Local Infiltration Analgesia for Pain After Total Knee Replacement Surgery: A Winner or Just a Strong Runner-Up?

Johan C. Raeder, PhD, MD

Local infiltration analgesia (LIA) has been introduced recently as a promising step forward in reducing postoperative pain and side effects from analgesics after knee arthroplasty and, so far, with less convincing results after hip artroplasty.[1]

As often with new methods, there is a way to go from the first, enthusiastic, nonblinded case series[2] to evidence-based recommendations for clinical, everyday use.[3,4] This way is paved with some important questions:

1. Does the method work at all?
2. What parts and components of the new method are efficient?
3. How does the method compare to other methods in terms of safety, quality, and cost efficacy?

It is tempting to throw all potential ingredients of a new method into a huge cocktail and show superiority versus controls who receive a stripped and nonoptimal regimen. This may give an answer to question 1, but certainly no or few answers to questions 2 and 3.

In the present issue of the *Journal*, Essving et al. present an interesting study on LIA versus intrathecal morphine for postoperative analgesia after knee artroplasty in bupivacaine spinal anesthesia.[5] The LIA group had less morphine consumption during 0- to 24-hour and 24- to 48-hour periods after surgery, less pain on movement at 24 and 48 hours, less pain at rest on 24 hours, better patient satisfaction at 24 hours, and shorter time to discharge readiness. No differences were demonstrated at 3 days, 1 week, or 3 months after surgery in any variable, including no difference in knee functional outcome.

Thus, the LIA method worked well for the patients in comparison with the simple alternative of a single shot of morphine 0.1 mg added intrathecally. Still, turning to question 2 on important components, we may look closer at the LIA method of Essving et al.:

(a) Multiple injections of local anesthesia in joint structures during the procedure, ketorolac and epinephrine added, whereas the control group receives 0.1 mg morphine intrathecally.
(b) Injection of ketorolac into joint at 21 and 45 hours, saline to control group.
(c) Injection of ropivacaine into joint at 21 and 45 hours, saline to control group.
(d) Injection of epinephrine into joint at 21 and 45 hours, saline to control group.

As to (a), we know that proper local anesthesia in all relevant wound structures pre- or perioperatively during knee replacement is efficient.[6] Also, in a study of hernia repair with complete single-shot bupivacaine infiltration analgesia, Aasboe et al. showed improved pain relief for as much as 1 week after the procedure.[7] Still, such results are to some extent procedure specific, and not reproduced with total knee arthroplasty in the literature. In a study of Andersen et al. on knee arthroplasty, the preoperative ropivacaine infiltration was superior to placebo at 6 hours but not at 24 hours.[6] The success may also have to do with how extensive the local infiltration technique is performed in terms of including all relevant structures, not only the superficial wound.[7] Although intrathecal morphine 0.1 mg in Essving et al.'s study had inferior effect at 24 hours, it may be that the control group would have improved with simple local anesthesia infiltration in the wounds by end of surgery, as is a frequent routine in many hospitals.

As to (b), (c), and (d), we may, as the authors also mention, ask whether things would have been different if the control group received a slow IV dose of ketorolac, ropivacaine, and epinephrine at 21 and 45 hours instead of just saline in the joint. We know that ketorolac[8] and ropivacaine have analgesic effects when given systemically and also that intra-articular administration will result in systemic absorption and systemic effects. We also know that infiltration of saline into the knee joint does have some analgesic effect, mostly as a placebo effect of the injection,[9] but also potentially by pharmacological volume effect per se,[10] tentatively explained by cooling and dilution of inflammatory local proteins.

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Accepted for publication June 7, 2011.

Funding: None.

The author declares no conflict of interest.

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DOI: 10.1213/ANE.0b013e3182288e14

The role of epinephrine in the LIA mixture has not been studied. Although epinephrine has an analgesic effect on the spinal α-2 receptors when given epidurally or spinally, there is no documentation on any specific analgesic effect or target mechanism of this drug when used peripherally.[11] Still, epinephrine is probably often included "just in case" because of potential strengthening of the effect of other locally active drugs, because their clearance from the local site is delayed owing to the epinephrine-induced vasoconstriction.

Thus, being the devil's advocate and to summarize: The prolonged (48 hours) analgesic effect from LIA may have been due to a specific effect or may have been a result of the meticulously administered perioperative local anesthesia infiltration and joint bolus, the systemic effects of ropivacaine given twice, and systemic effects of ketorolac given 3 times; none of such systemic effects actually being LIA specific. In addition, the control group was very simple and received just a single-shot spinal and morphine patient-controlled analgesia. This group could have been further improved by adding local anesthetic wound infiltration, as well as regular doses of paracetamol and nonsteroidal anti-inflammatory drugs throughout the perioperative phase.

Still, there is no doubt that in Essving et al.'s study the patients in the LIA group had a better quality of analgesia than did the morphine intrathechal group during their first postoperative 2 days, and these positive results should be used for the rest of our future research and clinical practice. There are data suggesting that ketorolac works better when given locally than systemically,[12] and it is certainly established that local anesthesia does so. Also, clinical impressions suggest that the morning injection the day after surgery seems to have a clear effect on patients in pain, although not shown convincingly in controlled studies.[4,10,13] This may be because control patients in studies usually get a placebo injection and often have low to moderate pain; thus there is not much potential or statistical power for showing improvements for the whole group.

