Review Article

Review of adjuvants to local anesthetics in peripheral nerve blocks: Current and future trends

ABSTRACT

In recent anesthetic practice, peripheral nerve blocks (PNBs) are used extensively for surgical anesthesia and nonsurgical analgesia. PNBs offer many benefits over other anesthetic techniques in a certain population of patients, and in some specific clinical setting, that may contribute to faster and safer pain relief, increased patient satisfaction, reduced hospital stay, and decreased overall healthcare cost. The technique involves the injection of the anesthetic in the vicinity of a specific nerve or bundle of nerves to block the sensation of pain transmitting to a specific portion of the body. However, the length of analgesia when a single anesthetic is used for PNB may not last long. Therefore, the practice of adding an additional agent called adjuvant has been evolved to prolong the analgesic effect. There are many such adjuvants available that are clinically being used for this purpose imparting great efficacy and safety to the anesthetic process. The adjuvants molecules are generally classified as opioids, alpha-2 agonist, steroids, etc. Most of them are safe to use and show little or no adverse event related to neurotoxicity and tissue damage. Although there is extensive use of such adjuvants in the clinical field, none of the molecules is approved by the FDA and is used as an off-label drug. The risk to benefit ratio must be assessed while using such an agent. This review will try to delineate the basic need of adjuvant in peripheral nerve block and will discuss the advantages and limitations of using different adjuvants and will discuss the future prospect of such application.

Key words: Additive; alpha-2 agonists; analgesia; opioids; peripheral nerve block; steroid

Introduction

Among several methods of surgical anesthesia, peripheral nerve blocks (PNB) are extensively used by anesthetists across the globe. PNBs are used for both perioperative and nonsurgical analgesia. Depending on the patient and clinical situation, PNBs may offer several benefits over neuraxial or general anesthesia (GA) and provide a superior outcome. Some benefits of PNB over GA include superior pain control, reduction in general anesthesia-related adverse events, etc.[1]

Peripheral nerve block generally lasts longer than local anesthesia and involves the injection of the regional anesthetic in the close vicinity of a specific nerve or bundle of nerves to block sensations of pain generated and transmitted from a specific area of the body to another. A nerve block can be useful when it is confined to a specific region of the body suitable for anesthesia. In addition, a nerve block is indicated when analgesia is required across a large surface area of the body where injection with a huge amount of local anesthetic may cause adverse effects affecting the other parts of the

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body or might cause distortion of that region that imparts difficulty to surgery.[2] Although there is no specific guideline for the indication of PNB, the preference may be given to patients who are at high risk of respiratory depression on exposure to general anesthesia, who want to avoid systematic medications and who are unresponsive to oral medications. Importantly, the onset of analgesia is generally faster than other local anesthetic techniques but lasts a few hours only.[3,4]

In-depth knowledge of pain mechanism guided by the peripheral nervous system (PNS) is required to understand the use of local anesthetics for PNB, to decide its dosage, and prolongation of analgesia. On the other hand, physicians must consider the reduction of central and peripherally mediated adverse effects. In general, the local anesthetics work by infiltrating the nerve and blocking the transmission of pain signals to the brain.[5] Such anesthetic effect lasts for a few hours. Therefore, a major issue with such anesthesia is that the patient may suffer moderate to severe postoperative pain once the effect of anesthesia is over. The situation demands a prolongation of such analgesia that can be done by increasing the dose of the anesthetic. However, a higher dose of local anesthetic poses a greater risk of the adverse outcome on the cardiovascular and nervous system. Some major complications of PNB include systemic toxicity related to local anesthetic, hematoma, allergy, infection, and in rare cases, peripheral nerve injury.[6]

To address this issue, several drugs have been clinically tested and proven useful as an adjunct agent to local anesthetics used for PNB or for local infiltration or intra-articular analgesia. These agents are termed as analgesic adjuvants. Adjuvants are injected perineurally in combination with local anesthetics to prolong the anesthesia without elevating the risk of adverse effects. However, the adjuvant itself may exhibit its own side effect that should be taken into consideration.[7]

This review will focus on the rationale, strategies, advantages, and limitations for using different classes of analgesic adjuvants based on current evidence. The article will also discuss the detailed mechanism, dosage, and application of individual adjuvants that are used for optimizing pain control and reducing adverse effects postsurgery under peripheral nerve block.

