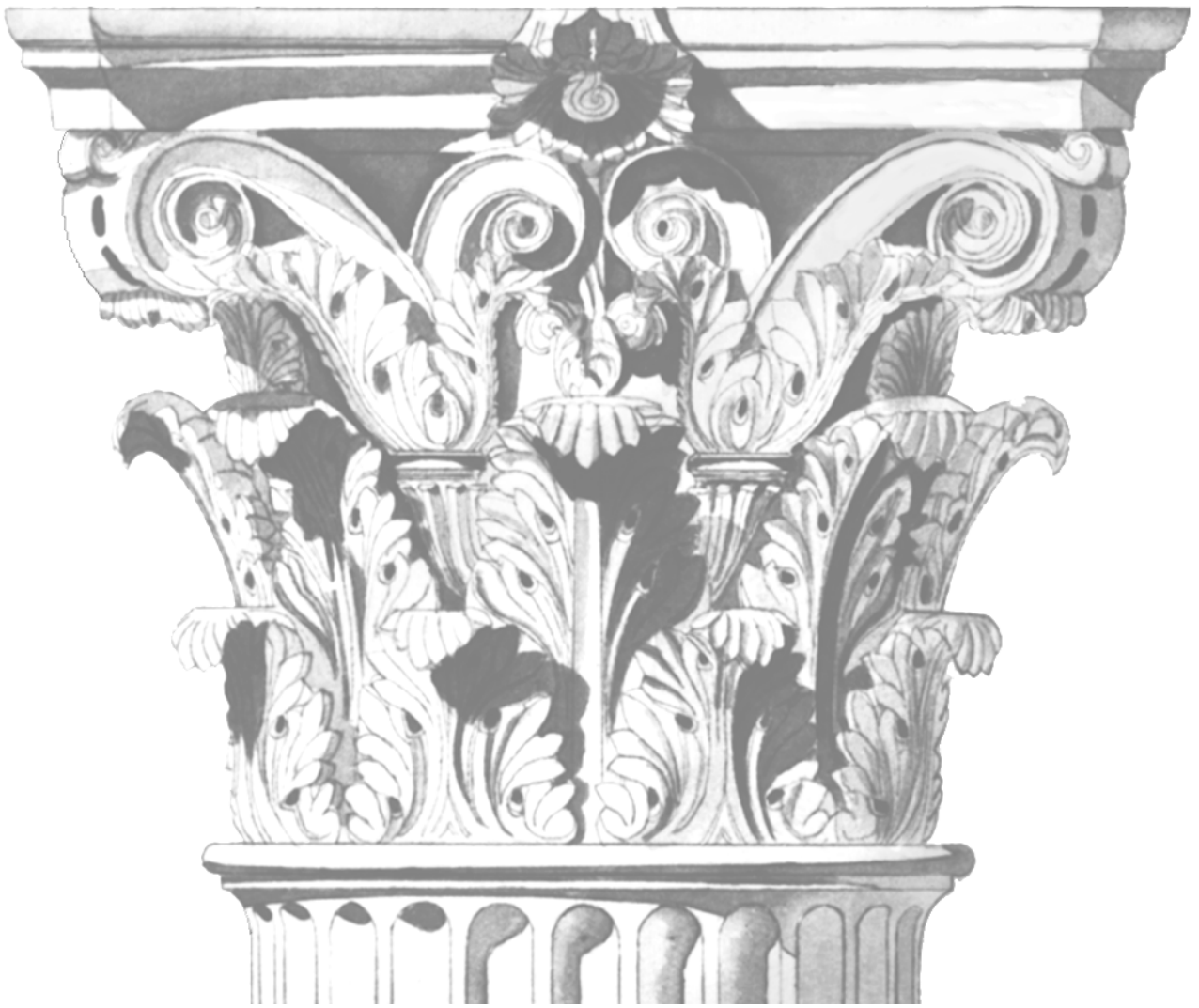
# PAIN RELIEF AFTER JOINT SURGERY

A clinical study

***PÄIVI LAURILA NÉE KOSTAMOVAARA***

Department of Anaesthesiology,
University of Oulu

OULU 2002



*PÄIVI LAURILA NÉE KOSTAMOVAARA*

# PAIN RELIEF AFTER JOINT SURGERY

A clinical study

Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in the Auditorium 1 of the University Hospital of Oulu, on October 11th, 2002, at 12 noon.

OULUN YLIOPISTO, OULU 2002

Reviewed by
Docent Mikko Pitkänen
Docent Marjatta Tuominen

ISBN 951-42-6795-8 (URL: http://herkules.oulu.fi/isbn9514267958/)

ALSO AVAILABLE IN PRINTED FORMAT
Acta Univ. Oul. D 694, 2002
ISBN 951-42-6794-X
ISSN 0355-3221 (URL: http://herkules.oulu.fi/issn03553221/)

OULU UNIVERSITY PRESS
OULU 2002

**Laurila née Kostamovaara, Päivi, Pain relief after joint surgery. A clinical study**
Department of Anaesthesiology, University of Oulu, P.O.Box 5000, FIN-90014 University of Oulu, Finland
Oulu, Finland
2002

## *Abstract*

Excessive pain after surgery causes many kinds of endocrine, metabolic and inflammatory responses, which may increase postoperative morbidity and mortality — especially among elderly patients. This study evaluated the effect of peripheral and central pain relief techniques after joint surgery.

Intravenously administered doses of 100 mg, 200 mg and 300 mg of ketoprofen decreased the requirement for opioid (fentanyl) in a dose-dependent manner by 38%, 45% and 53%, respectively, compared with a placebo, without any noticeable ceiling-effect, when administered after hip and knee arthroplasty. Patients receiving a 300 mg dose of ketoprofen had significantly lower postoperative pain scores than those receiving a placebo. There were no significant differences in incidences of nausea and vomiting, or in the amount of bleeding between the ketoprofen and placebo groups.

Intravenous doses of 200 mg of ketoprofen, 150 mg of diclofenac, and 120 mg of ketorolac produced similar postoperative pain scores and requirement for opioid (fentanyl) with no intergroup differences in the incidence of nausea and vomiting and in the amount of bleeding, when administered after hip arthroplasty.

The addition of ropivacaine, 1 $mg \cdot ml^{-1}$, did not decrease the requirement for epidural fentanyl administered via a patient-controlled analgesia device for postoperative pain relief after hip arthroplasty. Both drug infusions provided effective pain relief. The most common adverse effect was pruritus, which occurred in a similar number of patients in both groups.

An interscalene brachial plexus block with ropivacaine decreased the dose of PCA-delivered oxycodone by 78% after arthroscopic shoulder surgery while subacromial bursa blockade with ropivacaine decreased it by only 11% compared to a placebo during the 20 hour study period. Postoperative pain scores were significantly lowest with a interscalene brachial plexus block.

*Keywords:* analgesia, patient-controlled; analgesia, epidural; pain, postoperative; arthroplasty; arthroscopy; analgesics, opioid; anti-inflammatory agents, non-steroidal; anesthetics, local

# Acknowledgements

This research was carried out in the Department of Anesthesiology, University Hospital of Oulu, and in the Departments of Anesthesiology and Intensive Care, University Hospital of Kuopio and Lappi Central Hospital.

I wish to express my sincere thanks to Professor Seppo Alahuhta. M.D., Ph.D., the Acting Head of the Department of Anesthesiology, for his friendly support and guidance over the last years of my research work. This book never would have been finished without the encouragement and the good working possibilities he provided.

I owe my sincere thanks to my supervisors Professor Lauri Nuutinen, M.D., Ph.D., the former Head of the Department, and Timo Salomäki, M.D., Ph.D., for their everlasting encouragement throughout the years of this work. I would have given up this work many times during the darker moments without their friendly guidance and understanding. Their great knowledge in postoperative pain relief has been invaluable. I am also most grateful to my co-worker Jorma Laitinen, M.D., Ph.D., who first suggested this field of scientific research to me. Without his skilful help and knowledge the first manuscript would have never been published.

I am also deeply grateful to Docent Marjatta Tuominen, M.D., Ph.D., and Docent Mikko Pitkänen, M.D., Ph.D., the official examiners, for their critically constructive comments, which definitely helped to improve the final manuscript of this thesis.

I wish to express my warm thanks to Docent Tuula Kangas-Saarela, M.D., Ph.D., my co-worker, for her valuable assistance and advice in scientific work. My other co-workers Docent Heikki Hendolin, M.D., Ph.D., Docent Hannu Kokki, M.D., Ph.D., Merja Koivuranta, M.D., Ph.D., Ari Löppönen, M.D. and Tapio Flinkkilä, M.D. also fully deserve my grateful thoughts.

I am deeply grateful to my colleague Michael Spalding, M.D., Ph.D., and to Sirkka-Liisa Leinonen, M.Sc., who skilfully revised the English language of the original papers and this thesis.

My warmest thanks go to Pasi Ohtonen, M.Sc., for the discussions and his advice concerning biostatistics. He also taught me to create figures with Origin.

Special thanks are due to Docent Kai Kiviluoma, M.D., Ph.D., who always had the time and interest to read and comment on my manuscripts. I also warmly thank my colleagues Docent Vilho Vainionpää, M.D., Ph.D., for his patience and encouragement

during the last two years and Risto Hanhela, M.D., for his positive attitude towards teaching and scientific work. In addition, I owe a very special thanks to my friends and colleagues Pirjo Ravaska, M.D. and Kirsimarja Metsävainio, M.D., who offered me assistance in numerous ways during the years I lived in Rovaniemi. I also want to thank all my colleagues in Oulu and Rovaniemi for their support and understanding.

I am most grateful to all the nurses who took part in this study in Oulu, Rovaniemi and Kuopio. They unselfishly gathered data on the pain experienced by the patient during the postoperative hours.

I warmly thank all the patients who participated these studies. Without their understanding, it would not have been possible to write this thesis.

I warmly thank Ms. Airi Koivu for her secretarial assistance. Auvo Hietaharju, RN and Kauko Korpi, RN are especially acknowledged for their friendly technical assistance with computers. They never said “no” when I called them.

My brothers Raimo, Juha and Pasi with their families have always been very special to me. It has been a great relief to know that whatever happens I can always count on them. All my friends are remembered for the refreshing moments we have spent together. These have helped me forget work for a while.

Finally, I owe my loving thanks to my husband Jouko, who has spent numerous nights in discussion with me, standing beside my desk. His patience and unshakable calmness has guided me through the multiple moments of despair during this research. I also owe thanks to our children Mikko and Hanna, and the “big daughters” Katja and Elisa. You have reminded me of real life, laughter and joy which – unfortunately - are quite often far from the worktable.

This study has been supported by grants provided by the Professor Arno Hollmèn Fund and the Research Foundation of the Orion Corporation, which are gratefully acknowledged.

The permission of Acta Anaesthesiologica Scandinavica and the British Journal of Anaesthesia to reprint the original articles are acknowledged.

Oulu, July 17th, 2002 Päivi Laurila

# Abbreviations

| | |
|---|---|
| ANOVA | analysis of variance |
| ASA | American Society of Anesthesiologists |
| BS-11 | 11-point Box Pain Scale |
| CI | confidence interval |
| COX | cyclooxygenase enzyme |
| COX-1 | cyclooxygenase-1 enzyme |
| COX-2 | cyclooxygenase-2 enzyme |
| D | intravenous infusion of diclofenac (Study II) |
| e.g. | exempli grata (for example) |
| et al. | et alia (and others/coworkers) |
| F | epidurally administered infusion of fentanyl, 10 $\mu g \cdot ml^{-1}$ (Study III) |
| FR | epidurally administered infusion of fentanyl, 10 $\mu g \cdot ml^{-1}$, and ropivacaine 1 $mg \cdot ml^{-1}$, (Study III) |
| i.m. | intramuscular(ly) |
| ISB | interscalene brachial plexus blockade (with ropivacaine, Study IV) |
| i.v. | intravenous(ly) |
| K | intravenous infusion of ketorolac (Study II) |
| KP | intravenous infusion of ketoprofen (Study I, II) |
| LT | leukotriene |
| LX | lipoxin |
| n | number |
| n.s. | not significant |
| NSAID | nonsteroidal anti-inflammatory drug |
| PACU | postanaesthesia care unit |
| PCA | patient-controlled analgesia |
| PCEA | patient-controlled epidural analgesia |
| PG | prostaglandin |
| PLA | subacromial bursa block with saline (Study IV) |
| S | intravenous infusion of saline (Study I) |
| SD | standard deviation |
| SUB | subacromial bursa block (with ropivacaine) (Study IV) |
| TX | thromboxane |
| VAS | visual analogue scale |
| vs. | versus |

# List of original publications

This thesis was written based on the following original articles. These are referred to in the text by their corresponding Roman numerals.

I Kostamovaara PA, Laitinen JO, Nuutinen LS & Koivuranta MK (1996) Intravenous ketoprofen for pain relief after total hip or knee replacement. Acta Anaesthesiol Scand 40: 697-703.

II Kostamovaara PA, Hendolin H, Kokki H & Nuutinen LS (1998) Ketorolac, diclofenac and ketoprofen are equally efficacious for pain relief after total hip replacement surgery. Br J Anaesth 81: 369-372.

III Kostamovaara PA, Laurila JJ, Alahuhta S & Salomäki TE (2001) Ropivacaine 1 $mg \cdot ml^{-1}$ does not decrease the need for epidural fentanyl after hip replacement surgery. Acta Anaesthesiol Scand 45: 489-494.

IV Laurila PA, Löppönen A, Kangas-Saarela T, Flinkkilä T & Salomäki TE (2002) Interscalene brachial plexus is superior to subacromial bursa block after arthroscopic shoulder surgery. Acta Anaesthesiol Scand 46: 1031-1036.

# Contents

# 1 Introduction

The sensation of pain is one of the vital functions of the human body providing information on the occurrence of an injury. The function of acute pain is to protect the injured area while enabling healing and repair to occur. All surgical operations are followed by pain, which may amplify endocrine metabolic responses, autonomic reflexes, nausea, ileus, and muscle spasm, and which may increase postoperative morbidity and mortality (Kehlet 1997). Optimal postoperative pain treatment is therefore mandatory to enable early mobilisation and rehabilitation, to enhance recovery and to reduce morbidity. Despite continuous advances in anesthesia and postoperative pain relief, however, a review of the literature shows that there is still a significant number of patients which experience severe or moderate pain after surgery (Kuhn *et al.* 1990, Bruster *et al.* 1994, Oates *et al.* 1994).

Ever since the chemical synthesis of aspirin in 1899, the non-steroidal anti-inflammatory drugs (NSAIDs) have been among the most widely used drugs for the treatment of pain and inflammation. These drugs have also become popular for postoperative pain relief, as they decrease the need for opioids, and thus their adverse effects, such as respiratory depression, sedation, nausea and vomiting (Nissen *et al.* 1992, Laitinen & Nuutinen 1992). NSAIDs develop their mode of action by blocking the cyclooxygenase (COX) enzyme and thus the biosynthesis of PGs (Vane 1971). Two isoforms of the COX enzyme have been characterized: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (O'Banion *et al.* 1991). Because NSAIDs differ from each other in the inhibition property of these enzymes, they may also differ in analgesic efficacy and adverse effects.

Epidural blocks are one of the standard methods used in anesthesia for surgery. They have also been successfully used for postoperative pain. A variety of drugs have been administered into the epidural space for this purpose, for example (e.g.) opioids, local anesthetics or the combination of both (Etches *et al.* 1989, White *et al.* 1992, Salomäki *et al.* 1991, Salomäki *et al.* 1995, Badner *et al.* 1994). Constant research is still going on to determine the optimal drug or drug combination for epidural pain relief.

Peripheral nerve blocks have been widely used for anesthesia and postoperative analgesia. Although the majority of peripheral blocks in use today were first described in the early years of the 20$^{th}$ century, it is only in the last two decades that they have

undergone a marked resurgence in popularity. Peripheral blocks have been shown to reduce or avoid the need for parenteral opioids and therefore reduce the risk of delayed recovery, nausea, vomiting, and respiratory depression (Bridenbaugh 1983). Peripheral blocks can be performed as either a single injection or as a continuous infusion of a local anesthetic, depending on the requirements for the extent and duration of postoperative analgesia.

Multimodal analgesia employs a variety of drugs, such as NSAIDs, local anesthetics and opioids to achieve improved pain relief with a reduction in the incidence and severity of side effects (Kehlet 1997). The use of multimodal analgesia may thus improve recovery and reduce costs (Brodner *et al.* 1998). There are quite a few studies in the literature on the pain relief achieved with intravenous ketoprofen or comparisons of the analgesia achieved with different NSAIDs after orthopedic surgery. In the present study, the pain relief achieved with ketoprofen, ketorolac and diclofenac combined with patient-controlled fentanyl after hip and knee arthroplasty was evaluated. The analgesic effect of an addition of a new local anesthetic, ropivacaine, to fentanyl administered for epidural pain relief after hip arthroplasty was also studied. Pain after shoulder surgery is often severe. Subacromial bursa offers a suitable compartment for the injection of a local anesthetic. The scientific evaluation of the analgesic effect of subacromial bursa block (SUB), however, is meagre. The analgesia achieved with a SUB was compared with both the interscalene brachial plexus block (ISB) and a placebo.

# 2 Review of the literature

## 2.1 Nonsteroidal anti-inflammatory drugs

### *2.1.1 Eicosanoids and cyclooxygenase enzymes*

The activation of phospholipase A2 by pro-inflammatory cytokines leads to a production of arachidonic acid from membrane phospholipids. Arachidonic acid gives rise to eicosanoids, physiologically and pharmacologically active compounds known as prostaglandins (PG), thromboxanes (TX), leukotrienes (LT) and lipoxins (LX) (see Figure 1). PGs are considered to sensitise the nociceptors to natural stimuli and endogenous chemicals by modifying a voltage-sensitive Na+ current specific to nociceptors (Gold *et al.* 1996). Eicosanoids are synthesized via two pathways: the cyclooxygenase pathway and the lipooxygenase pathway. COX is the key enzyme in the synthesis of PGs, prostacyclin and TXs. Two isoforms of the COX enzyme have been characterized: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (O'Banion *et al.* 1991). These two isoforms of COX are almost identical in structure but have important differences in substrate and inhibitor selectivity. COX-1 is constitutively present in almost all tissues and it produces protective PGs maintaining homeostasis in many organs (e.g. stomach, kidney), while COX-2 is induced by inflammatory stimuli and by cytokines. In addition to the induction of COX-2 in inflammatory lesions, it is present constitutively in the brain and spinal cord, where it may be involved in nerve transmission, particularly that for pain and fever. PGs made by COX-2 are also important in ovulation and in the birth process. (Vane 2000) The discovery of COX-2 has made possible the design of drugs that reduce inflammation without removing the protective PGs in the stomach and kidney made by COX-1.

