Intraneural Ultrasound-guided Sciatic Nerve Block
Minimum Effective Volume and Electrophysiologic Effects

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ABSTRACT

Background: Both extra- and intraneural sciatic injection resulted in significant axonal nerve damage. This study aimed to establish the minimum effective volume of intraneural ropivacaine 1% for complete sensory-motor sciatic nerve block in 90% of patients, and related electrophysiologic variations.

Methods: Forty-seven consecutive American Society of Anesthesiologists physical status I-II patients received an ultrasound-guided popliteal intraneural nerve block following the up-and-down biased coin design. The starting volume was 15 ml. Baseline, 5-week, and 6-month electrophysiologic tests were performed. Amplitude, latency, and velocity were evaluated. A follow-up telephone call at 6 months was also performed.

Results: The minimum effective volume of ropivacaine 1% in 90% of patients for complete sensory-motor sciatic nerve block resulted in 6.6 ml (95% CI, 6.4 to 6.7) with an onset time of 19 ± 12 min. Success rate was 98%. Baseline amplitude of action potential (mV) at ankle, fibula, malleolus, and popliteus were 8.4 ± 2.3, 7.1 ± 2.0, 15.4 ± 6.5, and 11.7 ± 5.1 respectively. They were significantly reduced at the fifth week (4.3 ± 2.1, 3.5 ± 1.8, 6.9 ± 3.7, and 5.2 ± 3.0) and at the sixth month (5.9 ± 2.3, 5.1 ± 2.1, 10.3 ± 4.0, and 7.5 ± 2.7) (P < 0.001 in all cases). Latency and velocity did not change from the baseline. No patient reported neurologic symptoms at 6-month follow-up.

Conclusions: The intraneural ultrasound-guided popliteal local anesthetic injection significantly reduces the local anesthetic dose to achieve an effective sensory-motor block, decreasing the risk of systemic toxicity. Persistent electrophysiologic changes suggest possible axonal damage that will require further investigation. (Anesthesiology 2018; 129:241-8)
Therefore, the purposes of this prospective, up-and-down study were: (1) to assess the minimum effective volume of ropivacaine 1% to achieve a complete sensory-motor sciatic nerve block in 90% of patients, using an ultrasound-guided intraneural popliteal approach; and (2) to evaluate any variations of the electrophysiologic test both at 5 weeks and 6 months after surgery, considering the administered dose.

Materials and Methods

The IRCCS (Scientific Research and Care Institute) Policlinico of Milan Ethics Committee approved the study. Therefore, 47 American Society of Anesthesiologist physical status I-II patients, 18 yr or older, undergoing hallux valgus repair with an ultrasound-guided popliteal nerve block were enrolled. The study was previously registered at clinicaltrial.gov (NCT02589041, principal investigator Gianluca Cappelleri). Exclusion criteria included allergy to local anesthetics, diabetes, peripheral neurologic disorder, inability to perform the electrophysiologic evaluation either preoperatively or postoperatively, and patient refusal. For all patients, written informed consent for the study was obtained during the preoperative anesthesia evaluation, followed by a baseline electrophysiologic assessment before surgery.

In the operating room, standard monitoring including noninvasive arterial blood pressure, electrocardiography, heart rate, and pulse oximetry were used. An 18-gauge catheter was placed in the forearm opposite the blood cuff and IV premedication with midazolam (0.05 mg · kg⁻¹) was given in all patients. A single author (G.C.), skilled in ultrasound regional anesthetic techniques performed all blocks according to the up-and-down biased coin design described in the Statistical Methods section below. An investigator not involved in the management of the patient opened the envelope and gave it to the provider just before administration of regional anesthesia.

