REGIONAL ANAESTHESIA

High-volume local infiltration analgesia combined with intravenous or local ketorolac + morphine compared with epidural analgesia after total knee arthroplasty

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Key points

- After total knee arthroplasty, local infiltration analgesia (LIA) with intra-articular ketorolac and morphine was superior to epidural anaesthesia after the initial 24 h.
- Epidural anaesthesia offered better initial pain relief, despite more common side-effects such as hypotension at the post-anaesthetic care unit.
- Ketorolac and morphine showed a superior therapeutic balance when given as intra-articular adjuvants than when given i.v.
- Patients getting LIA had superior knee function, were mobilized faster, and were discharged earlier from hospital.

Background. Recently, high-volume local infiltration analgesia (LIA) in total knee arthroplasty (TKA) has been introduced, but dosage, timing, and effects of adjuvants are still debated.

Methods. We randomized 102 patients undergoing TKA to receive either epidural analgesia (EDA group) or LIA (ropivacaine 150 mg and epinephrine 0.5 mg) combined with ketorolac 30 mg and morphine 5 mg given either locally (LIA group) or i.v. (LIAiv group). Epidural analgesia was maintained for 48 h. Intra-articular re-injection via a catheter with ropivacaine 142.5 mg and either intra-articular or i.v. ketorolac 30 mg was given 24 h after surgery. Pain scores, morphine consumption, side-effects, and readiness for hospital discharge were studied.

Results. At discharge from the postoperative anaesthetic care unit, verbal pain scores were lower in the EDA group (P=0.004), but discharge was delayed (difference 101 min, 95% CI: (23, 178), P=0.007). Group LIA reported lower pain scores at rest beyond 24 h after surgery (mean VAS (so) at 24/48/72 h: LIA group 16/12/10 (13)/(13)/(11); LIAiv group 22/18/15 (17)/(15)/(12); EDA group 27/30/21 (21)/(29)/(19)). Both the LIA and the LIAiv groups were mobilized faster and were earlier ready for hospital discharge [3.5 days (LIA group) vs 4 days (LIAiv group) vs 5.5 days (EDA group); P<0.001]. Cumulated morphine consumption (72 h) was lowest for the LIA group [80 vs 101 mg (EDA group) vs 118 mg (LIAiv group), P=0.007].

Conclusions. LIA with local adjuvants compared with epidural analgesia results in reduced opioid consumption, faster mobilization, and earlier readiness for hospital discharge. Ketorolac and morphine are more efficient when given locally than systemically.

The study has been registered at clinicaltrials.gov (NCT00562627) before onset of participant enrolment: http://clinicaltrials.gov/ct2/show/NCT00562627?term=spreng&rank=2 (April 21, 2010).

Keywords: anaesthesia, infiltration; anaesthesia, local; analgesia, epidural; arthroplasty, replacement, knee

Accepted for publication: 6 July 2010

Total knee arthroplasty (TKA) is associated with moderate-to-severe postoperative pain.1 Traditionally, epidural analgesia or continuous peripheral nerve blocks have been used for postoperative pain treatment after TKA.2–5 Recently, Kerr and Kohan6 introduced the concept of ‘high volume–low concentration’ local infiltration analgesia (LIA) in a case series of patients undergoing hip and knee surgery. Studies have shown that LIA is consistently more effective in the treatment of postoperative pain after TKA, when compared with placebo.7,8 LIA has also been shown to accelerate rehabilitation and reduce the length of hospital stay when compared with placebo.8,9 The use of LIA has shown a better analgesic effect compared with epidural analgesia in patients after hip arthroplasty.10 In patients undergoing TKA, LIA has been compared with femoral nerve block,11 but no randomized study has compared LIA with epidural analgesia in this group of patients.
Also, it is disputed to what extent the observed benefits of LIA may be enhanced by adding non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and/or vasopressor. Further, it is not agreed upon whether these adjuvants have a specific local effect or merely have an effect through absorption to systemic circulation.

The main goal of this clinical trial was to compare multimodal peri- and intra-articular infiltration analgesia to standard epidural analgesia in patients undergoing TKA.

