Single-shot intraoperative local anaesthetic infiltration does not reduce morphine consumption after total hip arthroplasty: a double-blinded placebo-controlled randomized study

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Editor’s key points

- Combining several agents for local infiltration has previously been shown to provide effective analgesia for total hip arthroplasty.
- This study investigates the contribution of infiltration of local anaesthetic alone to postoperative analgesia.
- Local infiltration of ropivacaine had no effect on morphine consumption 24 h post-surgery.
- Further work is needed to establish the optimal combination of agents to use for local infiltration analgesia.

Background. The infiltration of local anaesthetic (LA), ketorolac, and epinephrine has been suggested to be effective for analgesia after total hip arthroplasty (THA). The part of action of each component of the mixture remains unclear. We investigated the contribution of infiltration of ropivacaine alone on the morphine consumption during the first 24 h after surgery.

Methods. Sixty patients undergoing primary THA were included in this prospective randomized double-blinded placebo-controlled trial, after IRB approval and informed consent. Surgical and general anaesthetic management were standardized. At the end of surgery, 80 ml of ropivacaine 0.2% (160 mg) or saline was infiltrated. The primary endpoint was morphine consumption 24 h after surgery. The secondary endpoints were: visual analogue scale scores and opioid side-effects at H2, H4, H8, H12, H24, D1, D2, D3, D4, D5, rehabilitation programme progress, chronic pain level, analgesic consumption, and surgical result at 3 months and 1 yr after surgery. The observation period was 1 yr.

Results. Groups were similar for patient characteristic and perioperative characteristics. The ropivacaine wound infiltration did not reduce morphine consumption at 24 h [median (25th and 75th inter-quartile) 27 (17–37) mg in the ropivacaine group vs 24 (18–34) mg in the placebo group, P=0.51] or its side-effects. No effect was found on rehabilitation progress or chronic pain after 3 months or 1 yr, but these were not the main endpoints of the study.

Conclusions. Ropivacaine infiltration alone did not reduce morphine consumption at 24 h after operation nor did it improve postoperative rehabilitation.

Keywords: anaesthesia, infiltration; anaesthetics, local; morphine; orthopaedics; pain, postoperative

Accepted for publication: 21 August 2013

Total hip arthroplasty (THA) is a current surgical procedure for reducing hip pain and improving articuler mobility, and quality of life in patients suffering from hip arthritis. Half of these procedures are performed on patients over 70 yr old, with frequent cardiovascular co-morbidities. Health authorities underline that the costs are mainly due to prolonged length of hospital stay needed to ensure sufficient analgesia and rehabilitation in order to enable the patient to perform activities of daily living independently.1

According to a systematic review published by Sharma and colleagues2 in 2009, the association of a minimally invasive surgical technique and an aggressive pain control seems to improve recovery by improving patient compliance in accelerated rehabilitation. A minimally invasive surgery alone is not sufficient for the purpose.

Despite the great number of THA performed, there was no consensus as to the pain management at the time this study was designed.3 In THA, several studies have shown potential interest in infiltration techniques: analgesia gain, 2 day shorter length of hospital stay, and less residual pain 2 weeks after surgery.4 5 In these studies, a catheter was left in the joint for a second injection several hours later.4 5 This technique is presented as sure, cheap, and needing no particular technique knowledge.6 In those studies, ketorolac is associated with local anaesthetics (LA). Therefore, we cannot distinguish the effects of each of the used drugs.

† Dr Emmanuel Nouvellon passed away during this study.
In order to do so, we evaluated the effect of a single-shot infiltration of ropivacaine alone in the pain management of THA, during the 5 days of hospital stay and a 3 month and 1 yr follow-up.

Methods
This study was approved by the Institutional Review Board (2008.12.08 bis) and by the French Agency for Sanitary Security of Medical Drugs in March 2009. It was registered in EudraCT (2008-007090-20).

Sixty patients undergoing primary homolateral THA operated on in the Orthopaedics ward of our university hospital were included after informed consent from June 2009 to May 2010.

We included patients aged from 18 to 80 yr undergoing THA by postero-lateral incision under general anaesthesia, with a general health state permitting independent ambulation after surgery, capable of understanding the usage of patient-controlled analgesia (PCA).

The exclusion criteria were chronic renal disease (clearance < 50 ml min⁻¹ calculated by the Cockroft and Gault formula), severe liver dysfunction (clinical coagulation disorder or INR > 1.31), known allergy, intolerance to or counter-indication for drugs used in the protocol, long-term morphine treatment, pregnancy or breastfeeding, and reoperation.