Aim of using adjuvants with local anesthetics

Looking at the details of the mechanism, it is easily understood that the pain transmission mechanism in the central and peripheral nervous system is highly complex and involves an array of neurotransmitters and several interconnected signaling pathways. A single method or agent may not be able to block the pain transmission by acting on such a complex network.[8]

Therefore, it would be useful to add another drug to local anesthetics that can act fast as a sensory block and prolong the analgesic effect. In turn, it reduces the requirement of a higher dose of anesthetic preventing the patient from adverse effects of anesthetics. Such use of additional agent along with local anesthetics is clinically termed as "multimodal perineural analgesia." This mode of analgesia is advantageous in terms of avoiding potential neurotoxicity and tissue damage caused by a higher dose of local anesthetics.[9]

A myriad of drugs from different classes, such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), α2-agonists, etc., exhibits synergistic effect when applied with local anesthetics during peripheral nerve block. Moreover, these agents show no neurotoxicity at clinically relevant doses. However, they have their associated effects, such as hypotension, sedation, bradycardia, etc.[10]

The application of adjuvants are in PNB is especially relevant in the case of outpatients and daycare surgery patients where prolongation of anesthesia is of greater importance. In addition, the use of adjuvants may eliminate the need for continuous catheter and thus reduce the risk of catheter-mediated infection. However, in clinical practice, adjuvants are being combined to local anesthetic with the objective to prolong analgesia; none of them are approved by the FDA. The use of such agents is completely off-label and depends on the assessment of risk to benefit ration by the anesthesiologists. Buprenorphine, dexmedetomidine, and dexamethasone are few of the adjuvants that have strong evidence-based support in favor of using in combination with local anesthetics in PNBs. Studies have shown that for these agents the benefit to risk ration is in favor of the benefit. Therefore, the debate regarding the advantage and limitation of using such an agent is a continuous topic in a medical fraternity.[11-13]

Classification of adjuvants

Adjuvants are classified according to their mode of action, application, and other parameters. The major categories of adjuvants are as follows:

Opioids

Opioids are by far oldest adjuvant used in the neuraxial block. They act by boasting the antinociception of local anesthetics. The opioids were clinically started being used soon after the discovery of peripheral opioid receptor. It causes hyperpolarization of the afferent sensory neuron

through G protein-coupled receptor mechanism. Following are few widely used opioids as adjuvants and their use in PNB.

Buprenorphine

It is a lipophilic partial opioid receptor agonist that acts by blocking voltage-gated Na^+ channels and thus acts as a local anesthetic. The metabolic intermediate of buprenorphine is norbuprenorphine, which act not only on μ opioid receptors but on κ and δ opioid receptors too. Therefore, it shows potential antihyperalgesic effects.[14]

Studies have shown that applying perineural buprenorphine along with levobupivacaine interscalene in shoulder arthroscopy almost doubles the length of analgesia. It was also found that bupivacaine supraclavicular blocks with perineural buprenorphine is far more superior (analgesia prolonged by 6 h) than bupivacaine blocks with intramuscular buprenorphine. Almost no studies showed any difference in the occurrence of post operative nausea and vomiting (PONV), respiratory depression, etc., as adverse effects in patients receiving opioids with anesthetics and not receiving anesthetics.[15,16]

Morphine

Intrathecal morphine (100–200 μg) and epidural morphine (1–5 mg) have shown good analgesic effect in obstetric, orthopedic surgery, and diverse subsets of the population across varied age groups.[17,18] However, the use of morphine as an adjuvant in PNB exhibits contradictory results in different studies. Some showing prolongation of analgesia and many of them showed no benefit.[19] Therefore, based on the weak evidence of benefit, the use of morphine in PNB is not recommended. Moreover, studies have failed to show any advantage of PNB aided by morphine over intravenous (IV) and intramuscular (IM) routes.[16]

Fentanyl

In comparison to morphine, intrathecal fentanyl (10–25 μg dose) has exhibited a prolonged and higher extent of the sensory block with less adverse effect. However, epidural fentanyl did not show much benefit and occurrence of adverse effects was also higher. Overall, studies do not show much benefit for the use of fentanyl with other local anesthetics, such as ropivacaine or lidocaine plus epinephrine, mepivacaine plus epinephrine (in supraclavicular blocks), ropivacaine (in sciatic/femoral blocks), and lidocaine (interscalene blocks).[20-22]

However, some recent studies were able to establish the effect of prolongation of analgesia by fentanyl. Studies have shown that the combination of fentanyl with 0.25% bupivacaine and epinephrine prolonged the anesthesia by 18 h in paravertebral blocks.[23] Similarly, fentanyl boosted the efficacy of bupivacaine and lidocaine mixture in cervical plexus blocks.[24]

