Intraoperative Local Infiltration Analgesia for Early Analgesia After Total Hip Arthroplasty

A Randomized, Double-Blind, Placebo-Controlled Trial

Troels H. Lunn, MD,*† Henrik Husted, MD,‡‡ Søren Solgaard, MD, DMSc,**§ Billy B. Kristensen, MD,*† Kristian S. Otte, MD,‡‡ Anne G. Kjersgaard, MD,**§ Lissi Gaarn-Larsen, RNA,† and Henrik Kehlet, MD, PhD†‡

Background and Objectives: High-volume local infiltration analgesia (LIA) is widely applied as part of a multimodal pain management strategy in total hip arthroplasty (THA). However, methodological problems hinder the exact interpretation of previous trials, and the evidence for LIA in THA remains to be clarified. Therefore, we evaluated whether intraoperative high-volume LIA, in addition to a multimodal oral analgesic regimen, would further reduce acute postoperative pain after THA.

Methods: Patients scheduled for unilateral, primary THA under spinal anesthesia were included in this randomized, double-blind, placebo-controlled trial receiving high-volume (150 mL) wound infiltration with ropivacaine 0.2% with epinephrine (10 µg/mL) or saline 0.9%. A multimodal oral analgesic regimen consisting of slow-release acetylsalicylic acid 2 g, celecoxib 400 mg, and gabapentin 600 mg was instituted preoperatively. Rescue analgesia consisted of oral oxycodone. Pain was assessed repeatedly the first 8 hrs after surgery using the 100-mm visual analog scale. The primary end point was pain during walking (5 m) 8 hrs after surgery. Secondary end points were pain at rest, pain on 45 degrees of passive flexion of the hip with the leg straight, and cumulative consumption of oxycodone.

Results: A total of 120 patients were included. Pain during walking (median [interquartile range] [95% confidence interval]) was low in the ropivacaine versus the placebo group (20 [14–38] [0–93] vs 22 [10–40] [0–83]) and did not differ significantly (P = 0.71). Consumption of rescue oxycodone (5 mg [0–10 mg] [0–24 mg] vs 10 mg [0–15 mg] [0–29 mg]) did not differ (P = 0.45).

Conclusions: Intraoperative high-volume LIA with ropivacaine 0.2% provided no additional reduction in acute pain after THA when combined with a multimodal oral analgesic regimen consisting of acetaminophen, celecoxib, and gabapentin and is therefore not recommended.

METHODS

Patients and Design

The trial was approved by the local research ethics committee (De Videnskabsstiske Komité for Region Hovedstaden, Hillerød, Denmark) and the Danish data protection agency and registered at www.clinicaltrials.gov (no. NCT00968955). Oral and written informed consent was obtained from all patients, and the study was carried out in accordance with the principles of the Helsinki Declarations. The CONSORT recommendations for reporting randomized controlled clinical trials was followed.16

Patients scheduled for elective, unilateral, primary THA by 1 of 3 orthopedic surgeons at Hvidovre University Hospital (from
September 2009 to March 2010) and by 1 of 2 orthopedic surgeons at Hørsholm Hospital (from November 2009 to June 2010), older than 18 years, and familiar with the Danish language were screened for inclusion in the study. Exclusion criteria were alcohol and medical abuse, daily use of strong opioids (morphine, fentanyl, hydromorphone, ketobemidone, methadone, nicomorphine, oxycodone, and pethidine) or glucocorticoids, body mass index (BMI) higher than 40 kg/m², allergies to local anesthetics, pregnancy or breast-feeding, diabetic neuropathy, rheumatoid arthritis, and neurological or psychiatric diseases potentially influencing pain perception. The design was a 2-center, prospective, randomised, double-blind, placebo-controlled trial.

Randomization and Blinding

One hundred twenty patients were randomly assigned to 2 groups of 60. A random allocation sequence concealed in 120 consecutively numbered, opaque, sealed envelopes determined active treatment or placebo was computer-generated by a project nurse not otherwise involved in the trial. The envelopes were opened on the morning of surgery, and the trial drug was prepared by an anesthetist not otherwise involved with data collection. The envelopes were divided between the 2 hospitals, and no stratification was made. Trial participants, care providers, and data collectors were all blinded to the allocation throughout the study.

