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Some Challenges of
Postoperative Pain Treatment

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the Small Auditorium of Building M,
Pirkanmaa Hospital District, Teiskontie 35,
Tampere, on January 28th, 2011, at 12 o’clock.

UNIVERSITY OF TAMPERE
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.


Etorikoksibi 120mg vähensi merkitsevästi leikkauksen jälkeistä opioidikulutusta. Sen sijaan parasetamolin lisääminen etorikoksibiin ei tuonut lisätehoa kivun lievitykseen. Myöskään parekoksibiin 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.

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### Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>APC</td>
<td>Adenoma prevention with Celecoxib</td>
</tr>
<tr>
<td>APPROV</td>
<td>Adenomatous Polyp Prevention on Vioxx</td>
</tr>
<tr>
<td>ARF</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>ASA</td>
<td>Anaesthetic risk groups according to the American Society of Anesthesiologists</td>
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<tr>
<td>ATP</td>
<td>Adenosintriphosphate</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CI</td>
<td>Confidence intervals</td>
</tr>
<tr>
<td>CLASS</td>
<td>Celecoxib in Long-term Arthritis Safety Study</td>
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<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclo-oxygenase</td>
</tr>
<tr>
<td>CT</td>
<td>Computer tomography</td>
</tr>
<tr>
<td>etCO₂</td>
<td>End-tidal carbon dioxide</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma-amino-butyric acid</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GST</td>
<td>Glutathione-S-transferases</td>
</tr>
<tr>
<td>GTP</td>
<td>Guanosine Triphosphate</td>
</tr>
<tr>
<td>IASP</td>
<td>International Association for the Study of Pain</td>
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<tr>
<td>IC₅₀</td>
<td>Half maximal inhibitory concentration</td>
</tr>
<tr>
<td>IMMPACT</td>
<td>Initiative on Methods, Measurement and Pain Assessment in Clinical Trials</td>
</tr>
<tr>
<td>LSD</td>
<td>Least significant difference</td>
</tr>
<tr>
<td>MEDAL</td>
<td>Multinational Etoricoxib and Diclofenac Arthritis Long-Term Programme</td>
</tr>
<tr>
<td>MEG</td>
<td>Magnetoencephalography</td>
</tr>
<tr>
<td>NaCl</td>
<td>Sodium Chloride</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NRS</td>
<td>Numeral Rating Scale</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>ORL</td>
<td>Opioid Receptor Like</td>
</tr>
<tr>
<td>P</td>
<td>p-value</td>
</tr>
<tr>
<td>PCA</td>
<td>Patient controlled analgesia</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PGE₂</td>
<td>Prostaglandin E₂</td>
</tr>
<tr>
<td>PGI₂</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td>POD</td>
<td>Postoperative day</td>
</tr>
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</table>
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\textsubscript{2} Thromboxane A\textsubscript{2}
U-Crea Urinary Creatinine
U-\textalpha-1-miglo Urinary \textalpha-1-microglobulin
U-\textalpha-GST Urinary \textalpha-glutathione-S-transferase
U-\pi-GST Urinary \pi-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


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; Aavang 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.
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: \(A\alpha\), \(A\beta\), \(A\delta\) and \(c\). \(A\alpha\)-fibres and \(A\beta\)-fibres are both large in diameter, myelinated and responsible in propriocepting (\(A\alpha\), \(A\beta\)) or heavy touch (\(A\beta\)). \(A\delta\)-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- \(A\delta\)-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 \(A\delta\)-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 (\(A\beta\), \(A\delta\), \(c\)) (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 propioceptive 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 Aβ 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.
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 resolve 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 nociceptive 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

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

* IC_{50} is indicated by lipopolysaccharide-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.
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 (McCorry 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 *.
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 lipoygenase pathways, resulting in increased leukotriene synthesis. This in turn increases the probability of bronchospasm. 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.
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

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

* IC_{50} is indicated by lipopolysaccharide-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). Similarly, 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, ORL₁) 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, cardiototoxicity) 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 1:16000 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 euvoletic, 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.