With the patients in prone position, a high frequency (8 to 12 MHz) linear array transducer (Snerve, Sonosite, USA) was placed in the popliteal fossa and tilted cranially to visualize the sciatic nerve in a transverse cross-sectional view. The point of needle insertion was 1 to 2 cm proximal to the bifurcation where the sciatic nerve appears circular. After the best visualization of needle insertion was 1 to 2 cm proximal to the bifurcation, a 20-ml syringe connected to a manometer (B-Smart, B. Braun Medical Inc., Germany) in order to achieve an injection pressure less than 15 psi. In case of paresthesia, pain reported by the patient, as well as an increase of the injection pressure, the needle was slightly withdrawn until complete resolution of the symptoms, and then the injection continued. A postinjection sciatic diameter and a couple of images of the nerve, 2 cm above and below the injection point (to visualize local anesthetic spread), were registered.

Sensory and motor blockade in the operated foot was evaluated every 5 min after local anesthetic injection by an observer blinded to randomization. Sensory block was evaluated as an absence of sensation to pinprick in the common peroneal and tibial nerve distributions (both dorsal and plantar region of the foot), and classified as follows: 1 = normal sensation within the nerve distribution (no block); 2 = blunted sensation (anaesthesia); 3 = absence of sensation (anesthesia). Motor block was assessed for voluntary motor response by asking the patient to plantar-flex or dorsiflex the foot, and was classified as follows: 1 = normal movement; 2 = decreased movement; 3 = absence of movement (complete motor block). Success was defined when a complete sensory and motor block (score = 3) was achieved within 40 min after local anesthetic injection. The time between local anesthetic injection and successful complete block was considered the onset, and thereby registered.

Surgery was performed in all patients in a bloodless field, using an ankle tourniquet application inflated to 100 mmHg above systolic blood pressure (maximum 250 mmHg).

All patients received both a clinical and baseline electrophysiologic follow-up assessment. An investigator, unaware of randomization, followed up by telephone to all patients at 1, 2, and 5 weeks, and 6 months after surgery, to detect any neurologic symptoms, using a standardized questionnaire (see appendix).

The electrophysiologic study was performed before surgery (baseline), and at 5 weeks and 6 months after surgery by a neurologist blinded to randomization. Both tibial and peroneal nerves were studied. The following motor nerve conduction data were obtainedbilaterally using surface electrodes: conduction velocity from knee level to ankle (in m/s); distal latency from ankle to the extensor digitorum brevis muscle for the peroneal (nerve) and the abductor hallucis muscle for the tibial (nerve) (ms); and muscle response amplitude for the distal stimulation (mV). Stimuli were obtained from ankle to fibular head, and from malleolus to popliteus, respectively. Nerve injury was defined based on the well-established criteria for the presence of nerve damage according to the normative reference values adopted in our own laboratory. These values included a change in amplitude and conduction velocity to less than 80% baseline data (i.e., a reduction of more than 20% from baseline), or a change in latency to more than 120% baseline data (i.e., an increase of more than 20% from baseline), obtained in the same patient. Yet, a variation in one of these three variables was considered significant of nerve injury.
Statistical Analysis and Sample Size Calculation

A “biased coin up-and-down sequential design” was applied to assess the minimum effective volume in 90% of patients for the popliteal intraneural approach. This statistical technique has been extensively reviewed in the current literature. The first subject received 15 ml ropivacaine, 1% solution. Each subsequent patient received a dose that depended on the response of the previous one, just as in classical up-and-down designs, but with different probability. In fact, in case of block failure, the subsequent patient received the same dose of the previous one, incremented by 2 ml; however, in case of a successful block, the subsequent patient could receive either the same dose decreased by 2 ml with a probability \( \beta = 0.11 \), or the same dose of the previous one with a probability \( 1-\beta = 0.89 \).

The initial dose was chosen based on our previous study, which reported 96% success after the intraneural injection of 15 ml ropivacaine, 1% solution.

Previous simulations, according to Stylianou et al., estimated the minimum sample size required for the stabilization of the minimum effective volume calculation. Assuming a fixed-sample biased coin design, and a fixed minimal number of successes for different dose distributions, sample sizes, and number of successes, stabilization of the estimated parameters occurred after the enrollment of 40 subjects, even when applying the assumption that the probability of receiving a lesser volume after a successful response is equal to the 0.11 theoretical value. Our aim was to obtain a fixed number of 45 successful blocks as defined per protocol. Hence, we continued recruitment until 45 successful cases were obtained, and the 45 presealed envelopes with dose allocation (each with 11% probability of decreased dose and 89% probability of unchanged dose) were opened.