Randomization was carried out using a computerized randomization process. The treatment was assigned with two different-sized blocks (three blocks of eight patients and six blocks of six patients). The patients were randomized in two groups: ropivacaine 2 mg ml⁻¹ and placebo (saline). The solution was prepared in a dish using non-blinded ropivacaine (4 blisters of 20 ml of ropivacaine 2 mg ml⁻¹) or saline. The randomizing anaesthesiologist served the dish to the assisting nurse without informing the surgical team of the drug used. Neither the anaesthesiologist nor the surgeon in charge of the patient knew which was the drug used, but there was still a possibility of immediate disclosure in the case of suspicion of intravascular injection of LA.

All the patients underwent standardized general anaesthesia using propofol (1–5 mg kg⁻¹), etomidate (0.3–0.5 mg kg⁻¹), or sufentanil (0.2–0.5 μg kg⁻¹) associated or not with cisatracrium (0.15 mg kg⁻¹) for induction and maintained by 0.5–1.5 MAC of sevoflurane or desflurane and boli of 0.1–0.3 μg kg⁻¹ of sufentanil. Administration of anaesthetic drugs was left to the discretion of the attending physician and based on usual monitoring.

The surgeon realized the infiltration of 80 ml of the chosen drug after putting in the implants. The infiltration technique used was the one described by Andersen and colleagues.⁴⁻⁵

- 40 ml in the deep tissues: capsula, gluteus maximus and medius muscles, and rotating muscles.
- 40 ml in the superficial tissues: fascia, subcutaneous tissues, and skin.

Drainage was used systematically for 24–48 h. The closing of the wound bandage defined H0.

Postoperative period
On the day of surgery and the first postoperative day, i.v. analgesia consisted of:

- paracetamol 1 g every 6 h,
- nefopam 60–120 mg per 24 h,
- initial i.v. morphine titration if the patients’ pain score was higher than 30 on a 100 mm visual analogue scale (VAS) (initial bolus of 4 mg if VAS > 30 followed by boli of 2 mg every 5 min if persistence of VAS > 30),
- in the case of persistence of a high VAS evaluation despite a well-conducted morphine titration, the anaesthesiologist was free to use one dose of non-steroidal anti-inflammatory drug (NSAID) (ketoprofene 100 mg),
- a PCA device was initiated (1 mg ml⁻¹, bolus of 1 ml every 6 min, no maximal dose per 4 h) when leaving the post-anesthesia care unit (PACU).

The postoperative nausea and vomiting were treated by a bolus of ondansetron 4 mg, a bolus of droperidol 1.25 mg, or both according to the Apfel score and French anaesthesia and intensive care society recommendations.⁷

From the second postoperative day onwards, analgesia was assured by oral intake of paracetamol 1 g every 6 h and morphine chlorhydrate 10–20 mg every 4 h.

Postoperative care, reintroduction of personal treatments when needed, and thromboprophylaxis were left at the discretion of the caring anaesthesiologist. All the patients followed the same rehabilitation programme.

Studied parameters
Primary endpoint
The primary endpoint was the total morphine consumption at 24 h after surgery (the sum of the morphine titration in PACU and the cumulated morphine consumption delivered by the PCA device at 24 h after surgery).

Secondary endpoints
Postoperative pain Patients’ pain scores were evaluated at rest at the 2nd, 4th, 8th, 12th, and 24th hour after surgery by the VAS by drawing a line on a 10 cm long graph representing the VAS scale, when presented to them by the attending nurse or the main investigators. After the first postoperative day, it was evaluated twice daily (at rest and at mobilization during the rehabilitation sessions) during the 5 days.

Morphine side-effects During the pain measurements, morphine side-effects were also noted: nausea, vomiting, pruritus, and acute urine retention.

Hyperalgesia zone measurement The length of the surgical wound and the surface of the pericicatricial hyperalgesia zone were measured with a Von Frey filament (396 mN) as described by Lavand’homme and colleagues.⁸

Rehabilitation process Patients’ day-to-day rehabilitation progress was noted.
Follow-up
All the patients were interviewed 3 months and 1 yr after surgery for chronic pain and chronic pain medication. The functional results of the arthroplasty were evaluated by walking distance, length of the upright position without pain, walking stick usage, and ability to climb stairs. We determined joint mobility and its stability by the ability to stand on the operated leg, and the existence of lameness. The functional results were measured by the change in the Postel Merle d’Aubigné score.9

The investigators and the ward nurses unaware of the allocated treatment collected the data. No specific training was given for data collection. A clinical research assistant verified all the charts to complete the missing data every 10 inclusions and at the end of the inclusion period before entering the data into the database system. After, 100% of items were data managed.