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.
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

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>Prevalence of persistent pain (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>60-80</td>
<td>(Perkins and Kehlet 2000; Nikolajsen and Jensen 2001)</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>40-60</td>
<td>(Perttunen et al. 1999; Kalso et al. 2001)</td>
</tr>
<tr>
<td>Sternotomy</td>
<td>20-50</td>
<td>(Eisenberg et al. 2001; Lahtinen et al. 2006; King et al. 2008)</td>
</tr>
<tr>
<td>Breast surgery</td>
<td>10-60</td>
<td>(Tasmuth et al. 1995; Wallace et al. 1996)</td>
</tr>
<tr>
<td>Inguinal hernia repair</td>
<td>5-30</td>
<td>(Poobalan et al. 2003; Aasvang and Kehlet 2005; Kalliomäki et al. 2008)</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>10-50</td>
<td>(Middelfart et al. 1998)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>12</td>
<td>(Nikolajsen et al. 2004)</td>
</tr>
<tr>
<td>Orthopaedic surgery</td>
<td>10-60</td>
<td>(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)</td>
</tr>
</tbody>
</table>
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 1β, 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 (Poloshuck 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; Poloshuck 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/m² 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

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>Laparoscopic cholecystectomy, ASA I-II, 30-60 years, 60-100kg</td>
<td>Laparoscopic cholecystectomy, ASA I-III, 16-70 years</td>
<td>Laparoscopic hysterectomy, ASA I-II, 30-60 years, 50-80kg</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>allergy to aspirin-like drugs/sulphonamide, bronchial asthma, liver or renal dysfunction, peptic ulcer, bleeding disorder, pregnancy, substance abuse, chronic pain</td>
<td>BMI&gt;40kg/m², 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</td>
<td>allergy to aspirin-like drugs/sulphonamide, bronchial asthma, liver or renal dysfunction, peptic ulcer, bleeding disorder, pregnancy, substance abuse, chronic pain</td>
</tr>
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</table>
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/O₂ 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. EtCO₂ 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 NDASAID 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 (α = 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 α = 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>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td>ANOVA</td>
<td>ANOVA</td>
<td>t-test</td>
</tr>
<tr>
<td>Categorized data</td>
<td>Pearson’s $\chi^2$</td>
<td>Pearson’s $\chi^2$</td>
<td>Pearson’s $\chi^2$</td>
</tr>
<tr>
<td>Data of fentanyl consumption, VAS scores, laboratory samples (skewed distribution)</td>
<td>Kruskall-Wallis</td>
<td>Kruskall-Wallis</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>Statistical programme</td>
<td>SPSS for Windows 11.5</td>
<td>SPSS for Windows 11.5</td>
<td>SPSS for Windows 14.02</td>
</tr>
</tbody>
</table>

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 (Q1, Q3). 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

Total 178 patients

Study I: 73 patients
- 9 patients excluded
- Placebo: 20 patients
- Parecoxib 40mg: 23 patients
- Parecoxib 80mg: 21 patients

Study II: 75 patients
- 3 patients excluded
- Placebo: 15 patients
- Parecoxib 80mg: 15 patients
- Parecoxib 80mg: 21 patients

Study III: 30 patients
- Etoricoxib 120mg: 24 patients
- Etoricoxib 120mg+ Paracetamol 1g: 25 patients
- Placebo: 23 patients

9 patients excluded, 3 patients excluded
<table>
<thead>
<tr>
<th></th>
<th>Px40 (n=23)</th>
<th>Px80 (n=21)</th>
<th>PlaI (n=20)</th>
<th>E (n=24)</th>
<th>E+P (n=25)</th>
<th>PlaII (n=23)</th>
<th>Px (n=15)</th>
<th>PlaIII (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>45±9</td>
<td>44±12</td>
<td>41±10</td>
<td>46±12</td>
<td>45±11</td>
<td>45±9</td>
<td>49±8</td>
<td>51±5</td>
</tr>
<tr>
<td>Gender (Female%)</td>
<td>74</td>
<td>81</td>
<td>70</td>
<td>79</td>
<td>80</td>
<td>70</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77±14</td>
<td>77±12</td>
<td>75±11</td>
<td>79±14</td>
<td>84±12</td>
<td>78±15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24.8±2.9</td>
<td>25.2±2.4</td>
</tr>
<tr>
<td>ASA I/II/III (%)</td>
<td>48/52/0</td>
<td>62/38/0</td>
<td>60/40/0</td>
<td>38/54/8</td>
<td>40/56/4</td>
<td>48/39/13</td>
<td>67/33/0</td>
<td>67/33/0</td>
</tr>
<tr>
<td>surgery duration (min)</td>
<td>63±37</td>
<td>56±24</td>
<td>54±25</td>
<td>55 (44,75)</td>
<td>63 (48,68)</td>
<td>72 (47,91)</td>
<td>103±28</td>
<td>103±34</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100.7±20.4</td>
<td>105.9±23.3</td>
</tr>
</tbody>
</table>