NSAIDs can be classified according to COX-1 and COX-2 inhibition: 1. irreversible inhibitors of COX-1 or COX-2 (aspirin); 2. reversible, competitive inhibitors of COX-1 and COX-2 (e.g. ibuprofen, piroxicam); 3. slow time-dependent, reversible inhibitors of COX-1 and COX-2 (e.g. indomethacin) and 4. slow, time-dependent, irreversible inhibitors inhibitors of COX-2 (e.g. celecoxib, rofecoxib) (Kurumbail *et al.* 1996). All

classic NSAIDs inhibit both COX-1 and COX-2 at standard anti-inflammatory doses, but the ratio between COX-1 and COX-2 inhibition is different.

The analgesic efficacy of these drugs is not totally and satisfactorily explainable by the inhibition of PG synthesis. In a dental pain model it has been shown that potent inhibitors of PG synthesis demonstrate analgesic efficacy comparable to the reference compound, aspirin 650 mg. On the other hand, weak inhibitors of PG synthesis demonstrate analgesic efficacy superior to aspirin 650 mg. (McCormack & Brune 1991) In addition to a well known peripheral action, a central component of the analgesic effect of NSAIDs has also been demonstrated. Diclofenac has been found to reduce the nociceptive response from the ventral nucleus of the thalamus evoked by stimulation of the sural nerve in normal and arthritic rats (Attal *et al.* 1988). Ketoprofen has been shown to inhibit spinal cord nociceptor reflex activity (Willer *et al.* 1989) and to reduce wind-up or central sensitisation in the spinal cord (Herrero *et al.* 1997).

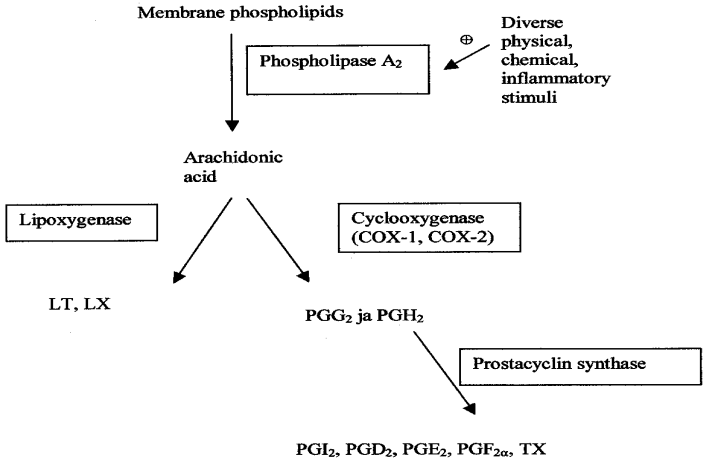



**Fig. 1. Prostaglandin synthesis.**

## *2.1.2 Ketoprofen*

Ketoprofen (2-(3-benzoyl phenyl)-propionic acid) was synthesised in 1967 and introduced to clinical practise in 1973 (Mills *et al.* 1973). It can be administered via a number of routes: orally, rectally, intramuscularly (i.m.), intravenously (i.v.) and topically.

The oral bioavailability of ketoprofen is over 90 % (Jamali & Brocks 1990), while absorption of the i.m. and rectal routes is 71-96% and 73-93%, respectively, of the equivalent oral dose. Maximum plasma concentrations are achieved within 45 to 80 minutes after single-dose i.m., rectal or oral administration. Ketoprofen binds extensively to plasma albumin (>90%). (Ishizaki *et al.* 1980) It is eliminated following extensive biotransformation to its inactive glucuroconjugated metabolite in the liver. Conjugates are

excreted in urine and the excretion is closely tied to renal function. An accumulation of conjugates occurs in the elderly, but not in young subjects (Jamali & Brocks 1990). The mean elimination half-life is from 1.1 to 1.3 hours for a single dose of 100 mg by oral, rectal or i.m. administration (Ishizaki *et al.* 1980) and 2.05 hours for the same dose by i.v. administration (Debruyne *et al.* 1987). The mean elimination half-life for elderly after a single oral dose of 150 mg of ketoprofen has been reported to be 2.72 hours, which is still sufficient to prevent clinically significant accumulation (Advenier *et al.* 1983).

Ketoprofen is a potent inhibitor of the cyclooxygenase enzyme and hence also of PG synthesis. In animal studies, a dose of less than 0.5 $mg \cdot kg^{-1}$ has resulted in a 50% reduction of urinary prostaglandin $E_2$ secretion (Matsuda *et al.* 1983) and a dose of 5 $mg \cdot kg^{-1}$ has produced an 87% inhibition of prostaglandin $E_2$ (Ligumsky *et al.* 1990). The opioid-sparing effect of i.v. or i.m. ketoprofen administered for postoperative pain relief after surgery has been reported in many studies (Rorarius *et al.* 1993, Tarkkila & Saarnivaara 1999, Rao *et al.* 2000). There have also been many studies comparing the analgesic effect of orally administered ketoprofen with other NSAIDs for rheumatoid arthritis or osteoarthrosis. In these studies, oral ketoprofen performs well (Veys 1991). The studies comparing the analgesic effect of i.v. or i.m. administered ketoprofen to that of diclofenac or ketorolac in postoperative pain relief are presented in Table 1. Diclofenac has offered better pain relief than ketoprofen in three out of four studies, while in one study they were equal.

### *2.1.3 Ketorolac*

Ketorolac is an enantiomeric (racematic) compound belonging to the nonsteroidal anti-inflammatory drug group and is available in both oral and parenteral forms (only parenteral in Finland).

The oral bioavailability of ketorolac is between 80 and 100% and is similar with i.m. and i.v. administration (Brocks & Jamali 1992). Maximum plasma concentrations are achieved within about 30 to 60 minutes after single-dose oral, rectal, subcutaneous or i.m. administration (Gillis & Brodgen 1997). Ketorolac is highly bound to plasma proteins (>99%). It is metabolised in the liver by conjugation and by para-hydroxylation and excreted via the kidney. The metabolites have no significant analgesic activity (Brocks & Jamali 1992). The mean terminal elimination half-life after single-dose administration is about 5 hours but is prolonged to 6 to 7 hours in the elderly and to 9 to 10 hours in those with renal impairment (Gillis & Brodgen 1997).

Ketorolac has been shown to reduce opioid consumption by 35-66% after orthopedic surgery when compared with placebo (Kinsella *et al.* 1992, Etches *et al.* 1995). Results from early clinical trials showed that ketorolac 30 mg i.m. was as effective as morphine 12 mg i.m. or meperidine 100 mg i.m. for postoperative pain relief after major surgery (Yee *et al.* 1986). Stouten *et al.* (1992) later reported similar results. Ketorolac 30 mg i.m. was better than ketorolac 10 mg or morphine 10 mg i.m. after major surgery. Ketorolac i.m. supplemented by oral oxycodone has been shown to offer less postoperative complications, such as nausea, vomiting and urinary retention than i.v. morphine administered via a patient-controlled analgesia (PCA) device (Popp *et al*. 1998).

Studies comparing i.v. administered PCA ketorolac with PCA morphine have shown conflicting results. The total dose of morphine and the incidence of side effects were significantly higher in patients receiving PCA morphine for postoperative pain relief in cancer patients (Bosek & Miguel 1994), but then after elective intra-abdominal operations PCA morphine provided a better quality of analgesia than PCA ketorolac (Cepeda *et al*. 1995).

### *2.1.4 Diclofenac*

Diclofenac sodium is one of the most potent inhibitors of the cyclooxygenase pathway (McCormack & Brune 1991). Reimann and Frölich (1981) found that a daily dose of 150 mg of diclofenac decreased urinary excretion of $PGE_2$ by about 50%.

Diclofenac sodium is almost totally absorbed after oral administration, peak serum levels being attained within 2 hours of ingestion. Similar to most other NSAIDs, diclofenac is highly bound (99.7%) to serum proteins. (Riess *et al.* 1978) Diclofenac is eliminated principally by metabolism and subsequent urinary and biliary excretion of glucuronide and sulphate conjugates of the metabolites (Stierlin *et al.* 1978). The principal metabolite has about $1/30^{th}$ the activity of the unchanged drug in animal models of inflammation (Menasse *et al.* 1978).

Diclofenac administered orally, intramuscularly, or rectally in single doses of 50-100 mg is an effective analgesic agent for the treatment of minor surgical pain (Kantor 1986). I.v. administered diclofenac decreased the need for PCA fentanyl by about 40 % after total hip replacement surgery (Laitinen & Nuutinen 1992). On the other hand, in a recent study, a continuous infusion of diclofenac failed to decrease opioid requirements in geriatric patients undergoing major orthopedic surgery (Fredman *et al.* 2000). Studies comparing the analgesic effect of diclofenac to that of ketoprofen or ketorolac are presented in Table 1.

*Table 1. Studies comparing the analgesic effect of intravenously or intramuscularly administered ketoprofen, ketorolac and diclofenac for postoperative pain relief.*

| Reference | Surgery | KP | K | D | RM |
|---|---|---|---|---|---|
| Tarkkila & Saarnivaara 1999 | TE | 200mg/12 h i.v. | 90mg/12h i.v. | 150mg/12h i.v. | P>KP>K=D |
| Rorarius *et al.* 1993 | Section | 200mg/24h i.v. | | 150 mg/24h i.v. | P>KP=D |
| Niemi *et al.* 1995 | Maxillofacial | 1.35 + 1.35 $mg{\cdot}kg^{-1}$ i.v. + i.m. | | 1.0 + 1.0 $mg{\cdot}kg^{-1}$ i.v. + i.m. | P, KP>D |
| Perttunen *et al.* 1999 | Thoracic | | 90 mg/24h i.v. | 150 mg/24h i.v. | P>K=D |
| O'Hanlon *et al.* 1996 | L-scopy | | 30 mg i.m. | 75 mg i.m. | K=D |
| Tarkkila *et al.* 1996 | Maxillofacial | | 0.4 $mg{\cdot}kg^{-1}$ qid i.v. | 1.0 $mg{\cdot}kg^{-1}$ bid i.v. | K=D |
| Chui & Gin 1995 | L-scopy | | 30 mg i.m. | 75 mg i.m. | K=D |
| Fredman *et al.* 1995 | L-scopy | | 60 mg i.m. | 75 mg i.m. | P>K=D |
| Morrow *et al.* 1993 | Arthroscopy | | 30 mg i.m. | 75 mg i.m. | D>K |

KP (ketoprofen), K (ketorolac), D (diclofenac), P (placebo), RM (rescue medication), TE (tonsillectomy), L-scopy (laparoscopy), gid (four times per day), bid (two times per day

### *2.1.5 Adverse effects of NSAIDs*

In addition to the response to tissue injury or inflammation, PGs have cytoprotective properties in the gastrointestinal tract and control of renal functions in the kidney (Vane 2000). Therefore, administration of non-selective, classical NSAIDs unavoidably leads to a lack of the PGs required for the physiological functions.

Their long-term use is limited by gastrointestinal effects such as dyspepsia, abdominal pain, and less often, hemorrhage and ulceration (Zfass *et al*. 1993). Current intake of NSAIDs, studied as a therapeutic class, has been associated with a four-fold to five-fold increase in upper gastrointestinal bleeding (Langman *et al.* 1994, Hernandez-Diaz & Garcia-Rodriguez 2001). The risk of serious gastrointestinal adverse effects is very low, however, after short-term use (Kehlet & Dahl 1992). In a recent report of 11245 patients receiving ketorolac, diclofenac or ketoprofen, only four patients (0.04%) suffered gastrointestinal bleeding (Forrest *et al.* 2002).

The reduced production of PGs also decreases the glomeruleric filtration. This leads to a retention of water, hypertension and, in some cases, to renal failure - especially in patients with reduced renal function. (Clive & Stoff 1984) Current long-term users of NSAIDs are estimated to experience a two-fold to four-fold increase in the risk of hospitalisation for acute renal failure (Perez-Gutthann *et al.* 1996, Henry *et al.* 1997). A recent meta-analysis on the effects of NSAIDs on postoperative renal function showed that NSAIDs cause a clinically unimportant reduction in renal function on the first day after surgery in patients with normal preoperative renal function. The reduction in creatinine clearance on the first day was between 21% and 28%. (Lee *et al.* 1999) NSAIDs may, however, cause postoperative renal failure in patients with pre-existing impaired renal blood flow, such as the elderly, those with heart failure or shock, or patients exposed to other nephrotoxic agents (Myles & Power 1998). In the study reported by Forrest *et al*. (2002) there were ten patients (0.1%) who had acute renal failure after administration of ketorolac, diclofenac or ketoprofen. No significantly increased risk of acute renal failure in patients with a history of renal insufficiency (n=42), or patients with a history of congestive heart failure (n=72) was detected.

Because ketoprofen, ketorolac and diclofenac have an inhibitory effect on platelet aggregation (Niemi *et al*. 1997), they may increase the risk of surgical site bleeding. However, the evidence of increased bleeding is conflicting (Bricker *et al.* 1987, Kenny 1992, Wierod *et al.* 1998). In a recent study the proportion of patients with postoperative bleeding while using ketorolac was 21% compared to 16% with diclofenac and ketoprofen. If the patients had any anticoagulant drugs used for thromboprophylaxis after surgery, however, the proportion was 39% in both groups. Some types of surgery were associated with higher risk of surgical site bleeding, independent of the use of postoperative anticoagulants. Plastic/ear-nose-throat surgery increased the risk by 3.5 times, gynecological surgery by 2.7 times, and urological surgery by 2.5 times. (Forrest *et al.* 2002)

## 2.2 Epidural pain relief

### *2.2.1 Fentanyl*

In addition to intravenous administration fentanyl has also been used epidurally for postoperative pain relief. Often a lower dose of opioid with a subsequent lower incidence of side effects is needed for postoperative pain relief when the opioid is administered epidurally rather than i.v. (Grant *et al.* 1992, Salomäki *et al.* 1995, Cooper *et al.* 1995). Most studies concerning the effects of epidural fentanyl administration suggest that epidural fentanyl causes a less clinically significant ventilatory depression (Etches *et al.* 1989) and less nausea (White *et al.* 1992) than epidural morphine. Pruritus also seems to be more severe and generalized with epidural morphine than with epidural fentanyl (White *et al.* 1992).

It is not clear whether the epidural administration of fentanyl results in systemic (Loper *et al.* 1990, Glass *et al.* 1992) or segmental analgesia (Gourlay *et al.* 1989, Coda *et al.* 1994, Cooper *et al.* 1995, Liu *et al*. 1996) or both. There are several studies with contradictory results comparing the epidural administration of fentanyl to i.v. administration (Sandler *et al*. 1992, Grant *et al*. 1992, Salomäki 1995, Loper *et al*. 1990, Glass *et al.* 1992, Cooper *et al*. 1995). Most studies demonstrating the superiority of the epidural route were patient-controlled epidural analgesia (PCEA) studies (Salomäki *et al*. 1991, Cooper *et al.* 1995). Results of the studies comparing patient-controlled epidural analgesia with continuous epidural infusion (bupivacaine-fentanyl mixture) show a reduction in analgesic requirement with PCEA (Lubenow *et al*. 1994, Silvasti & Pitkänen 2001). The ability of lipophilic opiates, such as fentanyl, to spread into the cerebrospinal fluid may be limited (Gourlay *et al*. 1987). Because of this it may be important to place the epidural catheter in the area of maximum nociceptive input. In many studies comparing the i.v. and epidural administration of fentanyl the epidural catheter has been placed faraway from the site of nociceptive input (e.g. Sandler *et al.* 1992, Grant *et al.* 1992).

### *2.2.2 Ropivacaine*

Ropivacaine is a new amide-type local anesthetic, an enantiomer (isomer) of the hydrochloride salt of S-(-)-1-propyl-2',6'-pipecoloxylidide (Markham & Faulds 1996).

Ropivacaine binds extensively (94%) to plasma proteins. It is metabolised by microsomal cytochrome P450 in the liver. The terminal elimination half-life of ropivacaine after epidural injection has been reported to vary between 4.1 and 6.5 hours after ropivacaine doses of 125-250 mg (Sandler *et al.* 1995).

Ropivacaine has the same pKa but is less lipid-soluble than is bupivacaine. In vitro studies have shown that ropivacaine is more selective for Aδ fibres (pain) than Aβ fibres (motor) and blocks Aδ fibres more potently than equimolar concentrations of bupivacaine (Rosenberg & Heinonen 1983). The results from clinical studies are contradictory. Some studies have shown that, in similar concentrations, ropivacaine causes less motor block

than bupivacaine (e.g. Meister *et al.* 2000, Bertini *et al.* 2001), while others have failed to show significant difference in motor block (e.g. Jorgensen *et al.* 2000). It has been difficult to determine an exact potency ratio between ropivacaine and bupivacaine. In a recent study assessing the minimum local analgesic concentration of bupivacaine and ropivacaine during the first stage of labour, ropivacaine was less potent than bupivacaine, with a potency ratio of 0.6 (Polley *et al.* 1999). In another study, however, the minimum local anesthetic volume of ropivacaine and bupivacaine, 5 $mg \cdot ml^{-1}$, required to produce an effective block of femoral nerve in 50% of cases was the same (Casati *et al.* 2001). Numerous other clinical studies comparing ropivacaine to bupivacaine describe an equipotent analgesia between these two local anesthetics (e.g. Owen *et al.* 1998, Casati *et al.* 2000, Hodgson & Liu 2001)

Ropivacaine is structurally similar to bupivacaine but less toxic to the heart and central nervous system (Reiz *et al.* 1989, Moller & Covino 1990, Pitkänen *et al.* 1992, Knudsen *et al*. 1997). A few cases of severe central neurological complications after administration of ropivacaine have, however, been reported (Korman & Riley 1997, Abouleish *et al.* 1998, Plowman *et al.* 1998, Ræder *et al.* 1999, Ruetsch *et al.* 1999, Müller *et al.* 2001).

