

Physiological and pharmacologic aspects of peripheral nerve blocks

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Abstract

A successful peripheral nerve block not only involves a proper technique, but also a thorough knowledge and understanding of the physiology of nerve conduction and pharmacology of local anesthetics (LAs). This article focuses on what happens after the block. Pharmacodynamics of LAs, underlying mechanisms of clinically observable phenomena such as differential blockade, tachyphylaxis, C fiber resistance, tonic and phasic blockade and effect of volume and concentration of LAs. Judicious use of additives along with LAs in peripheral nerve blocks can prolong analgesia. An entirely new group of drugs-neurotoxins has shown potential as local anesthetics. Various methods are available now to prolong the duration of peripheral nerve blocks.

Key words: Local anesthesia, nerve blockade, regional anesthesia

Introduction

Peripheral Nerve blocks have gained much popularity in recent times due to widespread acceptance and adoption of ultrasound guided techniques. Improved success rates with reduced incidence of complications are contributory. However, the knowledge of what happens after the drug is deposited near a nerve requires a thorough understanding of physiology of nerve blockade and pharmacology of local anesthetic (LA) agents. Recent knowledge about structure and function of sodium channel, the primary site of action of LAs has enabled us to understand the mechanism of action of existing LA agents and develop newer agents that are longer acting, more potent and less toxic.

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Anatomical Aspects

The structure of a peripheral nerve reveals individual axons covered by the endoneurium. Inside the axon, several nerve fibers are grouped together as fascicles which in turn are covered with the perineurium. The whole peripheral nerve is encased by the epineurium. Now, the fascicles are not continuous, but they divide every few millimeter and rejoin, thereby distributing the nerve fibers to the adjacent fascicles. The numbers of fascicles increase and their diameter decrease from proximal to distal.^[1]

This complex plexiform topography of nerve fibers is the reason for poor recovery after disruption of the fascicles, as by accidental intraneural injections. Further damage is inflicted because of the hampering of blood supply and axonal transport of various functionally important substances, such as proteins. The perineurium is a tough membrane with several layers consisting of fibroblasts. It forms a formidable barrier to the diffusion of LAs.

Nonneural-neural Tissue Ratio

As the nerve leaves the spinal cord, the density of an epineurium (composed of stroma and connective tissue) decreases, but the total volume increases. Thus, the ratio of nonneural to neural tissue is approximately 1:1 in proximal plexuses, 2:1 in distal plexus and a peripheral nerve might

contain up to 70% of connective tissue.^[2] Clinically, even if a needle enters a peripheral nerve, it might still be inside the connective tissue, not necessarily within the fascicle.^[3] This also explains the longer block onset times for peripheral nerve blocks as opposed to proximal plexus blocks [Figure 1].

Extrinsic and Intrinsic System

Nerves have a dual blood supply. The extrinsic system is located in the epineurium, are nonnutritive and respond to adrenergic stimulation. On the other hand, the intrinsic system located in the perineurium is mainly nutritive and has minimal adrenergic receptors.^[4] They have poorly developed smooth muscles and have limited ability to regulate intrafascicular blood flow.^[5] Peripheral nerves are richly supplied by an extensive vascular network in which the endoneurial capillaries have endothelial “tight junctions,” a peripheral analogy to the “blood-brain barrier.” Autoregulation is notably absent in the blood vessels supplying peripheral nerves.^[6]

Physiology of Nerve Impulse Conduction

The resting membrane potential (RMP) of neuronal membrane is brought about by ionic disequilibria. The membrane is less permeable to Na⁺ as compared to K⁺. It is not due to the size factor of the ions. Na⁺ ions are 30% smaller in diameter than K⁺, yet the membrane of most cells is 20-30 times more permeable to K⁺. This is explained in part by the tendency of ions to be hydrated. As a result, the K⁺ ions which diffuse inside are retained by the negatively charged intracellular proteins; hence they maintain a steep gradient resulting in a negative RMP. The RMP varies across different type of nerve fibers [Figure 2].

