Local Infiltration Analgesia in Knee Arthroplasty
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Abstract


Local infiltration analgesia (LIA) is a new technique for postoperative pain management following knee arthroplasty. LIA involves a long-acting local anesthetic (ropivacaine), a non-steroid anti-inflammatory drug (ketorolac) and epinephrine infiltrated into the knee joint during surgery and injected postoperatively via a catheter.

In the first two studies, LIA was compared with placebo in unicompartmental (I) and total (II) knee arthroplasty. Postoperative pain levels, morphine consumption and the incidence of side effects were lower in the LIA groups. In addition, we found a shorter length of hospital stay in the LIA group following unicompartmental knee arthroplasty compared with placebo (I), while the time to home readiness was shorter in the LIA group following total knee arthroplasty (II). In this study, we found that the unbound venous blood concentration of ropivacaine was below systemic toxic blood concentrations in a sub-group of patients.

In the third study, LIA was compared with intrathecal morphine for postoperative pain relief following total knee arthroplasty (III). Pain scores and morphine consumption were lower, length of hospital stay was shorter and patient satisfaction was higher in the LIA group.

In the final study, we investigated the effect of minimally invasive surgery (MIS) compared with conventional surgery in unicompartmental knee arthroplasty (IV). Both groups received LIA. We found no statistically significant differences in postoperative pain, morphine consumption, knee function, home readiness, hospital stay or patient satisfaction.

In conclusion, LIA provided better postoperative pain relief and earlier mobilization than placebo, both in unicompartmental and total knee arthroplasty. When compared to intrathecal morphine, LIA also resulted in improved postoperative pain relief and earlier mobilization. Minimally invasive surgery did not improve outcomes after unicompartmental knee arthroplasty, when both groups received LIA.

Keywords: Knee arthroplasty, minimally invasive surgery, ropivacaine, ketorolac, intrathecal morphine, local infiltration analgesia.

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## Abbreviations

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<tbody>
<tr>
<td>EDA</td>
<td>Epidural Anesthesia</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EuroQol 5 Dimensions</td>
</tr>
<tr>
<td>IT</td>
<td>Intrathecal</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>LA</td>
<td>Local Anesthetic</td>
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<td>LIA</td>
<td>Local Infiltration Analgesia</td>
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<tr>
<td>LOS</td>
<td>Length of Hospital Stay</td>
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<td>MIS</td>
<td>Minimally Invasive Surgery</td>
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<tr>
<td>NSAID</td>
<td>Non-Steroid Anti-Inflammatory Drug</td>
</tr>
<tr>
<td>PCA</td>
<td>Patient Controlled Analgesia</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<td>TUG-test</td>
<td>Time to Up and Go test</td>
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<td>TKA</td>
<td>Total Knee Arthroplasty</td>
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<tr>
<td>UKA</td>
<td>Unicompartmental Knee Arthroplasty</td>
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<tr>
<td>VAS</td>
<td>Visual Analog Scale</td>
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</table>
List of original papers

This thesis is based on the following papers, which will be referred to by roman numerals:

   Acta Orthopaedica 2009; 80:213-9

   Acta Orthopaedica 2010; 81:354-60

   Anesthesia & Analgesia 2011; 113: 926-33

   Submitted for publication

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Introduction

Osteoarthritis of the knee is a common disease, characterized by progressive breakdown of the articular cartilage, often resulting in pain, stiffness and reduced function of the knee. When non-surgical management, such as oral analgesics and physiotherapy, fail to provide sufficient relief of symptoms, surgery is often indicated.

There are three basic surgical options; osteotomy, unicompartmental or total knee arthroplasty. Osteotomy involves an extra-articular correction of the alignment in order to relieve the load from the affected part of the knee joint and thereby reduce pain. This procedure is generally reserved for the earlier stages of osteoarthritis in the younger population. Another option is knee arthroplasty, where the diseased parts of the knee are replaced with artificial joint surfaces. When only one compartment of the knee is affected, a unicompartmental arthroplasty (UKA) might be considered. UKA was first introduced in the mid 1970s and most often involves replacement of the joint surfaces of the medial compartment. If both the medial and the lateral parts of the joint show signs of osteoarthritis or if the deformity is severe, a total knee arthroplasty (TKA) is recommended. In the Swedish Knee Arthroplasty Register, TKA comprises approximately 94 % of knee arthroplasties and UKA 6 %. Knee arthroplasty is a successful procedure with excellent results, both in terms of pain relief and long-time durability. More than 12 000 knee replacements are performed yearly in Sweden.

Early postoperative pain following knee arthroplasty is often severe. Poor pain control may lead to major discomfort for the patient and also impaired early mobilization. Immobilization of the patient in bed increases the risk of deep vein thrombosis and prolonged hospital stay may increase the risk of nosocomial infection.

Several methods are available for pain management following knee arthroplasty. Peripheral nerve blocks often provide good pain relief, but can be technically demanding and may sometimes lead to motor block of the lower extremity, hindering early mobilization, and sometimes involves a risk of nerve damage.

A simple method for postoperative pain management is opioids, administered intravenously via a patient-controlled analgesia (PCA) pump. However, large doses of opioids are often required and the risk increases of side effects, such as sedation, nausea, vomiting, pruritus and respiratory depression. In addition, pain relief during movement is sometimes poor.
Epidural anesthesia (EDA) has traditionally been widely used for postoperative pain management following knee arthroplasty. If only local anesthetics are administered epidurally, there is risk of motor blockade and difficulty in mobilizing the patient. Epidural anesthesia with an indwelling catheter prolongs pain relief, but can lead to rare, but serious complications such as epidural hemorrhage, various degrees of nerve damage, meningitis or epidural infection.

Spinal anesthesia is commonly used in knee replacement surgery. It has the advantage of rapid onset of action, but has relatively short duration of postoperative analgesia. If a small dose of opioid is added to the local anesthetic during spinal anesthesia (intrathecal opioids), postoperative pain relief can be enhanced and prolonged. Several studies have demonstrated reduced pain intensity postoperatively and reduction in rescue analgesic medication, at least during the first 6–24 postoperative hours. However, there are several disadvantages of intrathecal opioids including the risk of side effects such as nausea, vomiting, pruritus, urinary retention and respiratory depression, that can be troublesome for the patient and costly for the health-care provider. Spinal anesthesia with intrathecal morphine is currently one of the most common methods used in Sweden for postoperative pain management following knee arthroplasty.

**Local infiltration analgesia (LIA)**

The side effects and disadvantages of these traditional methods of postoperative pain management have led to a search for alternative techniques. Dr. Dennis Kerr and Dr. Lawrence Kohan in Sydney, Australia, developed a simple technique called local infiltration analgesia (LIA), which has become increasingly popular during the last decade. The technique was designed for the management of the acute postoperative pain phase lasting approximately 36 hours, following hip or knee surgery. The method includes two well-defined moments, a periarticular infiltration during the operation and intraarticular infusion via a catheter postoperatively. At the end of the operation a mixture of local anesthetics and non-steroid anti-inflammatory drugs (NSAIDs) is infiltrated into the soft tissue around the surgical field by the surgeon. Before wound closure, a thin catheter is placed intraarticularly to allow for postoperative bolus injections.