The second aim was to study whether intra-articular administration of NSAIDs (ketorolac) and morphine resulted in a better analgesic effect compared with the same drugs given i.v.

**Methods**

The study protocol was approved by the National Committee for Medical and Health Research Ethics and the Norwegian Medicines Agency, and the study was registered at http://www.clinicaltrials.gov (NCT00562627). Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and conformed to the CONSORT guidelines. It was conducted in a prospective, randomized manner, with two study groups (double-blinded) and a control group (continuous lumbar epidural analgesia). Collection of data and data analysis have been externally monitored (Section for Good Clinical Practice, Oslo University Hospital, Ullevaal, Norway).

All patients at our county hospital during the period from November 2007 to June 2009 due for unilateral non-cemented poro-coated LCS® TKA without patella resurfacing were evaluated for enrolment. Inclusion criteria were age ≥18 yr and ASA grade ≤III. Patients with moderate or severe heart, lung, liver, kidney, or psychiatric disease and patients with a history of gastric ulcer disease or regular use of opioids, and also pregnant or breastfeeding patients were excluded from study participation.

After premedication with oral acetaminophen (weight <60 kg: 1000 mg; 60–90 kg: 1500 mg; >90 kg: 2000 mg), spinal anaesthesia (level L2–L5) was performed using bupivacaine (Marcain plain® 5 mg ml$^{-1}$) 13–15 mg with fentanyl 20 µg added. Propofol (10 mg ml$^{-1}$) up to 10 ml h$^{-1}$ was allowed for sedation if indicated. All patients got supplemental oxygen via a nasal catheter, 2 litre min$^{-1}$.

Permuted block randomization, blinding, and packing of the study medication were performed by the hospital pharmacy, and the patients were randomized to receive either epidural analgesia (EDA group) or LIA. Patients getting LIA were further randomized in two groups and got, in addition to standard LIA, both ketorolac 30 mg and morphine 5 mg injected either into the knee (LIA group) or i.v. (LIAiv group).

Patients randomized to postoperative lumbar epidural analgesia received an epidural catheter through a Touhy G 18 needle (at level L2–L5) immediately before spinal anaesthesia was performed. The epidural catheter was taped along the back of the patient and connected to an infusion pump, which was covered in an opaque bag. Patients randomized to LIA got an identical looking catheter taped along the back, but no Touhy needle puncture. This catheter was connected to a shunt pump, which was covered in an opaque bag.

The solutions which were infiltrated into the knee (150 ml) were prepared under aseptic conditions and contained ropivacaine 150 mg and epinephrine 0.5 mg added to isotonic saline. In the LIA group, ketorolac 30 mg + morphine 5 mg were added to the infiltration mixture.

The knee injections were administered in the same way in both local infiltrate groups: after surgical preparation of the knee joint, the surgeon injected 40 ml of the study medication into posterior capsule structures. After the joint replacement, 50 ml of the study medication was infiltrated circular around the prosthesis. An 18 G epidural catheter with a bacterial filter was placed from the lateral side into the knee joint. After closure of the capsule, the surgeon infiltrated another 50 ml of the study medication into the fascia and subcutis. At the end of the operation, 10 ml of the study medication was injected through the knee catheter.

Patients randomized to epidural analgesia received no knee infiltrations. An epidural catheter, which was not inserted into the knee joint, was taped along the knee after surgery. Only the bacterial filter could be seen after knee bandage in all patients.

After surgical knee joint preparation, the LIAiv group patients got an i.v. injection of ketorolac 1 ml (30 mg ml$^{-1}$) plus morphine 5 ml (1 mg ml$^{-1}$), whereas patients in the LIA group got isotonic saline 6 ml.

Unilateral TKA was performed by a computer-assisted method with minimal ligament release and tibia cut first. All patients got i.v. tranexamic acid (Cyclocapron®) 10 mg kg$^{-1}$ 15 min before tourniquet was released. No wound drains were inserted, and after the end of surgery, a cooling compression bandage (Cryocuff®) was applied around the operated knee.

