What is the ED$_{95}$ of prilocaine for femoral nerve block using ultrasound?†

P. K. Gupta$^{1,2}$, S. Chevret$^3$, S. Zohar$^3$ and P. M. Hopkins$^{1,2}$*

$^1$Section of Translational Anaesthetic and Surgical Sciences, Leeds Institute of Molecular Medicine, University of Leeds, Leeds LS9 7TF, UK
$^2$Leeds Teaching Hospital NHS Trust, Leeds LS9 7TF, UK
$^3$UMR-S717, Paris Diderot University; AP-HP, Paris, France

* Corresponding author: Academic Unit of Anaesthesia, St James’s University Hospital, Leeds LS9 7TF, UK. E-mail: p.m.hopkins@leeds.ac.uk

Editor’s key points

- Our aim was to estimate the ED$_{95}$ of prilocaine 1% w/v for femoral nerve block.
- The dose closest to the ED$_{95}$ for prilocaine 1% w/v was 17 ml.
- Dixon’s methods are useful for estimating the ED$_{50}$.
- Unlike Dixon’s methods, the continual reassessment method can provide a direct estimate of the ED$_{95}$.

Background. Our aim was to estimate the ED$_{95}$ of prilocaine 1% w/v for femoral nerve block.

Methods. This two-stage dose-finding sequential clinical trial followed an adaptive design based on the continual reassessment method (CRM). Adult patients undergoing Vastus medialis muscle biopsy under ultrasound-guided femoral nerve block were recruited. Data from previously published studies and our own previous experience were used to set the dose levels and their guesstimate probabilities of response.

Results. Forty patients were recruited in the trial ($n=26$ in the first stage and $n=14$ in the second stage). Using the CRM, the estimated response probabilities with 13 and 17 ml prilocaine 1% w/v were 90.4% (95% credibility interval: 68–98%) and 99.1% (95% credibility interval: 89–100%), respectively.

Conclusion. Our study demonstrates that the dose closest to the ED$_{95}$ of prilocaine 1% w/v for ultrasound-guided femoral nerve block is 17 ml. The study also illustrates the value of CRM in dose-finding experiments.

Keywords: anaesthetic techniques, regional; anaesthetics local, prilocaine; monitoring, ultrasound; pharmacology, dose–response; statistics

Accepted for publication: 9 November 2012

The femoral nerve is the largest branch of the lumbar plexus. The nerve can be easily identified with ultrasound deep to the inguinal ligament and lateral to the pulsating femoral artery.

The femoral nerve provides innervation to the anteromedial thigh, femur, knee joint, medial malleolus, and medial side of the foot. It supplies pectineus, sartorius, and the quadriceps femoris muscles. Femoral nerve block, therefore, can be used to provide pre- or postoperative analgesia for femoral neck fractures, femoral shaft fractures, total hip arthroplasty, surgical anaesthesia for outpatient saphenous vein stripping, anaesthesia for outpatient knee arthroscopy, postoperative analgesia for knee procedures or total knee arthroplasty, and surgical anaesthesia for muscle biopsies from the antero-medial thigh.

We use femoral nerve block routinely under ultrasound guidance for Vastus medialis muscle biopsy in patients undergoing investigation of malignant hyperthermia susceptibility. The aim of this dose-finding sequential clinical trial was to provide a valid estimate of the ED$_{95}$ of prilocaine 1% w/v for femoral nerve block.

†Preliminary data from this study were presented at a meeting of the European Society of Regional Anaesthesia.

Methods

With the approval of the local ethics committee, we recruited 40 ASA I, II, and III patients of either sex undergoing elective muscle biopsy. Patients aged <18 yr or with a BMI of more than 35 kg m$^{-2}$ were excluded. All patients received a patient information sheet and a verbal explanation of the trial before written consent was obtained.

Femoral nerve block was performed by a single anaesthetist (P.M.H.), with more than 20 yr experience of performing femoral nerve blocks. For the last 6 yr, P.M.H. has performed more than 80 blocks per year under ultrasound guidance. I.V. access and standard routine monitoring was established in all patients before the start of the procedure. A Sonosite M-Turbo ultrasound machine with a 13.6 MHz linear probe was used to visualize the femoral nerve in the groin below the inguinal ligament. The nerve was traced up and down to confirm its anatomy in relation to the surrounding structures. The nerve either appeared as an oval or a triangular shadow lateral to the pulsating femoral artery.