The theory behind LIA is to prevent pain at the site of its origin. This is achieved by systematically infiltrating the entire surgical site with local anesthetics and anti-inflammatory drugs, extending the duration of analgesia by bolus injections via the catheter and restricting the drugs to the site of injection using vasoconstrictors, compression bandage and cooling. The drugs used include a long-acting local anesthetic (ropivacaine), a di-
rectly acting non-steroid anti-inflammatory drug (ketorolac) and a vasocostrictr (epinephrine), which is believed to limit the absorption of the local anesthetic (LA).

Rapid, high quality recovery from surgery and anesthesia should be the goal following knee arthroplasty. Good pain management is central in achieving that goal. According to Kerr and Kohan, the pain management process begins at the preoperative visit, and proceeds through anesthesia and surgery, during the acute postoperative phase and all the way to home care (Kerr 2011, personal communication). LIA is known to be effective during the acute postoperative phase and is regarded as a key enabling technique in promoting rapid return to normal activities of daily living and early home discharge.

In an open study of 325 patients, Kerr and Kohan reported good postoperative pain relief and that 71% of patients were able to leave the hospital on the first postoperative day. A number of studies have supported the efficacy of LIA in TKA compared with placebo or no injections. However, to our knowledge, no prospective randomized studies have been conducted on unicompartmental knee arthroplasty.

To further address these questions we performed the first two studies comparing LIA with placebo following unicompartmental (Study I) and total (Study II) knee arthroplasty.

Several studies published in the literature compared the LIA technique to other standard methods for postoperative pain management after TKA, such as epidural analgesia and femoral nerve blocks. However, no previous study has compared LIA with intrathecal morphine. Therefore, we conducted the third study, comparing LIA with intrathecal morphine following TKA (Study III).

Minimally invasive surgery (MIS)

Another attempt to reduce postoperative pain and improve mobilization has been the development of minimally invasive surgery (MIS). Repicci et al. introduced the mini-arthrotomy or minimally invasive surgery in unicompartmental knee arthroplasty in the 1990s and during the procedure, a limited amount of local anesthetic was infiltrated, mainly in the anterior part of the joint. The procedure resulted in earlier mobilization and shorter hospital stay than conventional surgery, in which a longer incision was used that resulted in greater trauma. The work of Repicci et al. influenced Kerr and Kohan in developing the LIA technique (Kerr, 2011, personal communication). In another non-randomized study, Price found that patients undergoing UKA using MIS could be mobilized twice as fast as conventional surgery. In the only randomized controlled study
comparing MIS with conventional exposure in UKA, Carlsson et al. found shorter hospital stay in the MIS group, but no difference in postoperative pain or range of motion of the knee \(^{42}\). The use of MIS during total knee replacements has been debated \(^{43}\) and is not universally accepted.

In Sweden the MIS technique for unicompartmental knee arthroplasty quickly became popular and today more than 50% of UKAs are performed with MIS \(^{2}\). MIS is considered a more difficult technique and most orthopedic surgeons are more familiar with the conventional exposure. Therefore we were interested in evaluating whether MIS, compared to conventional surgery, would reduce postoperative pain and improve mobilization following UKA, when both groups received LIA (Study IV).
Aims of the thesis

General
To investigate the effect of local infiltration analgesia on postoperative pain and mobilization following knee arthroplasty.

Specific aims – Studies I–IV

I
To evaluate whether the local infiltration analgesia (LIA) technique would result in better postoperative analgesia and earlier mobilization, compared to placebo, following unicompartmental knee arthroplasty performed with minimally invasive technique.

II
To evaluate whether the local infiltration analgesia (LIA) technique would result in better postoperative analgesia and earlier mobilization compared to placebo, following total knee arthroplasty. To evaluate whether the local infiltration analgesia (LIA) technique would result in toxic blood concentrations of the local anesthetic.

III
To evaluate whether the local infiltration analgesia (LIA) technique would provide better postoperative analgesia and earlier mobilization than intrathecal morphine following total knee arthroplasty.

IV
To evaluate whether minimally invasive surgery (MIS) would result in reduced postoperative pain and earlier mobilization, compared to conventional surgery, following unicompartamental knee arthroplasty, when both groups received local infiltration analgesia (LIA).
Methods

Ethics
The Regional Ethics Committee in Uppsala, Sweden, approved the study protocols of all four studies and the Swedish Medical Products Agency approved the study protocols for studies I and II. All studies were conducted in accordance with the Declaration of Helsinki and according to Good Clinical Practice, and an independent body, the Clinical Research Support Unit at Örebro University Hospital, monitored studies I–III. All studies were registered in a central online database, maintained at ClinicalTrials.gov.

Patients
Patients scheduled for UKA (I, IV) and TKA (II, III) were screened for study eligibility by one of the researchers participating in the study. Inclusion criteria were: ASA physical status I–III, 20–80 years (I, IV), 20–85 years (II) and 40–85 years (III). Exclusion criteria were allergy or intolerance to any of the study drugs, severe liver, heart or renal disease, bleeding disorder or chronic pain requiring opioid medication.

Anesthesia
All patients received diazepam 10 mg orally 1 hour before planned surgery and all operations were performed under general anesthesia, except in study III, where spinal anesthesia was used. General anesthesia was induced with fentanyl 1–2 µg/kg and propofol 1–2 mg/kg IV. Tracheal intubation was performed after muscle relaxation with rocuronium 0.5 mg/kg and anesthesia was maintained with 1–3% sevoflurane and 33% oxygen in nitrous oxide.

In study III, spinal anesthesia was used and glucose-free bupivacaine 17.5 mg (3.5 mL) injected using a 27 G spinal needle at the L3/L4 or L2/L3 intervertebral space with the patient in the sitting position.

Study design
All studies were prospective, randomized, controlled trials and all but study IV were double-blinded. Surgery was performed at the Department of Orthopedics, Örebro University Hospital, Sweden, between September 2005 and March 2011.
Studies I and II
After randomization the patients were allocated to one of two groups, LIA or Placebo, with 20 patients in each group in study I (UKA) and 24 patients in each group in study II (TKA).
In the LIA groups, the LIA-mixture was infiltrated intraoperatively into the knee and on the following morning, injected via the knee catheter, while the Placebo groups received no injections intraoperatively and a saline injection via the knee catheter postoperatively.
A sub-study was first performed on 8 patients prior to the start of study II to investigate the unbound and total venous blood concentration of ropivacaine, the local anesthetic within the LIA-mixture.

