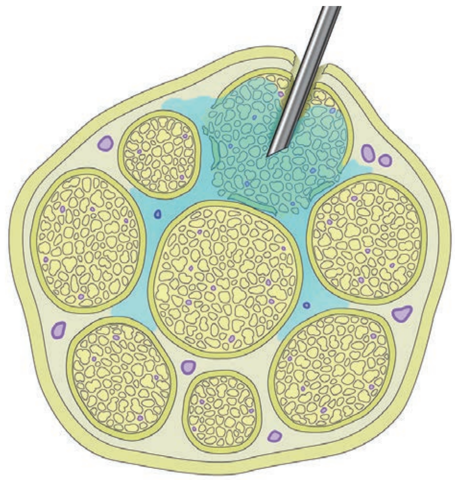
Intraneural Injection

Is the Jury Still Out?

Kamen Vlassakov, M.D., Philipp Lirk, M.D., Ph.D., James P. Rathmell, M.D.



"… the distinction between reversible nerve blockade and reversible nerve injury may be fuzzier than we dare to admit."

A SUCCESSFUL regional anesthetic has to result in a sensory (and often also motor) block that is reliable and completely reversible. From the site of injection all the way to the target nerve's voltage-gated sodium channels, local anesthetics must penetrate several tissue barriers, with the perineurium causing the largest drop in concentration.[1] The closer to the nerve fibers the local anesthetic is injected, in theory, the faster the onset and the more reliable the block.[2] Injecting local anesthetic directly into the nerve rather than onto its outer surface might well speed the onset of the block and increase the success rate. In this issue of ANESTHESIOLOGY, Cappelleri *et al.* test that hypothesis by conducting a dose-ranging study aimed to identify the smallest volume of *intraneural* local anesthetic needed to produce a reliable block of the sciatic nerve in the popliteal fossa.[3]

Conventional wisdom holds that direct intraneural injection is to be avoided, and generations of regional anesthesiologists in many institutions have been taught just that based on science, logic, and instinct. Since the introduction of ultrasound-guided regional anesthesia, both higher success rates and substantial reductions in local anesthetic volumes and doses have been achieved by depositing local anesthetic as precisely as possible,[4] *close to the nerve—not in the nerve.* Yet, we still seem to question whether intraneural injections are safe.

There is already significant evidence that intraneural injections should be avoided. Local anesthetics clearly produce direct chemical nerve injury in a dose-dependent manner.[5,6] Intraneural local anesthetic or saline injection as well as intraneural needle placement alone produce histologic evidence of nerve injury and inflammation in animals.[7,8] In clinical epidemiologic studies, the occurrence of a paresthesia during block placement, indicating that the needle is close enough to cause nerve activation by mechanical distortion, has been associated with an increased likelihood of nerve injury.[9,10] However, when small groups of patients have been followed after unintentional intraneural injections, gross neurologic function was intact several weeks later.[11] From this clinical evidence, it has been suggested that intraneural injection might not be as harmful as previously assumed.[12] This viewpoint is supported by studies showing that inadvertent intraneural injection into the sciatic nerve at the popliteal fossa using only nerve stimulation as guidance is surprisingly frequent, and again no immediate neurologic injury was clinically detectable.[13,14]

How can these viewpoints be reconciled? One potential explanation is that peripheral nerves, in particular the sciatic nerve, have substantial connective tissue,[15] which may serve as safeguard against nerve damage secondary to intraneural needle placement and/or local anesthetic injection. Even after deliberate puncture of the sciatic nerve *ex vivo*, most fascicles remain intact, suggesting nature to be "on our side" as far as safety is concerned.[16] Peripheral nerves also have a remarkable potential to heal. This is supported by the observation that transient neurologic symptoms occur in some patients after peripheral nerve blocks, but these tend to resolve in the large majority of cases.[17] Indeed, it is conceivable that nerve blocks cause minor injury that goes unnoticed by both patient and practitioner relatively frequently. Hence, the distinction between reversible nerve blockade and reversible nerve injury may be fuzzier than we dare to admit. Clearly, not every intraneural injection causes nerve injury that is of concern to or even detectable by the patient (small sample sizes).[11] But by following many patients over

Image: G. Nelson/J. P. Rathmell.

