REGIONAL ANAESTHESIA

Determination of the EC$_{50}$ of levobupivacaine for femoral and sciatic perineural infusion after total knee arthroplasty

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Background. Infusion of local anaesthetic through femoral and sciatic catheters is an accepted method of providing pain relief after knee arthroplasty. However, the minimum effective concentration of perineural local anaesthetics is not known.

Methods. Twenty-four patients received femoral and sciatic perineural infusions of levobupivacaine in order to prevent pain relief after total knee arthroplasty. The primary endpoint of the study was patient request for analgesic rescue for anterior or posterior knee pain within the first 36 h of perineural infusion. Treatment was determined by the method of sequential allocation, with a dosing interval of 0.002% w/v.

Results. Thirteen patients did not require rescue analgesia for anterior knee pain and 16 patients did not require rescue analgesia for posterior knee pain. Median duration of failed blocks until rescue analgesia was 25 h (24–27 h) for the femoral block and 27 h (24–29 h) for the sciatic block. The minimum concentration at which patients did not require rescue analgesia was 0.024% for the femoral nerve and 0.014% for the sciatic nerve. Comparison of EC$_{50}$ showed that local anaesthetic requirements were significantly ($P=0.03$) higher by a factor of 1.25 (95% CI 1.03–1.55) for the femoral compared with the sciatic nerve.

Conclusions. The EC$_{50}$ for femoral perineural infusion is greater than the EC$_{50}$ for sciatic perineural infusion.

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Ideally, postoperative analgesic techniques should provide sufficient pain relief to allow early function, physiotherapy, and movement after total knee replacement.$^{1,2}$ Unfortunately, many regional anaesthesia procedures still fail to provide these early postoperative benefits. Intrathecal morphine affords reasonable pain relief, albeit with supplemental patient-controlled analgesia; epidural infusions provide long-lasting analgesia, but at the expense of motor block; and single-injection femoral and sciatic nerve blocks provide good pain relief, but are of limited duration.$^{3,4}$ Extension of postoperative analgesia and improvement in function is possible by infusion of local anaesthetics through femoral and sciatic perineural catheters,$^{5}$ but invariably results in motor block when commercial concentrations of ropivacaine and levobupivacaine are used. The latter concentrations were principally derived from human volunteer$^{6}$ and regulatory studies of epidural analgesia before the development of perineural catheter techniques and their adoption into routine practice.

A need clearly exists to investigate the dose–response relationships of local anaesthetics$^{7}$ when infused via femoral and sciatic catheters in order to rationalize the practice of regional anaesthesia. This is particularly
important considering that peripheral nerve block has been shown in a recent meta-analysis\(^8\) to have a better side-effect profile compared with epidural analgesia after total knee arthroplasty. Thus, the primary aim of our study was to compare the EC\(_{50}\)s of levobupivacaine when infused through femoral and sciatic perineural catheters at a rate of 10 ml h\(^{-1}\) to prevent pain for 36 h after total knee replacement. Our secondary aims were to measure motor block using the Bromage and straight leg raising (SLR) scores and measure outcome using the Knee Society score before operation and 12 months after operation.

**Methods**

**Recruitment**

The study was approved by the Tayside Medical Ethics Committee, MREC 05/S1401/77, and registered on the EudraCT database, no. 2006-005667-26. Patient information leaflets were distributed to patients in the anaesthetic preadmission clinic 1–2 weeks before elective total knee replacement surgery. After admission to the ward, on the day before surgery, patients were approached for written informed consent to participate in the study. Patients were not approached if they were ASA IV, if they had received any investigational drug within the 90 days before the study, had any evidence of alcohol or drug abuse, had symptomatic cardiac failure, recent seizures, dementia, or encephalopathy, or had a terminal illness with a life expectancy <3 months. In addition, abnormal laboratory results or ECG findings on admission that were clinically significant in the investigator’s opinion excluded entry into the study.