What then are the alternatives to LIA for knee arthroplasty? In terms of "best" pain relief, it is probably hard to beat a well-functioning epidural, as long as the catheter is in place and used for regular top-ups, infusion, or adjustments.[12] Still, the epidural technique does not seem to provide any pain protection or benefits beyond the period of active use, and during this period the technique demands resources and may result in some motor block with subsequent limitations in mobilization and physiotherapy.[12] Furthermore, there are risks of urinary retention and hypotension and very rare, but serious, hematoma formation. Femoral nerve block provides a more limited area and time period of focused pain relief, but includes motor block and carries the rare risk of nerve damage. In a recent study comparing LIA and femoral block for knee arthroplasty, Affas et al. found less movement pain with LIA at 24 hours and therefore recommended it. They also found the LIA less expensive and easier to perform than femoral block.[14] There may also be other blocks for more focused single knee pain relief without motor block, as presented in a recent preliminary report on adductor canal block of the saphenus and obturator nerves.[15]

Finally, we should not forget the more common alternative: multimodal nonopioid pain propylaxis combined with the spinal 0.1 mg morphine. In the expert evidence-based procedure-specific recommendation for knee arthroplasty,[a] the combination of either spinal (without opioid) or general anesthesia with femoral block is recommended as first choice for anesthesia, supplemented with paracetamol, nonsteroidal anti-inflammatory drugs regularly and opioid top-up when needed. The recommendation to avoid intrathecal morphine was based on nausea in a study that used a morphine dose of 0.25 mg[16] and may not be relevant with the 0.1-mg dose as used by Essving et al. Finally, other components of a multimodal drug analgesic strategy for total knee replacement may also include glucocorticoid[17] and gabapentinoid.[18]

In conclusion, the LIA method seems promising as a routine tool for analgesia after total knee replacement. Still, we need more clinical research along 2 important paths to move the LIA concept into its proper clinical place: The first is to test each component individually (keeping the rest unchanged and standardized) in very controlled and standardized conditions, to elucidate that what is working is LIA specific. The second path, that Essving et al. have started on, is to compare LIA with the best potential alternatives used most optimally: intrathecal opioid, epidural analgesia, femoral nerve block, other nerve blocks, or just optimal multimodal analgesia including local anesthesia wound infiltration.

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Local Infiltration Analgesia Versus Intrathecal Morphine for Postoperative Pain Management After Total Knee Arthroplasty: A Randomized Controlled Trial

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BACKGROUND: Local infiltration analgesia (LIA)—using a combination of local anesthetics, nonsteroidal anti-inflammatory drugs, and epinephrine, injected periarticularly during surgery—has become popular in postoperative pain management after total knee arthroplasty (TKA). We compared intrathecal morphine with LIA after TKA.

METHODS: In this double-blind study, 50 patients scheduled to undergo TKA under spinal anesthesia were randomized into 2 groups: group M, 0.1 mg morphine was injected intrathecally together with the spinal anesthetic and in group L, LIA using ropivacaine, ketorolac, and epinephrine was infiltrated in the knee during the operation, and 2 bolus injections of the same mixture were given via an intraarticular catheter postoperatively. Postoperative pain, rescue analgesic requirements, mobilization, and home readiness were recorded. Patient-assessed health quality was recorded using the Oxford Knee Score and EQ-5D during 3 months follow-up. The primary endpoint was IV morphine consumption the first 48 postoperative hours.

RESULTS: Mean morphine consumption was significantly lower in group L than in group M during the first 48 postoperative hours: 26 ± 15 vs 54 ± 29 mg, i.e., a mean difference for each 24-hour period of 14.2 (95% confidence interval [CI] 7.6 to 20.9) mg. Pain scores at rest and on movement were lower during the first 48 hours in group L than in group M ($P < 0.001$). Pain score was also lower when walking in group L than in group M at 24 hours and 48 hours postoperatively ($P < 0.001$). In group L, more patients were able to climb stairs at 24 hours: 50% (11 of 22) versus 4% (1 of 23), i.e., a difference of 46% (95% CI 23.5 to 68.5) and at 48 hours: 70% (16 of 23) versus 22% (5 of 23), i.e., a difference of 48% (95% CI 23 to 73). Median (range) time to fulfillment of discharge criteria was shorter in group L than in group M, 51 (24–166) hours versus 72 (51–170) hours. The difference was 23 (95% CI 18 to 42) hours ($P = 0.001$). Length of hospital stay was also shorter in group L than in group M: median (range) 3 (2–17) versus 4 (2–14) days ($P = 0.029$). Patient satisfaction was greater in group L than in group M ($P = 0.001$), but no differences were found in knee function, side effects, or in patient-related outcomes, Oxford Knee score, or EQ-5D.

CONCLUSIONS: LIA technique provided better postoperative analgesia and earlier mobilization, resulting in shorter hospital stay, than did intrathecal morphine after TKA. (Anesth Analg 2011; 113:926–33)

Total knee arthroplasty (TKA) is generally associated with moderate to severe postoperative pain that often lasts for up to 48 hours and is particularly severe during mobilization.[1,2] Several methods are available for pain management including opioids, administered IV or intrathecally, peripheral nerve block, and the recently introduced method of local infiltration analgesia (LIA). Although IV opioids are effective, they have the major disadvantage of having disabling side effects, and analgesia is sometimes inadequate, specifically during mobilization. Therefore, intrathecal morphine has been used as an alternative method for pain relief and provides satisfactory analgesia for at least 24 hours, a period of time when pain is often most severe.[3–6] However, side effects of intrathecal morphine—including pruritus, urinary retention, and respiratory depression[7]—can be troublesome for the patient and require increased supervision and monitoring.

