
A Practical Review of Perineural Versus Intraneural Injections: A Call for Standard Nomenclature

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■ Introduction

Before ultrasound-guided regional anesthesia (UGRA), little information was available on the location of the needle necessary to accomplish successful and safe nerve blockade. This lack of information is because localization techniques without ultrasound guidance depend on an indirect assessment of needle location, such as electrical current intensity or patient reports of paresthesias (needle-nerve contact). The introduction of UGRA has allowed for greater precision of needle placement and deposition of local anesthetics (LA), and has helped in our understanding of many aspects of peripheral nerve block (PNB).¹ For instance, although nerve stimulation was thought to decrease the risk of needle-nerve contact, an evoked motor response during low-intensity currents (eg, <0.5 mA; 0.1 msec) with nerve stimulator-guided nerve localization seems to commonly result only after the needle enters the epineurium of the nerve.²⁻⁶

Several recently published clinical reports document the inadvertent intraneural placement of the needle and subsequent injection of LA without clinically apparent neurological injury.⁴⁻⁷ Although these reports represent only small clinical series that were not designed to study the risk of neurological complications, they reported no neurological complications associated with small-volume injections. This may have led to a misconception that intraneural needle injections are safe and may, in fact, be desirable to speed the onset and enhance the reliability of nerve blockade.⁸ However, case reports of neurological injuries suggest that neurological complications with PNB is a complex issue, and continues to occur even with UGRA, where avoiding intraneural insertion of the needle is often a procedural goal.^{9,10}

As nerve architecture varies from nerve to nerve, and within the same nerve at different locations, an understanding of what constitutes needle placement categories as intraneural (within the nerve) versus perineural (adjacent to the nerve) is important for understanding the efficacy and safety of PNBs. The purpose of this invited review is to define a functional anatomic classification of these categories and suggest their clinical implications. In particular, this review aims to provide a “delicate balance” to help anesthesiologists lay out a rational clinical algorithm based on the presently known information and available technology, rather than to provide a “definitive answer” on the subject. The information provided is a synthesis of the available data and clinical and imaging experiences of the undersigned international team of experts.

■ Anatomy of the Peripheral Nerve

Histologic Peripheral Nerve Anatomy

Axons are the essential conducting units of peripheral nerves. Axons are surrounded by supporting connective tissue called the endoneurium

or endoneural network. With their adjacent endoneurium, axons are protected by a dense layer of cells organized into a surrounding membrane called the perineurium. The perineurium creates both a physical and chemical barrier, which translates into a degree of protection for the peripheral nerve fascicles—akin to the blood-brain barrier. When fascicles coalesce together into fascicular bundles, they are embedded in the interfascicular epineurium, and bound by joint perineurium. The fascicles, or groups of fascicles, are embedded in a varying degree of protective fibroadipose tissue called the epineurium. The epineurium is classified into 2 distinct anatomic structures: (i) the interfascicular epineurium, and (ii) the outer epineurium that both houses the peripheral nerve contents and connects the nerve to the neighboring structures (Fig. 1).^{11,12}

It should be noted that multiple terminology can be found in the literature creating confusion with regards to what constitutes intraneural versus perineural needle placement. As an example, outer epineurium is often called epineural tissue or epineural membrane, whereas epineurium within the nerve proper and between the fascicular bundles is referred to as interfascicular epineurium. To simplify, we will adhere