Study I: Px40= parecoxib 40mg, Px80=parecoxib 80mg, PlaI=placebo
Study II: E=etoricoxib 120mg, E+P= etoricoxib 120mg+paracetamol 1g, PlaII=placebo
Study III: Px=Parecoxib 80mg, PlaIII=placebo
Table 7. Baseline data in Study IV

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>855</td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>562 (65.7)</td>
<td></td>
</tr>
<tr>
<td>*Age (years)</td>
<td>69±9</td>
<td></td>
</tr>
<tr>
<td>*BMI (kg/m²)</td>
<td>29.1±4.4</td>
<td></td>
</tr>
<tr>
<td>*Female gender</td>
<td>396 (70.5)</td>
<td></td>
</tr>
<tr>
<td>*Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>osteoarthritis</td>
<td>535 (95.2)</td>
<td></td>
</tr>
<tr>
<td>rheumatoid arthritis</td>
<td>18 (3.2)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>9 (1.6)</td>
<td></td>
</tr>
<tr>
<td>*Operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary arthroplasty</td>
<td>433 (77.0)</td>
<td></td>
</tr>
<tr>
<td>bilateral arthroplasty</td>
<td>95 (16.9)</td>
<td></td>
</tr>
<tr>
<td>revision arthroplasty</td>
<td>34 (6.1)</td>
<td></td>
</tr>
<tr>
<td>*Presurgical pain score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no pain or mild</td>
<td>40 (7.1)</td>
<td></td>
</tr>
<tr>
<td>moderate, occasional</td>
<td>271 (48.2)</td>
<td></td>
</tr>
<tr>
<td>moderate continuous</td>
<td>200 (35.6)</td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>44 (7.8)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>7 (1.3)</td>
<td></td>
</tr>
<tr>
<td>*Presurgical duration of pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤12months</td>
<td>51 (9.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;12months</td>
<td>493 (87.7)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>18 (3.2)</td>
<td></td>
</tr>
<tr>
<td>*Early postsurgical pain score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td>151 (26.9)</td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>244 (43.4)</td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>135 (24.0)</td>
<td></td>
</tr>
<tr>
<td>unbearable</td>
<td>24 (4.3)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>8 (1.4)</td>
<td></td>
</tr>
</tbody>
</table>

*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 (Q₁,Q₃)) during the first 20 hours in Studies I and II

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

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 ≤ 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(%))

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

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 (Q₁,Q₃)) with normal values

<table>
<thead>
<tr>
<th>Measurement, group</th>
<th>Baseline</th>
<th>2h after induction</th>
<th>2h after end of anaesthesia</th>
<th>1. POD</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-crea &lt;95 µmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parecoxib</td>
<td>14, 61(58.67)</td>
<td>14, 60(57.69)</td>
<td>14, 63(56.71)</td>
<td>13, 57(55.70)</td>
</tr>
<tr>
<td>placebo</td>
<td>14, 62(54.66)</td>
<td>14, 61(49.64)</td>
<td>14, 59(52.64)</td>
<td>12, 56(47.60)</td>
</tr>
<tr>
<td>S-urea 2.6-6.4 mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parecoxib</td>
<td>15, 3.7(2.8,4.8)</td>
<td>15, 3.3(2.9,4.0)</td>
<td>15, 3.3(3.0,4.8)</td>
<td>13, 2.4(2.2,3.8)</td>
</tr>
<tr>
<td>placebo</td>
<td>14, 4.2(3.6,5.4)</td>
<td>15, 4.0(3.5,5.0)</td>
<td>15, 4.2(3.5,5.0)</td>
<td>12, 2.7(2.3,3.1)</td>
</tr>
<tr>
<td>S-CysC &lt;1.4-1.5 mg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parecoxib</td>
<td>15, 0.74(0.66,0.85)</td>
<td>15, 0.67(0.55,0.76)</td>
<td>15, 0.66(0.57,0.83)</td>
<td>13, 0.68(0.60,0.78)</td>
</tr>
<tr>
<td>placebo</td>
<td>15, 0.71(0.64,0.84)</td>
<td>15, 0.65(0.56,0.78)</td>
<td>15, 0.66(0.56,0.72)</td>
<td>12, 0.67(0.55,0.78)</td>
</tr>
<tr>
<td>S-K 3.5-4.5 mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parecoxib</td>
<td>15, 4.1(4.0,4.3)</td>
<td>14, 4.1(4.0,4.4)</td>
<td>12, 4.1(4.0,4.6)</td>
<td>13, 4.0(3.8,4.2)</td>
</tr>
<tr>
<td>placebo</td>
<td>14, 4.2(4.0,4.2)</td>
<td>15, 4.2(4.0,4.4)</td>
<td>14, 4.0(3.9,4.2)</td>
<td>12, 3.6(3.4,3.8)</td>
</tr>
<tr>
<td>S-Na 137-145 mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parecoxib</td>
<td>15, 140(139-142)</td>
<td>15, 139(138,141)</td>
<td>15, 140(137,141)</td>
<td>13, 139(136,142)</td>
</tr>
<tr>
<td>placebo</td>
<td>14, 139(138,141)</td>
<td>15, 140(138,141)</td>
<td>14, 139(138,141)</td>
<td>11, 137(136,139)</td>
</tr>
</tbody>
</table>