Corresponding article on page 241.

Accepted for publication June 11, 2018. From the Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

 Anesthesiology 2018; 129:221-4

<zdoi;10.1097/ALN.0000000000002352>

time (large sample sizes), it becomes apparent that being too close to or inside the nerve can lead to symptomatic nerve injury in some.[10]

The controversy has been compounded by the continuing discussions over nomenclature. Conventionally, a needle position inside the epineurium is called "intraneural," but in the case of the sciatic nerve, especially in the popliteal fossa, the anatomy is more complex. Here, a connective tissue sheath surrounds the sciatic nerve as it splits into the tibial and the common peroneal nerve (fig. 1). And while the existence of this distinct structure is now unchallenged,[18] its accurate name is still debated (epineural sheath,[19] common epineural sheath, paraneural sheath, circumneural sheath,[20] paraneurium, perineural sheath, gliding apparatus of the nerve, and Vloka sciatic nerve sheath,[21] to name a few), and its role is still being clarified. A needle can thus be placed inside the compound structure we call the sciatic nerve (within the paraneurium), but not inside the tibial or the common peroneal nerve; this is not "intraneural" in the histopathologic sense. The neurostimulation parameters, injection pressure, patient symptoms (pain, paresthesia), and ultrasonographic criteria for intraneural injection have all been characterized, and most practitioners use some combination of these to avoid intraneural injection.[22]

Cappelleri *et al.* contribute another key piece of evidence to the ongoing controversy about the safety of intraneural injection.[3] They performed intentional intraneural injection in 47 patients and performed clinical and neurophysiologic examinations at 5 weeks and 6 months. They report the minimal effective local anesthetic volume of 1% ropivacaine estimated to be effective in 90% of patients (MEV90), as well as functional and neurologic consequences of intraneural injection into the sciatic nerve. The two main findings are a MEV90 of 6.6 ml and a sustained decrease of compound motor action potential amplitude persisting 6 months beyond intraneural nerve block, despite a lack of clinical neurologic deficits. A previous study by the same group comparing subepineural and subparaneural block with 15 ml of ropivacaine 1% found similar decreases in amplitude in both groups at 5 weeks, but normal clinical examination at 6 months.[23]

While the present study[3] sets the standard for investigations into sequelae of regional anesthesia by combining neurophysiology and clinical examinations, some aspects need clarification. The precise site of injection for individual patients in this specific study is not clearly illustrated, but referenced to a previously published study.[23] It remains unclear from the description provided in the present article whether the needle had pierced the paraneurium but not the tibial/common peroneal nerve, or whether it had indeed entered the individual nerves. In addition, only average numbers are given for neurologic parameters. Knowing the needle position, injected volume, and neurologic outcome for each individual patient is important for assessing what might have caused the injury and how profoundly each individual patient was affected. In future trials, true extraneural comparison groups should be included to assess whether the nerve damage observed in the present study is related to the nerve block in general, or to the intraneural injection specifically. Surprisingly, in the present study, pathologic reductions of compound motor action potential amplitude of 40 to 50% at 6 months, similar to those seen at 5 weeks, were not associated with signs of injury on clinical examination.[3]