Once the nerve was localized, the overlying skin was infiltrated with lidocaine 1% w/v. A short-bevel nerve block
needle was passed under ultrasound guidance in-plane with the ultrasound array, so that its tip was adjacent to the nerve. After a negative aspiration test, a small bolus of saline (up to 0.25 ml) was injected to rule out intravascular placement, to confirm tip position, or both. The study volume of prilocaine 1.0% w/v was injected by an assistant as requested by the anaesthetist performing the block who used real-time ultrasound visualization to maintain correct location of the needle. To ensure the nerve was surrounded on all sides with the local anaesthetic and to avoid compartmentalization of the local anaesthetic, we divided the dose into equal volumes in three syringes and injected these above, below, and on the lateral side of the nerve. The patients were blinded to the volume of local anaesthetic, which was also concealed from the anaesthetist performing the block by the use of white non-transparent tape applied to the local anaesthetic syringes.

After completion of the local anaesthetic injection, we identified the motor point of Vastus medialis using transcutaneous electrical stimulation: the motor point is usually located about 5 cm medial and cephalad to the knee cap. The block was then assessed to cold with an alcohol swab and ethyl chloride spray at 5, 10, and 15 min at this point. An effective block was defined as loss of cold sensation within 15 min.

Failure to achieve complete loss of cold sensation at the motor point of Vastus medialis was considered an ineffective block. After an ineffective block, 10–20 ml of local anaesthetic (prilocaine 1% w/v) was infiltrated locally at the surgical site. The block was assessed by the loss of power in the quadriceps muscle. With the knee flexed at 90°, the patients were asked to straighten their leg. The motor power was graded as no loss (full ability to straighten the leg), partial loss (partial ability to straighten the leg), or complete loss (complete inability to straighten the leg). In every respect, other than the study interventions described above, the anaesthetic and surgical management followed our standard practice.

The study design was based on the modified continual re-assessment method (CRM).7–9 It is an adaptive Bayesian design in the sense that it uses all of the available data before trial onset and all the data from the trial that have accumulated at the time each dose level is selected for new patients. It is designed to estimate the targeted percentile of response among several dose levels. Based on our previous experience of using prilocaine 1% w/v for femoral nerve block (since 1988), six dose levels were selected, with associated guesstimates of response probability reported in Table 1. A power model that fits the dose–response curve was chosen, with an exponential unit prior for its parameter (Fig. 1). The volume of prilocaine 1% w/v used for the first patient cohort (two patients per cohort) was 23 ml, which from our experience and available literature was our best guess of the ED95. On the basis of updated data, probabilities of response were re-estimated after each cohort (Fig. 2). The dose allocated to each further cohort was that dose level with updated response probability closest to the target rate of 95%. The CRM continued until one of the following discontinuation criteria was met:10 (i) when the planned number of 40 subjects was reached; (ii) when the estimated probability of response was either too low or too high for all dose levels; or (iii) when a suitable estimate of the ED95 was obtained, based on the predictive gains (mean and maximum) of the inclusion of further patients on the response probability and on the width of its credibility interval lower than 5%. The dose-finding allocation was performed using R software version 2.10 (R cran).11

Other data recorded included sex, age, weight, height, BMI, preoperative assessment of cold score, time of block, time of assessment, effect of block, bolus used for ineffective block, and sedation. These data were analysed using Excel 2000 for Windows (Microsoft, Redmond, WA, USA).

Results
The personal and surgical characteristics of the patients recruited in the study are shown in Table 2. The blocks in

<table>
<thead>
<tr>
<th>Volume (ml)</th>
<th>Guesstimate of response</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>0.50</td>
</tr>
<tr>
<td>17</td>
<td>0.75</td>
</tr>
<tr>
<td>20</td>
<td>0.90</td>
</tr>
<tr>
<td>23</td>
<td>0.95</td>
</tr>
<tr>
<td>26</td>
<td>0.98</td>
</tr>
<tr>
<td>30</td>
<td>0.99</td>
</tr>
</tbody>
</table>
the first cohort of two patients were performed with 23 ml and were effective. The dose level calculated for the next cohort after taking into account the success of the first two blocks was 20 ml and both of these patients again had an effective block. The probabilities were recalculated and the dose level for the next cohort was determined. After we had tested 13 cohorts (26 patients in the first stage), our statistical team suggested adding lower dose levels. This was because the results suggested that the ED95 may not lie in the initial dose range chosen. Two further dose levels (6 and 9 ml) were therefore chosen by the investigators and 14 additional patients were added in this second stage.

In total, 40 patients were recruited and all completed the study. There were no breaches of the protocol. The blocks were effective in 37 patients and not effective in three patients. Figure 2 shows the sequence of effective and ineffective blocks. Figure 3 displays how the prior distribution of the model parameter was modified into a posterior distribution at the end of the trial, with the actualized probabilities of success associated with each of 6, 9, 13, 17, 20, and 23 ml were 63%, 73%, 90%, 99%, 99%, and 100%, respectively (Fig. 4). At the end of the trial, the response probability associated with 13 ml was 90.4% (95% credibility interval: 67–98%) and that associated with 17 ml was 99.1% (95% credibility interval: 89–100%). It seems that the dose associated with a 95% response lies between 13 and 17 ml.