Statistical analysis
We aimed to show a 30% reduction in morphine consumption in the first 24 h. Considering that in the control group, the morphine consumption would be around 30 (10) mg, with a power of 90% and an α bilateral risk at 5%, 27 patients were needed in each group. To anticipate incomplete data, this sample size was increased to a total of 60 patients to be included.

Statistical results were expressed with mean (sd) for normally distributed quantitative variables, and median (25–75 IQ) for other quantitative variables. The number and associated percentage were given for qualitative variables.

The comparability between groups on main features and prognostic variables at inclusion was evaluated.

The main judgement criterion and quantitative secondary criteria were compared by a Wilcoxon–Mann–Whitney test.

The qualitative criterion ‘respect of the rehabilitation programme after surgery’ was compared between the two groups by a χ2 test or a Fisher exact test.

A general linear model was used to compare the quantitative criteria with repeated measures.

All statistical tests were conducted at 0.05 two-sided level.

Results
The inclusions followed the flow chart presented in Figure 1. The ropivacaine group included 30 patients and the placebo group 31 patients. In the placebo group, one patient was wrongly included. When the error was recognized (chronic renal failure that was discovered after randomization), the patient received no treatment and the data were not collected. A double-assignation error occurred with one patient assigned to the two groups (computer electric shut down during randomization) and this patient was excluded from analysis. When this occurred, a new randomization block was added in order to be able to include enough patients. This caused the different number of patients in each group. The surgeon forgot to infiltrate one patient in the ropivacaine group at the end of surgery. This patient’s data were collected and analysed with the intention of treating in the ropivacaine group. Therefore, 29 patients were analysed per group.

The patient characteristic and surgical characteristics of the two groups are shown in Table 1. The repartition of the ASA status of the patients was identical in the two groups (ASA I 9 patients, ASA II 19 patients, and ASA III two patients in each group). The length of stay in PACU was a median of 130 (90–170) min in the placebo group and 135 (100–170) min in the ropivacaine group, P=0.77. There were no clinically relevant differences between the groups.

Main endpoint
As shown in Table 2, single-shot infiltration of ropivacaine alone did not lessen the morphine consumption of the first 24 h: 27 (17–31) mg in the ropivacaine group vs 24 (18–34) mg in the placebo group (P=0.51). The per-protocol analysis showed P=0.76, median morphine consumption 27 (17–37) mg in the ropivacaine group vs 24 (18–34) mg in the placebo group.

Secondary endpoints
Postoperative pain evaluation
During the first 24 h, the median VAS scores at rest were comparable (Fig. 2). The pain scores at rest (Fig. 2) and during mobilization (Fig. 3) go down after postoperative day 2. There were no statistically significant differences between the groups.

The morphine dose for the second postoperative day onwards was retrieved retrospectively. The measured daily morphine consumption is shown in Table 2.

The measured median cumulated morphine consumption up to postoperative day 5 was 47 (32–80) mg in the ropivacaine group vs 35.5 (25.5–57) mg of morphine in the placebo group, P=0.21.

The hyperalgesia surfaces were not different between the groups [median: ropivacaine 0 (0–4) cm² vs placebo 0 (0–9) cm², P=0.28] (data not shown in tables or figures).

Observed side-effects
No immediate toxic effects of LA or immediate or delayed sign of local surgical site infection were observed (data not shown in tables or figures).

The incidence of morphine side-effects (nausea, vomiting, sedation, and hallucinations) was not different between the groups at all measurement times. All the patients received droperidol 5 mg in 100 ml of PCA mixture. Only one patient had severe nausea and vomiting and needed up to 50 mg of ondansetron during the 5 days in hospital. No patients presented respiratory depression.

Postoperative rehabilitation
The rehabilitation progress is shown in Table 3.

Follow-up results
We found very few patients with chronic pain. There was no statistical difference between the groups for pain scores at 3 months [median VAS 0.4 (0.0–2.7) vs 0 (0.0–0.1), P=0.06, in the ropivacaine vs placebo group, respectively] or at 1 yr
[median VAS 0 (0–3) vs 0 (0–0), P=0.17, in the ropivacaine vs placebo group, respectively].

There was no difference in the surgical result, evaluated by the Postel Merle d’Aubigné score at 3 months [median 17 (15–18) vs 18 (17–18), P=0.09 in the ropivacaine vs placebo group, respectively] (data not shown in tables or figures).

