Editor’s key points

- The effects of some nerve blocks depend on local anaesthetic dose rather than concentration or volume.
- It is uncertain whether this applies to continuous infusion popliteal-sciatic nerve block.
- In this volunteer study, the effects of ropivacaine 0.1% (at 8 ml h$^{-1}$) and 4% (at 2 ml h$^{-1}$) were similar.
- This suggests that higher concentrations of local anaesthetic at lower infusion rates may be as effective as lower concentrations.
- However, further clinical studies are needed.

Background. It remains unknown whether local anaesthetic dose is the only factor influencing continuous popliteal-sciatic nerve block effects, or whether concentration, volume, or both exert an influence as well.

Methods. Bilateral sciatic catheters were inserted in volunteers (n=24). Catheters were randomly assigned to ropivacaine of either 0.1% (8 ml h$^{-1}$) or 0.4% (2 ml h$^{-1}$) for 6 h. The primary endpoint was the tolerance to transcutaneous electrical stimulation within the tibial nerve distribution at hour 6. Secondary endpoints included current tolerance at other time points and plantar flexion maximum voluntary isometric contraction (22 h total).

Results. At hour 6, tolerance to cutaneous stimulation for limbs receiving 0.1% ropivacaine was [mean (standard deviation)] 27.0 (20.2) vs 26.9 (20.4) mA for limbs receiving 0.4% [estimated mean difference 0.2 mA; 90% confidence interval (CI) –8.2 to 8.5; P=0.02 and 0.03 for lower and upper boundaries, respectively]. Because the 90% CI fell within the prespecified tolerance ±10 mA, we conclude that the effect of the two concentration/volume combinations were equivalent. Similar negative findings were found for the secondary outcomes.

Conclusions. For continuous popliteal-sciatic nerve blocks, we found no evidence that local anaesthetic concentration and volume influence block characteristics, suggesting that local anaesthetic dose (mass) is the primary determinant of perineural infusion effects in this anatomic location. These findings suggest that for ambulatory perineural local anaesthetic infusion—for which there is usually a finite local anaesthetic reservoir—decreasing the basal rate while increasing the local anaesthetic concentration may allow for increased infusion duration without compromising postoperative analgesia.

Clinical trial registration. NCT01898689.

Keywords: continuous peripheral nerve block; perineural infusion; perineural local anaesthetic infusion

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patients who are permitted to ambulate on their operative foot. Therefore, portable infusion pumps’ local anaesthetic reservoir volume would be consumed at a lower rate, greatly increasing the duration of postoperative analgesia provided by ambulatory perineural infusion, and, possibly, the risk of postoperative falls might be decreased.

In fact, there is currently evidence that a low-rate, high-concentration continuous ropivacaine popliteal-sciatic block decreases the incidence of an unwanted insensate extremity compared with a high-rate, low-concentration infusion. However, this study in outpatients was not powered to determine analgesia equivalence, and the primary endpoint was subjective in nature. More importantly, the post-surgical subjects self-administered bolus doses, making it impossible to determine the total dose that each actually received and thus possible equivalence.

We therefore designed and executed this randomized, triple-masked (subjects, investigators/staff, statisticians), active-controlled, split-body clinical trial testing the hypothesis that providing ropivacaine at different concentrations and rates (0.1% at 8 ml h\(^{-1}\) vs 0.4% at 2 ml h\(^{-1}\) — but at an equivalent total dose (8 mg h\(^{-1}\) — produces comparable effects when infused for a continuous popliteal-sciatic nerve block. The primary endpoint was the tolerance to cutaneous electrical current applied on the plantar aspect of the foot after 6 h of infusion. Secondary endpoints included tolerance to transcutaneous electrical stimulation within the tibial nerve distribution at other time points, and, maximum voluntary isometric contraction (MVIC) during plantar flexion in the 22 h after local anaesthetic administration initiation.