Study Parameters

The primary end point was pain during walking with a walking aid (5 m) 8 hrs after surgery. Secondary end points were pain at rest (supine), pain on 45 degrees of passive flexion of the hip with the leg straight, and cumulative consumption of oxycodone 8 hrs after surgery. Pain during walking was assessed 4 and 8 hrs postoperatively and pain at rest and on hip flexion 2, 4, 6, and 8 hrs postoperatively using the 100-mm visual analog scale (VAS) (0 mm indicating no pain and 100 mm indicating worst pain imaginable). The investigator asked the patients at each time point: “Please show me how much pain you have right now on the VAS, where the lower limit indicates no pain and the upper limit indicates worst pain imaginable.” Complications occurring during hospitalization were registered.

Study Intervention

Local infiltration analgesia was performed intraoperatively using ropivacaine 0.2% (AstraZeneca, Södertälje, Sweden) with epinephrine (10 μg/mL) or saline 0.9% (placebo). A total volume of 150 mL was injected using a systematic technique ensuring uniform delivery to all tissues incised and instrumented during the surgery. The first 50 mL was systematically injected in the periacetabular tissues after reaming of the acetabulum and before insertion of the acetabular component. After insertion of the femoral component, another 50 mL was injected in the cut rotators and the gluteus muscles and the proximal part of the iliotibial tract. Finally, 50 mL was systematically injected in the subcutaneous layers. The subcutaneous injections (in case of allocation to ropivacaine) were without epinephrine to minimize the risk of subcutaneous blister formation. No intrarticular catheter was placed, and no postoperative injections were administered.

Anesthesia, Surgery, and Analgesia

Anesthesia, surgery, and analgesia were standardized for all patients. Thus, interventions were fixed for all but the modality under investigation. Surgery was performed under lumbar spinal anesthesia with 12.5 mg of isobaric bupivacaine (0.5%) and optional sedation with propofol (1–5 mg/kg per hour) by 1 of 5 surgeons all specialized in arthroplasty and the LIA technique. They agreed on a similar surgical and LIA technique before the study. Cefuroxime 1.5 g and tranexamic acid 1 g were administered intravenously. Intraoperative fluid therapy was standardized and consisted of saline 0.9% 5 mL/kg per hour and colloid (Voluven; Fresenius Kabi AB, Uppsala, Sweden) 7.5 mL/kg per hour. Total hip arthroplasty was performed using a standard posterior approach without the use of minimally invasive surgical techniques. Drains were not used. Prostheses were Bimetric with Ringloc-cup or Magnum-cup (Biomet-Merck, Inc, Warsaw, Ind) or CLS Spotorno with Trilogy-cup (Zimmer, Inc, Warsaw, Ind). A multimodal oral analgesic regimen consisting of slow-release acetaminophen 2 g, celecoxib 400 mg, and gabapentin 600 mg was instituted 1 to 2 hrs preoperatively. Rescue analgesics (administered if VAS >50 at rest) consisted of sufentanil 5 μg intravenously in the postanesthesia care unit (PACU) and subsequently, oral oxycodone 5 mg. Patients followed a well-defined, fast-track rehabilitation regimen and were discharged to their homes according to functional discharge criteria.

Statistical Analyses

The estimated sample size for the primary effect variable was calculated based on the results from a pilot study (n = 10), where average pain during walking (5 m) 8 hrs after primary, unilateral THA was found to be 28 mm with an SD of 22 mm. A total sample of 120 patients would allow the detection or rejection of a 50% reduction in pain in the ropivacaine group compared with the placebo group at a 2-sided 5% significance level with a power of 90% and 15% dropouts.

Continuous numeric variables were assessed for normality of distribution (Kolmogorov-Smirnov). Depending on whether variables were normally distributed (only the case for age, BMI, and duration of surgery), they were presented as mean with range, and otherwise as median with interquartile range (IQR). Categorical variables are presented as count with percentage, and tests for significant differences between groups were done with the χ² test. The Mann-Whitney rank sum test was used for comparison between groups because pain data were not normally distributed and no meaningful transformation could be performed (many values = 0 and skew was very positive). Subsequent Bonferroni adjustment for repeated measurements was applied. In addition, summarized (cumulated) pain was calculated for each of the 3 pain assessments by adding up pain scores from the different time points (2–8 hrs). Data analyses were conducted using SPSS for windows, version 12.0 (SPSS, Inc, Chicago, Ill). P < 0.05 was considered statistically significant.