Impulse Generation

During an impulse, the Na⁺ conductivity increases and the RMP becomes less negative. At threshold, more voltage gated Na channels (Na_v) opens up and RMP shoots up to positive values. Now Na_v channels close (or inactivated, as discussed subsequently) and K⁺ opens up, helping RMP to return to baseline values. Na⁺ K⁺ ATP-ase restores original ionic gradients by pumping 3 sodium ions out for two potassium ions.

Sodium Channels (Na_v)

It is obvious that Na channels play a vital role in impulse propagation and is the site of action of drugs exhibiting LA actions. Electron microscopic studies reveal the Na_v channel as a bell-shaped transmembrane glycoprotein with

4 domains, D1-D4. Each domain spans the membrane 6 times, s1-s6. The Na_v channel belongs to the superfamily of other transmembrane voltage-gated channels like calcium and potassium channels [Figure 3].

The channels can exist in three states, closed (or resting- below 70 mv) open (above 40 mV) and inactivated. Only the open state can conduct Na ions through them. Specific sites of the Na_v channel for sensing voltage and binding LAs

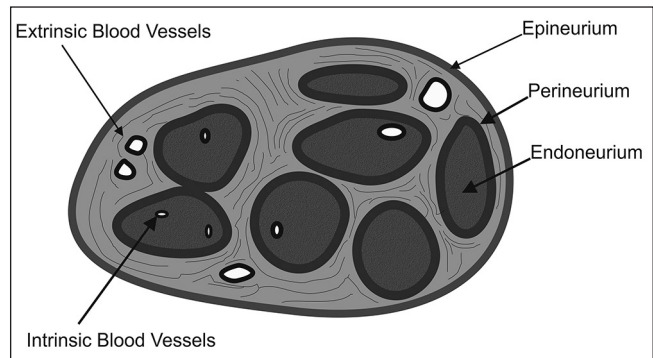


Figure 1: Intraneural arrangement

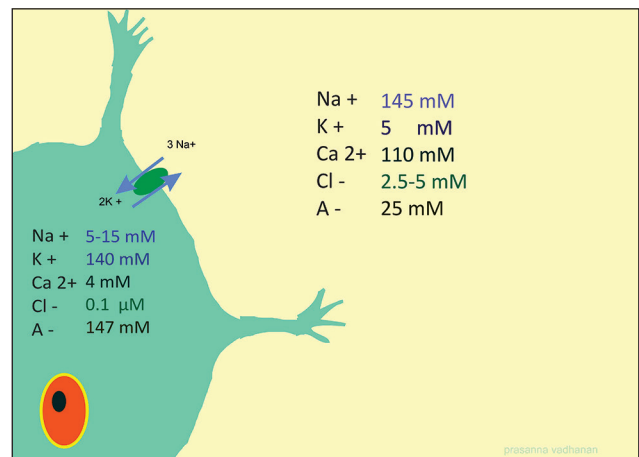


Figure 2: Ion distribution across neuronal membranes

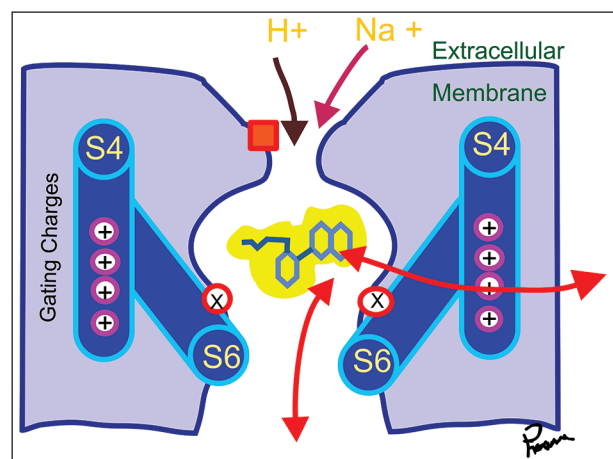


Figure 3: Na_v channel cross-section

have been elucidated (domain IV s6).^[7,8] Point mutations at these sites alter nerve impulse conduction as expected. More recent studies show other residues in D1 S6 and D3-S6 are also critical for LA binding. Overall multiple S6 segments of various domains together form the LA binding site, most prominent being those of D3 and D4.^[9]

Mechanism of Local Anesthetic Action

Local anesthetic binds to specific sites at the inner pore creating an electrostatic field that repels positively charged ions like Na. They don't physically occlude the pores as previously thought.^[10] All LAs are weak bases and exist in ionized and unionized forms, the percentage of which varies depending on their pKa. Three factors determine the clinical differences among the LAs.

