Local infiltration analgesia for total knee arthroplasty: should ketorolac be added?

K. V. Andersen1, L. Nikolajsen3*, V. Haraldsted2, A. Odgaard1 and K. Søballe1,4

1 Department of Orthopaedic Surgery and 2 Department of Anaesthesiology, Aarhus University Hospital, Tage-Hansens Gade 2, 8000 Aarhus C, Denmark
2 Department of Anaesthesiology, Aarhus University Hospital, Norrebrogade 44, 8000 Aarhus C, Denmark
3 The Lundbeckfond Center for Fast-Track Hip and Knee Arthroplasty, Tage-Hansens Gade 2, 8000 Aarhus C, Denmark
4 Corresponding author. E-mail: nikolajsen@dadlnet.dk

Editor’s key points
- Early mobilization in patients undergoing total knee arthroplasty benefits from accurate pain relief.
- Repeated high-volume local infiltration analgesia (LIA) through an intra-articular catheter was tested.
- The addition of ketorolac resulted in a reduced morphine consumption, reduced pain intensity, and earlier readiness for hospital discharge compared with ropivacaine alone or saline injections.

Background. Adequate postoperative analgesia with minimal side-effects is essential for early mobilization and recovery in patients undergoing total knee arthroplasty (TKA). High-volume local infiltration analgesia (LIA) with ropivacaine has been introduced, but effects of adjuvants are still debated. We tested the hypothesis that the addition of ketorolac to LIA significantly improves analgesia after TKA.

Methods. Sixty patients undergoing TKA were randomized to receive intraoperative LIA (ropivacaine 300 mg and epinephrine 0.5 mg) combined with either ketorolac 30 mg (ketorolac group) or saline (control group). After surgery, eight bolus doses of ropivacaine 100 mg combined with either ketorolac 15 mg (ketorolac group) or saline (control group) were administered every 6 h via an intra-articular catheter. The primary outcome was postoperative consumption of i.v. morphine patient-controlled analgesia (PCA). Secondary outcomes were time to first request of i.v. morphine PCA, pain intensity, side-effects, and readiness for hospital discharge.

Results. Consumption of i.v. morphine PCA was lower in the ketorolac group vs control group {0–6 h: 0 (0–0) vs 5 (0–10) mg, P<0.0001; 0–48 h: 10 (0–22.5) vs 48.75 (30–82.5) mg, P<0.0001 [median (inter-quartile range, IQR)]}. Time to first request of i.v. morphine PCA was longer in the ketorolac group vs the control group [490 (248–617) vs 223 (115–319) min, P=0.02, median (IQR)]. Early postoperative pain (<48 h) and readiness for hospital discharge were also significantly reduced in the ketorolac group.

Conclusions. LIA with ketorolac results in reduced morphine consumption, reduced pain intensity, and earlier readiness for hospital discharge.

Keywords: anti-inflammatory agents, non-steroidal; arthroplasty, replacement, knee; injections, intra-articular; pain, postoperative

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Total knee arthroplasty (TKA) is a common surgical procedure that often results in moderate-to-severe postoperative pain.1 2 Traditionally, epidural analgesia or continuous peripheral nerve blocks have been used for postoperative analgesia.3 –6 In recent years, there has been an increased interest in wound infiltration techniques with local anaesthetics for peri- and postoperative analgesia.7 13 A modification of the technique is high-volume local infiltration analgesia (LIA) developed by Kerr and Kohan7 for analgesia after TKA and total hip arthroplasty. LIA consists of a high-volume intraoperative infiltration, often combined with postoperative intra-articular injections of a mixture of ropivacaine, ketorolac, and epinephrine. Intraoperative LIA with either this mixture or local anaesthetics alone has been shown to provide effective analgesia after TKA compared with no injections,1 8 femoral nerve block,9 epidural analgesia,10 and placebo.11 12

Several of the studies on the LIA technique, however, have some methodological insufficiencies and the use of different LIA techniques and solutions mixtures makes the interpretation of the results difficult.13 It is not clear at the present time whether it is necessary to place an indwelling catheter for injections after surgery,14 and also, there is a need for studies that address the single components of the LIA solution.15 To be specific, there are limited data to support the
use of non-steroidal anti-inflammatory drugs (NSAIDs) in the solution.

We therefore decided to carry out a prospective, double-blind, randomized study to examine the effect of adding ketorolac to a high-volume local infiltration mixture of ropivacaine and epinephrine. The primary outcome measure was the consumption of i.v. morphine patient-controlled analgesia (PCA) during the first 48 h after surgery. Secondary outcome measures were time to first request of i.v. morphine PCA, intensity of pain during rest and activity, side-effects, time for readiness for hospital discharge, and length of hospital stay.