Sufentanyl

A lower dose range (1.5 μg) of sufentanyl is recommended for less adverse effect. However, some studies used 5-μg doses as an adjuvant to achieve better efficacy. Epidural administration of 0.75–1 μg/mL sufentanyl showed excellent potential in alleviating pain in various patient population.[25]

Tramadol

It is a weak opioid that acts by blocking Na^+ and K^+ channels as well as blocks the serotonin and norepinephrine receptors.[26] Tramadol used through intrathecal route at a dose of 10–50 mg has been used in various patients with varying degree of success. On the other hand, the epidural dose of 1–2 mg/kg of tramadol has been used in varied types of surgeries such as obstetric, pediatric abdominal surgeries, and lower abdominal surgeries.[27,28]

However, the use of tramadol as an adjuvant to local anesthetic in PNB has been presented with contradictory results with uncertain safety profile. Therefore, use of this agent is recommended only in postoperative epidural infusion, not as an adjuvant to local anesthetics in peripheral nerve block.[29-31]

Vasoactive agents/alpha-2 agonist

Clonidine

Clonidine is a derivative of imidazole that was used as an adjuvant to local anesthetics used for peripheral nerve blocks for almost 25 years.[32] It is an α2-selective adrenergic agonist that has analgesic, hemodynamic, and sedative effects in the neuraxial spaces and in the periphery.[33] Recent studies have suggested that the clonidine works through hyperpolarization of nucleotide-gated ion channels for *in vivo* elongation of nerve blockade by local anesthetics.[34] A meta-analysis showed that clonidine is capable of extending the duration of nerve blockade by almost 2 h. Moreover, it was also reported that when used with long-acting anesthetics clonidine shows a higher efficacy. Doses ranging from 30 to 300 μg of clonidine hydrochloride prolong the time of request for first analgesic by patient by approximately 2 to 2.5 h. In 70% of the trial studies, a dose of 150 μg of clonidine has been used as an effective dose. Moreover, it was shown that except mepivacaine, clonidine can extend the effect of all other regional anesthetics.[35]

When used with bupivacaine,[36] clonidine was shown to prolong the popliteal fossa nerve blockade but failed to show such an effect when used with 0.5% levobupivacaine.[37] Moreover,

studies have also pointed out that a high dose of clonidine has several systemic side effects including hypotension and bradycardia, and therefore, this should be avoided.

Epinephrine

Epinephrine has been used as an additive to local anesthetics for a very long period. A typical dose of 5–10 μg/mL concentration of epinephrine has been proved to effective in prolonging the action of local anesthetics by preventing the systematic reabsorption of local anesthetics.[10] This vasoconstrictive property also helps in decreasing the systematic toxicity exerted by the local anesthetics that prompts to allow for administration of larger doses in patients.[38] Moreover, it also has an alpha-2 adrenoreceptor mediated antinociceptive property.

In addition to its effect as an adjuvant for local anesthetics, studies have rarely reported undesirable hemodynamic side effects of epinephrine. However, systemic administration of epinephrine has been shown to cause hypertension or tachycardia.[39] Studies have shown that in lower dose epinephrine is effective in patients who have chances of getting hypertension or tachycardia. Dogru *et al.* have reported that a lower dose of epinephrine (25–200 μg/mL) had similar blockade with a more stable hemodynamic condition. They have recommended this additive for patients who undergo surgery of forearm and hand.[40]

In spite of several advantages as an adjuvant used in local anesthetics, studies have shown that epinephrine significantly decreases the nerve blood flow.[41] In addition to this Kroin *et al.* have shown that in diabetic rat models, epinephrine causes increased neurotoxicity making them less useful in patients suffering from diabetes.[42] However, researchers have suggested that epinephrine should be avoided in peripheral nerve blocks as minimal efficacy been reported for epinephrine neural tissues.[43]

Dexmedetomidine

Dexmedetomidine works as α-2 agonist and has analgesic and hypnotic effect. Studies have shown that dexmedetomidine also causes hypotension and bradycardia. It has been shown that a dose of 3 μg of this additive prolongs the motor and sensory blockade effect of intrathecal bupivacaine.[44]

Literature shows that dexmedetomidine can prolong the blockade of the peripheral nerve by 200 min in a dose of 1 μg/kg. In a systematic review and meta-analysis by Abdallah and Brull have shown that dexmedetomidine can further extend the action of long-acting local anesthetics used in spinal blocks. They have also mentioned that in the peripheral application category, dexmedetomidine even some times exceeds the effect of clonidine. Different doses ranging from 1 μg/kg, 30 μg, 100 μg to 0.75 μg/kg of additive were used in different studies. This meta-analysis showed the presence of reversible bradycardia in <10% time.[45]