Study III
Patients (n=50) were randomized into two groups, LIA and M (intrathecal morphine), with 25 patients in each group. In group M, morphine 0.1 mg (0.25 mL) was injected intrathecally, while in group LIA an equal volume of saline (0.25 mL) was administered together with the spinal anesthetic. Group LIA received LIA intraoperatively and then via the intraarticular catheter on postoperative day 1 and 2, while patients in group M received no injections intraoperatively and saline injection via the knee catheter postoperatively.

Study IV
Patients were allocated to either group MIS or CON (conventional), with 20 patients in each group. All patients received LIA intraoperatively and an injection via the intraarticular catheter postoperatively.
Surgery

Studies I and IV (Unicompartmental knee arthroplasty)
A medial unicompartmental knee arthroplasty was performed in all patients. In study I, a minimally invasive surgery (MIS) technique was used in all patients and in study IV, patients were randomized to either MIS or conventional surgery. All patients received the Link Endo-Model Sled Prosthesis (Link Sweden AB, Åkersberga, Sweden) (Fig. 1).

Conventional surgery
A 15- to 20-cm-long mid-line skin incision was made. A medial parapatellar arthrotomy was performed from the base of the patella and continued distally to the medial side of the tibial tuberosity. The arthrotomy was extended proximally 5–10 cm into the rectus tendon of the quadriceps muscle, in order to allow eversion and dislocation of the patella (Fig. 2).

Minimally invasive surgery (MIS)
An 8- to 10-cm-long medial parapatellar skin incision was made from the upper medial pole of the patella and carried distally to the medial side of the tibial tuberosity. A medial parapatellar arthrotomy was performed from the base of the patella, leaving the muscle fibers of the vastus medialis

Fig. 1. X-ray images of unicompartmental (UKA) and total knee arthroplasty (TKA).
untouched, and continued distally to 2–3 cm below the joint line, to the medial side of the tibial tuberosity. The patella was not dislocated or everted. (Fig. 2)

Studies II and III (Total knee arthroplasty)
Total knee arthroplasty was performed through a conventional medial para-patellar approach (Fig. 2) using AGC prostheses (Biomet, Warsaw, IN, USA) (Fig. 1).

Postoperative pain management
Local infiltration analgesia (LIA)
During the operation, the surgeon infiltrated a mixture of ropivacaine, ketorolac, and epinephrine systematically into all tissue that had been traumatized during surgery in the following way: 30–50 mL of the solution was infiltrated in the posterior capsule and the collateral ligaments after the bone cuts had been made and before insertion of the prosthesis (Fig. 3). The injections were performed using a systematic sequence of multiple injections from one side to the other in order to ensure uniform distribution of the mixture of drugs. After the prosthesis had been inserted, another 40–60 mL was injected in the capsule incision, the quadriceps tendon, and the infra-patellar ligament, and around the posterior cruciate ligament. The final 30–50 mL was infiltrated into the subcutaneous tissue.
before skin closure. When the conventional exposure was used, the subcutaneous injection was without epinephrine or ketorolac in order to avoid possible damage of the skin blood circulation \textsuperscript{36}. In study I, a total of 200 mg ropivacaine was infiltrated during the operation, while in studies II–IV, the dose was increased to 400 mg. In all studies 30 mg ketorolac and 0.5 mg epinephrine were injected (Table 1).

Table 1. Intraoperative LIA-mixture

<table>
<thead>
<tr>
<th>Study</th>
<th>ropivacaine (mg)</th>
<th>ketorolac (mg)</th>
<th>epinephrine (mg)</th>
<th>Total volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (UKA)</td>
<td>200</td>
<td>30</td>
<td>0.5</td>
<td>106</td>
</tr>
<tr>
<td>II (TKA)</td>
<td>400</td>
<td>30</td>
<td>0.5</td>
<td>166</td>
</tr>
<tr>
<td>III (TKA)</td>
<td>400</td>
<td>30</td>
<td>0.5</td>
<td>166</td>
</tr>
<tr>
<td>IV (UKA)</td>
<td>400</td>
<td>30</td>
<td>0.5</td>
<td>146 (group CON)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>116 (group MIS)</td>
</tr>
</tbody>
</table>

Fig. 3. Local infiltration analgesia. Intraoperative infiltration.
Before wound closure, a multi-hole 20-G catheter was tunneled under the skin, the tip of the catheter was placed intraarticularly and a bacterial filter was connected to the catheter in all patients (Fig. 4). No drains were used.

On the first postoperative morning, a bolus dose was injected via the intraarticular catheter. The bolus LIA mixture consisted of ropivacaine 150 mg (study I) or 200 mg (studies II–IV), ketorolac 30 mg and epinephrine 0.1 mg in a total volume of 22 mL. In study III, an additional bolus injection was administered on the second postoperative morning in an attempt to prolong the analgesic effect.

A cooling bandage was applied for the first 6 hours postoperatively and a compression bandage for 24 hours in all studies (I–IV).

**Intrathecal morphine**

In study III, glucose-free bupivacaine 17.5 mg (3.5 mL) was injected intrathecally in all patients together with morphine 0.1 mg (0.25 mL) in group M, or 0.25 mL of 0.9 % saline in group LIA.
Rescue medication
In all studies, all patients received paracetamol 1 g orally every 6 hours. In the recovery room, a Patient-Controlled Analgesia (PCA)-pump (Gemstar Abbott) with IV morphine (1-mg bolus and 6-min lockout time) was connected. The PCA-pump was discontinued at 24 h postoperatively in studies I and IV and at 48 h in studies II and III, if the Visual Analogue pain Score (VAS) 0-100 mm was < 40 mm during a 2 h period at rest. Thereafter, patients were permitted to take paracetamol 1 g and tramadol 50–100 mg orally up to 4 times daily, as required for pain relief.

Outcome measurements

Pain
Postoperative pain intensity was assessed both at rest and on motion (60 degrees of knee flexion) using VAS.

Analgesic consumption
PCA-morphine (primary endpoint in studies II and III) and oral analgesic consumption were recorded at different time periods postoperatively.

Patient satisfaction
The patients were asked to give a verbal rating for satisfaction with the quality of analgesia (excellent = 4, good = 3, inadequate = 2, poor =1) during the first, second and seventh postoperative days (I–IV).

Functional outcome
Maximum degree of knee flexion and extension was assessed (I–IV). In the UKA studies (I and IV) the ability to walk with a frame 6 h postoperatively was recorded. Time to Up and Go (TUG)-test was also assessed (II–IV). The TUG-test involves timing the patient while they rise from an armchair, walk three meters, turn, walk back and sit down again. Times < 20 s indicate that the patient is independently mobile. The Oxford Knee Score and EuroQol (EQ-5D) were determined (I–IV). Oxford Knee Score is a validated 12-item knee questionnaire that scores patients from 12 (best possible) to 60 (worst possible). EQ-5D is a standardized measure of health outcome. It provides a single index value from 0 to 1, where 0 represents poor health and 1 represents perfect health.