In order to calculate the minimum effective volume in 90% of patients, we employed the R translation of the dedicated software designed by Pace and Stylianou to obtain the isotonic regression estimator \( \mu^* \) by calculating the pool adjacent violators algorithm, and the relevant 95% CI by implementing a parametric bootstrap routine with 9,999 boot replications.

Statistical analysis was performed with the dedicated software Stata 11.1 (StataCorp., USA) and R version 3.4.1.

Two-tailed Hypothesis Testing Was Applied and \( P < 0.05 \) Was Considered Significant

Electrophysiologic latency (ms), velocity (m/s), and amplitude (mV) were recorded at four sites: ankle, fibula, malleolus, and popliteal fossa. Data obtained 5 weeks and 6 months after surgery are expressed as a fraction of the respective basal (presurgery) values.

After assessing normality with the Shapiro–Wilk test, the one-sample \( t \) test was applied to test the null hypothesis of ratio = 1 (no difference from baseline) for each electromyographic ratio.

Baseline electrophysiologic values of dropout patients, both at 5 and 6 months, were compared with those of corresponding non-dropouts with the two-sample Wilcoxon rank sum (Mann–Whitney) test.

Simple linear regression was used to evaluate a possible effect of the local anesthetic dose on each electrophysiologic ratio.

In order to take into account the repeated measure structure of our data and to investigate a possible dose × time interaction, we built panel data models for each anatomical site investigated. After reshaping data in the long format, mixed linear effect models were studied taking a local anesthetic dose as a fixed effect. Dose × time interaction was studied, modeling the between-patient variability as a random effect. Both random intercept and slope models were analyzed. Independent covariance matrices were applied therein.

Continuous variables are reported as mean ± SD and categorical variables are reported as number (percentage).

Results

From November 2015 to May 2016, 47 patients were enrolled. Only one patient (receiving 5 ml ropivacaine solution) did not show a complete sensory-motor sciatic nerve block after 40 min. Therefore, at the end of the study, after all 45 envelopes were opened, a 98% success rate (46/47 cases) was determined (fig 1). Six (12.8%) patients were male. The mean age of the total population was 58 ± 13 yr old, and they had a mean body weight of 65 ± 13 kg and mean height of 163 ± 10 cm (body mass index: 24.1 ± 4.2).

The minimum effective volume of ropivacaine 1% solution in 90% of patients, calculated using the up-and-down biased coin design to achieve a complete sensory-motor ultrasound-guided popliteal nerve block, resulted in 6.6 ml (95% CI, 6.4 to 6.7) with an onset time of 19 ± 12 min. The sensory and motor block is reported in figure 2.

Five (11%) patients reported pain just after needle placement or immediately after the injection was started. In all of these cases, we slightly withdrew the needle until the complete resolution of symptoms was obtained, and then continued the procedure with no further pain. In all patients we maintained an injection pressure less than 15 psi measured by the manometer.

No patients reported clinical neurologic symptoms throughout the 6-month follow-up.

Forty-three of 47 patients (91%) had an electrophysiologic test 5 weeks after surgery, but only 23 (49%) repeated the test again at 6 months. All of these patients showed a significant reduction of the amplitude of action potentials, compared with the baseline (table 1), while latency and velocity did not differ from the baseline in all tested anatomical sites (table 2).

Dropout patients at 5 weeks (4 patients, i.e., 9% of the 47 enrolled) had similar baseline electrophysiologic tests as non-dropouts (baseline values in the nondropouts are reported in...
tables 1 and 2). Ankle, fibula, malleolus, and popliteal fossa latency was respectively: 4.0 ± 0.6 ($P = 0.423$); 10.5 ± 1.5 ($P = 0.819$); 4.0 ± 0.9 ($P = 0.954$); and 11.5 ± 2.6 ($P = 0.253$). Ankle, fibula, malleolus, and popliteal fossa amplitude was respectively: 7.8 ± 2.5 ($P = 0.675$); 7.1 ± 2.5 ($P = 0.970$); 18.7 ± 5.5 ($P = 0.208$); and 14.0 ± 3.5 ($P = 0.195$). Fibula and popliteal fossa velocity was respectively: 50.5 ± 5.8 ($P = 0.492$) and 47.4 ± 2.5 ($P = 0.612$).