There are several dose-finding studies on the continuous epidural infusion of ropivacaine for postoperative pain relief after major orthopedic and abdominal surgery. Scott *et al.* (1995) and Badner *et al.* (1996) compared ropivacaine concentrations of 1, 2, and 3 $mg \cdot ml^{-1}$ at an infusion rate of 10 $ml \cdot h^{-1}$ with a placebo infusion. All the patients in these studies needed PCA morphine as rescue analgesic, thus ropivacaine infusion of up to 3 $mg \cdot ml^{-1}$ concentration without an opioid addition did not provide sufficient analgesia. Based on these studies it seems that ropivacaine, 2 $mg \cdot ml^{-1}$, is favourable, if no opioid addition is performed. Turner *et al.* (1996) compared the requirement for PCA morphine with epidural ropivacaine, 2 $mg \cdot ml^{-1}$, at an infusion rate of 6, 8, 10, 12, or 14 $ml \cdot h^{-1}$ to a control group with no infusion and reported that the infusion rate of 10 $ml \cdot h^{-1}$ was favourable.

### *2.2.3 Ropivacaine with fentanyl*

Laboratory studies have demonstrated a synergistic analgesic effect of a combination of an epidural opioid and a local anesthetic (Kaneko *et al.* 1994). Many clinical studies on the effect of adding low concentrations of bupivacaine to epidural fentanyl have produced conflicting results. In some studies, postoperative analgesia was superior with bupivacaine addition (Paech & Westmore 1994, Badner *et al.* 1994), while in others no improvement in analgesia was detected (Badner *et al*. 1991, Badner & Komar 1992, Salomäki *et al*. 1995). The advantage of adding ropivacaine to epidural fentanyl has not been studied.

The addition of fentanyl to epidural ropivacaine either produces lower pain scores or reduces the consumption of ropivacaine, or both. Scott *et al.* (1999) compared the analgesic effect of the addition of fentanyl, 1, 2 or 4 $\mu g \cdot ml^{-1}$ to epidural ropivacaine, 2 $mg \cdot ml^{-1}$, after abdominal surgery and showed the pain scores were lowest in the group with addition of fentanyl, 4 $\mu g \cdot ml^{-1}$. In the study reported by Berti *et al.* (2000) the

addition of fentanyl, 2 $\mu g \cdot ml^{-1}$, to patient-controlled epidural ropivacaine, 2$mg \cdot ml^{-1}$, resulted in a significant reduction in ropivacaine consumption after abdominal surgery. No significant difference, however, was found in pain scores between the study groups. Buggy *et al.* (2000) reported that the addition of fentanyl, 2 $\mu g \cdot ml^{-1}$, to ropivacaine, 1 $mg \cdot ml^{-1}$, resulted in lower pain scores and a significant reduction in ropivacaine consumption. According to these results, it would appear that the use of plain epidural ropivacaine infusion for postoperative pain relief is not recommendable.

## 2.3 Regional analgesia in shoulder surgery

### *2.3.1 Interscalene brachial plexus blockade*

The interscalene brachial plexus block (ISB) alone or in combination with general anesthesia is a very suitable technique for shoulder surgery. Winnie was the first to describe the single injection technique of ISB block (Winnie 1970). In this technique, the interscalene groove is palpated at the level of C6. After the groove is identified, a needle is inserted perpendicularly to all planes, directed caudally and advanced slowly until paresthesia below the level of the shoulder is detected. It has later been shown that the plexus can be well identified using a nerve stimulator to determine the accurate spot for the injection of local anesthetic (Yasuda *et al.* 1980, Tuominen *et al.* 1987a). Other approaches than that described by Winnie to the ISB block have been described (Rucci *et al.* 1993, Sharrock *et al.* 1996). A catheter with a continuous infusion of local anesthetic can be used to produce a prolonged postoperative analgesia (Tuominen *et al.* 1987b).

Reported complications associated with ISB are nerve damage (Barutell *et al.* 1980, Walton *et al.* 2000, Borgeat *et al.* 2001), diaphragmatic paralysis (Urmey *et al.* 1991, Pere *et al.* 1992), unintentional intravenous, intra-arterial (Tuominen *et al.* 1991), epidural (Mahoudeau *et al.* 1995), and subdural injection (Tetzlaff *et al.* 1994), as well as Horner's syndrome (Al-Khafaji & Ellias 1986). Auditory disturbance has also been reported after ISB (Rosenberg *et al.* 1995). In a recent report, the incidence of short- and severe long-term complications was 0.4%. When a continuous technique with placement of a catheter into the interscalene space was used, the rate of complications was not increased. (Borgeat *et al.* 2001)

### *2.3.2 Subacromial bursa block*

Vangsness *et al.* (1995) have studied the neural histology of the human shoulder and have found scattered free nerve endings throughout the subacromial bursa. Irritation of the subacromial space with hypertonic saline solution has been shown to produce pain in the region of the lateral acromion, the deltoid muscle, and occasionally in the forearm or the fingers (Gerber *et al.* 1998). Corticosteroids have been injected into this bursa for the treatment of symptomatic subacromial impingement syndrome (Blair *et al.* 1996).

Even though the subacromial bursa offers a suitable compartment for the injection of a drug, there are only a few studies in the literature assessing the analgesic efficacy of a local anesthetic injection to the subacromial bursa. Muittari and Kirvelä (1998) have reported that postoperative (approximately 24 hours) fentanyl consumption did not differ between the subacromial bursa block and ISB groups, when SUB was achieved with 10 ml of bupivacaine, 5 $mg \cdot ml^{-1}$, combined with oxycodone 5 mg. Unfortunately, this study was not placebo-controlled. In another study, SUB with bupivacaine was compared to a placebo, and no difference on patients' report of pain or on total dose of postoperative analgesic was found (de Nadal *et al.* 1998). In a recent study, a patient-controlled, continuous infusion of lidocaine to the subacromial space appeared to be a safe method for achieving high levels of pain control in patients undergoing an acromioplasty (Mallon *et al.* 2000).

## 2.4 Patient-controlled analgesia

PCA is a technique which allows patients to self-administer small doses of an analgesic drug within preset limits. The first experiences of this method in pain management were described in the late 1960's (Sechzer 1968). At first this technique was used as a research tool to accurately measure pain, while later it has also become a method for improving the treatment of postoperative pain. In addition, PCA can be used in diverse clinical settings including analgesia during labour (Frank *et al.* 1987) and in the treatment of cancer pain (Citron *et al.* 1986, Kalso & Vainio 1990).

A PCA device delivers a prescribed amount of drug (a bolus dose), when the patient presses a button connected to the device. To help prevent excessive drug administration, the device ignores further patient demands until a lockout period has passed. This lockout interval is programmed into the pump and is usually set at between 5 and 10 minutes. In addition to the bolus dose, a background infusion is also programmable in the device. The purpose of this background infusion is to maintain therapeutic drug levels in the blood while the patients are not self-initiating boluses, such as during sleep. As it is impossible to predict any patient's absolute requirement for the analgesic drug, however, the use of a continuous background infusion may lead to an increased risk of side effects (Notcutt & Morgan 1990). On most pumps it is possible to set a maximum dose over a period of time (usually 4 hours).

The literature concerning the efficacy of PCA is contradictory. There are studies which indicate that PCA is superior to i.m. supplementation of the same opioid (Wheatley *et al.* 1992, Boulanger *et al.* 1993), while in other studies no difference in postoperative analgesia between the PCA and i.m. groups have been detected (Kleiman *et al.* 1988, McGrath *et al.* 1989). A meta-analysis of randomised controlled trials comparing PCA and i.m. injections indicated that analgesic efficacy was better with PCA and the patients preferred PCA over conventional analgesia (Ballantyne *et al.* 1993). The results from a more recent meta-analysis show also that PCA provides a slightly better analgesia than conventional opioid treatment (Walder *et al.* 2001).

Morphine has been the opioid used in many studies for PCA-delivered rescue analgesic. Recent studies have suggested, however, that NSAIDs may reduce morphine

requirements by reducing the excretion of the active metabolite, morphine-6-glucuronide. A morphine sparing effect may not result in parallel reductions in opioid-related adverse effects (Tighe *et al.* 1999). Fentanyl has inactive metabolites and minimal renal excretion, and because of these properties it may be a better rescue analgesic than morphine for studies assessing the analgesic and adverse effects of NSAIDs. Fentanyl has been administered for postoperative pain as PCA bolus doses with and without background infusion (Lehmann *et al.* 1988, Rowbotham *et al.* 1989, Welchew & Breen 1991, Laitinen & Nuutinen 1992). In the PCA bolus mode, the bolus doses of fentanyl administered range from 20-50 µg with lockout intervals up to 10 minutes (Laitinen & Nuutinen 1992, Cooper *et al*. 1995, Howell *et al*. 1995). No published study has directly assessed the advantages of adding a background infusion to PCA fentanyl bolus dose. Oxycodone, 14-hydroxy-7,8-dihydrocodeinone, is a strong opioid agonist with properties similar to morphine (Pöyhiä & Kalso 1992). However, hallucinations may occur less frequently with oxycodone than with morphine (Kalso & Vainio 1990). In postoperative patient-controlled analgesia, oxycodone appears to be equipotent to morphine with no differences in side effects, such as nausea, vomiting, pruritus and urinary retention (Silvasti *et al*. 1998). At present, local anesthetics are also being infused using the PCA technique, e.g. into the intrascalenic plexus (Borgeat *et al.* 1997).

### *2.4.1 Adverse effects of PCA*

Respiratory depression is a frequently voiced concern of PCA. Clinical studies including over 10000 patients, however, suggest an incidence of significant respiratory depression requiring intervention in the range of 0,2% (Baird & Schug 1996). According to Schug, the incidence of respiratory depression is increased to 1,65% if a background infusion is used in the PCA device (Schug & Torrie 1993). In a recently published survey of 1057 patients receiving postoperative PCEA with bupivacaine and fentanyl the incidence of respiratory depression was 0,19% (Wigfull & Welchew 2001). Apart from drug-related respiratory depression, incorrect programming, accidental bolusing during syringe changes and concentration error of a drug can also be causes of respiratory depression. Technical problems with PCA pumps are becoming rare; serious opioid overdoses due to equipment failure have been described, however (Doyle & Vicente 2001). The incidence of nausea and vomiting seems to be similar with the use of PCA compared with traditional opioid administration methods (Ballantyne *et al*. 1993, Woodhouse & Mather 1997, Walder *et al.* 2001).

## 2.5 Measurement of pain

As pain is a subjective experience, its objective measurement is quite difficult. It is, however, essential to determine pain intensity, quality and duration, in order to determine the most effective analgesic drug and appropriate dose to control it and/or to evaluate the

relative effectiveness of different analgesic therapies. As pain is a subjective experience, the patient's self-assessment provides the most valid measure.

Approaches to the measurement of pain include verbal and numeric self-rating scales, behavioural observation scales and physiological responses. Verbal rating scales typically consist of a series of verbal pain descriptors ordered from least to most intense (e.g. no pain, mild, moderate, severe). VAS consists of a 10-cm horizontal line with two endpoints labelled as 0 (no pain) and 10 (worst pain ever). (Joyce *et al.* 1975) The scores obtained by VAS correlate highly with pain measured on a verbal scale (Ohnhaus & Adler 1975). A numerical 11-point box (BS-11) scale has also been used for the assessment of pain. It may be the most useful clinical index of pain intensity among postoperative patients (Jensen *et al.* 1989). A large number of levels have been used for numerical rating scale in literature, but the results of a recent study reported by Jensen *et al.* (1994) suggest that 10 and 21-point scales provide a sufficient breadth of levels to describe pain intensity for chronic pain patients.

Patient-controlled analgesia offers a valuable method for measuring the amount of rescue analgesic required to treat postoperative pain, and thus can be used as an indirect assessment of pain.

# 3 Aims of the study

The aim of this research was to evaluate pain relief after orthopedic surgery. The following issues were of particular interest:

1. to study the pain relief, fentanyl-sparing, and adverse effects of three different doses of intravenously administered ketoprofen (100mg, 200 mg, 300 mg) after total hip or knee replacement surgery (I).
2. to study whether a ceiling effect can be found when increasing the intravenous dose of ketoprofen from 100 mg to 300 mg (I).
3. to compare the pain relief effect of diclofenac, ketorolac and ketoprofen after hip replacement surgery (II).
4. to study whether the addition of ropivacaine, 1 $mg \cdot ml^{-1}$, reduces the dose of epidural fentanyl administered with PCA pump after hip replacement surgery (III).
5. to compare the analgesia achieved with a ropivacaine-induced subacromial bursa block to that achieved with a saline-induced subacromial bursa block and to that achieved with a ropivacaine-induced interscalene plexus blockade after arthroscopic shoulder surgery (IV).

# 4 Patients and methods

This study consists of four different substudies, which have previously been reported in publications hereafter referred to as Studies I-IV. The Studies were conducted in the Department of Anesthesiology, University Hospital of Oulu (I, III, IV) and in the Department of Anesthesiology and Intensive Care, University Hospital of Kuopio and Lappi Central Hospital (II). Each study was conducted in accordance with the declaration of Helsinki. The study protocols were approved by the Ethical committee of the Faculty of Medicine, University of Oulu (I, III, IV) and by the Ethical committee of the Kuopio University Hospital and by that of the Lappi Central Hospital (II). Informed, written consent was obtained from all patients.

## 4.1 Patients

A total of 245 patients scheduled for hip arthroplasty (n=186, I-III), knee arthroplasty (n=14, I) or arthroscopic shoulder surgery (n=45, IV) were prospectively examined. Patients with hypersensitivity to aspirin or other NSAIDs (I, II, IV), hepatic, renal or cardiac failure (I, II, IV), bleeding or coagulation disorders (I-IV), asthma (I, II, IV) or with peptic ulcer (I, II, IV) were excluded. In Study IV, patients were excluded if they were morbidly obese or had preoperatively used opioids orally or parenterally. In Studies II-IV those patients unable to understand the instructions concerning the use of PCA pump were excluded.

## 4.2 Study designs

Studies presented in this thesis were prospective (I-IV), randomised (I-IV), placebo-controlled (I, IV), and double-blind (I-III). The patients in Study IV undergoing a subacromial bursa block with ropivacaine (SUB) or saline (PLA) were treated in a

double-blind manner, while the patients in the interscalene plexus block (ISB) group were treated openly.

After written, informed consent all patients were randomised into study groups. Randomisation was performed in blocks of 6 (II, IV), or 8 (I, III). A person not associated with the investigators performed the randomisation, and the codes were kept in sealed envelopes. For each recruited patient in Studies I-III, a trained nurse opened the envelope and prepared the study drugs. In Study IV, an anesthesiologist prepared the drugs. The study drugs were masked by dilution to the same volume of saline (I-IV).

Studies I and II began in the postanesthesia care unit (PACU) when the spinal anesthesia had disappeared from the operation site (0h). This was indicated by a pin-prick response: the patient was able to detect a sharp pinprick (22-gauge blunt needle) at the operation site. Study I assessed the effectiveness of i.v. administered ketoprofen in postoperative pain relief after hip and knee replacement surgery. The patients were randomly assigned in equal ratio to receive saline (n=19) (S), ketoprofen 100 mg (KP100, n=19), ketoprofen 200 mg (KP200, n=20), or ketoprofen 300 mg (KP300, n=18) (see Figure 2).

| GROUP | PACU | PACU |
|---|---|---|
| | 0-30 minutes | 31 minutes - 12 hours |
| S<br>KP100<br>KP200<br>KP300 | saline, 9 mg·ml$^{-1}$ (bolus)<br>KP 50 mg i.v (bolus)<br>KP 100 mg i.v (bolus)<br>KP 150 mg i.v (bolus) | infusion of saline, 9 mg·ml$^{-1}$<br>KP infusion of 4.3 mg/h (50mg)<br>KP infusion of 8.7 mg/h (100mg)<br>KP infusion of 13.0 mg/h (150 mg) |
| | Rescue analgesic<br>PCA: Fentanyl i.v., bolus 0.05 mg | |

**Fig. 2. Administration of ketoprofen in Study I.**

Study II compared the postoperative pain relief achieved with three i.v. administered NSAIDs: diclofenac 150 mg (D, n=28), ketorolac 120mg (K, n=28) and ketoprofen 200 mg (KP, n=29) after hip relacement surgery (see Figure 3). The sample size was estimated to demonstrate with 90 % power and at the 5 % significance level a difference of 30 % in fentanyl consumption between the study groups.

| Group | PACU | PACU |
|---|---|---|
| | 0-30 minutes | 31 minutes - 16 hours |
| K 120<br>KP 200<br>D 150 | K 30 mg i.v (bolus)<br>KP 100 mg i.v (bolus)<br>D 75 mg i.v (bolus) | K infusion of 5.8 mg/h (90mg)<br>KP infusion of 6.5 mg/h (100mg)<br>D infusion of 4.8 mg/h (75 mg) |
| | Rescue analgesic<br>PCA: Fentanyl i.v., bolus 0.05 mg | |

**Fig. 3. Administration of ketorolac, ketoprofen and diclofenac in Study II.**

To ensure adequate pain relief throughout the study, all patients in Studies I and II received a PCA pump (Graceby PCAS, Medical Limited, Watford, Herts, UK). The PCA pump was programmed to deliver on demand an i.v. bolus dose of 0.05 mg of fentanyl. The infusion time and the lockout time were 5 minutes, thus the maximal dose of fentanyl was 0.30 mg per hour. The patients were instructed to take a bolus dose whenever they required pain relief, and all successful demands were recorded.

