Chapter

Adjuvant Drugs to Local Anesthetics

Nandita Mehta and Sayyidah Aasima tu Nisa Qazi

Abstract

Local anesthetics have a potential to be used in a wide variety of situations including central neuraxial blocks, peripheral nerve blocks, intravenous, and local infiltration both for surgeries and acute and chronic pain management. Their use can be limited by their duration of action and the dose-dependent adverse effects on the cardiac and central nervous system. Adjuvants are drugs which, when co-administered along with local anesthetic agents, improve the latency of onset and duration of analgesia and counteract disadvantageous effects of local anesthetics. There is a wide armamentarium of adjuvant drugs to choose to be added in neuraxial and peripheral nerve blocks. They can be broadly divided into non-opioids and opioids, with non-opioids being vasoconstrictors, α2-adrenoceptor agonists, anti-inflammatory agents, acetylcholine esterase inhibitors (neostigmine), adenosine, ketorolac, midazolam, magnesium, and sodium bicarbonate and opioids being lipophilic (fentanyl and sufentanil) and hydrophilic (morphine).

Keywords: local anesthetics, adjuvants, neuraxial blocks, peripheral nerve blocks, opioids, neurotoxicity

1. Introduction

Local anesthetics (LA) are widely used in clinical practice for regional anesthesia or analgesia in various locations like central neuraxial blockade, peripheral nerve block, intravenously, and local infiltration. Infiltration with LA around the nerve produces analgesia by interrupting pain signals to the brain. The analgesic effect of a nerve block with LAs lasts only a few hours. Therefore, after surgery patients may suffer from moderate to severe acute pain. The duration of the action of LA can be prolonged by either increasing the dose or administering a continuous infusion of the drug, which can lead to dose-dependent side effects on the cardiovascular system and/or central nervous system (CNS) [1, 2]. The popularity of peripheral nerve blocks for surgical anesthesia as well as for postoperative analgesia has increased significantly due to anesthetists becoming more familiar with ultrasound-guided techniques. While the use of catheters for continuous infusions allows for sustained pain relief during the perioperative period, they can increase the challenges related to patient management, catheter displacement, and the potential for increased infection risk. In the case a long-acting LA or continuous block is used, sensory block is also associated with prolonged motor block in the postoperative period. Prolonged motor blockade in the postoperative period is undesirable as it leads to delayed mobilization of the patient and hence increased risk of complications.

The adjuvant drugs of regional LAs improve the quality and duration of anesthesia and analgesia and patient safety, thus increasing patient satisfaction and comfort [3, 4]. The aim of this chapter is to discuss the past, present, and future trends in the use of adjuvants, as well as their benefits and side effects.

2. Adjuvants drugs

Adjuvants are drugs which, when administered along with LA agents, may improve the latency of onset and duration of analgesia and counteract the undesirable effects associated with large doses of LAs. The use of adjuvant drugs has the potential to improve the efficacy of peripheral and central neuraxial blocks and decrease LA systemic toxicity by chiefly prolonging the duration of sensory block,

Opioids
• Morphine
• Pethidine
• Fentanyl
• Sufentanil
• Hydromorphone
• Buprenorphine
• Diamorphine
• Tramadol
Vasoactive agents
• Epinephrine
• Phenylephrine
Alpha-2 adrenergic agonists
• Clonidine
• Dexmedetomidine
Steroids
• Dexamethasone
Nonsteroidal anti-inflammatory drugs
• Parecoxib
• Lornoxicam
Other agents
• Ketamine
• Midazolam
• Neostigmine
• Droperidol
• Magnesium sulfate
• Sodium bicarbonate
• Potassium chloride
• Adenosine
• Dextran

Table 1.
Classification of adjuvant drugs.

enhancing motor blockade, and limiting the overall dose requirement of LAs. An ideal adjuvant should not only shorten the speed of onset of action of the LA drug but also reduce its dosage along with providing hemodynamic stability, optimal sedation, and minimum adverse effects.

A wide variety of adjuvant drugs have been used for both neuraxial and peripheral nerve blocks (**Table 1**). They can be broadly divided into non-opioids and opioids.

Current research is directed toward a search for agents and techniques which would prolong LA action while limiting its side effects and giving the patient its maximum benefit. These include techniques like the use of charged molecules to produce LA action (tonicaine and n-butyl tetracaine), newer delivery mechanisms for prolonged bioavailability (liposomal, cyclodextrin, and microsphere systems), and the use of other drugs (dextrans, adenosine, neuromuscular blockers) [3, 4].

While the use of LA adjuvants in regional anesthesia [5, 6] is in widespread clinical off-label use and has been subject to multiple clinical trials, we would like to emphasize on the fact that only a few adjuvants have been approved by the Food and Drug Administration (FDA), so absolute caution must be exercised while using these adjuvants.