The patients were transferred to the post-anæsthetic care unit (PACU) and observed there for at least 4 h by a study nurse not knowing the group allocation. Patients randomized to epidural analgesia got epidural infusion with fentanyl 2 µg ml$^{-1}$, epinephrine 1 µg ml$^{-1}$, bupivacaine 1 mg ml$^{-1}$ started as soon as the spinal anaesthesia started to wear off. The infusion rate was programmed according to body height (<160 cm: 6 ml h$^{-1}$; 160–190 cm: 8 ml h$^{-1}$; >190 cm: 10 ml h$^{-1}$). Continuous epidural analgesia was maintained for 48 h after operation.

All patients were treated with acetaminophen 1000 mg every 6 h during the hospital stay and were equipped with an i.v. patient-controlled morphine pump (PCA) for the first 48 h after surgery (2 mg bolus with 10 min lockout time). Pain intensity at rest and during cautious active knee flexion was assessed by a study nurse after 30 min and thereafter every hour until discharge from PACU, using a visual analogue scale (VAS, 0–100) and a verbal scale (none, mild, moderate, severe, and very severe). At the same time intervals, the patients were asked if they suffered from postoperative nausea and vomiting (PONV) and, in the case of nausea or vomiting, treated with i.v. odansetron.
Between 22 and 24 h after surgery, patients in the LIA group and in the LIAiv group got injections both into the knee and i.v. The solutions which were injected into the knee (20 ml) were prepared under aseptic conditions containing ropivacaine 19 ml (7.5 mg ml\(^{-1}\)) and either ketorolac 1 ml (30 mg ml\(^{-1}\)) in the LIA group patients or isotonic saline 1 ml in the LIAiv group patients. The knee catheter was removed immediately after injection. Additionally, the patients in these two groups got an i.v. injection with either ketorolac 1 ml (30 mg ml\(^{-1}\)) in the LIAiv group patients or isotonic saline 1 ml in the LIA group patients. Patients randomized to continuous epidural analgesia did not get injections in the sham knee catheter.

From the day when PCA was stopped, all patients got 10 mg slow release oxycodone (Oxycontin\(^{®}\)) p.o. twice a day. Five milligrams standard oxycodone (Oxynorm\(^{®}\)) were administered by nurses on patient request as rescue analgesic medication.

The patients were evaluated daily with VAS and verbal scale at rest and during 45° of knee flexion by the hospital’s specially trained pain nurses, who were not involved in patient treatment. Physiotherapists helped to mobilize the patients as early as possible, and walking distance was measured on the first two postoperative days.

Each postoperative day, discharge readiness was assessed by an orthopaedic surgeon, a pain nurse, a ward nurse, and a physiotherapist according to the following criteria: no evidence for surgical complications, VAS pain at rest ≤30 which is controlled by oral analgesics, ability to eat and drink, ability to walk with elbow crutches, and ability to climb ≥8 stairs. At the end of the hospital stay, the patients were interviewed by nurses, evaluating pain, patient satisfaction, and complications.

**Statistics**

On the basis of earlier studies, we hypothesized a standard deviation of ±20% regarding pain intensity and assumed the effect of LIA as clinically relevant if it provided 20% better analgesia as measured by either VAS at rest or VAS at knee flexion 48 h after surgery.\(^{15}\) Given a power of 80% and a significance level of 5%, the number of patients needed in each treatment arm was calculated to be 25. After compensating for missing data, a total of 102 patients, 34 patients in each group, were planned to include in this study. For tests of differences in continuous variables between the three groups, one-way ANOVA tests were used. Pairwise comparisons were done with the Bonferroni correction. The distributions of all dependent variables were examined to assess the appropriateness of using parametric tests.\(^{16}\) Categorical data were analysed with \(\chi^2\) tests and the Kruskal–Wallis tests adjusted for ties. Analyses for mean effects over repeated measurements (longitudinal data) were performed with linear mixed models. For data analysis, SPSS\(^{®}\) (version 16.0), StatXact 8 (Cytel Inc., 2007), and CIA (www.som.soton.ac.uk/cia) were used.