Table 10b. Urinary renal measurements (n, median (Q₁,Q₃)) with normal values

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

POD=postoperative day  
* p<0.05 when compared to baseline measurement and tested by Mann-Whitney test
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**

![Pie chart showing pain intensity at rest](image)

**Figure 7. Pain during exercise**

![Pie chart showing pain intensity during exercise](image)
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pain Yes/No</th>
<th>Univariate analysis OR(95%CI)</th>
<th>Multivariate analysis OR(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>101/304</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>22/70</td>
<td>0.95(0.55-1.58)</td>
<td>0.89(0.48-1.56)</td>
</tr>
<tr>
<td>Revision</td>
<td>7/22</td>
<td>0.96(0.37-2.20)</td>
<td>1.09(0.37-2.89)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, squared and centred at 70 years</td>
<td></td>
<td></td>
<td>1.0027(1.0007-1.0048)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25/128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>105/268</td>
<td>2.00(1.25-3.31)</td>
<td>1.90(1.14-3.28)</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>6/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>124/378</td>
<td>0.98(0.40-2.76)</td>
<td></td>
</tr>
<tr>
<td>Presurgical pain score:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pain or mild</td>
<td>7/31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate, occasional</td>
<td>59/196</td>
<td>1.33(0.59-3.43)</td>
<td></td>
</tr>
<tr>
<td>Moderate, continuous</td>
<td>48/139</td>
<td>1.53(0.66-3.98)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>15/24</td>
<td>2.77(1.00-8.26)</td>
<td></td>
</tr>
<tr>
<td>Presurgical duration of pain:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤12 months</td>
<td>5/42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>122/342</td>
<td>3.00(1.27-8.82)</td>
<td>2.84(1.14-8.65)</td>
</tr>
<tr>
<td>Early postsurgical pain score:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>11/128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>50/179</td>
<td>3.25(1.69-6.80)</td>
<td>3.11(1.59-6.62)</td>
</tr>
<tr>
<td>Severe</td>
<td>56/74</td>
<td>8.81(4.50-18.70)</td>
<td>8.17(4.04-17.83)</td>
</tr>
<tr>
<td>Unbearable</td>
<td>13/11</td>
<td>13.75(5.09-39.10)</td>
<td>10.69(3.63-32.63)</td>
</tr>
</tbody>
</table>
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 herniorrhaphy (Beaussier et al. 2005)

Combining paracetamol 1g with etoricoxib 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 Rømsing 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. Rømsing 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 oliguric 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 13cmH₂O 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 (Kalbo 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.
Acknowledgements

This research has taken many years to complete which means numerous situations and contacts to be remembered and people to be acknowledged. If someone is missing from this section, I apologize and hope that I have understood to cordially thank them already at the time we passed together.

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I wish express my gratitude to another member of supervisory board, Docent Jorma Laitinen who introduced me into the research of pain and taught me both anaesthesiological skills and empathy.