RESULTS

One hundred twenty patients were included, and all received their allocated intervention (Fig. 1). Baseline demographic and perioperative characteristics of study patients are shown in Table 1. Groups were comparable. Pain hindering walking (5 m) was not different to a significant degree between the 2 groups (count [%], ropivacaine vs placebo: 7 patients [0.12] vs 2 patients [0.03], P = 0.08) (Fig. 1). For secondary end points (pain at rest and pain on passive hip flexion), data were only missing once (1 patient in the ropivacaine group was asleep 8 hrs postoperatively).

For the first 8 hrs after surgery, pain was low for all pain assessments (pain during walking, pain at rest, and pain on passive hip flexion) at all time points investigated, and no significant difference between the ropivacaine and placebo groups was seen (Fig. 2). No significant difference in summarized pain (added pain scores) for each of the 3 pain assessments (walking P = 0.11, rest P = 0.84, passive hip flexion P = 0.52) was
observed. Furthermore, no significant difference was observed in cumulative consumption of oxycodone for the first 8 hrs postoperatively (median [IQR] [95% confidence interval], ropivacaine vs placebo: 5 mg [0–10 mg] [0–24 mg] vs 10 mg [0–15 mg] [0–29 mg], \( P = 0.45 \)), in number of patients having sufentanil in PACU (count [%], ropivacaine vs placebo: 5 patients [0.08] vs 13 patients [0.22], \( P = 0.07 \) [range, 0–30 mg]), or in length of stay (median [IQR], 3 nights [2–3] in both groups, \( P = 0.86 \)).

One patient in the placebo group developed computed tomographic scan verified cerebral infarction after surgery. A patient in the ropivacaine group had quadriceps muscle palsy, and electromyography suggested that the complication was due to an intraoperative local mechanical injury on the femoral nerve rather than related to the ropivacaine infiltration because the nerve injury was limited to the branches innervating the quadriceps muscle.

A post hoc power analysis yields a power of 93% for the primary end point, pain during walking 8 hrs after surgery (mean [SD], ropivacaine vs placebo: 28 [23] vs 26 [21]).

**DISCUSSION**

This randomized, double-blind, placebo-controlled trial demonstrated that intraoperative high-volume LIA with ropivacaine 0.2% provided no additional reduction in acute pain after

---

**TABLE 1. Baseline Demographic and Perioperative Characteristics of Study Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ropivacaine (n = 60)</th>
<th>Placebo (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>67 (47–82)</td>
<td>67 (35–87)</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>27/33 (45/55)</td>
<td>21/39 (35/65)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27 (19–40)</td>
<td>27 (17–40)</td>
</tr>
<tr>
<td>ASA, I/II/III</td>
<td>18/37/5 (30/62/8)</td>
<td>14/43/3 (23/72/5)</td>
</tr>
<tr>
<td>Smoking, yes/no</td>
<td>9/51 (15/85)</td>
<td>17/43 (28/72)</td>
</tr>
<tr>
<td>Perioperative data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital, HvH/HH</td>
<td>25/35 (42/58)</td>
<td>24/36 (40/60)</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>49 (25–84)</td>
<td>51 (25–110)</td>
</tr>
<tr>
<td>Prosthesis, BR/BM/ST</td>
<td>17/8/35 (28/13/58)</td>
<td>19/5/36 (32/8/60)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (range) or count (%) where appropriate.

ASA indicates American Society of Anesthesiologists physical status; BR, Bimetric with Ringloc-cup; BM, Bimetric with Magnum-cup; HH, Hørsholm Hospital; HvH, Hvidovre University Hospital; ST, CLS Spotorno with Trilogy-cup.
THA when combined with a multimodal oral analgesic regimen. Furthermore, no significant reduction in consumption of rescue oxycodone was achieved.

Our findings are in contrast to previous results from randomized trials in the orthopedic literature, all reporting superior analgesia in the LIA group. Reduced pain (20–96 hrs postoperatively) and opioid requirement (96 hrs postoperatively) were reported when intraoperative and postoperative LIA was compared with continuous epidural analgesia. When intraoperative and postoperative LIA was compared with saline infiltration, a reduction in pain (up to 2 weeks postoperatively) and opioid requirement (96 hrs postoperatively) was reported. Finally, reduced pain (in PACU) and opioid requirement (24 hrs postoperatively) were reported when intraoperative LIA was compared with no infiltration. However, some methodological problems hinder the exact interpretation of these trials. First, NSAID was not administered in the control group in any of the 3 trials, making the interpretation of the local anesthetic component and the LIA technique in particular difficult; second, 1 trial was not blinded, and pain not sufficiently assessed/reported; third, 1 trial was not placebo-controlled, and the surgeon was not blinded; and fourth, in 2 trials, administration of morphine in LIA versus control groups was unmatched.