1. P_{ka} : Lower the P_{ka} means more unionized drug at physiological pH, hence the onset is faster as the unionized drug diffuses freely across lipid membranes.
2. Protein binding: More protein bound drugs has a longer duration of action, as the protein bound fraction acts like a reservoir.
3. Lipid solubility (expressed as octanol buffer partition coefficient): Determines the potency of the drug.

The Aftermath

What happens after the LA is injected in close proximity to the nerve? Two factors determine the amount of drug that actually reaches the nerve.^[11]

Relative mass

This is the mass of the nerve as opposed to the mass of the tissues surrounding the volume of the LA agent injected. The LA has to reach equilibrium with all these tissues. The tissues include muscles, bone, connective tissue etc., the mass of other tissues is 5-10 times more than the mass of the nerve, hence only a small portion of the drug is taken up by the nerve.

Perineurium

As already mentioned the perineurium forms a formidable barrier for the diffusion of drugs. The rate of diffusion across the perineurium is much slower than the rate at which the drug is absorbed into the systemic circulation. Thicker the perineurium and more vascular the area, lesser the amount of drug that reaches the actual site of action, that is the inner pore of the Na_v channels clustered around the Nodes of Ranvier.

The effective concentration of lignocaine to block 50% maximum obtainable impulses (IC50) is 10 times more if injected percutaneously when compared to the concentration required for equilibrating the nerves when perfused with lignocaine.^[12]

Perception of Conducted Impulses and Effective Blocks

As we have seen Na_v channels are clustered around the nodes of Ranvier. The internodal distance varies according to the nerve fiber size. Furthermore, impulses are known to "jump" across blocked nodes. Hence the concept of minimum length of nerve fiber to be exposed to LA was created. The more the length of the nerve exposed to the LA, more the percentage of impulses blocked.^[13] However, ultrasound guided (USG) techniques have demonstrated even volumes < 1 ml per nerve can cause clinical results.^[14]

It is possible for the block to be successful even if nerve conduction is not blocked completely. This brings the question — Are all conducted impulses perceived? Pinprick sensation, carried by $A\delta$ -nociceptors may be totally absent when conduction remains in C-nociceptors, which are only activated by more intense noxious stimuli. Furthermore, repeated activation of C-nociceptors "sensitizes the receiving neurons in the dorsal horn, setting up a situation where a partial block, reduces impulse activity below the perceived minimal" level at first, later becomes ineffectual as the dorsal horn neurons become sensitized. There is evidence from clinical blocks that afferent activity still arrives at the central nervous system during local anesthesia in patients who are completely pain-free that is, acutely, all sensation can be lost without blocking all impulses.^[15]

C Fiber Resistance

Traditionally myelinated small fibers are most sensitive to LAs and dull visceral pain mediated by unmyelinated C fibers are resistant to LAs. The clinical picture is wherein patient is unresponsive to skin incision but complains of visceral pain as the surgery proceeds. Several mechanisms are proposed for the apparent C fiber resistance. Na_v isoforms and tetrodotoxin (TTX) resistant channels are the most plausible explanation. TTX is a toxin which binds to the Na_v channel from its outside unlike LA, and their use is limited to experimental *in vitro* studies because of their high systemic toxicity. There are a group of Na_v channels which are resistant to TTX^[16] particularly Na_v 1.8.^[17] They require more than the usual concentrations of LA to, block them (3-4 times more).^[18] These channels are predominant in C fibers.

Differential Blockade

The ability of the LA to block sensory impulses while sparing motor and proprioception is called a differential blockade. This is highly desirable where motor function needs to be preserved as in labor analgesia. Several theories were put forth for selective sensory blockade.