**Methods**

**Enrolment**

All study procedures were approved by the local Institutional Review Board (Human Research Protection Program, University California, San Diego, CA, USA). Volunteers were recruited from the community by IRB-approved advertisements and databases, and also through clinicaltrials.gov where the trial was prospectively registered (NCT01898689). Included were ASA I and II adult (≥18 yr) men and women. Exclusion criteria included daily analgesic use, opioid use within the previous 4 weeks, any neuromuscular deficit of the sciatic nerve or within its distribution, a BMI >35 kg m\(^{-2}\), pregnancy, and incarceration.

**Perineural catheter insertion**

After written, informed consent, subjects were admitted, an i.v. line was placed in an upper extremity, and external monitors were applied (pulse oximeter, arterial pressure, and EKG). Oxygen was provided by nasal cannula, and oral diazepam (10 mg) and hydromorphone (4 mg) were provided for sedation. After sterile preparation (chlorhexidine gluconate and isopropyl alcohol) and draping, bilateral popliteal-sciatic catheters were placed using an identical insertion protocol by one of two investigators (S.J.M. or A.M.M.). The dominant side (right vs left) was always inserted first.

With subjects in the prone position, the sciatic nerve was identified by ultrasound imaging with a high-frequency linear array transducer (HFL 38 ×, SonoSite M-Turbo, Bothell, WA, USA) in a transverse cross-sectional (short axis) view immediately proximal to the popliteal fossa. The bifurcation of the sciatic nerve into the tibial and common peroneal nerves was identified and the block was performed immediately proximal to this point. A local anaesthetic skin wheal was raised lateral to the ultrasound transducer, and a non-insulated 17 G Tuohy-tip needle (FlexTip Plus, Teleflex Medical, Research Triangle Park, NC, USA) was inserted through the skin wheal and directed medially in-plane beneath the ultrasound transducer towards the sciatic nerve. Once the needle tip was positioned immediately posterior to the sciatic nerve, normal saline was injected in 1–2 ml increments to ensure spread to the medial and lateral aspects of the nerve (maximum 10 ml). A flexible 19 G catheter was placed through the needle and positioned just posterior to the sciatic nerve, between the two branches if they had separated apart with the initial injection. The needle was then withdrawn over the catheter, with care taken to leave the catheter in its original position. The catheter was subsequently secured with an anchoring device and sterile occlusive dressing.

**Treatment group assignment**

For each subject, the dominant-sided catheter was randomly assigned to one of the two treatment groups: a ropivacaine concentration of 0.1% or 0.4%. Subjects acted as their own controls, with the contralateral side receiving the alternative concentration. The Investigational Drug Service prepared the randomization list and also the two ropivacaine reservoirs and two electronic infusion pumps (SIGMA Spectrum Infusion System, Baxter Healthcare International, Deerfield, IL, USA) used to infuse the ropivacaine for each subject. The basal rate of each infusion was determined by the ropivacaine concentration in each pump reservoir: 0.1% (8 ml h\(^{-1}\)) or 0.4% (2 ml h\(^{-1}\)). While the basal rate differed for each concentration, the total dose of local anaesthetic remained the same for both treatments (8 mg h\(^{-1}\)). The infusion pump with the reservoir of 0.1% ropivacaine was labelled ‘0.1%’ and the opposite end of its tubing was labelled either ‘dominant’ or ‘other’, depending upon the randomization for each subject. The other pump was labelled ‘0.4%’ and the opposite end of its tubing was labelled either ‘dominant’ or ‘other’ as well. The two pieces of tubing were then gently wound at least five rotations and covered with opaque tape, masking from all but the Investigational Drug Service pharmacists of the treatment group assignment of each limb (ropivacaine is clear, so the flow through the clear tubing from the tape to the perineural catheters was not visually distinguishable). The Investigational Drug Service delivered this apparatus to the investigators, ensuring masking for both the subjects and observers (clinical research nurse taking the measurements). The catheters were removed after 6 h of infusion (48 mg).

**Outcome measurements**

We selected measures that have established reliability, validity, and minimal inter-rater discordance. Measurements were
performed at hour 0 (baseline), and on the hour until hour 14, and also the following morning at hour 22. In all cases, measurements were taken in the supine position with the dominant side measured first, followed by the non-dominant side.