**Results**

**Patient flow and characteristic data**

A total of 153 patients were assessed for eligibility, 120 fulfilled the criteria for participation, of which 18 refused to participate (Fig. 1). A total of 102 patients were included and randomized; three patients were withdrawn from the study: in one patient, abuse of opioids before operation was noticed 1 day after surgery; one patient was unable to complete postoperative pain registrations due to a non-diagnosed dementia; and one patient received general anaesthesia because spinal anaesthesia was technically impossible (Fig. 1).

The three study groups had a similar distribution of sex, age, weight, height, and ASA classification. Heart rate, arterial pressure, and pain scores (VAS) and also KOOS (Knee Osteoarthritis Outcome Score) measured before operation did not differ significantly between the groups (Table 1).

**Perioperative period**

Insertion of the epidural catheter in the EDA group took mean 9 min. TKA was performed by two different surgeons (90/9 patients). Mean duration of surgery was longer in the two groups where the surgeon used LIA (LIA group: mean 9.1 min, 95% CI: −1.57 to 19.88; LIAiv group: mean 9.5 min, 95% CI: −1.24 to 20.21, \(P=0.055\)) (Table 2).

**PACU period**

Verbal pain scores at discharge from PACU were significantly lower in the epidural group both at rest and during active knee flexion, but the time to discharge from the PACU was significantly longer in the EDA group (Table 2). Hypotension occurred only in the EDA group (three of 33 patients). There was no difference between the groups regarding PONV (Table 2). In five patients, the epidural analgesia regimen had to be modified <4 h after end of surgery: in three patients, the epidural catheter had to be withdrawn 2–3 cm to optimize analgesia; and in two patients, the epidural catheter had to be replaced by a new one due to insufficient analgesia.

**Post-PACU period**

Patients randomized to the LIA group had significantly lower pain scores (VAS) at rest compared with the EDA group on days 1, 2, and 3 after surgery (Fig. 2). The mean reduction
in VAS at rest for the LIA group compared with the EDA group from discharge PACU until 72 h after surgery was 7.52, 95% CI: 2.49–12.5, \(P=0.004\). For the comparison of the LIA group with the LIAiv group, the mean reduction was 5.26, 95% CI: 0.25–10.3, \(P=0.040\). VAS during active knee flexion was significantly higher in the EDA group 72 h after surgery compared with patients in the LIA group (Fig. 3). The mean reduction in VAS during knee flexion for the LIA group compared with the EDA group from discharge PACU until 72 h after surgery was 4.35, 95% CI: –3.03 to 11.7, \(P=0.25\). For the comparison of the LIA group with the LIAiv group, the mean reduction was 7.11, 95% CI: –0.23 to 14.5, \(P=0.058\).

Morphine consumption was lowest in the epidural group during the first day after surgery (ns), but thereafter morphine consumption was lowest in the LIA group (Fig. 4). There was a significant difference between the amounts of oral oxycodone, in favour of both the LIA group and the LIAiv group from the day when the patients were ready to be discharged (Table 3). Patients in both the LIA group and the LIAiv group could be mobilized earlier after operation

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**Table 1** Patient characteristic data. Data are means or numbers. Values in parentheses indicate SD. No significant differences between the groups were found (ANOVA and \(\chi^2\) test). *Mean VAS during the week before operation. KOOS, Knee Osteoarthritis Outcome Score; EDA, epidural analgesia; LIA, local infiltration analgesia with i.v. placebo injection; LIAiv, local infiltration analgesia plus i.v. injections with ketorolac and morphine; BMI, body mass index; ASA, American Society of Anesthesiologists