Study III tested the hypothesis that the addition of ropivacaine to epidural fentanyl administered via PCA pump (Graceby PCAS, Medical Limited, Watford, Herts, UK) would reduce the need for epidural fentanyl after hip replacement surgery. There were 20 patients in the fentanyl group and 19 patients in the fentanyl-ropivacaine group. The sample was estimated to demonstrate with 90 % power at a 5 % significance level that the mean fentanyl consumption in the two groups differed by 25 %. Study III started immediately when the patients arrived in the PACU. The patients received a PCA pump, which was programmed to deliver either fentanyl, 10 $\mu g \cdot ml^{-1}$ in the F group, or ropivacaine, 1 $mg \cdot ml^{-1}$, combined with fentanyl 10 $\mu g \cdot ml^{-1}$ in the FR group. The flowchart of administration of the pain medication in the study is presented in Figure 4.

| Group | PACU |
|---|---|
| | 0-20 hours |
| F | PCEA: background infusion of F, 30 $\mu g \cdot h^{-1}$<br>bolus of F, 30$\mu g$, lockout 15 minutes |
| FR | PCEA: background infusion of F, 30 $\mu g \cdot h^{-1}$ and R 3 $mg \cdot h^{-1}$<br>bolus of F, 30 $\mu g$, and R, 3 mg, lockout 15 minutes |
| | Rescue analgesic (pain score > 5 more than 30 minutes):<br>epidural catheter: R bolus of 20 mg |

**Fig. 4. Administration of epidural drugs for pain relief in Study III. F (fentanyl), R (ropivacaine).**

Study IV compared the postoperative analgesia achieved with subacromial bursa block combined with infiltration of the arthroscopic port areas (15 ml of ropivacaine, 5 mg·ml$^{-1}$, n=15, group SUB, or saline, 9 mg·ml$^{-1}$, n=15, group PLA) to that achieved with an interscalene brachial plexus block (15 ml ropivacaine, 5 mg·ml$^{-1}$, n=15, group ISB) after arthroscopic shoulder surgery. The patients in the ISB group also received a subacromial bursa block with saline, 9 mg·ml$^{-1}$ (n=15) (see Figure 5). All medications injected into the subacromial bursa contained 75 μg of adrenaline. The ISB block was performed before general anesthesia, while the patient was awake. A successful sensory block in the shoulder area was verified by the absence of cold sensation. Immediately after arriving into the PACU, the patients received a PCA pump (Abbott Pain Management Provider®, Abbott laboratories, North Chicago, U.S). The pump was programmed to deliver a 2 mg i.v. bolus of oxycodone as rescue medication. The lockout time was 10 minutes and the maximal dose was therefore 12 mg per hour. The nurses in the PACU were advised to give extra 2 mg boluses of oxycodone, if the pain score was high (>7) and PCA-delivered oxycodone was not sufficient during the first hour postoperatively. In addition, all patients received two 100 mg doses of oral ketoprofen at eight-hour intervals. The sample size was estimated to demonstrate with 90 % power at a 5 % significance level that the mean oxycodone consumption differed by 50 % in the ISB and SUB groups compared with the PLA group during the first six postoperative hours.

| Group | | PACU |
|---|---|---|
| ISB | ISB + SUB (saline)<br>ketoprofen 1 mg·kg$^{-1}$ | PCA: Oxycodone, bolus 2 mg<br>ketoprofen 100 mg+100 mg orally |
| SUB | SUB (ropivacaine)<br>ketoprofen 1 mg·kg$^{-1}$ | PCA: Oxycodone, bolus 2 mg<br>ketoprofen 100 mg+100 mg orally |
| PLA | SUB (saline)<br>ketoprofen 1 mg·kg$^{-1}$ | PCA: Oxycodone, bolus 2 mg<br>ketoprofen 100 mg+100 mg orally |

**Fig. 5. The flowchart of trial design in study IV.**

## 4.3 Anesthesia

All patients in Studies I-III were premedicated with oral diazepam 10-15 mg 40-60 minutes before the induction of anesthesia. No premedication was administered to the patients in Study IV.

Patients in Studies I-III received a spinal anesthesia. A bolus dose of 15-20 mg of plain bupivacaine, 5 mg·ml$^{-1}$, was administered into the lumbar 2-3 or 3-4 interspace to achieve the required sensory and motor block for the operation area. A midline or a lateral

puncture was performed in a lateral horizontal position using Quincke spinal needles of size 25 or 27 Gauge. After completion of surgery, all patients were transferred into the PACU.

An epidural catheter for postoperative pain relief was inserted before spinal anesthesia for the patients in Study III. The catheter was inserted about 5 cm into the epidural space at the thoracic 12-lumbar 1 or lumbar 1-2 interspace. A test dose of 3 ml lidocaine, 20 $mg \cdot ml^{-1}$, with adrenaline, 5 $\mu g \cdot ml^{-1}$, was injected to confirm satisfactory placement of the epidural catheter. The epidural catheter was not used during the surgery.

In Study IV operations were performed under standardized general anesthesia. Propofol, 2-3 $mg \cdot kg^{-1}$, and fentanyl, 3 $\mu g \cdot kg^{-1}$, were administered i.v. for the induction of anesthesia and rocuronium, 0.6 $mg \cdot kg^{-1}$, for tracheal intubation. The lungs were ventilated with 70 % nitrous oxide in oxygen and sevoflurane (end-tidal minimal alveolar concentrations 1-1.5) Supplementary doses of fentanyl, 1 $\mu g \cdot kg^{-1}$, were administered to maintain adequate anesthesia if the patient's blood pressure exceeded its preoperative value by 25 % and sevoflurane concentration was at the aforementioned level. All patients received an i.v. ketoprofen bolus of 1 $mg \cdot kg^{-1}$ during surgery. After extubation, patients were transferred into the PACU.

During anesthesia patients received i.v. Ringer acetate (I-III) or saline, 9 $mg \cdot ml^{-1}$, (I-IV) or hydroxyethyl starch (I-III) infusions to maintain adequate blood volume. Packed red cells were given (I-III) if needed to maintain a hemoglobin concentration above 90-100 $g \cdot l^{-1}$.

## 4.4 Subjective assessment of pain relief

The patients assessed their experience of postoperative pain at rest (I, II) by indicating a point on a 10-cm visual analogue scale (VAS) between the extremes 0 cm – no pain and 10 cm – worst pain imaginable at 0, 2, 4, and at 12 hours (I) and at 0, 0.5, 3, 6, 10, 13, and at 16 hours (II). In Studies III-IV the pain intensity was assessed both at rest and on movement with a visual 11-point Box Pain Scale (BS-11) which consisted of 11 numbered boxes (0=no pain, 10=worst pain imaginable) (Jensen *et al.* 1989) at 0, 2, 4, 6, 8, 10, 15, and 20 hours (III) and at 0, 1, 2, 4, 6, 8, and at 20 hours (IV). In Study III pain graphs at rest and on movement were drawn for each patient with BS-11 values on the y-axis and time on x-axis. The area under the curve (AUC) for pain was then calculated using the formula:

$$AUC = \tfrac{1}{2} \sum_{i=0}^{k-1} (t_{i+1}-t_i)(BS\text{-}11_i+BS\text{-}11_{i+1})$$

where $t_i$ is time for measurement point (i=0,…,k).

At the end of the study periods the patients were asked to rate the overall quality of their pain treatment on a four-point scale: 1=excellent/very good, 2=good, 3=fair, 4=poor (I, III). The patients in Study IV were asked to rate their postoperative analgesia on a scale of 1(very poor) to 10 (excellent).

## 4.5 Required doses of fentanyl and oxycodone

The PCA-administered doses of i.v. fentanyl (I, II) or oxycodone (IV), and of epidural fentanyl (III) were measured during and at the end of the study periods.

## 4.6 Motor and sensory block (III)

The extent of the motor and sensory block was assessed at 0, 2, 4, 6, 8, 10, 15, and 20 hours. The motor block was evaluated in the non-operated leg using a modified Bromage scale (0=no motor block, 1=inability to raise an extended leg, 2=inability to flex the knee, 3=inability to flex the ankle joint) (Bromage 1965). The distribution of sensory block was determined bilaterally over all dermatomes as a loss of sharp sensation, using a 22-gauge blunt needle.

## 4.7 Orthostatic test (III)

An orthostatic test was performed at 20 hours if allowed by the patient's clinical condition. The decision to perform the test was made by a doctor blinded to patient allocation. A physiotherapist helped the patient to get up and to stand erect for 2 minutes, during which time continuous heart rate and invasive blood pressure were measured. Thereafter the patient was allowed to lie down. If systolic blood pressure dropped below 80 mmHg, the test was interrupted.

## 4.8 Hemodynamic and respiratory data

Non-invasive arterial blood pressure (I, II, IV), invasive arterial blood pressure (III), heart rate (I-IV), respiratory rate (I-IV) and peripheral blood oxygen saturation (I-IV) were measured during the study. In Study III the patients were connected to a monitor (Datex AS3, Datex-Ohmeda, Helsinki, Finland), which was set to give an alarm when systolic blood pressure fell below 80 mmHg, heart rate below 40 beats·min$^{-1}$, respiratory rate below 6·min$^{-1}$, or oxygen saturation below 90%. Any activated alarm was verified and recorded by the nursing staff. Patients were given supplementary oxygen 2 litres·min$^{-1}$ if oxygen saturation was less than 90% (I-IV).

## 4.9 Sedation, nausea and vomiting

The incidence and severity of postoperative sedation (II-IV), and nausea and vomiting (I-IV) were recorded simultaneously with pain intensity. Sedation was evaluated by a

trained nurse on a scale of 0-3 (II, IV): 0=awake, oriented, 1=asleep, answers questions normally, 2=asleep, but arousable to painful stimuli, 3=asleep, not arousable. In study III a sedation scale of 0-5 was used: 0=oriented and able to initiate conversation, 1=answers questions normally, 2=dozing, 3=asleep, responds to verbal commands, 4=asleep, responds to painful stimulation but not verbal commands, 5=not responsive to painful stimuli. Nausea and vomiting were evaluated on a scale of 0-3 (I, III, IV): 0=no nausea, 1=mild nausea, no medication needed, 2=severe nausea, medication needed, 3=vomiting (I, IV) or 0= no nausea, 1=patient felt dizzy, 2= patient felt sick, 3= patient vomited (III). In Study II a scale of 1-2 for nausea and vomiting was used: 1=yes, 2=no.

## 4.10 Pruritus and pain at infusion site

The incidence of pruritus was evaluated on a scale of 1-2 (1=yes, 2=no)(II) or on a scale of 0-3 (III): 0=no pruritus present, 1=mild, no medication needed, 2=moderate, the patients needs medication, 3=severe, medication ineffective. Pain in the infusion vessel was registered on a verbal scale of 0-2 as: 0=no pain, 1=mild pain, 2=harmful pain and the redness of the infusion site was graded as: 0=no, 1=yes (I). In Study II pain at the infusion site during the bolus dose was graded as: 0=no, 1=yes.

## 4.11 Laboratory assessments and postoperative bleeding

In study I hemoglobin, hematocrit and plasma activated partial thromboplastin time using the Cephotest® (Nycomed Hg), were determined preoperatively, and on the first and second postoperative days. Platelet count, serum urea and serum creatinine were assessed preoperatively and on the second postoperative day.

Samples for arterial blood gas analyses were obtained at 0, 4, 10, 16 and 20 hours in Study III.

Postoperative blood loss was determined by measuring the contents of the suction bottles at the beginning and end of the study (I, II).

## 4.12 Statistical methods

The data are expressed as mean and standard deviation (SD), range, or 95 % confidence interval (CI) for mean, as median and range or as median and 25 and 75 percentiles. The incidences of adverse effects are expressed as accurate number or as the percentual proportion of patients suffering from it.

The statistical analyses were performed using the SPSS® for Windows versions 6.0-10.0 (I-IV). The Chi-squared test was used for discrete demographic parameters. Analysis of variance (ANOVA) was used for the analysis of continuous parameters if the distribution of the variable was normal. Otherwise, the Kruskall-Wallis test was applied,

and when P>0.05, the groups were compared pair-wise using the Mann-Whitney U-test. (Study I, II, IV) In Studies II and III, the Student's t-test for two independent samples was used for continuous parameters. Analysis of variance with repeated measures was used for heart rate, respiratory rate, blood pressure and peripheral oxygen saturation. In all studies, a P value less than 0.05 was considered statistically significant.

# 5 Results

## 5.1 Patients

Of the 255 patients recruited 10 were excluded from the study after randomisation. Three patients were withdrawn from Study I: one patient in the S group did not want to continue the study because of nausea caused by PCA administered fentanyl and two patients in the KP300 group: one needed reoperation and one did not properly understand the instructions concerning the use of PCA device. One patient from the FR group was excluded in Study III due to administration of i.v. opioids for ischemic cardiac pain. Six patients were excluded from Study IV after their arthroscopic procedure was converted to open surgery (two patients in each group).

*Table 2. Patient characteristics, mean (SD), [range].*

| Study | I | II | III | IV |
|---|---|---|---|---|
| Number of patients | 76 | 85 | 39 | 45 |
| ASA | I-II | I-III | I-III | I-II |
| Age (years) | 61 [40,76] | 64 [45,81] | 61 [34,74] | 47 [21,66] |
| Sex female/male | 50/26 | 40/45 | 16/23 | 12/33 |
| Weight (kilograms) | 73 (12) | 77 (14) | 78 (11) | 79 (14) |
| Height (centimeters) | 165 (8) | 167 (9) | 167 (8) | 173 (9) |

## 5.2 Pain at rest

Pain scores at rest in Studies I-IV are presented in Figures 6 and 7. In Study I, those patients receiving a total administered dose of ketoprofen of 300 mg i.v. had the lowest pain scores throughout the study, and this resulted in significant difference at 12 hours postoperatively. In Study II and III no significant differences in pain scores at rest were found between the groups. Postoperative pain scores in the ISB group were lower during the first 4 hours at rest compared with those in the PLA and SUB groups (IV).

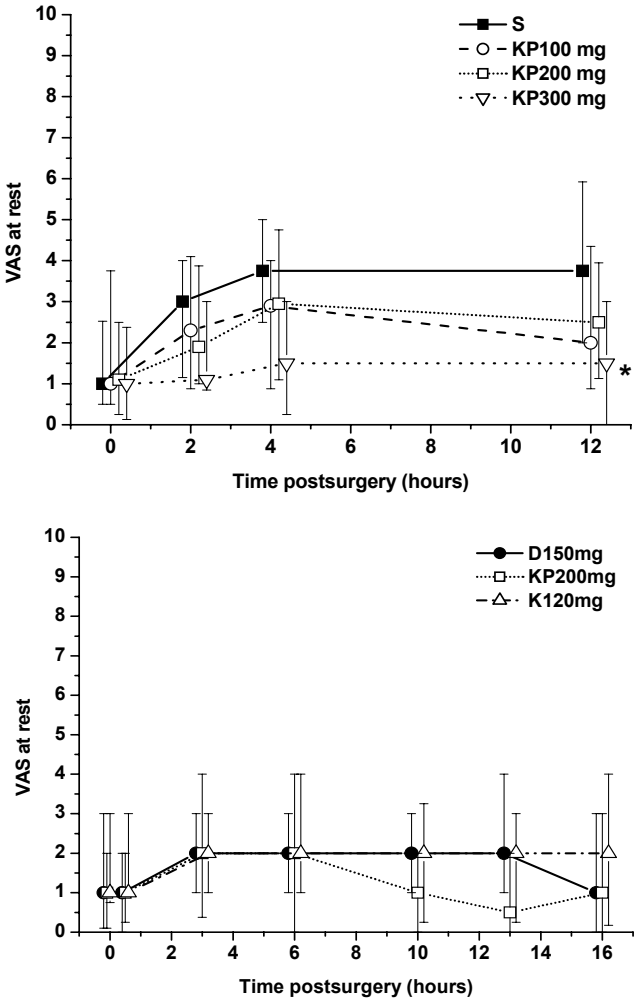



**Fig. 6. Median ($25^{th}$, $75^{th}$ percentiles) postoperative pain scores at rest (Studies I, II). * P<0.05, Mann-Whitney U-test.**

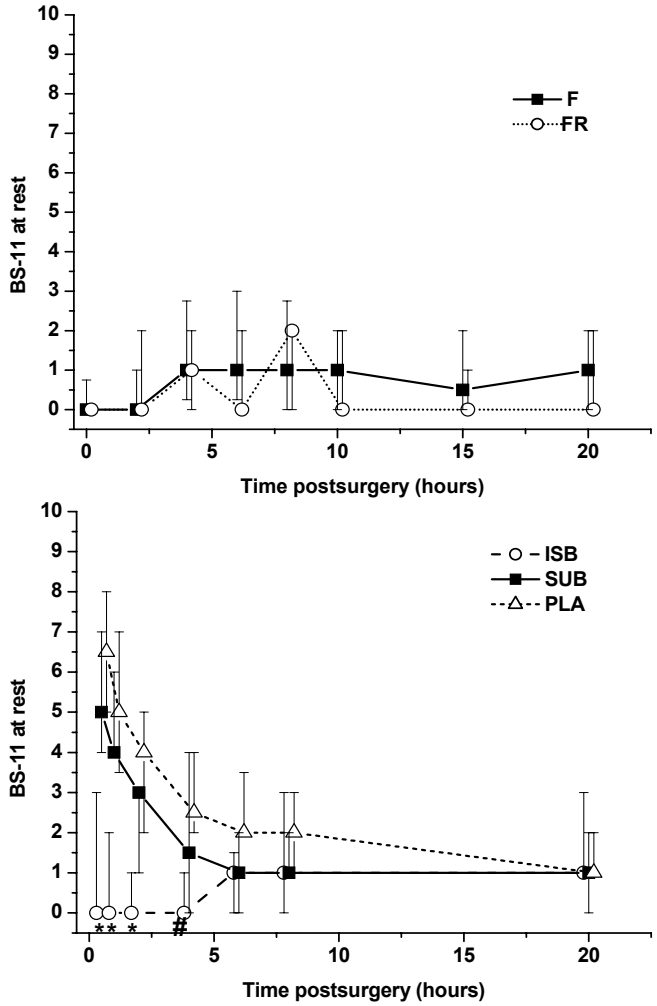



**Fig. 7. Median (25 th, 75 th percentiles) postoperative pain scores at rest (Study III, IV). * P<0.02 ISB vs. SUB, PLA # P=0.013 ISB vs. PLA.**

## 5.3 Pain on movement

Pain scores on movement are presented in Figure 8 (III, IV). The AUC (0,20h) pain values at rest were 27.1 in F group and 21.7 in group FR (P= 0.506, 95% CI of the mean difference from –10 to 21.5), and on movement 61.2 and 45.2 (P=0.246, 95% CI from –11 to 43.4), respectively (III).