The LIA technique has increasingly become popular over the last 5 to 10 years, especially in the Scandinavian countries. A long-acting local anesthetic (ropivacaine), a nonsteroidal anti-inflammatory drug (NSAID) (ketorolac), and epinephrine are infiltrated intraoperatively in the LIA technique, and this solution is also injected via a catheter placed in the knee joint, postoperatively. A number of studies supporting the efficacy of LIA in TKA have been published recently,[8–12] but only a few have compared this technique with other standard techniques for postoperative pain management after TKA.[13–16] Lower pain scores were found in all these studies, and mobilization could be achieved earlier after LIA. However, no decrease in hospital length of stay (LOS) was shown.

In this prospective, randomized, double-blind study, we compared the LIA technique with intrathecal morphine

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Accepted for publication May 25, 2011.

Funding: Research Committee, Örebro University Hospital.

The authors declare no conflict of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0b013e3182288deb

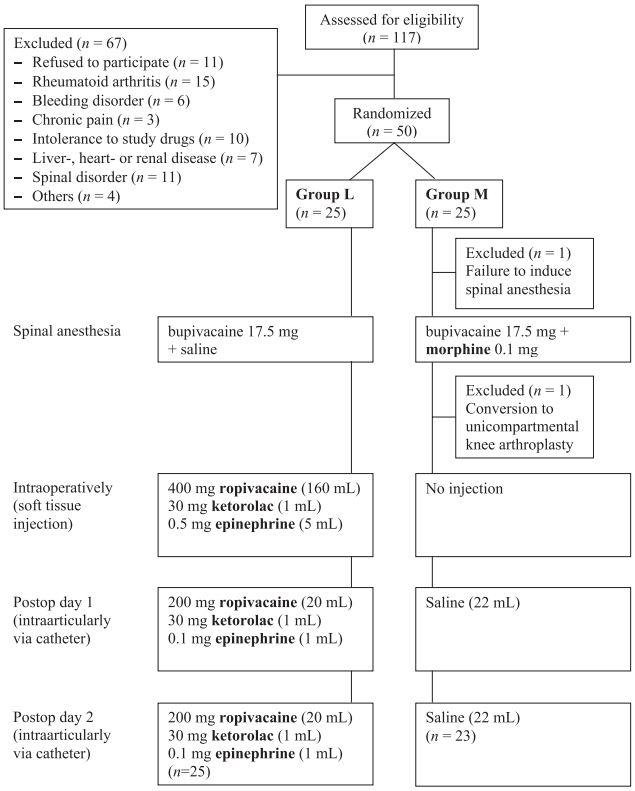

Figure 1. Flow chart for the study. Group L = local infiltration analgesia; group M = intrathecal morphine.

during TKA. In an attempt to prolong the postoperative analgesia and improve mobilization, the intra-articular catheter was left in situ for 48 hours to allow an additional bolus injection on the first and second postoperative days. Our hypothesis was that LIA would provide better postoperative analgesia than intrathecal morphine and thereby reduce IV morphine consumption during the first 48 postoperative hours.

METHODS

The regional ethics committee in Uppsala, Sweden (March 25, 2009, Dnr 2009/069), and the Swedish Medical Products Agency approved this study. It was also registered at the ClinicalTrials.gov (Code NCT992082) on October 7, 2009, and conducted in accordance with the Helsinki declaration and monitored by the Clinical Research Support Unit at Örebro University Hospital.

Patients

Fifty patients scheduled to undergo TKA because of osteoarthritis gave written, informed consent and were enrolled in this trial (Fig. 1). The inclusion criteria were age 40 to 85 years and ASA I–III. Exclusion criteria were allergy or intolerance to any of the study drugs, severe liver, heart or renal disease, inflammatory joint disease, chronic pain requiring opioid medication, bleeding disorder, and any other contraindication for spinal anesthesia. Patients fulfilling the above criteria had surgery between August 2009 and June 2010 at the Department of Orthopedic Surgery, Örebro University Hospital.

Randomization and Blinding

The hospital pharmacy randomized the patients into 2 groups: group M (morphine) and group L (local infiltration), 25 patients in each group, using computer-generated randomized numbers (Fig. 1). The surgeon was not blinded to group randomization and was not allowed to participate in postoperative patient care. All other persons involved directly or indirectly in the study—including the patients, the other investigators, the physiotherapist, and staff involved in postoperative patient care—were blinded to the study arm.

Anesthesia

All patients received diazepam 10 mg orally 1 hour before planned surgery, and all operations were performed under spinal anesthesia using a 27-G pencil-point spinal needle at the L3/L4 or L2/L3 intervertebral space with the patient in the sitting position. In group M, morphine 0.1 mg (0.25 mL) was injected intrathecally, and in group L an equal volume of 0.9% saline, together with glucose-free bupivacaine 17.5 mg (3.5 mL) (Fig. 1). The study drug mixtures were prepared by the hospital pharmacy. If the spread of the sensory block (pinprick) was insufficient, the patient was excluded from the study, and general anesthesia was administered. All patients could receive propofol IV on demand or as continuous infusion during the operation. If the patient had pain during the operation, fentanyl IV was administered in bolus doses of 25 to 50 μg up to a maximum of 300 μg. If insufficient analgesia was achieved, the patient was excluded from the study, and general anesthesia was administered.

Surgery

All patients received an AGC prosthesis (Biomet, Warsaw, IN) using a standard medial parapatellar approach. Surgery was performed using a femoral tourniquet to minimize blood loss and improve operative conditions. No drains were left in the knee joint after the operation. Cloxacillin 2 g was given IV preoperatively and continued until the intra-articular catheter was withdrawn after 48 hours. Dalteparin (5.000 IU) was administered subcutaneously for thromboprophylaxis once each evening for 10 days, starting on the evening before surgery. Ice packs were applied around the knee joint during the first 6 hours, which is a routine in our hospital. The whole lower limb had a compression bandage for the first 21 postoperative hours.

