikolajsen et al. 2006).

Advanced age seems to reduce the risk of persistent pain after general surgery (Smith et al. 1999; Poobalan et al. 2001; Aasvang and Kehlet 2005; Poleshuck et al. 2006; Kalliomäki et al. 2008) . In our study age was not a linear risk factor for persistent pain, which concurs with other orthopaedic studies (Brander et al. 2003; Lundblad et al. 2008). In the study by Singh et al. younger patients (61-70 years) even had reduced risk of persistent pain after revision hip arthroplasty (Singh and Lewallen 2009).

Other factors associated with increased postsurgical persistent pain are anxiety and depression (Tasmuth et al. 1996; Tasmuth et al. 1996; Brander et al. 2003; Rolfson et al. 2009; Singh and Lewallen 2009), but our questionnaire was not designed to identify depression or anxiety.

The hypothesis of this study was that the larger the tissue injury (bilateral vs. unilateral arthroplasty group), the higher the prevalence of persistent pain. Surprisingly there was no association in this respect. These results are in line

with those of an earlier study (Powell et al. 2006) and support the consensus on offering bilateral knee arthroplasty when needed.

4. Strengths and weaknesses of the studies

Both dose efficacy studies (I-II) were equally well designed: prospective, randomized, double-blinded and placebo controlled. The sample size was based on calculations to enroll an ideal number of patients in the studies.
The weaknesses were in Studies III and IV. The major limitation of Study III was small sample size with wide variation in the data. This increases the risk of type II error. We had assumed that our physiological stressful study setting would have increased the sensitive renal marker values even in this small study population. Awareness of wide data variation in a clinical setting provides valuable information for other researchers.
The major limitations in Study IV were the relatively low response rate (65.7%) and the variable time period from surgery to the questionnaire. Psychosocial factors were likewise not included in the questionnaire. The response rate was considered sufficient to draw conclusions from the results, but a higher response rate might have been obtained with several reminders. This would have increased the power of the results. Fortunately, the original size of study sample (855 patients) is much larger than in earlier prevalence studies (Brander et al. 2003; Garcia et al. 2003; Lundblad et al. 2008).
The time interval from surgery to the questionnaire varied from four to 22 months. The minimum duration for persistent pain is two months (Macrae 2008). This requirement was met in our study. However, the long time interval for some responders may have affected the memory of acute postoperative pain. This was well illustrated in the study, where the women who had chronic pain after breast cancer surgery remembered having had more severe postoperative pain than those women who had no chronic pain (Tasmuth et al. 1996). Preoperative pain scores were not influenced by memory because they were taken from the hospital registry. Moreover, a long interval usually increases the likelihood of false negatives (Poobalan et al. 2001) or in other words increases the likelihood of true positives (Dworkin et al. 2010). This in turn underlies the significance of the high prevalence of persistent pain found in our study. A fixed time interval between surgery and the questionnaire would have improved the quality of this study.

5. Challenges in studying postsurgical pain

Pain is always a subjective experience, which makes it difficult to assess (Merskey 1994). Pain assessment method should be valid and comparable. Visual analogue scale (VAS) and numeral rating scale (NRS) are the most

reliable methods (Breivik et al. 2008), but still useless in some patient groups such as infants or older adults with dementia (Karp et al. 2008).

Pain is also culturally dependent, which means that the results from one study cannot be directly applied to some other population. The same problem occurs with different genders and races (Kalso et al. 2009).

Pain has many components which should be evaluated separately. Several pharmacotherapeutic studies have reported only spontaneous pain relief, although pain relief in movement might be even more important in regarding the patient's rehabilitation (Breivik et al. 2008).

The efficacy of pain medication seems to also vary between surgical procedures (Rømsing and Møiniche 2004) suggesting different components of pain: incisional, visceral, bone related, neuropathic etc. Efficacy differences also arise from different time intervals between the investigated drugs used (Dworkin et al. 2010). Pharmacodynamic and pharmacokinetic profiles should be noted in advance.

The assessment of baseline pain is essential in analgesic efficacy studies (Breivik et al. 2008) making the evaluation of pre-emptive analgesia demanding.

The aetiology of persistent postsurgical pain is always multifactorial (Kehlet et al. 2006b; Macrae 2008). Reliable risk analysis of persistent pain needs a wide perspective to include all possible risk factors in the model tested. The more risk factors are included, the more patients must be enrolled.

Challenges in studying pain are faced by different pain organizations, which have led to detailed recommendations about the study designs to be followed (Dworkin et al. 2010). This means that studies in the future should be more reliable and easier to compare against each other.

6. Future aspects

The efficacy of COX-2 inhibitors has been proven in several studies and meta-analyses (Gilron et al. 2003; Rømsing and Møiniche 2004; Elia et al. 2005). A cardiovascular risk profile is also well established (Bresalier et al. 2005; Nussmeier et al. 2005; Solomon et al. 2005). Future studies should concentrate on other adverse effects of COX-2 inhibitors. There is some controversy on the both renal effects (Hermann et al. 2005) and the bone healing (Beck et al. 2005; Vuolteenaho et al. 2008; Boursinos et al. 2009), which should be investigated. In addition, the positive role of coxibs in the inhibition of carcinogenesis (Rostom et al. 2007) could be studied in a perioperative model. An ideal coxib is still lacking in clinical practice.

Assessment of risk factors for persistent postsurgical pain is essential in the future, too (Macrae 2008). Risk factors identified might open a curative window to persistent pain. Most efforts will also be invested in solving genetic susceptibility (Stamer and Stuber 2007b). The patient at elevated risk of persistent pain should in turn be optimally treated. The optimal combination of medications needs to be solved for these patients (Dworkin et al. 2010).

Conclusions

Based on these studies the following conclusions can be drawn:

1. Neither the recommended dose of parecoxib, 40mg nor the double dose 80mg, reduced the fentanyl consumption during early postoperative period after laparoscopic cholecystectomy.

2. The recommended dose of etoricoxib, 120mg given in premedication, is effective for the treatment of pain during the early postoperative period after laparoscopic cholecystectomy. Combining paracetamol 1000mg with etoricoxib 120mg had no additional effect.

3. A single dose of 80mg parecoxib was well tolerated by the kidneys during the next 20 postoperative hours in patients undergoing laparoscopic hysterectomy with ASA physiological status I-II and age under 60 years.

4. The type of surgery in knee arthroplasty did not correlate with the prevalence of persistent pain. Persistent pain after knee arthroplasty seems to be a far more frequent problem than assumed. The preoperative duration of pain and the intensity of early postoperative pain are the risk factors to be addressed in prevention of postsurgical persistent pain.

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References

Aasvang E and Kehlet H (2005): Chronic postoperative pain: the case of inguinal herniorrhaphy. British journal of anaesthesia 95: 69-76.

Abassi Z, Brodsky S, Gealekman O, Rubinstein I, Hoffman A and Winaver J (2001): Intrarenal expression and distribution of cyclooxygenase isoforms in rats with experimental heart failure. American journal of physiology.Renal physiology 280: F43-53.

Abdullah TI, Iddon J, Barr L, Baildam AD and Bundred NJ (1998): Prospective randomized controlled trial of preservation of the intercostobrachial nerve during axillary node clearance for breast cancer. The British journal of surgery 85: 1443-1445.

Aida S, Fujihara H, Taga K, Fukuda S and Shimoji K (2000): Involvement of presurgical pain in preemptive analgesia for orthopedic surgery: a randomized double blind study. Pain 84: 169-173.

Akerström B, Logdberg L, Berggard T, Osmark P and Lindqvist A (2000): alpha (1)-Microglobulin: a yellow-brown lipocalin. Biochimica et biophysica acta 1482: 172-184.

Andrew D and Craig AD (2001): Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. Nature neuroscience 4: 72-77.

Angst MS and Clark JD (2006): Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 104: 570-587.

Apfelbaum JL, Chen C, Mehta SS and Gan aTJ (2003): Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged. Anesthesia & Analgesia 97: 534-540.

Bach S, Noreng MF and Tjellden NU (1988): Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 33: 297-301.

Bagge E, Bjelle A, Eden S and Svanborg A (1991): Factors associated with radiographic osteoarthritis: results from the population study 70-year-old people in Goteborg. The Journal of rheumatology 18: 1218-1222.

Barkin RL and Buvanendran A (2004): Focus on the COX-1 and COX-2 agents: renal events of nonsteroidal and anti-inflammatory drugs-NSAIDs. American Journal of Therapeutics 11: 124-129.

Beaussier M, Weickmans H, Paugam C, Lavazais S, Baechle JP, Goater P, Buffin A, Loriferne JF, Perier JF, Didelot JP, Mosbah A, Said R and Lienhart A (2005): A randomized, double-blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients.[see comment]. Anesthesia & Analgesia 100: 1309-1315.

Beck A, Salem K, Krischak G, Kinzl L, Bischoff M and Schmelz A (2005): Nonsteroidal anti-inflammatory drugs (NSAIDs) in the perioperative phase in traumatology and orthopedics effects on bone healing. Operative Orthopadie und Traumatologie 17: 569-578.

Belfer I, Wu T, Kingman A, Krishnaraju RK, Goldman D and Max MB (2004): Candidate gene studies of human pain mechanisms: methods for optimizing choice of polymorphisms and sample size. Anesthesiology 100: 1562-1572.

Bernardes SF, Keogh E and Lima ML (2008): Bridging the gap between pain and gender research: A selective literature review. European Journal of Pain, 12: 427-440.

Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ and VIGOR Study Group (2000): Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. The New England journal of medicine 343: 1520-1528.

Bonica JJ (1984): Management of pain with regional analgesia. Postgraduate medical journal 60: 897-904.

Bonnefont J, Courade JP, Alloui A and Eschalier A (2003): Antinociceptive mechanism of action of paracetamol. Drugs 63 Spec No 2: 1-4.

Borly L, Andersen IB, Bardram L, Christensen E, Sehested A, Kehlet H, Matzen P, Rehfeld JF, Stage P, Toftdahl DB, Gernow A and Højgaard L (1999): Preoperative Prediction Model of Outcome after Cholecystectomy for Symptomatic Gallstones. Scandinavian journal of gastroenterology 34: 1144-1152.

Boursinos LA, Karachalios T, Poultsides L and Malizos KN (2009): Do steroids, conventional non-steroidal anti-inflammatory drugs and selective Cox-2 inhibitors adversely affect fracture healing? Journal of Musculoskeletal Neuronal Interactions 9: 44-52.

Braden GL, O'Shea MH, Mulhern JG and Germain MJ (2004): Acute renal failure and hyperkalaemia associated with cyclooxygenase-2 inhibitors. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 19: 1149-1153.

Brander VA, Stulberg SD, Adams AD, Harden RN, Bruehl S, Stanos SP and Houle T (2003): Predicting total knee replacement pain: a prospective, observational study. Clinical orthopaedics and related research 416: 27-36.

Brandsborg B, Nikolajsen L, Kehlet H and Jensen TS (2008): Chronic pain after hysterectomy. Acta Anaesthesiologica Scandinavica 52: 327-331.

Breivik EK, Barkvoll P and Skovlund E (1999): Combining diclofenac with acetaminophen or acetaminophen-codeine after oral surgery: a randomized, double-blind single-dose study. Clinical pharmacology and therapeutics 66: 625-635.

Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Breivik Hals EK, Kvarstein G and Stubhaug A (2008): Assessment of pain. British journal of anaesthesia 101: 17-24.

Breivik H, Bang U, Jalonen J, Vigfusson G, Alahuhta S and Lagerkranser M (2010): Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. Acta Anaesthesiologica Scandinavica 54: 16-41.

Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA and Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators (2005): Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. The New England journal of medicine 352: 1092-1102.

Breyer MD, Hao C and Qi Z (2001): Cyclooxygenase-2 selective inhibitors and the kidney. Current opinion in critical care 7: 393-400.

Breyer MD and Harris RC (2001): Cyclooxygenase 2 and the kidney. Current opinion in nephrology and hypertension 10: 89-98.

Bruce J, Drury N, Poobalan AS, Jeffrey RR, Smith WCS and Chambers WA (2003): The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. Pain 104: 265-273.

Brune K and Hinz B (2004): Selective cyclooxygenase-2 inhibitors: similarities and differences. Scandinavian journal of rheumatology 33: 1-6.

Burkart BC, Bourne RB, Rorabeck CH and Kirk PG (1993): Thigh pain in cementless total hip arthroplasty. A comparison of two systems at 2 years' follow-up. The Orthopedic clinics of North America 24: 645-653.

Camu F, Beecher T, Recker DP and Verburg KM (2002): Valdecoxib, a COX-2-specific inhibitor, is an efficacious, opioid-sparing analgesic in patients undergoing hip arthroplasty. American Journal of Therapeutics 9: 43-51.

Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, Reicin AS, Bombardier C, Weinblatt ME, van der Heijde D, Erdmann E, Laine L and MEDAL Steering Committee (2006): Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 368: 1771-1781.

Chan CC, Reid CM, Aw TJ, Liew D, Haas SJ and Krum H (2009): Do COX-2 inhibitors raise blood pressure more than nonselective NSAIDs and placebo? An updated meta-analysis. Journal of hypertension 27: 2332-2341.

Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS and Simmons DL (2002): COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proceedings of the National Academy of Sciences of the United States of America 99: 13926-13931.

Chang DJ, Desjardins PJ, King TR, Erb T and Geba GP (2004): The analgesic efficacy of etoricoxib compared with oxycodone/acetaminophen in an acute postoperative pain model: a randomized, double-blind clinical trial. Anesthesia and Analgesia 99: 807-15, table of contents.

Cheer SM and Goa KL (2001): Parecoxib (parecoxib sodium). Drugs 61: 1133-1143.

Cheng HF, Wang CJ, Moeckel GW, Zhang MZ, McKanna JA and Harris RC (2002): Cyclooxygenase-2 inhibitor blocks expression of mediators of renal injury in a model of diabetes and hypertension. Kidney international 62: 929-939.

Cochrane DJ, Jarvis B and Keating GM (2002): Etoricoxib. Drugs 62: 2637-2653.

Courtney CA, Duffy K, Serpell MG and O'Dwyer PJ (2002): Outcome of patients with severe chronic pain following repair of groin hernia. The British journal of surgery 89: 1310-1314.

Dahan A, Kest B, Waxman AR and Sarton E (2008): Sex-specific responses to opiates: animal and human studies. Anesthesia and Analgesia 107: 83-95.
Dahan A, Aarts L and Smith TW (2010): Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. Anesthesiology 112: 226-238.
Dharnidharka VR, Kwon C and Stevens G (2002): Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation 40: 221-226.
Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, Goldman D, Xu K, Shabalina SA, Shagin D, Max MB, Makarov SS and Maixner W (2005): Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Human molecular genetics 14: 135-143.
D'Mello R and Dickenson AH (2008): Spinal cord mechanisms of pain. British journal of anaesthesia 101: 8-16.
Drenth JP and Waxman SG (2007): Mutations in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. The Journal of clinical investigation 117: 3603-3609.
Duggan ST and Scott LJ (2009): Intravenous Paracetamol (Acetaminophen). Drugs 69: 101-113.
Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, Chappell A, Chartier K, Cleeland CS, Costello A, Cowan P, Dimitrova R, Ellenberg S, Farrar JT, French JA, Gilron I, Hertz S, Jadad AR, Jay GW, Kalliomäki J, Katz NP, Kerns RD, Manning DC, McDermott MP, McGrath PJ, Narayana A, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Reeve BB, Rhodes T, Sampaio C, Simpson DM, Stauffer JW, Stucki G, Tobias J, White RE and Witter J (2010): Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain 149: 177-193.
Eisenberg E, Pultorak Y, Pud D and Bar-El Y (2001): Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). Pain 92: 11-17.
Elia N, Lysakowski C, Tramer M and Phil D (2005): Does Multimodal Analgesia with Acetaminophen, Nonsteroidal Antiinflammatory Drugs, or Selective Cyclooxygenase-2 Inhibitors and Patient-controlled Analgesia Morphine Offer Advantages over Morphine Alone?: Meta-analyses of Randomized Trials. Anesthesiology 103: 1296-1304.
Elson DW and Brenkel IJ (2007): A conservative approach is feasible in unexplained pain after knee replacement: a selected cohort study. Journal of Bone and Joint Surgery - British Volume 89-B: 1042-1045.
Faccenda KA and Finucane BT (2002): Epidural block: technical aspects and complications. Current Opinion in Anaesthesiology 15: 519-523.
Feldman HI, Kinman JL, Berlin JA, Hennessy S, Kimmel SE, Farrar J, Carson JL and Strom BL (1997): Parenteral ketorolac: the risk for acute renal failure. Annals of Internal Medicine 126: 193-199.

Fitzgibbons RJ,Jr, Giobbie-Hurder A, Gibbs JO, Dunlop DD, Reda DJ, McCarthy M,Jr, Neumayer LA, Barkun JS, Hoehn JL, Murphy JT, Sarosi GA,Jr, Syme WC, Thompson JS, Wang J and Jonasson O (2006): Watchful waiting vs repair of inguinal hernia in minimally symptomatic men: a randomized clinical trial. JAMA: the journal of the American Medical Association 295: 285-292.

Fong HJ and Cohen AH (1982): Ibuprofen-induced acute renal failure with acute tubular necrosis. American Journal of Nephrology 2: 28-31.