Dropout patients at 6 months (24 patients, i.e., 51% of the 47 enrolled) also had similar baseline electrophysiologic tests as nondropouts (baseline values in the nondropouts are reported in tables 1 and 2). Ankle, fibula, malleolus, and popliteal fossa latency was respectively: 3.8 ± 0.5 ($P = 0.572$); 10.6 ± 1.1 ($P = 0.173$); 4.1 ± 0.8 ($P = 0.091$); and 12.0 ± 1.5 ($P = 0.551$). Ankle, fibula, malleolus, and popliteal fossa amplitude was respectively: 8.5 ± 2.7 ($P = 0.882$); 7.1 ± 2.3 ($P = 0.856$); 16.6 ± 7.2 ($P = 0.229$); and 12.3 ± 5.6 ($P = 0.565$). Fibula and popliteal fossa velocity was respectively: 48.1 ± 3.8 ($P = 0.209$) and 47.4 ± 3.9 ($P = 0.524$).

Simple linear regression showed that the local anesthetic dose used had no effect on each electrophysiologic ratio at...
any anatomical site. At 5 weeks, the ankle, fibula, malleolus, and popliteal fossa local anesthetic dose linear regression coefficients were respectively: –0.006 (95% CI, –0.024 to 0.013; \( P = 0.554 \)); 0.001 (95% CI, –0.007 to 0.009; \( P = 0.762 \)); –0.019 (95% CI, –0.039 to 0.001; \( P = 0.064 \)); and –0.003 (95% CI, –0.012 to 0.005; \( P = 0.430 \)) for the latency; –0.011 (95% CI, –0.036 to 0.0138; \( P = 0.369 \)); –0.018 (95% CI, –0.048 to 0.012; \( P = 0.229 \)); –0.014 (95% CI, –0.032 to 0.005; \( P = 0.147 \)); and –0.009 (95% CI, –0.030 to 0.012; \( P = 0.386 \)) for the amplitude, and 0.035 (95% CI, –0.091 to 0.162; \( P = 0.578 \)) and –0.006 (95% CI, –0.016 to 0.004; \( P = 0.204 \)) for the fibula and posterior fossa velocity.

Table 1. Electrophysiologic Variations of the Amplitude of the Action Potential from Baseline

<table>
<thead>
<tr>
<th>Site</th>
<th>Baseline (45 Cases)</th>
<th>5 Weeks (43 Cases)</th>
<th>6 Months (23 Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle</td>
<td>8.4 ± 2.3</td>
<td>4.3 ± 2.1</td>
<td>5.9 ± 2.3</td>
</tr>
<tr>
<td>Fibula</td>
<td>7.1 ± 2.0</td>
<td>3.5 ± 1.8</td>
<td>5.1 ± 2.1</td>
</tr>
<tr>
<td>Malleolus</td>
<td>15.4 ± 6.5</td>
<td>6.9 ± 3.7</td>
<td>10.3 ± 4.0</td>
</tr>
<tr>
<td>Popliteal fossa</td>
<td>11.7 ± 5.1</td>
<td>5.2 ± 3.0</td>
<td>7.5 ± 2.7</td>
</tr>
</tbody>
</table>

The mean ± SD values of the amplitude of action potential for all four sites evaluated. Mean amplitudes are reduced from baseline (ratio less than 1) in all sites \( P < 0.001 \) for all sites.