<table>
<thead>
<tr>
<th>Variable</th>
<th>EDA (n = 33)</th>
<th>LIA (n = 33)</th>
<th>LIAiv (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.8 (10.1)</td>
<td>67.2 (8.9)</td>
<td>66.5 (11.0)</td>
</tr>
<tr>
<td>Sex (male/female) (n)</td>
<td>11/22</td>
<td>13/20</td>
<td>13/20</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (7.7)</td>
<td>170 (10.6)</td>
<td>174 (12.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.9 (14.9)</td>
<td>82.8 (17.3)</td>
<td>89.0 (20.0)</td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>28.4 (5.1)</td>
<td>28.5 (5.2)</td>
<td>29.2 (4.8)</td>
</tr>
<tr>
<td>Heart rate before operation (beats min(^{-1}))</td>
<td>71 (9.9)</td>
<td>70 (9.6)</td>
<td>70 (12.8)</td>
</tr>
<tr>
<td>Systolic arterial pressure before operation (mm Hg)</td>
<td>148 (19.5)</td>
<td>151 (24.3)</td>
<td>153 (22.1)</td>
</tr>
<tr>
<td>Diastolic arterial pressure before operation (mm Hg)</td>
<td>87 (11.5)</td>
<td>90 (11.4)</td>
<td>87 (12.1)</td>
</tr>
<tr>
<td>ASA class (I/II/III)</td>
<td>4/27/2</td>
<td>5/26/2</td>
<td>8/23/2</td>
</tr>
<tr>
<td>VAS before operation (0–100 mm)*</td>
<td>42 (20.0)</td>
<td>47 (18.3)</td>
<td>50.2 (18.6)</td>
</tr>
<tr>
<td>KOOS pain before operation</td>
<td>46.4 (17.5)</td>
<td>47.9 (17.9)</td>
<td>48.8 (14.4)</td>
</tr>
<tr>
<td>KOOS symptoms before operation</td>
<td>56.5 (20.7)</td>
<td>54.4 (17.7)</td>
<td>56.7 (15.3)</td>
</tr>
</tbody>
</table>

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**Fig 1** Patient flow (according to CONSORT guidelines). EDA, epidural analgesia; LIA, local infiltration analgesia; LIAiv, local infiltration analgesia plus i.v. ketorolac and morphine.

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in VAS at rest for the LIA group compared with the EDA group from discharge PACU until 72 h after surgery was 7.52, 95% CI: 2.49–12.5, \(P=0.004\). For the comparison of the LIA group with the LIAiv group, the mean reduction was 5.26, 95% CI: 0.25–10.3, \(P=0.040\). VAS during active knee flexion was significantly higher in the EDA group 72 h after surgery compared with patients in the LIA group (Fig. 3). The mean reduction in VAS during knee flexion for the LIA group compared with the EDA group from discharge PACU until 72 h after surgery was 4.35, 95% CI: –3.03 to 11.7, \(P=0.25\). For the comparison of the LIA group with the LIAiv group, the mean reduction was 7.11, 95% CI: –0.23 to 14.5, \(P=0.058\).

Morphine consumption was lowest in the epidural group during the first day after surgery (ns), but thereafter morphine consumption was lowest in the LIA group (Fig. 4). There was a significant difference between the amounts of oral oxycodone, in favour of both the LIA group and the LIAiv group from the day when the patients were ready to be discharged (Table 3). Patients in both the LIA group and the LIAiv group could be mobilized earlier after operation
The relative risk of not being able to walk more than 10 m about 48 h after surgery was 3.5 [95% CI: (1.6, 7.5)] for patients randomized to the EDA group compared with the LIA group and the LIAiv group. Delayed mobilization for patients in the epidural group during the first postoperative day was mainly due to muscle weakness (six patients), pain (six patients), dizziness (two patients), and nausea (four patients). Mean time to readiness for hospital discharge was shorter in the LIA group compared with the LIAiv group and the EDA group. Patient satisfaction during the first 48 h after surgery was highest in the LIA group (Table 3). Epidural analgesia had to be modified in three patients after PACU discharge (<24 h after surgery), and epidural analgesia was satisfying after catheter manipulation in all three.

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

**Discussion**

In the present study, we found that LIA with intra-articular adjuvants was superior to epidural anaesthesia after the initial 24 h. Intra-articular adjuvants were superior to i.v. administration for the whole study period.

This is, to our knowledge, the first randomized study comparing LIA with epidural analgesia in patients undergoing total knee replacement.