Gajraj NM (2003): Cyclooxygenase-2 inhibitors. Anesthesia and Analgesia 96: 1720-1738.

Gambaro G and Perazella MA (2003): Adverse renal effects of anti-inflammatory agents: evaluation of selective and nonselective cyclooxygenase inhibitors. Journal of internal medicine 253: 643-652.

Gan TJ, Joshi GP, Zhao SZ, Hanna DB, Cheung RY and Chen C (2004): Presurgical intravenous parecoxib sodium and follow-up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduces opioid requirements and opioid-related adverse effects. Acta Anaesthesiologica Scandinavica 48: 1194-1207.

Garcia JA, Bewley B and Redden JF (2003): The St. Leger total knee replacement--a 7-year clinical assessment and survivorship analysis. The Knee 10: 173-177.

Gatchel RJ, Peng YB, Peters ML, Fuchs PN and Turk DC (2007): The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychological bulletin 133: 581-624.

George SZ, Wallace MR, Wright TW, Moser MW, Greenfield WH, Sack BK, Herbstman DM and Fillingim RB (2008): Evidence for a biopsychosocial influence on shoulder pain: pain catastrophizing and catechol-O-methyltransferase (COMT) diplotype predict clinical pain ratings. Pain 136: 53-61.

Gilron I, Milne B and Hong M (2003): Cyclooxygenase-2 inhibitors in postoperative pain management: current evidence and future directions. Anesthesiology 99: 1198-1208.

Graham GG and Scott KF (2005): Mechanism of Action of Paracetamol. American Journal of Therapeutics 12: 46-55.

Granot M and Ferber SG (2005): The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. The Clinical journal of pain 21: 439-445.

Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P, Fletcher D and Chauvin M (2000): Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology 93: 409-417.

Gureje O, Simon GE and Von Korff M (2001): A cross-national study of the course of persistent pain in primary care. Pain 92: 195-200.

Harden RN, Bruehl S, Stanos S, Brander V, Chung OY, Saltz S, Adams A and Stulberg SD (2003): Prospective examination of pain-related and psychological predictors of CRPS-like phenomena following total knee arthroplasty: a preliminary study. Pain 106: 393-400.

Harkness EF, Macfarlane GJ, Nahit E, Silman AJ and McBeth J (2004): Mechanical injury and psychosocial factors in the work place predict the onset of widespread body pain: a two-year prospective study among cohorts of newly employed workers. Arthritis and Rheumatism 50: 1655-1664.

Harmoinen A, Lehtimäki T, Korpela M, Turjanmaa V and Saha H (2003): Diagnostic accuracies of plasma creatinine, cystatin C, and glomerular filtration rate calculated by the Cockcroft-Gault and Levey (MDRD) formulas. Clinical chemistry 49: 1223-1225.

Harris RC (2006): COX-2 and the kidney. Journal of cardiovascular pharmacology 47: S37-42.

Harris RC (2008): An update on cyclooxygenase-2 expression and metabolites in the kidney. Current opinion in nephrology and hypertension 17: 64-69.

Hauser B, Froba G, Bracht H, Strater J, Chkhouta AB, Vassilev D, Schoaff MJ, HuberLang M, Bruckner UB, Radermacher P and Schelzig H (2005): Effects of intrarenal administration of the COX-2 inhibitor parecoxib during porcine suprarenalaortic cross-clambing. Shock 24: 476-481.

Hegi TR, Bombeli T, Seifert B, Baumann PC, Haller U, Zalunardo MP, Pasch T and Spahn DR (2004): Effect of rofecoxib on platelet aggregation and blood loss in gynaecological and breast surgery compared with diclofenac. British journal of anaesthesia 92: 523-531.

Hermann M, Shaw S, Kiss E, Camici G, Buhler N, Chenevard R, Luscher TF, Grone HJ and Ruschitzka F (2005): Selective COX-2 inhibitors and renal injury in salt-sensitive hypertension. Hypertension 45: 193-197.

Ho SC, Royse CF, Royse AG, Penberthy A and McRae R (2002): Persistent pain after cardiac surgery: an audit of high thoracic epidural and primary opioid analgesia therapies. Anesthesia and Analgesia 95: 820-823.

Hogan Q, Dotson R, Erickson S, Kettler R and Hogan K (1994): Local anesthetic myotoxicity: a case and review. Anesthesiology 80: 942-947.

Horackova M, Schuck O, Komers R, Charvat J, Teplan V and Kvapil M (2005): Effect of rofecoxib on the glomerular filtration rate, proteinuria and the renin-angiotensin-aldosterone system in elderly subjects with chronic renal impairment. International journal of clinical pharmacology and therapeutics 43: 413-419.

Hubbard RC, Naumann TM, Traylor L and Dhadda S (2003): Parecoxib sodium has opioid-sparing effects in patients undergoing total knee arthroplasty under spinal anaesthesia. British journal of anaesthesia 90: 166-172.

Hyllested M, Jones S, Pedersen JL and Kehlet H (2002): Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. British journal of anaesthesia 88: 199-214.

Jensen MK and Andersen C (2004): Can chronic poststernotomy pain after cardiac valve replacement be reduced using thoracic epidural analgesia? Acta Anaesthesiologica Scandinavica 48: 871-874.

Jess P, Jess T, Beck H and Bech P (1998): Neuroticism in relation to recovery and persisting pain after laparoscopic cholecystectomy. Scandinavian journal of gastroenterology 33: 550-553.

Johnsson R and Thorngren KG (1989): Function after total hip replacement for primary osteoarthritis. International orthopaedics 13: 221-225.

Juhl GI, Norholt SE, Tonnesen E, Hiesse-Provost O and Jensen TS (2006): Analgesic efficacy and safety of intravenous paracetamol (acetaminophen) administered as a 2 g starting dose following third molar surgery. European journal of pain 10: 371-377.
Jung BF, Johnson RW, Griffin DR and Dworkin RH (2004): Risk factors for postherpetic neuralgia in patients with herpes zoster. Neurology 62: 1545-1551.
Kallanagowdar C, LeBreton A and Aviles DH (2006): Acute renal failure. Clinical pediatrics 45: 771-773.
Kalliomäki ML, Meyerson J, Gunnarsson U, Gordh T and Sandblom G (2008): Long-term pain after inguinal hernia repair in a population-based cohort; risk factors and interference with daily activities. European journal of pain 12: 214-225.
Kalso E, Perttunen K and Kaasinen S (1992): Pain after thoracic surgery. Acta Anaesthesiologica Scandinavica 36: 96-100.
Kalso E, Mennander S, Tasmuth T and Nilsson E (2001): Chronic post-sternotomy pain. Acta Anaesthesiologica Scandinavica 45: 935-939.
Kalso E, Haanpää M and Vainio A (2009): Kipu. Kustannus Oy Duodecim, Helsinki.
Karp JF, Shega JW, Morone NE and Weiner DK (2008): Advances in understanding the mechanisms and management of persistent pain in older adults. British journal of anaesthesia 101: 111-120.
Katz J, Poleshuck EL, Andrus CH, Hogan LA, Jung BF, Kulick DI and Dworkin RH (2005): Risk factors for acute pain and its persistence following breast cancer surgery. Pain 119: 16-25.
Kehlet H, Jensen TS and Woolf CJ (2006a): Persistent postsurgical pain: risk factors and prevention. Lancet 367: 1618-1625.
Kehlet H, Jensen TS and Woolf CJ (2006b): Persistent postsurgical pain: risk factors and prevention. The Lancet 367: 1618-1625.
Keller SM, Carp NZ, Levy MN and Rosen SM (1994): Chronic post thoracotomy pain. The Journal of cardiovascular surgery 35: 161-164.
Khuder SA, Herial NA, Mutgi AB and Federman DJ (2005): Nonsteroidal antiinflammatory drug use and lung cancer: a metaanalysis. Chest 127: 748-754.
King KM, Parry M, Southern D, Faris P and Tsuyuki RT (2008): Women's Recovery from Sternotomy-Extension (WREST-E) study: examining long-term pain and discomfort following sternotomy and their predictors. Heart 94: 493-497.
Kis B, Snipes JA, Isse T, Nagy K and Busija DW (2003): Putative cyclooxygenase-3 expression in rat brain cells. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism 23: 1287-1292.
Koppert W, Frotsch K, Huzurudin N, Boswald W, Griessinger N, Weisbach V, Schmieder RE and Schuttler J (2006): The effects of paracetamol and parecoxib on kidney function in elderly patients undergoing orthopedic surgery. Anesthesia and Analgesia 103: 1170-1176.
Korpela R, Korvenoja P and Meretoja OA (1999): Morphine-sparing effect of acetaminophen in pediatric day-case surgery. Anesthesiology 91: 442-447.

Lahtinen P, Kokki H and Hynynen M (2006): Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. Anesthesiology 105: 794-800.
Laisalmi M, Eriksson H, Koivusalo AM, Pere P, Rosenberg P and Lindgren L (2001): Ketorolac is not nephrotoxic in connection with sevoflurane anesthesia in patients undergoing breast surgery. Anesthesia and Analgesia 92: 1058-1063.
Liu SS, Zayas VM, Gordon MA, Beathe JC, Maalouf DB, Paroli L, Liguori GA, Ortiz J, Buschiazzo V, Ngeow J, Shetty T and Ya Deau JT (2009): A prospective, randomized, controlled trial comparing ultrasound versus nerve stimulator guidance for interscalene block for ambulatory shoulder surgery for postoperative neurological symptoms. Anesthesia and Analgesia 109: 265-271.
Lundblad H, Kreicbergs A and Jansson K (2008): Prediction of persistent pain after total knee replacement for osteoarthritis. Journal of Bone and Joint Surgery - British Volume 90-B: 166-171.
Macrae WA (2001): Chronic pain after surgery. British Journal of Anaesthesia 87: 88-98.
Macrae WA (2008): Chronic post-surgical pain: 10 years on. British Journal of Anaesthesia 101: 77-86.
Malan TP, Marsh G, Hakki SI, Grossman E, Traylor L and Hubbard RC (2003): Parecoxib sodium, a parenteral cyclooxygenase 2 selective inhibitor, improves morphine analgesia and is opioid-sparing following total hip arthroplasty. Anesthesiology 98: 950-956.
Malmstrom K, Kotey P, Cichanowitz N, Daniels S and Desjardins PJ (2003): Analgesic efficacy of etoricoxib in primary dysmenorrhea: results of a randomized, controlled trial. Gynecologic and obstetric investigation 56: 65-69.
Mann B, Hartner A, Jensen BL, Hilgers KF, Hocherl K, Kramer BK and Kurtz A (2001): Acute upregulation of COX-2 by renal artery stenosis. American journal of physiology.Renal physiology 280: F119-25.
Markowitz GS and Perazella MA (2005): Drug-induced renal failure: a focus on tubulointerstitial disease. Clinica chimica acta; international journal of clinical chemistry 351: 31-47.
Martinez V, Fletcher D, Bouhassira D, Sessler DI and Chauvin M (2007): The Evolution of Primary Hyperalgesia in Orthopedic Surgery: Quantitative Sensory Testing and Clinical Evaluation Before and After Total Knee Arthroplasty. Anesthesia & Analgesia 105: 815-821.
McCartney CJ, Brull R, Chan VW, Katz J, Abbas S, Graham B, Nova H, Rawson R, Anastakis DJ and von Schroeder H (2004): Early but no long-term benefit of regional compared with general anesthesia for ambulatory hand surgery. Anesthesiology 101: 461-467.
McCrory CR and Lindahl SG (2002): Cyclooxygenase inhibition for postoperative analgesia. Anesthesia and Analgesia 95: 169-176.
Melzack R and Wall PD (1965): Pain mechanisms: a new theory. Science 150: 971-979.
Merskey H and Bogduk N (1994): Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. IASP Press, Seattle.

Merskey H (1994): Logic, truth and language in concepts of pain. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation 3: S69-76.
Middelfart HV, Kristensen JU, Laursen CN, Qvist N, Hojgaard L, Funch-Jensen P and Kehlet H (1998): Pain and dyspepsia after elective and acute cholecystectomy. Scandinavian journal of gastroenterology 33: 10-14.
Miranda HF, Puig MM, Prieto JC and Pinardi G (2006): Synergism between paracetamol and nonsteroidal anti-inflammatory drugs in experimental acute pain. Pain 121: 22-28.
Moen V, Dahlgren N and Irestedt L (2004): Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. Anesthesiology 101: 950-959.
Møiniche S, Kehlet H and Dahl J (2002): A Qualitative and Quantitative Systematic Review of Preemptive Analgesia for Postoperative Pain Relief: The Role of Timing of Analgesia. Anesthesiology 96: 725-741.
Morse HN (1878): Ueber eine neue Darstellungsmethode der Acetylamidophenole. Berichte der deutschen chemischen Gesellschaft 11: 232-233.
Mukherjee D, Nissen SE and Topol EJ (2001): Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 286: 954-959.
Munsterhjelm E, Munsterhjelm N, Niemi T, Ylikorkala O, Neuvonen P and Rosenberg P(2005): Dose-dependent Inhibition of Platelet Function by Acetaminophen in Healthy Volunteers. Anesthesiology 103: 712-717.
Neal JM (2010): Ultrasound-Guided Regional Anesthesia and Patient Safety: An Evidence-Based Analysis. Regional Anesthesia & Pain Medicine 35: S59-67.
Ng A, Smith G and Davidson AC (2003): Analgesic effects of parecoxib following total abdominal hysterectomy. British journal of anaesthesia 90: 746-749.
Nikolajsen L, Hansen PO and Jensen TS (1997a): Oral ketamine therapy in the treatment of postamputation stump pain. Acta Anaesthesiologica Scandinavica 41: 427-429.
Nikolajsen L, Ilkjaer S, Christensen JH, Kroner K and Jensen TS (1997b): Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. Lancet 350: 1353-1357.
Nikolajsen L, Ilkjaer S, Kroner K, Christensen JH and Jensen TS (1997c): The influence of preamputation pain on postamputation stump and phantom pain. Pain 72: 393-405.
Nikolajsen L and Jensen TS (2001): Phantom limb pain. British journal of anaesthesia 87: 107-116.
Nikolajsen L, Sorensen HC, Jensen TS and Kehlet H (2004): Chronic pain following Caesarean section. Acta Anaesthesiologica Scandinavica 48: 111-116.
Nikolajsen L, Brandsborg B, Lucht U, Jensen TS and Kehlet H (2006): Chronic pain following total hip arthroplasty: a nationwide questionnaire study. Acta Anaesthesiologica Scandinavica 50: 495-500.
Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, Boyce SW and Verburg KM (2005): Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. New England Journal of Medicine 352: 1081-1091.

O'Dwyer PJ, Alani A and McConnachie A (2005): Groin hernia repair: postherniorrhaphy pain. World journal of surgery 29: 1062-1065.
Ott E, Nussmeier NA, Duke PC, Feneck RO, Alston RP, Snabes MC, Hubbard RC, Hsu PH, Saidman LJ and Mangano DT (2003): Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. The Journal of thoracic and cardiovascular surgery 125: 1481-1492.
Page B, Paterson C, Young D and O'Dwyer PJ (2002): Pain from primary inguinal hernia and the effect of repair on pain. The British journal of surgery 89: 1315-1318.
Pamuk ON and Cakir N (2006): The renal effects of the addition of low-dose aspirin to COX-2 selective and nonselective antiinflammatory drugs. Clinical rheumatology 25: 123-125.
Papaioannou M, Skapinakis P, Damigos D, Mavreas V, Broumas G and Palgimesi A (2009): The role of catastrophizing in the prediction of postoperative pain. Pain Medicine10: 1452-1459.
Pavy TJ, Gambling DR, Merrick PM and Douglas MJ (1995): Rectal indomethacin potentiates spinal morphine analgesia after caesarean delivery. Anaesthesia and Intensive Care 23: 555-559.
Perazella MA and Eras J (2000): Are selective COX-2 inhibitors nephrotoxic? American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation 35: 937-940.
Perkins FMMD and Kehlet HMD, Ph.D. (2000): Chronic Pain as an Outcome of Surgery: A Review of Predictive Factors. Anesthesiology 93: 1123-1133.
Perttunen K, Tasmuth T and Kalso E (1999): Chronic pain after thoracic surgery: a follow-up study. Acta Anaesthesiologica Scandinavica 43: 563-567.
Peters ML, Sommer M, de Rijke JM, Kessels F, Heineman E, Patijn J, Marcus MA, Vlaeyen JW and van Kleef M (2007): Somatic and psychologic predictors of long-term unfavorable outcome after surgical intervention. Annals of Surgery 245: 487-494.
Plaisance KI and Mackowiak PA (2000): Antipyretic Therapy: Physiologic Rationale, Diagnostic Implications, and Clinical Consequences. Archives of Internal Medicine 160: 449-456.
Poleshuck EL, Katz J, Andrus CH, Hogan LA, Jung BF, Kulick DI and Dworkin RH (2006): Risk factors for chronic pain following breast cancer surgery: a prospective study. The journal of pain 7: 626-634.
Poobalan AS, Bruce J, King PM, Chambers WA, Krukowski ZH and Smith WC (2001): Chronic pain and quality of life following open inguinal hernia repair. The British journal of surgery 88: 1122-1126.
Poobalan AS, Bruce JM, Smith S, Cairns W, King PM, Krukowski ZH and Chambers WA (2003): A Review of Chronic Pain After Inguinal Herniorrhaphy. Clinical Journal of Pain 19: 48-54.
Powell RS, Pulido P, Tuason MS, Colwell J, Clifford W. and Ezzet KA (2006): Bilateral vs Unilateral Total Knee Arthroplasty: A Patient-Based Comparison of Pain Levels and Recovery of Ambulatory Skills. The Journal of Arthroplasty, 21: 642-649.
Prescott LF, Roscoe P, Wright N and Brown SS (1971): Plasma-paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage. Lancet 1: 519-522.