Tolerance of transcutaneous electrical stimulation
Sensory perception—depth of analgesia—was evaluated using tolerance of transcutaneous electrical stimulation with a similar quantitative procedure validated and used in multiple previously published clinical trials. Electrocardiogram pads were placed on the lateral aspect of the plantar surface of the foot. Tolerance to cutaneous electrical current was obtained using a nerve stimulator (EZstimII, Model ES400; LifeTech, Stafford, TX, USA): current was increased from 0 mA until subjects detected the electrical current (up to a maximum of 80 mA), at which time the current was recorded and the nerve stimulator turned off.

Muscle strength
Muscle strength was evaluated with an isometric force electromechanical dynamometer (MicroFET2, Lafayette Instrument Company, Lafayette, IN, USA) to measure the force produced during an MVIC during plantar flexion. The dynamometer was placed against the bed’s foot board (immobile) and the subjects were asked to take 2 s to come to maximum effort plantar flexing, maintaining this effort for 5 s, and then relaxing. The measurements immediately before perineural ropivacaine administration were designated as baseline measurements, and all subsequent measurements were expressed as a percentage of the pre-infusion baseline.

Statistical analysis
We tested the hypothesis that 0.1% ropivacaine (8 ml h⁻¹=8 mg h⁻¹) was equivalent to 0.4% ropivacaine (2 ml h⁻¹=8 mg h⁻¹) on the mean tolerance to transcutaneous electrical stimulation at hour 6 (the primary endpoint). The a priori equivalence region for the difference in means between the two concentrations was specified as ±10 mA. This value was considered the minimal clinically relevant current since it approximates the tolerated electrical current range at baseline considered the minimal clinically relevant current since it because a 10% side-to-side strength difference is common, yet functionally unnoticeable in healthy individuals.

With 24 evaluable subjects, we had 90% power at the 0.05 significance level to detect equivalence of 0.1% and 0.4% ropivacaine concentration on the mean tolerance to transcutaneous electrical stimulation at hour 6 (primary outcome) using an a priori equivalence interval of ±10 mA. This assumed, based on previously published data, a standard deviation (SD) of tolerance difference between legs of 13 mA. Subjects were deemed non-responders and excluded from the primary analyses if both extremities failed to exhibit any increase in tolerance to cutaneous electrical current by hour 6. SAS software 9.3 (SAS Institute, Cary, NC, USA) and R software versions 2.15.3 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all analyses.

Results
Twenty-six subjects were enrolled during a 4 month period beginning from July 2013 (Fig. 1). All had bilateral popliteal-sciatic perineural catheters successfully inserted per protocol. Each subject’s dominant side was randomized to either one of the two ropivacaine concentration/rate combinations—0.1% at 8 ml h⁻¹ or 0.4% at 2 ml h⁻¹—and the non-dominant side received the opposite treatment. One subject did not exhibit any increased tolerance to cutaneous electrical current bilaterally, and was deemed a non-responder. An additional subject was excluded because of equipment
nerve stimulator) failure that failed to deliver electrical current. The remaining 24 subjects were included in the primary analyses (Table 1).

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Summary statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>21–63</td>
</tr>
<tr>
<td>Gender (female, %)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175 (11)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 (17)</td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>26 (4)</td>
</tr>
<tr>
<td>Dominant side (right, %)</td>
<td>24 (100%)</td>
</tr>
</tbody>
</table>

### Primary outcome

At hour 6, tolerance to cutaneous stimulation for limbs receiving 0.1% ropivacaine was a mean (SD) of 27.0 (20.2) mA, compared with 26.9 (20.4) mA for limbs receiving 0.4% (estimated mean difference of 0.2 mA; 90% CI –8.2 to 8.5). P-values from the TOST procedure were 0.02 and 0.03 for the mean being inside the lower and upper boundaries, respectively. Because the 90% CI decreased within prespecified tolerances, we conclude that the effect of the two concentration/volume combinations was equivalent.