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The study population was gathered from different hospitals. The District Hospitals of Valkeakoski, Vammala and Mänttä were included in addition to the Department of Anaesthesiology and Surgery in University Hospital of Tampere. I am deeply grateful to all the doctors and nurses involved in this study from the operating theatres to the wards. I likewise want to thank Professor, Matti Lehto, former head of the Coxa, Hospital for Joint Replacement for opportunity to use the hospital registry in my thesis.

I want to thank my colleagues Marika Ala-Peijari and Rami Puustinen and all the staff from the Neurosurgery Department for understanding my EVO-weeks and taking care of business while I was away.

I am also grateful to my colleague Nils Hoffman for helping me with picture editing. You were always polite - the problem was in the program, not with me.

Writing a dissertation in a foreign language is challenging. I wish to express my gratitude to Virginia Mattila, M.A. for editing my manuscript pleasantly with amazing quickness. The first page with the flower sticker will be saved.
My warmest thanks also go to the official reviewers of this dissertation—Docent Tuula Manner and Docent Timo Salomäki. You were able to highlight the weak points in the manuscript which I could not have noticed on my own. Your comments improved the manuscript and provided me with some new insights in studying pain.

Great support was provided by those sharing the dream about the dissertation. All the knowledge shareable was shared by this anaesthesiologist team. I want to thank you all: Antti Aho, Kati Järvelä, Maija Kalliomäki, Sari Karlsson, Antti Kämäräinen, Heli Leppikangas, Markku Rantanen and Ilkka Virkkunen. Some of you have already completed your dissertation - I am grateful for lovely events around them - and some of you will get there soon. Congratulations!

I want especially to thank my good friend and neighbour of mine, Tuire Sannisto. We have done our studies alongside each other. At first, you introduced me to the life of Refworks and finally to the numerous functions rooms of Tampere. Our dissertations are going to be defended in the same month, which means special challenges to our caretakers. Let the winter not be too snowy!

I also wish to express my sincere gratitude to the competitive research funding of the Pirkanmaan Hospital District and the Finnish Society of Anaesthesiologists for the financial support of this study.

Finally I owe my deepest gratitude to those I love most.

I want to thank mother Ritva for endless support on the way I have chosen. Without your help almost nothing could have happened. You have proficiently run our family business whenever needed.

Fortunately I have friends like Hellu, Harri, Raija, Niko, Hannele, Memma, Pauliina, Eeva, both Maijas and Helena, who have not only encouraged during this journey but also offered something else to think and do - endless discussions, outdoor and country living, travelling, riding, singing, dining and dancing. Thank you for your friendship.

My children, Elina, Hanna and Tuomas, you are the dearest to me. I have always enjoyed the time spent with you which is one of the reasons to the long time period needed to this dissertation. Anyway, there have been moments when I have been more or less absent-minded: thank you for showing me the life around me.

I want to thank my loving husband Timo. You have always supported me and my career although it had meant some periods of loneliness and single parenthood for you.

The dog is Man’s Best Friend. This has been true with this dissertation, too. Thank you, Nelli.

Tampere, November 2010

Pia Puolakka
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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
Lack of analgesic effect of parecoxib following laparoscopic cholecystectomy

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1Department of Anaesthesiology, University Hospital, Tampere, 2Department of Anaesthesiology, District Hospital, Varkaus, 3Department of Anaesthesiology, District Hospital, Vammala, 4Department of Surgery, District Hospital, Varkaus, 5Tampere School of Public Health, University of Tampere and Research Unit, Tampere University Hospital, Tampere and 6Medical School, University of Tampere, Tampere, Finland

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.

Accepted for publication 24 May 2006

Key words: cyclo-oxygenase-2 inhibitor; non-steroidal anti-inflammatory drug; parecoxib; visceral pain.
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-medications 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) CO₂ insufflation was used and the intra-abdominal pressure was kept at 12 mmHg. Anaesthesia was maintained with sevoflurane 2–3% in air–O₂ (66% : 34%). Muscle relaxation was maintained between train-of-four (TOF) 0/4–2/4 with rocuronium. E₂CO₂ 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 $\chi^2$ 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 ($3.9 \pm 1.9$) than in the placebo group ($5.8 \pm 3.0$) ($P = 0.014$).

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 $\leq 6$). Blurred vision (VAS $\leq 2$) 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 $\pm$ SD or range).