Prescott LF (2000a): Paracetamol: past, present, and future. American Journal of Therapeutics 7: 143-147.
Prescott LF (2000b): Therapeutic misadventure with paracetamol: fact or fiction? American Journal of Therapeutics 7: 99-114.
Prielipp RC and Warner MA (2009): Perioperative nerve injury: a silent scream? Anesthesiology 111: 464-466.
Rasmussen GL, Malmstrom K, Bourne MH, Jove M, Rhondeau SM, Kotey P, Ang J, Aversano M and Reicin AS (2005): Etoricoxib Provides Analgesic Efficacy to Patients After Knee or Hip Replacement Surgery: A Randomized, Double-Blind, Placebo-Controlled Study. Anesthesia & Analgesia 101: 1104-1111.
Reimann F, Cox JJ, Belfer I, Diatchenko L, Zaykin DV, McHale DP, Drenth JP, Dai F, Wheeler J, Sanders F, Wood L, Wu TX, Karppinen J, Nikolajsen L, Mannikko M, Max MB, Kiselycznyk C, Poddar M, Te Morsche RH, Smith S, Gibson D, Kelempisioti A, Maixner W, Gribble FM and Woods CG (2010): Pain perception is altered by a nucleotide polymorphism in SCN9A. Proceedings of the National Academy of Sciences of the United States of America 107: 5148-5153.
Reynolds LW, Hoo RK, Brill RJ, North J, Recker DP and Verburg KM (2003): The COX-2 specific inhibitor, valdecoxib, is an effective, opioid-sparing analgesic in patients undergoing total knee arthroplasty. Journal of pain and symptom management 25: 133-141.
Rigler ML, Drasner K, Krejcie TC, Yelich SJ, Scholnick FT, DeFontes J and Bohner D (1991): Cauda equina syndrome after continuous spinal anesthesia. Anesthesia and Analgesia 72: 275-281.
Rolfson O, Dahlberg LE, Nilsson JA, Malchau H and Garellick G (2009): Variables determining outcome in total hip replacement surgery. The Journal of bone and joint surgery.British volume 91: 157-161.
Romundstad L, Stubhaug A, Niemi G, Rosseland LA and Breivik H (2006): Adding propacetamol to ketorolac increases the tolerance to painful pressure. European Journal of Pain 10: 177-183.
Rorarius MG, Suominen P, Baer GA, Romppanen O and Tuimala R (1993): Diclofenac and ketoprofen for pain treatment after elective caesarean section. British journal of anaesthesia 70: 293-297.
Rosseland LA and Stubhaug A (2004): Gender is a confounding factor in pain trials: women report more pain than men after arthroscopic surgery. Pain 112: 248-253.
Rosseland LA, Solheim N and Stubhaug A (2008): Pain and disability 1 year after knee arthroscopic procedures. Acta Anaesthesiologica Scandinavica 52: 332-337.
Rostom A, Dube C, Lewin G, Tsertsvadze A, Barrowman N, Code C, Sampson M, Moher D, U.S and Preventive Services Task F (2007): Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Annals of Internal Medicine 146: 376-389.
Rømsing J, Møiniche S and Dahl JB (2002): Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia. British journal of anaesthesia 88: 215-226.

Rømsing J and Møiniche S (2004): A systematic review of COX-2 inhibitors compared with traditional NSAIDs, or different COX-2 inhibitors for post-operative pain. Acta Anaesthesiologica Scandinavica 48: 525-546.
Rømsing J, Møiniche S, Mathiesen O and Dahl JB (2005): Reduction of opioid-related adverse events using opioid-sparing analgesia with COX-2 inhibitors lacks documentation: a systematic review. Acta Anaesthesiologica Scandinavica 49: 133-142.
Saastamoinen P, Leino-Arjas P, Laaksonen M and Lahelma E (2005): Socio-economic differences in the prevalence of acute, chronic and disabling chronic pain among ageing employees. Pain 114: 364-371.
Schmelz M (2001): A neural pathway for itch. Nature neuroscience 4: 9-10.
Schwab JM, Beiter T, Linder JU, Laufer S, Schulz JE, Meyermann R and Schluesener HJ (2003a): COX-3--a virtual pain target in humans? The FASEB journal: official publication of the Federation of American Societies for Experimental Biology 17: 2174-2175.
Schwab JM, Schluesener HJ and Laufer S (2003b): COX-3: just another COX or the solitary elusive target of paracetamol? Lancet 361: 981-982.
Sciulli MG, Seta F, Tacconelli S, Capone ML, Ricciotti E, Pistritto G and Patrignani P (2003): Effects of acetaminophen on constitutive and inducible prostanoid biosynthesis in human blood cells. British journal of pharmacology 138: 634-641.
Sear JW (2005): Kidney dysfunction in the postoperative period. British journal of anaesthesia 95: 20-32.
Seeff LB, Cuccherini BA, Zimmerman HJ, Adler E and Benjamin SB (1986): Acetaminophen hepatotoxicity in alcoholics. A therapeutic misadventure. Annals of Internal Medicine 104: 399-404.
Senturk M, Ozcan PE, Talu GK, Kiyan E, Camci E, Ozyalcin S, Dilege S and Pembeci K (2002): The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesthesia and Analgesia 94: 11-5, table of contents.
Shlipak MG, Praught ML and Sarnak MJ (2006): Update on cystatin C: new insights into the importance of mild kidney dysfunction. Current opinion in nephrology and hypertension 15: 270-275.
Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM and Geis GS (2000): Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 284: 1247-1255.
Singh JA and Lewallen D (2009): Age, gender, obesity, and depression are associated with patient-related pain and function outcome after revision total hip arthroplasty. Clinical rheumatology 28: 1419-1430.
Smirnov, Grigori T, Markku T, Henri H, Kimmo S, Marjatta K and Hannu (2008): Etoricoxib for pain management during thyroid surgery-a prospective, placebo-controlled study. Otolaryngology - Head & Neck Surgery 138: 92-97.
Smith WC, Bourne D, Squair J, Phillips DO and Chambers WA (1999): A retrospective cohort study of post mastectomy pain syndrome. Pain 83: 91-95.

Soinila S, Kaste M and Somer H (2006): Neurologia. Kustannus Oy Duodecim, Helsinki.
Solomon DH, Glynn RJ, Levin R and Avorn J (2002): Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. Archives of Internal Medicine 162: 1099-1104.
Solomon DH, Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H and Avorn J (2004): Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 109: 2068-2073.
Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E and Bertagnolli M (2005): Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. The New England journal of medicine 352: 1071-1080.
Stamer UM and Stuber F (2007a): The pharmacogenetics of analgesia. Expert opinion on pharmacotherapy 8: 2235-2245.
Stamer UM and Stuber F (2007b): Genetic factors in pain and its treatment. Current opinion in anaesthesiology 20: 478-484.
Svendsen KB, Bech JN, Sorensen TB and Pedersen EB (2000): A comparison of the effects of etodolac and ibuprofen on renal haemodynamics, tubular function, renin, vasopressin and urinary excretion of albumin and alpha-glutathione-S-transferase in healthy subjects: a placebo-controlled cross-over study. European journal of clinical pharmacology 56: 383-388.
Swan SK, Rudy DW, Lasseter KC, Ryan CF, Buechel KL, Lambrecht LJ, Pinto MB, Dilzer SC, Obrda O, Sundblad KJ, Gumbs CP, Ebel DL, Quan H, Larson PJ, Schwartz JI, Musliner TA, Gertz BJ, Brater DC and Yao SL (2000): Effect of Cyclooxygenase-2 Inhibition on Renal Function in Elderly Persons Receiving a Low-Salt Diet: A Randomized, Controlled Trial. Annals of Internal Medicine 133: 1-9.
Tacconelli S, Capone ML, Sciulli MG, Ricciotti E and Patrignani P (2002): The biochemical selectivity of novel COX-2 inhibitors in whole blood assays of COX-isozyme activity. Current medical research and opinion 18: 503-511.
Taenzer P, Melzack R and Jeans ME (1986): Influence of psychological factors on postoperative pain, mood and analgesic requirements. Pain 24: 331-342.
Tang J, Li S, White PF, Chen X, Wender RH, Quon R, Sloninsky A, Naruse R, Kariger R, Webb T and Norel E (2002): Effect of parecoxib, a novel intravenous cyclooxygenase type-2 inhibitor, on the postoperative opioid requirement and quality of pain control. Anesthesiology 96: 1305-1309.
Tasmuth T, von Smitten K, Hietanen P, Kataja M and Kalso E (1995): Pain and other symptoms after different treatment modalities of breast cancer. Annals of Oncology 6: 453-459.
Tasmuth T, Estlanderb AM and Kalso E (1996): Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer. Pain 68: 343-347.
Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejim J, Marian C, Scholz J, Wu T, Allchorne A, Diatchenko L, Binshtok AM, Goldman D, Adolph J, Sama S, Atlas SJ, Carlezon WA, Parsegian A, Lotsch J, Fillingim RB, Maixner W, Geisslinger G, Max MB and Woolf CJ (2006): GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nature medicine 12: 1269-1277.

Tiippana E, Nilsson E and Kalso E (2003): Post-thoracotomy pain after thoracic epidural analgesia: a prospective follow-up study. Acta Anaesthesiologica Scandinavica 47: 433-438.
Toivonen J, Pitko VM and Rosenberg PH (2007): Etoricoxib pre-medication combined with intra-operative subacromial block for pain after arthroscopic acromioplasty. Acta Anaesthesiologica Scandinavica 51: 316-321.
Vane JR (1971): Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature: New biology 231: 232-235.
Veering BT (2003): Complications and local anaesthetic toxicity in regional anaesthesia. Current Opinion in Anaesthesiology 16: 455-459.
Vogt L, de Zeeuw D, Woittiez AJ and Navis G (2009): Selective cyclooxygenase-2 (COX-2) inhibition reduces proteinuria in renal patients. Nephrology, dialysis, transplantation 24: 1182-1189.
Vuolteenaho K, Moilanen T and Moilanen E (2008): Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 and the bone healing process. Basic & Clinical Pharmacology & Toxicology 102: 10-14.
Wallace MS, Wallace AM, Lee J and Dobke MK (1996): Pain after breast surgery: a survey of 282 women. Pain 66: 195-205.
Wang JL, Cheng HF, Shappell S and Harris RC (2000): A selective cyclooxygenase-2 inhibitor decreases proteinuria and retards progressive renal injury in rats. Kidney international 57: 2334-2342.
Welch MB, Brummett CM, Welch TD, Tremper KK, Shanks AM, Guglani P and Mashour GA (2009): Perioperative peripheral nerve injuries: a retrospective study of 380,680 cases during a 10-year period at a single institution. Anesthesiology 111: 490-497.
Whelton A (1999): Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. The American Journal of Medicine 106: 13S-24S.
Whelton A (2000): Renal and related cardiovascular effects of conventional and COX-2-specific NSAIDs and non-NSAID analgesics. American Journal of Therapeutics 7: 63-74.
Winkelmayer WC, Waikar SS, Mogun H and Solomon DH (2008): Nonselective and cyclooxygenase-2-selective NSAIDs and acute kidney injury. The American Journal of Medicine 121: 1092-1098.
Wright D, Paterson C, Scott N, Hair A and O'Dwyer PJ (2002): Five-year follow-up of patients undergoing laparoscopic or open groin hernia repair: a randomized controlled trial. Annals of Surgery 235: 333-337.

http://www.who.int/cancer/palliative/painladder/en/
http://www.thecochranelibrary.com
http://www.biomedcentral.com/1471-2253/2/4
http://www.biomedcentral.com/1471-2253/3/1
http://www.tga.gov.au/recalls/2007/lumiracoxib.htm
http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD002765/frame.html

Appendix

The questionnaire of Study IV

Background:

1. Weight_____kg
2. Height_____cm

Pre/Post-surgical status

3. How long did you suffer from pain in the operated knee before surgery?_____months
4. How much did this pain disturb your daily life?
   1 not at all
   2 a little
   3 to some extent
   4 a lot
5. How long did you have pain after surgery?_____weeks/months
6. How would you describe the pain during the first week after the operation?
   1 mild
   2 moderate
   3 severe
   4 unbearable

At present

7. Do you still have pain in your operated knee?
   1 yes, go to Question 9
   2 no (no further questions)
8. Do you have pain at rest?
   1 yes
   2 no
9. How would you describe the degree of pain at rest?
   1 mild
   2 moderate
   3 severe
   4 unbearable

10. Do you have pain during exercise?
    1 yes
    2 no, go to Question 12
11. How would you describe the degree of pain during exercise?
    1 mild
    2 moderate
    3 severe
    4 unbearable
12. How much does this pain disturb your daily life?
    1 not at all
    2 a little
    3 to some extent
    4 a lot
13. How much does this pain disturb your sleep?
    1 not at all
    2 a little
    3 to some extent
    4 a lot
14. Do you still use any medicine against postsurgical knee pain?
    Which?_____

Original publications

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Lack of analgesic effect of parecoxib following laparoscopic cholecystectomy

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Background: The cyclo-oxygenase-2 inhibitor, parecoxib, can be administered parenterally. The recommended dose for post-operative use is 40 mg twice daily, which may not be the appropriate dose for the treatment of visceral pain. We studied the effect of a single dose of parecoxib of either 40 or 80 mg in laparoscopic cholecystectomy, and its effect on opioid-induced side-effects.
Methods: Seventy-three patients scheduled for elective laparoscopic cholecystectomy were enrolled in this prospective, randomized, double-blind study. Patients were randomized into three groups: a placebo-treated control group, a 40-mg parecoxib-treated group (P40) and an 80-mg parecoxib-treated group (P80). We recorded the cumulative fentanyl consumption during the first 20 h post-operatively by patient-controlled analgesia equipment, the pain scores during rest, coughing and mobilization (visual analogue scale, 0–10), the worst pain during the first 2 h post-operatively and in the following 18 h, and the side-effects by questionnaire.
Results: No significant differences in fentanyl consumption between the three groups could be detected. The worst pain experienced between 2 and 20 h post-operatively on the ward was significantly lower in the P80 group than in the control group.
Conclusion: The recommended dose of parecoxib, 40 mg, is not effective for the treatment of pain during the early post-operative period after laparoscopic cholecystectomy. Doubling the dose to 80 mg seems to improve the results.

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Key words: cyclo-oxygenase-2 inhibitor; non-steroidal anti-inflammatory drug; parecoxib; visceral pain.

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OPIOIDS are commonly used for post-operative pain treatment, although their side-effects are well known. Non-steroidal anti-inflammatory drugs (NSAIDs), used for post-operative pain, are valuable because they reduce the use of opioids by about 20–50% depending on the pain model employed (1–3). Because cyclo-oxygenase-2 (COX-2) inhibitors are not associated with the various side-effects of traditional NSAIDs, such as peptic irritation and, in particular, interference with haemostasis (1–3), they can be used more often for pain treatment during the peri-operative period. However, renal side-effects are similar (1–3). The risk for cardiovascular events may be increased when COX-2 inhibitors are used (4, 5).

Parecoxib is a COX-2 inhibitor which can be administered parenterally. It is a pro-drug metabolized by the liver to valdecoxib. The analgesic effect of valdecoxib starts at 10 min, but the maximum effect (t_{max}) is seen between 2 and 4 h. The $t_{1/2}$ of valdecoxib is 6–10 h (1). Its peri-operative use has been studied in dental (6, 7), orthopaedic (8, 9), gynaecological (10–13) and coronary artery bypass (14) surgery, reducing the need for additional pain treatment with opioids by 20–40%. The peri-operative use of parecoxib improved the quality of patient recovery following laparoscopic cholecystectomy (15–17). The dose of parecoxib effective for post-operative pain relief varies from 20 to 80 mg depending on the type of surgery. The recommended dose for peri-operative use is 40 mg twice daily.

Visceral pain is more therapy resistant than pain following orthopaedic or dental surgery, for example (18). In addition, the results of previous studies on the effect of parecoxib on post-operative pain relief following surgery of the viscera, published so far, have been biased by the fact that the statistical analyses of the results have been performed in a manner not adhering to the rules of statistical assumptions. Mostly, only parametric analyses have been employed in the measurements, although a non-normal distribution of

the outcome variables, such as patient behaviour during pain and the cumulative consumption of analgesics, is well known (19, 20). We therefore decided to study the effect of a single dose of parecoxib of either 40 or 80 mg on post-operative pain, and its possible influence on opioid-induced side-effects, such as nausea, in patients undergoing laparoscopic cholecystectomy. Pain after laparoscopic cholecystectomy has incisional, visceral and shoulder pain components (21). The hypothesis was that parecoxib 80 mg would be a more appropriate dose than 40 mg in this mixed pain model. The primary end point was the reduced cumulative consumption of analgesics during the first 20 h post-operatively. We gave parecoxib at the end of surgery because it has been judged to perform better when given as treatment than as prophylaxis (22).