Local Infiltration Technique

In group L, 300 mg ropivacaine, 30 mg ketorolac, and 0.5 mg epinephrine (total volume 116 mL) were infiltrated by the surgeon into the soft tissues periarticularly during the operation. The injections were done systematically into all tissue that had been traumatized during surgery by injecting 40 to 50 mL in the posterior capsule and the collateral ligaments after the bone cuts had been made and before insertion of the prosthesis. After the prosthesis had been inserted, another 50 to 70 mL was injected in the capsule incision, in the quadriceps tendon, in the infrapatellar ligament, and around the posterior cruciate ligament. Finally, 50 mL ropivacaine (100 mg) without epinephrine or ketorolac was

infiltrated into the subcutaneous tissue before skin closure. Thus, a total of 400 mg ropivacaine was administered in a volume of 166 mL. Patients in group M received no injection (Fig. 1).

Before wound closure, the surgeon placed an intra-articular catheter in all patients in both groups using a Tuohy 18-G needle, a multihole 20-G epidural catheter ,and a bacterial filter (B. Braun Medical, Melsungen, Germany). The needle was introduced percutaneously from the lateral side about 10 cm proximal to the skin incision through the vastus lateralis and into the knee joint. The catheter was inserted via the needle and passed along the medial femoral condyle, leaving the tip of the catheter in the posterior part of the knee joint. The needle was removed, the bacterial filter was connected, and the filter and the catheter were filled with 1 to 2 mL of ropivacaine for bacteriostasis as well as to ensure functional patency of the system.

On the first and second postoperative morning, after 21 and 45 hours, 200 mg ropivacaine, 30 mg ketorolac, and 0.1 mg epinephrine, total volume 22 mL, were injected intra-articularly via the catheter in group L, and a similar volume of saline was injected in group M (Fig. 1). These drugs were prepared by the hospital pharmacy to ensure blinding. The intra-articular catheter was removed after 45 hours, and the tip of the catheter was sent for culture.

The first attempt to mobilization was made on the first postoperative morning 1 hour after the intra-articular injection. The patients were encouraged to stand and to walk 6 to 8 steps. If the patients could not be mobilized, another attempt was made the following day, after the second intra-articular injection.

A visual analog scale (VAS; 0 mm = no pain, 100 mm = worst imaginable pain) was used for assessment of pain. At 48 hours, if pain at rest was VAS <40 mm during a 2-hour period, the patient-controlled analgesia (PCA) pump was discontinued, and tramadol was administered 100 mg orally up to 4 times daily as required to achieve VAS <40 mm.

Recordings and Measurements

Morphine consumption. PCA-morphine consumption was recorded during 0 to 24 hours and 24 to 48 hours postoperatively, and 0 to 48 hours was calculated.

Pain relief. Pain assessment (VAS) was made preoperatively and at 6, 12, 21, 22, 24, 45, and 46 hours postoperatively. Pain was assessed both at rest and on flexion of the knee by 60 degrees. Pain when walking was also recorded at 24 and 48 hours. After discharge home, all patients were asked to complete a questionnaire regarding postoperative pain on days 1, 3, and 14 and after 3 months.

Patient satisfaction. The patients were also asked to give a verbal rating scale for satisfaction with the quality of analgesia (excellent = 4, good = 3, inadequate = 2, poor = 1) during the first and second postoperative days and after 7 days.

Functional recovery. Maximum knee extension and flexion were assessed preoperatively, on day 3, at discharge, and after 2 weeks and 3 months postoperatively. Ability to climb 8 stairs was recorded at 24 and 48 hours. Time to Up and Go (TUG) test[17] was assessed preoperatively and postoperatively on days 3, 7, and 14, and after 3 months. The TUG test involves timing the patient when he or she rises from an armchair, walks 3 meters, turns, walks back, and sits down again. Values <20 seconds indicate that the patient is independently mobile. Oxford Knee Score was determined preoperatively and at 2 weeks and 3 months postoperatively. Oxford Knee Score is a validated 12-item knee questionnaire that scores patients from 12 (best possible) to 60 (worst possible).[18] EuroQol (EQ-5D) questionnaire was collected preoperatively and postoperatively at 3 months. EQ-5D is a standardized instrument for use as a measure of health outcome.[19] It provides a single index value from 0 to 1 for which 0 represents poor health and 1 represents perfect health.

Home readiness and hospital stay. After the second injection via the catheter at 45 hours, the time to fulfillment of discharge criteria (home readiness) was recorded by a physician and the study physiotherapist, who were unaware of group randomization. The discharge criteria were mild 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. Time to fulfillment of discharge criteria was defined as the time from the end of the operation until the patient fulfilled the discharge criteria, which was assessed 3 times a day. Hospital LOS was recorded (day 0 = the day of operation) as actual time to home discharge.

Adverse events. The incidence of nausea, vomiting, pruritus, and sedation were recorded on the first and second postoperative days. Sedation was recorded at 24 hours and 48 hours using a 4-grade scale (1 = fully awake, 2 = drowsy [light sedation], 3 = asleep, 4 = deeply asleep [heavily sedated]). As part of our routine in our hospital, respiratory rate and arterial oxygen saturation were recorded during the first 24 hours, and respiratory depression is defined as respiratory rate <10/min combined with Sao_2 <90%. All complications and adverse events were registered intra- and postoperatively, as well as after discharge. Any hospital readmission during the 3-month follow-up period postoperatively was also recorded.