Patients in the EDA group had lower verbal pain scores in the subsequent hours after surgery. This may be due to the fact that an epidural bolus dose was given just before the end of spinal anaesthesia. Also, epidural analgesia involves

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### Table 2 Perioperative and PACU period. Data are means or numbers. Values in parentheses indicate sd. *Significant differences between the groups (Student’s t, ANOVA, and χ² test). Verbal pain score (a/b/c/d/e): a, no pain; b, little pain; c, moderate pain; d, severe pain; e, very severe pain. EDA, epidural analgesia; LIA, local infiltration analgesia with i.v. placebo injection; LIAiv, local infiltration analgesia plus i.v. injections with ketorolac and morphine; PACU, post-anaesthetic care unit; PONV, postoperative nausea and vomiting.

<table>
<thead>
<tr>
<th>Variable</th>
<th>EDA (n = 33)</th>
<th>LIA (n = 33)</th>
<th>LIAiv (n = 33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period patient in, start surgery (min)</td>
<td>73 (15.5)</td>
<td>62 (12.4)</td>
<td>65 (10.0)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>98 (16.5)</td>
<td>108 (19.4)</td>
<td>107 (17.8)</td>
<td>0.055</td>
</tr>
<tr>
<td>PACU stay (min)</td>
<td>428 (199)</td>
<td>327 (62)</td>
<td>360 (81)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Pain at rest, at discharge PACU*</td>
<td>13/16/4/0/0</td>
<td>3/22/8/0/0</td>
<td>4/24/5/0/0</td>
<td>0.015*</td>
</tr>
<tr>
<td>Pain knee flexion, at discharge PACU*</td>
<td>8/13/8/3/1</td>
<td>1/9/15/6/2</td>
<td>0/5/16/9/2</td>
<td>0.004*</td>
</tr>
<tr>
<td>PONV in PACU</td>
<td>8</td>
<td>6</td>
<td>10</td>
<td>0.517</td>
</tr>
<tr>
<td>Hypotension (&lt;80 mm Hg syst)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0.045*</td>
</tr>
<tr>
<td>Respiratory depression (&lt;8 min)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Fig 2 Progress of mean VAS at rest from the time of surgery through discharge. Vertical lines indicate 95% CIs for the means. One-way ANOVA tests were used to test the null hypothesis of equal means of the three groups (EDA, LIA, and LIAiv) for each time point. The primary endpoint was 48 h after surgery. EDA, epidural analgesia; LIA, local infiltration analgesia; LIAiv, local infiltration analgesia plus i.v. ketorolac and morphine; PACU, post-anaesthetic care unit.
global analgesia of all structures surrounding the painful knee, whereas an LIA technique may miss some painful anatomical tissue structures. However, the epidural patients had to stay significantly longer in the PACU due to side-effects of epidural analgesia (hypotension) and necessary modifications of epidural setup due to suboptimal analgesia in several patients.

Patients getting LIA with intra-articular ketorolac and morphine had lower pain scores at rest from 24 h after surgery until discharge from the hospital. All patients getting LIA had superior knee function, were mobilized faster, and were discharged earlier from hospital.

Choi and colleagues\textsuperscript{17} discussed epidural analgesia or systemic analgesia in patients undergoing hip or knee replacement in a Cochrane review and concluded that the beneficial effect of epidural analgesia on pain relief was limited to the early postoperative period (4–6 h). However, side-effects such as hypotension, urinary retention, and itching were more frequent with epidural analgesia.\textsuperscript{17} Campbell and colleagues\textsuperscript{18} who compared epidural analgesia with lumbar plexus infusions after TKA reported that only 50% of the patients with epidural analgesia could sit and stand on the first postoperative day, 77% were able to this on the second postoperative day. Length of hospital stay was 6 days. These results are comparable with our data. The reason for delayed discharge compared with LIA was both delayed mobilization and difficult pain management after epidural analgesia was discontinued.

Our results are comparable with a recently published study where continuous epidural analgesia was compared with LIA (ropivacaine 200 mg, ketorolac 30 mg, and epinephrine 0.5 mg) in patients undergoing total hip arthroplasty.\textsuperscript{10} The authors found significantly reduced narcotic consumption and reduced length of stay in patients treated with LIA.

