Pathophysiology of Peripheral Nerve Injury During Regional Anesthesia

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Background and Objectives: Despite attention to technical details in performance of regional anesthetics, damage to nerves continues to be a concern. Understanding of pathophysiological mechanisms may aid in decreasing the incidence and severity of such injuries.

Methods: Studies from both clinical and basic science perspective are reviewed.

Results: Exposure of peripheral nerves to local anesthetics may result in axonal damage, particularly if the solution is injected intrafascicularly, if the concentration is high, and if duration of exposure is prolonged. Disruption of numerous cellular functions may contribute to neuronal damage by local anesthetics, but elevated intracellular calcium levels may play a central role. Needle penetration of a nerve results in minimal lasting damage unless this is combined with local anesthetic administration within the nerve fascicle. Direct compression by a pronged tourniquet application may damage axons particularly of large myelinated fibers. Ischemia may also contribute to neuronal injury in proportion to the duration of blood flow interruption.

Conclusions: The relative importance of these pathogenic factors in cases of nerve injury after regional anesthesia is not resolved. *Reg Anesth Pain Med 2008;33:435-441.*

Key Words: Nerve injury, Neuropathy, Regional anesthesia, Local anesthetics.

Although the great majority of peripheral nerve block anesthetics are followed by complete return to normal nerve activity, a small number result in persisting deficits of motor or sensory performance, or in the generation of pain. This may not be considered too surprising because the purpose of nerves as generators of motion and sensation equips them to reveal imperfections in their function with exquisite sensitivity. Furthermore, local anesthetics are drugs with diverse actions, and are applied in formidable concentrations during nerve block. For instance, injection of 1.5% lidocaine exposes the neural tissue to a 64 mM concentration, whereas medications given by means other than regional anesthesia arrive at their target in micromolar or nanomolar concentrations. Finally, we direct sharp devices into close proximity with the nerves in order to deliver these drugs, thereby risking mechanical injury. General aspects of the pathogenic processes associated with nerve block are introduced in the subsequent sections.

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Toxicity of Injected Solution

Local anesthetics produce a variety of cytotoxic effects in cell cultures, including inhibition of cell growth, motility, and survival, and may also produce morphologic changes.[1] The extent of these effects is proportionate to the duration that the cells are exposed to the local anesthetic solution and occur using local anesthetic concentrations in the range used clinically. Within this range, the cytotoxic changes are greater as concentrations increase. Relevant to the clinical setting, the exact site of the local anesthetic deposition plays a critical role in determining the pathogenic potential. Normally, the internal milieu of the nerve fascicle is maintained by barriers in the perineurium, which regulates entry of substances from adjacent tissues, and in the blood vessel endothelium, which regulates entry from the vascular compartment. After application of local anesthetics outside the perineurium that delimits a nerve fascicle, the regulatory function of the perineurial and endothelial blood-nerve barrier is only minimally compromised. The normally hypertonic endoneural fluid that permeates between the neuronal fibers within the fascicle becomes hypotonic, with the accumulation of edema,

increased perineural permeability, and increased fluid pressures within the fascicles.[2] Inflammatory changes as well as myelin and Schwann cell injury have been identified.[2-4]

High concentrations of extrafascicular anesthetics produce axonal injury independent of edema formation and elevated endoneurial fluid pressure.[5] Ester local anesthetics in comparison to amides have been said to be somewhat more prone to producing these changes,[3] although this is not supported by more recent investigation.[6] As with the effects of local anesthetics in cell cultures, the duration of exposure and concentration of local anesthetic determines the degree and incidence of local anesthetic-induced residual paralysis.[7-9] The importance of these changes after extrafascicular injections in contributing to clinical cases of nerve injury has not been determined, but it is prudent to use only the minimum necessary local anesthetic concentrations. Because small fiber neurons are more sensitive to chemical damage, the manifestations of local anesthetic nerve damage would include spontaneous paresthesias, and deficits in pain and temperature perception, but not loss of motor, touch, or proprioceptive function.[10]

Topical application of local anesthetics decreases blood flow in nerves,[11,12] which may either cause injury directly by ischemia, or potentiate direct cytotoxic effects. As with other toxic effects, local anesthetic vasoconstriction is related to the concentration of the drug.[13] The mechanisms of these vascular changes may be inhibition of endothelial processes regulating nerve vessel tone.[14]