Home readiness and Length of hospital stay
Time to fulfillment of discharge criteria (home readiness) was recorded in study II–IV (primary endpoint in study IV), using the following discharge
criteria: Mild or no pain (VAS < 30 at rest) sufficiently controlled by oral  
analgesics, able to walk with elbow crutches, ability to climb 8 stairs, eat  
and drink normally, and no evidence of any surgical complication. Length  
of hospital stay (LOS) was also recorded (day 0 = the day of operation) as  
actual time to home discharge in all four studies (primary endpoint in  
study I).

Adverse events
The incidence of nausea, vomiting, pruritus and sedation were recorded on  
the first and second postoperative days. All complications and adverse  
events were registered intra- and postoperatively and also after discharge.  
Any hospital readmission during the postoperative follow-up period was  
also recorded.

Plasma concentrations of ropivacaine
A sub-study of 8 patients investigating the plasma concentration of ropiva-
caine was performed prior to the start of study II. Venous blood was col-
lected postoperatively after 30, 60, 90, 120 and 180 min and just before  
and after the catheter injection at 30, 60, 90, 120 and 180 min for analyses  
of total and free (unbound) concentrations of ropivacaine.

Statistics
Power analyses were performed prior to the start of each study using data  
from previously published studies, when available, or data from some pilot  
patients for sample-size calculations. The length of hospital stay (primary  
endpoint in study I) and home readiness (primary endpoint in study IV)  
were analyzed using the Mann-Whitney U test.

VAS pain scores were analyzed using the Mann-Whitney U test at each  
time point in studies I, II and IV. In study III, a median value for the first  
48 postoperative hours was calculated as a summary measure for each  
patient; the difference between the groups was then analyzed using the  
Mann-Whitney U test.

The Mann-Whitney U test was used to analyze morphine consumption  
in studies II (primary endpoint), I and IV, while repeated measures analysis  
of variance (ANOVA) was used in study III (primary endpoint).

Patient satisfaction scores and knee function scores, including Oxford  
Knee Score and EQ-5D, were also analyzed using the Mann-Whitney U  
test. In study IV repeated measures analysis of variance (ANOVA) was  
used to analyze knee extension and flexion.
The Bonferroni-Holm method was used to correct for multiple measurements. Dichotomous data was analyzed using the chi-square test or Fisher's exact test, as appropriate.

A value of $p < 0.05$ was considered to be statistically significant. SPSS (version 15.0 for windows, SPSS Inc., Chicago, IL) and STATA (release 11, StataCorp., College Station, TX) were used in statistical analysis.
Results

A total of 178 patients were enrolled in these four studies (Table 2). Of these 178 patients, 7 were excluded after randomization: 2 in study I, 1 in study II, 2 in study III and 2 in study IV.

Table 2. Demographic data and type of surgery.

<table>
<thead>
<tr>
<th>Paper</th>
<th>n</th>
<th>Age</th>
<th>Female/male</th>
<th>ASA I/II/III</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>40</td>
<td>65 (6)</td>
<td>20/20</td>
<td>16/24/0</td>
<td>UKA</td>
</tr>
<tr>
<td>II</td>
<td>48</td>
<td>71 (9)</td>
<td>26/22</td>
<td>12/35/1</td>
<td>TKA</td>
</tr>
<tr>
<td>III</td>
<td>50</td>
<td>71 (8)</td>
<td>31/19</td>
<td>6/40/4</td>
<td>TKA</td>
</tr>
<tr>
<td>IV</td>
<td>40</td>
<td>64 (7)</td>
<td>23/17</td>
<td>16/24/0</td>
<td>UKA</td>
</tr>
</tbody>
</table>

n = number of patients. Age is shown as mean (SD). ASA physical status I: normal health; II: systemic disease with no limited activity; III: systemic disease with limited activity. UKA = unicompartmental knee arthroplasty. TKA = total knee arthroplasty.

Pain

In the first three studies, postoperative pain scores were lower at rest in the LIA groups and this was even more pronounced on flexion. The lower pain intensity at rest lasted until 27 h postoperatively when compared with placebo (I, II) and up to 24 h when compared with intrathecal morphine (III).

On flexion there was lower pain intensity up to 27 h postoperatively in the LIA group following unicompartmental arthroplasty (I) (Fig. 5) and up to 48 h during total knee arthroplasty in studies II (Fig. 6) and III (Fig. 7). No differences in postoperative pain intensity were found when comparing minimally invasive to conventional surgery where both groups received LIA (IV) (Fig. 8).
**Fig. 5.** Pain on flexion (UKA) (Study I). Group A: LIA and Group P: Placebo. a) p < 0.05.

**Fig. 6.** Pain on flexion (TKA) (Study II). Group A: LIA and Group P: Placebo. a) p < 0.05.
Fig. 7. Pain on flexion (TKA) (Study III). Group L: LIA and Group M: Intrathecal morphine. a) p < 0.05.

Fig. 8. Pain on flexion (UKA) (Study IV). Group MIS and Group CON: Conventional surgery.
Morphine consumption
Morphine consumption was lower in the LIA groups than in the placebo groups in unicompartmental (I), and in total knee arthroplasty (II), and also compared to intrathecal morphine (III) (Table 3). No differences were found when comparing minimally invasive and conventional surgery in unicompartmental knee arthroplasty, where both groups received LIA (IV).

Tab. 3. Morphine consumption 0–48 h.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Median (range)</th>
<th>Median (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (UKA)</td>
<td>21 (0-68)</td>
<td>67 (17-126)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II (TKA)</td>
<td>18 (1-74)</td>
<td>87 (36-160)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III (TKA)*</td>
<td>23 (2-80)</td>
<td>42 (19-138)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV (UKA)</td>
<td>14 (0-63)</td>
<td>8 (0-51)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

IV PCA-morphine in mg. Studies I–II: LIA vs. Placebo; Study III: LIA vs. intrathecal morphine; Study IV: MIS vs. Conventional surgery (LIA in both groups). * Reported as mean (SD) in the published paper: 26 (15) vs. 54 (29) mg.

Home readiness, length of hospital stay
Time to fulfillment of discharge criteria (home readiness) was shorter in the LIA groups compared to the placebo group (II) and compared to the intrathecal morphine group (III) during total knee arthroplasty. In study IV, there were no differences between the minimally invasive and conventional surgery, both groups were home ready after a median time of 24 hours.