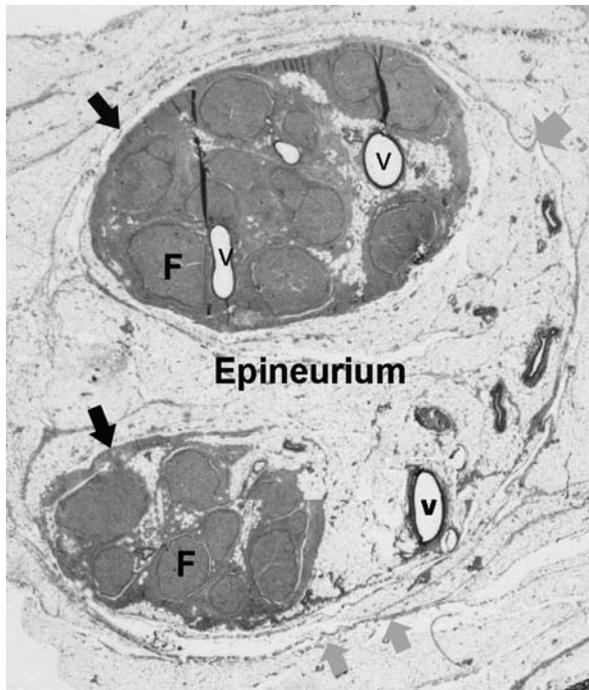


Figure 1. Histologic anatomy of the peripheral nerve. Fascicles are grouped into fascicular bundles and protected by perineurium. A large amount of epineurium is seen within outer epineurium (gray arrows). Black arrows indicates perineurium; F, nerve fascicles; V, blood vessels.

to the terms interfascicular epineurium and outer epineurium. Most importantly, an injection that occurs outside the outer epineurium will be referred to as perineural (adjacent to the outer epineurium), whereas an injection within outer epineurium (under the epineural membrane) will be considered intraneural.

As will be discussed, an intraneural injection can occur in 2 functionally and distinctly different locations, under the outer epineurium and (i) within the interfascicular epineurium (without breaching the fascicle's perineurium) or (ii) within fascicles or fascicular bundles (indeed breaching the perineurium).

The interstitial fluid inside the endoneurium in the brachial plexus roots has been demonstrated to consist of cerebrospinal fluid with retrograde communication to the spinal cord. The roots are also surrounded by a dural sleeve (connected to the dura mater), whereas fascicles within the nerve roots are extensions of the spinal nerve. Practical implications of the latter feature is that injection within a nerve root can result in a syrinx, epidural anesthesia, or spinal anesthesia.^{13,14}

Functional Anatomy of the Peripheral Nerve

From the functional anatomy standpoint with respect to UGRA, peripheral nerves consist of 2 distinctly different parts: the epineurium or connective tissue of the nerve, and the conducting (neurologically functional) elements of the nerve fascicles, often organized into bundles of fascicles. Peripheral nerves and plexuses have varying proportions of epineurium and the number of fascicles and/or fascicular bundles. In general, fascicles comprise between 20% and 70% of the cross-sectional surface of a peripheral nerve.¹¹ Different fascicular patterns also exist at various cross-sectional levels, even within one single nerve. The number and size of the fascicles are more numerous in areas where nerves traverse mobile areas, such as in the vicinity of the joints.

Multiple elaborate interconnections exist among the fascicles throughout the path of the peripheral nerve on its journey from the neuraxis to the periphery. Fascicles divide and regroup, interconnect, and form new groups, clusters, divisions, bridges, and other elaborate organizational formations called intraneural plexuses. Elaborate patterns occur, particularly when the rami separate or when the nerves divide or diverge. Along their path toward distal locations, peripheral nerves are often accompanied by blood vessels and held together by loose, fibrous tissue organized into neurovascular sheaths.

At other times, nerves pass through, underneath, or between the muscle fasciae. Various tissues which surround peripheral nerves function as “nerve sheaths,” and serve as (i) a conduit for the injected LA, (ii) a path allowing for nerve gliding, and (iii) a layer of protection against nerve trauma. These tissue sheaths should not be confused with

outer epineurium, a thickened outer section of epineurium that connects the nerve to the neighboring structures.

From a hydrodynamic point of view, the various tissues that comprise a peripheral nerve can be also divided into the loose, high-compliance, expansible connective tissue-epineurium and the low-compliance, disruptable fascicles and fascicular bundles, densely packed within the perineurium. The anatomic differences between connective tissue and fascicles or fascicular bundles serve as a logical explanation as to why an injection into the latter requires more force (pressure) to initiate an injection, when compared with injecting into the loose connective tissue-epineurium.^{14,15}

■ Classification of Intraneural Injections

As the location, mechanics, and chemistry of the injection within a nerve all determine the likelihood of complications, the functional classification of intraneural injections is of utmost relevance in clinical practice. Table 1 outlines the possible microanatomic sites of LA deposition during PNBs. The following findings, when seen during ultrasound-guided PNBs, are considered signs of an intraneural injection (Fig. 2).³⁻⁶

- Visualization of the needle inside the nerve (within outer epineurium) at the time of injection
- Increase in nerve diameter and cross-sectional area of the nerve by $\geq 15\%$
- Separation of the fascicles and/or fascicular bundles by the injectate
- Diffusion of the LA within epineurium in a proximal and distal direction