Injection of local anesthetic within a nerve fascicle is clearly neurotoxic. Although axonal degeneration and a damaged blood-nerve barrier are inconsistent[15] or absent[16] after the intrafascicular injection of saline alone, lidocaine 1% and bupivacaine 0.5% injection results in evidence of axonal degeneration and barrier changes. Findings are progressively worse with increasing concentrations of both agents, especially in concentrations above the clinically used range.[15,16] Ester local anesthetics and carbonated lidocaine produce widespread and severe damage of the nerve fibers and the blood-nerve barriers when injected within the fascicles.[16] Together, these various observations lead to the conclusion that the surrounding perineurium plays an important role in protecting the fascicular contents from the cytotoxic effects of local anesthetics.

A large array of studies has revealed disturbances of a diversity of cellular processes that may contribute neuronal damage by local anesthetics, but no single pathway is established as the clinically dominant mechanism. Disruption of cytoplasmic calcium signaling after local anesthetic injection induces elevations in cytoplasmic calcium concentrations through plasmalemmal influx and release of calcium from intracellular stores.[17-19] This leads to neuronal death from activation of kinases and altered energy metabolism. Triggering of apoptosis (programmed cell death) is closely linked to calcium alterations, and has been noted as a delayed finding after local anesthetic injection.[19-21] Mitochondrial damage as a contributing factor is suggested by loss of mitochondrial potential[22] and leakage of cytochrome C,[20,22] but this is not a consistent finding.[21,23] Other studies focus on direct neuronal membrane damage by local anesthetics,[19,24,25] and inhibition of axonal transport has likewise been implicated,[26,27] probably through loss of axonal microtubules.[28] There is also evidence of damage from the generation of oxygen free radicals.[19,29] This diversity of potential pathogenic mechanisms is a testament to the highly nonspecific actions of local anesthetics, through their potency at receptors and pathways other than the intended voltage-gated sodium channels of the cell membrane. For many of these alterations of cellular function, lidocaine has proved to be more potent than other local anesthetics.

In addition to direct actions of local anesthetics on nerves, these agents additionally may alter peripheral nerve blood flow in an agent-specific fashion. Doppler blood flow measurements have shown that lidocaine and bupivacaine decrease neuronal blood flow, whereas tetracaine does not.[13] Interestingly, progressive increase in perineural bupivacaine concentrations show less interference in blood flow, possibly indicating a concurrent dilating effect at higher doses. These data are not entirely conclusive, however, since an alternate technique using entrapment of radiolabeled microspheres shows minimal change in peripheral nerve perfusion with perineural lidocaine injection.[30] Epinephrine may be added to local anesthetic injections to prolong and intensify blockade or to serve as a marker for intravascular injection. While the data are again variable on the ability of customary concentrations of perineural epinephrine to vasoconstrict vascular supply to peripheral nerves,[11,13,30] the combination of epinephrine and local anesthetics clearly has vasoconstrictive effects.[13,30] The addition of epinephrine has been shown to increase the neurotoxicity of bisulfite-containing chloroprocaine solutions,[31] and to increase the axonal degeneration that follows intrafascicular bupivacaine injection.[15,16] However, a contribution of vasoconstriction to peripheral nerve injury has not been proved, and clinical observations suggest that this aspect of toxicity generally plays a minor role.[32] For instance, peripheral nerves are tolerant

to full ischemia from the use of an occlusive tourniquet for hours (see below). Nonetheless, in the context of predisposing factors such as diabetes or peripheral vascular disease, it is prudent to add epinephrine to local anesthetic solutions only if prolongation of the block cannot be achieved by use of a different local anesthetic, or if maximal doses are used and systemic toxicity is possible.

Other adjuvant agents injected together with the local anesthetics for neural blockade may also play a role in causing nerve damage. Chlorocresol, an antimicrobial preservative added to multiuse vials, is neurotoxic and should not be used in nerve block solutions. Sodium bisulfite, an antioxidant added to preparations of chloroprocaine, is neurotoxic intrathecally when combined with low pH solutions.[33,34] Peripheral nerves appear to be more tolerant of the neurotoxic effects of bisulfite.[35]