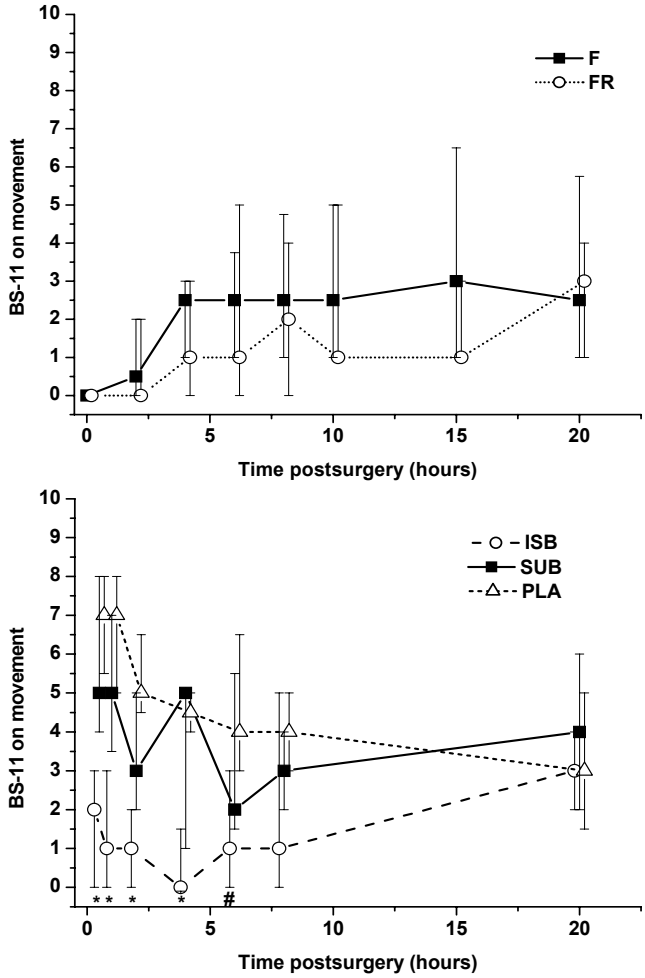



**Fig. 8. Median (25 th, 75 th percentiles) postoperative pain scores on movement (III, IV). * P<0.05 ISB vs. SUB, PLA # P=0.012 ISB vs. PLA.**

## 5.4 Requirements for fentanyl and oxycodone

The patients in the ketoprofen groups (I) required significantly less PCA administered fentanyl than patients in the placebo group. An i.v. dose of 100 mg, 200 mg and 300 mg ketoprofen decreased the need for fentanyl 38%, 44% and 52% respectively compared to placebo. A ketoprofen dose of 300 mg was most effective in decreasing the need for rescue analgesic. No significant difference was found between i.v. administered ketoprofen, diclofenac and ketorolac in fentanyl requirement (II). The mean hourly consumptions of fentanyl were comparable to those measured in Study I. (Table 3) An

addition of ropivacaine, 1 mg·ml$^{-1}$, to epidural fentanyl failed to produce any significant difference in consumption of epidural fentanyl (III) (Table 4). The mean hourly requirement for epidural fentanyl was comparable to the need for i.v. fentanyl in those patients receiving ketoprofen, ketorolac or diclofenac.

*Table 3. The mean (95% CI) consumptions of fentanyl administered intravenously via PCA device in Studies I-II.*

| Group | Study hours | Intravenous fentanyl mg | Intravenous fentanyl µg/h | P-value |
|---|---|---|---|---|
| S (I) | 12 | 1.25 (0.98-1.51) | 104 (82-126) | |
| KP100 (I) | 12 | 0.78 (0.63-0.94) | 65 (52-78) | 0.008 vs. S |
| KP200 (I) | 12 | 0.69 (0.52-0.87) | 58 (43-72) | 0.003 vs. S |
| KP300 (I) | 12 | 0.59 (0.46-0.73) | 50 (38-61) | 0.0002 vs. S, 0.005 vs. KP100 |
| D 150 (II) | 16 | 0.92 (0.70-1.14) | 57 (44-71) | n.s. |
| KP 200 (II) | 16 | 0.85 (0.72-0.97) | 53 (45-61) | |
| K 120 (II) | 16 | 0.89 (0.73-1.04) | 55 (46-65) | |

*Table 4. The mean (95% CI) consumptions of fentanyl administered epidurally via PCA device in Study III.*

| Group | Study hours | Epidural fentanyl mg | Epidural fentanyl µg/h | P-value |
|---|---|---|---|---|
| F (III) | 20 | 1.11 (1.02-1.19) | 55 (51-60) | n.s. |
| FR (III) | 20 | 1.08 (0.94-1.23) | 54 (47-62) | |

The mean cumulative oxycodone consumption (see Figure 9) during the first six hours was significantly lower in the ISB group (6mg, 95% CI for mean 3.4-8.6 mg) than in the SUB group (24.1 mg, 95% CI for mean 17.2-30.9 mg), P=0.001 or in the PLA group (27 mg, 95% CI for mean 18.5- 35.5 mg), P<0.001 and this difference lasted over the entire study period.

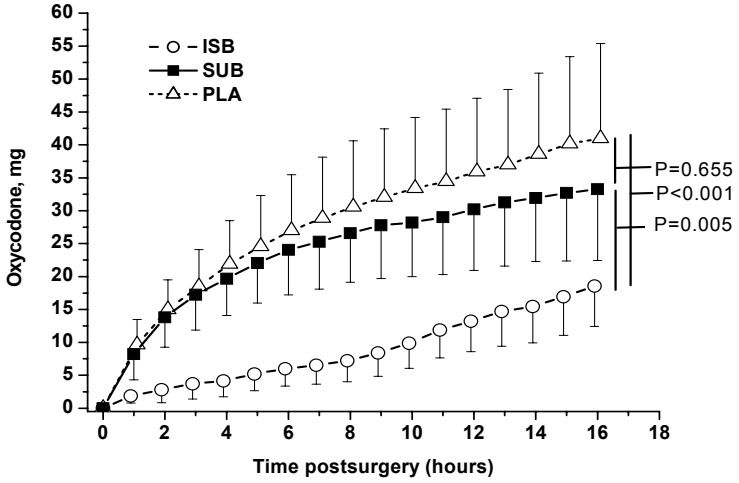



**Fig. 9. Mean (95 % CI) cumulative consumption of oxycodone (IV). Repeated measurements of ANOVA.**

## 5.5 Satisfaction with pain relief

There were no statistically significant differences between the study groups as to satisfaction with pain relief (see Table 5 and 6). The proportion of patients grading their pain relief as excellent or good in study I was 79 % in the placebo group and 84%, 100% and 83% among those patients receiving ketoprofen at 100 mg, 200 mg or 300 mg, respectively. In study II the proportion of patients grading their pain relief as excellent or good was 95% in the F group and 89% in the FR group. The proportion of patients in study IV grading their satisfaction to pain relief as 10 or 9 was 66% in the PLA group, 73% in the SUB group and 87% in the ISB group.

*Table 5. The number of patients grading their postoperative pain relief as excellent, good or fair (I,III).*

| Study | Group (n) | Excellent | Good | Fair | P-value |
|---|---|---|---|---|---|
| I | S (19) | 4 | 11 | 4 | 0.228 |
| I | KP100 (19) | 6 | 10 | 3 | |
| I | KP200 (20) | 10 | 10 | | |
| I | KP300 (18) | 9 | 6 | 3 | |
| III | F (20) | 12 | 7 | 1 | 0.686 |
| III | FR (19) | 13 | 4 | 1 | |

*Table 6. The number of patients grading their postoperative pain relief as 8,9 or 10 (Study IV).*

| Study | Group (n) | 10 | 9 | 8 | P-value |
|---|---|---|---|---|---|
| IV | PLA (15) | 5 | 5 | 3 | 0.920 |
| IV | SUB (13) | 4 | 7 | 2 | |
| IV | ISB (13) | 6 | 7 | 2 | |

## 5.6 Motor and sensory block (III)

The degree of motor block decreased in the F and FR groups during the study. At the time of induction of epidural analgesia, 15% of the patients in the F group and 5% of those in the FR group showed no motor block. At 4 hours, these percentages were 95% and 75%, and at 8 hours 95% and 100%, respectively. After 8 hours, all patients in both groups were free from motor block.

There were no differences between the F and FR group regarding the distribution of sensory block at any time during the study. The median upper segmental level at the beginning of the study was thoracic 4-6 in the F group and thoracic 7-10 in the FR group. The median lower level was lumbar 4- sacral 1 in both groups. At and beyond 4 hours, all patients in both groups had intact cutaneous sensation.

## 5.7 Orthostatic test (III)

There were 8 patients in the F group and ten patients in the FR group whose clinical condition enabled the performance of an orthostatic test. One patient in the FR group had to interrupt the test because of the drop in systolic blood pressure (< 80 mmHg). No intergroup differences were found regarding changes in blood pressure or heart rate (see Table 7).

*Table 7. Mean (SD) systolic blood pressure (SBP) and heart rate (HR) at 0, 1, and 2 minutes during orthostatic test (Study III).*

| Group | SBP 0 | SBP1 | SBP2 | HR0 | HR1 | HR2 |
|---|---|---|---|---|---|---|
| F (n=7) | 143 (29) | 127 (34) | 122 (35) | 80 (16) | 91 (20) | 91 (23) |
| FR (n=10) | 124 (21) | 122 (17) | 120 (19) | 80 (6) | 91 (12) | 88 (9) |

## 5.8 Adverse effects

No patients needed mechanical respiratory support because of excessive respiratory depression. Postoperative arterial carbon dioxide tension values were similar in the F and FR groups, with mean values within the normal range (III). Cardiovascular functions were well maintained in all patients (I-IV). No evidence of excessive sedation existed (II-IV).

The mean amounts of postoperative drainage volume were 688 ml, 667 ml, 607 ml and 414 ml in the S, KP100, KP200 and KP300 groups, respectively (I). The mean drainage volumes in Study II were 795 ml, 725 ml and 798 ml in the K, D and KP groups, respectively. No statistical difference was detected between the groups in either study.

No significant difference was found between the S and KP100, KP200 and KP300 groups in hemoglobin concentrations, platelet counts, activated thromboplastin times, serum creatinine or serum urea concentrations (I).

The overall incidence of postoperative nausea and vomiting varied from 10 to 40 %, but was similar between the groups (I-IV) (see Table 8). The number of patients suffering from pain at infusion site (I, II) or pruritus (II, III) is presented in Table 8.

*Table 8. Patients (%) with adverse effects and complaints about the analgesic therapy during Studies I-IV.*

| Study | Group | $Sa0_2$<90 | Nausea and vomiting | Pain at infusion site | Pruritus |
|---|---|---|---|---|---|
| I | S | 2 (11) | 3 (16) | 4 (21) | - |
| | KP100 | 2 (11) | 4 (21) | 4 (21) | - |
| | KP200 | 0 (0) | 5 (25) | 6 (30) | - |
| | KP300 | 2 (11) | 3 (17) | 7 (39) | - |
| II | KP | 10 (34) | 10 (34) | 3 (10) | 1 (3) |
| | D | 7 (25) | 9 (32) | 4 (14) | 3 (11) |
| | K | 12 (43) | 9 (32) | 1 (4) | 4 (14) |
| III | F | 11 (55) | 2 (10) | - | 8 (40) |
| | FR | 7 (37) | 5 (26) | - | 9 (47) |
| IV | PLA | 0 (0) | 6 (40) | - | - |
| | SUB | 0 (0) | 6 (40) | - | - |
| | ISB | 2 (13) | 5 (33) | - | - |

# 6 Discussion

## 6.1 Ketoprofen, ketorolac and diclofenac

### *6.1.1 Fentanyl-sparing effect*

In the present study, the fentanyl-sparing effect was 38, 44, and 52% in the KP100, KP200, and KP300 groups (I), respectively. The larger the dose of ketoprofen, the better the fentanyl-sparing effect was; no ceiling effect was noticed with the doses used in this study. After cesarean section, a dose response of oral ketoprofen was also observed: a dose of 100 mg provided significantly greater analgesia than one of 50 mg (Sunshine *et al.* 1993). However, after extraction of impacted third molars it has been shown that a ketoprofen dose of 12.5 mg and 25 mg provided similar analgesia, and no additional benefit was obtained by increasing the dose of ketoprofen to 25 mg (Sunshine *et al.* 1998). The extent of prostaglandin synthesis inhibition might be the explanation to this. In an animal study, a dose of 5 $mg \cdot kg^{-1}$ of ketoprofen has produced an 87% inhibition of prostaglandin $E_2$ (Ligumsky *et al.* 1990). It is possible that the doses administered in the present study were not sufficient to completely inhibit inducible PG synthesis after major orthopedic trauma. In a recent study assessing the dose-dependent effects of ketoprofen on the human gastric mucosa in comparison with ibuprofen it was shown that an oral dose of ketoprofen 50 mg three times daily (t.d.s.) suppressed prostaglandin synthesis to a significantly greater extent and caused more gastroduodenal injury than ketoprofen 12.5 mg t.d.s., or ibuprofen 400 mg t.d.s. (Donnelly *et al.* 2000). In the present study, no increase in the incidence of side effects was noticed when increasing the dose of ketoprofen from 100 mg to 300 mg. However, the administration of ketoprofen was very short-term. It might be that increasing the dose of ketoprofen still further would produce better analgesia, but the incidence of renal and gastroduodenal side effects might also increase, as shown in the study reported by Donnelly *et al*. A ceiling analgesic effect has been reported in a meta-analysis assessing the efficacy and safety of NSAIDs in the treatment of cancer pain (Eisenberg *et al.* 1994). In this study, the recommended and supramaximal single doses of NSAIDs produced comparable changes in pain scores,

which indicates a ceiling analgesic effect. The incidence of side effects, however, showed a trend to increase with dose, without a ceiling effect.

The fentanyl-sparing effect of ketoprofen seems to be similar to that reported for other NSAIDs. In the literature on clinical studies, the opioid-sparing effect of NSAIDs have been shown to vary from 30 to 60 % (Rorarius *et al.* 1993, Etches *et al.* 1995, Kinsella *et al*. 1992, Tarkkila & Saarnivaara 1999, Rao *et al*. 2000). These studies include different types of surgical procedures. Laitinen and Nuutinen (1992) reported a fentanyl-sparing effect of 40 % in patients receiving i.v. diclofenac compared with patients in a placebo group after hip replacement surgery.

In Study II, we compared the fentanyl-sparing effect of ketorolac, diclofenac and ketoprofen to each other, a placebo group was not included. The total consumptions of fentanyl in this study in the K120, D150 and KP200 groups were 0.89 mg, 0.92 mg and 0.85 mg, respectively, during the first 16 hours postoperatively with no significant differences between the groups. The mean hourly consumption of fentanyl in all study groups in Study II was comparable to that of all ketoprofen groups measured in Study I. According to these results, ketoprofen, diclofenac and ketorolac each have a similar opioid-sparing effect after hip and knee replacement surgery. In the literature, studies comparing the opioid-sparing effect of i.v. or i.m. administered ketoprofen, ketorolac or diclofenac have conflicting results (see Table 1). After tonsillectomy and maxillofacial surgery diclofenac has decreased the opioid requirement more than ketoprofen (Tarkkila & Saarnivaara 1999, Niemi *et al.* 1995), while after Cesarean section they were equal (Rorarius *et al.* 1993). In most studies, ketorolac has been shown to have an opioid-sparing effect comparable to that of diclofenac (Perttunen *et al.* 1999, O'Hanlon *et al.* 1996, Tarkkila *et al.* 1996, Chui & Gin 1995, Fredman *et al*. 1995), while in one study in pain after arthroscopy, ketorolac was better than diclofenac (Morrow *et al.* 1993).

### *6.1.2 Pain scores*

In Study I, the mean VAS scores were lower throughout the study period in the ketoprofen groups than in the placebo group. A statistically significant difference in VAS scores between the placebo group and the KP300 group was only measured, however, at 12 hours. The results are in accord with those of a study on i.v. diclofenac administered for pain relief after hip replacement surgery (Laitinen & Nuutinen 1992). Even though the mean VAS scores were higher in the placebo group, they were still under 4, which has been considered to indicate mild pain. It may be that this is the level at which side effects of PCA fentanyl are confronted with the level of tolerable pain. Similarly, other investigators have found that patients will remain in mild or even moderate pain without making the maximum number of demands for PCA available to them (Lehmann 1995, Doyle *et al.* 1994, Taylor *et al*. 1996). Kalso *et al*. (1991) also reported that patients did not want more analgesic when the VAS was 33-45 mm after abdominal surgery. On the other hand, a bolus dose of fentanyl may produce a larger drop in VAS scores if an NSAID is administered in addition to fentanyl. NSAIDs may also provide better relief than fentanyl for any possible musculoskeletal pain caused by the lateral position during the operation.

At the beginning of Studies I and II VAS scores were similar and quite low. The explanation for this is that in order to begin the surveys and administer the bolus dose of NSAIDs at the same phase in all patients, we waited until the spinal anesthesia began to withdraw from the operation site.