Paradoxically, visualization of an intraneurally placed needle during UGRA may be the least sensitive sign of an intraneural injection, because it is easily missed on ultrasound if the operator is not very facile or vigilant.¹⁶ High-resolution ultrasound can differentiate injection outside the outer epineurium from the injection into the epineurium, whereas very high-resolution ultrasound can differentiate the fascicle in superficial nerves. However, reliable imaging of peripheral nerves and their anatomic components requires significant expertise, which may not be available consistently.¹⁶

■ Ultrasonographic Signs of an Intraneural Injection

As the outer epineurium is anatomically a part of a peripheral nerve, an intraneural injection can be defined as an injection that occurs anywhere within the epineurium. However, as the consequences of a

Table 1. Classification of the Peripheral Nerve Block Injections According to the Location of the Injectate

	Intrafascicular Injection	Injection Into Interfascicular Epineurium	Injection Under Outer Epineurium	Perineural Injection
Frequency	Very rare	Uncommon	Frequent	Frequent
Paresthesia*	Paresthesia common but not always present in unpremedicated patients*	Paresthesia common but not always present in unpremedicated patients	Occasional paresthesia or general discomfort on injection	Occasional paresthesia or general discomfort on injection
Evoked motor response with nerve stimulation (0.1 msec)	Often present with $\leq 0.2\text{--}0.3$ Ma	Often present with <1.0 mA	May be absent even with current intensity up to 1.5 mA	May be absent even with current intensity up to 1.5 mA
Injection pressure	High opening pressure (≥ 15 psi), initially; the pressure rapidly declines upon needle dislodgment or perineural rupture	Normal opening pressure (≤ 15 psi), may increase during the injection	Normal opening pressure (≤ 15 psi), the pressure remains constant throughout injection	Normal opening pressure (≤ 15 psi), the pressure remains constant throughout injection
Patient symptoms [†]	Pain or paresthesia common	Paresthesia, sensation of numbness, cold or warm temperatures	Often asymptomatic	Often asymptomatic
Block onset	Rapid	Rapid	Normal	Slow, block may fail or be partial
Risk of nerve injury	High	Low	Very low	No risk

*Unpredictable/absent with multiple injections.

†Unpredictable/absent with multiple injections.

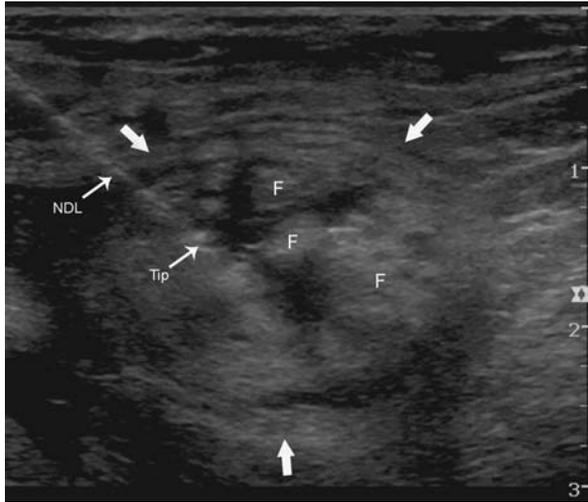


Figure 2. *Ultrasound image of intraneural needle placement. The needle is seen within the epineurium of the popliteal sciatic nerve. Fascicular bundles are being separated by the injection of the local anesthetic. NDL indicates needle; Tip, tip of the needle; F, nerve fascicles; Arrows, outer epineurium.*

needle insertion within the connective tissue stroma (epineurium) of the nerve versus its fascicles are starkly different, the designation of all intraepineural injections as “intraneural” fails to recognize the differences in the risk of neurological injury between the (two).^{4,15,17} As unintended intraneural injections within the nerve structures seem to be a common occurrence with some nerve blocks, familiarity with the classification of the various injection patterns should help to specify the needle tip location more accurately.