Table 2. Electrophysiologic Variations of Latency and Velocity from Baseline

<table>
<thead>
<tr>
<th>Site</th>
<th>Baseline (45 Cases)</th>
<th>5 Weeks (43 Cases)</th>
<th>6 Months (23 Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle</td>
<td>3.8 ± 0.7</td>
<td>3.5 ± 0.5</td>
<td>3.5 ± 0.5</td>
</tr>
<tr>
<td>Fibula</td>
<td>10.4 ± 1.2</td>
<td>10.2 ± 1.2</td>
<td>9.8 ± 1.0</td>
</tr>
<tr>
<td>Malleolus</td>
<td>4.0 ± 0.7</td>
<td>3.7 ± 0.6</td>
<td>3.7 ± 0.9</td>
</tr>
<tr>
<td>Popliteal fossa</td>
<td>11.9 ± 1.4</td>
<td>11.7 ± 1.3</td>
<td>11.6 ± 1.2</td>
</tr>
<tr>
<td>Fibula</td>
<td>48.0 ± 7.4</td>
<td>48.3 ± 3.3</td>
<td>49.3 ± 3.9</td>
</tr>
<tr>
<td>Popliteal fossa</td>
<td>47.0 ± 3.5</td>
<td>46.5 ± 4.0</td>
<td>46.1 ± 2.8</td>
</tr>
</tbody>
</table>

No difference from baseline was observed in any 5-week or 6-month measurement.

Panel data model repeated measure analysis showed no significant effect of the administered local anesthetic dose both on any mean electrophysiologic values and on their time-course in any anatomical site.

Discussion

This prospective, up-and-down biased coin design study demonstrated that the minimum anesthetic volume of ropivacaine 1% needed to achieve a complete sensory-motor nerve block in patients receiving an ultrasound-guided popliteal intraneural solution of ropivacaine 1%.
sciatic nerve block in 90% of patients by an ultrasound-guided popliteal intraneural injection is 6 ml. Unfortunately, such dose reduction, also compared to the higher local anesthetic volumes employed in our previous investigation, did not decrease the risk of having a significant loss of amplitude of action potential, both at 5 and 6 months after surgery.

The findings of our study lead to a number of interpretations. The effectiveness of the technique was already documented by previous reports in which unintentional intraneural injection resulted in a faster onset and a greater success rate if compared to extraneural techniques. Furthermore, a minimum ropivacaine 1% effective volume of only 6 ml determines a significant decreased risk of systemic local anesthetic toxicity. This is worthy of consideration, especially for fragile patients, such as elderly patients or children, or when multiple peripheral nerve blocks are done on the same patient.

By contrast, although half of the studied patients received a total ropivacaine volume of 7 ml or less, no relationship was found between the reduction of amplitude of the action potential and the administered dose. Moreover, in the 26 patients who also received the 6-month evaluation, the recovery of the action potential remained limited.

We have demonstrated in our recent study that a significant reduction of the amplitude of action potential 5 weeks after surgery was observed in every patient who received the ultrasound-guided sciatic nerve block, irrespective of the intra- or extraneural local anesthetic injection. Therefore, we have hypothesized that the axonal nerve damage could be due to the local anesthetic cytotoxicity, or to ischemia caused by high local anesthetic volume deposited around the nerve fascicles. As a consequence, a significant reduction of the local anesthetic volume possible with the intraneural technique could have led to a reduction of the axonal damage. Unfortunately, the findings of the current study seem to reject this hypothesis, leaving many questions open regarding both local anesthetic toxicity on the nerve tissue and the true risks of the intraneural injection.

Although the deleterious effects on nerve fascicles of both mechanical needle injury and the intraneural injection of bupivacaine have been known for more than 30 yr, lasting neurologic dysfunction significant enough to arouse patient complaints is rare, despite unintended intraneural injection being frequent. A recent large experimental animal model showed that intraneural injection of only 2 ml of bupivacaine could lead to mild histopathologic demonstrable inflammation. Unexpectedly, the authors also found the same result in the control group, using a 2 ml of lactated Ringer’s solution. Therefore, they concluded that inflammation may be prevented only by strictly avoiding nerve perforation. In fact, inflammation could be a consequence of mechanical trauma, as also an intraneural hematoma. Unfortunately, the above-mentioned study assessing the electrophysiologic effects of the subparaneural injection showed comparable axonal damage, even in absence of a needle trauma.