Materials and methods

The study was approved by the ethics committees of the participating institutions (District Hospitals of Valkeakoski and Vammala, Finland) and the Finnish National Medical Board. Written informed consent was obtained from each patient. Seventy-three patients scheduled for elective laparoscopic cholecystectomy were enrolled in this prospective, randomized, double-blind study. The inclusion criteria were as follows: age between 30 and 60 years; ASA physiological status I–II; weight between 60 and 100 kg. The exclusion criteria included allergy to aspirin-like drugs or sulphonamide, bronchial asthma, liver or renal disturbances, peptic ulcer, bleeding disorder, pregnancy, substance abuse and chronic pain.

Patients were randomized into three groups: placebo-treated control group (placebo group), 40-mg parecoxib-treated group (P40 group) and 80-mg parecoxib-treated group (P80 group). The randomization procedure involved computer-generated random numbers in opaque envelopes. The study medication was given at the end of anaesthesia. All solutions were colourless in a volume of 4 ml and were prepared by a staff nurse not involved in the study.

Pre-medication was oxazepam (15 mg) in all groups. Anaesthesia was standardized. Induction was with fentanyl (2 μg/kg), propofol (2 mg/kg) and rocuronium (0.6 mg/kg). An equal amount of fentanyl was given about 3 min before skin incision for trocars. All operations were performed by experienced laparoscopic surgeons using the standard technique with two 12-mm trocars and two 5-mm trocars. Warm (37 °C) CO_2 insufflation was used and the intra-abdominal pressure was kept at 12 mmHg. Anaesthesia was maintained with sevoflurane 2–3% in air–O_2 (66% : 34%). Muscle relaxation was maintained between train-of-four (TOF) 0/4–2/4 with rocuronium. E_tCO_2 was maintained between 5.0 and 5.5% by adjusting the ventilation. Residual neuromuscular block was antagonized with neostigmine and glycopyrrolate. The wounds were not infiltrated with local anaesthetics.

All patients were instructed pre-operatively and assisted post-operatively in the use of the patient-controlled analgesia (PCA) device, programmed to deliver 50 μg of fentanyl over 2 min. The lockout time was 5 min, and the maximum dose was 10 ml/h (= 500 μg) during the first 2 h in the recovery room and 5 ml/h (= 250 μg) on the ward until 20 h after the end of surgery. During emergence from anaesthesia, the recovery room nurses were allowed to give additional fentanyl boluses via the PCA device on request of the patients.

During the pre-anaesthetic round, the patients were instructed in the use of a visual analogue scale (VAS, 0–10). Pain intensity at rest, during coughing and during leg elevation was assessed using VAS at the pre-operative round, on arrival in the operating theatre, and at 1, 2, 4, 6, 8, 10 and 20 h after the end of surgery (0, no pain at all; 10, unbearable pain). The patients were asked to evaluate the worst pain score at rest encountered during the previous period at 2 and 20 h after the end of surgery. The times from the end of surgery until the first bolus of fentanyl delivered by the PCA device and the times to eye opening and head raising on demand were recorded. The need for additional pain treatment was evaluated by the frequency and amount of fentanyl boluses during the first 20 h post-operatively.

The patients were asked about nausea using VAS during the pre-operative round, on arrival at the operating theatre, and at 1, 2, 4, 6, 8, 10 and 20-h post-operatively (0, not at all; 10, worst imaginable). At the same time points, the patients were also asked about the type and degree (VAS) of other possible side-effects of any kind. The anti-emetics used were recorded at 2 and 20 h post-operatively. At the end of the observation period, the patients were asked to express their opinion concerning the efficacy of the pain-relieving treatment (0, excellent; 1, good; 2, unknown; 3, fair; 4, poor).

The sample size estimation was based on our hypothesis that parecoxib would reduce the need for post-operative pain treatment during the first 20 h post-operatively to the same degree as traditional NSAIDs (18, 23). We calculated that, with 20 patients

per group, the sample size would be sufficient to detect a difference of 40% in the overall amount of fentanyl boluses during the first 20 h post-operatively between the P80 and control groups ($\alpha = 0.05$, power = 80%).

The cumulative fentanyl doses and VAS score variables for pain measurements and fatigue were treated as continuous. Most were non-normally distributed and medians and quartiles are reported. The significance test between the study groups was the Kruskall–Wallis test. Normally distributed data was reported by means and tested by analysis of variance (ANOVA) (*post hoc* least-significant difference). Categorized variables are presented as percentage frequencies, with χ^2 tests as the significance test. $P < 0.05$ was considered to be statistically significant. The analysis was performed using SPSS for Windows, version 11.5.

Results

Seventy-three patients consented to participate in the study. Of these, nine were excluded for the following reasons: the laparoscopic operation was changed to open cholecystectomy in four patients; local anaesthetics were used in one patient; one non-Finnish-speaking patient was unable to answer the questions; two patients were rejected because of violations of the protocol (weight of more than 100 kg); one patient was rejected because of an extremely difficult and time-consuming operation (more than 120 min). Of the remaining 64 patients, there were no significant differences between the treatment groups with regard to age, weight, gender, ASA risk qualification and the duration of the operation (Table 1).

The cumulative consumption of fentanyl, expressed as medians and quartiles, is shown in Table 2. There was a tendency to use less fentanyl in the P40 and P80 groups compared with the placebo group throughout the entire post-operative study period from 1 to 20 h post-operatively. The difference was not statistically or clinically significant. PCA demands were almost equal to delivered doses in all groups (correlation, 0.9).

There were no significant differences between the groups with regard to pain scores at rest or during coughing and leg elevation at any time point (Table 3). The worst pain on the ward, evaluated by VAS and expressed by means and standard deviations, was significantly lower in the P80 group (3.9 ± 1.9) than in the placebo group (5.8 ± 3.0) ($P = 0.014$).

In the global evaluation of the quality of post-operative analgesia, patients rated it from good to excellent in each group, but there were two patients in the placebo group who evaluated their analgesia as fair or poor (Table 4). Four patients did not answer the question about the quality of analgesia.

There was no clinically or statistically significant difference between the groups with regard to post-operative nausea when evaluating nausea by VAS or comparing the anti-emetic doses used.

The frequency of other side-effects was rare and of a slight to moderate degree. Three patients in each group complained of slight to moderate headache (VAS < 5) and one patient in each group suffered from dizziness (VAS ≤ 6). Blurred vision (VAS ≤ 2) was experienced by one patient in the placebo group and one in the P80 group.

Discussion

In this study in patients undergoing elective laparoscopic cholecystectomy, we demonstrated that there was no significant difference in the cumulative fentanyl consumption during the first 20 h post-operatively in the 40- or 80-mg parecoxib-treated groups compared with the placebo group.

The original studies evaluating the recommended dose of parecoxib were mostly performed in patients undergoing minor surgery, e.g. dental or orthopaedic surgery (6–9). Clinical studies on orthopaedic patients have managed to reduce opioid consumption by 40% (8, 9). Pain after laparoscopic cholecystectomy is intense if local anaesthesia is not employed: the degree of pain until the first post-operative morning has been shown to be strong or even unbearable in about half of patients (24). Pain after laparoscopic cholecystectomy has several components (incisional, visceral and shoulder pain) and pain intensity varies between patients (21). In addition, visceral pain seems to be more resistant to the

Table 1

Baseline characteristics of the three study groups (mean ± SD or range).

	Placebo n = 20	P40 n = 23	P80 n = 21
Age (years)	41 ± 10	45 ± 9	44 ± 12
Weight (kg)	75 ± 11	77 ± 14	77 ± 12
ASA I/II	12/8	11/12	13/8
Sex (male/female)	6/14	6/17	4/17
Duration of surgery (min)	54 (19–106)	63 (10–150)	56 (19–103)

P40, parecoxib 40 mg; P80, parecoxib 80 mg.
No significant differences between the groups.

Table 2

Cumulative post-operative fentanyl consumption during the study [median (Q_1, Q_3)].

Group	1 h	2 h	4 h	6 h	8 h	10 h	20 h
Placebo	2 (1, 3)	4 (2.5, 5.5)	5 (4, 11)	6 (4, 12.5)	7 (5, 14.5)	8 (5, 15)	10 (6, 22)
P40	2 (1, 3.5)	3 (2, 4.75)	5 (3, 7.75)	5 (3.25, 10.75)	5.5 (4, 11)	6 (5, 12.75)	8 (6, 16.75)
P80	1 (1, 2)	2 (1, 4.75)	4 (2, 5.75)	4 (2.25, 7)	5.5 (4.25, 8)	6.5 (4.25, 8)	8.5 (5.5, 11.75)

P40, parecoxib 40 mg; P80, parecoxib 80 mg.
No significant differences between the groups (Kruskall–Wallis test).

analgesic effect of NSAIDs (18). Therefore, the recommended dose cannot be regarded as similar in a visceral pain model as in orthopaedic or dental pain models.

In contrast with other published studies on mixed pain (10–12, 15–17), parecoxib, 40 mg, failed to demonstrate any analgesic effect in our study. Some of the previous studies have used parametric tests, although the normality of the data was not clear (10, 12). The duration of our study was 20 h post-operatively; however, the evaluation of only the first 20 h may not be the appropriate end point to determine the efficacy of coxibs. Some studies have demonstrated that the analgesic efficacy of parecoxib increases during the study period (15). One study demonstrated the efficacy of parecoxib in relieving acute post-operative pain following gynaecological laparotomy, but the study started on the first post-operative day (11). This phenomenon may be explained by the fact that NSAIDs work better when pain is less intense (25). Alexander (26) concluded in his review that NSAIDs are ineffective for shoulder pain, commonly seen after laparoscopy. We did not investigate shoulder pain separately.

The relatively small number of patients may also explain some of the discrepancies with other studies. In our power analysis, we calculated the sample size to be 20 patients per group to demonstrate a 40% decrease in cumulative opioid consumption, a decrease we believe to be clinically meaningful when treating moderate pain. A statistically significant difference may have been reached by gathering more data, but this would not have resulted in a significant clinical difference (20%).

We chose to give only a single dose of parecoxib, because the maximum daily dose recommended by the drug company is 80 mg. The drug companies also advise that valdecoxib be prescribed on a once-daily basis. The $t_{1/2}$ of parecoxib (*c.* 8 h) should be sufficiently long to secure sufficiently high plasma levels during the first 20 h following administration. The maximum effect of parecoxib was seen 6–8 h post-operatively, which matches the pharmacokinetics of parecoxib.

The opioid-sparing effect of a coxib is most beneficial when it also results in a decrease in post-operative side-effects (27, 28). Our study was not powered for side-effects, but the reported opioid-related side-effects did not differ between the groups. This has also been found in lower abdominal and orthopaedic pain models (8–10). Gan et al. (17)

Table 3

Medians of the pain scores (visual analogue scale, 0–10) at rest, during coughing and during leg elevation.

	1 h	2 h	4 h	6 h	8 h	10 h	20 h
At rest							
Placebo	4.5	3.3	2.0	2.0	1.0	1.0	1.0
P40	4.0	3.0	2.0	1.0	1.0	1.0	1.0
P80	4.0	2.0	2.0	1.5	1.5	1.0	1.0
Coughing							
Placebo	6.0	5.0	4.0	3.0	3.0	3.0	2.0
P40	5.0	4.0	4.0	3.0	3.0	2.0	3.0
P80	4.0	4.0	3.0	2.8	3.0	2.0	2.0
Leg elevation							
Placebo	5.0	4.3	4.0	3.0	2.5	2.0	2.5
P40	5.0	4.0	3.0	3.0	3.0	2.0	3.0
P80	5.0	4.0	3.0	2.5	2.0	2.0	2.0

P40, parecoxib 40 mg; P80, parecoxib 80 mg.
No significant differences between the groups (Kruskall–Wallis test).

Table 4

Global evaluation of analgesia (*n*).

	Placebo $n = 17$	P40 $n = 22$	P80 $n = 21$
Excellent	9	17	14
Good	6	5	7
Unknown	1	0	0
Fair	1	0	0
Poor	1	0	0

P40, parecoxib 40 mg; P80, parecoxib 80 mg.
No significant differences.

showed a decrease in opioid-related side-effects in patients recovering from laparoscopic cholecystectomy and receiving parecoxib pre-operatively and valdecoxib post-operatively. They used the opioid-related Symptoms Distress Scale questionnaire every 24 h for 7 days, accumulating data from each individual, not spontaneous complaints as in our and most other studies.

Publications on the effect of analgesics should include information about the normality of the data to provide the reader with more accurate information on the statistical analysis of the study results. Normality should be tested at least by histogram (19, 20), and parametric tests should be used only if the results are normally distributed. Parametric tests in non-normally distributed data may be misleading. They may find a statistical difference when there is none. However, in the published literature, parametric tests are often used to compare opioid consumption (8, 9, 17), although normality is not demonstrated.

We conclude that the recommended dose of parecoxib (40 mg) during the early post-operative period is not effective for laparoscopic cholecystectomy. Doubling the dose to 80 mg seems to improve the results.

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References

1. Gilron I, Milne B, Hong M. Cyclooxygenase-2 inhibitors in postoperative pain management. *Anesthesiology* 2003; **99**: 1198–208.
2. Noor M. Cyclooxygenase-2 inhibitors. *Anesth Analg* 2003; **96**: 1720–38.
3. Brune K, Hintz B. Selective cyclooxygenase-2 inhibitors: similarities and differences. *Scand J Rheumatol* 2004; **33**: 1–6.
4. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; **345**: 433–42.
5. Solomon SD, Murray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352**: 1071–80.
6. Daniels SE, Grossman EH, Kuss ME, Talwalker S, Hubbard RC. A double-blind, randomized comparison of intramuscularly and intravenously administered parecoxib sodium versus ketorolac and placebo in a post-oral surgery pain model. *Clin Ther* 2001; **23**: 1018–31.
7. Desjardins PJ, Grossman EH, Kuss ME, et al. The injectable cyclooxygenase-2-specific inhibitor parecoxib sodium has analgesic efficacy when administered preoperatively. *Anesth Analg* 2001; **93**: 721–7.
8. Hubbard RC, Naumann TM, Traylor L, Dhadda S. Parecoxib sodium has opioid-sparing effects in patients undergoing total knee arthroplasty under spinal anaesthesia. *Br J Anaesth* 2003; **90**: 166–72.
9. Malan TP, Marsh G, Hakki S, Grossman E, Traylor L, Hubbard RC. Parecoxib sodium, a parenteral cyclooxygenase 2 selective inhibitor, improves morphine analgesia and is opioid-sparing following total hip arthroplasty. *Anesthesiology* 2003; **98**: 950–6.
10. Tang J, Shitong L, White P, et al. Effect of parecoxib, a novel intravenous cyclooxygenase type-2 inhibitor, on the postoperative opioid requirement and quality of pain control. *Anesthesiology* 2002; **96**: 1305–9.
11. Barton S, Langeland F, Snabes M, et al. Efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynecologic laparotomy surgery. *Anesthesiology* 2002; **97**: 306–14.
12. Ng A, Smith G, Davidson AC. Analgesic effects of parecoxib following total abdominal hysterectomy. *Br J Anaesth* 2003; **90**: 746–9.
13. Ng A, Temple A, Smith G, Emembolu J. Early analgesic effects of parecoxib versus ketorolac following laparoscopic sterilization: a randomized controlled trial. *Br J Anaesth* 2004; **92**: 846–9.
14. Ott E, Nussmeier N, Duke P, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2003; **125**: 1481–92.
15. Joshi G, Viscusi E, Gan T, et al. Effective treatment of laparoscopic cholecystectomy pain with intravenous followed by oral COX-2 specific inhibitor. *Anesth Analg* 2004; **98**: 336–42.
16. Gan T, Joshi G, Viscusi E, et al. Preoperative parenteral parecoxib and follow-up oral valdecoxib reduce length of stay and improve quality of patient recovery after laparoscopic cholecystectomy surgery. *Anesth Analg* 2004; **98**: 1665–73.
17. Gan T, Joshi G, Zhao Z, Hanna D, Cheung R, Chen C. Presurgical intravenous parecoxib sodium and follow-up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduces opioid requirements and opioid-related adverse effects. *Acta Anaesthesiol Scand* 2004; **48**: 1194–207.
18. Rorarius MGF. Perioperative use of non-steroidal anti-inflammatory drugs – evaluation of their effects on analgesia, anaesthesia, haemostasis and stress response. *Acta Univ Tamper Ser A* 1993; **368**: 12–83.
19. Altman DG. *Practical Statistics for Medical Research*. Boca Raton, FL: Chapman & Hall/CRC, 1999.
20. Mutapi F, Roddam A. P values for pathogens: statistical inference from infectious-disease data. *Lancet Infect Dis* 2002; **2**: 219–30.
21. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain* 2001; **90**: 261–9.
22. Kranke P, Morin A, Roewer N, Eberhart L. Patients' global evaluation of analgesia and safety of injected parecoxib for postoperative pain: a quantitative systematic review. *Anesth Analg* 2004; **99**: 797–806.
23. Blackburn A, Stevens JD, Wheatley RG, Madej TH, Hunter DH. Balanced analgesia with intravenous ketorolac and patient controlled morphine following lower abdominal surgery. *J Clin Anesth* 1995; **7**: 103–8.
24. Scheinin B, Kellokumpu I, Lindgren L, Haglund C, Rosenberg PH. Effect of intraperitoneal bupivacaine on pain after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 1995; **39**: 195–8.