**Anaesthesia**

All patients received temazepam 20 mg for premedication, before transfer to the anaesthetic room. In the anaesthetic room, patients received oxygen 5 litre min\(^{-1}\) via a facemask, i.v. cefuroxime 1.5 mg, and a target-controlled infusion (TCI) of propofol at a blood level of 0.5 mg ml\(^{-1}\) for sedation. Regional anaesthesia was standardized and performed by two experienced consultant anaesthetists (G.A.M. and M.O.C.). All nerve blocks were performed using full aseptic technique and nerves localized using a peripheral nerve stimulator (B. Braun, Sheffield, UK), set at a pulse duration 0.1 ms, pulse frequency 2 Hz, and an initial electrical current of 2 mA. Acceptable electrical currents for local anaesthetic injection were between 0.3 and 0.5 mA. Femoral, obturator, and sciatic nerve blocks were performed as follows:

(i) **Femoral nerve block.** A 50 cm 19 g Touhy needle was inserted 1 cm lateral and 1 cm inferior to the femoral artery in the groin. Once quadriiceps contractions, including tapping of the patella, had been elicited 10 ml of levobupivacaine 0.375% w/v was injected slowly in 5 ml increments, then a perineural catheter (Stimuplex, Pajunk, Germany) passed cephalad through the needle and positioned 5 cm within the femoral sheath. Once the femoral catheter was secured, a further 5 ml of levobupivacaine 0.375% w/v was injected through the catheter.

(ii) **Obturator nerve block.** A 100 mm single regional anaesthesia needle (B. Braun) was inserted in the groin, lateral to adductor magnus, and advanced until adduction was obtained between 0.3 and 0.5 mA. At this point, 7.5 ml of levobupivacaine 0.375% w/v was injected.

(iii) **Sciatic nerve block.** With the patient in the lateral position and hips fully flexed, a 100 cm 19 g Tuohy needle was inserted at a point midway between the greater trochanter and the ischial tuberosity (subgluteal block). After eliciting tibialis posterior muscle contractions and plantar flexion of the ankle, 10 ml of levobupivacaine 0.375% w/v was injected slowly in 5 ml increments and then a perineural catheter (Stimuplex, Pajunk, Germany) passed caudal through the needle and positioned 5 cm within the sciatic sheath. Once the sciatic catheter was secured, the remaining 5 ml of levobupivacaine 0.375% w/v was injected through the catheter.

(iv) **Spinal anaesthesia.** With the patient in the lateral position and the operative side uppermost, 3.2 ml of 0.5% w/v plain bupivacaine and preservative-free morphine 0.1 mg were injected into the intrathecal space.

Additionally, ondansetrone 4 mg, cyclizine 50 mg, and dexamethasone 4 mg were injected i.v. 20 min before the end of the operation to prevent nausea and vomiting.

At the end of the procedure, two infusion bags of levobupivacaine in saline 0.9% were prepared by one of the investigators. The concentration of levobupivacaine given to the first patient was 0.03% w/v in the femoral and sciatic catheters, which were labelled ‘femoral study drug’ and ‘sciatic study drug’, respectively. The femoral and sciatic catheters were attached and infused at 10 ml h\(^{-1}\) via two Hospira Gemstar infusion pumps (Lake Forest, IL, USA). All other medical investigators, patients, and ward staff were blinded to the study drug.

Postoperative analgesia was supplemented with acetaminophen 1 g, 6 hourly, and oxycodone 20 mg, 12 hourly, as our experience of treating patients after total knee replacement is that patients tend to experience pain from other joints, particularly when kept in bed.

**Study assessments**

For the purposes of the study, the time of spinal injection was regarded as time zero. All study assessments including pain, motor block, nausea and vomiting, sedation, arterial pressure, heart rate, and ventilatory frequency were made...
at 4 h intervals thereafter for 36 h. Pain was scored as anterior knee pain or posterior knee pain using a verbal rating scale measured every 4 h by ward nurses blinded to the study concentrations. These measurements are routine for ward nurses caring for patients after arthroplasty in our unit.

The primary endpoint of the study was pain relief defined according to the following criteria.