Moreover, our study results confirm that local administration of ketorolac and morphine has a specific local effect regarding pain, narcotic consumption, mobilization, and length of stay. These effects were significantly stronger than after giving the same total dose of adjuvants i.v. Still, some effect of systemic absorption cannot be ruled out with our study design. It is also unclear if only one of these two substances is responsible for the beneficial effects or

![Fig 3](image1.png)

**Fig 3** Progress of mean VAS at knee flexion from the time of surgery through discharge. Vertical lines indicate 95% CIs for the means. One-way ANOVA tests were used to test the null hypothesis of equal means of the three groups (EDA, LIA, and LIAiv) for each time point. The primary endpoint was 48 h after surgery. EDA, epidural analgesia; LIA, local infiltration analgesia; LIAiv, local infiltration analgesia plus i.v. ketorolac and morphine; PACU, post-anaesthetic care unit.

![Fig 4](image2.png)

**Fig 4** Mean morphine consumption per 24 h during the first 3 days after surgery. Vertical lines indicate 95% CIs for the means. One-way ANOVA tests were used to test the null hypothesis of equal means of the three groups (EDA, LIA, and LIAiv) for each time interval. EDA, epidural analgesia; LIA, local infiltration analgesia; LIAiv, local infiltration analgesia plus i.v. ketorolac and morphine.
both. Further studies are needed to address both the content and dosing of components for the optimal ‘LIA-cocktail’.

To our knowledge, only one previous study with LIA has defined specific discharge criteria after major knee surgery. The authors report a median length of postoperative hospital stay of only 1 day in patients treated with LIA. Different from our study, these patients were operated with unicompartmental knee arthroplasty which is considered less painful than TKA. Kerr and Kohan describe a mean length of hospital stay of 3.2 days after TKA, but without defining what criteria have to be fulfilled to be ready for discharge.

This study has some limitations: despite the fact that several studies have shown superior analgesic effects of wound infiltration compared with control regimens, it is unclear which ‘cocktail’ of LIA is the best. We cannot rule out that our results could have been different with different dosing and timing of drugs in our groups. Further, the patients were not informed what kind of treatment they were randomized to receive. Postoperative nurse assessments at 240 min after operation, at discharge from PACU, and in the whole post-PACU period were done by nurses who were not involved in patient treatment and who did not know the group allocation. Nevertheless, in spite of dummy catheters and syringe pumps, it is possible that some patients, researches, or both could have found out whether patients had been randomized to the EDA group or not. Therefore, we defined the epidural analgesia (EDA) after TKA as not fully blinded.

In conclusion, LIA with intra-articular ketorolac and morphine was added to the ‘LIA-cocktail’. Timing, content, and frequency of ‘top-up’ intra-articular analgesia is also different between the studies. Whereas some authors already give injections through the knee catheter after 6–8 h, others wait until the next day. Rasmussen and colleagues used continuous intra-articular injection of morphine and ropivacaine which was maintained from 24 to 72 h after operation.

The technique of LIA is not standardized, and different approaches have been used in the published studies. It is unclear which injection volumes should be used and where the injections should be placed (intra-articular, periarticular, or both). Andersen and colleagues recently conducted a randomized study where they showed an insignificant analgesic effect from additional ropivacaine with epinephrine which was administered to the extra-articular tissues.

Our study did not include a placebo group. Several double-blinded and randomized studies have compared either LIA or epidural analgesia with placebo in major knee and hip surgery. They consistently show that these methods are better than placebo. Thus, we decided that another placebo-controlled study was not needed, as including placebo groups may also be ethically controversial.

The study was conducted in a fully double-blind manner regarding patients’ randomization to the LIA and LIAiv groups. Further, the patients were not informed what kind of treatment they were randomized to receive. Postoperative nurse assessments at 240 min after operation, at discharge from PACU, and in the whole post-PACU period were done by nurses who were not involved in patient treatment and who did not know the group allocation. Nevertheless, in spite of dummy catheters and syringe pumps, it is possible that some patients, researches, or both could have found out whether patients had been randomized to the EDA group or not. Therefore, we defined the epidural control (EDA group) as not fully blinded.