Till date, no studies on human subjects have shown the presence of neurotoxicity when dexmedetomidine was used. However, no neurotoxicity of dexmedetomidine was reported in spinal anesthesia models of animals.[46]

Anti-inflammatory agents/Steroids

Dexamethasone

Dexamethasone has been used extensively for the past decade as an adjunct agent to local anesthetics in peripheral and neuraxial nerve blocks. Till date, researchers were failed to decipher the exact mechanism of its effect on local anesthetics. However, studies have indicated that it may act on the K+ channels on nociceptive C fibers through the glucocorticoid receptor, thus affecting the activity of the fiber.[47]

In a meta-analysis of placebo-controlled trials, it was mentioned that dexamethasone when administered perineurally can prolong the effect of brachial plexus nerve block local anesthetics (LA) in a significant way. A dose of 4–10 mg of dexamethasone can prolong the effect of long-acting LA from 730 to 1,306 min. For intermediate acting LAs, this difference was 175 min. On the other hand, the motor blockade was prolonged from 664 to 1102 min with a mean difference of 438 min.[11]

Parrington *et al.* have shown that dexamethasone phosphate modestly increased the median pain reporting time from 228 to 332 min compared with placebo in patients undergoing supraclavicular brachial plexus blockade when used with 1.5% mepivacaine hydrochloride solution. However, the time of onset of motor and sensory blockade between the placebo and the subject group was found to be similar.[48]

In contrast to the advantages of dexamethasone as an additive, *in vitro* studies have also shown a risk of dexamethasone-induced peripheral neurotoxicity. In mice model, dexamethasone was reported increased neuronal death.[49]

Verapamil

Verapamil belongs to the calcium channel blocker category that is used as adjuvant to local anesthtics for peripheral nerve block. Verapamil has been used in addition to lignocaine/bupivacaine solution for brachial plexus and exhibited significant result in prolonging the duration of action of local anaesthetic. It lengthens the sensory block by reducing permeability of calcium ion. The use of verapamil in supraclavicular brachial plexus block has been studied extensively and found effective

as an adjuvant to levobupivacaine in terms of faster onset and prolonged analgesia.[50,51]

Ketorolac

Ketorolac is known to prolong the local anesthesia in conjunction with regional anesthetics by inhibiting prostaglandin. The drug belongs to the class of parenteral NSAIDs. Studies have shown that addition of ketorolac to another local anesthetic lidocaine (1.73% lidocaine plus IV ketorolac) improved the length of analgesia in peripheral nerve block at ankle in pediatric surgery.[52] In other study, ketorolac failed to perform better than dexmedetomidine as an adjuvant in infraclavicular brachial plexus block in terms of duration and onset of motor sensory block.[53]

Methylprednisolone

The drug belongs to corticosteroid group and long been used in analgesia. The literature supporting its role as adjuvant to local anesthetic in peripheral nerve block is scanty. However, some studies showed that depo-methylprednisolone as an adjuvant to 0.5% lidocaine showed excellent result in neuropathic pain resulting from nerve injury. The adjuvant and anesthetic were administered at the proximal site of the injury through peripheral nerve block.[54]

Adenosine

Adenosine has been extensively studied for its analgesic effect mediated through the spinal adenosine receptors and minimal neurotoxicity in laboratory animals.[55,56] However, Apan *et al.* have shown when used in combination with the local anesthetics for brachial plexus block, adenosine had no effect on extending the duration of analgesia.[57]

Other additives

Ketamine

Ketamine has been shown to poses the local anesthetic effect and affects nerve conduction significantly. The mechanism of ketamine-induced anesthesia lies in its ability to antagonize the NMDA-receptor.[39] In spite of the several studies that have shown the neuraxial effect of ketamine, very few studies have reported the use of ketamine as a peripheral nerve block agent. In a study by Lee *et al.*, it was reported that the use of 30 mg of ketamine with ropivacaine has no effect on the sensory or motor nerve blockade. In contrast, a high rate of adverse events including hallucination, nausea, and drowsiness was reported in the group that received ketamine as an additive.[58] Thus, ketamine is presently not recommended as an additive in peripheral nerve block.

Midazolam

This additive is mainly used as an additive for neuraxial anesthetics and indirectly acts as a gamma-aminobutyric acid receptor agonist.[59] In animal models, the intrathecal use of midazolam has shown to display neurotoxic effects.[60-62] In addition, use of this additive is not FDA approved and should be avoided as a peripheral nerve block additive.