25. Römsing J, Möiniche S. A systematic review of COX-2 inhibitors compared with traditional NSAIDs, or different COX-2 inhibitors for post-operative pain. *Acta Anaesthesiol Scand* 2004; **48**: 525–46.
26. Alexander JI. Pain after laparoscopy. *Br J Anaesth* 1997; **79**: 369–78.
27. Römsing J, Möiniche S, Mathiesen O, Dahl JB. Reduction of opioid-related adverse events using opioid-sparing analgesia with COX-2 inhibitors lacks documentation: a systematic review. *Acta Anaesthesiol Scand* 2005; **49**: 133–42.
28. Straube S, Derry S, McQuay HJ, Moore RA. Effect of pre-operative Cox-II-selective NSAIDs (coxibs) on postoperative outcomes: a systematic review of randomized studies. *Acta Anaesthesiol Scand* 2005; **49**: 601–13.

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Etoricoxib pre-medication for post-operative pain after laparoscopic cholecystectomy

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Background: Etoricoxib alleviates and prevents acute pain. The hypothesis of our study was that the pre-operative use of etoricoxib would reduce the post-operative need for additional pain treatment.
Methods: In this double-blind, randomized and active placebo-controlled study, 75 patients were pre-medicated 1.5 h before elective laparoscopic cholecystectomy with 120 mg of etoricoxib (E120 group), the same dose of etoricoxib combined with 1 g of paracetamol (E + P group) or placebo (Pla group). To alleviate post-operative pain, a patient-controlled analgesia (PCA) device was programmed to deliver 50 μg of fentanyl intravenously (lockout time, 5 min). The pain intensity and nausea were assessed using a visual analogue scale (VAS). The number of patients with post-operative nausea and vomiting was recorded. Blood loss was compared between the groups. Because the operations are almost blood-less, the operation time was also recorded to compare the possible effect on bleeding time.
Results: Pre-medication with etoricoxib or etoricoxib plus paracetamol had a statistically significant fentanyl-sparing effect 2–20 h post-operatively compared with placebo ($P = 0.001$). No significant differences were demonstrated in fentanyl-sparing effect between the E120 and E + P groups. No significant differences in pain intensity were found between the three study groups. No significant differences were observed between the groups with regard to nausea, blood loss, duration of anaesthesia or duration of surgery.
Conclusion: Etoricoxib is suitable for pre-medication before laparoscopic cholecystectomy as it reduces the need for post-operative opioids. Opioid-related side-effects, however, were not reduced in the present study, despite the observed opioid-sparing effect of etoricoxib and combined etoricoxib and paracetamol.

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Key words: clinical trial; cumulative fentanyl; etoricoxib; laparoscopic cholecystectomy; nausea; outcome; post-operative pain; pre-operatively; side-effects; surgery.

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NON-STEROIDAL anti-inflammatory drugs (NSAIDs) are effective analgesics for the control of moderate post-operative pain (1). The combination of opioids with, for example, NSAIDs reduces the dose of opioid needed to achieve pain relief (2), and may reduce the incidence of side-effects, either by reducing the need for opioids or by improving pain relief (3).

The inhibition of cyclo-oxygenase (COX) is the principal mechanism for both the efficacy and toxicity of NSAIDs (4), and it has been demonstrated that COX exists as at least two isoenzymes: COX-1 and COX-2 (5). The major reason for the development of specific COX-2 inhibitors was the maintenance of the anti-inflammatory and analgesic effects without altering the homeostatic functions of COX-1.

Although opioids are suitable for intense post-operative pain, they have common side-effects, such as post-operative nausea and vomiting (PONV) and fatigue. These unpleasant side-effects may be avoided by reducing the need for opioids by combining NSAIDs and opioids. Reports on the analgesic efficacy and adverse effects of different COX-2 inhibitors for acute post-operative pain have been the subject of recent systematic reviews (6–9). However, the data did not support the common opinion that opioid sparing with COX-2 inhibitors provides a clinical beneficial effect with respect to opioid-related adverse events.

Etoricoxib is effective in low back pain, osteoarthritis, rheumatoid arthritis, acute gout and primary dysmenorrhoea (10), but etoricoxib pre-medication before surgical operations has not been studied in

detail. The duration of action of etoricoxib is sufficiently long to enable dosing once a day. After the oral administration of etoricoxib, the maximum serum concentration is achieved in 1 h and the bioavailability is almost 100%. The half-life ($T_{1/2}$) of etoricoxib is 22 h (11).

Paracetamol is commonly used for the management of peri-operative pain. In the studies reviewed, paracetamol seems to have almost equal efficacy to NSAIDs, but there is no clear evidence as to whether the combination of paracetamol and NSAIDs is beneficial.

Because etoricoxib seems to alleviate and prevent acute pain and may reduce post-operative pain more generally, we planned the following active placebo-controlled, double-blind, randomized study in patients undergoing elective laparoscopic cholecystectomy. The aim of this study was to test the analgesic efficacy of etoricoxib pre-medication for post-operative pain relief. In addition, we examined pre-medication with a combination of paracetamol and etoricoxib.

The primary endpoint was as follows: (i) does pre-operative etoricoxib reduce the post-operative need for additional pain treatment in patients undergoing elective laparoscopic cholecystectomy under general anaesthesia (i.e. the post-operative opioid-sparing effect of etoricoxib in humans). The secondary endpoints were as follows: (ii) does the addition of paracetamol to etoricoxib improve the analgesic effect of the pre-medication; (iii) does the pre-medication have an impact on PONV or fatigue; and (iv) does the pre-medication influence the operation time and/or blood loss during surgery.

Materials and methods

The study was approved by the ethics committees of the participating institutions (University Hospital of Tampere, District Hospital of Valkeakoski) and the Finnish National Medical Board. Written informed consent was obtained from each patient. The inclusion criteria were as follows: age of 16–70 years; ASA physiological status of I–III (physiological status score of the American Society of Anesthesiologists); patient scheduled for elective laparoscopic cholecystectomy. The exclusion criteria were as follows: allergy to NSAIDs; chronic pain syndrome; psychiatric disorder; substance abuse; gastrointestinal bleeding; any disease of the liver or the kidneys; pregnancy; congestive heart disease; angina pectoris; cerebrovascular circulatory symptoms; body mass index (BMI) over 40. Our intention was to include overweight patients in the study in order to represent the Finnish cholecystectomy population in the results.

All patients were operated on at Valkeakoski District Hospital. The patients were divided into three groups using a random number table. A nurse from a department not involved in the study prepared the drug-containing bags, each containing four tablets according to the list. In the E120 group, the bag contained one 120-mg tablet of etoricoxib, one 15-mg tablet of oxazepam and two placebo tablets; in the E + P group, the bag contained one 120-mg tablet of etoricoxib, two 500-mg tablets of paracetamol and one 15-mg tablet of oxazepam; in the Pla group, the bag contained three placebo tablets and one 15-mg tablet of oxazepam. We used a very small dose of oxazepam in all groups as sedative pre-medication and as an active placebo in the Pla group. The medication was given to the patients about 1.5 h before the induction of anaesthesia.

The name of the study and the running number of the patient were stated on the bags. For safety reasons, the randomization list, including the contents of the study bag of each patient, was kept in the recovery room.

Anaesthesia was induced with 2 μg/kg of fentanyl adjusted to the nearest 25 μg/kg, followed by 2–3 mg/kg of propofol. The same dose of fentanyl was given again 4 min before incision. After induction, one dose of 15 μg/kg of dehydrobenzperidole was administered as a prophylactic anti-emetic agent. Anaesthesia was further maintained with sevoflurane in 66% air in O_2. During the maintenance of anaesthesia, the sevoflurane concentration was adjusted to keep the systolic blood pressure between 85 and 130 mmHg. Neuromuscular blockade was kept at the level of T1 0–15% and the block was antagonized with glycopyrrolate combined with glycostigmine. Mechanical ventilation was adjusted to keep the end-tidal CO_2 between 5 and 5.5%. The sizes of the four troacars were: 12 mm, 10 mm and 2 × 5 mm. The pressure of CO_2 insufflation was kept under 12 cmH_2O. At the end of the operation, the four incisions were infiltrated with 20 ml of 5 mg/ml of bupivacaine with epinephrine by the surgeon. The durations of anaesthesia and operation were recorded. The weight of blood loss was measured and adjusted to the nearest 5 ml. One litre of Ringer's acetate was infused intra-operatively, a second one during the first six post-operative hours, and 1 l of 0.3 M sodium chloride in 5% glucose during the next 12 h.

Monitoring during anaesthesia comprised continuous electrocardiogram and heart rate, pulse oximetry,

non-invasive arterial pressure, measurement of the end-tidal CO_2 and measurement of the expiratory end-tidal sevoflurane concentration. All of these parameters were recorded at 5-min intervals.

All patients were instructed pre-operatively and assisted post-operatively to use a patient-controlled analgesia (PCA) device, programmed to deliver 50 μg of fentanyl during 1 min. The lockout time was 5 min, and the maximum dose was 500 μg/h during the first 2 h in the recovery room and 250 μg/h on the ward until 20 h after the end of surgery. During emergence from anaesthesia, the recovery room nurses were allowed to give additional fentanyl boluses via the PCA device on request of the patients.

During the pre-anaesthetic round, the patients were also instructed in the use of a visual analogue scale (VAS; 0–10: 0, no pain at all; 10, unbearable pain). Pain intensity at rest, during coughing and during leg elevation were assessed using VAS at the pre-operative round, on arrival in the operating theatre, and at 1, 2, 4, 10 and 20 h after the end of surgery. The patients were asked to evaluate the worst pain score at rest encountered during the previous period at 2 h and at 20 h after the end of surgery. The need for additional pain treatment was evaluated by the frequency and amount of fentanyl boluses during the first 20 post-operative hours. At the end of the observation period, the patients were asked to express their opinion concerning the efficacy of the pain-relieving treatment on a 1–5 satisfaction scale (1, very satisfied; 5, very unsatisfied).

The patients were also asked about fatigue and nausea using VAS during the pre-operative round, on arrival in the operating theatre, and at 1, 2, 4, 10 and 20 h post-operatively (0, none at all; 10, worst imaginable). On arrival in the operating theatre, as well as at 4 and 20 h post-operatively, the patients who had vomited or suffered from nausea during the previous period were recorded, together with any use of anti-emetic medication.

Statistical methods

The sample size estimation was based on the assumption that etoricoxib would reduce the need for opioids by 33% as do NSAIDs (12). Thus, with $\alpha = 0.05$ and power = 80%, the sample size was 23 patients in each group.

Demographic and other background data are presented as frequencies, means and standard deviations (SD). Measures of PONV, having only a few non-zero values, were dichotomized according to the presence of PONV, and are presented as percentage frequencies For single variables, including time point-specific ones, the significance tests between the study groups included chi-squared, one-way analysis of variance and independent sample *t*-test, as appropriate. The PONV score includes nausea and/or vomiting. Retching was not recorded separately.

The original VAS values (0–100) were divided by 10 and rounded to the nearest integer. Factors measured before or during the operation had non-normal distributions and were therefore reported as medians and quartiles; the significance test for group differences was the Kruskall–Wallis or Mann–Whitney test, as appropriate. The non-normality of the repeatedly measured post-operative cumulative fentanyl doses, as well as the pain and fatigue measurements, was corrected by applying a square-root transformation. The differences in these transformed variables between the study groups over time could then be examined by repeated measures analysis of variance with the least significant difference multiple comparisons test. The reported descriptives of the results were, however, re-transformed by squaring. *P* values of less than 0.05 were considered to be statistically significant. Except in the repeated measures analysis of variance, Bonferroni correction was not considered to be appropriate. The analysis was performed with SPSS for Windows, version 11.5.

Results

Seventy-five patients consented to participate in the study over 13 months. Two patients in the Pla group needed open cholecystectomy and were excluded from the data. In addition, one operation in the E120 group was cancelled as a result of severe macroscopic hepatic cirrhosis, which was diagnosed at the start of laparoscopy. Apart from these three patients, the evaluation of the pre-operative status and the need for PCA fentanyl was performed in all other patients ($n = 72$). VAS scores for post-operative pain and PONV were analysed only for 66 patients, because some of the data sheets were incompletely filled during the night time period.

There were no statistically significant differences between the groups with regard to age, sex, weight, height and ASA group (Table 1). There were also no differences in pre-operative VAS scores for pain and PONV.

Pre-medication with etoricoxib had a statistically significant fentanyl-sparing effect 2–20 h post-operatively ($P = 0.001$). The fentanyl-sparing effects were 43%, 57%, 44% and 23%, respectively, when the E120 group was compared with the Pla group 2, 4, 10

Table 1

Demographic data and ASA physical status in the different pre-medication groups [mean and standard deviation (SD) or percentage]. All differences between the groups were non-significant.

	Pre-medication group*								
	E120 ($n = 24$)			E + P ($n = 25$)			Pla ($n = 23$)		
	Mean	SD	%	Mean	SD	%	Mean	SD	%
Age (years)	46.0	12.2		45.2	10.7		45.3	8.8	
Sex									
Male			21			20			30
Female			79			80			70
Weight (kg)	79	14		84	12		78	15	
Height (cm)	169	8		170	8		170	9	
ASA†									
I			38			40			48
II			54			56			39
III			8			4			13

*E120, etoricoxib 120 mg; E + P, etoricoxib 120 mg combined with 1 g of paracetamol; Pla, placebo.
†ASA, physical status score of the American Society of Anesthesiologists.

and 20 h post-operatively. Etoricoxib combined with paracetamol reduced the fentanyl consumption by 23%, 53%, 48% and 21%, respectively, when compared with the Pla group (Fig. 1). The addition of paracetamol to etoricoxib pre-medication did not improve the analgesic effect of the pre-medication (Fig. 1).

With respect to post-operative pain intensity, there were no statistically significant differences between the groups in the repeated measures analysis, or when analysing the time points separately and across all groups.

There were no statistically significant differences between the groups in the repeated measures analysis of PONV or fatigue, although the Pla group needed more fentanyl. The proportions of patients whose highest PONV score at the ward was above three were, however, 33% in the Pla group, 18% in the E120 group and 5% in the E + P group. The difference between the Pla and E + P groups was significant ($P = 0.033$). However, there was no difference between the groups with regard to the number of doses of rescue anti-emetic.

There were no statistically significant differences between the groups with regard to blood loss, duration of anaesthesia or duration of surgery (Table 2). All patients were satisfied or very satisfied with their pain management (five-point scale) 20 h post-operatively. There was, however, a significant ($P = 0.041$) difference in the proportion of very satisfied patients between the groups, the proportions being 50%, 73% and 86% in the Pla, E120 and E + P groups, respectively. The difference between the Pla and E + P groups was the only statistically significant difference ($P = 0.018$).

Discussion

We found that etoricoxib pre-medication reduced the need for supplemental analgesics after laparoscopic cholecystectomy. An opioid-sparing effect was seen throughout the study when compared with placebo. Combining paracetamol with etoricoxib in the pre-medication did not result in a further reduced fentanyl consumption. Our findings do not agree with a recent study by Romundstad et al. (13), which supports the practice of combining paracetamol with an NSAID for the relief of acute pain. Hyllested et al. (14) reviewed post-operative pain management when using NSAIDs, paracetamol or a combination. They also found very limited data concerning the

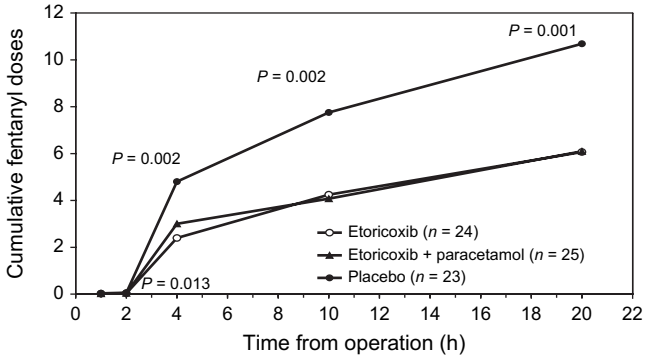

Fig. 1. Mean cumulative number of fentanyl doses (50 μg) 1, 2, 4, 10 and 20 h post-operatively in the three pre-medication groups (etoricoxib 120 mg, etoricoxib 120 mg combined with paracetamol 1 g, and placebo). The number of fentanyl doses normalized by square-root transformation; the difference in these transformed variables was examined by repeated measures analysis of variance with the least significant difference multiple comparisons test.

Table 2

Duration of anaesthesia and surgery, and blood loss [median (Md) and quartiles (Q_1, Q_3)].

	Pre-medication group*					
	E120 ($n = 23$)		E + P ($n = 24$)		Pla ($n = 17$–19)	
	Md	Q_1, Q_3	Md	Q_1, Q_3	Md	Q_1, Q_3
Duration of anaesthesia (min)	93	75, 105	94	82, 105	105	88, 122
Duration of surgery (min)	55	44, 75	63	48, 68	72	47, 91
Blood loss (g)	10	10, 20	15	10, 20	10	10, 35

*E120, etoricoxib 120 mg; E + P, etoricoxib 120 mg combined with 1 g of paracetamol; Pla, placebo.

combination, but their results suggested some benefit. The power of the present study, however, was planned to reveal the fentanyl-sparing effect of etoricoxib and a combination of etoricoxib with paracetamol, not the difference between the two.