(i) Successful pain relief defined as: no demand for perineural rescue within the 36 h study period.
(ii) Unsuccessful pain relief defined as: demand for perineural rescue within the 36 h study period, and pain treated successfully with perineural injection of 15 ml of levobupivacaine 0.125% w/v.
(iii) Technical failure defined as: demand for perineural rescue within the 36 h study period, but pain remaining despite injection of 15 ml of levobupivacaine 0.125% w/v.

The EC50 was calculated using the method of up–down sequential allocation,9 whereby the concentration of local anaesthetic given to a patient was determined by the response of the previous patient. For example, if the previous patient had no demand for rescue in the 36 h period, this was regarded as a clinical ‘success’ and the next patient would receive a concentration 0.002% w/v less. If the previous patient received rescue levobupivacaine, then this was regarded as a clinical ‘failure’ and the next patient would receive a concentration 0.002% w/v greater.

Secondary endpoints were degree of motor block, excessive sedation, low ventilatory frequency or arterial pressure, nausea and vomiting, and 12 month outcomes.

The motor block was assessed by two methods. The first was the MRC scale, whereby 0 represents no active contraction; 1, the visible palpable contraction without active movement; 2, the movement possible with gravity eliminated; 3, the movement possible against gravity; 4, the movement against gravity and resistance but weaker than normal; and 5, the normal power. The second motor block scale was the modified Bromage scale, whereby 0 represents full power; 1, unable to straighten leg; 2, just able to flex knees; and 3, foot movement only.

Outcome scores such as the Knee Society score, functional score, and degree of knee bending were measured before operation and 12 months after operation. The Knee Society score combines a relatively objective knee score that is based on clinical parameters and a functional score based on how the patient perceives the knee functions with specific activities. The maximum knee score is 100 points and the maximum functional score is 100 points.

Justification of sample size

A pilot study of 10 patients was conducted using the same protocol as the main study. Median duration of block until rescue analgesia was 23.5 h (22.8–26 h) for the femoral block and 25 h (24–25 h) for the sciatic block. Pooled femoral and sciatic data showed the EC50 of levobupivacaine to be 0.022% (95% CI 0.019–0.026%) using the formula of Dixon and Massey and 0.023% (95% CI 0.020–0.025%) using up–down analysis. Data from both sequences when pooled showed that the testing interval of 0.002% w/v would provide good precision and was well matched to the standard deviations of between 0.0012% and 0.0020% w/v for each nerve. Using these preliminary data, we calculated that 24 patients would be needed to show a difference in levobupivacaine concentration between femoral and sciatic nerves.

Statistical analysis

Data are presented as mean (sd), median (inter-quartiles), and frequency as appropriate. Minimum local anaesthetic concentration (MLAC) for continuous infusion was estimated from the up–down sequences using the method of Dixon–Massey and probit regression. The Dixon–Massey method used the failures as the less frequent outcome in order to estimate the MLAC for continuous infusion, whereas Probit regression was used as the backup or sensitivity analysis. Analyses included Student’s paired t-test, Wilcoxon’s matched pairs test, McNemar’s χ2 test, and exact logistic regression. Software used included: Excel 2000 (Microsoft Inc., Redmond, VA, USA), Prism 5.0 (GraphPad Inc., San Diego, CA, USA), Minitab 15.0 (Minitab Inc., State College, PA, USA), and LogXact 8.0 (Cytel Inc., Cambridge, MA, USA). Significance was defined at P<0.05 (two-sided).

Results

Twenty-four patients successfully completed the study. One obese patient was excluded because of difficulty inserting a sciatic catheter. Patient characteristics were consistent with patients having total knee arthroplasty in our unit (Table 1). All nerve stimulator endpoints (patellar tap, leg inversion, and plantar flexion) were achieved between 0.3 and 0.5 mA, and all muscle contractions disappeared after injection of 1 ml of levobupivacaine 0.375% w/v. Thirteen patients did not require rescue analgesia for anterior knee pain and 16 patients did not require rescue analgesia for posterior knee pain. Median duration of block until rescue analgesia was 25 h (24–27 h) for the femoral block and 27 h (24–29 h) for the sciatic block (Table 2). The minimum concentration at which