Statistics

Sample-size calculations were done using morphine consumption for 48 hours postoperatively as the primary endpoint. In an earlier study on patients undergoing TKA during general anesthesia,[10] the mean ± SD morphine consumption for 48 hours postoperatively was 91 ± 36 mg in the placebo group versus 24 ± 23 mg in the LIA group. In a pilot study of 5 patients receiving spinal anesthesia with morphine added to the local anesthetic, the PCA-morphine consumption was 45 ± 11 mg. Therefore, assuming a mean of 45 mg in group M and 24 mg in group LIA, with SD of 23 in both groups, we calculated that 23 patients would be required in each group to detect this difference with an α of 0.05 and β of 0.2. Considering the risk of dropouts and the uncertainty in SD, 25 patients were included in each of the 2 groups. Repeated-measurements analysis of variance (ANOVA) with Huynh–Feldt corrected P values were used for the analysis of the primary endpoint (morphine consumption during the first 48 postoperative hours), and post hoc test from the ANOVA for the first 24

Table 1. Demographic Data and Duration of Surgery

	Group L (n = 25)	Group M (n = 25)
No. of females/males	16/9	15/10
Age, years	71 ± 8	71 ± 9
Weight, kg	85 ± 16	85 ± 17
Height, cm	168 ± 9	169 ± 9
BMI	30 ± 5	29 ± 4
ASA, I/II/III	2/20/3	4/20/1
Operation time, minutes	83 ± 12	78 ± 13

Values are shown as mean ± SD. Group L = local infiltration analgesia; group M = intrathecal morphine; BMI = body mass index; ASA physical status I = normal health; II = systemic disease with no limited activity; III = systemic disease with limited activity.

postoperative hours was also performed. Mean difference between groups and time points and their interaction were tested. To summarize each patient's VAS pain scores for the first 48 postoperative hours, the median value was calculated for each patient. The difference between groups was then analyzed using Mann–Whitney U test. Hospital stay, time to fulfillment of discharge criteria, knee function scores, and patient satisfaction scores were also analyzed using the Mann–Whitney U test. The Bonferroni–Holm method was used to correct for multiple measures when $P < 0.05$ in the secondary endpoints.[20] Dichotomous data were analyzed using the χ^2 test or Fisher's exact test, as appropriate. $P < 0.05$ was considered to be statistically significant. Confidence interval around median was calculated with Hodges–Lehmann method using Confidence Interval Analysis (CIA) Software (Statistics with Confidence, 2nd ed., BMJ Books 2000). All other analyses were made using computer software SPSS version 15.0 for windows (SPSS Inc., Chicago, IL).

RESULTS

Two patients in group M were excluded after randomization, the first because of failure to induce spinal anesthesia and the second because of an intraoperative conversion to unicompartmental knee arthroplasty (Fig. 1). The patient characteristics of the study groups were similar (Table 1).

Primary Endpoint: Morphine Consumption

Mean morphine consumption was less in group L than in group M for the first 48 postoperative hours: 26 ± 15 vs 54 ± 29, i.e., a mean difference for each 24-hour period of 14.2 (95% confidence interval [CI] 7.6 to 20.9) mg from the ANOVA (Table 2) with between- subjects effects (group) $P < 0.001$, within-subject effects (time) $P = 0.001$, and interaction effects (time × group) $P = 0.335$. Because of a slight significance in Shapiro–Wilk test for skewness, a sensitivity analysis with square-root transformation (resulting in nonsignificant Shapiro–Wilk test) was performed, resulting in the same overall conclusions. Post hoc test from the same ANOVA during the first 24 hours showed a mean difference of 15.7 (95% CI 7.9 to 23.6) mg. There was a protocol violation in 6 patients, 3 in each group, who received 1 dose of oral tramadol postoperatively in the ward.

Table 2. Descriptive Data of Morphine Consumption

	Group L (n = 25)	Group M (n = 23)
Morphine IV (mg)		
0–48 hours	26 ± 15	54 ± 29
0–24 hours	15 ± 10	30 ± 17
24–48 hours	11 ± 8	24 ± 14

Values are shown as mean ± SD. Group L = local infiltration analgesia; group M = intrathecal morphine. When 0–48 hours was analyzed with repeated-measurement analysis of variance, we found a mean difference for each 24-hour period of 14.2 (95% confidence interval of 7.6–20.9) mg.

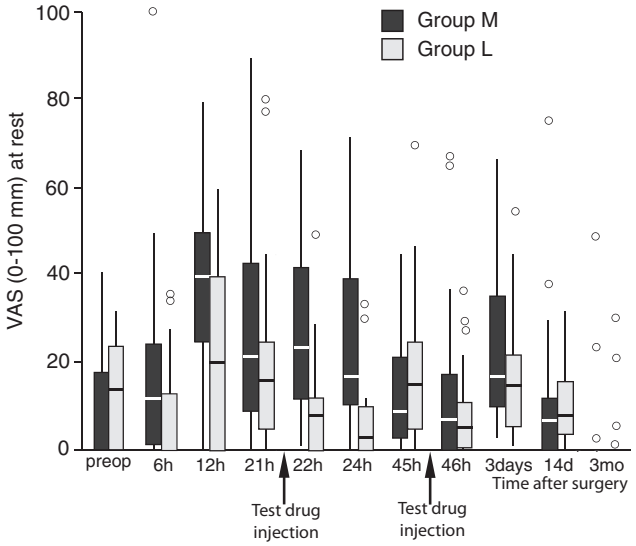

Figure 2. Pain at rest. Visual analog scale (VAS) scores are presented as median and interquartile range. Group L = local infiltration analgesia; group M = intrathecal morphine.

