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

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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. A modification of the technique is high-volume local infiltration analgesia (LIA) developed by Kerr and Kohan[7] 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 (LOS).

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[16] 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) 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,