A shorter length of hospital stay was found in the LIA groups compared to the placebo group (I) (Fig. 9) and compared to the intrathecal group (III). However, this shorter hospital stay in patients in the LIA group vs. placebo in study II (4 vs. 6 day), did not reach statistical significance (p = 0.06) (Table 4). In study IV there was no difference between the groups in terms of hospital stay and the proportions of patients who were discharged during the first postoperative day were similar between the groups; 80 % in group MIS compared to 83 % in group CON (p = 1.0). After 2 days, only one patient in group MIS remained in the hospital and was discharged on postoperative day 3. These results correspond well with the LIA group in study I (Fig. 9).
Hospital stay after knee surgery

<table>
<thead>
<tr>
<th>No. of patients discharged from hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tbody>
</table>

Fig. 9. Length of Hospital Stay (Study I). Group A: LIA and Group P: Placebo.

Tab. 4. Length of Hospital Stay.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Median (range)</th>
<th>Median (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (UKA)</td>
<td>1 (1-6)</td>
<td>3 (1-6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II (TKA)</td>
<td>4 (2-8)</td>
<td>6 (3-10)</td>
<td>0.06</td>
</tr>
<tr>
<td>III (TKA)</td>
<td>3 (2-17)</td>
<td>4 (2-14)</td>
<td>0.03</td>
</tr>
<tr>
<td>IV (UKA)</td>
<td>1 (1-3)</td>
<td>1 (1-2)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Length of hospital stay (number of days). Study I–II: LIA vs. Placebo; Study III: LIA vs. intrathecal morphine; Study IV: MIS vs. Conventional surgery (LIA in both groups).

Surgical outcome

The only difference in knee function in the UKA study (I) was found after 27 h, with better knee extension and knee flexion in the LIA group compared to the placebo group (medians of 5 degrees vs. 10; and 90 degrees vs. 80). In the TKA study (II) comparing LIA with placebo, we found that the LIA group showed better knee flexion at 24 h (90 vs. 60 degrees); and at
48 h (75 vs. 60 degrees). No differences in knee function scores were found in Studies III and IV.

In study I, 16 of 19 patients in the LIA group compared to 9 of 19 in the placebo group were able to walk with a frame at 6 h postoperatively (p=0.04). In study IV, comparing minimally invasive and conventional surgery, no difference was found between the groups in the ability to walk with a frame (14 of 17 patients vs. 13 of 15).

A greater proportion of patients given LIA compared to intrathecal morphine (III) were able to climb stairs at 24 h (20 % vs. 4 %) and at 48 h (70 % vs. 22 %).

No differences were found between the groups in any of the studies in the TUG-test, Oxford Knee Score or EQ-5D.

**Patient satisfaction**

Patient satisfaction was greater in the LIA groups in the TKA studies (II and III), but no statistically significant differences between the groups were found in the UKA studies (I and IV).

**Side effects**

There was a lower incidence of nausea, pruritus and sedation in the LIA groups compared with placebo groups (I and II), but no differences were found when LIA was compared with intrathecal morphine (III).

It was found that 14 of 171 cultures taken from the catheter tips were positive for solitary coagulase-negative Staphylococcus, but no signs of clinical infections were found in any of these patients. One patient in study III was readmitted due to a swollen knee and mild fever, which resolved following oral antibiotic administration. However, wound cultures were negative and no deep infection developed in this patient.

**Sub-study on ropivacaine blood concentration (II)**

The individual maximum unbound venous plasma concentration of ropivacaine varied between 0.032 and 0.121 µg/mL in the subgroup of 8 patients studied, which was below the toxic level of 0.35 µg/mL (Fig. 10). The individual maximum total venous plasma concentration of ropivacaine varied between 0.062 and 2.458 µg/mL (Fig. 11). The highest individual value of total venous plasma concentration (2.458 µg/mL) corresponded to an unbound venous plasma concentration of 0.093 µg/mL. None of the patients displayed any symptoms or signs of systemic LA toxicity.
Fig. 10. Unbound venous plasma concentration of ropivacaine.

Fig. 11. Total venous plasma concentration of ropivacaine.
Discussion

Knee arthroplasty is considered one of the most successful orthopedic procedures, usually resulting in a pain-free knee, restored function and with excellent long-term outcomes for patients. Although successful, the procedure is generally associated with moderate to severe postoperative pain.

This thesis addresses the important issue of postoperative pain management using a new and promising technique, often called local infiltration analgesia (LIA), which we have studied in patients undergoing knee arthroplasty.

The technique

The LIA technique has been used by several groups of researchers, particularly in Scandinavia. However, there are many descriptions and variations in the technique used, which may partly explain the variability in reported results. In the studies performed by our group, we used the original method outlined by Kerr and Kohan with some minor modifications. In our initial study on patients undergoing UKA, we decided to use a lower dose of ropivacaine (200 mg), since we were concerned about potential LA toxicity when infiltrating large doses into the soft tissue around the knee joint. In that study, we found no signs or symptoms of LA toxicity. Therefore, in our second study, in patients undergoing TKA, we decided to increase the dose of intraoperative ropivacaine to 400 mg and the postoperative bolus dose to 200 mg. This was for two reasons: firstly, TKA involves more extensive surgery and therefore the volume of injectate had to be increased; secondly, we thought there may be a dose-response effect, with increased dosage producing improved analgesia. To ensure the safety of such high doses of ropivacaine, we first performed a sub-study investigating the plasma concentration of ropivacaine prior to starting the main study. We found that, although ropivacaine is absorbed to a significant extent from the knee joint, the plasma concentration of ropivacaine continued to be low despite these high doses, and no patient showed any symptoms of clinical LA toxicity. This could be because we used epinephrine in the mixture of drugs, which may have prevented rapid LA absorption from the tissues. Additionally, we used compression dressings and hypothermic pads around the knee joint, which may also have reduced LA absorption. However, no specific splint was applied to stabilize the knee, except for the splinting effect of the compression and cooling bandages.

The effect-duration of LIA appears to vary between studies and the effect could be short-lasting. Therefore, several authors used catheters...
placed intraarticularly in order to prolong the duration of action. We did not use any additional top-up bolus injections, except for the one on the first postoperative morning. It is possible that intermittent injections during the evening and night may have improved pain-relief. However, this method has two problems: firstly, there is a risk of LA toxicity when using several doses after the large initial bolus. Secondly, administering intermittent injections on hospital wards could be personnel-intensive and require frequent patient monitoring to detect possible LA toxicity, so therefore we decided to give a single dose the following day in order to prolong the effect.

In addition, it is important to perform the intraoperative injections carefully and in a standardized way in order to achieve the best effect. Not only is sterility important in this situation, but also a careful injection protocol is required to ensure proper spread of the drug into traumatized tissues and therefore effective analgesia.

**Catheter injections**

The definition of LIA is not universally agreed upon at the present time and therefore, in the studies published to date, either bolus injections, continuous infusions or single dose at the end of the procedure have been used to describe the same technique. In our studies, we used the intraarticular catheter for one bolus injection, using a smaller volume of the same mixture on the first postoperative morning, except in study III, where we injected another dose of this mixture on the second postoperative morning in order to further prolong the effect of LIA.