3. Opioids

Opioids are the most common and the earliest used LA adjuvants. Their use in neuraxial and peripheral nerve blocks has evolved greatly over the last 30 years. It is advisable to use specific opioids, at appropriate doses and routes of administration that result in a primarily spinal site of action rather than a systemic opioid [7]. Afferent noxious stimuli from peripheral tissues converge in the dorsal horn of the spinal cord, where the primary nociceptive neuron synapses with the interneurons and the second-order nociceptive neuron in the spinothalamic tract. Blockade of these opioid receptors by agonists helps to suppress afferent nociceptive input from pain sites by modulating the release of pain-pathway associated peptides [8]. Opioids produce analgesia by mimicking the actions at specific receptors of endogenous opioid peptides. These peptides are beta-endorphin, met-enkephalin, and dynorphin. The three main types of opiate receptors, each with its own subtypes, are mu (μ), delta (δ), and kappa (*κ*) [9]. The most important target for opioids is the μ-receptor (endorphin), and intrathecal opioids appear to selectively modulate C- and A-fibers with minimal impact on dorsal root axons. The enkephalins are the primary endogenous ligands of the delta receptor and are involved with spinal analgesia. Dynorphin is the ligand for the kappa receptor. Activation of the kappa receptor results in segmental spinal analgesia and sedation. Most of the mixed agonist–antagonist opioids like butorphanol bind to the kappa receptor.

The exact mechanism of action of opioids at peripheral nerve is still uncertain. Evidences have begun to support the presence of peripheral opioid receptors [10]. The possible mechanism of prolonged analgesia by peripheral opioid administration could be through direct binding at opioid receptors of dorsal nerve root aided by axonal flow, diffusion through brachial plexus sheath to extradural or subarachnoid space to dorsal horn, and central action after peripheral systemic uptake [11].

3.1 Morphine

The first opioid to be used intrathecally was morphine with the initial clinical study published in 1979 [12]. Morphine being relatively less hydrophobic than other opioids remains in the CSF for a longer time and therefore occupies the rostral receptor sites for a longer duration than other opioids [13]. Consequently, morphine

produces a long-lasting and adequate analgesia with intrathecal use [14]. However, this huge advantage is offset by the increased risk of adverse effects, especially post-operative respiratory depression [15], which remains a particular concern among anesthetists. Intrathecal and epidural morphine are associated with a high incidence of side effects like nausea, vomiting, pruritus, urinary retention, sedation, and delayed respiratory depression [13, 16]. The recommended dose for intrathecal administration is 50–300 μg, while as 2–5 mg of epidural loading dose is considered adequate. The risk of side effects increases exponentially with the increase in the dose [16, 17].

3.2 Pethidine

Pethidine (meperidine) is a lipophilic phenylpiperidine derivate that is 30 times more lipid soluble and 10 times less potent than morphine, leading to a faster onset and a shorter duration of action than morphine. Pethidine possesses some local anesthetic properties (motor and sensory fiber block) which lets it stand out from the rest of the opioid agents. Pethidine is a popular choice for obstetric analgesia used mainly in epidural analgesia during labor. Intrathecal use of pethidine is not recommended. The incidence of nausea, vomiting, and hypotension is more with pethidine than with morphine. Pethidine can be injected as a loading dose of 25–50 mg in the epidural space.

3.3 Fentanyl

In addition to acting on the spinal cord receptors and peripheral receptors, fentanyl is also reported to have a local anesthetic like action, but this requires a very high concentration (50 g/mL) which is not clinically feasible [18]. Fentanyl as an adjuvant to LA causes significant prolongation of duration of analgesia but delays the onset of both sensory and motor blockade compared to LAs alone [19]. The change in pH of the anesthetic solution resulting in slower penetration of nerve membrane by LA is considered to be responsible for this effect [20]. The recommended intrathecal dose is 10–25 μg, and the epidural loading dose is 50–100 μg. Fentanyl as adjuvant does not prolong motor block, so it allows early ambulation, thereby reducing the morbidity. The duration of action is 2–4 h, and the risk of respiratory depression is very low and of short duration [17].

3.4 Sufentanil

A potent agonistic opioid was synthesized in the mid-1970s. A piperidine derivative is 6–10 times more potent than fentanyl, depending on the route of administration; it has been registered for intravenous, epidural, and subarachnoid administration. It is considered to be more lipid soluble than its counterparts, a better μ receptor ligand. It is an extremely potent opioid with a faster onset of action than its counterparts. Its use in clinical practice is limited by its short duration of action and high side effect profile. The recommended intrathecal dose is 2.5–10 μg, and epidural loading dose is 10–50 μg [17].

3.5 Hydromorphone

This opioid has intermediate lipid solubility. Due to its hydrophilicity, epidural hydromorphone can cross the blood-brain barrier faster and provide fast onset and modest duration of action.

3.6 Buprenorphine

Buprenorphine is a highly lipophilic partial opioid receptor agonist. It is also considered to have local-anesthetic-like capacity by blocking voltage-gated sodium channels. Buprenorphine and its metabolite nor-buprenorphine have been shown to act on κ and δ opioid receptors in addition to μ receptors which account for its anti-hyperalgesic effects. The risk of side effects like postoperative nausea and vomiting (PONV) is more with the use of perineural buprenorphine [21].

3.7 Diamorphine

It is a diacetylated analogue of morphine with a potency of approximately 1.5–2 times that of morphine. This leads to a faster onset and slightly shorter duration of action than morphine. It is a lipophilic semi-synthetic opioid and is a prodrug that is converted to its active metabolites (morphine and 6-monoacetyl morphine) by deacetylation in the liver and neural tissues. The recommended intrathecal dose is 300–400 μg, and epidural loading dose is 2–5 mg [17, 22].