### Secondary outcomes

Equivalence between 0.1% and 0.4% ropivacaine concentration was claimed for both maximum tolerance to

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**Fig 1** Consolidated Standards of Reporting Trials (CONSORT) flow diagram.
Continuous popliteal-sciatic nerve blocks

Discussion

This randomized, triple-masked, active-controlled, split-body clinical investigation provides strong evidence that dose alone is the primary determinant of perineural effects for continuous popliteal-sciatic nerve blocks, and varying the concentration and infusion rate while keeping dose constant does not have any significant effect on block characteristics.

While our results do not support the practice of minimizing local anaesthetic concentration to reduce motor block, they...

Table 2 Mixed-effect model estimates for tolerance to transcutaneous electrical stimulation (n=24). The a priori equivalence region is –10 to 10 mA. The P-value for group–time interaction was >0.99. The table includes P-values adjusted for multiple comparisons using the single-step method for simultaneous inference from parametric models, and also unadjusted P-values. All P-values are derived from the TOST procedure for equivalence; significance criterion is P<0.05. *P >0.05 testing whether the mean is above lower limit or below upper limit means equivalence cannot be claimed.

<table>
<thead>
<tr>
<th>Hour</th>
<th>Estimated difference (0.1% vs 0.4%)</th>
<th>90% CI</th>
<th>P-value for equivalence testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For &gt; –10 mA</td>
<td>For &lt;10 mA</td>
</tr>
<tr>
<td>Overall</td>
<td>0.23</td>
<td>–1.19</td>
<td>1.66</td>
</tr>
<tr>
<td>0</td>
<td>0.67</td>
<td>–4.87</td>
<td>6.20</td>
</tr>
<tr>
<td>1</td>
<td>–1.42</td>
<td>–6.95</td>
<td>4.12</td>
</tr>
<tr>
<td>2</td>
<td>–1.54</td>
<td>–7.08</td>
<td>3.99</td>
</tr>
<tr>
<td>3</td>
<td>–0.29</td>
<td>–5.83</td>
<td>5.24</td>
</tr>
<tr>
<td>4</td>
<td>3.38</td>
<td>–2.16</td>
<td>8.91</td>
</tr>
<tr>
<td>5</td>
<td>0.96</td>
<td>–4.58</td>
<td>6.49</td>
</tr>
<tr>
<td>6</td>
<td>0.13</td>
<td>–5.41</td>
<td>5.66</td>
</tr>
<tr>
<td>7</td>
<td>0.42</td>
<td>–5.12</td>
<td>5.95</td>
</tr>
<tr>
<td>8</td>
<td>–0.71</td>
<td>–6.24</td>
<td>4.82</td>
</tr>
<tr>
<td>9</td>
<td>–1.08</td>
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<td>4.45</td>
</tr>
<tr>
<td>10</td>
<td>0.75</td>
<td>–4.79</td>
<td>6.29</td>
</tr>
<tr>
<td>11</td>
<td>–0.92</td>
<td>–6.45</td>
<td>4.62</td>
</tr>
<tr>
<td>12</td>
<td>3.17</td>
<td>–2.37</td>
<td>8.70</td>
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<tr>
<td>13</td>
<td>–2.13</td>
<td>–7.66</td>
<td>3.41</td>
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<tr>
<td>14</td>
<td>2.58</td>
<td>–2.95</td>
<td>8.12</td>
</tr>
<tr>
<td>22</td>
<td>–0.21</td>
<td>–5.74</td>
<td>5.33</td>
</tr>
</tbody>
</table>

Transcutaneous electrical stimulation and MVIC when collapsing over time. Since the time-by-treatment interaction was not significant either for maximum tolerance (P>0.99) or muscle strength (P=0.98), equivalence in the treatment effect was assessed marginally by collapsing over time. The mean difference (0.1–0.4%) was 0.2 (90% CI: –2.3 to 2.8) mA for maximum tolerance and 0.7 (90% CI: –4.1 to 5.6)% for MVIC, both of which were well contained within the a priori equivalence regions of –10 to 10 mA and –20 to 20%, respectively (P<0.001 for both outcomes).