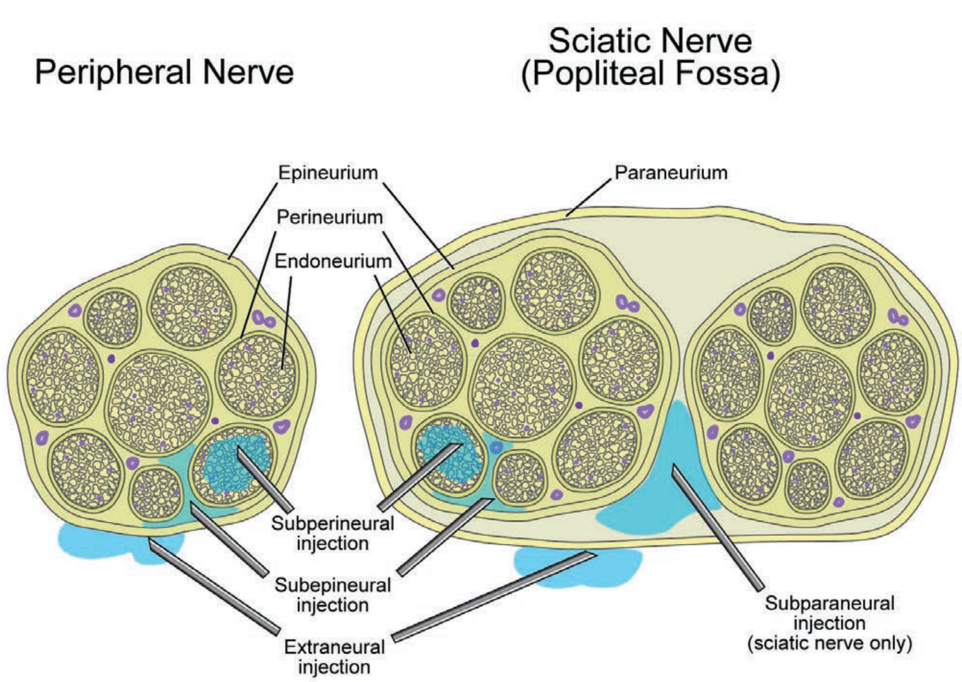


Fig. 1. Anatomy and needle-nerve relationships in peripheral nerves and the sciatic nerve at the popliteal fossa.

Also important is the optimal choice of local anesthetic concentration.[3,23] Ropivacaine 1% is not universally used for conventional peripheral nerve blocks, and such concentration may be considered too high, especially for the direct "intimate" delivery to the unprotected axons as intended in an intraneural injection. The use of 5% lidocaine for spinal anesthesia decades ago and the associated persistent neurologic symptoms underscores the risks of nerve injury associated with concentrated local anesthetic solutions.[24] Satisfactory surgical anesthesia can be readily achieved with 0.5% and 0.75% solutions of ropivacaine.[25]

The rationale given for performing the present study[3] using intraneural injection was to reduce the dose of local anesthetic to minimize the likelihood of local anesthetic systemic toxicity. However, the notion that intraneural injection may actually *increase* the safety of regional anesthesia by decreasing the amount of local anesthetic necessary to achieve a block, is not well founded. First, the volume described here as the MEV90 (6.6 ml)[3] is not clinically different from the effective volume (estimated to be effective in 99% of patients—EV99) of less than 6 ml (or 0.1 ml/mm^2) of mepivacaine reported by Latzke *et al.,* after extraneural subgluteal sciatic nerve block.[26] Second, the use of ultrasound guidance itself has already decreased the incidence of local anesthetic toxicity from 1:1,000 to 1:1,600 patients,[27] and large case series have been reported with zero incidence of serious local anesthetic toxicity.[28] The clinical problem of local anesthetic toxicity is certainly relevant, but perhaps not pressing enough to warrant a move toward intraneural injection. An increase in block efficacy and reliability would be a plausible argument for intraneural injection, but clinical success rates in studies by expert groups are already near ideal,[29] and local anesthetic volumes used in contemporary practice are low enough for rescue blocks to be entirely feasible when needed. The potential additional gain from intraneural injections may not be worth the known risk. Finally, both Cappelleri *et al.*[23] and Choquet *et al.*[2] reported significant numbers of unintended intraneural injections when the objective was to inject subparaneurally, indicating that even for experienced operators armed with state-of-the-art high-definition ultrasound technology, pinpointing the exact needle position within the sciatic nerve is not always straightforward.