Neostigmine

Neostigmine increases the analgesic effect by increasing the secretion of acetylcholine at the nerve terminals as it works by an acetylcholinesterase inhibitor. Very few studies that have used neostigmine as a peripheral nerve block and *in vitro* studies have shown that the use of this additive is positively associated with gastrointestinal adverse events. However, a dose of <50 μg has found to have no adverse effects.[63,64] Perineural use of this additive also has been shown to cause neurotoxicity in experimental models.[62] Thus presently, the use of this additive in peripheral nerve block is not recommended.

Magnesium

Magnesium mainly modulates the calcium influx in the cell by acting as an NMDA (*N*-methyl-d-aspartate) antagonist. It was mentioned in the previous studies that the addition of magnesium can prolong the peripheral nerve block when added into bupivacaine,[65,66] prilocaine,[67] and levobupivacaine.[68] In addition, it was also reported that magnesium increases the activity of lidocaine by raising the threshold of A-beta fibers in experimental rat models.[69]

The main advantage of magnesium is that none of these papers have reported adjuvant related adverse events. In a study by Lee *et al.*, nausea was reported in the first 12 h after interscalene nerve block when a higher dose of magnesium was used (200 μg).[65] Similarly, in another animal study, severe nerve damage caused by intrathecal administration of magnesium is reported.[70] These studies have indicated that although magnesium reliably prolongs the nerve block, its administration is not recommended because of less number of clinical trials performed.

Sodium bicarbonate

Usually, sodium bicarbonate is added to any local anesthetic solution for alkalization that facilitates the passage of the chemical across the lipid membrane resulting in increased nerve blockade action.[71] Among some of the local anesthetic, bupivacaine may be alkalized with a lower concentration of sodium bicarbonate to prevent the precipitation of bases present in the solution.[72] Hence, it can be safely concluded that the effect of sodium bicarbonate is unclear and it should be used with only selected few peripheral nerve blocks.

Limitations

Most of the studies and randomized controlled trials reported little or no adverse effect based on the route of

administration of opioids.[9] However, studies investigating the peripheral administration of opioids reported adverse effects, such as pruritus, vomiting, nausea, etc., which are characteristic effects of systemic administration. A study on dogs showed that continuous exposure to sufentanyl, fentanyl, and morphine for 28 days showed no characteristics of neurotoxicity.[73]

In contrary, *in vitro* studies showed the potential neurotoxic effect of opioids. The study showed that morphine enhanced the lidocaine-induced apoptosis in rat astrocytes, whereas sulfentanyl did not show any such effect.[64]

Although in clinical practice buprenorphine is proven as an efficacious and safe adjuvant in PNB, studies in isolated rat primary sensory neurons exhibited considerable cell death on exposure to a high dose of buprenorphine for 24 h.[74] Therefore, further studies elucidating the risk to benefit ratio of opioid use as an adjuvant to local anesthetic in peripheral nerve block are warranted to standardize the dose and duration of clinical application.

As mentioned earlier, the use of adjuvants in peripheral nerve block is not approved by any competent authorities across the world including FDA. However, the use of different classes of adjuvants creeped into clinical practice owing to the compelling reasons, such as prolonging the duration of anesthesia/analgesia, hemodynamic stability, severe pain, and palliative care. In addition, many a times such use is not registered and adverse event such as neurotoxicity is overlooked. Therefore, proper registration of such use with appropriate informed consent from patient after assessing benefit-to-risk ratio may avoid untoward medicolegal implication for clinicians.[75]

Future trends

Ongoing research is in place for agents that can prolong the analgesic effect of local anesthetics without causing any neurotoxicity or deleterious effect. Butyl-amino-benzoate has shown an increased pain relief effect though this is strictly not an additive.[76] Studies have used charged molecules that can produce local anesthetic effects.[77] Similarly, dextrans have also been shown to have a promising result by prolonging the duration of local anesthesia.[78,79] However, no clinical trial has been performed that can prove the efficacy of dextrans as adjuvants.[80]

Conclusion

Use of adjuvants to local anesthetics is a continuously evolving field in anesthesiology where newer agents and techniques are being added to improve the efficacy and safety of analgesia. Among different classes of drugs, opioids remain the most extensively used adjuvant. In addition, alpha-2 receptor antagonists (e.g., dexmedetomidine) are also becoming the adjuvant of choice in anesthesiology practice. With the increasing number of adjuvants in the armamentarium of the clinicians, it has become more important to acquire the knowledge of adverse effect profile, associated life-threatening complications, making the user aware of postapplication monitoring, etc. Future efforts should be directed toward conducting more controlled studies that will be aimed at reducing the perineural doses of local anesthetic, increasing the analgesic effect, and zeroing the adverse effect of the adjuvants.

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Conflicts of interest

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