| Table 1 Patient characteristics. Data presented as mean (range), mean (sd) and n (%) |
|------------------|------------------|------------------|
| Age              | 72.9 (57–83)     | Height           | 163.1 (8.3)      |
| Weight           | 77.5 (16.2)      | BMI              | 29.1 (5.6)       |


patients did not require rescue analgesia was 0.024% for the femoral nerve and 0.014% for the sciatic nerve. Comparison of EC50 showed that local anaesthetic requirements were significantly (P=0.03) higher by a factor of 1.25 (95% CI 1.03–1.55) for the femoral compared with the sciatic nerve (Table 3). Significance tests for difference in sequences were: Wilcoxon’s matched pairs test: P=0.03, exact logistic regression: P=0.012, and Clopper–Pearson binomial exact: P=0.023. Six patients were able to straight leg raise and the remaining 18 were able to flex the operative knee between 50° and 90° (Table 4). No patient had a ventilatory frequency <10 bpm or a sedation score ≥2. Five patients had an episode of nausea or vomiting and five patients were hypotensive (systolic arterial pressure between 90 and 100 mm Hg) on at least one occasion. From before operation to 12 months after operation, the mean (sd) Knee Society score improved significantly from 31.9 (14.1) to 85.0 (13.7), P<0.001, and the mean (sd) functional score increased from 47.9 (12.4) to 68.6 (23.5), P<0.001 (Table 5).

Discussion

This study has shown that the concentration of levobupivacaine needed to prevent pain after total knee replacement is 25% higher when infused via a femoral perineural catheter compared with a sciatic perineural catheter. In addition, a range of knee flexion from 50° to 90° was possible in patients, one in four of which was able to fully straight leg raise. Differential split of analgesia and motor block was possible by reducing the concentration of levobupivacaine four- to six-fold compared with commercial preparations of levobupivacaine and ropivacaine.

Our decision to use the up–down sequential approach to measure EC50 was based on knowledge of the likely side-effects using a traditional dose–response design. High concentrations of levobupivacaine in a traditional design invariably ensure good pain relief but are associated with unacceptably dense motor block, whereas a similar proportion of patients, given low concentrations of levobupivacaine would have some movement, but be restricted by severe pain. Thus, we felt that a study protocol designed to measure EC50 was more appropriate in this population. Although criticism of MLAC studies has questioned the ethics of the technique by suggesting that half of patients suffer excessive pain, there is little awareness of the quality of analgesia available to protocol ‘failures’ in these studies. In our trial, the ‘failure’ group of patients was pain-free for a median duration of 25–27 h, a period of time by and large greater than that associated with bolus anaesthesia but with much less motor block. Our opinion is that the use of a high-quality primary endpoint in MLAC studies ensures that patients are treated to a high clinical standard.

In fact, our primary endpoint of 36 h pain-free time was extremely demanding and reflected our clinical ability to now provide extended pain relief well into the second postoperative day. In addition, we feel that local anaesthesia by whatever route should be part of a multimodal analgesic regime designed to prevent pain at various perioperative stages. Therefore, spinal anaesthesia with bupivacaine and intrathecal morphine was supplemented with levobupivacaine around the femoral, obturator, and sciatic nerves at our standard concentration of 0.375%.

Table 2 Number of patients succeeding and failing to experience 36 h of pain relief without need for rescue bolus. Third row represents median (inter-quartile range) duration of pain relief in ‘failures’ as defined by time to first patient request for analgesia

<table>
<thead>
<tr>
<th></th>
<th>Femoral</th>
<th>Sciatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success (n)</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Failures (n)</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Duration of pain relief in failures (h)</td>
<td>25 (24–26)</td>
<td>27 (24–29)</td>
</tr>
</tbody>
</table>

Table 3 MLAC (95% CI) of femoral and sciatic nerves. Ratio: 1.25 (95% CI 1.03–1.55)

<table>
<thead>
<tr>
<th>Nerve block</th>
<th>Dixon and Massey</th>
<th>Probit analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>0.024 (0.023–0.025)</td>
<td>0.024 (0.020–0.027)</td>
</tr>
<tr>
<td>Sciatic</td>
<td>0.019 (0.015–0.024)</td>
<td>0.018 (0.015–0.020)</td>
</tr>
</tbody>
</table>