We would like to thank Cappelleri *et al.* for their contributions to further clarifying the risks of intraneural injection. We feel that the results are best interpreted as yet more proof that intraneural injections should be avoided and not encouraged as a safer alternative, since even small injected volumes consistently cause long-term electrophysiologic changes indicating nerve injury. The unique morphology of the sciatic nerve and the regenerative capacity of peripheral nerves that allow for many manifestations of peripheral nerve damage to remain subclinical, or fade over time, may be masking the true danger. We respectfully submit that in expert hands, true intraneural injections are unnecessary, and in less qualified hands, they are prohibitively dangerous.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Rathmell: jrathmell@bwh.harvard.edu

References

1. Lirk P, Hollmann MW, Strichartz G: The science of local anesthesia: Basic research, clinical application, and future directions. Anesth Analg 2018; 126:1381–92
2. Choquet O, Noble GB, Abbal B, Morau D, Bringuier S, Capdevila X: Subparaneural *versus* circumferential extraneural injection at the bifurcation level in ultrasound-guided popliteal sciatic nerve blocks: A prospective, randomized, double-blind study. Reg Anesth Pain Med 2014; 39:306–11
3. Cappelleri G, Ambrosoli AL, Gemma M, Cedrati VLE, Bizzarri F, Danelli GF: Intraneural ultrasound-guided sciatic nerve block: Minimum effective volume and electrophysiologic effects. Anesthesiology 2018; 129:241–8
4. Renes SH, van Geffen GJ, Rettig HC, Gielen MJ, Scheffer GJ: Minimum effective volume of local anesthetic for shoulder analgesia by ultrasound-guided block at root C7 with assessment of pulmonary function. Reg Anesth Pain Med 2010; 35:529–34
5. Selander D: Neurotoxicity of local anesthetics: Animal data. Reg Anesth 1993; 18(6 Suppl):461–8
6. Werdehausen R, Fazeli S, Braun S, Hermanns H, Essmann F, Hollmann MW, Bauer I, Stevens MF: Apoptosis induction by different local anaesthetics in a neuroblastoma cell line. Br J Anaesth 2009; 103:711–8
7. Kirchmair L, Strohle M, Loscher WN, Kreutziger J, Voelckel WG, Lirk P: Neurophysiological effects of needle trauma and intraneural injection in a porcine model: a pilot study. Acta Anaesth Scand 2016; 60:393–9
8. Wiesmann T, Steinfeldt T, Exner M, Nimphius W, De Andres J, Wulf H, Schwemmer U: Intraneural injection of a test dose of local anesthetic in peripheral nerves—Does it induce histological changes in nerve tissue? Acta Anaesthesiol Scand 2017; 61:91–8
9. Auroy Y, Benhamou D, Bargues L, Ecoffey C, Falissard B, Mercier FJ, Bouaziz H, Samii K, Mercier F: Major complications of regional anesthesia in France: The SOS Regional Anesthesia Hotline Service. Anesthesiology 2002; 97:1274–80
10. Fredrickson MJ, Kilfoyle DH: Neurological complication analysis of 1000 ultrasound guided peripheral nerve blocks for elective orthopaedic surgery: A prospective study. Anaesthesia 2009; 64:836–44
11. 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
12. Bigeleisen PE, Chelly J: An unsubstantiated condemnation of intraneural injection. Reg Anesth Pain Med 2011; 36:95; author reply 95–7, 98–9
13. Sala Blanch X, López AM, Carazo J, Hadzic A, Carrera A, Pomés J, Valls-Solé J: Intraneural injection during nerve stimulator-guided sciatic nerve block at the popliteal fossa. Br J Anaesth 2009; 102:855–61
14. Sala-Blanch X, López AM, Pomés J, Valls-Sole J, García AI, Hadzic A: No clinical or electrophysiologic evidence of nerve injury after intraneural injection during sciatic popliteal block. Anesthesiology 2011; 115:589–95
15. Moayeri N, Groen GJ: Differences in quantitative architecture of sciatic nerve may explain differences in potential

vulnerability to nerve injury, onset time, and minimum effective anesthetic volume. ANESTHESIOLOGY 2009; 111:1128–34