They include length of the nerve fiber (in epidural space), frequency of firing (motor fibers fire slower, they need higher concentration of drug) and 'Use dependent blockade' as described later. Currently, a combination of factors are deemed responsible for the differential blockade, that include Na_v isoforms, use dependent blockade and particular LA used.

Use Dependent Blockade-Tonic and Phasic Blockade

Tonic block

All LAs decrease Na current (I_{Na}) as determined by infrequent stimuli — due to binding of LA to resting or closed Na channels. This is called tonic block.

Phasic block

When stimuli become more frequent, further inhibition of I_{Na} binding to open channels occur. This phasic block is lesser in 'neutral' drugs like benzocaine. Phasic block is also seen with volatile agents.

Hille-modulated Receptor Theory and Hydrophilic Pathway

Modulated receptor theory was proposed by Hille^[19] to explain tonic and phasic blockade. It was proposed that the LA receptor site is modulated by state transitions during membrane depolarization. Also the open and inactivated states of voltage-gated Na^+ channels have higher affinities toward LA drugs than that of the resting state. In fact as the Na^+ channel cycles from resting to open and inactivated states during a pulse, the LA receptor site also changes its configuration and thereby displaying higher affinity to LAs.^[20] More recently, Sheets and Hanck^[21] show that stabilizing the S4 segments into the outward configuration locks the sodium channels into the high affinity state, essentially providing proof for the concept behind the modulated receptor hypothesis. Hille's hypothesis has a wide-reaching application in ion channel physiology. Numerous ion channel receptors are modulated by ion channel gating.

LA binds to Na_v channel in inactivated and open states preferentially than closed states. In other words fibers which fire faster are blocked earlier. Motor fibers whose frequency of impulse generation is slower is the last sensory modality to be blocked.

Clinically can it be used to hasten the onset of block by increasing the activity? Isometric hand contraction after interscalene block for shoulder surgery has failed to appreciably hasten the onset of block for shoulder arthroscopy.^[22]

Guarded Receptor Hypothesis

According to the Guarded receptor hypothesis proposed by Starmer *et al.*,^[23] the LA binds to a constant affinity receptor, but the access to it is regulated by channel gates. During an action potential, the gates change conformation in response to the transmembrane potential. Conducting channels have their gates open and expose the binding site to the drugs, whereas the nonconducting channel restrict drug access or trap the drug if it is already bound. The guarded receptor hypothesis is mathematically identical to the Modulated receptor hypothesis, they differ only in the reasons why drug binding is state dependent.

Volume and Concentration for Nerve Blocks

It is well-known that if the volume of LA agents is increased to improve the diffusion of the drug, the density of the block decreases. If the concentration of LA is decreased due to excessive dilution, the steep concentration gradient needed to penetrate the perineurium might not be achieved. Also, sparing of certain sensory modalities and motor function ensues. This has given way to the concept of mean effective volume (MEV) and minimum effective anaesthetic concentration (MEAC).

MEV and MEAC

The minimum effective volume to abolish all sensory modalities is denoted by the term MEV. This varies according to the site of injection. In short, tighter the space, lesser the volume required. For example sciatic nerve block needs lesser volume than popliteal nerve block.

Effect of ultrasound-guidance on MEV

Studies have shown the minimum volume for brachial plexus block is around 32 ml irrespective of the technique used.^[24] However, volumes as low as 1.8 ml and 2 ml has been administered per nerve (radial, ulnar, median and axillary) by USG guided techniques with success.^[25] The total volume in these cases were only around 10 ml. But the surgeries done did not include major bone manipulation, and patients needed opioid supplementations intravenously.

What if the volume is kept constant and concentration decreased? Thicker the nerve, more the concentration required. As already mentioned, a steep concentration gradient is needed to penetrate thicker perineurium. Thus sciatic nerve blocks need more concentration and lesser volume^[26] than popliteal nerve blocks. Hence, blocks where the nerves are 'tightly packed' like sciatic nerve

block depends mainly on concentration, whereas blocks like popliteal nerve block and plexus blocks also depend on sufficient volume.