Mechanical Nerve Damage

Interruption of the perineural tissue around the nerve fascicles breaches the blood-nerve barrier and produces edema of the nerve and herniation of the endoneural contents through the rent. A fascicular injury is more likely to result from nerve contact with sharp beveled needles than with a blunt beveled needle,[36] but if penetration of a fascicle is achieved, a sharp bevelled needle causes greater damage.[37] Needle tip penetration of the nerve may not itself be the cause of clinical complications,[38] and no functional change is evident in humans after the passage of a needle into the ulnar nerve if local anesthetic is not injected intraneurally.[39] No changes in microscopic anatomy or adequacy of diffusion barriers within the nerve follow penetration of the fascicle with a needle and the injection of saline solution,[16] despite the creation of intrafascicular pressures that transiently exceed the nerve capillary perfusion pressure.[40] There has been little experimentation directly examining the mechanism by which needle injury disrupts the biophysics of peripheral nerves. One study has noted, however, that spontaneous activity may result from impalement of a nerve, which results in myelin damage or accumulation of K^+ outside the axonal membrane, producing depolarization.[41] As noted above, the main source of substantial peripheral nerve damage associated with injection techniques is injection of local anesthetic into a fascicle, causing axonal degeneration.

Insertion of a needle toward a nerve often fails to produce evidence of contact with neural structures, manifest as an induced sensory event (paresthesia) or, if current is being passed through the needle, as an induced motor event. While this may be due to bad aim, it is also evident that needles may pass through a nerve without contacting fascicles comprising bundles of axons enclosed in a perineurial sheath. Nerves are not homogeneous unitary struc-

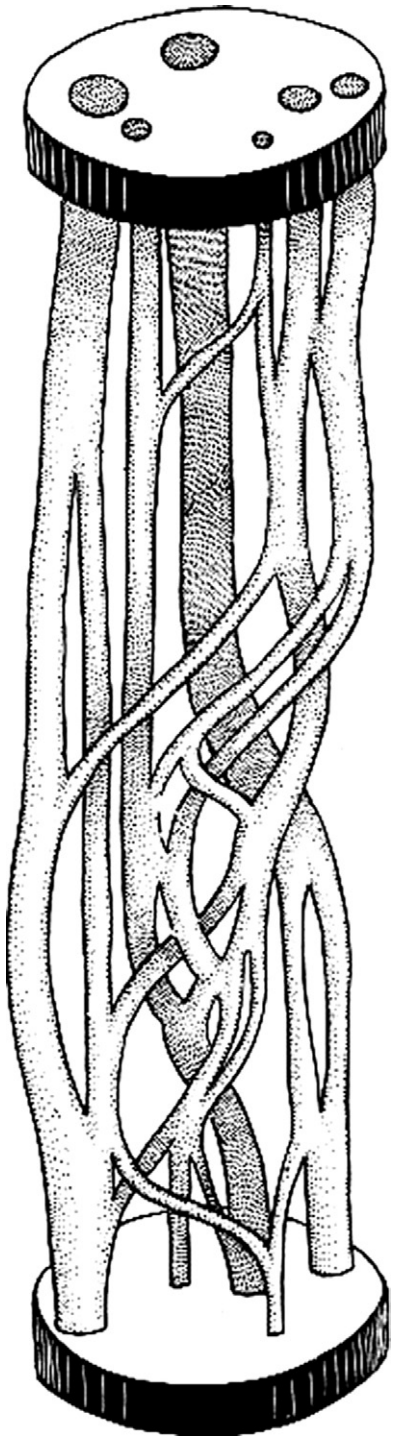

Fig 1. Nerves are not homogeneous unitary structures, but instead the axons are gathered up into fascicles that join and divide repeatedly to form a complicated network inside the bulk of the nerve.[42] (Reprinted with permission).

tures, but instead the axons are gathered up into fascicles that join and divide repeatedly to form a complicated network inside the bulk of the nerve (Fig 1).[42] Fascicles may number in the dozens and occupy as little as a quarter of the cross-sectional area of a peripheral nerve. The rest is taken up by epineurial connective tissue. The surplus path length and dispersion of fascicles inside nerves enhances tensile strength and flexibility, and allows fascicles to slide away from an encroaching needle without damage. The ratio of the area of fascicles to epineural tissue is lowest where nerves cross joints, which are also common sites of neural blockade. It is therefore possible, and even likely, for a needle to enter a nerve without contacting any neuronal tissue and without causing damage.