3.8 Tramadol

Tramadol is a weak centrally acting opioid. A potency ratio of oral morphine to oral tramadol has been reported to be between 1:4 and 1:10. It has been shown to have Na^+ and K^+ channel blocking properties and can block motor and nociceptive signals similar to that of LAs. The central and peripheral analgesic effects of tramadol have not been fully explained, but it is a selective agonist of μ-receptors. Tramadol also prevents reuptake of noradrenaline and enhances both serotonin and noradrenaline release. The monoaminergic activity of tramadol increases the inhibitory activity of the descending pain pathways, resulting in a suppression of nociceptive transmission at the spinal level [23].

4. Vasoactive agents

Vasoactive drugs are the oldest adjuvants that have been used, although at the beginning their action was attributed more to the fact that their vasoconstrictor effect prolonged the anesthetic and analgesic results of LAs by decreasing the blood flow of the site where they were injected. Adrenaline was the first vasopressor used.

4.1 Epinephrine

Epinephrine has been used along with LA in neuraxial and peripheral nerve blocks since Heinrich Braun first experimented with its use as a "chemical tourniquet" in the early 1900s [24]. Epinephrine potentiates the LA action. The substantia gelatinosa of the dorsal horn of the spinal cord houses alpha-2 adrenoreceptors wherein the epinephrine by its direct action mediates its antinociceptive properties resulting in presynaptic inhibition of transmitter release from Aδ and C fibers. Also its vasoconstrictive properties limit the systemic absorption of LA leading to prolonged duration of action. There are concerns about epinephrine being a potent vasoconstrictive agent can place the blood supply of the spinal cord at risk and may lead to ischemia of the spinal cord leading to permanent damage. Epinephrine is typically administered in doses of 0.2–0.3 mg [25].

4.2 Phenylephrine

Phenylephrine has a mechanism of action similar to that of epinephrine. It has vasoconstrictive abilities, thus limiting the uptake of LA and prolonging their duration of action. Phenylephrine in the dose of 2–5 mg prolongs both lidocaine and tetracaine spinal anesthesia to a similar extent as epinephrine. The use of phenylephrine has declined in popularity because of its association with transient neurologic symptoms (TNS) [26].

5. Alpha-2 adrenergic agonists

Alpha-2 adrenergic receptor agonists have recently been the focus of interest for their sedative, analgesic, perioperative sympatholytic, anesthetic sparing, and hemodynamic stabilizing properties. The central α-2-AR agonists inhibit nociceptive impulses by activating post-junctional α-2-adrenoceptors in the dorsal horn of the spinal cord. These receptors are located on primary afferent terminals (both at peripheral and at spinal endings), on neurons in the superficial lamina of the spinal cord, and within several brainstem nuclei responsible for analgesia. They block the conduction of C- and A-delta fibers and increase potassium conductance, thus intensifying conduction block. They also cause local vasoconstriction, thereby reducing vascular uptake of the LA from around the neural structures and in turn prolonging the duration of action [27–29].

5.1 Clonidine

Clonidine is an imidazole derivative with selective partial agonist properties which inhibit the nociceptive impulses by acting on the post-junctional alpha-2 adrenoreceptors in the dorsal horn of the spinal cord. In neuraxial blocks, it has a local effect leading to decreased sympathetic outflow, while in peripheral nerve blocks it prolongs the duration of analgesia by hyperpolarization of cyclic nucleotide-gated cation channels. Clonidine enhances and prolongs sensory and enhances motor blockade when used along with LA for epidural or peripheral nerve blocks [30]. The alpha-2 adrenergic agonists also enhance analgesia from intraspinal opioids by interactions with both pre- and post-synaptic receptors within the spinal cord.

Although there is no agreement on the doses of intrathecal clonidine [31], the most commonly used doses vary widely. The most recommended dose for intrathecal use is 15–150 μg, with the incidence of adverse effects (bradycardia, sedation, hypotension) increasing with doses above 150 μg. Clonidine can be used via epidural route with a bolus dose of 75–150 μg. In pediatric anesthesia, the use of clonidine (1 μg/kg) as an adjuvant along with LA for caudal blocks doubles the duration of analgesia when compared to LA alone but causes marked sedation [17].

Clonidine has been found to prolong the action of local anesthetics in peripheral blocks in the postoperative period. This effect of clonidine is dose-related. After brachial plexus block with mepivacaine, the minimum doses which significantly prolong analgesia and anesthesia are 0.1 and 0.5 μg/kg, respectively [32].

5.2 Dexmedetomidine

Dexmedetomidine is seven times more selective agonist to alpha-2 receptor than clonidine (seven times more specific for alpha-2 than alpha-1) but has a similar mechanism of blocking hyperpolarization-activated cation channels. When used as an adjuvant to LA for neuraxial block, dexmedetomidine leads to reduced onset

time of sensory and motor block, increased duration of sensory block, and delayed recovery from motor blockade. It leads to prolongation of postoperative analgesia, decreased requirement of additional analgesics, delayed first rescue analgesic, and decreased postoperative shivering. Dose in spinal anesthesia varies from 3 to 15 μg as an adjuvant to LA [33]. For caudal epidural block, 1–2 μg/kg of dexmedetomidine along with bupivacaine can lead to prolonged analgesia without significant side effects [34].

The most common reported adverse effects are bradycardia and hypotension. Bradycardia due to dexmedetomidine is resistant to atropine, and higher doses are needed; although rare, even cardiac arrest can occur.

It has been shown that clonidine and dexmedetomidine administered orally, intramuscularly, and intravenously also prolong the anesthetic effect of intrathecal LA [35–40].