Discussion

In our study, infiltration of LA alone did not lessen the morphine consumption or morphine side-effects after THA surgery. At H24, the median consumption of morphine was 27 (17–37) mg in the ropivacaine group vs 24 (18–34) mg in the placebo group, P=0.51.
Comparison with other local infiltration analgesia studies for THA

Several studies using different types of drugs showed a beneficial analgesic effect of infiltration in THA and total knee arthroplasty (TKA). All of these studies used a mixture of drugs, making it difficult to clearly explain the mechanism or efficacy of local infiltration analgesia (LIA). Parvataneni and colleagues\textsuperscript{10} used a solution containing an LA (bupivacaine 200–400 mg), morphine (4–10 mg), corticosteroids (methylprednisolone 40 mg), epinephrine (300 µg), and an antibiotic (cefuroxime 750 mg). Andersen and colleagues\textsuperscript{4} used a solution containing 300 mg, and Andersen and colleagues\textsuperscript{5} 200 mg of ropivacaine. Both used an NSAID (ketorolac 30 mg) and epinephrine (0.5 mg). Andersen and colleagues\textsuperscript{4} showed a 2 day reduction in length of stay, a 32% reduction in morphine consumption 20 h after operation, and a 20% reduction at 96 h after operation. Andersen and colleagues\textsuperscript{5} showed a 62% reduction in morphine consumption during the first postoperative day.

In our study, we used 160 mg of ropivacaine, whereas in previous studies, the authors used 300 and 200 mg of the same LA in the initial injection respectively.\textsuperscript{6,5} We chose this dosage because it is close to the dosage authorized for infiltrations in France. Our trial is the second one to find no effect for LA infiltration alone. Indeed, Lunn and colleagues\textsuperscript{11} showed that ropivacaine single-shot infiltration had no effect on pain and morphine consumption during the first 8 h after operation. To prolong LA efficacy, several authors added a second injection at H8–H24. Therefore, a dose effect cannot be excluded in these studies. In an editorial accompanying this article, Rawal\textsuperscript{12} underlined the possibility that the difference is made later than the first 8 h. In our study, the pain scores and morphine consumption were followed up to 24 h after operation and no difference was shown. As was underlined by Rawal, the patients in Lunn and colleagues’ study had only morphine medication after operation.\textsuperscript{11,12} In our study, a multimodal regimen of paracetamol, nefopam, and morphine was used after operation for all patients. Moreover, the pain score follow-

### Table 1: Patient characteristic and perioperative characteristics. Data are mean (SD), medians (25th–75th), or number (%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ropivacaine group (n = 29)</th>
<th>Placebo group (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range, yr)</td>
<td>38–70</td>
<td>42–80</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28 (26–30)</td>
<td>27 (25–28)</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>15/14</td>
<td>19/10</td>
</tr>
<tr>
<td>ASA score I/II/III</td>
<td>9/18/2</td>
<td>9/18/2</td>
</tr>
<tr>
<td>Side of surgery L/R</td>
<td>19/10</td>
<td>12/17</td>
</tr>
<tr>
<td>Preoperative Postel Merle d’Aubigné score</td>
<td>13 (12–15)</td>
<td>14 (13–15)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>98 (72–120)</td>
<td>90 (70–110)</td>
</tr>
<tr>
<td>Surgical incision size (cm)</td>
<td>12 (9–15)</td>
<td>13 (11–15)</td>
</tr>
<tr>
<td>Perioperative sufentanil consumption (µg kg(^{-1}))</td>
<td>0.6 (0.2)</td>
<td>0.6 (0.2)</td>
</tr>
<tr>
<td>PACU NSAID use (n)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Haemoglobin day 0 (g litre(^{-1}))</td>
<td>139 (18)</td>
<td>139 (11)</td>
</tr>
<tr>
<td>Haemoglobin day 1 (g litre(^{-1}))</td>
<td>115 (15)</td>
<td>115 (17)</td>
</tr>
<tr>
<td>Haemoglobin day 3 (g litre(^{-1}))</td>
<td>113 (17)</td>
<td>110 (13)</td>
</tr>
<tr>
<td>Nausea, number of patients days 0–5</td>
<td>9 (31)</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Vomiting, number of patients days 0–5</td>
<td>6 (21)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Ondansetron (mg)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