One small dose (1 g) of paracetamol was given before the operation as pre-medication, and the duration of paracetamol action was limited to the first few hours after surgery. In addition, the fentanyl doses used during the operation (total of 4 μg/kg) and the local infiltration of bupivacaine in the incisions have an important effect on the additional pain treatment needed during the first few hours post-operatively. However, we wanted to use maximal pain-relieving methods in order to represent the usual Finnish peri-operative care. Infiltration with bupivacaine and moderate doses of fentanyl during cholecystectomy may have attenuated the possible opioid-sparing effect of paracetamol.

No differences between the three groups were encountered with respect to the duration of the operation or to bleeding during the operation. There is a causal relationship between the bleeding time and the operation time. NSAIDs prolong the bleeding time but, according to our results, pre-medication with etoricoxib did not increase the operation time.

In summary, pre-medication with etoricoxib had a statistically significant fentanyl-sparing effect 2–20 h after laparoscopic cholecystectomy. Combining paracetamol with etoricoxib in the pre-medication did not have any additional fentanyl-sparing effect. Pre-treatment with etoricoxib or combined etoricoxib and paracetamol did not have an effect on the degree of post-operative nausea and incidence of vomiting/retching, although the Pla group needed more fentanyl. Etoricoxib pre-medication did not alter the operation time and/or blood loss during surgery. All patients were satisfied or very satisfied with the pain management 20 h post-operatively.

In conclusion, etoricoxib is suitable for pre-medication before laparoscopic cholecystectomy as it reduces the need for supplemental post-operative opioids. Opioid-related side-effects, however, were not reduced in the present study, despite the observed opioid-sparing effect of etoricoxib and combined etoricoxib and paracetamol. The effectiveness of etoricoxib pre-medication should be confirmed in other more painful procedures.

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References

1. McQuay HJ. Acute pain. In: Tramér, MR, ed. *Evidence-Based Resource in Anaesthesia and Analgesia*. London: BMJ Books, 2000: 87–106.
2. Rorarius MGF, Suominen P, Baer GA, Romppanen O, Tuimala R. Diclofenac and ketoprofen for pain treatment after elective caesarean section. *Br J Anaesth* 1993; **70**: 293–7.
3. Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. *Br J Anaesth* 2001; **87**: 62–72.
4. Vane J. Inhibition of prostaglandin synthesis as a mechanism of action for the aspirin-like drugs. *Nature* 1971; **231**: 231–5.
5. Rømsing J, Møiniche S. A systematic review of COX-2 inhibitors compared with traditional NSAIDs, or different COX-2 inhibitors for post-operative pain. *Acta Anaesthesiol Scand* 2004; **48**: 525–46.
6. Barden J, Edwards JE, McQuay HJ, Moore RA. Single-dose rofecoxib for acute postoperative pain in adults: a quantitative systematic review. *BMC Anesthesiol* 2002; **2**: 4.
7. Barden J, Edwards JE, McQuay HJ, Moore RA. Single dose oral celecoxib for postoperative pain. *Cochrane Database Syst Rev* 2003; **2**: CD004233.
8. Barden J, Edwards JE, McQuay HJ, Moore RA. Oral valdecoxib and injected parecoxib for acute postoperative

pain: a quantitative systematic review. *BMC Anesthesiol* 2003; **3**: 1–8.
9. Rømsing J, Møiniche S, Mathiesen O, Dahl JB. Reduction of opioid-related adverse events using opioid-sparing analgesia with COX-2 inhibitors lacks documentation: a systematic review. *Acta Anaesthesiol Scand* 2005; **49**: 133–42.
10. Cochrane DJ, Jarvis B, Keating GM. Etoricoxib. *Drugs* 2002; **62**: 2637–51.
11. Dallob A, Hawkey CJ, Greenberg H et al. Characterization of etoricoxib, a novel, selective COX-2 inhibitor. *J Clin Pharmacol* 2003; **43**: 573–85.
12. Rorarius MGF. Perioperative use of non-steroidal anti-inflammatory drugs – evaluation of their effects on analgesia, anaesthesia, haemostasis and stress response. *Acta Univ Tamperensis Ser A* 2006; **10**: 177–183.
13. Romundstad L, Stubhaug A, Niemi G, Rosseland LE, Breivik H. Adding propacetamol to ketorolac increases the tolerance to painful pressure. *Eur J Pain* 2005.
14. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in post-operative pain management: a qualitative review. *Br J Anaesth* 2002; **88**: 199–214.

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CLINICAL STUDY

The Effect of Parecoxib on Kidney Function at Laparoscopic Hysterectomy

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Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) have a well-documented nephrotoxic action. Still, there are only few studies that have investigated the nephrotoxicity of cyclooxycenase-2-inhibitors during the perioperative period. Thirty patients scheduled for elective laparoscopic hysterectomy were enrolled in this prospective, randomized double-blind study. Patients were randomized into two groups: a saline-treated control group (placebo) and 80 mg parecoxib-treated group (parecoxib). The samples for the analyses of serum and urine were collected at the induction of anesthesia, two hours thereafter, two hours from the end of anesthesia, and on the first postoperative day (POD). S-crea, S-urea, S-cystatin C, S-Na, S-K, U-1mikroglobulin/U-crea, U-GST/U-crea, and U-GST/U-crea were analyzed from the samples. Urine output was measured every hour for the first five hours, and total amount of urine was measured until the first postoperative day. There were no clinical and few statistical significant differences between the two groups in the renal measurements during the study period. The urinary output was also similar in the two groups. A single dose of 80 mg of parecoxib was well tolerated by the kidneys in the short-term perioperative use in patients undergoing laparoscopic hysterectomy with ASA physiological status I-II and age under 60 years.

Keywords COX-2-inhibitor, parecoxib, laparoscopy surgery, drug safety, kidney function, glutathione-S-transferases

INTRODUCTION

The nephrotoxic effects of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are well documented. The adverse renal effects occur because of inhibition of the synthesis of cyclooxygenase-derived prostaglandins. Coxibs, selective COX-2-inhibitors, raised the hope that this kind of drugs would reduce adverse effects on both the gastrointestinal track and the kidneys. COX-2 is inducible in most tissues in response to injury or inflammation, but both COX-1 and COX-2 are constitutively expressed in the kidneys. COX-2 has been detected both in the tubular component, macula densa, and the renal vascular component, podocytes and arteriolar smooth muscle cells.

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COX-2-synthesized prostaglandins play certain roles in the kidneys, like regulating perfusion pressure, handling salt and water intake, and renin release.[1–5] These roles become more important in stressed states like hypovolemia, sepsis, and heart failure, when the glomerular filtration rate is already compromised.[1–5]

Pneumoperitoneum for laparoscopy has been associated with transient oliguria.[6] In spite of oliguria, renal tubular ischaemia was not detected in laparoscopic operations when measuring urinary N-acetyl-β-D-glucosaminidase.[7] Possible causes of oliguria include diminished renal blood flow secondary to renal vascular compression, direct renal parenchymal compression, ureter obstruction, and changed systemic hormonal levels.

There are only a few studies investigating the nephrotoxicity of NSAID or coxibs during perioperative period.[8–10] We decided to study the renal adverse effect of a single dose of the COX-2 inhibitor, parecoxib 80mg, in patients undergoing laparoscopic hysterectomy. We assumed that the combination with laparoscopic surgery might reveal renal adverse effects of parecoxib in the perioperative period when measuring sensitive markers of both tubular and glomerular damage. Urinary glutathione-S-transferases (GSTs) have been used to detect tubular injury.[7,11] GSTs are cytosolic enzymes that have many isomers. GST and GST are the main isomers in the kidney. Elevated urinary GST- levels are correlated with the proximal tubular injury and GST levels with distal tubular injury.[12] Serum cystatin C is a cysteine protease inhibitor, for which production is independent of age, sex, and muscle mass.[13] It is freely filtered at the glomerulus, which makes it an ideal marker of the glomerular filtration rate (GFR).

The COX-2 inhibitors have lost their popularity because of documented risk of cardiovascular events.[14] However, their single, acute use at surgery can be safe, especially when coxibs unlike conventional NSAIDs do not enhance surgical bleeding.[15]

MATERIALS AND METHODS

The study was approved by the local ethic committee and the Finnish National Agency for Medicines. Written informed consent was obtained from each patient. Thirty patients scheduled for elective laparoscopic hysterectomy were enrolled in this prospective, randomized double-blind study. The inclusion criteria were age between 30 and 60 years, ASA physiological status I-II, and weight between 50 and 80 kg. The exclusion criteria were allergy to aspirin-like drugs or sulphonamide, bronchial asthma, liver or renal disturbances, peptic ulcer, bleeding disorder, pregnancy, substance abuse, and chronic pain.

Patients were randomized into two groups: a saline-treated control group (group placebo) and 80 mg parecoxib treated group (group parecoxib). The randomization procedure involved computer-generated random numbers in opaque envelopes. The study medication was given intravenously before the induction of anesthesia in the operation room. All solutions were colorless in a volume of 4 ml and were prepared by a staff nurse otherwise not involved in the study.

Anesthesia was standardized. Induction was with fentanyl 2 g/kg, propofol 2–3 mg/kg, and rocuronium 0.6 mg/kg. An equal amount of fentanyl was given about 3 minutes before skin incision. Warm (37°C) CO_2 insufflation was used, and intra-abdominal pressure was kept at 12 mmHg. A semi-closed breathing system with fresh gas flow of 2–3 l/min was used. Anesthesia was maintained with sevoflurane in air/O_2 66/34% and adjusted to keep systolic blood pressure level between 85–130 mmHg (sevoflurane end tidal concentration, about 2%). Muscle relaxation was maintained between TOF 0/4 and 2/4 with rocuronium. $EtCO_2$ was maintained between 5.0 and 5.5% by adjusting the ventilation. Residual neuromuscular block was antagonized with neostigmine and glycopyrrolate. Ringer's acetated solution, bolus 5 mL/kg continued by 5 mL/kg/h, was administered during the operation. Five hundred ml of 4% gelatin solution was used if surgical blood loss was over 400 ml. One liter of mixture 0.3% of NaCl in 5% glucose was administered during the next 12 hours after operation.

A urinary bladder catheter was inserted after induction of anesthesia to measure urine output and collect urine samples. The samples for the analyses of serum and urine were collected during the induction of anesthesia, two hours thereafter, two hours after anesthesia, and on the first postoperative day (POD). The samples of serum creatinine, urea, sodium, potassium, α-1-microglobulin, and cystatin C were analyzed on the consecutive working day. Serum creatinine clearance was calculated by the Cockroft and Gault formula.[16] Samples for GST were conserved in a tube with stabilizer (containing mertiolate and azide) and stored at −20°C before analysis. S-crea, S-urea, S-cysC, S-Na, s-K, U-α-1-microglobulin/U-crea, U-αGST/U-crea, and U-πGST/U-crea were analyzed according to good laboratory practice (GLP) by the laboratory of Tampere University Hospital. Abbreviations, method with analyzer, and normal limits of the laboratory data are listed in the Table 1. Urine output was measured hourly for the first four hours, and total amount of urine output was measured until the first post-operative day.

Post-operative pain was managed by patient-controlled analgesia device (PCA), programmed to deliver 50 g of fentanyl during two minutes. The lockout time was 5 min, and the maximum dose was 500 g/h during the first

Table 1
Abbreviations, methods for analyses, and normal values of the laboratory data

Measured parameters	Abbreviation	Method and analyzer	Normal values
Serum creatinine	S-Crea	Cobas Integra (Roche Diagnostic, Basel, Switzerland)	<95 µmol/L
Serum urea	S-Urea	Cobas Integra	2.6–6.4 mmol/L
Serum sodium	S-Na	Cobas Integra	137–145 mmol/L
Serum potassium	S-K	Cobas Integra	3.5–4.5 mmol/L
Serum cystatin C	S-CysC	Turbidimetric Dako (Dako Cytomation, Glostrup, Denmark)	< 1.4 mg/L under 50 yr < 1.5 mg/L over 50 yr
Urinary α-1-mikroglobulin/ urinary creatinine	U-α-1-miglo/u-crea	Behring Nephelometric Analyzer, Behring AG, Mahrburg, Germany/ Cobas Integra	0.04–0.7 mg/mmol
Urinary α-glutathione-S-transferase/urinary creatinine	U-αGST/u-crea	NEPHKIT (Biotrin International Ltd, Dublin, Ireland), measured with Multiscan EX analyzer (Labsystems, Helsinki, Finland)/ Cobas Integra	0.10–1.93 µg/mmol
Urinary π-glutathione-S-transferase/ urinary creatinine	U- πGST/u-crea	NEPHKIT (Biotrin International Ltd, Dublin, Ireland), measured with Multiscan EX analyzer (Labsystems, Helsinki, Finland)/ Cobas Integra	0.25–7.41 µg/mmol

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two hours in the recovery room and 250 g/h on the ward until 20 hours after the end of the surgery. During emergence from anesthesia, the recovery room nurses were allowed to give additional fentanyl boluses via the PCA device on request of the patients. No other pain treatment was allowed during the study period.

Normally distributed, continuous, demographic data are expressed by means and standard deviations and tested by t-test. Categorized variables (ASA status) are presented as percent frequencies, with Pearson^2-test as the significance test. The laboratory data are treated as continuous. Due to skewed distribution of S-crea, S-urea, S-cysC, S-Na, S-K, U--1-micro/U-crea, U-GST/U-crea, and U-GST/U-crea, the data are expressed by medians and interquartile ranges and the difference between treatment groups is tested by Mann-Whitney test. $p < 0.05$ was considered statistically significant. The analysis was accomplished with SPSS for Windows, version 14.02.

RESULTS

There were no significant differences between the treatment groups concerning age, BMI, ASA risk classification, serum creatinine clearance, the duration of the surgery or anesthesia, and total blood loss (see Table 2). The baseline renal measurements did not differ between the two groups (measurement 1 in Table 3). There were few statistically but no clinically significant differences between groups in any renal measurement during the study period (measurements 2, 3, and 4 in Table 3). The values of U-πGST/U-crea were increased two hours after the

Table 2
Demographic factors

	Placebo, n = 15	Parecoxib, n = 15	*p*
Age, mean (SD) year	50.5 (4.5)	48.5 (7.9)	0.389
BMI, mean (SD) kg/m^2	25.2 (2.4)	24.8 (2.9)	0.725
Frequencies, n (%) of ASA 1	10 (67)	10 (67)	1.000
Duration of surgery, mean (SD) min	103 (34)	103 (28)	0.971
Duration of anesthesia, mean (SD) min	138 (36)	134 (38)	0.810
Total blood loss, med (min-max) ml	100 (50–200)	150 (50–400)	0.186
Creatinine clearance, mean (SD) mL/min	105.9 (23.3)	100.7 (20.4)	0.517

Differences were tested by t-test, Mann-Whitney test, or Pearson chi-squared test.

Table 3
Distributions of renal measurements

	Measurement 1		Measurement 2			Measurement 3		Measurement 4	
	n	Md [IQ]	n	Md [IQ]		n	Md [IQ]	n	Md [IQ]
S-Crea									
Placebo	14	62 [54–66]	15	61 [49–64]		15	59 [52–64]	12	56 [47–60]
Parecoxib	14	61 [58–67]	14	60 [57–69]		14	63 [56–71]	13	57 [55–70]
p		0.662		0.370			0.347		0.127
S-Urea									
Placebo	14	4.2 [3.6–5.4]	15	4.0 [3.5–5.0]		15	4.2 [3.5–5.0]	12	2.7 [2.3–3.1]
Parecoxib	15	3.7 [2.8–4.8]	15	3.3 [2.9–4.0]		15	3.3 [3.0–4.8]	13	2.4 [2.2–3.8]
p		0.101		0.124			0.229		0.978
S-CysC									
Placebo	15	0.71 [0.64–0.84]	15	0.65 [0.56–0.78]		15	0.66 [0.56–0.72]	12	0.67 [0.55–0.78]
Parecoxib	15	0.74 [0.66–0.85]	15	0.67 [0.55–0.76]		15	0.66 [0.57–0.83]	13	0.68 [0.60–0.78]
p		0.534		0.967			0.663		0.624
S-Na									
Placebo	14	139 [138.5–141]	15	140 [138–141]		14	139 [138–141]	11	137 [136–139]
Parecoxib	15	140 [139–142]	15	139 [138–141]		15	140 [137–141]	13	139 [136–142]
p		0.504		0.705			0.965		0.253
S-K									
Placebo	14	4.2 [4.0–4.2]	15	4.2 [4.0–4.4]		14	4.0 [3.9–4.2]	12	3.6 [3.4–3.8]
Parecoxib	15	4.1 [4.0–4.3]	14	4.1 [4.0–4.4]		12	4.1 [4.0–4.6]	13	4.0 [3.8–4.2]
p		0.965		0.774			0.091		0.001
U-αGST/u-crea									
Placebo	13	0.62 [0.17–1.75]	13	0.15 [0.02–0.93]		12	0.13 [0.04–0.98]	11	0.58 [0.15–0.99]
Parecoxib	14	2.07 [0.33–2.46]	13	0.42 [0.05–0.77]		13	0.15 [0.05–0.67]	10	0.50 [0.01–0.98]
p		0.133		0.554			0.723		0.597
U-πGST/u-crea									
Placebo	13	4.5 [1.6–5.5]	13	17.3 [11.8–22.9]	*	12	2.1 [0.7–3.6]	10	1.7 [0.9–4.0]
Parecoxib	14	2.8 [1.2–6.5]	13	12.2 [1.9–36.6]	*	13	3.1 [0.3–7.1]	10	2.1 [0.6–3.7]
p		0.808		0.457			0.663		0.821

Differences between the groups were tested by Mann-Whitney test.
*$p < 0.05$ compared with measurement 1 levels.