6. Steroids: dexamethasone

Acute inflammation from tissue injury has an important role in surgical pain, and glucocorticoids may be useful for its anti-inflammatory effect. Johansson et al. [41] investigated the corticosteroid effect on the plantar nerve of rats finding that methylprednisolone suppresses transmission in thin unmyelinated C fibers but not in myelinated A-beta fibers. The effect was reversed when the corticosteroid was removed, suggesting a direct action in the membrane.

Dexamethasone-induced prolongation of peripheral nerve blockade following LA injection is commonly attributed to its anti-inflammatory action. It also improves the quality and duration of analgesia over LAs alone. This is thought to be mediated by its capacity to alter the release of inflammatory mediators, reduce ectopic neuronal discharge, and inhibit potassium channel-mediated discharge of nociceptive C fibers [41]. Its action on glucocorticoid receptor is considered to alter the functioning of ion channels and produce acidosis around the nerve cell, thereby reducing the concentration of LA required to produce blockade of signal transmission or trapping the highly ionized bupivacaine molecule into the neuronal cell. Studies using dexamethasone for postoperative pain relief have produced positive results mainly in surgery involving large amounts of tissue trauma. A systematic review and meta-analysis included 1695 patients distributed in 29 controlled clinical trials where dexamethasone 4 and 8 mg perineural was used as adjuvant to LA. These authors found that dexamethasone increased the mean (95% CI) duration of analgesia by 233 (172–295) min when injected with short- or medium-term action LA and by 488 (419–557) min when injected with long-term action LA, $p < 0.00001$ for both. However, these results should be taken with caution due to the great heterogeneity of results, with I2 exceeding 90% for both analysis. Meta-regression did not show an interaction between dose of perineural dexamethasone (4–10 mg) and duration of analgesia ($r2 = 0.02$, $p = 0.54$). There were no differences between 4 and 8 mg dexamethasone on subgroup analysis [42]. After reviewing the current literature, Wiesmann et al. [43] prefer a systemic application mode (intravenously) over a perineural route of dexamethasone administration as a complement to peripheral nerve blocks. A single dose of dexamethasone could be a useful complement to prolong peripheral nerve blocks. In a randomized controlled triple-blind crossover study in 24 male volunteers, the authors used ultrasound-guided ulnar nerve blocks (ropivacaine 0.75% wt/vol, 3 ml, with saline 1 ml with or without dexamethasone 4 mg) which were performed on three occasions in each volunteer along with an IV injection of saline 1 ml with or without dexamethasone 4 mg. The median [inter-quartile range (IQR)] duration of sensory block was 6.87

(5.85–7.62) h in the control group, 7.37 (5.78–7.93) h in the perineural group, and 7.37 (6.10–7.97) h in the IV group (P = 0.61). There was also no significant difference in block onset time between the three groups. Dexamethasone 4 mg had no clinically significant effect on the duration of sensory block provided by ropivacaine applied to the ulnar nerve [44]. The role of dexamethasone as an adjunct in peripheral nerve blockades is still unclear.

7. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Several studies have demonstrated that the presence of COX-2 receptors in the dorsal horn of the spinal cord could regulate spinal nociceptive transmission [45]. Some studies suggest that administering a COX-2 antagonist directly on the central or peripheral nerve might have a better analgesic profile than intravenous administration of the same drug [46]. Basically COX-2 inhibitors reduce inflammation and pain sensation by inhibiting prostaglandin production. However, the role of COX-2 in the central nervous system is of more importance. Inflammation can induce COX-2 production and will lead to the release of prostanoids that sensitize the peripheral nociceptor terminals and produce localized hyperalgesia. It is hence thought that the administration of COX-2 antagonist on spinal or peripheral nerves may be a more effective mode of pain relief than the intravenous or intramuscular route. There are very less studies on this subject. Further research and studies need to be conducted to verify the use of NSAIDs as adjuvants.

8. Miscellaneous agents

8.1 Ketamine

Ketamine is a noncompetitive antagonist of NMDA receptor that has been shown to have local anesthetic properties. Ketamine acts on more than one region. It has actions at monoaminergic receptors, opioid receptors, voltage-sensitive calcium channels, and muscarinic receptors, in addition to local anesthetic actions through sodium channel blockade. Systemic ketamine causes central summation in the second-order pain neuron and decreases severe pain [3, 47, 48]. Epidural administration of ketamine at 0.5–1 mg/kg has been shown to reduce intraoperative and postoperative analgesic requirements without increased side effects [25]. Preservative-free S(+)-ketamine administered during caudal block for children at a dose of 0.5 mg/kg has been shown to extend analgesia time by several hours [17]. Intrathecal administration of ketamine is not recommended.

The risk of psychomimetic adverse effects such as hallucinations is a worrying factor for most anesthetists, limiting its use, but it can be easily overcome by using intravenous benzodiazepines as premedication prior to the block.

8.2 Midazolam

Midazolam, a water-soluble benzodiazepine, an indirect agonist of the gamma-aminobutyric acid (GABA) receptor, has been studied primarily as an adjuvant for neuraxial anesthesia. Addition of preservative-free midazolam to 0.5% hyperbaric bupivacaine for subarachnoid block in infraumbilical surgery has been found to prolong the duration of effective analgesia as compared to the same concentration of bupivacaine alone and delays the need for postoperative rescue analgesics

without having any reported significant side effects or hemodynamic instability. The use of intrathecal midazolam also decreases the incidence of postoperative nausea and vomiting. A small diluted intrathecal dose (1–2.5 mg) of preservative-free midazolam is reported to have few systemic side effects and is free of short-term neurotoxicity [49]. An infusion of epidural midazolam at 10–20 μg/kg/h for up to 12 h is considered safe.