A number of studies reported that an intraarticular injection of local anesthetics, without infiltration into periarticular tissues, after TKA had no effect on postoperative pain. At present, there is little information in the literature regarding the specific effect of bolus injections following intraoperative infiltrations and the scientific evidence for these bolus injections has been questioned. Only one study has specifically addressed this issue. In that study on hip arthroplasty, both groups received LIA during the operation. Postoperatively at 10 and 22 hours, one group received the LIA-mixture via the catheter while the other group received saline via the catheter. The authors found no clinically important effect of bolus injection following total hip arthroplasty. Although our studies were not designed to examine the catheter-injections specifically, we believe that the decrease in pain intensity following the catheter injections in the LIA groups indicates a definitive but short-lasting effect of the bolus injection. The advantage of catheter-use in relation to the potential risk of infection needs to be addressed in future studies.
Pain intensity and morphine consumption

Effective pain relief is central to improving patient satisfaction and possibly long-term outcomes. Therefore, it is important to confirm the efficacy of LIA compared to placebo. We found lower VAS pain scores in the LIA groups than the placebo groups (I, II) at rest and this difference was more pronounced on flexion. This is an important finding, since adequate flexion of the knee prevents stiffness and promotes mobilization.

Thus, we found a statistically significant difference between the LIA and placebo groups that lasted up to 27 h postoperatively following UKA (study I) and up to 48 h following TKA (study II). One explanation for the difference in duration of analgesia between the two studies could be that the pain intensity decreases faster following UKA, which is a less invasive procedure than TKA. Another explanation could be that the dose of ropivacaine in LIA was increased from 200 mg (study I) to 400 mg in the TKA study (II). In addition to the lower pain intensity in patients receiving LIA, we also found that morphine consumption was lower in the LIA groups compared to the placebo groups in studies I and II. Our results are in accordance with those of other authors comparing LIA with placebo 26, 28, 29.

Having shown that LIA is beneficial compared to placebo in both UKA and TKA, we were interested to assess its efficacy with intrathecal morphine, another common technique for postoperative pain management. The duration of action of intrathecal morphine varies between 8 and 24 h. However, at least two recent studies reported reduced rescue analgesic consumption up to 48 h after intrathecal morphine injection 58, 59. We found that patients receiving LIA had lower pain intensity and reduced morphine consumption for up to 48 h postoperatively (study III). However, the prolonged analgesia seen in this study could be because we gave a bolus injection on the second postoperative morning (study III).

In study IV, comparing MIS with conventional surgery in UKA, we found no differences between the groups regarding pain intensity or morphine consumption. Traditionally, knee replacements have been performed with a 20–25 cm-long skin incision and a medial parapatellar capsule incision. The capsule incision is extended proximally into the quadriceps tendon and the patella is everted and dislocated laterally. This approach generally gives good access, but results in a fairly great trauma to soft tissue around the knee.

MIS involves an 8–10 cm-long skin incision. The patella is not everted or dislocated, and the extensor mechanism is left unharmed. The “quadriiceps-sparing” rather than the shorter skin incision is thought to be the key factor in MIS knee surgery 60. We had expected greater postoperative pain...
in the conventional exposure with a longer skin incision, but we were surprised that the pain scores were rather low. Interestingly, we found that median pain scores at rest were below 6 mm and on flexion below 20 mm at all time points during the first 27 hours postoperatively in both groups. Furthermore, the doses of morphine used were generally very low in study IV. These findings relating to pain intensity are in agreement with another randomized, controlled trial by Carlsson et al. There could be several possible explanations for the low pain intensity and low morphine consumption in our study. For one, we used the local infiltration technique in both groups, including a bolus injection on the first postoperative morning. In addition, we had increased the dose of the local anesthetic (ropivacaine) from 200 mg to 400 mg during the operation and from 150 mg to 200 mg postoperatively in study IV compared to study I. Thus, the patients in the conventional surgery group had the best possible pain management protocol that we had found over several years of research, with the result that pain intensity was low in this group.

**Knee function, patient satisfaction**

In addition to satisfactory pain relief, good knee function and high patient satisfaction are important patient-related end-points. Thus, our aim was to achieve good pain relief in the expectation that this would lead to improved knee function as well as patient satisfaction. It was previously shown that severe pain may hinder mobilization.

We assumed that mobilization could be assessed, indirectly, by the maximum degree of knee flexion and extension. In other words, good knee flexion and extension were taken to be prerequisites for early mobilization. However, we saw only a small difference between LIA and placebos in studies I and II during the first 48 postoperative hours; however, a significantly greater proportion of LIA patients were able to walk using a frame at 6 h postoperatively following UKA (study I). This is probably a more direct measure of mobilization and a better predictor of early home discharge than knee flexion/extension. This was also seen in study III, where more patients were able to climb stairs at 24 and 48 h postoperatively, indicating earlier mobilization in the LIA group compared to the intrathecal morphine group. However, no differences were found in the TUG-test. Although the TUG-test has been used as an objective measure of mobilization in previous studies, we did not find that it was sensitive in detecting differences between pain management techniques.

When comparing the two surgical techniques (study IV), we found no differences in knee function scores. This is in contrast to another study on MIS. Price found that patients undergoing UKA using MIS could be mo-
bilized twice as fast as conventional UKA. We could not confirm those results. One explanation for these differences could be that all patients in our study were mobilized early and more than 80% were discharged home on the first postoperative day.

Although greater patient satisfaction was found in the LIA groups in studies II and III, only minor differences were seen in functional outcomes as assessed by the Oxford Knee Score or in the health-related quality of life as determined by EQ-5D, in all studies. This could partly be explained by the fact that these assessments took place first after 2 weeks and after 3 and 6 months (I, IV), when the likely benefits of LIA were no longer present. On the other hand, this supports the findings of other studies, that the LIA technique with early home discharge is safe following unicompartmental knee arthroplasty 37-39.

**Home readiness, length of hospital stay**

Early home readiness and discharge are important parameters for quality of care. Not only does this mean that patients are able to look after themselves but the costs of health-care are reduced. Indeed, we demonstrated significantly earlier discharge from hospital in the LIA groups in studies I and III. However, in study II, where we compared LIA with placebo during TKA, the differences did not reach statistical significance. Thus, although we demonstrated a definite reduction in pain intensity in the LIA group during TKA, this did not result in earlier home discharge. Since length of hospital stay can be influenced by several non-medical factors (administrative reasons or the availability of a home-carer), it is not always possible to demonstrate a difference in home discharge in small studies. Furthermore, when we initially investigated the LIA technique, we did not adopt the entire protocol outlined by Kerr and Kohan, which included pre-operative patient education and post-discharge follow-up. Thus, it is possible that we did not fully exploit the potential advantages of good postoperative pain management in our protocol. Another explanation could be that this study was not powered to detect a difference in home readiness.