In study II, all NSAIDs administered offered similar VAS scores. In most studies comparing the analgesic efficacy of NSAIDs in different types of surgery, no significant difference in VAS scores has been found (Tarkkila & Saarnivaara 1999, Rorarius *et al.* 1993, Perttunen *et al.* 1999, O'Hanlon *et al.* 1996, Tarkkila *et al.* 1996, Chui & Gin 1995).

## 6.2 Epidural fentanyl vs. fentanyl-ropivacaine

### *6.2.1 Fentanyl-sparing effect*

Laboratory studies have demonstrated a synergistic analgesic effect of a combination of an epidural opioid and a local anesthetic (Kaneko *et al.* 1994). In Study III, the addition of ropivacaine, 1 $mg \cdot ml^{-1}$, to epidural fentanyl, 10 $\mu g \cdot ml^{-1}$, did not significantly decrease the requirement for fentanyl. One reason for this might be the concentration of epidurally administered fentanyl. The fentanyl concentration of 10 $\mu g \cdot ml^{-1}$ was chosen based on the results of Welshew's study on the optimal concentration of a bolus dose of epidural fentanyl (Welchew 1983). Although this concentration does not necessarily apply to the continuous infusion, it has been widely used in previous studies of postoperative epidural pain relief (e.g. Badner *et al.* 1991, Badner *et al*. 1994, Paech & Westmore 1994, Salomäki *et al*. 1995). The continuous hourly dose of epidural fentanyl was 30 µg, which is quite low, however, if used as the sole analgesic for postoperative pain relief (Peng & Sandler 1999). The continuous fentanyl dose was not sufficient, as all patients required bolus doses of epidural fentanyl.

To the author's knowledge, there are no other studies in the literature evaluating on whether the addition of ropivacaine to epidural fentanyl offers any benefit. The explanation for this might be due to the discussion on whether the epidural administration of fentanyl results in systemic (Glass *et al*. 1992, Loper *et al*. 1990) or segmental analgesia (Gourlay *et al*. 1989, Coda *et al.* 1994, Cooper *et al.* 1995, Liu *et al.* 1996), or in both. In an editorial of the British Journal of Anesthesia, Chrubasik and Chrubasik wrote that the serum concentrations of opioids (except morphine and pethidine) and the quality of postoperative analgesia are the same using both the epidural and i.v. routes during continuous administration (Chrubasik & Chrubasik 1995). In the present study, the requirement for intravenous PCA fentanyl in the placebo group (Study I) was higher than the requirement for epidurally administered PCA-fentanyl in the F group (Study III) after hip replacement surgery (88 $\mu g \cdot h^{-1}$, and 55 $\mu g \cdot h^{-1}$, respectively).

### *6.2.2 Pain scores*

The BS-11 scores were measured both at rest and on movement in Study III with no significant differences between the F and FR groups. Patients undergoing hip replacement surgery are not usually mobile during the first 24 hours, so pain scores were obtained on passive movement of the operated leg. Even though BS-11 scores were higher on movement than at rest in both groups, the median values were still below three. Explanation for the higher pain scores on movement might be that the patients were not able to take a bolus from PCA pump in advance, as they were not aware of the timetable for assessing pain scores. The duration of movement was very short, so the pain period caused by this movement was probably also short. BS-11 scores on movement had a tendency to be higher in the F group than in the FR group, but no statistical difference was found in AUC pain between the groups. It might be that the addition of ropivacaine could offer some benefit in pain control during mobilisation. BS-11 scores at rest from Study III are similar when compared with the VAS scores in Studies I and II. It would therefore seem that the same level of pain relief could be achieved using either method. There is a lack of studies in the literature comparing the analgesia achieved by NSAIDs combined with PCA opioid to that achieved by PCEA.

### *6.2.3 Motor block and orthostatic test*

The addition of a local anesthetic to epidural opioid has been shown to produce various degrees of motor block depending on concentration and the volume administered. This motor block may hinder the mobilisation of the patients and there are therefore a good deal of studies attempting to determine an ideal mixture of opioid and local anesthetic. Badner *et al.* (1996) reported that ropivacaine 1 and 2 $mg \cdot ml^{-1}$ produced similar sensory anesthesia with less motor blockade than the 3 $mg \cdot ml^{-1}$ concentration. Results from another study show that ropivacaine 2 $mg \cdot ml^{-1}$ produces a higher degree of motor block than ropivacaine 1 or 0.5 $mg \cdot ml^{-1}$ (Liu *et al.* 1999). Kampe *et al*. (1999) assessed the motor block produced by an epidural bolus of 15 ml of ropivacaine, 7.5 $mg \cdot ml^{-1}$, continued with an infusion of ropivacaine, 1 $mg \cdot ml^{-1}$, at a rate of 5-9 $ml \cdot h^{-1}$ after total hip replacement surgery (n=15). The motor block resolved rapidly, with only two patients experiencing a grade 2 motor block on a modified Bromage scale at 4 hour, and one patient a grade 3 motor block. This reported motor block at 4 hours is most likely a consequence of prolonged duration of the bolus dose of ropivacaine, 7.5 $mg \cdot ml^{-1}$, epidurally administered at the beginning of the operation. The results concerning the motor block in our study are in accord with these above mentioned. All patients were free from motor block after 8 hours. The hip arthroplasty in our study was performed under spinal anesthesia, and the motor block seen during the first four hours postoperatively was most likely a residual effect of the spinal anesthesia.

Similarly to bupivacaine (Leith *et al.* 1994), ropivacaine causes hypotension in a dose-dependent manner (Schug *et al.* 1996). An orthostatic test was performed in Study III to determine whether or not the epidurally administered doses of ropivacaine were large enough to cause postural hypotension on the first postoperative morning. Postural

hypotension is not desirable as it can hinder mobilisation. The orthostatic test in the present study was performed in a way which simulates the normal clinical mobilisation routine (short orthostatic test, Piha 1994). In a normal reaction over the first three minutes, the SBP should remain constant and HR should increase by about ten beats per minute. In a vasovagal reaction, the SBP and HR should both decrease. In the present study, only one patient in the FR group suffered a vasovagal reaction with a systolic blood pressure below 80 mmHg and the test had to be interrupted. However, the number of patients participating in this test was small.

## 6.3 Subacromial bursa block vs. interscalene brachial plexus block

Shoulder surgery is often associated with severe postoperative pain and all the methods available to solve this important problem must be evaluated. The ISB alone or in combination with general anesthesia is highly suitable for surgery of the upper extremity and particularly for shoulder surgery (e.g. Tuominen *et al.* 1987b, Sandin *et al.* 1992). A single bolus injection of 30 ml of ropivacaine 5 $mg \cdot ml^{-1}$ or 7.5 $mg \cdot ml^{-1}$ as an ISB has been shown to provide good analgesia for 10 to 12 hours (Klein *et al.* 1998). Krone *et al.* (2001) reported that analgesia after an ISB with 10 ml of ropivacaine 2.5 $mg \cdot ml^{-1}$ or 5 $mg \cdot ml^{-1}$ lasted 10 hours. This is in accord with our results. The mean pain scores in our study were 0 at rest during the first 4 hours, remaining below 2 for the 20 hour study period. Good analgesia is achieved by blocking the axillary nerve via the interscalene brachial plexus block. As there is a possibility of serious adverse effects with this technique, however, such as nerve damage (Barutell *et al.* 1980, Walton *et al.* 2000, Borgeat *et al.* 2001), diaphragmatic paralysis (Urmey *et al.* 1991, Pere *et al.* 1992) unintentional intravenous, intra-arterial (Tuominen *et al.* 1991), epidural (Mahoudeau *et al.* 1995) and subdural injection (Tetzlaff *et al.* 1994), alternative methods for pain relief have been researched.

The SUB with local anesthetic containing adrenaline is widely performed by orthopedic surgeons during arthroscopic shoulder surgery to hinder perioperative bleeding and to reduce postoperative pain. Scientific evaluation of the analgesic effect of SUB, however, has been meagre and controversial. In the present study, SUB decreased the dose of PCA-delivered oxycodone by 11 % only compared to a placebo during the 20 hour study period, while ISB decreased it by 78 %. Some analgesic effect was seen, however, as the pain scores were lower at any measurement in the SUB group than in the PLA group, although this difference was not statistically significant. It seems that an injection of a local anesthetic into the subacromial space produces some analgesia via peripheral nerve endings, but the quality of this analgesia is much lower than that achieved by blocking the axillary nerve via ISB. According to our results, ISB with even a low dose of ropivacaine effectively relieves early postoperative pain and reduces the need for opioids more than SUB and should be the first choice for pain relief after shoulder surgery whenever possible.

## 6.4 Adverse effects

The most important possible adverse effects induced by NSAIDs are renal insufficiency and perioperative bleeding during short-term, postoperative use. A recent meta-analysis showed that NSAIDs cause a clinically unimportant reduction in renal function on the first day after surgery in patients with normal preoperative renal function (Lee *et al*. 1999) In a study with 11245 patients reported by Forrest *et al.* (2002) the incidence of acute renal failure was 0.1 % after administration of ketorolac, diclofenac or ketoprofen for postoperative pain relief. In the present study, as is presumable, no signs of renal insufficiency were noted (I, II). Postoperatively measured blood loss was also similar between the patients receiving NSAIDs or saline. The sample size in these studies was, however, too small to show any significant differences in adverse effects with this low incidence.

Severe respiratory depression is a dreaded complication with opioids administered for postoperative pain relief. The measurement of respiratory depression is often difficult. Respiratory rate measurement is easy to perform, but it has been shown to be a relatively poor indicator by itself. In a study reported by Whipple *et al.* (1994) only half of the narcotic overdose patients had a respiratory rate below 8 breaths per minute, but all overdose patients showed a decrease in mental status. Continuous pulse oximetry (Leino *et al*. 1999) is a more sensitive method than respiratory rate alone, but easily produces false alarms, especially if the patient is moving or sleeping. The false alarms are rather annoying to the patients, for which reason this method is somewhat impractical on the ward. All these methods were in use in the present study, and no severe respiratory depression was noted. The number of patients with a peripheral oxygen saturation below 90 % varied somewhat between the substudies, but no intergroup differences were found within a discrete study. The variation may simply be a result of different timetables for the measurements in each study. Intermittent blood gas analyses were used in study III with no signs of respiratory depression.

Postoperative nausea and vomiting (PONV) in addition to pain is the most frequent complication in the patients' perceptions of their previous postoperative symptoms. The use of opioids, female gender, a longer duration of surgery, a previous history of PONV, a history of motion sickness and non-smoking have been suggested as probable reasons or predictive characteristics associated with an increased risk for PONV (Cohen *et al.* 1994, Koivuranta *et al.* 1997). The type of anesthesia also affects the risk, the incidence of PONV following regional anesthesia being generally lower than that observed with general anesthesia techniques (Cohen *et al.* 1994). The incidence in the present study varied from 10 to 34 % in operations performed under regional anesthesia (I, II, III) and from 33 to 40 % in operations performed under general anesthesia (IV) with no intergroup differences in separate studies. Even though the ISB group required significantly less postoperative opioid than the other two groups, no significant reduction in PONV was seen (IV). The incidence of PONV seen in the present study is in accord with those reported in the literature.

## 6.5 Research methodology

Studies I, II, III were performed in a prospective, randomised, and double-blind fashion with a standardised technique for spinal anesthesia. Study I was placebo-controlled. A placebo group in Study II was not considered to be necessary, as the study compared the pain relief achieved with different NSAIDs. A placebo group was not included in Study III, as the main interest was to evaluate whether the addition of local anesthetic to epidural fentanyl offers any benefit in pain relief. In these three studies analgesics other than the study drugs were not allowed during the study in order to confirm that any possible differences observed were the result of differences in effect of study drugs and not a result of other rescue analgesics.

Study IV was performed in a prospective and randomised fashion. The SUB was performed in a double-blind manner with saline or ropivacaine, but the ISB was performed openly. The ISB should not be performed during general anesthesia, as unintentional intravenous, intra-arterial or epidural injection would be difficult to detect. On the other hand, performing the ISB with saline alone is not ethically recommendable as there is always a risk of neural deficit. In this study, SUB was compared to the golden standard, ISB, on the one hand and to a placebo on the other.

The sample sizes in Studies II, III and IV were determined according to power analysis.

### *6.5.1 The choice of patient-controlled analgesic*

Measuring the amount of rescue analgesic required to treat postoperative pain can be used for the assessment and comparison of the pain relief effect of the analgesics or regional analgesia techniques. Because the PCA allows patients to titrate the dose of analgesic needed for adequate pain relief by themselves, it has been widely used for research in postoperative pain (e.g. Scott *et al.* 1995, Turner *et al.* 1996, Laitinen & Nuutinen 1992). In the present study, PCA (I, II, IV) and PCEA (III) techniques were used for comparisons of pain relief of different regimens. All patients were preoperatively instructed in the use of a PCA or PCEA pump.

In many studies, morphine has been the opioid used for PCA-delivered rescue analgesic. However, recent studies have suggested that NSAIDs may reduce morphine requirements by reducing the excretion of the active metabolite, morphine-6-glucuronide. The morphine-sparing effect may not result in parallel reductions in opioid-related adverse effects (Tighe *et al.* 1999). Fentanyl has inactive metabolites and minimal renal excretion, and because of these properties it may be a more suitable rescue analgesic than morphine for studies assessing the analgesic and adverse effects of NSAIDs (I, II).

Oxycodone was chosen for PCA-delivered rescue analgesic instead of morphine in Study IV for several reasons. Oxycodone has been our routine opioid for postoperative pain relief and in postoperative patient-controlled analgesia oxycodone has been shown to be equipotent to morphine with no differences in side effects (Silvasti et al. 1998). The pharmacokinetics of oxycodone seems to be comparable to those of morphine (Pöyhiä *et*

*al.* 1993). Hallucinations may, however, occur less frequently with oxycodone than with morphine (Kalso & Vainio 1990).

## 6.6 Clinical implications

Patients are usually concerned about postoperative pain, and may find it frightening and distressing before, during, and after the operation. Surgery and pain cause many types of endocrine, metabolic and inflammatory responses, which may increase postoperative morbidity and mortality, especially among elderly patients with chronic diseases, e.g. cardiovascular. Excessive pain at the operation area can also be harmful to mobilization and rehabilitation.

Postoperative pain after hip and knee replacement surgery can be effectively relieved with a combination of NSAID and PCA-delivered fentanyl or with epidurally administered fentanyl alone or combined with ropivacaine. The new COX-2 inhibitors appear to have only minor effect on hemostasis with an analgesic effect similar to that of the older NSAIDs, which is why investigations as to their effectiveness in pain relief after joint surgery are warranted. Pain after shoulder surgery usually varies from moderate to severe. It can be effectively managed with an interscalene brachial plexus block using a low dose of ropivacaine, when surgery is performed under general anesthesia.

# 7 Conclusions

1. An intravenous dose of 100 mg, 200 mg and 300 mg of ketoprofen decreased the requirement for PCA-delivered fentanyl by 38%, 45% and 53 %, respectively compared to a placebo, when administered for pain after hip and knee replacement surgery. Postoperative pain scores at rest were lower in all the ketoprofen groups compared with placebo, but a significant difference was found only between the patients receiving 300 mg of ketoprofen and those receiving a placebo. The incidence of postoperative nausea and vomiting varied from 16 to 25 % with no intergroup differences. No serious adverse effects were noted.
2. The fentanyl-sparing effect of intravenously administered ketoprofen increased in a dose-dependent manner without a noticeable ceiling-effect.
3. Intravenous doses of 200 mg of ketoprofen, 150 mg of diclofenac, and 120 mg of ketorolac produced similar postoperative pain scores and requirement for PCA-delivered fentanyl with no intergroup differences in adverse effects, when administered for pain relief after hip replacement surgery. Adverse effects consisted mainly of postoperative nausea and vomiting at an incidence of 32-34 %.
4. The addition of ropivacaine 1 $mg \cdot ml^{-1}$ did not decrease the requirement for fentanyl, when administered epidurally via a PCA device for pain relief after hip replacement surgery.
5. A subacromial bursa block with ropivacaine had only a minor effect on postoperative analgesia after arthroscopic shoulder surgery, with no significant differences to that achieved with an injection of saline, whereas an interscalene brachial plexus block effectively relieved early postoperative pain.

# References


Abouleish EI, Elias M & Nelson C (1998) Ropivacaine-induced seizure after extradural anaesthesia. Br J Anaesth 80: 843–844.

Advenier C, Roux A, Gobert C, Massias P, Varoquaux O & Flouvat B (1983) Pharmacokinetics of ketoprofen in the elderly. Br J Clin Pharmacol 16: 65-70.

Al-Khafaji JM & Ellias MA (1986) Incidence of Horner syndrome with interscalene brachial plexus block and its importance in the management of head injury. Anesthesiology 64: 127.

Attal N, Kayser V, Eschalier A, Benoist JM & Guilbaud G (1988) Behavioural and electrophysiological evidence for an analgesic effect of a non-steroidal anti-inflammatory agent, sodium diclofenac. Pain 35: 341-348.

Badner NH, Bhandari R & Komar WE (1994) Bupivacaine 0.125% improves continuous postoperative epidural fentanyl analgesia after abdominal or thoracic surgery. Can J Anaesth 41: 387-392.

Badner NH & Komar WE (1992) Bupivacaine 0.1% does not improve post-operative epidural fentanyl analgesia after abdominal or thoracic surgery. Can J Anaesth 39: 330-336.

Badner NH, Reid D, Sullivan P, Ganapathy S, Crosby ET, McKenna J & Lui A (1996) Continuous epidural infusion of ropivacaine for the prevention of postoperative pain after major orthopaedic surgery: a dose-finding study. Can J Anaesth 43: 17-22.

Badner NH, Reimer EJ, Komar WE & Moote CA (1991) Low-dose bupivacaine does not improve postoperative epidural fentanyl analgesia in orthopedic patients. Anesth Analg 72: 337-341.

Ballantyne JC, Carr DB, Chalmers TC, Dear KB, Angelillo IF & Mosteller F (1993) Postoperative patient-controlled analgesia: meta-analyses of initial randomized control trials. J Clin Anesth 5: 182-93.