Methods

Patients

The study was approved by the Committee on Health Research Ethics, Central Denmark Region (M-20080112), the Danish Medicines Agency (EudraCT. no 2008-003180-39), and the Danish Data Protection Agency. It was registered at clinicaltrial.gov (NCT00868388), conducted in accordance with the guidelines for Good Clinical Practice (GCP), and monitored by the GCP unit at Aarhus University Hospital.

After obtaining written informed consent, 60 patients were enrolled at the Department of Orthopaedic Surgery at Aarhus University Hospital, Denmark. Inclusion criteria were planned primary unilateral TKA on the basis of osteoarthritis, planned spinal anaesthesia, and age > 18 yr. Exclusion criteria were known allergy/intolerance to study drugs (ketorolac, ropivacaine, epinephrine, and morphine), opioid consumption on a daily basis, rheumatoid arthritis, bleeding disorders, previous major bone operation in the knee to be operated on, obesity (BMI > 35 kg m⁻²), and inability to communicate in Danish. A secondary exclusion criterion was intraoperative conversion to general anaesthesia.

Randomization and blinding

An independent pharmacist generated the allocation sequence using computer-generated randomized numbers (block size: 12 and allocation ratio: 1:1). Patients were randomized to receive LIA and intra-articular reinjections with either ropivacaine, epinephrine, and ketorolac (ketorolac group) or ropivacaine and epinephrine (control group). Allocation concealment was ensured using sequentially numbered, opaque-sealed envelopes. The allocation list was stored at the local pharmacy until all patients had been included and all 4 month follow-ups were completed.

The study medication was prepared by the hospital pharmacy. After obtaining the patient’s consent, the hospital pharmacy was contacted by the investigator, and the study medication consisting of 1 bag (150 ml ropivacaine 2 mg ml⁻¹) with either 1 ml ketorolac 30 mg ml⁻¹ (ketorolac group) or 1 ml sodium chloride 9 mg ml⁻¹ (control group) and 1 cassette (80 ml ropivacaine 10 mg ml⁻¹) with either 4 ml ketorolac 30 mg ml⁻¹ (ketorolac group) or 4 ml sodium chloride 9 mg ml⁻¹ (control group) was delivered on the day of surgery.

Blinding of patients, surgeons, healthcare providers, and outcome assessors was obtained by using tamper-proof study medication delivered in sequentially numbered bags and cassettes similar in appearance, weight, smell, and viscosity.

Anaesthesia and surgical technique

Oral paracetamol 2000 mg was given 2 h before anaesthesia as premedication. I.V. cefuroxime 1.5 g was administered before surgery, and i.v. tranexamic acid 10 mg kg⁻¹ was given at the end of surgery and 3 h after surgery. Spinal anaesthesia was induced at the L3–4 level by using a 25 G spinal needle with a dose of 3 ml bupivacaine 5 mg ml⁻¹. The same four orthopaedic specialists performed all surgical procedures using a standard medial parapatellar approach for the arthroplasty. A tourniquet above the knee was used in all patients.

At the end of surgery, 50 ml of the study medication (150 ml ropivacaine 2 mg ml⁻¹ with either 1 ml ketorolac 30 mg ml⁻¹ or 1 ml sodium chloride 9 mg ml⁻¹) was loaded into one 50 ml syringe. Epinephrine 0.5 ml 1 mg ml⁻¹ was added to the remaining 100 ml study medication and loaded into two 50 ml syringes. The LIA technique was administered in the same way in both groups. After implant insertion, the surgeon injected 50 ml of the study medication with epinephrine into the posterior capsule structures; another 50 ml was injected around the prosthesis. A multi-hole epidural catheter with a bacterial filter was inserted with the tip placed intra-articularly and connected to an infusion pump (dose 10 ml, lockout time 6 h). After closure of the capsule, the surgeon used 50 ml of the study medication without epinephrine for infiltration of the fascia and subcutis. An elastic compression bandage and a low-pressure suction drain were applied and kept for the first 48 h. The patients were transferred to the post-anaesthesia care unit (PACU) and observed there for at least 3 h after surgery. Ice packs were applied around the knee for the first 4 h after surgery.