We did, however, assess the time to fulfillment of all discharge criteria (home readiness) in studies II–IV. In assessing home readiness it is important to use objective parameters that can easily be assessed and have relevance for both the patient and the care-giver. Since home readiness depends on a composite of several factors, delay in one of these factors would influence outcome. This outcome coincided well with hospital stay and showed statistical significance in studies II and III, in favor of the LIA groups.
In contrast to our findings, other authors did not report a shorter hospital stay when comparing LIA with placebo. One possible explanation for this could be that Busch et al. used no bolus injections after 24 h as in our study, while Vendittoli et al. used ropivacaine alone in the bolus injection. Of the other studies comparing LIA with other methods for postoperative pain relief, only one (LIA vs. EDA) demonstrated a reduction in hospital stay. The other studies, where the authors compared LIA with EDA or femoral nerve block, did not find any difference in length of hospital stay. We do not have any clear explanation for the difference between these studies but, as mentioned earlier, it could be due to a multitude of factors that influence home discharge, some of which can be difficult to control in clinical studies. Additionally, if the whole protocol is not adopted, the benefit of LIA in terms of early mobilization and discharge might not be evident.

In the final study, comparing minimally invasive surgery and conventional surgery in unicompartmental knee arthroplasty (both groups received LIA), we found no differences in home readiness or length of hospital stay between the groups. This was somewhat surprising and contrary to the study by Carlsson et al., who found a difference of 3 days (3 vs. 6 days) in hospital stay in favor of the MIS group. There could be several explanations for this. It is possible that LIA provides excellent analgesia even during more extensive surgery and therefore differences in postoperative pain and mobilization were less obvious between the two operative techniques. Another explanation could be that the bone preparations and implant insertion during MIS are made through a limited exposure, which may involve more extensive use of wound retractors and associated damage to soft tissue, resulting in postoperative pain.

**Adverse events**

Lower morphine consumption reduces the risk of opioid-related side effects, such as nausea, pruritus and sedation. Indeed, we found lower incidence of such side effects in the LIA groups when compared to placebo (I, II), and, although a similar tendency was found in comparison with intrathecal morphine (III), this did not reach statistical significance. A greater difference may have been anticipated between the groups in study III, since the control group in this study received both intrathecal morphine and PCA-morphine. However, the intrathecal morphine dose was relatively low and the study was not powered to detect a difference in this parameter.
**Systemic and local toxicity**

The possible hazards of the LIA technique need to be discussed. Injecting such high doses of ropivacaine as we did presents a risk of systemic and local toxicity. Ropivacaine is less cardiotoxic than bupivacaine. When increasing the dose from 200 mg (I) to 400 mg (II), we assessed the possible systemic toxicity of ropivacaine. The unbound venous blood concentration of ropivacaine was below known systemic toxic blood concentrations and we found no clinical signs of systemic toxicity in any patient. These results are in accordance with other studies, which also reported low blood concentrations of ropivacaine. Therefore, 400 mg ropivacaine appears to be safe when injected using the method described.

Another important question is whether there is a risk of local toxicity of ropivacaine injected intraarticularly. In recent years, there were reports of chondrolysis associated with the use of another LA, bupivacaine, when administered intraarticularly via a pump during shoulder surgery. However, this appears to have been specifically when using bupivacaine since there are no published reports of similar effects for ropivacaine. Piper did not find any evidence for chondrotoxicity of ropivacaine in vitro. Furthermore, chondrotoxicity is mainly of concern in unicompartmental knee arthroplasty, since all or nearly all of the cartilage is replaced by the implant in TKA. However, in the 57 UKA patients receiving LIA in our studies, we saw no clinical evidence of any chondrolysis during the 6 months follow-up. Two patients in study IV had residual pain in the medial part of the knee after the 6 months follow-up. Clinical and radiological follow-up of these patients did not show any signs of implant loosening or lateral chondral damage. This may indicate that the proposed risk of toxic chondrolysis caused by the local infiltration analgesia is probably not evident in unicompartmental knee arthroplasty. Additionally, we have used ropivacaine during knee as well as shoulder arthroscopies for over 10 years in our institution without any evidence of chondrolysis.

The next question is whether ketorolac injected periarticularly has any negative effect on implant fixation. There has long been a concern in the orthopedic community regarding the effect of NSAIDs on bone-healing. However, a recent study on NSAIDs administered during a 3-weeks period did not show any negative effect on prosthesis fixation in total knee replacement. Therefore, it is our belief that NSAIDs are safe when used in the LIA mixture as descibed.

Finally, there is a debate over whether it is safe to leave an intraarticular catheter for 1–2 days following knee surgery. As an orthopedic surgeon, one is always concerned when there is a possible risk of bacterial invasion via the catheter and into the prosthesis. A number of studies in
addition to ours, using LIA and intraarticular catheters, have not reported any infections related to the use of the wound catheter. However, two studies did report deep infections. DeWeese et al. reported one deep infection in 91 patients, while Rasmussen et al. found one case in 136 TKAs when a catheter was left in situ for 72 hours. This low incidence of deep infection following TKA can be expected even without intraarticular catheters. In the 171 patients included in this thesis, where catheters were left in situ, we found no case of deep infection. It is important to stress that all our patients were given antibiotics until the catheter was removed, that the catheters were inserted during the operation under sterile conditions and a bacterial filter was used during all postoperative intraarticular injections. Furthermore, local anesthetics have been reported to possess anti-inflammatory, bacteriostatic and antimicrobial effects, which may help explain the lack of any deep infection in our patients. In conclusion, it seems safe to use an indwelling knee catheter in the method described in these studies.

Limitations
There are some limitations with the three initial studies (I, II, III) that need to be addressed. Should the control group have received systemic NSAIDs, in order to exclude a possible systemic effect of ketorolac in patients receiving LIA? In our studies, the aim was to compare the concept of LIA to placebo (I, II) or intrathecal morphine (III), rather than to investigate the individual drugs. Furthermore, some studies have indicated a local (rather than systemic) effect of NSAIDs. For example, Spreng et al. reported a superior effect of ketorolac injected locally in the LIA-mixture than when administered intravenously. To our knowledge, there are no published studies where the systemic concentrations of ketorolac were measured following peri- and intraarticular injections. Unpublished data from Kerr in Australia show that peak blood-levels following local infiltration were significantly lower than when given intramuscularly, 0.28 µg/mL compared to 2.6 µg/mL (Kerr 2011, personal communication). However, it is possible that some of the analgesic effect of LIA could be contributed by its systemic absorption of both LA and ketorolac, but we believe that this is of minor importance. Although LA administered intraarticularly is absorbed into the systemic circulation, the concentrations are low. Nevertheless, this systemic absorption may contribute to the observed analgesic effect.