Because an intraoperative catheter was not applied, we did not evaluate the effect of repeated postoperative LIA injections. The role of catheter administration and its placement and type is unknown, and we consider in keeping with results from a recently published trial that a significant analgesic effect of postoperative injections is unlikely, when it is not observed with the systematic intraoperative infiltration.
In contrast to previous trials, we omitted ketorolac from the LIA-mixture because celecoxib was included in the comprehensive multimodal oral analgesic regimen. The analgesic benefit of LIA previously reported in THA might be due to an analgesic effect of NSAID in combination with a less comprehensive multimodal oral analgesia. This assumption is based on the results from the present study in combination with previous results indicating that NSAID provides analgesia whether administered locally or systemically and probably without important difference.9

Our study might be limited by pain scores a little less than 30 mm in both groups, which challenge the demonstration of an intervention effect.15,16 However, because LIA is already widely used in THA, our aim was to clarify if LIA in addition to a simple multimodal oral analgesic regimen would reduce acute postoperative pain additionally. Furthermore, the large sample size made the trial sufficiently powered ensuring final evaluation. At the same time, our study does not exclude that intraoperative LIA may have a minor, short-lasting analgesic effect with a less comprehensive oral analgesic regimen or in selected patients (high pain responders).

It may also be argued that the absent effect of LIA may be explained by a continuous effect of the spinal anesthesia. However, a small dose of bupivacaine was used, which should not have prolonged analgesic effects.17

The results from the present study illustrate that a simple multimodal oral analgesic regimen with acetaminophen, celecoxib, and gabapentin provides sufficient analgesia with acceptable low opioid requirements in opioid naive patients after THA, and it emphasizes the need for procedure-specific trials because LIA might be effective in other procedures.3 In our opinion, the applied multimodal oral analgesic regimen seems effective, simple, and easy and may be preferable compared with more invasive techniques. However, further data are required on the specific role of gabapentin regarding efficacy and adverse effects, especially the concerns about sedation in older patients (we did not measure sedation level). Although acceptable immediate postoperative pain relief after THA was achieved in opioid-naive patients with a simple multimodal oral nonopioid analgesic regimen in this study, higher pain scores have been reported by other investigators.1,20 This difference may relate to study design (basic analgesic regimen and duration of follow-up) or surgical technique. Therefore, further studies in subacute and late postoperative recovery and rehabilitation are needed.18 In this context, it remains noteworthy that not only pain but also multiple factors may limit ambulation ability and other functional recovery parameters.3 In future pain trials, the effects of long-duration administration of simple oral analgesics on long-term outcome need to be studied. Moreover, continuous low-dose peripheral nerve blockade and systemic administration of high-dose glucocorticoids may play important roles because they may be provided on an ambulatory basis, thereby possibly prolonging their benefits. However, potential risks of motor adverse effects resulting in delayed mobilization or falls and risk of deep infection, respectively, need to be clarified. Finally, these modalities need to be evaluated against the efficacy, safety, and costs of other evidence-based components of multimodal analgesia.

In conclusion, intraoperative high-volume LIA with ropivacaine 0.2% provided no additional reduction in acute pain after THA when combined with a multimodal oral analgesic regimen consisting of acetaminophen, celecoxib, and gabapentin. Acceptable acute postoperative pain relief was achieved with the oral analgesic regimen, and LIA is not recommended in THA.

ACKNOWLEDGMENTS

The authors thank Research Nurse Susan Randall, Harsholm Hospital, Denmark, for helpful assistance with data collection and Dr. Henning Erik Holm, Harsholm Hospital, Denmark, for implementation of the standardized anesthetic procedure. Furthermore, we acknowledge assistance from Dr. Kerr and Dr. Kohan, St. Luke’s Hospital, Australia, in teaching us the technique of high-volume infiltration analgesia, and Steen Ladellund, Clinical Research Centre, Hvidovre University Hospital, Denmark, for helpful advice regarding the statistical method.

REFERENCES


© 2011 American Society of Regional Anesthesia and Pain Medicine

Copyright © 2011 American Society of Regional Anesthesia and Pain Medicine. Unauthorized reproduction of this article is prohibited.