Based on these data, the dose level closest to the ED95 was estimated to be 17 ml.

Two patients had vasovagal bradycardia before the local anaesthetic injection and these responded immediately to i.v. atropine. Three patients were very anxious in the anaesthetic room and were sedated using 10–20 mg of propofol before injection of the local anaesthetic. All three ineffective blocks were supplemented with 10 ml of prilocaine 1% w/v locally at the surgical site. Motor power was recorded for all patients. Table 3 shows the results of motor assessment in all the successful blocks. Our mean block performance time was 2 min and 45 s (range 1–7 min).
Discussion

Dixon's methods\textsuperscript{12–14} (Dixon–Mood, Dixon–Massey, and Dixon’s small sample method) have been used most frequently in anaesthetic dose-finding research. Dixon’s ‘up and down’ methods provide an accurate indication of the ED\textsubscript{50} (dose which will produce an effective block in 50% of patients). However, Dixon’s methods are not good for estimating small or large percentage points [the dose which will be effective in 95% (ED\textsubscript{95}) or 99% (ED\textsubscript{99}) of patients] since testing is concentrated in the 16–84% response.

Fig 3 Prior and posterior (after the inclusion of 40 patients) densities of the dose–response model parameter $a$.

Fig 4 Estimated mean probability of success at various dose levels (with 95% credibility intervals).
CRM and ED95 for femoral nerve block

The CRM has been used successfully in dose-finding trials, and most recently for regional anaesthesia studies.

Femoral nerve block is perhaps one of the easier ultrasound-guided blocks as the nerve can be easily identified under the fascia lata and fascia iliaca next to the pulsating femoral artery. Real-time visualization of the block with ultrasound has been shown to reduce the time of onset and improve the quality of femoral nerve block when compared with using nerve stimulator location. Ultrasound not only allows the identification of intraneural and intravascular injections, but it also helps in detection of non-neural pathology such as femoral vein thrombosis.

Casati and colleagues reported the ED95 of ropivacaine 0.5% w/v for femoral nerve block to be 22 ml (95% CI, 13–36 ml). However, we found the ED95 of prilocaine 1% w/v to be 17 ml. This could be accounted for by the difference in the nature of the local anaesthetic agent. However, there are technical factors, such as transducer angle, ultrasound machine, frequency of probe, settings on the machine, and skill of the assistant, which can affect the dose required for a peripheral nerve block. Two important factors which may have a significant influence on the dose are the approach (in plane and out of plane) and the fractionation of the total dose (single injection and multiple injection). We used a three injection approach to surround the nerve on all sides, while Casati and colleagues used a single injection on the lateral aspect of the nerve in their study. This may have influenced the difference observed in the ED95 between the two studies. Compartmentalization of local anaesthetics for supraclavicular block. It will be interesting to see if similar differences could be found for the ED95 using a multiple injection technique. One may argue that a single large dose injected inadvertently in the nerve carries a high risk of nerve damage compared with a multiple injection technique that may be relatively safe as it allows injection of lower volume at any given place and thus generation of lower pressures and less chance of permanent nerve damage.

In conclusion, our estimate of the dose closest to the ED95 for prilocaine 1% w/v was 17 ml. It provides a clinically relevant guide for the femoral nerve block. We also recommend the use of the CRM for dose-finding studies looking at the point estimates of doses on the dose–response curves.

Declaration of interest

P.M.H. has the use of ultrasound equipment loaned by SonoSite UK Ltd and has received funding from SonoSite UK Ltd for expenses relating to speaking engagements.

References


9 Zohar S, Resche-Rigon M, Chevret S. Using the continual reassessment method to estimate the minimum effective dose in phase II dose-finding studies: a case study. Clin Trials 2011; 0: 1–8


20 Kant A, Gupta PK, Zohar S, Chevret S, Hopkins PM. Application of the continual reassessment method to dose-finding studies in regional anesthesia: an estimate of the ED50 dose for 0.5% bupivacaine for ultrasound-guided supraclavicular block. Anesthesiology 2013, in press


27 Gupta PK, Pace NL, Hopkins PM. Effect of body mass index on the ED50 volume of bupivacaine 0.5% for supraclavicular brachial plexus block. Br J Anaesth 2010; 104: 490–5

28 Bigeleisen PE. Nerve puncture and apparent intraneural injection during ultrasound-guided axillary block does not invariably result in neurologic injury. Anesthesiology 2006; 105: 779–83