8.3 Neostigmine

Neostigmine is an acetylcholinesterase inhibitor that can enhance analgesia by acting on muscarinic receptors and increasing endogenous acetylcholine at the nerve terminal. It produces spinal analgesia in the preclinical models. Intrathecal neostigmine produces analgesia by the inhibition of (endogenous spinal neurotransmitter) acetylcholine destruction via muscarinic and cholinergic receptors located at dorsal horn of spinal cord, substantia gelatinosa, and in lesser amounts at laminae III and V [50]. There is a high incidence of nausea and vomiting and prolongation of recovery from spinal anesthesia following intrathecal administration of neostigmine, implying that it may not be a useful additive for ambulatory spinal anesthesia. The dose of intrathecal neostigmine ranges from 10 to 50 μg with the side effects increasing as the dose rises.

8.4 Magnesium sulfate

Magnesium is an N-methyl-D-aspartate (NMDA) antagonist that plays a role in moderating calcium influx into neurons. Research has demonstrated that magnesium decreases peripheral nerve excitability and enhances the ability of lidocaine to raise the excitation threshold of A-beta fibers.

Intrathecal and epidural use of magnesium has shown variable results. It may prolong LA/opioid block in women in labor at a dose of 50 mg, but a very high dose of magnesium has been reported to produce transient neurological toxicity [17]. Farzanegan et al. compared the combination of bupivacaine 12.5 mg and morphine 2 mg versus bupivacaine 12.5 mg and morphine 2 mg and magnesium 50 mg versus placebo epidurally for postoperative analgesia after thoracotomy. These authors achieved better analgesia and lower consumption of postoperative morphine significantly in the magnesium group [51]. In preeclamptic parturients doses of 50 mg of intrathecal magnesium with epidural ropivacaine significantly prolonged postoperative analgesia compared with 1 mg intrathecal midazolam without any complications [52]. In a recent meta-analysis, 11 studies showed that the use of epidural magnesium as an adjuvant to bupivacaine is still controversial. Although epidural magnesium prolonged the time of the first rescue analgesic and reduced the number of patients who required rescue analgesics, as well as the requirement of these analgesics, further studies are needed to assess their usefulness [53].

8.5 Sodium bicarbonate

Local anesthetic agents are usually packed at low pH to enhance their shelf life. In anesthetic practice, there has been considerable interest in studying the effect of pH on the onset, duration, and potency of blockade of LAs. It is proven that alkalinization of the LA improves the quality of block by influencing the portioning coefficient of anesthetic between aqueous solution and biological membranes [20]. Adding sodium bicarbonate to lidocaine decreases the latency of onset and enhances the depth of epidural blockade by increasing the concentration

of non-ionized drug. The alkaline pH increases the extraneural amount of non-ionized LA, which is the form that diffuses through the lipid phase of the neural membrane leading to more rapid diffusion across perineural tissue barriers [54]. CO_2 produced by the addition of bicarbonate and bicarbonate per se reduces the margin of conduction safety of the neural membrane. Moreover, CO_2 penetrates into the nerve, where it may determine trapping of the active cationic form of LA by acidifying the axoplasm [55].

8.6 Potassium chloride

Movements of ions through the nerve membrane are considered one of the main steps in the process of excitation and propagation of nerve stimuli. A nerve impulse can be effectively blocked by accumulation of potassium ions outside the neuron [56]. Thus, administration of exogenous potassium chloride will reinforce and prolong the blockade produced by LA. The addition of potassium chloride to LA increases the extracellular concentration and depolarizes the nerve membrane and thus blocks the conduction of nerve impulses. Potassium chloride up to 4 mmol/l to isotonic solutions of lidocaine enhances the clinical effectiveness of the combination [57]. The addition of physiological amounts of potassium chloride shortens the latency period and prolongs the duration of the blockade.

8.7 Adenosine

Adenosine receptors are expressed on the surface of most cells. Five classes of adenosine receptors have been identified. The A1 and A2 receptors are present centrally and peripherally, with agonism of the A1 receptor leading to antinociceptive response and that of the A2 receptor being algogenic (i.e., activation results in pain). The diagnostic and therapeutic role for intrathecal adenosine in acute and chronic pain states is under investigation by several research groups. Intrathecal adenosine decreases the spontaneous and evoked pain intensity in patients with neuropathic pain involving hyperalgesia/dysesthesia/allodynia [58]. Its interaction along with spinal LA is just beginning to be studied.

8.8 Dextran

Low molecular weight dextran (LMWD) was used as an adjuvant with LA as early as in the 1970s, but the efficacy of dextrans including LMWD remained controversial, as several studies reported an absence of any substantial difference in analgesic duration with their addition. That might have been due to poor techniques of regional anesthesia. The use of USG regional blocks has rekindled the use of LMWD as adjuvant. The addition of LMWD to a LA and epinephrine mixture when used as an infiltration anesthesia [59], or to a LA alone when performing a regional block [33], safely prolongs the effective action by reducing systemic absorption. More studies need to be conducted to elicit the exact mechanism and dosing ranges.

A word of caution regarding the use of additives in LAs is that only preparations without preservatives should be used, since these can be neurotoxic. Also, only adjuvants in clinically safe doses should be used in order to avoid getting the side effects due to excessive dosages.