Baird M & Schug SA (1996) Safety aspects of postoperative pain relief. Pain Digest 6: 219-225.

Barutell C, Vidal F, Raich M & Montero A (1980) A neurological complication following interscalene brachial plexus block. Anaesthesia 35: 365-367.

Berti M, Casati A, Fanelli G, Albertin A, Palmisano S, Danelli G, Comotti L & Torri G (2000) 0.2% ropivacaine with or without fentanyl for patient-controlled epidural analgesia after major abdominal surgery: a double-blind study. J Clin Anesth 12: 292-297.

Bertini L, Mancini S, Di Benedetto P, Ciaschi A, Martini O, Nava S & Tagariello V (2001) Postoperative analgesia by combined continuous infusion and patient-controlled epidural analgesia (PCEA) following hip replacement: ropivacaine versus bupivacaine. Acta Anaesthesiol Scand 45: 782-785.

Blair B, Rokito AS, Cuomo F, Jarolem K & Zuckerman JD (1996) Efficacy of injections of corticosteroids for subacromial impingement syndrome. J Bone Joint Surg - Am 78: 1685-1689.

Borgeat A, Ekatodramis G, Kalberer F & Benz C (2001) Acute and nonacute complications associated with interscalene block and shoulder surgery: a prospective study. Anesthesiology 95: 875-880.

Borgeat A, Schappi B, Biasca N & Gerber C (1997) Patient-controlled analgesia after major shoulder surgery: patient-controlled interscalene analgesia versus patient-controlled analgesia. Anesthesiology 87: 1343-1347.

Bosek V & Miguel R (1994) Comparison of morphine and ketorolac for intravenous patient-controlled analgesia in postoperative cancer patients. Clin J Pain 10: 314-318.

Boulanger A, Choiniere M, Roy D, Boure B, Chartrand D, Choquette R & Rousseau P (1993) Comparison between patient-controlled analgesia and intramuscular meperidine after thoracotomy. Can J Anaesth 40(5 Pt 1): 409-415.

Bricker SRW, Savage ME & Hanning CD (1987) Perioperative blood loss and non-steroidal anti-inflammatory drugs: an investigation using diclofenac in patients undergoing transurethral resection of the prostate. Eur J Anaesthesiol 4: 429-434.

Bridenbaugh LD (1983) Regional anaesthesia for outpatient surgery--a summary of 12 years' experience. Canadian Anaesthetists' Society Journal 30: 548-552.

Brocks DR & Jamali F (1992) Clinical pharmacokinetics of ketorolac tromethamine. Clin Pharmacokinet 23: 415-427.

Brodner G, Pogatzki E, Van Aken H, Buerkle H, Goeters C, Schulzki C, Nottberg H & Mertes N (1998) A multimodal approach to control postoperative pathophysiology and rehabilitation in patients undergoing abdominothoracic esophagectomy. Anesth Analg 86: 228-234.

Bromage PR (1965) A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand 20: 55-69.

Bruster S, Jarman B, Bosanquet N, Weston D, Erens R & Delbanco TL (1994) National survey of hospital patients. BMJ 309 :1542-1546.

Buggy DJ, Hall NA, Shah J, Brown J & Williams J (2000). Motor block during patient-controlled epidural analgesia with ropivacaine or ropivacaine/fentanyl after intrathecal bupivacaine for caesarean section. Br J Anaesth 85: 468-470.

Casati A, Fanelli G, Albertin A, Deni F, Anelati D, Antonino FA & Beccaria P (2000) Interscalene brachial plexus anesthesia with either 0.5% ropivacaine or 0.5% bupivacaine. Minerva Anestesiologica 66: 39-44.

Casati A, Fanelli G, Magistris L, Beccaria P, Berti M & Torri G (2001) Minimum local anesthetic volume blocking the femoral nerve in 50% of cases: a double-blinded comparison between 0.5% ropivacaine and 0.5% bupivacaine. Anesth Analg 92: 205-208.

Cepeda MS, Vargas L, Ortegon G, Sanchez MA & Carr DB (1995) Comparative analgesic efficacy of patient-controlled analgesia with ketorolac versus morphine after elective intraabdominal operations. Anesth Analg 80: 1150-1153.

Chrubasik S & Chrubasik J (1995) Selection of the optimum opioid for extradural administration in the treatment of postoperative pain. Br J Anaesth 74: 121-122.

Chui PT & Gin T (1995) A comparison between ketorolac and diclofenac in laparoscopic sterilization. Eur J Anaesth 12: 597-601.

Citron ML, Johnston-Early A, Boyer M, Krasnow SH, Hood M & Cohen MH (1986) Patient-controlled analgesia for severe cancer pain. Arch Intern Med 146: 734-736.

Clive D & Stoff J (1984) Renal syndromes associated with nonsteroidal anti-inflammatory. N Engl J Med 310: 563-572.

Coda BA, Brown MC, Schaffer R, Donaldson G, Jacobson R, Hautman B & Shen DD (1994) Pharmacology of epidural fentanyl, alfentanil, and sufentanil in volunteers. Anesthesiology 81: 1149-1161.

Cohen MM, Duncan PG, DeBoer DP & Tweed WA (1994) The postoperative interview: assessing the risk factors for nausea and vomiting. Anesth Analg 78: 7-16.

Cooper DW, Ryall DM & Desira WR (1995) Extradural fentanyl for postoperative analgesia: predominant spinal or systemic action? Br J Anaesth 74: 184-187.

Debruyne D, Hurault de Ligny B, Ryckelynck JP, Albessard F & Moulin M (1987) Clinical pharmacokinetics of ketoprofen after single intravenous administration as a bolus or infusion. Clin Pharmacokinet 12: 214-212.

de Nadal M, Agreda G, Massenet S, Salgado I, Lacasta A, Cabre B & Gancedo VA (1998) Efficacy of bupivacaine infiltration upon postoperative pain after ambulatory shoulder arthroscopy under general anaesthesia. Br J Anaesth 80 (Suppl 1): A595.

Donnelly MT, Richardson P, Hawkey CJ, Courtauld E & Stack WA (2000) Dose-dependent effects of ketoprofen on the human gastric mucosa in comparison with ibuprofen. Aliment Pharm Therap 14: 543-549.

Doyle E, Mottart KJ, Marshall C & Morton NS (1994) Comparison of different bolus doses of morphine for patient-controlled analgesia in children. Br J Anaesth 72: 160-163.

Doyle J & Vicente KJ (2001) Electrical short circuit as a possible cause of death in patients on PCA machines: report on an opiate overdose and a possible preventive remedy. Anesthesiology 94: 940.

Eisenberg E, Berkey CS, Carr DB, Mosteller F & Chalmers TC (1994) Efficacy and safety of nonsteroidal anti-inflammatory drugs for cancer pain: a meta-analysis. J Clin Oncol 12: 2756-2765.

Etches RC, Sandler AN & Daley MD (1989) Respiratory depression and spinal opioids. Can J Anaesth 36: 165-185.

Etches RC, Warriner CB, Badner N, Buckley DN, Beattie WS, Chan VW, Parsons D & Girard M (1995) Continuous intravenous administration of ketorolac reduces pain and morphine consumption after total hip or knee arthroplasty. Anesth & Analg 81: 1175-1180.

Forrest JB, Camu F, Greer IA, Kehlet H, Abdalla M, Bonnet F, Ebrahim S, Escolar G, Jage J, Pocock S, Velo G, Langman MJS, Bianchi Porro G, Samama MM & Heitlinger E (2002) Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. Br J Anaesth 88: 227-233.

Frank M, McAteer EJ, Cattermole R, Loughnan B, Stafford LB & Hitchcock AM (1987) Nalbuphine for obstetric analgesia. A comparison of nalbuphine with pethidine for pain relief in labour when administered by patient-controlled analgesia (PCA). Anaesthesia 42: 697-703.

Fredman B, Olsfanger D & Jedeikin R (1995) A comparative study of ketorolac and diclofenac on post-laparoscopic cholecystectomy pain. Eur J Anaesth 12: 501-504.

Fredman B, Zohar E, Tarabykin A, Shapiro A & Jedeikin R (2000) Continuous intravenous diclofenac does not induce opioid-sparing or improve analgesia in geriatric patients undergoing major orthopedic surgery. J Clin Anesth 12: 531-536.

Gerber C, Galantay RV & Hersche O (1998) The pattern of pain produced by irritation of the acromioclavicular joint and the subacromial space. J Shoulder Elb Surg 7: 352-355.

Gillis JC & Brodgen RN (1997) Ketorolac. A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. Drugs 53: 139-188.

Glass PSA, Estok P, Ginsberg B, Golberg JS & Sladen RN (1992) Use of patient-controlled analgesia to compare the efficacy of epidural to intravenous fentanyl administration. Anesth Analg 74: 345-351.

Gold MS, Reichling DB, Shuster MJ & Levine JD (1996) Hyperalgesic agents increase a tetradotoxin-resistant Na+ current in nociceptors. Proc Natl Acad Sci USA 93:1108-1112.

Gourlay GK, Cherry DA, Plummer JL, Armstrong PJ & Cousins MJ (1987) The influence of drug polarity on the absorption of opioid drugs into CSF and subsequent cephalad migration following lumbar epidural administration: application to morphine and pethidine. Pain 31: 297-305.

Gourlay GK, Murphy TM, Plummer JL, Kowalski SR, Cherry DA & Cousins MJ (1989) Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. Pain 38: 253-259.

Grant RP, Dolman JF, Harper JA, White SA, Parsons DG, Evans KG & Merrick CP (1992) Patient-controlled lumbar epidural fentanyl compared with patient-controlled intravenous fentanyl for postthoracotomy pain. Can J Anaesth 39: 214-219.

Henry D, Page J, Whyte I, Nanra R & Hall C (1997) Consumption of nonsteroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects. Results of a case-control study. Br J Clin Pharmacol 44: 85-90.

Hernandez-Diaz S & Garcia-Rodriquez LA (2001) Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. Am J Med 110: 20-27.

Herrero JF, Parrado A & Cervero F (1997) Central and peripheral actions of the NSAID ketoprofen on spinal cord nociceptive reflexes. Neuropharmacology 36: 1425-1431.

Hodgson PS & Liu SS (2001) A comparison of ropivacaine with fentanyl to bupivacaine with fentanyl for postoperative patient-controlled epidural analgesia. Anesth Analg 92: 1024-1028.

Howell PR, Gambling DR, Pavy T, McMorland G & Douglas MJ (1995) Patient-controlled analgesia following Caesarean section under general anaesthesia: a comparison of fentanyl with morphine. Can J Anaesth 42: 41-45.

Ishizaki T, Sasaki T, Suganuma T, Horai Y, Chiba K, Watanabe M, Asuke W & Hoshi H (1980) Pharmacokinetics of ketoprofen following single oral, intramuscular and rectal doses and after repeated oral administration. Eur J Clin Pharmacol 18: 407-414.

Jamali F & Brocks DR (1990) Clinical pharmacokinetics of ketoprofen and its enantiomers. Clin Pharmacokinet 19: 197-217.

Jensen MP, Karoly P, O'Riordan EF, Bland F Jr & Burns RS (1989) The subjective experience of acute pain. An assessment of the utility of 10 indices. Clin J Pain 5: 153-159.

Jensen MP, Turner JA & Romano JM (1994) What is the maximum number of levels needed in pain intensity measurement? Pain 58: 387-392.

Jorgensen H, Fomsgaard JS, Dirks J, Wetterslev J & Dahl JB (2000) Effect of continuous epidural 0.2% ropivacaine vs 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy. Br J Anaesth 84: 144-150.

Joyce CR, Zutshi DW, Hrubes V & Mason RM (1975) Comparison of fixed interval and visual analogue scales for rating chronic pain. Eur J Clin Pharmacol 8: 415-420.

Kalso E, Pöyhiä R, Onnela P, Linko K, Tigerstedt I & Tammisto T (1991) Intravenous morphine and oxycodone for pain after abdominal surgery. Acta Anaesthesiol Scand 35: 642-646.

Kalso E & Vainio A (1990) Morphine and oxycodone hydrochloride in the management of cancer pain. Clin Pharmacol Ther 47: 639-646.

Kampe S, Weigand C, Kaufmann J, Klimek M, Konig DP & Lynch J (1999) Postoperative analgesia with no motor block by continuous epidural infusion of ropivacaine 0.1 % and sufentanil after total hip replacement. Anesth Analg 89: 395-398.

Kaneko M, Saito Y, Kirihara Y, Collins JG & Kosaka Y (1994) Synergistic antinociceptive interaction after epidural coadministration of morphine and lidocaine in rats. Anesthesiology 80: 137-150.

Kantor TG (1986) Use of diclofenac in analgesia. Am J Med 80(4B): 64-9.

Kehlet H (1997) Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth 78: 606-617.

Kehlet H & Dahl JB (1992) Are perioperative nonsteroidal anti-inflammatory drugs ulcerogenic in the short-term. Drugs 44 (Suppl 5): S38-41.

Kenny GN (1992) Potential renal, haematological and allergic adverse effects associated with nonsteroidal anti-inflammatory drugs. Drugs 44 (Suppl 5): S31-37.

Kinsella J, Moffat AC, Patrick JA, Prentice JW, McArdle CS & Kenny GN (1992) Ketorolac trometamol for postoperative analgesia after orthopaedic surgery. Br J Anaesth 69: 19-22.

Kleiman RL, Lipman AG, Hare BD & MacDonald SD (1988) A comparison of morphine administered by patient-controlled analgesia and regularly scheduled intramuscular injection in severe, postoperative pain. J Pain Sympt Manage 3: 15-22.

Klein SM, Greengrass RA, Steele SM, D'Ercole FJ, Speer KP, Gleason DH, DeLong ER & Warner DS (1998) A comparison of 0.5% bupivacaine, 0.5% ropivacaine, and 0.75% ropivacaine for interscalene brachial plexus block. Anesth Analg 87: 1316-1319.

Knudsen K, Beckman Suurküla M, Blomberg S, Sjövall J & Edvardsson N (1997) Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine, and placebo in volunteers. Br J Anaesth 78: 507–514.

Koivuranta M, Läärä E, Snåre L & Alahuhta S (1997) A survey of postoperative nausea and vomiting. Anaesthesia 52: 443-449.

Korman B & Riley RH (1997) Convulsions induced by ropivacaine during interscalene brachial plexus block. Anesth Analg 85: 1128-1129.

Krone SC, Chan VW, Regan J, Peng P, Poate EM, McCartney C & Miniaci A (2001) Analgesic effects of low-dose ropivacaine for interscalene brachial plexus block for outpatient shoulder surgery-a dose-finding study. Reg Anesth Pain Med 26: 439-443.

Kuhn S, Cooke K, Collins M, Jones JM & Mucklow JC (1990) Perceptions of pain relief after surgery. BMJ 300: 1687-1690.

Kurumbail RG, Stevens AM, Gierse JK, McDonald JJ, Stegeman RA, Pak JY, Gildehaus D, Miyashiro JM, Penning TD, Seibert K, Isakson P & Stallings WC (1996) Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents. Nature 384: 644-648.

Laitinen J & Nuutinen L (1992) Intravenous diclofenac coupled with PCA fentanyl for pain relief after total hip replacement. Anesthesiology 76: 194-198.

Langman MJ, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RF, Murphy M, Vessey MP & Colin-Jones DG (1994) Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 343:1075-1078.

Lee A, Cooper MG, Craig JC, Knight JF & Keneally JP (1999) The effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on postoperative renal function: a meta-analysis. Anaesth Intensive Care 27: 574-580.

Lehmann KA (1995) New developments in patient-controlled analgesia. Ann Med 27: 271-282.

Lehmann KA, Heinrich C & van Heiss R (1988) Balanced anesthesia and patient-controlled postoperative analgesia with fentanyl: minimum effective concentrations, accumulation and acute tolerance. Acta Anaesth Belg 39: 11-23.

Leino K, Mildh L, Lertola K, Seppälä T & Kirvelä O (1999) Time course of changes in breathing pattern in morphine- and oxycodone-induced respiratory depression. Anaesthesia 54: 835-840.

Leith S, Wheatley RG, Jackson IJ, Madej TH & Hunter D (1994) Extradural infusion analgesia for postoperative pain relief. Br J Anaesth 73: 552-558.

Ligumsky M, Sestieri M, Karmeli F, Zimmerman J, Okon E & Rachmilewitz D (1990) Rectal administration of nonsteroidal antiinflammatory drugs. Effect on rat gastric ulcerogenicity and prostaglandin E2 synthesis. Gastroenterology. 98: 1245-1249.

Liu SS, Gerancher JC, Bainton BG, Kopacz DJ & Carpenter RL (1996) The effects of electrical stimulation at different frequencies on perception and pain in human volunteers: epidural versus intravenous administration of fentanyl. Anesth Analg 82: 98-102.

Liu SS, Moore JM, Luo AM, Trautman WJ & Carpenter RL (1999) Comparison of three solutions of ropivacaine/fentanyl for postoperative patient-controlled epidural analgesia. Anesthesiology 90: 727-733.

Loper KA, Ready LB, Downey M, Sandler AN, Nessly M, Rapp S & Badner N (1990) Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesth Analg 70: 72-75.

Lubenow TR, Tanck EN, Hopkins EM, Mc Carthy RJ & Ivankovich AD (1994) Comparison of patient-assisted epidural analgesia with continuous-infusion epidural analgesia for postoperative patients. Reg Anesth 19: 206-211.

Mahoudeau G, Gaertner E, Launoy A, Ocquidant P & Loewenthal A (1995) Interscalenic block: accidental catheterization of the epidural space. Ann Fr Anaesth 14: 438-41.

Mallon WJ & Thomas CW (2000) Patient-controlled lidocaine analgesia for acromioplasty surgery. J Shoulder Elb Surg 9: 85-88.

Markham A & Faulds D (1996) Ropivacaine. A review of its pharmacology and therapeutic use in regional anaesthesia. Drugs 52: 429-449.