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beginning of anesthesia in both groups. The increase was also statistically significant (Wilcoxon signed ranks test), $p = 0.013$ in the parecoxib and $p = 0.033$ in the placebo groups, when compared to baseline levels. The number of patients is mentioned at each measurement because the data was either missing or the outliers were omitted (seven measurements). One-third of the measurements of urinary α-1-microglobulin was undetectable (<5.2 mg/L), which makes statistical analysis impossible. However, there was no clinical difference between the groups in urinary α-1-microglobulins. The urinary output during the first four hours was small in volume, but there was no difference between the groups (see Figure 1). On the first postoperative day, the total amount of urine output was recorded only in few patients.

DISCUSSION

The aim of our study was to reveal renal adverse effects of the COX-2-inhibitor, parecoxib 80 mg, by measuring the sensitive markers of both tubular and glomerular damage in patients undergoing laparoscopic hysterectomy. However, we were not able to find any clinical and few statistical significant differences between the placebo and the parecoxib groups during the study period, the first 20 perioperative hours.

Renal adverse events reported with COX-2-inhibitors occur in less than 2% of the population,[5] which means that a much larger sample size than ours would be needed to find differences in such outcomes. Therefore, we recruited patients with relatively increased risk for renal

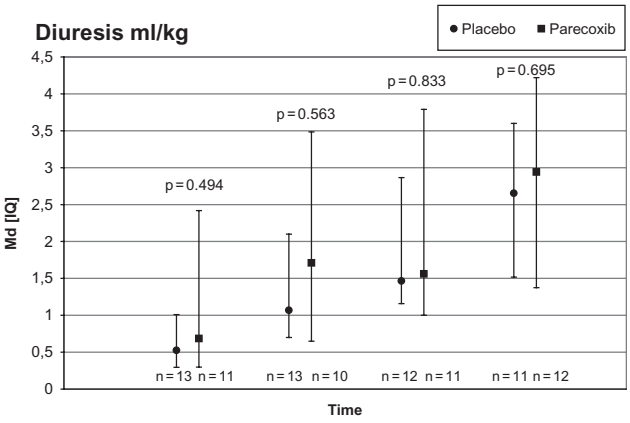

Figure 1. The cumulative urine output (mL/kg) during the first four hours, expressed by medians and IQ.

incidents. The risk factors were laparoscopic surgery, anesthesia, moderate rather than abundant fluid administration, and high dose of parecoxib. The dose of parecoxib was 80mg intra venously, which is same as maximal daily dose. The recommended dose of parecoxib for perioperative use is 40 mg twice daily. Furthermore, sensitive markers of renal adverse effects were used.

Oliguria was detected in both groups and might be explained by the laparoscopic surgery. The measured increase in U-πGST/U-crea ratio two hours after the beginning of anesthesia in both groups was statistically but also clinically significant (see normal values, Table 1). It can be explained by the operation itself and indicates some distal tubular damage to occur. The values normalized during the first 20 postoperative hours. Between the groups there was no difference, although there was a tendency of higher values in the control group. This underlines the safety of parecoxib, because COX-2 is expressed in the distal tubular component, macula densa, which damage can be detected by U-πGST.

In our study, the preoperative level of U-αGST/U-crea was surprisingly high in both groups. In the parecoxib group, it was even over normal values. One explanation is a preoperative fasting, which causes a relative dehydration. The values were lowest two hours after anesthesia, which differs from the study showing an increase at that time point when comparing ketorolac to normal saline in patients undergoing breast surgery.[9] This emphasizes the differences in the action sites of the kidneys between the traditional NSAIDs and coxibs.

Cystatin C was employed as a sensitive marker of GFR.[13,17,18] Because there was no increase in its levels, we can assume that there was no clinically significant decrease in GFR during the study period in either group. The Cochrane meta-analysis of effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function did not find any clinically meaningful difference between NSAIDs and placebo.[19] There is no such meta-analysis of coxibs available. Koppert et al. were able to show a small parecoxib-associated decrease in creatinine clearance perioperatively in elderly patients whose creatinine varied between 44–144 mol/L.[10] There are also studies where short term use of COX-2 inhibitors had no effect on glomerular filtration rate[20–22] or even protected the kidney from other harmful effects.[21,22] There might also be heterogeneity in COX-2 inhibitors because celecoxib seemed to be more tolerated by the kidneys than rofecoxib in animal model.[23] This emphasizes the importance of clinical studies.

The major limitations of this study are small sample size and large variation of data. Both increase the risk of type II error. We had assumed that our stressful study setting would have increased sensitive renal markers' values even in this small study population. The knowledge of large data variation in a clinical setting provides valuable information for other researchers.

We conclude that a single dose of 80 mg parecoxib was well tolerated by the kidneys during the next 20 perioperative hours in patients undergoing laparoscopic hysterectomy with ASA physiological status I–II and age under 60 years. It should not be withheld from such patients because of concerns about postoperative renal impairment.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

1. Gambaro G, Perazella MA. Adverse renal effects of anti-inflammatory agents: Evaluation of selective and non-selective cyclooxygenase inhibitors. *J Intern Med.* 2003;253:643–652.
2. Breyer MD, Harris RC. Cyclooxygenase 2 and the kidney. *Curr Opin Nephrol Hypertens.* 2001;10:89–98.
3. Breyer MD, Hao C-M, Qi Z. Cyclooxygenase 2 selective inhibitors and the kidney. *Curr Opin Crit Care.* 2001;7:393–400.

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4. Harris RC. COX-2 and the kidney. *J Cardiovasc Pharmacol.* 2006;47:S37–S42.
5. Barkin RL, Buvanendran A. Focus on the COX-1 and COX-2 agents: Renal events of nonsteroidal and anti-inflammatory drugs-NSAIDs. *Am J Ther.* 2004;11:124–129.
6. Hassan AR, Fields D, Vargas JC, Vaughan ED, Vukasin A, Sosa RE. Oliguria during laparoscopic surgery: Evidence for direct renal parenchymal compression as an etiologic factor. *J Endour*. 1996;10:1–4.
7. Micali R, Silver RI, Kaufman HS, et al. Measurements of urinary N-acetyl-β-D-glucosaminidase to assess renal ischemia during laparoscopic operations. *Surg Endosc.* 1999;13:503–506.
8. Laisalmi M, Eriksson H, Koivusalo A-M, Pere P, Rosenberg P, Lindgren L. Ketorolac is not nephrotoxic in connection with sevoflurane anesthesia in patients undergoing breast surgery. *Anesth Analg.* 2001;92:1058–1063.
9. Laisalmi M, Teppo A-M, Koivusalo A-M, Honkanen E, Valta P, Lindgren L. The effect of ketorolac and sevoflurane anesthesia on renal glomerular and tubular function. *Anesth Analg.* 2001;93:1210–1213.
10. Koppert W, Frötsch K, Huzurudin N, et al. The effects of paracetamol and parecoxib in kidney function in elderly patients undergoing orthopedic surgery. *Anesth Analg.* 2006;103:1170–1176.
11. Svendsen KB, Bech JN, Sørensen TB, Pedersen EB. A comparison of the effect of etodolac and ibuprofen on renal haemodynamics, tubular function, renin, vasopressin and urinary excretion of albumin and α-glutathione-S-trasferase in heathy subjects: A placebo-controlled cross-over study. *Eur J Clin Pharmacol.* 2000;56:383–388.
12. Branten AJW, Mulder TPJ, Peters WHM, Assmann KJM, Wetzels JFM. Urinary excretion of glutathione S transferases alpha and pi in patients with proteinuria: Reflection of the site of tubular injury. *Nephron.* 2000;85:120–126.
13. Harmoinen A, Lehtimäki T, Korpela M, Turjanmaa V, Saha H. Diagnostic accuracies of plasma creatinine, cystatin C and glomerular filtration rate calculated by the Cockcroft-Gault and Levey (MDRD) formulas. *Clin Chem.* 2003;49:1223–1225.
14. Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppi PA, Egger M. Risk of cardiovascular events and rofecoxib: Cumulative meta-analysis. *Lancet.* 2004;364:2021–2029.
15. Hegi TR, Bombeli T, Seifert B, et al. Effect on platelet aggregation and blood loss in gynaecological and breast surgery compared with diclofenac. *Br J Anaesth.* 2004;92:523–531.
16. Cockcroft DW, Gault MH. Prediction of craetinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
17. Sear JW. Kidney dysfunction in the postoperative period. *Br J Anaesth.* 2005;95:20–32.
18. Shilipak MG, Praught ML, Sarnak MJ. Update on cystatin C: New insights into the importance of mild kidney dysfunction. *Curr Opin Nephrol Hypertens.* 2006;15:270–275.
19. Cooper LA, Craig JC, Knight JF, Keneally JP. Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. *Cochrane Database Systematic Review* 2006:2.
20. Horackova M, Schuck O, Komers R, Charvat J, Teplan V, Kvapil M. Effect of rofecoxib on the glomerular filtration rate, proteinuria and rennin-angiotensin-aldosterone system in elderly subjects with chronic renal impairment. *Int J Clin Pharmacol Ther.* 2005;43:413–419.
21. Hauser B, Froba G, Bracht H, et al. Effects of intrarenal administration of the cox-2 inhibitor parecoxib during porcine suprarenal aortic cross-clamping. *Shock* 2005;24:476–481.
22. Pamuk ON, Cakir N. The renal effects of the addition of low aspirin to COX-2 selective and nonselective anti-inflammatory drugs. *Clin Rheumatol.* 2006;25:123–125.
23. Hermann M, Shaw S, Kiss E, et al. Selective COX-2 inhibitors and renal injury in salt-sensitive hypertension. *Hypertension* 2005;45:193–197.

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Persistent pain following knee arthroplasty

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Background and objective The prevalence of persistent pain after orthopaedic surgery has been the subject of only few studies and the risk factors for persistent pain have been evaluated even more rarely. The purpose of the present study was to evaluate the degree and the risk factors of persistent pain after knee arthroplasty.

Methods The prevalence of persistent postoperative pain after knee replacement was evaluated with a questionnaire in a large, register-based cross-sectional prevalence study. The main hypothesis was that the type of operation (primary, bilateral, revision) would influence the prevalence of persistent postoperative pain. Logistic regression analysis was performed to test the hypothesis and to find other possible risk factors for the development of persistent pain.

Results The total number of patients was 855. The operation was a primary arthroplasty in 648 patients (75.7%), a bilateral arthroplasty in 137 patients (21.1%) and a revision arthroplasty in 70 patients (8.2%). The response rate was 65.7%. The type of operation was not associated with the prevalence of persistent pain, but the degree of early postoperative pain was the strongest risk factor. If the degree of pain during the first postoperative week was from moderate to intolerable, the risk for the development of persistent pain was three to 10 times higher compared with patients complaining of mild pain during the same period. Other risk factors were the long duration of preoperative pain and female sex.

Conclusion Intensity of early postoperative pain and delayed surgery increase the risk of the persistent pain after knee arthroplasty.

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Keywords: knee arthroplasty, orthopaedic surgery, persistent pain, questionnaire study

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Introduction

Persistent postoperative pain, which is defined as pain lasting for more than 3 months, is today a well known problem independent of the type of surgery.[1–3] The highest prevalences are reported after leg amputation (60–80%),[4] thoracotomy and sternotomy (20–50%).[5–9] Futhermore, routine operations such as mastectomy,[10] hernioplasty,[11–13] cholecystectomy[14] and caesarean section[15] may also lead to persistent pain in approximately 12–30% patients.

The prevalence of persistent pain after orthopaedic surgery has been the subject of only few studies[16–24] and the risk factors for persistent pain have been evaluated even more rarely.[17,18,21–23] The purpose of the present study was to evaluate the degree and the risk factors of persistent pain after knee arthroplasty with a questionnaire in a large, register-based cross-sectional prevalence study. Primary injury influences the intensity of forthcoming pain.[25,26] The main hypothesis, therefore, was that the type of operation (primary, bilateral, revision) would influence the development of persistent postoperative pain.

Patients and methods

Patients who had undergone knee arthroplasty during the period from 1st September 2002 to 28th February 2004 were recruited from the arthroplasty registry of the arthroplasty specialized hospital. The study was approved by the Ethic Committee of the hospital. Written informed consent was obtained from each patient. The total number of patients was 855. The operation was a primary arthroplasty in 648 patients (75.7%), a bilateral arthroplasty in 137 patients (21.1%) and a revision arthroplasty in 70 patients (8.2%). If a patient was operated several times, the last operation was taken into account. The preoperative pain intensity was evaluated by a surgeon and taken from the hospital registry (none, mild, moderate, severe). All patients were operated on spinal anaesthesia and an epidural catheter was inserted for postoperative pain relief. Epidural analgesia was discontinued on the first postoperative day to ensure early rehabilitation. The early complications such as deep infection and/or dislocation of prosthesis during first 2 months were taken from the hospital registry.

A questionnaire and a consent form with a prestamped return envelope were mailed to all patients in July 2004. In the case of no reply, a reminder was sent once. The time interval between the performed operation and the questionnaire was minimum 4 months and maximum 22 months. The demographics were asked. All the other questions considered preoperative and postoperative pain. The duration of preoperative pain and the intensity of postoperative pain during the first week (mild, moderate, severe, unbearable) were asked. If the patient still was suffering any pain in operated knee while receiving the questionnaire, the pain intensity during rest and exercise was evaluated. The degree of disturbance of daily life and sleep due to pain (none, mild, moderate,

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severe) and the consumption of analgesics for persistent pain at the operated knee were asked.

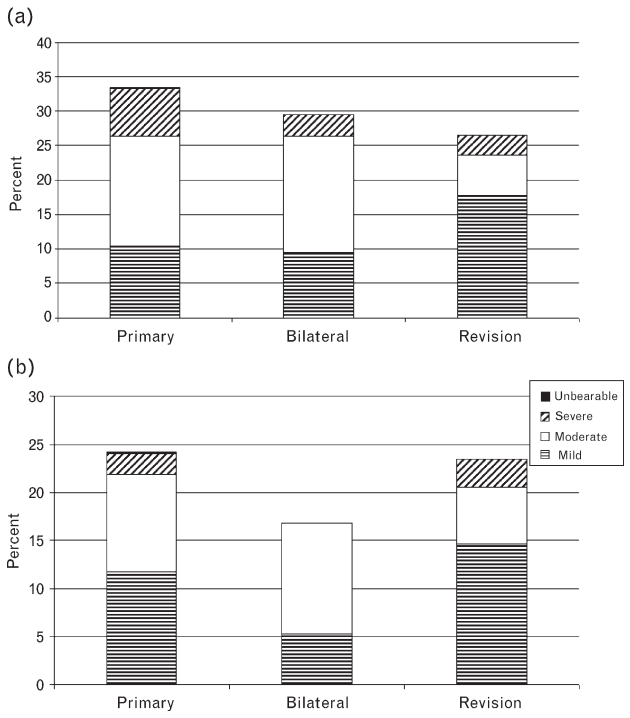
The data from the returned questionnaires and from the hospital registry were analysed using multiple logistic regression analysis. The dependent variable was the pain at the time of the questionnaire. The explanatory variables were treatment, age (centred at the age of 70 years and including a quadratic term), sex, BMI, pain score and duration prior to surgery, pain score during the first week after operation, type of prosthesis and diagnosis. The numeric variables are reported by means with standard deviations (SD) and the categorical variables are presented as absolute and relative frequencies. The results of the univariate and multivariate logistic regressions are presented as odds ratios (ORs) with 95% confidence intervals (CI). *P*-values are also given for univariate analysis. Logistic regression was used instead of linear regression because the object of the study-persistent pain or not was binominal.

All computations have been made by using R.[27]

Results

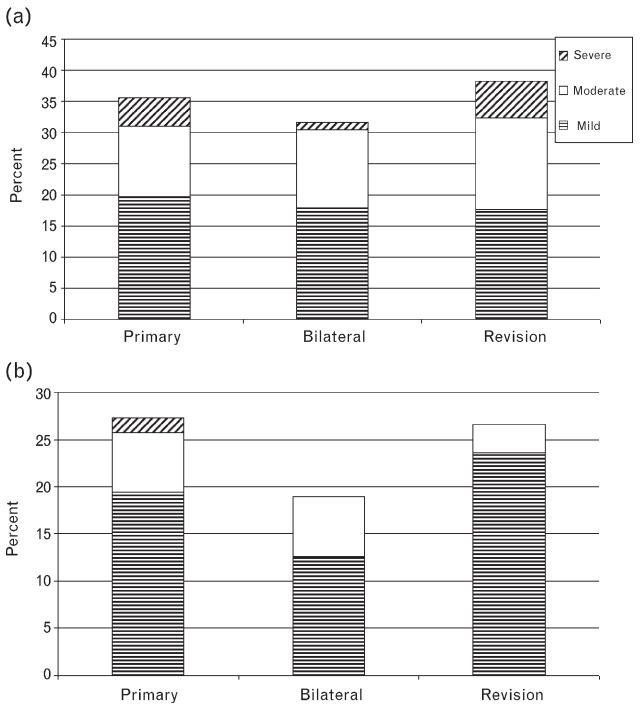
The response rate of the questionnaire was 65.7% in total; 66.8% in the primary arthroplasty group, 69.3% in the bilateral arthroplasty group and 48.6% in the revision arthroplasty group. Pain was not experienced only during exercise (Fig. 1a) but also during rest (Fig. 1b). Thirty-five

Fig. 1



Persistent pain during exercise (a) and rest (b) in primary, bilateral and revision arthroplasty groups. *P*-value is 0.32 (a, b).