Table 4 Side-effects. No. of patients with best SLR score, best Bromage score, ventilatory frequency <10 bpm, sedation score ≥2, systolic arterial pressure <100 and <90 mm Hg, and nausea and vomiting

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR 5</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>SLR 4</td>
<td>16 (67%)</td>
</tr>
<tr>
<td>SLR 3</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Bromage 0</td>
<td>20 (83%)</td>
</tr>
<tr>
<td>Bromage 1</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Ventilatory frequency &lt;10 bpm</td>
<td>0</td>
</tr>
<tr>
<td>Systolic arterial pressure &lt;100 mm Hg</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Systolic arterial pressure &lt;90 mm Hg</td>
<td>0</td>
</tr>
<tr>
<td>Sedation score ≥2</td>
<td>0</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>5 (21%)</td>
</tr>
</tbody>
</table>

Table 5 Patient outcomes. Data collected before operation and 12 months after operation. Data represent mean (sd). Analysis using paired t-test for parametric data and the Wilcoxon signed-rank test for difference in medians, P<0.05

<table>
<thead>
<tr>
<th></th>
<th>12 months postoperative</th>
<th>P-value</th>
<th>Difference CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee Society score</td>
<td>31.9 (14.1)</td>
<td>85.0 (13.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Functional score</td>
<td>47.9 (12.4)</td>
<td>68.6 (23.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Flexion</td>
<td>107.3 (100.0–111.3)</td>
<td>107.9 (101.2–118.5)</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Science concentrations compared with the narrow spread of femoral concentrations may reflect the relative contribution of afferent pain pathways to pain transmission to the spinal cord from the knee joint. For example, Allen and colleagues in a randomized, double-blind study of total knee replacement found no benefit in pain scores by adding a sciatic nerve block to an established femoral block, whereas in a study by Pham Dang and colleagues, pain scores at rest were significantly higher for 36 h in patients given a continuous femoral perineural infusion compared with those using combined femoral and sciatic nerve infusions.

Despite the use of ultra-low concentrations of levobupivacaine, mild motor block—manifest as impaired SLR or inability to dorsiflex—still occurred in the majority of patients, and prevented early mobilization. Furthermore, patients felt that movement was restricted by the weight of the blocked distal leg. Inaccurate placement of perineural catheters may account for some variability of response and inconsistent motor block, but was negated somewhat by using only two experienced consultant anaesthetists. All per protocol blocks provided anaesthesia for at least 16 h, and no technical failure occurred during the course of infusion. We did not use ultrasound for catheter placement because at the time of the study the equipment was not available.

Other side-effects which govern the acceptability of any interventional technique in postoperative pain relief are respiratory depression, excessive sedation, and nausea and vomiting. Although we administered intrathecal morphine 0.1 mg for spinal anaesthesia and oxycodone 20 mg, 12 hourly, we recorded no ventilatory frequency <10 bpm and no sedation score ≥2. This result is in agreement with our own internal audit of arthroplasty patients which has not recorded one episode of ventilatory frequency depression since the introduction of perineural catheters for arthroplasty and amputation in 2004. Nausea and vomiting occurred in five patients, often >20 h after operation and probably reflects the dose of oxycodone. We now intend to compare the MLAC of levobupivacaine with ropivacaine both as a bolus and as an infusion in order to determine which local anaesthetic offers the best balance of pain relief and motor block when given as a femoral block alone.

In conclusion, we have shown that the ED50 of levobupivacaine is greater after knee arthroplasty when infused through a femoral catheter compared with a sciatic catheter. The ED50 of femoral and sciatic infusions of levobupivacaine are substantially less than the concentrations used clinically.

References


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**Fig 1** Patient sequences, concentrations of levobupivacine (%w/v), and patient response.
5 Ben-David B, Schmalenberger K, Chelly JE. Analgesia after total knee arthroplasty: is continuous sciatic blockade needed in addition to continuous femoral blockade? Anesth Analg 2004; 98:747–9