Matsuda K, Ohnishi K, Misaka E & Yamazaki M (1983) Decrease of urinary prostaglandin E2 and prostaglandin F2 alpha excretion by nonsteroidal anti-inflammatory drugs in rats. Relationship to anti-inflammatory activity. Biochem Pharmacol 32: 1347-1352.

McCormack K & Brune K (1991) Dissociation between the antinociceptive and anti-inflammatory effects of the nonsteroidal anti-inflammatory drugs. A survey of their analgesic efficacy. Drugs 41: 533-547.

McGrath D, Thurston N, Wright D, Preshaw R & Fermin P (1989) Comparison of one technique of patient-controlled postoperative analgesia with intramuscular meperidine. Pain 37: 265-270.

Meister GC, D'Angelo R, Owen M, Nelson KE & Gaver R (2000) A comparison of epidural analgesia with 0.125% ropivacaine with fentanyl versus 0.125% bupivacaine with fentanyl during labor. Anesth Analg 90: 632-637.

Menasse R, Hedwall PR, Kraetz J, Pericin C, Riesterer L, Sallmann A, Ziel R & Jaques R (1978) Pharmacological properties of diclofenac sodium and its metabolites. Scand J Rheumatol Suppl.22: 5-16.

Mills SB, Bloch M & Bruckner FE (1973) Double-blind cross-over study of ketoprofen and ibuprofen in management of rheumatoid arthritis. BMJ 4: 82-84.

Moller R & Covino BG (1990) Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. Anesthesiology 72: 322–329.

Morrow BC, Bunting H & Milligan KR (1993) A comparison of diclofenac and ketorolac for postoperative analgesia following day-case arthroscopy of the knee joint. Anaesthesia 48: 585-587.

Muittari P & Kirvelä O (1998) The safety and efficacy of intrabursal oxycodone and bupivacaine in analgesia after shoulder surgery. Reg Anesth Pain Med 23: 474-478.

Müller M, Litz RJ, Hübler M & Albrecht DM (2001) Grand mal convulsion and plasma concentrations after intravascular injection of ropivacaine for axillary brachial plexus blockade**.** Br J Anaesth 87: 784-787.

Myles PS & Power I (1998) Does ketorolac cause postoperative renal failure how do assess the evidence? Br J Anaesth 80: 420-421.

Niemi L, Tuominen M, Pitkänen M & Rosenberg PH (1995) Comparison of parenteral diclofenac and ketoprofen for postoperative pain relief after maxillofacial surgery. Acta Anaesthesiol Scand 39: 96-99.

Niemi TT, Taxell C & Rosenberg PH (1997) Comparison of the effect of intravenous ketoprofen, ketorolac and diclofenac on platelet function in volunteers. Acta Anaesthesiol Scand 41: 1353-1358.

Nissen I, Jensen KA & Öhrström JK (1992) Indomethacin in the management of postoperative pain. Br J Anaesth 69: 304-306.

Notcutt WG & Morgan RJ (1990) Introducing patient-controlled analgesia for postoperative pain control into a district general hospital. Anaesthesia 45: 401-406.

Oates JD, Snowdon SL & Jayson DW (1994) Failure of pain relief after surgery. Attitudes of ward staff and patients to postoperative analgesia. Anaesthesia 49: 755-758.

O'Banion MK, Sadowski HB, Winn V & Young DA (1991) A serum- and glucocorticoid-regulated 4-kilobase mRNA encodes a cyclooxygenase-related protein. J Biol Chem 266: 23261-23267.

O´Hanlon JJ, Beers H, Huss BK & Milligan KR (1996) A comparison of the effect of intramuscular diclofenac, ketorolac or piroxicam on postoperative pain following laparoscopy. Ulster Med J 65: 51-54.

Ohnhaus EE & Adler R (1975) methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. Pain 1: 374-384.

Owen MD, D'Angelo R, Gerancher JC, Thompson JM, Foss ML, Babb JD & Eisenach JC (1998) 0.125% ropivacaine is similar to 0.125% bupivacaine for labor analgesia using patient-controlled epidural infusion. Anesth Analg 86: 527-531.

Paech MJ & Westmore MD (1994) Postoperative epidural fentanyl infusion – is the addition of 0.1% bupivacaine of benefit. Anaesth Intensive Care 22: 9-14.

Peng PWH & Sandler AN (1999) A review of the use of fentanyl analgesia in the management of acute pain in adults. Anesthesiology 90: 576-599.

Pere P, Pitkänen M, Rosenberg PH, Bjorkenheim JM, Linden H, Salorinne Y & Tuominen M (1992) Effect of continuous interscalene brachial plexus block on diaphragm motion and on ventilatory function. Acta Anaesthesiol Scand 36: 53-57.

Perez-Gutthann S, Garcia-Rodriques LA, Raiford DS, Duque Oliart A & Romeu JR (1996) Nonsteroidal anti-inflammatory drugs and the risk of hospitalisation for acute renal failure. Arch Intern Med 156: 2433-2439.

Perttunen K, Nilsson E & Kalso E (1999) I.v. diclofenac and ketorolac for pain after thoracoscopic surgery. Br J Anaesth 82: 221-227.

Piha Juhana (1994) Autonomisen hermoston tutkimusmenetelmät. In Sovijärvi A, Uusitalo A, Länsimies E & Vuori I (eds) Kliininen fysiologia, Duodecim, Jyväskylä, 328-329.

Pitkänen M, Feldman HS, Arthur GR & Covino BG (1992) Chronotropic and inotropic effects of ropivacaine, bupivacaine, and lidocaine in the spontaneously beating and electrically paced isolated, perfused rabbit heart. Reg Anesth 17: 183-192.

Plowman AN, Bolsin S & Mather LE (1998) Central nervous system toxicity attributable to epidural ropivacaine hydrochloride. Anaesth Intensive Care 26: 204–206.

Polley LS, Columb MO, Naughton NN, Wagner DS & van de Ven CJ (1999) Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: implications for therapeutic indexes. Anesthesiology 90: 944-950.

Popp JE, Sanko WA, Sinha AK & Kaeding CC (1998) A comparison of ketorolac tromethamine/oxycodone versus patient-controlled analgesia with morphine in anterior criciate ligament reconstruction patients. Arthroscopy 14: 816-819.

Pöyhiä R & Kalso E (1992) Antinociceptive effects and central nervous system depression caused by oxycodone and morphine in rats. Pharmacol Toxicol 70: 125-130.

Pöyhiä R, Vainio A & Kalso E (1993) A review of oxycodone's clinical pharmacokinetics and pharmacodynamics. J Pain Symptom Manage 8: 63-67.

Ræder JC, Drosdahl S, Klaastad Ø, Kvalsvik O, Isaksen B, Stromskag KE, Mowinckel P, Bergheim R & Selander D (1999) Axillary brachial plexus block with ropivacaine 7.5 mg/ml. A comparative study with bupivacaine 5 mg/ml. Acta Anaesthesiol Scand 43: 794–798.

Rao AS, Cardosa M & Inbasegaran K (2000) Morphine-sparing effect of ketoprofen after abdominal surgery. Anaesth Intensive Care 28: 22-26.

Reimann IW & Frölich JC (1981) Effects of diclofenac on lithium kinetics. Clin Pharmacol Ther 30: 348-352.

Reiz S, Haggmark S, Johansson G & Nath S (1989) Cardiotoxicity of ropivacaine: A new amide local anaesthetic agent. Acta Anaesthesiol Scand 33: 93–98.

Riess W, Stierlin H, Degen P, Faigle JW, Gerardin A, Moppert J, Sallmann A, Schmid K, Schweizer A, Sulc M, Theobald W & Wagner J (1978) Pharmacokinetics and metabolism of the anti-inflammatory agent Voltaren. Scand J Rheumatol Suppl. (22): 17-29.

Rorarius MG, Suominen P, Baer GA, Romppanen O & Tuimala R (1993) Diclofenac and ketoprofen for pain treatment after elective caesarean section. Br J Anaesth 70: 293-297.

Rosenberg PH & Heinonen E (1983) Differential sensitivity of A and C nerve fibres to long-acting amide local anaesthetics. Br J Anaesth 55: 163-167.

Rosenberg PH, Lamberg TS, Tarkkila P, Marttila T, Bjorkenheim JM & Tuominen M (1995) Auditory disturbance associated with interscalene brachial plexus block. Br J Anaesth 74: 89-91.

Rowbotham DJ, Wyld R & Nimmo WS (1989) A disposable device for patient-controlled analgesia with fentanyl. Anaesthesia 44: 922-924.

Rucci FS, Pippa P, Barbagli R & Doni L (1993) How many interscalenic blocks are there? A comparison between the lateral and posterior approach. Eur J Anaesth 10: 303-307.

Ruetsch YA, Fattinger KE & Borgeat A (1999) Ropivacaine-induced convulsions and severe cardiac dysrhythmia after sciatic block. Anesthesiology 90: 1784–1786.

Salomäki T (1995) Epidural fentanyl for pain relief after major surgery. Acta Univ Oul D 333: 47.

Salomäki TE, Laitinen JO & Nuutinen LS (1991) A randomised double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after thoracotomy. Anesthesiology 75: 790-795.

Salomäki TE, Laitinen JO, Vainionpää V & Nuutinen LS (1995) 0.1 % bupivacaine does not reduce the requirement for epidural fentanyl infusion after major abdominal surgery. Reg Anesth 20: 435-443.

Sandin R, Stam H & Sternlo JE (1992) Interscalene plexus block for arthroscopy of the humeroscapular joint. Acta Anaesthesiol Scand 36: 493-494.

Sandler A, Finucane B & McKenna J (1995) A pharmacokinetic comparison between ropivacaine 0.5 %, 0.75 %, 1.0 % and bupivacaine 0.5 % in epidural anaesthesia: a double blind multi center study in women undergoing hysterectomy. Can J Anaesth 42 (Pt2): A 43.

Sandler AN, Stringer D, Panos L, Badner N, Friedlander M, Koren G, Katz J & Klein J (1992) A randomized, double-blind comparison of lumbar epidural and intravenous fentanyl infusions for post-thoracotomy pain relief: analgesic, pharmacokinetic and respiratory effects. Anesthesiology 77: 626-634.

Schug SA, Scott DA, Payne J, Mooney PH & Hagglof B (1996) Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery. Br J Anaesth 76: 487-491.

Schug SA & Torrie JJ (1993) Safety assessment of postoperative pain management by an acute pain service. Pain 55: 387-391.

Scott DA, Blake D, Buckland M, Etches R, Halliwell R, Marsland C, Merridew G, Murphy D, Paech M, Schug SA, Turner G, Walker S, Huizar K & Gustafsson U (1999) A comparison of epidural ropivacaine infusion alone and in combination with 1, 2, and 4 microg/mL fentanyl for seventy-two hours of postoperative analgesia after major abdominal surgery. Anesth Analg 88: 857-864.

Scott DA, Chamley DM, Mooney PH, Deam RK, Mark AH & Hagglöf B (1995) Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery-a dose finding study. Anesth Analg 81: 982-986.

Sechzer PH (1968) Objective measurement of pain. Anesthesiology 29: 209-210.

Sharrock NE, Hotchkiss R, Ennis WJ & Weiland A (1996) Brachial plexus surgery through the infraclavicular approach using an interscalene block. J Hand Surg - Am 21: 271-272.

Silvasti M & Pitkänen M (2001) Patient-controlled epidural analgesia versus continuous epidural analgesia after total knee arthroplasty. Acta Anaesthesiol Scand 45: 471-476.

Silvasti M, Rosenberg P, Seppälä T, Svartling N & Pitkänen M (1998) Comparison of analgesic efficacy of oxycodone and morphine in postoperative intravenous patient-controlled analgesia. Acta Anaesthesiol Scand 42: 576-580.

Stierlin H, Faigle JW & Colombi A (1978) Pharmacokinetics of diclofenac sodium (Voltaren) and metabolites in patients with impaired renal function. Scand J Rheumatol Suppl. 22. 30-35.

Stouten EM, Armbruster S, Houmes RJ, Prakash O, Erdmann W & Lachmann B (1992) Comparison of ketorolac and morphine for postoperative pain after major surgery. Acta Anaesthesiol Scand 36: 716-721.

Sunshine A, Olson NZ, Marrero I & Tirado S (1998) Onset and duration of analgesia for low-dose ketoprofen in the treatment of postoperative dental pain. J Clin Pharmacol 38: 1155-1164.

Sunshine A, Olson NZ, Zighelboim I & De Castro A (1993) Ketoprofen, acetaminophen plus oxycodone, and acetaminophen in the relief of postoperative pain. Clin Pharmacol Ther 54: 546-555.

Tarkkila P & Saarnivaara L (1999) Ketoprofen, diclofenac or ketorolac for pain after tonsillectomy in adults? Br J Anaesth 82: 56-60.

Tarkkila P, Tuominen M & Rosenberg PH (1996) Intravenous ketorolac vs diclofenac for analgesia after maxillofacial surgery. Can J Anaesth 43: 216-220.

Taylor NM, Hall GM & Salmon P (1996) Patients' experiences of patient-controlled analgesia. Anaesthesia 51:525-528.

Tetzlaff JE, Yoon HJ, Dilger J & Brems J (1994) Subdural anesthesia as a complication of an interscalene brachial plexus block. Reg Anesth 19: 357-359.

Tighe KE, Webb AM & Hobbs GJ (1999) Persistently high plasma morphine-6-glucuronide levels despite decreased hourly patient-controlled analgesia morphine use after single-dose diclofenac: potential for opioid-related toxicity. Anesth Analg 88: 1137-1142.

Tuominen MK, Pere P & Rosenberg PH (1991) Unintentional arterial catheterisation and bupivacaine toxicity associated with continuous interscalene brachial plexus block. Anesthesiology 75: 365-358.

Tuominen MK, Pitkänen MT, Numminen MK & Rosenberg PH (1987a) Quality of axillary brachial plexus block. Comparison of success rate using perivascular and nerve stimulator techniques. Anaesthesia 42: 20-22.

Tuominen M, Pitkanen M & Rosenberg PH (1987b) Postoperative pain relief and bupivacaine plasma levels during continuous interscalene brachial plexus block. Acta Anaesthesiol Scand 31: 276-278.

Turner G, Blake D, Buckland M, Chamley D, Dawson P, Goodchild C, Mezzatesta J, Scott D, Sultana A, Walker S, Hendrata M, Mooney P & Armstrong M (1996) Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery. Br J Anaesth 76: 606-610.

Urmey WF, Talts KH & Sharrock NE (1991) One hundred percent insidence of hemidiaphragmatic paresis associated with interscalene brachial plexus anesthesia as diagnosed by ultrasonography. Anesth Analg 72: 498-503.

Vane JR (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature - New Biology. 231: 232-235.

Vane J (2000) Aspirin and other anti-inflammatory drugs. Thorax 55 (Suppl 2): S3-S9.

Vangsness CT Jr, Ennis M, Taylor JG & Atkinson R (1995) Neural anatomy of the glenohumeral ligaments, labrum, and subacromial bursa. Arthroscopy 11: 180-184.

Veys EM (1991) 20 Years' experience with ketoprofen. Scand J Rheumatol Suppl 90: 3-44.

Walder B, Schafer M, Henzi I & Tramer MR (2001) Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. Acta Anaesthesiol Scand 45: 795-804.

Walton JS, Folk JW, Friedman RJ & Dorman BH (2000) Complete brachial plexus palsy after total shoulder arthroplasty done with interscalene block anesthesia. Reg Anesth Pain Med 25: 318-321.

Welchew EA (1983) The optimum concentration for epidural fentanyl. A randomised, double-blind comparison with and without 1:200000 adrenaline. Anaesthesia 38: 1037-1041.

Welchew EA & Breen DP (1991) Patient-controlled on-demand epidural fentanyl. A comparison of patient-controlled on-demand fentanyl delivered epidurally or intravenously. Anaesthesia 46: 438-441.

Wheatley RG, Shepherd D, Jackson IJB, Madej TH & Hunter D (1992) Hypoxaemia and pain relief after upper abdominal surgery: comparison of i.m. and patient-controlled analgesia. Br J Anaesth 69: 558-561.

Whipple JK, Quebbeman EJ, Lewis KS, Gottlieb MS & Ausman RK (1994) Difficulties in diagnosing narcotic overdoses in hospitalized patients. Ann Pharmacother 28: 446-450.

White MJ, Berghausen EJ, Dumont SW, Tsueda K, Schroeder JA, Vogel RL, Heine MF & Huang KC (1992) Side effects during continuous epidural infusion of morphine and fentanyl. Can J Anaesth 39: 576-582.

Wierod FS, Frandsen NJ, Jacobsen JD, Hartvigsen A & Olsen PR (1998) Risk of haemorrhage from transurethral prostatectomy in acetylsalicylic acid and NSAID-treated patients. Scand J Urol Nephrol 321: 20-22.

Wigfull J & Welchew E (2001) Survey of 1057 patients receiving postoperative patient-controlled analgesia. Anaesthesia 56: 70-75.

Willer JC, De Broucker T, Bussel B, Roby-Brami A & Harrewyn JM (1989) Central analgesic effect of ketoprofen in humans: electrophysiological evidence for a supraspinal mechanism in a double-blind and cross-over study. Pain 38: 1-7.

Winnie AP (1970) Interscalene brachial plexus block. Anesth Analg 49: 455-466.

Woodhouse A & Mather LE (1997) Nausea and vomiting in the postoperative patient-controlled analgesia environment. Anaesthesia 52: 770-775.

Yasuda I, Hirano T, Ojima T, Ohira N, Kaneko T & Yamamuro M (1980) Supraclavicular brachial plexus block using a nerve stimulator and an insulated needle. Br J Anaesth 52: 409-411.

Yee JP, Brown CR, Allbon C & Koshiver JE (1986) Analgesia from intramuscular ketorolac tromethamine compared to morphine in severe pain following major surgery. Pharmacotherapy 6: 253-261.

Zfass AM, McHenry L & Sanyal AJ (1993) Nonsteroidal antiinflammatory drug-induced gastroduodenal lesions: prophylaxis and treatment. Gastroenterologist 1:165-169.