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>P40</th>
<th>P80</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>41 $\pm$ 10</td>
<td>45 $\pm$ 9</td>
<td>44 $\pm$ 12</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 $\pm$ 11</td>
<td>77 $\pm$ 14</td>
<td>77 $\pm$ 12</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>12/8</td>
<td>11/12</td>
<td>13/8</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>6/14</td>
<td>6/17</td>
<td>4/17</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>54 (19–106)</td>
<td>63 (10–150)</td>
<td>56 (19–103)</td>
</tr>
</tbody>
</table>

P40, parecoxib 40 mg; P80, parecoxib 80 mg.
No significant differences between the groups.
The 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>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative post-operative fentanyl consumption during the study [median ($Q_1$, $Q_3$)].</td>
</tr>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>P40</td>
</tr>
<tr>
<td>P80</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
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<tbody>
<tr>
<td>Medians of the pain scores (visual analogue scale, 0–10) at rest, during coughing and during leg elevation.</td>
</tr>
<tr>
<td>At rest</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>P40</td>
</tr>
<tr>
<td>P80</td>
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<tr>
<td>Coughing</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>P40</td>
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<tr>
<td>P80</td>
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<tr>
<td>Leg elevation</td>
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<tr>
<td>Placebo</td>
</tr>
<tr>
<td>P40</td>
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<tr>
<td>P80</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Table 4</th>
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<tbody>
<tr>
<td>Global evaluation of analgesia ($n$).</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>n = 17</td>
</tr>
<tr>
<td>Excellent</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Fair</td>
</tr>
<tr>
<td>Poor</td>
</tr>
</tbody>
</table>

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.

Acknowledgements

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References


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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.

Accepted for publication 5 March 2006

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 $\mu$g/kg of fentanyl adjusted to the nearest 25 $\mu$g/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 $\mu$g/kg of dehydrobenzperidole was administered as a prophylactic anti-emetic agent. Anaesthesia was further maintained with sevoflurane in 66% air in O2. 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 Ti 0–15% and the block was antagonized with glycopyrrolate combined with glycostigmine. Mechanical ventilation was adjusted to keep the end-tidal CO2 between 5 and 5.5%. The sizes of the four troacars were: 12 mm, 10 mm and 2 x 5 mm. The pressure of CO2 insufflation was kept under 12 cmH2O. 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 CO₂ 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 α = 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
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

### 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.

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

*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.

![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.](image-url)
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.

Acknowledgements

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References


Table 2

Duration of anaesthesia and surgery, and blood loss [median (Md) and quartiles (Q1, Q3)].

<table>
<thead>
<tr>
<th>Pre-medication group*</th>
<th>E120 (n = 23)</th>
<th>E + P (n = 24)</th>
<th>Pla (n = 17–19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>93 75, 105</td>
<td>94 82, 105</td>
<td>105 88, 122</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>55 44, 75</td>
<td>63 48, 68</td>
<td>72 47, 91</td>
</tr>
<tr>
<td>Blood loss (g)</td>
<td>10 10, 20</td>
<td>15 10, 20</td>
<td>10 10, 35</td>
</tr>
</tbody>
</table>

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


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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 a few studies that have investigated the nephrotoxicity of cyclooxygenase-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.
COX-2-synthesized prostaglandins play certain roles in the kidneys, like regulating perfusion pressure, handling salt and water intake, and renin release. These roles become more important in stressed states like hypovolemia, sepsis, and heart failure, when the glomerular filtration rate is already compromised.

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

There are only a few studies investigating the nephrotoxicity of NSAID or coxibs during perioperative period. 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. GSTs are cytosolic enzymes that have many isoforms. GST and GST are the main isoforms in the kidney. Elevated urinary GST levels are correlated with the proximal tubular injury and GST levels with distal tubular injury. Serum cystatin C is a cysteine protease inhibitor, for which production is independent of age, sex, and muscle mass. 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. However, their single, acute use at surgery can be safe, especially when coxibs unlike conventional NSAIDs do not enhance surgical bleeding.