Hence further research is required to find the exact mechanism of action and the safe dose of various adjuvants in order to avoid cardiovascular and neurological complications. The practice of making off-label use of drugs without getting FDA approval should be discouraged.

9. Conclusion

Locoregional anesthesia is increasingly used as it has demonstrated efficacy, safety, and low costs. Patients and surgeons have realized its enormous advantages. Although the use of LA in the management of locoregional anesthesia, postoperative pain, and chronic pain is limited by its duration of action and dose-dependent adverse effects that mainly affect the cardiovascular and CNS systems, this has been improved with the use of various LA adjuvant drugs. Adjuvants are medications that work synergistically with LAs to improve the onset, duration, and quality of anesthesia-analgesia in regional techniques, as well as greatly reducing the use of opioid analgesics.

The arsenal of adjuvants has developed from adrenaline, opioids, to a large group of non-opioid medications with various mechanisms of action. Opioids are the most commonly used adjuvants and range from morphine, fentanyl, and sufentanil to hydromorphone, buprenorphine, and tramadol with very different results. Its use has been limited by its adverse effects such as respiratory depression, nausea, vomiting, and pruritus, especially with its neuraxial use. Other adjuvants include alpha-2 agonists such as clonidine and dexmedetomidine, midazolam, NMDA antagonists including ketamine and magnesium, neostigmine, sodium bicarbonate, and nonsteroidal anti-inflammatory drugs. Concern regarding the safety profile of these adjuvants is due to their potential neurotoxicity and neurological complications that may limit their use and require further investigation.

Conflict of interests

The authors declare no conflict of interest.

Author details

Nandita Mehta* and Sayyidah Aasima tu Nisa Qazi
Department of Anaesthesia and Critical Care, ASCOMS Jammu, J&K, India

*Address all correspondence to: drnanditamehta@gmail.com

References

[1] Becker DE, Reed KL. Local anesthetics: Review of pharmacological considerations. Anesthesia Progress. 2012;**59**(2):90-101. DOI: 10.2344/0003-3006-59.2.90

[2] Shah J, Votta-Velis EG, Borgeat A. New local anesthetics. Best Practice & Research. Clinical Anaesthesiology. 2018;**32**(2):179-185. DOI: 10.1016/j.bpa.2018.06.010

[3] Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: Current understanding and future trends. World Journal of Clinical Cases. 2017;**5**(8):307-323. DOI: 10.12998/wjcc.v5.i8.307.x

[4] Schäfer M, Mousa SA, Shaqura M, Tafelski S. Background and current use of adjuvants for regional anesthesia: From research to evidence-based patient treatment. Der Anaesthesist. 2019;**68**(1):3-14. DOI: 10.1007/s00101-018-0522-6

[5] Krishna Prasad GV, Khanna S, Jaishree SV. Review of adjuvants to local anesthetics in peripheral nerve blocks: Current and future trends. Saudi Journal of Anaesthesia. 2020;**14**:77-84. DOI: 10.4103/sja.SJA_423_19

[6] Prabhakar A, Lambert T, Kaye RJ, Gaignard SM, Ragusa J, Wheat S, et al. Adjuvants in clinical regional anesthesia practice: A comprehensive review. Best Practice & Research. Clinical Anaesthesiology. 2019;**33**(4):415-423. DOI: 10.1016/j.bpa.2019.06.001

[7] Bujedo BM. Current evidence for spinal opioid selection in postoperative pain. The Korean Journal of Pain. 2014;**27**(3):200-209. DOI: 10.3344/kjp.2014.27.3.200

[8] Buvanendran A, Kroin JS. Useful adjuvants for postoperative pain management. Best Practice & Research. Clinical Anaesthesiology. 2007;**1**:31-49. DOI: 10.1016/j.bpa.2006.12.003

[9] Guany Y, Borzan J, Meyer RA, Raja SN. Windup in dorsal horn neurons is modulated by endogenous spinal mu-opioid mechanisms. The Journal of Neuroscience. 2006;**26**:4298-4307. DOI: 10.1523/JNEUROSCI.0960-06.2006

[10] Stein C, Lang LJ. Peripheral mechanisms of opioid analgesia. Current Opinion in Pharmacology. 2009;**9**:3-8. DOI: 10.1016/j.coph.2008.12.009

[11] Wajima Z, Shitara T, Nakajima Y, Kim C, Kobayashi N, Kadotani H, et al. Comparison of continuous brachial plexus infusion of butorphanol, mepivacaine and mepivacaine-butorphanol mixtures for post-operative analgesia. British Journal of Anaesthesia. 1995;**75**:548-551. DOI: 10.1093/bja/75.5.548

[12] Wang JK, Naus LA, Thomas JE. Pain relief by intrathecal applied morphine in man. Anaesthesiology. 1979;**50**:149-151

[13] Ummenhofer WC, Arends RH, Shen DD, Bernards CM. Comparative spinal distribution and clearance kinetics of intrathecally-administered morphine, fentanyl, alfentanil and sufentanil. Anaesthesiology. 2000;**92**:739-753. DOI: 10.1097/00000542-200003000-00018

[14] Liu SS, Block BM, Wu CL. Effects of post-operative central neuraxial analgesia on outcome after coronary artery bypass surgery: A meta-analysis. Anesthesiology. 2004;**101**:153-161. DOI: 10.1097/00000542-200407000-00024