Pain Relief

The median VAS pain score at rest and on flexion for the first 48 postoperative hours was determined for each subject. The medians at rest were lower in group L than in group M: 5 (0–33) versus 20 (3–48) mm ($P < 0.001$) (Fig. 2).

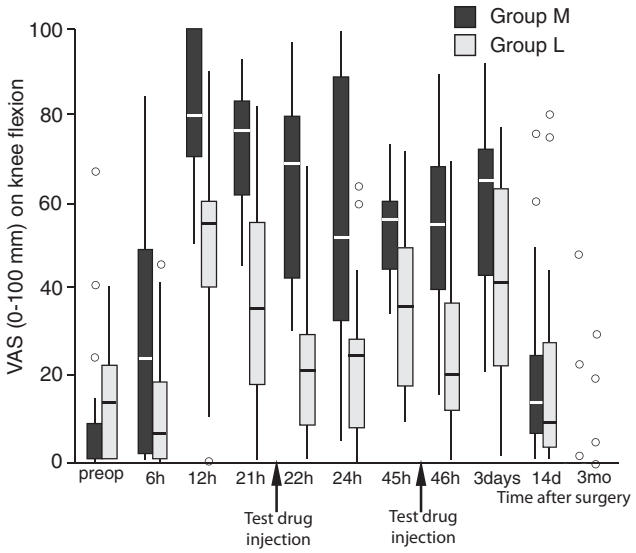

Figure 3. Pain on movement. Visual analog scale (VAS) scores are presented as median and interquartile range. Group L = local infiltration analgesia; group M = intrathecal morphine.

Table 3. Functional Outcome and Patient Satisfaction

	Group L		Group M		
Outcome	Median (range)	N	Median (range)	n	P value
Knee extension (degrees)					
Preoperative	5 (0–15)	24	5 (0–15)	23	
3 days postoperative	10 (0–15)	21	10 (0–25)	12	0.33
Discharge	10 (5–15)	22	10 (5–25)	21	0.35
7 days postoperative	5 (5–20)	21	15 (5–15)	15	0.11
14 days postoperative	10 (5–20)	25	10 (5–15)	23	0.80
3 months postoperative	0 (0–10)	20	0 (0–15)	22	0.82
Knee flexion (degrees)					
Preoperative	110 (75–125)	25	110 (75–130)	23	
3 days postoperative	75 (35–90)	21	65 (35–90)	12	0.10
Discharge	75 (60–95)	22	70 (35–90)	21	0.13
7 days postoperative	70 (35–90)	21	72 (35–90)	16	0.32
14 days postoperative	75 (50–105)	25	80 (40–100)	23	0.98
3 months postoperative	100 (70–115)	20	100 (70–120)	22	1.00
TUG test (seconds)					
Preoperative	11 (6–26)	24	13 (5–23)	23	
3 days postoperative	29 (16–49)	10	30 (18–59)	15	na[a]
7 days postoperative	15 (9–40)	21	18 (12–32)	16	0.31
14 days postoperative	14 (8–25)	25	16 (8–33)	23	0.22
3 months postoperative	10 (6–31)	20	10 (6–19)	22	0.87
Patient satisfaction					
1 day postoperative	4 (3–4)	24	3 (1–4)	21	0.001*
2 days postoperative	3.5 (3–4)	24	3 (2–4)	22	0.052
7 days postoperative	3 (2–4)	24	3 (2–4)	21	0.63
Oxford Knee Score					
Preoperative	39 (24–50)	25	38 (20–46)	23	
14 days postoperative	33 (28–48)	23	34 (23–47)	18	0.68
3 months postoperative	24 (12–43)	22	24 (14–42)	23	0.98
EQ-5D					
Preoperative	0.69 (0.09–0.81)	25	0.69 (0.02–0.89)	23	
3 months postoperative	0.80 (0.62–1)	21	0.80 (0.36–1)	19	0.98

Group L = local infiltration analgesia; group M = Intrathecal morphine; *n* = number of patients who participated varied depending on patients' ability to cooperate; TUG test = Time Up and Go test; No statistical calculations were done because of the small number of patients in each group. Patient satisfaction: excellent = 4, good = 3, inadequate = 2, poor =1. Oxford Knee Score: 12 (the best possible) to 60 (the worst possible). EQ-5D health outcome: 1 = perfect health, 0 = poor health.

* After correction with Bonferroni–Holm, the critical value for statistical significance was 0.0025.

[a] na = not applicable.

Even on flexion, the median (range) VAS pain score was lower in group L than in group M: 30 (0–60) versus 59 (22–93) mm ($P < 0.001$) for the first 48 postoperative hours (Fig. 3). When walking, the median (range) VAS pain score was lower in group L at 24 hours, 19 (0–49) versus 58 (40–92) ($P < 0.001$), and at 48 hours, 10 (10–50) versus 39 (4–74) ($P = 0.001$).

Patient Satisfaction

Patients' satisfaction was greater in group L than in group M on postoperative day 1 ($P = 0.001$). No difference was found in patient satisfaction on days 2 and 7 (Table 3).

Functional Recovery

Knee extension, knee flexion, and the TUG test did not show any differences between groups postoperatively (Table 3). However, a significantly larger proportion of patients in group L were able to climb stairs at 24 hours: 50% (11 of 22) versus 4% (1 of 23), i.e., a difference of 46% (95% CI 23.5 to 68.5); and at 48 hours: 70% (16 of 23) versus 22% (5 of 23), i.e., a difference of 48% (95% CI 23 to 73). Oxford Knee Score and EQ-5D did not reveal any differences between the groups at any time postoperatively (Table 3).