**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) CO2 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/O2 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. EtCO2 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 Cockcroft and Gault formula. 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-γGST/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...
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 $\chi^2$-test as the significance test. The laboratory data are treated as continuous. Due to skewed distribution of S-crea, S-urea, 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 not 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 1**

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

**Table 2**

<table>
<thead>
<tr>
<th>Demographic factors</th>
<th>Placebo, n = 15</th>
<th>Parecoxib, n = 15</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) year</td>
<td>50.5 (4.5)</td>
<td>48.5 (7.9)</td>
<td>0.389</td>
</tr>
<tr>
<td>BMI, mean (SD) kg/m²</td>
<td>25.2 (2.4)</td>
<td>24.8 (2.9)</td>
<td>0.725</td>
</tr>
<tr>
<td>Frequencies, n (%) of ASA 1</td>
<td>10 (67)</td>
<td>10 (67)</td>
<td>1.000</td>
</tr>
<tr>
<td>Duration of surgery, mean (SD) min</td>
<td>103 (34)</td>
<td>103 (28)</td>
<td>0.971</td>
</tr>
<tr>
<td>Duration of anesthesia, mean (SD) min</td>
<td>138 (36)</td>
<td>134 (38)</td>
<td>0.810</td>
</tr>
<tr>
<td>Total blood loss, mean (min-max) ml</td>
<td>100 (50–200)</td>
<td>150 (50–400)</td>
<td>0.186</td>
</tr>
<tr>
<td>Creatinine clearance, mean (SD) mL/min</td>
<td>105.9 (23.3)</td>
<td>100.7 (20.4)</td>
<td>0.517</td>
</tr>
</tbody>
</table>

Differences were tested by t-test, Mann-Whitney test, or Pearson chi-squared test.
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 $\alpha$-1-microglobulin was undetectable (<5.2 mg/L), which makes statistical analysis impossible. However, there was no clinical difference between the groups in urinary $\alpha$-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, 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
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 40mg 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-\(\pi\)GST/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-\(\pi\)GST.

In our study, the preoperative level of U-\(\alpha\)GST/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 importance of clinical studies.

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.

**ACKNOWLEDGMENTS**

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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**


Original Article

Persistent pain following knee arthroplasty

Pia A.E. Puolakka, Michael G.F. Rorarius, Miika Roviola, Timo J.S. Puolakka, Klaus Nordhausen and Leena Lindgren

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.

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 Furthermore, routine operations such as mastectomy,10 hernioplasty,11–13 cholecystectomy,14 and caesarean section15 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 studies16–24 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,
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 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
(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
Results of multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral versus primary arthroplasty</td>
<td>0.8864</td>
<td>0.4802–1.5875</td>
</tr>
<tr>
<td>Revision versus primary arthroplasty</td>
<td>1.0904</td>
<td>0.3950–2.8885</td>
</tr>
<tr>
<td>Duration of presurgical pain &gt;12 months</td>
<td>2.8401</td>
<td>1.1449–8.6517</td>
</tr>
<tr>
<td>Age, centred at 70 years</td>
<td>1.0141</td>
<td>0.9855–1.0434</td>
</tr>
<tr>
<td>Age, squared and centred at 70 years</td>
<td>1.0027</td>
<td>1.0007–1.0048</td>
</tr>
<tr>
<td>Sex, female</td>
<td>1.9084</td>
<td>1.1434–3.2787</td>
</tr>
<tr>
<td>Moderate postsurgical pain versus mild</td>
<td>3.1135</td>
<td>1.5857–6.1866</td>
</tr>
<tr>
<td>Severe postsurgical pain versus mild</td>
<td>8.1686</td>
<td>4.0428–17.8303</td>
</tr>
<tr>
<td>Unbearable postsurgical pain versus mild</td>
<td>10.6857</td>
<td>3.6304–32.6282</td>
</tr>
</tbody>
</table>

Table 3

CI, confidence interval; OR, odds ratio. as in some earlier studies. 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 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. Our strongest risk factor for persistent pain was the intensity of early (the first week) postsurgical pain. Earlier studies with knee replacement have not included the intensity of early postsurgical pain to their risk analysis, which has left the intensity of preoperative pain as a risk factor. Instead, the study with total hip arthroplasty revealed that persistent postsurgical pain was related to the recalled intensity of early postsurgical pain rather than the intensity of preoperative pain.

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

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

Other factors associated with increased postsurgical pain are anxiety and undiagnosed depression, 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 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.

The time interval from surgery to the questionnaire varied from 4 to 22 months. Thus, definition for persistent postoperative pain is filled. 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, 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. 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

Persistent pain following knee arthroplasty


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 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 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?______