An intraneural injection that occurs within fascicles (with consequent disruption of the perineum, its contents and/or feeding blood vessels) is obviously the least desired and most hazardous location. However, an intraneural injection inside the epineurium but outside of the fascicles seems to represent an acceptable risk/effectiveness ratio for rapid onset, successful sciatic popliteal block.^{4,5} Reports of intraneural injections for the sciatic nerve block in the popliteal fossa to date have not led to neurological complications in the absence of motor response to low-current nerve stimulation and abnormally high resistance to injection. It is assumed that the intraneural injections in these reports occurred within epineurium but outside of the fascicles. However, as no clinically applicable imaging technique has the ability to detect this delicate balance, an intentional intraneural injection with other peripheral nerve blocks cannot be recommended as safe or acceptable practice. This is particularly important if intraneural injection is performed without risk-reduction modalities (avoidance of high resistance to

injection, motor response at ≤ 0.2 to 0.3 mA) to reduce likelihood of intrafascicular injection or hydraulic disruption of any fascicle architecture.

■ **Intraneural Needle Insertion, Injection, and Risk of Neurological Injury**

The neurological consequences of an intraneural needle insertion and injection of LA depend on many factors, such as the design of the needle tip, injection force, and the chemical structure and concentration of the injectate. However, the anatomic specifics of a given nerve and how its organization can protect it against external injury may be the most significant factor that determines the likelihood of injury. In addition, preexisting pathology of the peripheral nerve also contributes to the risk of postblock neurological symptoms.

The most important anatomic factor that determines the vulnerability of a given nerve to an intraneural needle insertion or injection of LA is probably (i) the ratio of connective (epineural) tissue to axonal tissue (fascicles), and (ii) the size of nerve fascicles or fascicular bundles. The lesser quantity of connective tissue, and the larger the fascicles (eg, nerve roots, larger peripheral nerves), the higher the chances are that an advancing needle can enter the fascicles. The mechanisms of injection injury include (i) direct needle injury, and (ii) intraneural hydraulic distention (injection) of the nerve and disruption of the communication among fascicles (interfascicular plexus) and nutrient vessels. Finally, the anatomic organization of the nerve vasculature (vasa nervorum) also plays a role; vasa nervorum injury can lead to an intraneural hematoma and potential nerve ischemia from blood flow disruption to a watershed area (as occurs in the brain and spinal cord). Pressure of the intraneurally injected LA may also add to the potential for ischemia by compression of capillaries and venules. Direct chemical toxicity from the LA itself, or additives such as epinephrine, is also enhanced in the presence of a mechanical trauma to the nerve fascicles and disruption of the perineurium. Perineural analgesics (eg, clonidine, buprenorphine, low-dose dexamethasone) injected without LA warrant additional research to determine neurotoxicity in the setting of an intrafascicular injection, as these adjuvants have not been reported to result in neuronal cytotoxicity when administered in clinically used concentrations.¹⁸

■ **Intraneural Injections in Patients**

The absence of neurological injury with intraneural injections during sciatic popliteal block is at apparent odds with conventional thinking that intraneural injection invariably leads to nerve injury.^{19–23}

However, the physical location of the needle insertion, injection, and magnitude of the hydraulic forces used to inject are the key factors that determine whether or not neurological injury will result from an intraneural injection.^{17,24}

The low incidence of complications after intraneural injections with sciatic popliteal block is likely due to the anatomic characteristics of the sciatic nerve within the popliteal fossa, where epineurium comprises the bulk of the nerve. In other words, as connective tissue of the sciatic nerve comprises up to 80% of the cross-sectional area of the sciatic nerve at this level, the needle trajectory favors the path of lesser resistance through epineurium, rather than through more densely packed fascicles.^{23–25}

Studies in animal models suggest that low-pressure injection for sciatic nerve block indicates perineural or interfascicular, rather than intrafascicular injection.^{14,26} In patients, resistance to injection was reported as “normal” in all studies with intraneural injections that resulted in no neurological complications.^{19,21} In contrast, motor response during low current-intensity nerve stimulation, high injection pressure, and pain on injection were simultaneously present in several instances with suspected intraneural intrafascicular needle insertion.^{5,6} As none of the monitoring methods may be fail-safe with regards to causing nerve injury, their use in combination is suggested as a routine to help reduce the risk of an intraneural-intrafascicular injection. Concordant documentation is also important for assistance in understanding the factors involved with nerve injury associated with regional anesthesia when it occurs.