In conclusion, LIA with intra-articular ketorolac and morphine was superior to continuous epidural analgesia after TKA regarding pain scores at rest beyond 24 h after surgery, and also knee function and rehabilitation. Patients were more satisfied during the first 2 days after operation and could be discharged earlier from the hospital. Side-effects were more common in patients getting epidural analgesia with i.v. placebo injection; LIAiv, local infiltration analgesia plus i.v. injections with ketorolac and morphine; PONV, postoperative nausea and vomiting.

### Table 3 Post-PACU period. Data are means or numbers. Values in parentheses indicate SD. *Significant differences between the groups (one-way ANOVA, χ² test, and Kruskal–Wallis test). †Walking distance (a/b/c): a, 0–3 m; b, >3 and <10 m; c, >10 m. ‡Satisfaction with pain management (a/b/c/d/e): a, much better than expected; b, better than expected; c, as expected; d, worse than expected; e, much worse than expected. EDA, epidural analgesia; LIA, local infiltration analgesia with i.v. placebo injection; LIAiv, local infiltration analgesia plus i.v. injections with ketorolac and morphine; PONV, postoperative nausea and vomiting.

<table>
<thead>
<tr>
<th>Variable</th>
<th>EDA (n = 33)</th>
<th>LIA (n = 33)</th>
<th>LIAiv (n = 33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1: active knee flexion (grades)</td>
<td>77 (17)</td>
<td>79 (13)</td>
<td>81 (9)</td>
<td>0.461</td>
</tr>
<tr>
<td>Day 1: walking distance †</td>
<td>14/4/15</td>
<td>2/7/24</td>
<td>6/8/19</td>
<td>0.015*</td>
</tr>
<tr>
<td>Day 1: satisfaction †</td>
<td>6/12/6/6/3</td>
<td>6/19/5/3/0</td>
<td>5/7/14/7/0</td>
<td>0.013*</td>
</tr>
<tr>
<td>Day 1: PONV</td>
<td>8</td>
<td>9</td>
<td>6</td>
<td>0.649</td>
</tr>
<tr>
<td>Day 2: active knee flexion (grades)</td>
<td>75 (13)</td>
<td>82 (8)</td>
<td>78 (9)</td>
<td>0.034*</td>
</tr>
<tr>
<td>Day 2: walking distance †</td>
<td>10/4/19</td>
<td>0/1/32</td>
<td>4/3/26</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Day 2: satisfaction †</td>
<td>5/7/7/7/7</td>
<td>10/14/7/1/1</td>
<td>7/8/10/7/1</td>
<td>0.019*</td>
</tr>
<tr>
<td>Day 2: PONV</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>0.303</td>
</tr>
<tr>
<td>Day 3: active knee flexion (grades)</td>
<td>77 (11)</td>
<td>84 (7)</td>
<td>80 (8)</td>
<td>0.042*</td>
</tr>
<tr>
<td>Day 3: satisfaction †</td>
<td>3/6/7/5/4</td>
<td>7/12/7/1/0</td>
<td>6/7/8/4/3</td>
<td>0.234</td>
</tr>
<tr>
<td>Day 3: PONV</td>
<td>8</td>
<td>4</td>
<td>7</td>
<td>0.247</td>
</tr>
<tr>
<td>Discharge (days)</td>
<td>5.5 (1.6)</td>
<td>3.5 (0.7)</td>
<td>4.0 (1.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Discharge: oxycodone (mg)</td>
<td>24 (16)</td>
<td>16 (9)</td>
<td>21 (8)</td>
<td>0.016*</td>
</tr>
</tbody>
</table>
analgesia, and no serious adverse events were seen in the LIA patients. Local administration of ketorolac and morphine had a specific local effect.

Further studies are needed, addressing the single components of the LIA method, and also the optimal injection volumes and timing of the injections.

Authors’ roles

Acknowledgements
We thank our research nurse Elisabet Andersson and our pain nurses Helena Blom and Lena Windingstad for good support during the study.

Conflict of interest
None declared.

Funding
This study has been funded by institutional means. In addition, U.J.S. has been granted a research grant (5000€) for this study from the European Society of Regional Anaesthesia and Pain Therapy.

References