[15] Bromage PR, Camporesi EM, Durant PA, Nielsen CH. Rostral spread of epidural morphine. Anesthesiology. 1982;**56**:431-436. DOI: 10.1097/00000542-198206000-00004

[16] Yurashevich M, Habib AS. Monitoring, prevention and treatment of side effects of long-acting neuraxial opioids for post-cesarean analgesia. International Journal of Obstetric Anesthesia. 2019;**39**:117-128. DOI: 10.1016/j.ijoa.2019.03.010

[17] Musokota MJ, Kasandji KF, Tshebeletso NC. Pharmacology of local anaesthetics and commonly used recipes in clinical practice. In: Hakan ER, editor. Current Topics in Anesthesiology. Croatia: IntechOpen; 2017. pp. 5-27. DOI: 10.5772/67048

[18] Gissen AJ, Gugino LD, Datta S, Miller J, Covino BG. Effects of fentanyl and sufentanil on peripheral mammalian nerves. Anesthesia and Analgesia. 1987;**66**(12):1272-1276

[19] Kaniyil S, Radhakrishnan P. Does fentanyl prolong the analgesia of local anaesthetics in brachial plexus block? A randomized controlled study. International Journal of Research in Medical Sciences. 2017;**5**:583-587

[20] Capogna G, Celleno D, Costantino P, Muratori F, Sebastiani M, Baldassini M. Alkalinization improves the quality of lidocaine-fentanyl epidural anaesthesia for caesarean section. Canadian Journal of Anaesthesia. 1993;**40**:425-430

[21] Kosel J, Bobik P, Tomczyk M. Buprenorphine—The unique opioid adjuvant in regional anesthesia. Expert Review of Clinical Pharmacology. 2016;**9**(3):375-383. DOI: 10.1586/17512433.2016.1141047

[22] Elrazek EA. The analgesic effects of epidural diamorphine and levobupivacaine on established lower limb post-amputation stump pain—A comparative study. Middle East Journal of Anaesthesiology. 2005;**18**(1):149-160

[23] Bravo L, Mico JA, Berrocoso E. Discovery and development of tramadol for the treatment of pain. Expert Opinion on Drug Discovery. 2017;**12**(12):1281-1291. DOI: 10.1080/17460441.2017.1377697

[24] Braun H. Ueber die bedeutung des adrenalins fur die chirurgie. Munchener Medizinische Wochenschrift. 1903;**50**:352-353

[25] Abdalla IA. Additives for spinal anaesthesia. Sudan Medical Journal. 2016;**52**(3):109-113

[26] Miller RD, editor. Miller's Anesthesia. New York: Elsevier, Churchill Livingstone; 2005

[27] Christiansson L. Update on adjuvants in regional anaesthesia. Periodicum Biologorum. 2009;**111**:161-170

[28] Llorca-Torralba M, Borges G, Neto F, Mico JA, Berrocoso E. Noradrenergic locus Coeruleus pathways in pain modulation. Neuroscience. 2016;**338**:93-113. DOI: 10.1016/j.neuroscience.2016.05.057

[29] Valenzuela-Harrington M, Negrete-Díaz V, Rodríguez-Moreno A. Núcleo Coeruleus. Neurotransmisores, funciones y patología. Anest Mex. 2007;**19**:155-166

[30] Dobrydnjovi A, Guptaa L, Holmstrom B, Granath B. Improved analgesia with clonidine when added to local anesthetic during combined spinal-epidural anesthesia for hip arthroplasty: A double-blind, randomized and placebo-controlled study. Acta Anaesthesiologica Scandinavica. 2005;**49**:538-545

[31] Whizar LV, Flores CJC, Preciado RS. Intrathecal clonidine as spinal anaesthesia adjuvant. Is there a magical dose? In: Topics in Spinal Anaesthesia. Croatia: IntechOpen; 2014. DOI: 10.5772/58712

[32] Singelyn FJ, Gouverneur JM, Robert A. A minimum dose of clonidine added to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. Anesthesia and Analgesia. 1996;**83**:1046-1050

[33] Gupta M, Shailaja S, Hegde KS. Comparison of intrathecal dexmedetomidine with buprenorphine as adjuvant to bupivacaine in spinal anaesthesia. Journal of Clinical and Diagnostic Research. 2014;**8**(2):114-117. DOI: 10.7860/JCDR/2014/7883.4023

[34] El-Hennawy AM, Abd-Elwahab AM, Abd-Elmaksoud AM, El-Ozairy HS, Boulis SR. Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. British Journal of Anaesthesia. 2009;**103**(2):268-274. DOI: 10.1093/bja/aep159

[35] Dziubdziela W, Jałowiecki P, Kawecki P. Prolongation of bupivacaine spinal anaesthesia by oral and intramuscular clonidine. Wiadomości Lekarskie. 2003;**56**:520-526

[36] Rhee K, Kang K, Kim J, Jeon Y. Intravenous clonidine prolongs bupivacaine spinal anesthesia. Acta Anaesthesiologica Scandinavica. 2003;**47**:1001-1005. DOI: 10.1034/j.1399-6576.2003.00158.x

[37] Whizar-Lugo V, Gómez-Ramírez IA, Cisneros-Corral R, Martínez-Gallegos N. Intravenous dexmedetomidine vs. intravenous clonidine to prolong bupivacaine spinal anesthesia. A double blind study. Anest Mex. 2007;**19**:143-146