We did not use any oral NSAID in the protocols for our studies. The use of oral NSAIDs may have further reduced postoperative pain. However, we decided not to include these for several reasons. We were con-
cerned about possible systemic toxicity, since we used another NSAID (ketorolac) in the LIA-mixture. It is possible that we could have used oral NSAIDs in the placebo group but this would have confounded the evaluation of the LIA concept. Finally, there was an ongoing debate concerning the cardiotoxic effects of NSAIDs at the time of writing the study protocols, which possibly contributed to the decision to avoid oral NSAIDs.

Could a higher dose of morphine injected intrathecally resulted in better pain relief and a minimal difference between the groups in study III? In one study, the authors reported that morphine 0.1 or 0.2 mg resulted in similar postoperative pain relief after hip arthroplasty. In addition, 0.1 mg morphine was found to provide the best balance between efficacy and side effects in elderly patients. We found few side effects at this dose and no serious complications such as respiratory depression were seen in that study, further supporting the use of this dose intrathecally.

The final study also has some limitations. Firstly, would a larger sample-size have detected a difference between the groups in our primary endpoint? Although this is possible, small differences between groups in larger studies may be of statistical importance but are unlikely to have practical clinical relevance. In addition, even the confidence interval calculated for the primary endpoint in this small study was very narrow and far less than would be clinically relevant, suggesting that a larger study may have likely resulted in even narrower confidence intervals, which would be clinically meaningless. Furthermore, the lack of differences in our secondary endpoints also supports that the differences between these groups, if any, are rather small. Taken together, we believe that there is no clinically important difference between the two surgical methods. One final limitation is that this study was not blinded and therefore it is open to issues of observer bias. However, despite this potential bias in favor of MIS, we found no real differences between the groups.

To summarize, the results from our studies indicate that the LIA technique provides good postoperative analgesia and promotes early mobilization, when compared with placebo following knee arthroplasty. The LIA technique also seems to be superior to intrathecal morphine following total knee arthroplasty. Moreover, when LIA is used, minimally invasive surgery does not seem to improve the outcome compared with conventional surgery in unicompartmental knee arthroplasty.

Clinical implications
In light of our results, LIA seems to be a simple, safe and potent technique for postoperative pain management and early mobilization following knee arthroplasty. The early mobilization has the potential to reduce the risk for
venous thrombo-embolism and nosocomial infection. Shorter hospital stay reduces health-care costs and waiting time for surgery and patients also feel more comfortable in the home environment.

Unicompartmental knee arthroplasty using LIA, might routinely be performed as a day-surgery procedure in future. Furthermore, when using LIA in unicompartmental knee arthroplasty, the type of surgery (MIS or conventional surgery) can be guided by individual surgeon preference and local hospital practices.

**Future research**

Further studies should be performed in order to investigate the role of the different components of the LIA technique. What are the optimal doses of the drugs used in the LIA-mixture? Should corticosteroids be added to this? What is the role of the drugs administered after 24 h via the catheter and do the advantages outweigh the risk of infection? Would larger long-term follow-up studies reveal any side effects of the technique? More studies, using a different implant system are warranted in order to evaluate the concept of MIS in UKA when LIA is used.

Postoperative pain protocols aiming to minimize pain and promote early mobilization often consist of several phases, such as patient information, anesthesia protocols, MIS, LIA, pain management protocols, early physical therapy protocols and home care. The exact role of each of these components is yet to be explored. Visiting Drs Kerr and Kohan in Sydney recently, I understand today that the LIA technique is merely one component in the process of achieving good quality recovery after major orthopedic surgery. However, LIA should be regarded as a key enabling technique, promoting the rapid return of patients to normal activities of daily living.
Conclusions

I  Local infiltration analgesia (LIA) resulted in better postoperative analgesia and earlier mobilization, compared to placebo, following unicompartmental knee arthroplasty performed with minimally invasive surgery (MIS).

II  Local infiltration analgesia (LIA) resulted in better postoperative analgesia and earlier mobilization, compared to placebo, following total knee arthroplasty. Blood concentrations of the local anesthetic were below known toxic levels.

III  Local infiltration analgesia (LIA) provided better postoperative analgesia and earlier mobilization, compared to intrathecal morphine, following total knee arthroplasty.

IV  Minimally invasive surgery (MIS) did not result in reduced postoperative pain or earlier mobilization, compared to conventional exposure in unicompartmental knee arthroplasty, when both groups received local infiltration analgesia (LIA).
Summary in Swedish

Knäartros är en vanlig åkomma och årligen utförs över 12000 knäprotesoperationer i Sverige.

Om endast en ledkammare är angripen kan man överväga en enkammarprotes. Om hela knäet uppvisar artros används oftast totalprotes.

Den postoperativa smärtan efter en knäprotesoperation är ofta svår. Flea försök att förbättra smärtlindring och mobilisering efter knäprotesoperationer har gjorts de senaste åren. Lokal infiltrationsanalgesi (LIA) är en teknik där en blandning av lokalbedövningsmedel, inflammationshämmande medel och adrenalin infiltreras i operationsåret i slutet av operationen och injiceras via en kvarliggande knäkateter efter operationen. En annan metod är utvecklingen av mini-invasiv kirurgi (MIS), som innebär en minskad friläggning vid operationen.

I de inledande två studierna jämfördes LIA med placebo vid enkamar- och totalprotesoperationer. Postoperativ smärta, morfinåtgång och biverkningsfrekvensen var lägre i LIA-grupperna. I enkammarprotes-studien var vårdtiden kortare och i totalprotes-studien var tid till hemgångsklar kortare i LIA-gruppen. Blodkoncentrationen av lokalbedövningsmedlet (ropivakain) var under toxisk nivå.

I den tredje studien jämfördes LIA med en annan vanligt förekommande metod för postoperativa småttbindring, morfin givet tillsammans med lokalbedövningsmedlet vid ryggbedövning (spinalt morfin). Postoperativ smärta och morfinåtgång var lägre, vårdtiden kortare och patienttillfredsställelsen högre i LIA-gruppen jämfört med spinalt morfin-gruppen.

I den sista studien undersökt med mini-invasiv kirurgi (MIS) jämfört med konventionell kirurgi vid enkammarprotesoperationer, där båda grupperna erhöll LIA. Vi fann ingen skillnad i tid till hemgångsklar, vårdtid, postoperativ smärta eller morfinåtgång.

Sammanfattningsvis visade våra studier att LIA resulterade i bättre smärtlindring och mobilisering än placebo, både vid enkamar- och totalprotesoperationer. LIA gav också bättre småttbindring och mobilisering än spinalt morfin vid total knäprotesoperationer. Mini-invasiv kirurgi (MIS) resulterade inte i bättre småttbindring och mobilisering, när LIA användes i bågge grupperna.
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