Home Readiness and Hospital Stay

Median (range) time to fulfillment of discharge criteria was shorter in group L than in group M, 51 (24–166) hours versus 72 (51–170) hours. The difference was 23 (95% CI 18 to 42) hours ($P = 0.001$). The hospital LOS was shorter in group L than in group M, median (range) 3 (2–17) versus 4 (2–14) days ($P = 0.029$) (Fig. 4). One patient in group M was admitted for 14 days because of a fall in the ward and sustained a hip contusion, which delayed discharge. One patient in group L remained in the hospital for 17 days because of persistent urinary retention requiring repeated catheterization.

Adverse Effects

We found no differences in the incidence of nausea, vomiting, pruritus, or sedation between groups (Table 4). We found only sedation grade 1 (fully awake) or 2 (drowsy), and no patient had sedation grade 3 or 4. Therefore we analyzed the incidence of sedation, as shown in Table 4. We found 13 episodes of respiratory rate <10/min in the LIA group in comparison with 8 in the morphine group, but none of those with Sao_2 <90%. There were 3 episodes of Sao_2 <90% in the LIA group in comparison with 2 in the morphine group, but none of those with a respiratory rate

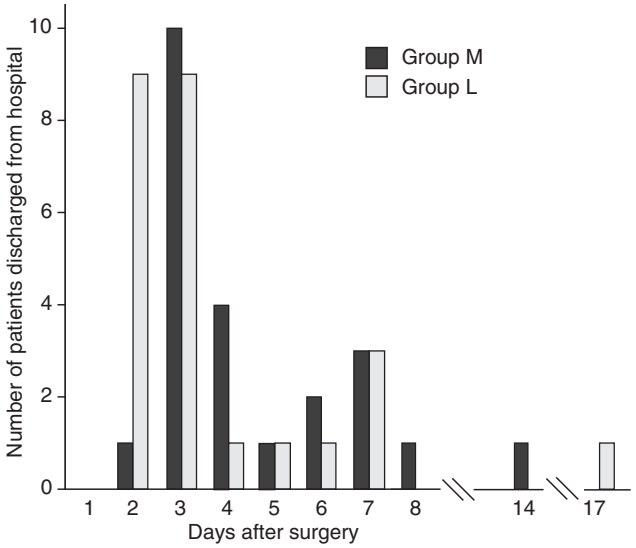

Figure 4. Length of hospital stay. Group L = local infiltration analgesia; group M = intrathecal morphine; day 0 = the day of operation.

<10/min. None of the patients was treated with naloxone. There were 7 positive cultures from the catheter tips, all with solitary coagulase-negative *Staphylococcus*, 3 in group L and 4 in group M, but no antibiotics were given, and no clinical signs of infection were found during the follow-up period. One patient in group M was readmitted after discharge because of a swollen knee and mild fever, 37.8°C. The maximum C reactive protein was 38 mg/L, and wound cultures were negative. Oral antibiotics were administered, and wound healing was complete and satisfactory. No evidence of deep infection was found at admission or during the 3-month follow-up. No other complications were reported.

DISCUSSION

Good pain relief after TKA is important as it aids physiotherapy and promotes mobilization, which is central for a satisfactory outcome. Several recent studies have confirmed the efficacy of the LIA technique during TKA, and today the method is commonly used in Scandinavia as an alternative to regional blocks for postoperative pain management. Therefore, the main aim of our present study was to elucidate whether this method is equally effective as intrathecal morphine after TKA. To the best of our knowledge, this is the first study comparing the LIA technique with intrathecal morphine during TKA. We used intrathecal morphine as a comparator for several reasons. It is a simple method used routinely for pain management after major orthopedic surgery of the lower extremity. Many studies have been published using intrathecal morphine, and the method is well established in clinical practice. In a review on postoperative analgesia after TKA, Fischer et al. recommended the use of spinal injection of local anesthetic plus spinal morphine as an alternative to general anesthesia combined with femoral nerve block (FNB).[21] Although intrathecal morphine may be associated with some side effects, the incidence of serious side effects such as respiratory depression is low. Respiratory depression is a cause for major concern and therefore the need for close monitoring may demand increased hospital resources. One drawback with intrathecal morphine is the relatively short duration of action, which limits analgesia to 24 hours and at best up to 48 hours.[22,23] Results from our present study show several advantages of LIA over intrathecal morphine. First, we found significantly lower total rescue morphine consumption for 0 to 48 hours in the LIA group, which was our primary endpoint. In contrast, we found that the effect of intrathecal morphine was shorter than 24 hours, which resulted in significantly more morphine consumption during the first 24 postoperative hours in group M. Although morphine consumption is a surrogate endpoint, nevertheless our study demonstrates that the LIA technique is effective because we used PCA in both groups and patients were clearly instructed to self-administer morphine as required to achieve VAS <30 mm. In addition to the local infiltrations during the operation, we injected the drugs intra-articularly after 21 and 45 hours in the LIA group, which prolonged the analgesic duration and reduced morphine consumption, which is an advantage when using this method. In contrast, the inability of prolonging analgesia is a major disadvantage when using intrathecal morphine and severely limits its potential during TKA. Furthermore, the injection of drugs intra-articularly after 45 hours prolonged analgesia during mobilization, and this beneficial effect may also have resulted in earlier home readiness and discharge in comparison with our previous study in which the catheter was removed after 21 hours.[10] Second, we found significantly lower pain scores in the LIA group on movement as well as when walking for 0 to 48 hours, which is important because better pain relief allows patients to be mobilized easily and aids physiotherapy. The latter is particularly important after knee surgery because it may promote quicker discharge home and earlier rehabilitation. Indeed, we did find a shorter time to home readiness as well as to home discharge in the LIA group. Because personnel evaluating home readiness were blinded to the study arm and we used previously described objective criteria for its assessment,[10] we believe that our results are valid on this point. Therefore, less pain resulted in earlier mobilization, which in turn led to earlier home readiness in the LIA group. Finally, a subjective measurement of patient