Mixture of Local Anesthetics

It is a common practice to mix Lignocaine with bupivacaine to hasten the onset and prolong the duration of the block. But studies using this mixture reveal lesser duration, when compared to bupivacaine alone. Also, the plasma levels of the long-acting agent were lower than when given alone.^[27] A mixture of LAs do not provide any significant benefit and cannot be recommended routinely.

Tachyphylaxis

Tachyphylaxis is the clinically observed decrease in drug's effectiveness when given repeatedly. Bromage *et al.* described it as "a form of acute tolerance or tachyphylaxis, develops in response to repeated applications of LAs."^[28] Tachyphylaxis is established when the block is waning, and the noxious stimuli persists.^[29]

The key factor in tachyphylaxis appears to be the timing between subsequent doses. If the second dose is delayed till the effect of the first dose has been completely worn off, tachyphylaxis is definitely possible. But if the time interval between loss of analgesia and reinjection is less than few minutes, tachyphylaxis can be avoided.^[30] However the exact molecular mechanism is still debatable. On the contrary, pseudotachyphylaxis is a term used to denote time-dependent variations in pain or circadian changes in the duration of LA.^[31]

Probable pharmacokinetic mechanisms include: Formation of local edema, an increase in epidural protein concentrations, an alteration in the distribution of the drug or a decrease in perineural pH. All of these mechanisms could result in decreased diffusion of the LAs to their binding sites.^[31,32] In terms of pharmacodynamics, antagonistic effects of nucleotides, increased sodium concentrations, increased afferent input from nociceptors, or receptor down-regulation of the sodium channels have been suggested as possible mechanisms.

More recently, Nitric oxide has been implicated in the development of tachyphylaxis.^[33] N-methyl-D-aspartic acid (NMDA)-antagonists as well as NO-synthase-inhibitors appear to prevent the development of tachyphylaxis. Nitric oxide could be a potential second messenger for NMDA pathways in the spinal cord and involved in spinal mechanisms of hyperalgesia.^[34]

Similar to opioids, changing over to lignocaine from bupivacaine has been shown to be successful in managing tachyphylaxis to the latter drug.^[35]

Extra Axonal Effects of Local Anesthetic

A variety of extra axonal actions of LAs has been identified. They exert potent anti-inflammatory effects, particularly on neutrophil priming reactions.^[36] LAs inhibit local inflammatory response to injury that can sensitize nociceptive receptors and contribute to pain and hyperalgesia. LAs reduce the release of inflammatory mediators from neutrophils, reduce neutrophil adhesion to the endothelium, reduce the formation of free oxygen radicals, and decrease edema formation.^[37] Antithrombotic and neuroprotective actions of intravenous LAs are independent of Na⁺ channel blockade and may account for additional pain relief after surgery.^[37,38]

Lignocaine also has some modulatory effect on NMDA receptors.^[39] LAs have long been known to inhibit the growth of different species in vitro^[39] Bupivacaine was shown to have the most efficient activity against microorganisms.^[40] Intravenous lignocaine has shown to be effective in enhancing bowel function recovery after surgery.^[41] Surgery induced immune alterations are also reduced by perioperative lignocaine.^[39]

Adjuvants

Adrenaline, sodium bicarbonate, clonidine, opioids and several other drugs have been used as additives to improve the duration of the block and to enhance postoperative analgesia.

Adrenaline

Adrenaline is useful as a marker for accidental intravascular injection, decrease systemic absorption, and increase the duration of action. Adrenaline itself has been shown to exhibit analgesic properties in central neuraxial blockade. The duration and intensity of peripheral nerve blocks are consistently enhanced by adrenaline, especially with lignocaine. A pharmacodynamic action that transiently enhances LA and a pharmacokinetic action that prolongs the duration have been proposed.^[42] But such a consistent action has not been observed when adrenaline is added to other LAs like ropivacaine.^[43]