[38] Reddy VS, Shaik NA, Donthu B, Reddy Sannala VK, Jangam V. Intravenous dexmedetomidine versus clonidine for prolongation of bupivacaine spinal anesthesia and analgesia: A randomized double-blind study. Journal of Anaesthesiology Clinical Pharmacology. 2013;**29**(3):342-347. DOI: 10.4103/0970-9185.117101

[39] Kaya FN, Yavascaoglu B, Turker G, Yildirim A, Gurbet A, Mogol EB, et al. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. Canadian Journal of Anaesthesia. 2010;**57**(1):39-45. DOI: 10.1007/s12630-009-9231-6

[40] Srinivas DB, Lakshminarasimhaiah G. Comparison of subcutaneous dexmedetomidine versus clonidine as an adjuvant to spinal anesthesia: A randomized double blind control trial. Local and Regional Anesthesia. 2019;**12**:29-36. DOI: 10.2147/LRA.S197386

[41] Johansson A, Hao J, Sjölund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. Acta Anaesthesiologica Scandinavica. 1990;**34**(5):335-338. DOI: 10.1111/j.1399-6576.1990.tb03097.x

[42] Albrecht E, Kern C, Kirkham KR. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. Anaesthesia. 2015;**70**(1):71-83. DOI: 10.1111/anae.12823

[43] Wiesmann T, Volk T, Steinfeldt T. Glucocorticoids as an adjunct in peripheral regional anesthesia. Move to the "holy grail of perineural analgesia". Der Anaesthesist. 2016;**65**(4):295-298. DOI: 10.1007/s00101-016-0143-x

[44] Marhofer P, Columb M, Hopkins PM, Greher M, Marhofer D, Levi Bienzle MR, et al. Dexamethasone as an adjuvant for peripheral nerve blockade: A randomised, triple-blinded crossover study in volunteers. British Journal of Anaesthesia. 2019;**122**(4):525-531. DOI: 10.1016/j.bja.2019.01.004

[45] Resnick DK, Graham SH, Dixon CE, Marion DW. Role of cyclooxygenase-2 in

acute spinal cord injury. Journal of Neurotrauma. 1998;**15**(12):1005-1013

[46] Liu X, Zhao X, Lou J, Wang Y, Shen X. Parecoxib added to ropivacaine prolongs duration of axillary brachial plexus blockade and relieves postoperative pain. Clinical Orthopaedics and Related Research. 2013;**471**(2):562-568

[47] Reboso Morales JA, González MF. Ketamina. Revista Española de Anestesiología y Reanimación. 1999;**46**(3):111-122

[48] Tawfic QA. A review of the use of ketamine in pain management. Journal of Opioid Management. 2013;**9**(5): 379-388. DOI: 10.5055/jom.2013.0180

[49] Shadangi BK, Garg R, Pandey R, Das T. Effects of intrathecal midazolam in spinal anaesthesia: A prospective randomised case control study. Singapore Medical Journal. 2011;**52**(6):432

[50] Lauretti GR, Lima IC. The effects of intrathecal neostigmine on somatic and visceral pain: İmprovement by association with a peripheral anticholinergic. Anesthesia and Analgesia. 1996;**82**(3):617-620

[51] Farzanegan B, Zangi M, Saeedi K, Khalili A, Rajabi M, et al. Effect of adding magnesium sulphate to epidural bupivacaine and morphine on post-thoracotomy pain management: A randomized, double-blind, clinical trial. Basic & Clinical Pharmacology & Toxicology. 2018;**123**(5):602-606. DOI: 10.1111/bcpt.13047

[52] Paleti S, Prasad PK, Lakshmi BS. A randomized clinical trial of intrathecal magnesium sulfate versus midazolam with epidural administration of 0.75% ropivacaine for patients with preeclampsia scheduled for elective cesarean section. Journal of Anaesthesiology Clinical Pharmacology. 2018;**34**(1):23-28. DOI: 10.4103/joacp.JOACP_74_17

[53] Li LQ, Fang MD, Wang C, Lu HL, Wang LX, Xu HY, et al. Comparative evaluation of epidural bupivacaine alone and bupivacaine combined with magnesium sulfate in providing postoperative analgesia: A meta-analysis of randomized controlled trials. BMC Anesthesiology. 2020;**20**(1):39. DOI: 10.1186/s12871-020-0947-8

[54] Strobel GE, Bianchi CB. The effects of pH gradients on the action of procaine and lidocaine in intact and desheathed sciatic nerves. The Journal of Pharmacology and Experimental Therapeutics. 1970;**172**:1-17

[55] Wong K, Strichartz GR, Raymond SA. On the mechanisms of potentiation of local anesthetics by bicarbonate buffer: Drug structure-activity studies on isolated peripheral nerve. Anesthesia and Analgesia. 1993;**76**:131-143

[56] Aldrete JA, Barnes DR, Sidon MA, et al. Studies on effects of potassium chloride to lidocaine. Anesthesia & Analgesia. 1969;**48**(2):269-276

[57] Kircha S, Barsa J, Fink BR. Potentiation of nerve block in vivo by physiological adjuvants in the solution. British Journal of Anaesthesia. 1983;**55**(6):549-553

[58] Belfrage M, Segerdahl M, Arner S, Sollevi A. The safety and efficacy of intrathecal adenosine in patients with chronic neuropathic pain. Anesthesia and Analgesia. 1999;**89**:136-142

[59] Ueda W, Hirakawa M, Mori K. Inhibition of epinephrine absorption by dextran. Anesthesiology. 1985;**62**:72-75