Table 4. Side Effects

	Group L (n = 25)	Group M (n = 23)	P value
Nausea			
0–24 h	13	17	0.12
24–48 h	12	11	0.99
Vomiting			
0–24 h	7	12	0.09
24–48 h	3	5	0.89
Pruritus			
0–24 h	4	7	0.24
24–48 h	4	6	0.49
Sedation			
0–24 h	1	3	0.34
24–48 h	0	0	na

Values are number of patients in each category. Group L = local infiltration analgesia; group M= intrathecal morphine; na = not applicable.

satisfaction with postoperative analgesia was also greater in the LIA group. When combined, our findings would confirm that LIA is effective and results in good pain relief, earlier mobilization, and quicker home readiness and discharge.

It could be argued that intrathecal morphine is not the "gold standard" for pain relief after TKA, and therefore an alternative comparator group could have been epidural analgesia (EDA) or FNB. In view of the highlighted risks of EDA in older patients,[24] we were reluctant to use this method for pain management after orthopedic surgery. Furthermore, previous studies using EDA for TKA did not demonstrate better analgesia than did LIA.[13–15] Could FNB then have been a better alternative to spinal morphine as a comparator? One study found the LIA technique to be better than FNB in terms of earlier mobilization, reduced pain intensity, and lower morphine requirements.[16] Although the study by Carli et al. showed greater morphine consumption in the LIA group than in the FNB group, this study could be questioned in view of the fact that the FNB group also received a modified LIA technique, which may be a confounding factor.[25] Therefore, these results are difficult to interpret.

In our study, the incidence of side effects was similar between the groups. Although urinary retention, pruritus, and nausea and vomiting are frequent side effects of intrathecal opioids,[4,26,27] we were unable to find any significant differences between the groups. This could be because of the small number of patients we studied and because the difference between the 2 groups in rescue morphine consumption was small. Thus, it is possible that side effects of morphine are dose dependent and that when larger doses are administered, the incidence of side effects increases and then becomes more clinically important and significant.

The patients in this study received a high dose of ropivacaine (400 mg) initially, followed by 2 bolus injections of 200 mg each over a 48-hour period. No patient had any clinical symptoms of systemic toxicity. In an earlier study using 400 mg ropivacaine injected periarticularly, followed by 200 mg intra-articularly after 21 hours, we could show that the individual maximum unbound plasma concentrations were far below toxic levels.[10,28] Our data are similar to those of other authors[9,12] and confirm that the risk of local anesthetic toxicity is small or absent when injected intra-articularly in these doses.

The safety of leaving in an intra-articular catheter for 1 or 2 days can be questioned. A number of studies using LIA and intra-articular catheters have not reported any infections related to the use of the wound catheter.[10,12,16,29,30] However, 2 studies did report deep infections. DeWeese et al. reported 1 deep infection in 91 patients, and Rasmussen et al. found 1 in 136 TKA when a catheter was left in situ for 72 hours.[31,32] This low incidence of deep infection after TKA can be expected even without intra-articular catheters.[33] It is important to stress that all of our patients were given antibiotics until the catheter was removed; the catheters were inserted during the operation by an orthopedic surgeon under sterile conditions; and a bacterial filter was used during all intra-articular injections postoperatively.

No differences were found at 3 months when comparing the general health outcome EQ-5D or the disease-specific Oxford Knee Score, because earlier mobilization and shorter hospital stay do not seem to affect the long-term outcome in any significant way.

One possible limitation of this study could be that group L received NSAID in the mixture injected in the knee perioperatively, whereas group M did not. Therefore, a systemic effect of NSAID administered intra-articularly cannot be excluded.[34] It may have been an advantage to inject a similar dose of ketorolac IV postoperatively in group M to confirm a beneficial local effect. However, some studies in the literature have reported significantly better pain relief when ketorolac was administered intra-articularly in comparison with IV injection.[13,14,35]

Could a higher dose of morphine injected intrathecally have a better analgesic effect? In one study, the authors found that 0.1 mg or 0.2 mg resulted in similar postoperative pain relief after hip arthroplasty.[4] In addition, 0.1 mg morphine was also found to provide the best balance between efficacy and side effects in elderly patients. Therefore, we chose to use this dose and also found few side effects in the present study.

In conclusion, the LIA technique was found to be superior to intrathecal morphine in providing good pain relief and resulted in early mobilization and greater patient satisfaction after TKA. These advantages translated into earlier home readiness and quicker home discharge without increasing any adverse effects. However, there was no improvement in patient-assessed long-term outcomes when using the LIA technique. Further clinical trials are warranted to define the best composition of drugs involved in the LIA mixture and the role of the intra-articular catheter in prolonging postoperative analgesia.

DISCLOSURES

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Attestation: This author reviewed the original study data and data analysis, approved the final manuscript, and is the archival author.
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Name: Anil Gupta, MD, PhD.
Contribution: Study design, manuscript preparation.
Attestation: This author approved the final manuscript.
Name: Anders Lundin, MD, PhD.
Contribution: Data analysis.
Attestation: This author approved the final manuscript.
This manuscript was handled by: Spencer S. Liu, MD.

ACKNOWLEDGMENTS

We thank Anders Magnuson of the Department of Epidemiology and Statistics for his expert help on statistic issues.

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