Postoperative treatment

Postoperative pain treatment consisted of eight intra-articular bolus injections of 10 ml ropivacaine 10 mg ml⁻¹ with either 0.5 ml ketorolac 30 mg ml⁻¹ (ketorolac group) or 0.5 ml sodium chloride 9 mg ml⁻¹ (control group) or 0.5 ml sodium chloride 9 mg ml⁻¹ (control group) via a catheter initiated 6 h after surgery and repeated every 6 h (dose 10 ml, lockout 6 h) and i.v. morphine PCA (1 mg ml⁻¹, dose 2.5 mg, lockout 10 min) for the first 48 h after surgery. The intra-articular bolus injections after 6, 24, and 48 h were administered by one of the investigators and the remaining five bolus injections were given by the nursing staff. All patients were treated with oral paracetamol 1000 mg every 6 h, initiated 4 h after surgery, and continued during the hospital stay. Nausea was treated with i.v. ondansetron 4 mg (first choice) or i.v. metoclopramide 10 mg. No other analgesic, anti-emetic, or sedative drugs were used during the 48 h study period. Oral oxycodone 5–10 mg was allowed as rescue analgesic medication from 48 h until
discharge from hospital. For thromboprophylaxis, an injection of 5000 IE dalteparin was administered subcutaneously, starting 8 h after surgery on the day of surgery until discharge. All patients received laxatives.

Outcome measures
The primary outcome measure was consumption of i.v. PCA morphine from 0 to 48 h after surgery. Consumption of i.v. morphine PCA was also registered from 0 to 6 and 0 to 24 h after surgery. Secondary outcome measures were time to first i.v. morphine PCA request after surgery; postoperative pain intensity scores both at rest and during coughing (2–4 h after surgery), and at rest and during walking (6–96 h after surgery); side-effects [nausea, vomiting, itching, and constipation (the latter defined as no bowel function for 72 h)]; time to fulfilment of discharge criteria (home readiness); and LOS.

Before surgery, all patients were instructed in the use of the visual analogue scale (VAS; 0, no pain, and 100, worst pain possible) and the i.v. PCA pump. The patients used diaries to record their pain intensity and side-effects. Pain intensity was recorded every 2 h on the day of surgery and every 4 h on postoperative days 1–4, except during night time, and side-effects were recorded for the postoperative periods 0–6, 6–24, 24–48, 48–72, and 72–96 h. Nausea and itching were described on a four-point verbal scale (none, mild, moderate, and severe), and vomiting as the number of vomiting. All patients were visited by one of the investigators (K.V.A.) 2, 4, 6, 24, and 48 h after surgery in order to ensure compliance. K.V.A. also recorded the consumption of i.v. morphine PCA after 6, 24, and 48 h.

Ability to meet discharge criteria (home readiness) was recorded by the nursing staff every afternoon. The discharge criteria were mild pain (VAS≤30 at rest), pain sufficiently controlled by oral analgesics, no evidence of any surgical complications, and ability to maintain personal hygiene, eat and drink, get in and out of bed, sit and rise from chair, walk safely with elbow crutches, and to climb stairs. LOS was recorded as the actual time to home discharge once the home discharge criteria were fulfilled (day 0, the day of operation).

Three, 6, and 16 weeks after surgery, each patient received a questionnaire about pain intensity (VAS) at rest and during daily activity. Sixteen weeks after surgery, all patients came to a control visit at the hospital.

Statistical analysis
The sample size calculation was based on an expected difference of 25% in i.v. morphine PCA consumption. With 80% power (α=0.05, β=0.2), a sample size of 27 per group was required, that is, a total of 54 patients. A sample size of 60 was chosen to allow for incomplete data collection.

Categorical data were analysed using the χ² test or Fisher’s exact test. Normally distributed data were statistically tested with Student’s t-test, and data that did not fulfil the assumptions of normal distribution were analysed with the Mann–Whitney U-test. Results are presented as either frequencies, mean (±sd), or median with inter-quartile range (IQR), as appropriate. The level of significance was chosen to be 0.05. EpiData, version 3.1 (EpiData Association, Odense, Denmark) was used for double data entry, and statistical analysis was performed with STATA software version 10.0 (StatCorp, TX, USA).

Results
A total of 361 patients were assessed for eligibility from May 2009 through March 2011; 62 patients participated in other studies, 54 patients declined to participate, and 185 patients were excluded based on the exclusion criteria. Sixty patients (30 in each group) were enrolled, and data for the primary endpoint were registered in all patients. Response rates for self-reported questionnaires 3, 6, and 16 weeks after surgery ranged from 90% to 97% (Fig. 1). Baseline characteristics were similar between the two groups (Table 1). The higher number of women in the control group was not significant.

I.V. morphine PCA consumption was significantly reduced in the ketorolac group compared with the control group at 0–6, 0–24, and 0–48 h after surgery (P<0.0001), and time to first consumption of i.v. morphine PCA was significantly prolonged in the ketorolac group vs control group [490 (248–617) vs 223 (115–319) min, P=0.02, median (IQR)] (Table 2). VAS pain scores at rest and during movement were lower in the ketorolac group during the first 48 h after surgery. There was no significant difference in pain intensity scores from 48 to 96 h, or at 3, 6, and 16 weeks after surgery (Tables 3 and 4). Oxycodone consumption 48–96 h was significantly reduced in the ketorolac group vs control group [17.5 (5–35) vs 40 (20–60) mg, P=0.03 median (IQR)]. All side-effects recorded, except nausea 0–6 h after surgery (P=0.04) in favour of the ketorolac group, were found to be similar in the two groups. These included incidence of constipation (2 vs 6), episodes of nausea 6–96 h after surgery, and vomiting and itching 0–96 h after surgery (Table 5).