Adrenaline and nerve damage

Concerns arise due to possible neural ischemia due to vasoconstriction mediated by adrenaline. But adrenaline in usual doses does not decrease spinal cord blood flow as long as mean arterial blood pressure is maintained within

autoregulatory limits. (50 mmHg). On the other hand, peripheral nerve blood flow (PNBF) has been shown to be consistently decreased by adrenaline, especially when used in doses more than 2.5 µg/ml. But this is usually inconsequential in healthy adults. The extrinsic system of blood vessels respond to sympathetic stimuli, hence drugs with alpha 1 agonistic action decreases PNBF. In rats Lignocaine decreases PNBF to 81% of control and 1 in 200000 adrenaline decreased it to 55%. Their combination decreased PNBF to 20% of control.^[44] On the other hand, increasing doses of bupivacaine has been shown to cause *lesser* decrease in PNBF.^[45]

Lower plasma levels of LA if administered with adrenaline is supposed to be due to perineural vasoconstriction decreasing the drug clearance, but an opposite effect was observed in muscle arterioles where low concentration of Lignocaine caused vasodilation and higher doses caused vasoconstriction.^[46]

It is clear that Lignocaine and adrenaline combination decreases PNBF upto 20% of baseline but is well tolerated by healthy individuals. This reduction is comparable to pneumatic tourniquets.^[47] However, it is prudent to use lesser concentration of adrenaline in diabetics, peripheral vascular disease patients, geriatric patients etc. Similarly, injured peripheral nerves have been shown to be more susceptible to adrenaline-induced damage. PNBF was transiently increased with low concentrations of adrenaline (2.5 µg/ml) in rat sciatic nerve.^[45] In conclusion, a 1 in 400,000 adrenaline can be preferred in patients with diabetes, arteriosclerosis, and postchemotherapy state etc. Here PNBF is transiently increased, and the duration of block prolongation is only slightly less as compared to 1 in 200,000 adrenaline.^[47]

Some authors even recommend adrenaline as an additive only for blocks done without ultrasound guidance, as a safety measure against accidental intravascular injection.^[48]

Sodium Bicarbonate

Sodium bicarbonate is frequently added in nerve blocks to hasten the onset. It raises the pH of the solution making more of the drug in its base form available that makes it easier to penetrate neural membranes. In peripheral nerve blocks, the results are not uniform. Some studies show a rapid onset of motor block, without affecting other parameters.^[49] The degree and duration of block was decreased when sodium bicarbonate was added with lignocaine plain, but not with adrenaline, even though the onset was hastened.^[50] Currently, there are no evidences to warrant routine use of sodium bicarbonate as an adjunct in peripheral nerve blocks.

Clonidine

The alpha 2 agonist clonidine has been claimed to prolong the analgesia when mixed with LAs. However, alpha 2 receptors are not clearly demonstrated in a normal peripheral nerve. Hyperpolarization activated cation current has been suggested as a possible mechanism, independent of alpha 2 receptors.^[51] clinical studies have consistently demonstrated enhancement of analgesia by adding clonidine to nerve and plexus blocks. In a 2009 meta-analysis, clonidine as an adjuvant in peripheral nerve or plexus block with long and intermediate onset agents do prolong analgesia and motor block by 2 h.^[52] The side-effects like orthostatic hypotension, bradycardia and sedation might affect its usefulness in day care surgeries. Similar analgesic prolongation has been observed with dexmedetomidine also.^[53]

Calcium and Magnesium

Calcium and magnesium has been known to affect nerve impulse conduction. In the presence of LAs, the effects are different. These may be relevant in certain pathological states affecting their levels.

Decreasing calcium concentrations enhanced both tonic and phasic blocks with or without the lignocaine, whereas increasing Ca^{2+} concentrations decreased both tonic and phasic blocks. The proposed mechanism is that Ca^{2+} ions can occupy Na_v and stabilize them in closed states, thereby making them unavailable to LA, as LA affinity of open channels is more than closed channels (modulated receptor hypothesis). The absence of calcium causes an increase in the number of open and inactivated channels, thereby enhancing LA binding.^[54] The clinical projection would be enhanced action of LAs in hypocalcemia and resistance in hypercalcemia.