Although, the role of needle trauma in the development of an inflammatory response on the nerve fibers has already been investigated, no study has shown the histologic effects of local anesthetic deposited immediately out of the epineurium in sciatic nerve. The relationship between the histologic changes and the axonal nerve damage at the electrophysiologic test has also not been demonstrated.

The nerve axon is a delicate structure, probably more sensitive to ischemia as thought before. In such a structure, the compression due to a few milliliters of fluid (either local anesthetic or other solutions) may be sufficient to develop a mild inflammatory response, as well as lead to a loss of action potential.

The lack of evident clinical neural symptoms in our series suggests that the observed electrophysiologic impairment could run a subclinical course. This is in keeping with the paucity of significant neural adverse effects of local anesthetic reported in current literature, although electrophysiologic axonal damage has been shown to be more frequent, irrespective of the neural target. This latter point adds new knowledge with regards to possible complications after peripheral nerve blocks. The consequences on a long-term outcome, as well as on a compromised peripheral nerve system, as in severe diabetes, need to be addressed in future studies.

Limitations

We routinely applied an ankle tourniquet during surgery. In a previous trial, which reported neurophysiologic examinations of 20 consecutive patients undergoing total knee arthroplasty with a bloodless field without peripheral nerve block, only one patient showed an increased latency. Another eight patients had minor electromyographic alterations 2 months after surgery without significant reduction in the amplitude of action potentials.

The most fearsome event of an intraneural injection is the unintentional intrafascicular injection, since the current ultrasound resolution is not able to distinguish between intra- or extraneural. Considering that in a previous animal study, 4 ml of direct intraneural local anesthetic injection resulted in a neurologic deficit only in cases of high injection pressure (greater than 25 psi; 172 kPa), we adopted injection pressure monitoring in order to maintain a pressure less than 15 psi throughout the procedure. This lower threshold and the absence of pain during injection should help to avoid this worrisome complication.

Finally, in our protocol, the time for the complete sensory and motor block was set at 40 min after local anesthetic injection. One could easily anticipate a higher minimum effective volume in case of a shorter timeframe. Nevertheless, a small increase in such value did not change the clinical information of the study.

Even if the intraneural approach cannot be recommended at the moment, the challenging conclusion of our results, and the available evidence may be that sciatic intraneural local anesthetic injection allows a drastic reduction of the local anesthetic dose, achieving an
effective sensory-motor block and decreasing the risk of systemic toxicity. However, the exact mechanism of action potential reduction still remains unclear. Since an electrophysiologic impairment after peripheral nerve blocks may be much more frequent than thought before, rare major neurologic sequelae are rarely reported, and future studies should directly compare the nerve histologic changes after intra- and extraneural local anesthetic injection in order to assess the relationship between such changes and axonal damage. Moreover, the time course of the observed electrophysiologic impairment should be defined by larger studies extending their follow-up beyond 6 months from anesthesia. Finally, future studies should also clarify the possibly subtle clinical consequences of the axonal damage through focused serial neurologic examinations. All of these observations would contribute to defining how much the physician could close the neural tissue for a safe and effective local anesthetic injection.

Lastly, it is important to observe that these findings are not applicable to other peripheral nerve approaches.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: gianluca.cappelleri@ausl.re.it. Raw data available at: gianluca.cappelleri@ausl.re.it.

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References


Appendix: Neurologic Screening Tool

1) Subjective assessment of sensory function
   A. Do you feel any sensations such as numbness, tingling, or pins in your foot after the anesthesia wore off?
   B. If so, which part of your foot is involved, internal or external?
   C. Is there any numbness in your limb? Please indicate the exact point
   D. Is it mild, moderate, or severe? (Mild = barely noticeable, moderate = definitely noticeable, severe = very preoccupied by the sensation)
   E. When did you first notice it? If it wore off, when did it wear off?

2) Subjective assessment of motor function
   A. Have you noticed any weakness in your limb or foot?
   B. If so, is it mild, moderate, or severe?
   C. Do you have difficulty to move your ankle up and down?
   D. Do you have difficulty to move your feet up and down?