When assessed at individual time points, equivalence was concluded for tolerance to current at all time points using raw P-values, and at most time points when adjusting for multiple comparisons (Table 2, Fig. 2). Equivalence was claimed for the mean MVIC at most time points using raw P-values but at only a few time points when adjusting for multiple comparisons (Table 3, Fig. 3).
The practice would greatly decrease local anaesthetic volume consumption and, during ambulatory perineural infusion, result in a dramatic increase in reservoir longevity and postoperative analgesia duration. In addition, hospitalized patients consuming less volume of local anaesthetic results in fewer changes of the medication reservoir and time savings for both nursing and pharmacy staff. Lastly, because providing continuous peripheral nerve blocks on an ambulatory basis requires patients to carry a local anaesthetic reservoir,12 decreasing the volume of local anaesthetic consumption by increasing local anaesthetic concentration—and therefore not sacrificing analgesic potency—allows for a smaller reservoir volume and less weight.

The current study’s results are also important because they suggest that lowering concentration while increasing the basal rate is not an effective strategy for decreasing motor weakness during continuous popliteal-sciatic nerve blocks. Moreover, the optimal local anaesthetic concentration, basal rate, and dose remain unknown for continuous popliteal-sciatic nerve blocks. With the determination that it is solely dose that is the main determinant of perineural infusion effects, the search for the optimal combination becomes far simpler: instead of requiring a huge number of concentration/rate/dose variations to be examined, a far more simple dose–response study may be used.

The results of this clinical trial build upon data available from published investigations. In a previous study, comparing two different dosing regimens in continuous popliteal-sciatic nerve blocks, patients undergoing foot/ankle surgery were more likely to have an insensate limb with a basal infusion of ropivacaine 0.2% at 8 ml h⁻¹ than with 0.4% at 4 ml h⁻¹.
Continuous popliteal-sciatic nerve blocks

(both 16 mg h⁻¹). This study is similar to ours, in that it compared two different dosing regimens that delivered the same total hourly drug mass. However, it differs in one critical respect: in the previous study, subjects self-administered bolus doses in response to pain since they were postoperative patients, making it impossible to determine the total dose that each actually received and thus possible equivalence. The present study protocol involving non-surgical volunteers enabled us to ensure each treatment received precisely identical local anaesthetic doses and treatment duration.

The relative importance of local anaesthetic dose, concentration, and volume (rate) within continuous peripheral nerve blocks has been studied in two additional tightly controlled trials.² ³ In the first, subjects undergoing hip arthroplasty received a posterior lumbar plexus (psoas compartment) catheter, and were then randomized to receive ropivacaine at either 0.1% (12 ml h⁻¹ basal; bolus 4 ml) or 0.4% (3 ml h⁻¹ basal; bolus 1 ml) for 48 h.⁵ Similar to the current study involving popliteal-sciatic perineural infusion, the two administration regimens were found to be equivalent for both induced muscle weakness (quadriceps femoris, hip flexor, and hip adductor muscles) and tolerance to cutaneous electrical current. Importantly, in this study including patients undergoing a relatively painful surgical procedure, the lack of difference between the two treatments was found for both cutaneously applied electrical current and pain scores (resting, average dynamic, and worst dynamic pain). This latter correlation increases confidence that for the current study involving volunteers, the finding of tolerance to cutaneous current equivalence will be reflected in pain scores for patients undergoing painful foot and ankle surgery.

In the second study, subjects undergoing bilateral knee arthroplasty received bilateral femoral perineural catheters.⁶ After the operation, the right-sided catheters were randomly assigned to receive perineural ropivacaine of either 0.1% (basal 12 ml h⁻¹; bolus 4 ml) or 0.4% (basal 3 ml h⁻¹; bolus 1 ml), with the left catheter receiving the alternative concentration-rate combination in a subject- and observer-masked fashion for 2 days. Just as for the investigation involving psosas compartment catheters, muscle strength, tolerance to cutaneous current, and pain scores between the treatments were all equivalent. Therefore, the current study involving popliteal-sciatic perineural infusion mirrors the findings of the two previously published investigations of local anaesthetic dose-concentration relationship involving two different anatomical catheter locations.