■ Practical Considerations and Current Recommendations

As an intraneural injection is much more likely to occur in the nonconducting connective tissue elements of the peripheral nerve (interfascicular epineurium) rather than into the fascicles,²⁴ it is not surprising that neurological injury is uncommon during PNBs. In fact, it seems that the long-established practice of low current-intensity nerve stimulator guidance during PNBs often results in intraneural but extrafascicular placement of the needle and injection.^{4–7,27} This not surprising, as a motor response to nerve stimulation at low-current intensities (0.3 to 0.5 mA) can be accomplished only when the needle tip is placed within the nerve or pressed against the outer epineurium.^{5,6}

The absence of neurological complications reported in a recent small series, however, should not be mistakenly interpreted to justify the indiscriminate practice of intraneural injection in all PNB models. On the basis of available information and collective clinical experience, injection within epineurium of the popliteal sciatic nerve or within tissue

sheaths (space) that envelop major plexuses (eg, brachial plexus) are often done, and is considered a common and acceptable practice.^{4,5,23,24} However, intraneural injection with other peripheral nerves may be associated with an unacceptable risk of complications, and cannot be recommended. This is because most peripheral these nerves have a greater nerve-to-connective tissue ratio, and less defined outer epineurium, making such nerves more prone to disruptive injury to the fascicles. The smaller proportion of the connective tissue in these nerves also allows perineural injections to be effective even with small volumes of LA, making intentional intraneural injections unnecessary altogether.^{28,29}

■ **Summary**

Intraneural but extrafascicular injection of LA is a common occurrence with low-current intensity nerve stimulator-guided popliteal sciatic nerve blocks. Such injections seem to be associated with high success rate and low risk of neurological injury when the motor response is not present at $\leq 0.2\text{-}0.3\text{ mA}$ (0.1 msec), injection pressure is low ($\leq 15\text{ psi}$), and/or the patient is asymptomatic. Therefore, based on available data, it may be suggested that the goal of ultrasound-guided blocks of the brachial plexus and popliteal sciatic nerve should be similar to that of nerve stimulation—*injection within the outer epineurium or tissue space (sheath), but outside of the fascicles or fascicular bundles.*

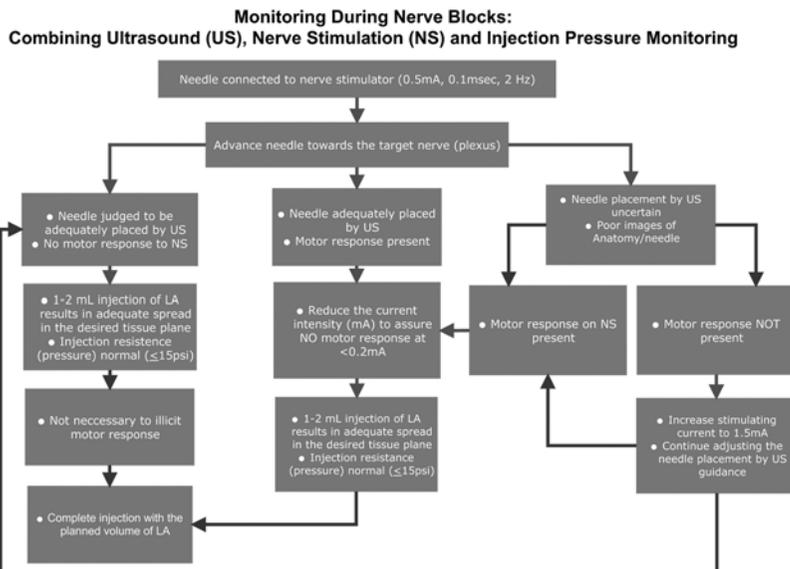


Figure 3. A flowchart with suggested monitoring methods to avoid an intrafascicular injection.

By contrast, no data exist to suggest that injections into nerve roots (including interscalene blocks) or intraneural injections with distal peripheral nerves are equally safe, and therefore they cannot be recommended as safe practice.

As none of the methods of nerve localization are fail-safe, a multimodal combination of needle tip location monitoring by ultrasound, electrostimulation, and assessment of resistance to injection is recommended. To decrease the risk of intrafascicular injection, LA should not be injected when the needle is inserted into fascicles or roots of a nerve plexus, motor response is present with low-current nerve stimulation, or when pain or high resistance to injection (≤ 15 psi) are present (Fig. 3).

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