16. Sala-Blanch X, Ribalta T, Rivas E, Carrera A, Gaspa A, Reina MA, Hadzic A: Structural injury to the human sciatic nerve after intraneural needle insertion. Reg Anesth Pain Med 2009; 34:201–5
17. Brull R, McCartney CJ, Chan VW, El-Beheiry H: Neurological complications after regional anesthesia: Contemporary estimates of risk. Anesth Analg 2007; 104:965–74
18. Andersen HL, Andersen SL, Tranum-Jensen J: Injection inside the paraneural sheath of the sciatic nerve: Direct comparison among ultrasound imaging, macroscopic anatomy, and histologic analysis. Reg Anesth Pain Med 2012; 37:410–4
19. Vloka JD, Hadzić A, Lesser JB, Kitain E, Geatz H, April EW, Thys DM: A common epineural sheath for the nerves in the popliteal fossa and its possible implications for sciatic nerve block. Anesth Analg 1997; 84:387–90
20. Boezaart AP: Microanatomy of the sciatic nerve, The Anatomical Foundations of Regional Anesthesia and Acute Pain Medicine. Edited by Boezaart AP. Bentham eBooks, 2016, pp 229–34
21. Sala-Blanch X, López A, Prats-Galino A: Vloka sciatic nerve sheath: A tribute to a visionary. Reg Anesth Pain Med 2015; 40:174
22. Sala-Blanch X, Vandepitte C, Laur JJ, Horan P, Xu D, Reina MA, Karmakar MK, Clark TB, Hadzic A: A practical review of perineural *versus* intraneural injections: A call for standard nomenclature. Int Anesthesiol Clin 2011; 49:1–12
23. Cappelleri G, Cedrati VL, Fedele LL, Gemma M, Camici L, Loiero M, Gallazzi MB, Cornaggia G: Effects of the intraneural and subparaneural ultrasound-guided popliteal sciatic nerve block: A prospective, randomized, double-blind clinical and electrophysiological comparison. Reg Anesth Pain Med 2016; 41:430–7
24. Drasner K: Lidocaine spinal anesthesia: A vanishing therapeutic index? ANESTHESIOLOGY 1997; 87:469–72
25. Keplinger M, Marhofer P, Marhofer D, Schroegendorfer K, Haslik W, Zeitlinger M, Mayer CV, Kettner SC: Effective local anaesthetic volumes for sciatic nerve blockade: A clinical evaluation of the ED99. Anaesthesia 2015; 70:585–90
26. Latzke D, Marhofer P, Zeitlinger M, Machata A, Neumann F, Lackner E, Kettner SC: Minimal local anaesthetic volumes for sciatic nerve block: Evaluation of ED 99 in volunteers. Br J Anaesth 2010; 104:239–44
27. Barrington MJ, Kluger R: Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. Reg Anesth Pain Med 2013; 38:289–99
28. Sites BD, Taenzer AH, Herrick MD, Gilloon C, Antonakakis J, Richins J, Beach ML: Incidence of local anesthetic systemic toxicity and postoperative neurologic symptoms associated with 12,668 ultrasound-guided nerve blocks: An analysis from a prospective clinical registry. Reg Anesth Pain Med 2012; 37:478–82
29. Kapral S, Krafft P, Eibenberger K, Fitzgerald R, Gosch M, Weinstabl C: Ultrasound-guided supraclavicular approach for regional anesthesia of the brachial plexus. Anesth Analg 1994; 78:507–13