While this correlation may appear unsurprising in retrospect, it was not necessarily predicted by previous literature. For example, previous investigations of interscalene,⁴³ axillary,⁴⁴ fascia iliaca,⁴⁵ extended femoral,⁴⁶ and subgluteal⁴⁷ catheters have shown that the optimal infusion method of local anaesthetic administration (basal vs bolus vs combination) varies with anatomic location. Therefore, data from the previous two studies involving dose/concentration/volume combinations for psosas compartment and femoral catheter locations could not automatically be applied to popliteal-sciatic placement.

While including only non-surgical volunteers avoided confounding the study results with uncontrolled bolus doses ethically required in patients experiencing post-surgical pain, it also makes extrapolation of our results to clinical practice somewhat theoretical. Similarly, it remains unknown how well cutaneous sensation correlates with postoperative pain after surgical procedures of the foot and ankle. Lastly, the current findings involving flexible catheters and 0.1%/0.4% ropivacaine for continuous sciatic nerve blocks may not be applicable to other catheter designs or insertion techniques; local anaesthetic types, concentrations, or doses; infusion delivery methods or durations; and anatomic catheter locations. Of note, the maximum recommended hourly total dose of local anaesthetic during perineural infusion remains unknown,¹⁸ but a wide safety margin has been documented in numerous clinical trials,¹ with one study reporting no toxicity signs or symptoms with perineural ropivacaine 0.2% administered at basal rates up to 14 ml h⁻¹ and large, repeated boluses of ropivacaine 0.5% (10–60 ml) provided for up to 27 days.¹⁹

It remains to be established whether the current findings in healthy volunteers may be reproduced in patients undergoing painful surgical procedures of the foot and ankle.⁴ ²⁰⁻²² In addition, future studies should investigate local anaesthetic concentrations in lower/higher combinations. For example, would ropivacaine 1% at 1 ml h⁻¹ produce equivalent results as 0.1% at 10 ml h⁻²? Similarly, additional catheter insertion locations other than the popliteal fossa may be used along the sciatic nerve to provide postoperative analgesia.¹⁷ ²³⁻²⁵ It remains unknown if the current results apply equally to these other anatomic locations. Additionally, the implications for clinicians should be further elucidated. For example, pharmacoeconomic studies might examine the fiscal impact of using a higher concentration local anaesthetic—allowing for a smaller volume of fluid—for patients discharged home with a disposable, portable infusion pump—since concentration often is correlated with medication cost; the size of an infusion pump is often correlated with device costs; and diluting medication often requires the assistance of a pharmacist, often increasing total treatment costs.²⁶⁻²⁹ Furthermore, patients' perspectives remain unexamined regarding the maximum acceptable volume of anaesthetic, considering that decreasing concentration and increasing reservoir volume are directly correlated with increased bulk and weight for ambulatory patients to carry.³⁰

In summary, this study documents strong evidence that for continuous popliteal-sciatic nerve blocks, local anaesthetic dose is the overwhelming factor in determining perineural infusion effects, and that concentration and basal rate do not affect the block to a clinically significant degree within the dose-range included in this protocol. These findings suggest that for ambulatory perineural local anaesthetic infusion—for which there is a finite local anaesthetic reservoir—decreasing the basal rate while increasing the local anaesthetic concentration may allow for increased infusion duration without compromising postoperative analgesia.

Authors’ contributions

S.J.M. and A.M.M.: participated in protocol design, study execution, and manuscript authorship; R.R.A. and T.J.F.: participated in study...
execution, and manuscript authorship; E.J.M. and Z.X.: participated in data analysis and manuscript authorship; M.C.D.: participated in protocol design and manuscript authorship; A.C.M.: participated in study execution, data entry, and manuscript authorship; B.M.I.: participated in protocol design, study execution, data analysis, and manuscript authorship.

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Declaration of interest

None declared.

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