The median (IQR) LOS was 3 days (2–3) in the ketorolac group and 3 days (3–3) in the control group (P=0.02); however, time to home readiness was reduced with 1 day in the ketorolac group [2 (2–3) vs 3 (2–3) days, P=0.004, median (IQR)].

There were no major surgical complications. One patient in the RK group was re-admitted to the hospital due to hematoma, but no signs of infection, deep venous thrombosis, or insufficient wound healing were found during the 16 week follow-up period.

Discussion
In this study, the use of ketorolac in the LIA solution resulted in a significant reduction in i.v. morphine PCA consumption after surgery in patients undergoing TKA under spinal anaesthesia. This opioid-sparing effect was also associated with prolonged time to first consumption of i.v. morphine PCA, reduced pain intensity at rest and during activity in the
early postoperative period (<48 h), and reduced time to home readiness. We chose to use the time for home readiness using objective criteria as an outcome parameter instead of the actual time of discharge as the latter can be influenced by several non-medical factors.

There may be some concerns about the local use of NSAIDs. In the present study, there were no cases of infection or delayed wound healing. However, the inclusion of only 60 patients does not provide sufficient study power to detect serious adverse advents. To the best of our knowledge, no publications on the LIA technique have reported an increased incidence of adverse events after local injection of ketorolac.

In spite of the lower consumption of morphine in the ketorolac group, we did not observe any reduction in opioid-related side-effects such as nausea, vomiting, and itching. The non-significantly higher proportion of women in the saline group may be a co-factor to this finding as women are more susceptible to postoperative nausea and vomiting than men; however, the lack of reduced PCA morphine side-effects is consistent with findings in several other studies.

Some methodological issues must be considered. First, we did not include a control group that received NSAIDs systemically. Thus, it can be argued that similar or even better results could have been achieved if ketorolac was given i.v. Other studies, however, have suggested that intra-articular ketorolac has a local rather than a systemic effect. Recently, Spreng and colleagues conducted a study in which 102 patients undergoing TKA were randomized into
three groups, each including 34 patients. One group had epidural analgesia for 48 h after operation; the two other groups had intraoperative LIA (ropivacaine 150 mg and epinephrine 0.5 mg) combined with 30 mg ketorolac and 5 mg morphine given either intra-articularly (LIA group) or i.v. (LIA i.v. group).
Both LIA groups were mobilized faster and discharged earlier than the epidural group. Cumulated morphine consumption (72 h) was lowest for the LIA group [80 vs 101 (epidural group) vs 118 mg (LIA i.v. group)].

Secondly, our study did not include a placebo group that only received saline as LIA. We did not find the inclusion of such a group useful as at least two randomized double-blind studies have shown that LIA with ropivacaine or ropivacaine combined with ketorolac results in better analgesia than saline. For example, Andersen and colleagues randomized 12 patients undergoing bilateral knee arthroplasty to receive 170 ml ropivacaine 2 mg ml\(^{-1}\) with epinephrine in one knee and a similar infiltration with 170 ml saline in the other knee. The intraoperative infiltration was followed by bolus injections of the study drug 8 and 24 h after surgery. Intensity of pain was significantly lower in the knee infiltrated with ropivacaine and epinephrine compared with the knee infiltrated with saline.

Thirdly, we chose to administer bolus injections after surgery, although the effect of bolus injections is unclear. The use of top-up bolus injections in an attempt to prolong the analgesic effect of the intraoperative high-volume infiltration was described in the first studies on the LIA technique and has since been used in most recent studies on the LIA technique with some modifications regarding frequency and volume.

Finally, the external validity of the study can be questioned as only 60 out of 361 patients were included. Thus, it is unknown whether our results are directly relevant to all patients undergoing TKA. Unfortunately, this problem applies to many clinical studies. We have previously assessed the external validity of a randomized trial, including patients undergoing total hip replacement. Non-consenters were older, less healthy, and were discharged later from hospital.

In conclusion, our study has provided information about one aspect of the LIA technique, that is, the effect of adding ketorolac to the solution. We showed that the addition of ketorolac to the LIA solution results in better analgesia in the early postoperative period (<48 h), reduced morphine consumption, and earlier readiness for hospital discharge.

**Declaration of interest**

None declared.

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