### Table 2: Morphine consumption. Data are medians (25th–75th)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ropivacaine group (n = 29)</th>
<th>Placebo group (n = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACU morphine consumption (mg)</td>
<td>6 (2–10)</td>
<td>8 (0–10)</td>
<td>0.96</td>
</tr>
<tr>
<td>24 h PCA morphine consumption (mg)</td>
<td>19 (14–28)</td>
<td>18 (13–28)</td>
<td>0.43</td>
</tr>
<tr>
<td>Total 24 h morphine consumption (mg)</td>
<td>27 (17–37)</td>
<td>24 (18–34)</td>
<td>0.51</td>
</tr>
<tr>
<td>Day 2 morphine consumption (mg)</td>
<td>12 (3–20)</td>
<td>6 (3–11.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Day 3 morphine consumption (mg)</td>
<td>10 (0–15)</td>
<td>0 (0–10)</td>
<td>0.04</td>
</tr>
<tr>
<td>Day 4 morphine consumption (mg)</td>
<td>0 (0–10)</td>
<td>0 (0–0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Day 5 morphine consumption (mg)</td>
<td>0 (0–5)</td>
<td>0 (0–10)</td>
<td>0.66</td>
</tr>
<tr>
<td>Cumulated overall morphine consumption (mg)</td>
<td>47 (32–80)</td>
<td>35.5 (25.5–57)</td>
<td>0.21</td>
</tr>
</tbody>
</table>
up at rest and mobilization continued during the first 5 days and a chronic pain evaluation was done at 3 months and 1 yr after operation. We found no difference at any measure time.

The originality of our study is that ropivacaine without NSAIDs or epinephrine was used. The effects of NSAIDs according to the administration route are debated in the literature. Most studies performed LIA with a mixture containing NSAIDs. In our study, NSAIDs were used for i.v. rescue. According to Romsing and colleagues' meta-analysis, NSAIDs have the same efficacy when used by infiltration and by systemic administration. When compared with placebo, NSAIDs reduce morphine consumption and lower VAS scores. Marret and colleagues' meta-analysis showed that the addition of NSAIDs reduced nausea and vomiting by 30% and sedation by 29%. However, recent literature seems to prove a higher efficiency of locally administered NSAIDs in several surgical procedures, such as Caesarean delivery and TKA. Indeed, Spreng and colleagues compared LIA containing ketorolac and morphine with LIA with LA alone associated with systemic ketorolac and morphine. The pain relief was more efficient in the local administration group. Therefore, the lack of efficiency of LA alone further confirms their findings.

Simplicity of the technique and side-effects

Several authors have presented LA infiltration as a simple and safe technique. Two explanations of the technique during the surgical staff meeting were needed to form all the surgeons to the technique as described roughly by Anderson. Indeed, although Kerr and Kohan described their technique in a congress communication, the publication of the precise description took 3 yr. Therefore, the two Danish studies and ours had begun (or had been concluded) before the publication. In order not to introduce a bias to our study, we did not intervene again after this publication to modify the taught technique. As underlined by Rawal, the Kerr and Kohan LIA technique was part of a multifactor programme including icing and compression of the wound and early and aggressive rehabilitation. Therefore, their findings are not applicable to a population that is not using all the components of their package. The rehabilitation programme was not modified on our ward for this study. Unlike the Kerr and Kohan case report, our trial evaluated the impact of LA infiltration alone in a public teaching hospital setting.

Limits

Our study has some limits. First, it is a monocentric study, but several surgeons having performed the surgeries, the bias of the unique operator has been waved aside.

Secondly, even though our physical trainers were informed of this study, no specific means had been put into the rehabilitation of our patients. Also, our study was not designed to modify the rehabilitation protocol and the length of stay of our patients. Therefore, these parameters were not evaluated.

We chose to evaluate pain by the VAS at rest and mobilization. Evaluation of the pain component of the WOMAC score could have permitted a more global approach taking into account the different levels of pain.
account various painful times: in the sitting position, in the upright position, at night lying in bed, while walking, and while climbing stairs. The primary endpoint of our study was at 24 h after operation, when patients are still in bed. The WOMAC score is more adapted to everyday life settings and VAS to acute post-surgical pain. VAS is the simplest and most known method for acute pain evaluation.

In conclusion, single-shot periarticular infiltration of LA did not permit to reduce morphine consumption during the first 24 postoperative hours or its side-effects. It did not have any clinically pertinent effect on rehabilitation.

Authors’ contributions
L.Z.: main investigator, patient follow-up, and writing the article. P.C.: inclusion and follow-up of patients and writing the article. S.A.: statistical analysis and data management. C.D.: study design, supervision of statistical analysis, and writing the article. N.V.: inclusion and follow-up of patients. G.A.: head of the department of surgery where all the patients were taken care of. J.R.: head of the department of anaesthesiology where all the patients were taken care of. E.N.: main investigator, patient inclusion and follow up, and data management.

Acknowledgement
Dr Emmanuel Nouvellon passed away during this study. In loving memory.

Declaration of interest
None declared.

Funding
This study was funded by institutional research funding only.

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Handling editor: L. Colvin