Fig. 2



Disturbance of daily life (a) and sleep (b) because of persistent pain in primary, bilateral and revision arthroplasty groups. *P*-values are 0.52 (a) and 0.70 (b), respectively.

percent of patients suffered from daily life disturbing pain (35.6% in primary, 31.6% in bilateral and 38.2% in revision arthroplasty groups, respectively) a minimum of 4 months after the operation (Fig. 2a). Twenty-five percent of patients had disturbances of sleep due to pain (Fig. 2b). The intensity of pain was mostly mild or moderate. The proportion of patients who still used analgesics because of pain in the operated knee was 45.5% after primary arthroplasty, 43.2% after bilateral arthroplasty and 41.2% after revision arthroplasty ($P = 0.86$).

The variables listed in Table 1 were all assumed to be risk factors for persistent pain. The results of univariate logistic regressions are presented in Table 2. Backward selection in the multivariate logistic regression left only age and its quadratic term, sex, the duration of pain prior to surgery and early postoperative pain in the final model. Age was entered in the model also quadratically and a possible interaction between age and treatment was considered. According to the primary hypothesis, the operation itself, primary, bilateral or revision arthroplasty and the type of prosthesis, demi-arthroplasty or total arthroplasty, were still left to the final model. The surgical complications checked from the registry were so few that they were left out from the regression analysis. Following Harrell,[28] Somer's D_{xy} rank correlation of the final model was 0.50, which corresponds to a value of the area under the Receiver Operating Characteristic

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Table 1 Variables evaluated for persistent pain

	Primary $N=433$	Bilateral $N=95$	Revision $N=34$
Age (years; mean±SD)	69.2 (8.9)	65.1 (8.9)	71.2 (10.3)
BMI (kg/m^2; mean ± SD)	29.5 (4.7)	29.6 (4.5)	28.1 (4.0)
Sex F/M (*N*)	304/129	64/31	28/6
Diagnosis OA/RA (*N*)	412/12	93/2	30/4
Presurgical pain score *N* (%); no pain/mild pain	29 (7.0)	4 (4.0)	7 (21.0)
Moderate, occasional pain	219 (51.0)	39 (41.0)	13 (38.0)
Moderate, continuous pain	149 (35.0)	42 (45.0)	9 (26.0)
Severe pain	30 (7.0)	9 (10.0)	5 (15.0)
Presurgical duration of pain	$N=419$	$N=94$	$N=30$
≤12 months *N* (%)	43 (10.0)	3 (3.0)	5 (17.0)
>12 months *N* (%)	377 (90.0)	91 (97.0)	25 (83.0)
Early postsurgical pain	$N=417$	$N=93$	$N=34$
Mild *N* (%)	111 (27.0)	26 (28.0)	14 (41.0)
Moderate *N* (%)	194 (45.0)	36 (39.0)	14 (41.0)
Severe *N* (%)	104 (24.0)	26 (28.0)	5 (15.0)
Unbearable *N* (%)	18 (4.0)	5 (5.0)	1 (3.0)

F, female; M, male; OA, osteoarthritis; RA, rheumatoid arthritis.

(ROC) curve of 0.75. The indices of unreliability and discrimination were $U=-0.0039$ and $D=0.1443$.

The results of the multivariate logistic regression (OR with 95% CI) are shown in Table 3. ORs for continuous variables refer to one unit changes.

Discussion

The aim of the present study was to find out whether the magnitude of the primary injury, the type of surgery, influences the development of persistent postoperative pain. Logistic regression analysis was chosen to test our hypothesis and to find any other risk factors for the development of persistent pain. Persistent pain after knee arthroplasty was relatively common (35.0%), but the type of surgery did not correlate with pain. Instead, female sex, long duration of pain prior to surgery and high intensity of pain during the first postoperative week led to persistent pain.

Pain is the main indication for knee arthroplasty and pain relief is the most important postoperative outcome. However, there are only few studies concerning persistent pain as an outcome measure after knee arthroplasty,[16–18,20–22,24] although most studies focus on the survival of prosthesis.

The prevalence of persistent pain in the present study was significantly higher than in the majority of the earlier studies. The study of Brander *et al.*[17] reported 22.6% prevalence of significant pain [Visual Analog Scale (VAS) >4] at 3 months, 18.4% at 6 months and 13.1% at 1 year. In another study the prevalence of moderate pain was 10%, but their time point was at 7 years.[20] Lundblad *et al.*[23] reported prevalences that are more in line with our study. The prevalence of persistent pain was 24% at rest and 66% with movement at 18 months after operation.[23]

The differences between the studies may be explained by study methods. Pain was not assessed by clinician such

Table 2 Results of univariate logistic regression analysis

Variable	Persistent pain Yes/No (*N*)	OR	95% CI	*P*
Treatment; primary	101/304			
Treatment; bilateral	22/70	0.9460	0.5473–1.5844	0.8370
Treatment; revision	7/22	0.9577	0.3695–2.2048	0.9230
Age	130/396	0.9792	0.9580–1.0007	0.0577
BMI	127/388	1.0126	0.9686–1.0580	0.5779
Sex: Male	25/128			
Sex: Female	105/268	2.0060	1.2530–3.3124	0.0049
Diagnosis; RA	6/18			
Diagnosis; OA	124/378	0.9841	0.4026–2.7638	0.9736
Presurgical duration of pain; ≤12 months	5/42			
Presurgical duration of pain; >12 months	122/342	2.9965	1.2677–8.8217	0.0236
Presurgical pain score; no pain or mild	7/31			
Moderate, occasional	59/196	1.3331	0.5876–3.4339	0.5173
Moderate, continuous	48/139	1.5293	0.6639–3.9819	0.3459
Severe	15/24	2.7679	1.0021–8.2608	0.0558
Early postsurgical pain score; mild	11/128			
Moderate	50/179	3.2504	1.6861–6.8002	0.0008
Severe	56/74	8.8059	4.4952–18.6975	<0.0001
Unbearable	13/11	13.7521	5.0873–39.0962	<0.0001

CI, confidence interval; OA, osteoarthritis; OR, odds ratio; RA, rheumatoid arthritis.

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Table 3 Results of multivariate logistic regression analysis

Variable	OR	95% CI
Bilateral versus primary arthroplasty	0.8864	0.4802–1.5875
Revision versus primary arthroplasty	1.0904	0.3650–2.8885
Duration of presurgical pain >12 months	2.8431	1.1448–8.6517
Age, centred at 70 years	1.0141	0.9855–1.0434
Age, squared and centred at 70 years	1.0027	1.0007–1.0048
Sex, female	1.9084	1.1434–3.2787
Moderate postsurgical pain versus mild	3.1135	1.5857–6.6186
Severe postsurgical pain versus mild	8.1686	4.0428–17.8303
Unbearable postsurgical pain versus mild	10.6857	3.6304–32.6282

CI, confidence interval; OR, odds ratio.

as in some earlier studies.[17,20] The patients were able to express their feelings confidentially by the questionnaire used, which might have increased the prevalence of pain. Pain was not graded by VAS[17,23] but by verbal terms. Mostly patients suffered from mild to moderate pain. The percentile from severe and unbearable pain (up to 21.4%) was more consistent with the study by Brander *et al.*[17]

Our strongest risk factor for persistent pain was the intensity of early (the first week) postoperative pain. Earlier studies with knee replacement have not included the intensity of early postoperative pain to their risk analysis, which has left the intensity of preoperative pain as a risk factor.[17,23] Instead, the study with total hip arthroplasty revealed that persistent postoperative pain was related to the recalled intensity of early postoperative pain rather than the intensity of preoperative pain.[22]

Women had an increased risk for persistent pain, which is related to many biological and psychosocial factors as discussed previously elsewhere.[29,30]

Advanced age seems to reduce the risk of persistent pain after general surgery.[31–33] In our study, age was not a linear risk factor for persistent pain, which is in line with other orthopaedic studies.[17,23]

Other factors associated with increased postoperative pain are anxiety and undiagnosed depression,[17] but our questionnaire was not designed to diagnose depression or anxiety.

The hypothesis of this study was that the larger the tissue injury (bilateral versus unilateral arthroplasty group), the higher the prevalence of persistent pain. Surprisingly there was no association in this respect. These results are in line with a previous study[34] and support the consensus to offer bilateral knee arthroplasty when needed.

The retrospective nature of data, the response rate (65.7%) and the variable time period from surgery to the questionnaire were the major limitations in the present study. To minimize the effect of retrospectivity, the original size of the study was designed to be large enough to draw conclusions. The response rate can be considered sufficient, but a higher response rate may have been obtained with several reminders. This in turn would have increased the power of the results. Especially the patients after revision knee arthroplasty were less likely to answer than others and the response rate 48.6% among them could not be regarded high enough. Anyway, the original size of study sample was 855 patients, which is enormous compared with previous prevalence studies.[17,20,23]

The time interval from surgery to the questionnaire varied from 4 to 22 months. Thus, definition for persistent postoperative pain is filled.[3] However, the long time interval for some responders may have affected the memory for preoperative pain. This problem was addressed by gaining the scores for preoperative pain scores from the hospital registry. Moreover, a long interval usually increases the possibility of false negatives,[35] which in turn underlies the significance of postoperative pain score as a risk factor for persistent postoperative pain. Altogether a fixed time interval between surgery and the questionnaire would have increased the quality of this study.

Although we found that the intensity of postoperative pain was a strong risk factor for persistent pain, a prospective study with observed pain intensities and the amounts of used analgesics should be carried out to confirm this finding.

Persistent pain after knee arthroplasty seems to be a far more frequent problem than assumed. The preoperative duration of pain and the intensity of early postoperative pain are the risk factors that we are able to influence by our own practice.[3] Surgery should be planned before the patients develop long lasting pain conditions and pain management during postoperative period and early rehabilitation should be considered as a challenge for the entire team. Prioritization according these findings is suggested in the healthcare system.

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References

1 Perkins FM, Kehlet H. Chronic pain as an outcome of surgery: a review of predictive factors. *Anesthesiology* 2000; **93**:1123–1133.
2 Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001; **87**:88–98.
3 Macrae WA. Chronic postsurgical pain: 10 years on. *Br J Anaesth* 2008; **101**:77–86.
4 Nikolajsen L, Jensen TS. Phantom limb pain. *Br J Anaesth* 2001; **87**:107–116.
5 Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. *Acta Anaesthesiol Scand* 1999; **43**:563–567.
6 Kalso E, Mennander S, Tasmuth T, Nilsson E. Chronic poststernotomy pain. *Acta Anaesthesiol Scand* 2001; **45**:935–939.
7 Eisenberg E, Pultorak Y, Pud D, Bar-El Y. Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). *Pain* 2001; **92**:11–17.
8 Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. *Anesthesiology* 2006; **105**:794–800.

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9 King KM, Parry M, Southern D, *et al.* Women's recovery from sternotomy-extension (WREST-E) study: examining long-term pain and discomfort following sternotomy and their predictors. *Heart* 2008; **94**:493–497.
10 Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: a survey of 282 women. *Pain* 1996; **66**:195–205.
11 Poobalan AS, Bruce JM, Smith S, *et al.* A review of chronic pain after inguinal herniorrhaphy. *Clin J Pain* 2003; **19**:48–54.
12 Aasvang E, Kehlet H. Chronic postoperative pain: the case of inguinal herniorrhaphy. *Br J Anaesth* 2005; **95**:69–76.
13 Kalliomaki ML, Meyerson J, Gunnarsson U, *et al.* Long-term pain after inguinal hernia repair in a population-based cohort: risk factors and interference with daily activities. *Eur J Pain* 2008; **12**:214–225.
14 Middelfart HV, Kristensen JU, Laursen CN, *et al.* Pain and dyspepsia after elective and acute cholecystectomy. *Scand J Gastroenterol* 1998; **33**:10–14.
15 Nikolajsen L, Sorensen HC, Jensen TS, Kehlet H. Chronic pain following caesarean section. *Acta Anaesthesiol Scand* 2004; **48**:111–116.
16 Burkart BC, Bourne RB, Rorabeck CH, Kirk PG. Thigh pain in cementless total hip arthroplasty: a comparison of two systems at 2 years' follow-up. *Orthop Clin North Am* 1993; **24**:645–653.
17 Brander VA, Stulberg SD, Adams AD, *et al.* Predicting total knee replacement pain: a prospective, observational study. *Clin Orthop Relat Res* 2003; **416**:27–36.
18 Harden RN, Bruehl S, Stanos S, *et al.* Prospective examination of pain-related and psychological predictors of CRPS-like phenomena following total knee arthroplasty: a preliminary study. *Pain* 2003; **106**:393–400.
19 Martinez V, Fletcher D, Bouhassira D, *et al.* The evolution of primary hyperalgesia in orthopedic surgery: quantitative sensory testing and clinical evaluation before and after total knee arthroplasty. *Anesth Analg* 2007; **105**:815–821.
20 Garcia JA, Bewley B, Redden JF. The St. Leger total knee replacement: a 7-year clinical assessment and survivorship analysis. *Knee* 2003; **10**:173–177.
21 Johnsson R, Thorngren KG. Function after total hip replacement for primary osteoarthritis. *Int Orthop* 1989; **13**:221–225.
22 Nikolajsen L, Brandsborg B, Lucht U, *et al.* Chronic pain following total hip arthroplasty: a nationwide questionnaire study. *Acta Anaesthesiol Scand* 2006; **50**:495–500.
23 Lundblad H, Kreicbergs A, Jansson K. Prediction of persistent pain after total knee replacement for osteoarthritis. *J Bone Joint Surg Br* 2008; **90-B**:166–171.
24 Elson DW, Brenkel IJ. A conservative approach is feasible in unexplained pain after knee replacement: a selected cohort study. *J Bone Joint Surg Br* 2007; **89-B**:1042–1045.
25 Costigan M, Woolf CJ. Pain: molecular mechanisms. *J Pain* 2000; **1**:35–44.
26 Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; **367**:1618–1625.
27 R Development Core Team (2009). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2009. ISBN 3-900051-07-0, URL http://www.R-project.org.
28 Harrell FE. *Regression Modelling Strategies*. New York, USA: Springer; 2001.
29 Rosseland LA, Stubhaug A. Gender is a confounding factor in pain trials: women report more pain than men after arthroscopic surgery. *Pain* 2004; **112**:248–253.
30 Bernardes SF, Keogh E, Lima ML. Bridging the gap between pain and gender research: a selective literature review. *Eur J Pain* 2008; **12**:427–440.
31 Smith WC, Bourne D, Squair J, *et al.* A retrospective cohort study of post mastectomy pain syndrome. *Pain* 1999; **83**:91–95.
32 Poleshuck EL, Katz J, Andrus CH, *et al.* Risk factors for chronic pain following breast cancer surgery: a prospective study. *J Pain* 2006; **7**:626–634.
33 Poobalan AS, Bruce J, King PM, *et al.* Chronic pain and quality of life following open inguinal hernia repair. *Br J Surg* 2001; **88**:1122–1126.
34 Powell RS, Pulido P, Tuason MS, *et al.* Bilateral vs unilateral total knee arthroplasty: a patient-based comparison of pain levels and recovery of ambulatory skills. *J Arthroplasty* 2006; **21**:642–649.
35 Tasmuth T, Estlanderb AM, Kalso E. Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer. *Pain* 1996; **68**:343–347.

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Appendix

Background:

1. Weight _____kg
2. Height _____cm

Pre/Post-surgical status

3. How long did you suffer from pain at the operated knee before surgery?_____months
4. How much did this pain disturb your daily life?
   1 not at all
   2 little
   3 to some extent
   4 a lot
5. How long did you have pain after surgery? _____weeks/months
6. How would you describe the pain during the first week after the operation?
   1 mild
   2 moderate
   3 severe
   4 unbearable

At present

7. Do you still have pain at your operated knee?
   1 yes, move to the question 9
   2 no (no futher questions)
8. Do you have pain at rest?
   1 yes
   2 no
9. How would you describe the degree ofpain at rest?
   1 mild
   2 moderate
   3 severe
   4 unbearable
10. Do you have pain at exercise?
    1 yes
    2 no, move to the question 12
11. How would you describe the degree of pain at exercise?
    1 mild
    2 moderate
    3 severe
    4 unbearable
12. How much does this pain disturb your daily life?
    1 not at all
    2 little
    3 to some extent
    4 a lot
13. How much does this pain disturb your sleep?
    1 not at all
    2 little
    3 to some extent
    4 a lot
14. Do you still use any medicine against post-surgical knee pain? Which?_____

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