On the other hand, magnesium has been claimed to potentiate the action of LAs by a different mechanism. Mg potentiates only use-dependent block, which can be explained by the surface charge hypothesis.^[55] This theory suggests the external surface of the nerve membrane has a net negative charge.

Mg^{2+} gets attracted by these charges and interferes with the gating of the Na_v channels. They neutralize the negative charge and alter the local field near the voltage sensing parts of the Na_v channel. The membrane is hyperpolarized making it difficult to reach the threshold hence conduction block ensues. Also Mg^{2+} has been suggested, to delay the closing of Na_v channels and enhance the number of inactivated channels, hence phasic blockade is enhanced.^[54]

More recently magnesium sulfate has been shown to decrease the effects of amide LAs on rat sciatic nerves *in vivo*.^[56] The previous studies demonstrating potentiation of LA by Mg are mainly *in vitro* studies. This apparent discrepancy may be due to study design and species selection. However, magnesium induced vasodilation may be responsible for shortening the block duration observed *in vivo*. Also, magnesium has several other actions including action on NMDA, K⁺ channels etc., the relative contribution of which can vary. Some studies have shown magnesium potentiates and prolongs LA action. This might be due to its action on NMDA receptors. Hence, currently magnesium cannot be recommended as an adjuvant to enhance nerve blocks.

Corticosteroids

Corticosteroids have been shown to specifically inhibit C-fibre transmission.^[57] Dexamethasone has been shown to prolong peripheral nerve and plexus blocks.^[58] The addition of 8 mg of dexamethasone extends the duration of analgesia after interscalene block using ropivacaine or bupivacaine by up to 22 h.^[59] In supraclavicular block with mepivacaine, dexamethasone has been shown to provide analgesia for 5 h.^[60] However concerns about neurotoxicity of perineural dexamethasone has been put forth.^[61]

Opioids

Opioid receptors have been demonstrated in peripheral afferent nerves,^[62,63] especially upregulated after inflammation. A review article examining the efficacy of adding opioids to LAs for brachial plexus blocks considering ten trials involving 413 patients found that six were supportive and four negative. The authors concluded that there was little evidence for any analgesic benefit of using opioid analgesics in brachial plexus block over systemic administration.^[64] But more recently buprenorphine has been shown to prolong analgesia in peripheral nerve and plexus blocks.^[65-67]

To summarize, the only adjuvants that can be considered in peripheral nerve blocks are adrenaline, alpha 2 agonists and possibly buprenorphine.

Future of Local Anesthetics

Newer local anesthetics

The ideal LA would have the following attributes. Long acting, better sensory motor separation and lesser systemic side-effects. To this, longer shelf life, stability, less tissue irritation can also be added.

Future local anesthetics-neurotoxins?

By the current knowledge of Na_v isoforms, it would be ideal for LAs to specifically block neuronal Na channels. The main drawback of currently available LAs is they are nonspecific blockers of Na_v channels. Hence prone for cardiac and neurological side-effects. The affinity of LAs for Na_v channels is quite low. Low affinity clinically translates to more systemic toxicity.

Neurotoxins have gained much attention and there are few agents which show promise. They differ from conventional LAs in these key aspects:

1. Neurotoxins have very high affinity for neuronal Na_v channels as compared to LAs. The dissociation constants are in the range of 10⁻⁹ to 10⁻⁶ mol/L (neurotoxins) as of 10⁻⁴ to 10⁻³ mol/L (LAs).^[68]
2. They are very specific to neuronal Na_v channels, hence cardiac and neurological side effects are low. For example, The affinity of cardiac purkinje fibers to neurotoxin is 200 fold lesser than that of axons.^[69] Hence, cardiac side-effects should be lesser.
3. They are extremely potent, hence need very small doses. At pH 7.2, 2 nM neo-saxitoxin (neo-STX) produces 50% inhibition of compound action potentials in peripheral nerves.^[70] In other words, neo-STX is roughly 1 million fold more potent than lignocaine.
4. The site of action is different. While LAs inhibit sodium channel activity by binding to the inner pore entering from the intracellular side, the toxins bind to the outer pore of the channel.^[71]