While it is clear that needle trauma can result in nerve damage, it is uncertain whether block techniques that seek to elicit mechanical contact paresthesias during block needle insertion increase the risk of lasting injury. One study demonstrates that seeking paresthesias may increase postoperative lesions,[43] but a contrasting study[44] shows only a 0.36% rate of neuropathy from brachial plexus blocks done with intentional production of paresthesias. It is unresolved whether using electrical stimulation through the needle reduces the incidence of nerve damage. However, advancement of a needle beyond the depth that produces a motor response by current stimulation will typically cause a mechanical paresthesia by contact,[45] indicating that electrical nerve location works at a somewhat greater distance than mechanical paresthesia.[46] Nonetheless, the stimulator technique cannot guarantee safety, since it has been shown that the needle may enter the nerve without producing a detectable motor response.[47,48]

Using a variety of rodent models of partial nerve injury, research has revealed a vast array of cellular changes following peripheral nerve trauma.[49-51] Injury to the primary sensory neuron causes a shift in membrane channel expression, sensitivity to algogenic substances, neuropeptide production, and activation of intracellular signal transduction, both at the injury site and in the cell soma in the dorsal root ganglion, leading to increased excitability at both sites. Further alterations evolve in the dorsal horn of the spinal cord as the result of neuronal and synaptic plasticity and glial activation. Altered pain processing at even more central sites includes dysregulation of descending modulatory influences. While this large body of research does not duplicate the events associated with mechanical trauma during regional anesthesia, the multitude of changes observed in a model such as nerve ligation makes it likely that comparable complexity is involved in generating lasting pain and paresthesias that may follow injury associated with peripheral nerve block.

Tourniquets may cause nerve damage either by ischemia or mechanical deformation. The initial effect of direct compression of the nerve by the tourniquet is failure of transmission by fast conducting myelinated fibers.[52] Prolonged nerve dysfunction results from damage to the portion of the nerve under the edge of the pneumatic cuff, where the mechanical distortion of the nerve is maximal. Irreversible damage, including substantial distortion of myelin lamellae and axonal shrinkage, may ensue as early as 2 to 4 hours after tourniquet inflation,[53] and predominantly affects large diameter neurons.[54] Thus, the main findings of tourniquet-induced neuropathy are motor loss and diminished touch, vibration, and position sense, with preserved senses of heat, cold, and pain, and the absence of spontaneous paresthesias.[55] One may minimize nerve damage by using wide cuffs and inflation pressures just adequate for arterial occlusion,[56] but periodic deflation of the cuff (even as much as 10 minutes down every hour) has no beneficial effects on the compression trauma.[57] Alternating between the 2 cuffs of a double cuff tourniquet may allow prolonged blood flow interruption with diminished mechanical damage to the nerves, because each site is compressed for only half the total duration.[58]

Ischemia

Failure of blood flow to the primary afferent neuron results in metabolic stress. The earliest response of the peripheral sensory neuron to ischemia is depolarization and generation of spontaneous activity, perceived by the subject as paresthesias. This is followed by blockade of slow conducting myelinated fibers and eventually all neurons,[52] possibly through accumulation of excess intracellular calcium,[59] which accounts for the loss of sensation with initiation of limb ischemia.

Nerve function returns within 6 hours if ischemic times are less than 2 hours,[60] and ischemic periods of up to 6 hours may fail to produce permanent structural changes in nerves.[61] However, more detailed pathological examination after 3 hours of reperfusion shows edema and fiber degeneration that lasts for 1 to 2 weeks, followed by a phase of regeneration lasting 6 weeks.[62] In addition to neuronal damage, oxidative injury associated with ischemia and reperfusion also affects the Schwann cells, initiating apoptosis.[63] Recently, sensory testing of rats 2 to 4 hours after a 3-hour period of hindpaw ischemia demonstrated hypersensitivity to cold and innocuous or nociceptive

mechanical stimuli reminiscent of human hyperalgesic syndromes.[64]

Conclusion

While numerous mechanisms have been delineated that may contribute to nerve damage during the performance of regional anesthesia, the relative importance of local anesthetic and adjuvant toxicity, needle injury, tourniquet compression, and ischemia to the generation of nerve injury is unknown. It is likely that the combined effects of several mechanisms increase the probability of injury. Further uncertainty in discerning the roles of these factors in any particular case is introduced by the growing recognition of genetic variability in the sensitivity of subjects to pharmacologic traumatic processes. It is likely that improved imaging techniques will permit more sophisticated evaluation of neuronal structure and function, and aid in the understanding of the complex processes leading to injury.

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