Neo-saxitoxin

Saxitoxin is a neurotoxin produced by certain species of dinoflagellates and cyanobacteria. Ingestion of STX (usually through shellfish contaminated by toxic algal blooms) is responsible for the human illness known as paralytic shellfish poisoning. Neo-STX differs from STX by the addition of an oxygen atom wherein the hydrogen (-H) at nitrogen 1 of STX is replaced by a hydroxyl (-OH) group. Neo STX has been shown to be more potent than STX and TTX both *in vitro* and *in vivo*.^[71,72]

In a first ever study to assess the clinical efficacy of neo STX on human volunteers 50 µg of neo-STX was injected subcutaneously on the skin of the calf and sensory parameters were assessed. All sensory modalities (warmth, cold, heat pain, cold pain, touch) were reliably abolished for an average of 3 h. Return to baseline values took as long as 9-12 h.^[73]

Wound infiltration with neo-STX after laparoscopic cholecystectomy provided lower pain scores after 12 hours as

compared to bupivacaine, and adverse events were no more frequent in the neo-STX group.^[74]

Tetrodotoxin

Tetrodotoxin is a naturally occurring neurotoxin of puffer fish. They are specific blockers of Na channel, but differently from LAs. TTX is known to plug the Na⁺ channel from the external side of the permeation pathway adjacent to the narrow selectivity filter region.^[75] When combined with adrenaline, it caused prolonged block of rat sciatic nerve. Considerable systemic toxicity precludes its clinical use.^[76]

Other such toxins which are of interest include ralfinamide, 5 Aryl 2 furfurramides, ziconotide and pro TX II. Among these, ziconotide is a conotoxin (neurotoxic peptides isolated from the venom of the marine cone snail, genus *Conus*.) blocks neuronal calcium channels and operates at the spinal cord level. Prolonged intrathecal administration of ziconotide has been shown to be useful in chronic pain and does not cause addiction or tolerance.^[77]

Prolonging the Block

Analgesia for days to weeks is highly desirable for certain patient sub sects. The following modalities are available.

Liposomes

Liposomes act as reservoirs for drugs. Lysosomal vesicles are sealed sacs containing a lipid bilayer, usually phospholipids. Following a single injection at the time of surgery, they remain in subcutaneous tissues (around the surgical incision) around a neural plexus or in the epidural space for a much longer period of time compared to the free drug.^[78,79] Liposomal bupivacaine has been approved by the US Food and Drug Administration for local infiltration for pain relief after bunionectomy and hemorrhoidectomy.

Microspheres and nanospheres

Micro and nano spheres are prepared from biodegradable synthetic hydrophobic materials such as homo-or copolymers of polylactic and polyglycolic acids. Clinically, in human intercostal blockade studies, dexamethasone added to microcapsules containing bupivacaine showed a longer duration of anesthesia affect compared with microcapsules without dexamethasone.^[80]

Hyaluronic acid-based hydrogels

Hyaluronic acid is a nonimmunogenic naturally occurring mucopolysaccharide, used as a viscous carrier solution to prolong LA action. Cross linked hyaluronic acid has been shown to double the duration of action of bupivacaine.^[81]

Controlled-release local anesthetic matrix

An absorbable, controlled-release, LA delivery system containing 16% (w/w) lignocaine (Xybrex) is capable of providing up to several days of reversible rat sciatic nerve block in a dose-(mass-) dependent fashion.^[82]

Injectable liquid polymers

There are three types of polymers for encapsulation, namely, nondegradable synthetic polymers, natural biodegradables (that degrade to nontoxic products that are completely eliminated from the body), and drug-conjugated polymers (where a drug is attached to water-soluble polymer by a cleavable bond). The use of a 15% bupivacaine lactic acid-co-castor oil copolymer prolonged the *in vivo* effect to 96-h sensory block.^[83]

Conclusion

A fine knowledge of LA action and nerve conduction physiology and sodium channels will help is in administering better blocks. The future of LAs hold much promise with possible development of drugs with prolonged action, low systemic toxicity and better sensory-motor separation. Also, prolonged analgesia is possible by long-acting preparations.

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