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Adjuvants in clinical regional anesthesia practice: A comprehensive review

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Adjuvants are medications that work synergistically with local anesthetics to help enhance the duration and quality of analgesia in regional techniques. Regional anesthesia has become more prevalent as evidence continues to show efficacy, enhancement of patient care, increased patient satisfaction, and improved patient safety. Practitioners in the perioperative setting need to not only be familiar with regional techniques but also the medications used for them. Some examples of adjuvant medications for regional

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non-steroidal anti-inflammatory medications

techniques include dexamethasone, alpha 2 agonists such as clonidine and dexmedetomidine, midazolam, buprenorphine, NMDA antagonists, including ketamine and magnesium, neostigmine, sodium bicarbonate, epinephrine, and non-steroidal anti-inflammatory drugs. The aim of the present investigation, therefore, is to provide a comprehensive review of the most commonly used non-opioid adjuvants in clinical practice today. Regional adjuvants can improve patient safety, increase patient satisfaction, and enhance clinical efficacy. Future studies and best practice techniques can facilitate standardization of regional anesthesia adjuvant dosing when providing nerve blocks in clinical practice.

Introduction

Regional anesthesia has become a cornerstone in modern clinical practice. This has been primarily driven by advancements in technology, improved patient satisfaction, quicker recovery, increased clinician awareness, and enhanced patient safety. Adjuvants are medications that work synergistically with local anesthetics to help enhance the quality and efficacy of regional techniques. Adjuvants can help to quicken the onset of action, increase the duration of analgesia, improve the quality of analgesia, and limit potential medication related adverse effects. Adjuvants have been studied using a variety of different routes including systemic, perineural, and topical administration. This paper will review the pharmacology, physiology, efficacy, and safety of the most common non-opioid adjuvants for regional anesthesia.

Adjuvants utilized in clinical practice

Dexamethasone

Dexamethasone is a long acting synthetic corticosteroid that has a wide range of physiologic effects. These include but are not limited to immunosuppression and anti-inflammatory properties mediated primarily by preventing cytokine release via inhibition of cyclo-oxygenase 2. Recently, more research has been performed to better understand its role in supplementing regional anesthetics. Dexamethasone has been studied as an adjuvant in conjunction with several different peripheral nerve blocks including transverse abdominis, brachial plexus, ankle, and paravertebral blocks [1]. Several studies suggest favorable outcomes such as lower pain scores, decreased post-operative opioid usage, and decreased nausea and vomiting [2].

A 2011 meta-analysis that included twenty four randomized controlled trials (RCTs) and 2751 patients showed decreased post-operative pain with intravenous supplementation of dexamethasone in doses greater than 0.1 mg/kg [3]. A recent randomized control trial looked at systemic administration of dexamethasone in conjunction with paravertebral blocks in breast surgery. Results were significant for decreased post-operative pain for up to 12 h in patients who received IV dexamethasone compared to those in the control group who did not receive systemic dosing [4]. Perineural dexamethasone administration has also been shown to provide superior analgesia when compared to local anesthetic only. A meta-analysis reviewing 9 RCTs with perineural dexamethasone supplementation in transverse abdominal plane blocks found that perineural administration was associated with decreased post-operative pain scores at 2, 6, and 12 h [5].

Reduced pain scores correlate well with decreased opioid consumption in the post-operative period. A meta-analysis performed by De Oliveira et al. found that intravenous doses greater than .1 mg/kg resulted in both a reduction of pain scores as well as opioid consumption [3]. Another meta-analysis including

forty-five studies and 5796 patients showed significantly less usage of morphine equivalents at 2 h and 24 h post operatively in those receiving a single 1.25 mg–20 mg IV dose of dexamethasone [6].

However, there are some studies which show either increased or no change in post-operative opioid consumption. A prospective randomized double-blind clinical trial looked at 110 patients undergoing upper extremity orthopedic operations. The control group was given a 40-ml solution of 2 mg/kg lidocaine while the intervention group was given a 40-ml solution of 2 mg/kg lidocaine plus 8 mg dexamethasone. The results showed the intervention group consumed significantly more opioids compared to the control group [7]. Another recent randomized clinical trial looked at administration of 8 mg of dexamethasone intravenously in 52 post-cesarean deliveries and found no reduction in 24 h post-operative opioid use [8]. It is worth noting that both randomized clinical trials are limited by sample size and potential variability in quality of the regional technique.

The use of systemic steroids as an anti-emetic has been well established in literature and is routinely used in regular anesthetic practice. Interestingly, perineural administration has also been shown to reduce the incidence of post-operative nausea and vomiting. A recent meta-analysis of nine randomized clinical trials involving 575 patients with dexamethasone used in transverse abdominis plane (TAP) blocks observed decreased post-operative nausea and vomiting [9]. While this finding may be a byproduct of better analgesia resulting in decreased rescue opioid use, it is still a significant and relevant observation.

Potential adverse effects of corticosteroids include immune suppression, increased risk of infection, impaired wound healing, and hyperglycemia. Several studies have looked at whether dexamethasone used as adjuvant therapy with regional anesthesia also results in these same adverse effects. Two large meta analyses found no difference in infection rates or wound healing in treatment groups compared to controls [3,6]. Hyperglycemia resulting from adjuvant use remains controversial with some literature suggesting an increased risk while others note no change [3,6]. Tien et al. looked specifically at adjuvant dexamethasone use in diabetic patients and non-diabetic patients [10]. While there was an increase in blood glucose levels post-operatively, there was no clinically significant difference in outcomes between the two groups [10].

Alpha 2 agonists

The two most common alpha agonists used in clinical practice today are clonidine and dexmedetomidine. Clonidine is selective for alpha 2 adrenergic receptors that are located on primary afferent terminals within the spinal cord and the brainstem. When used in peripheral nerve blocks, it is proposed that clonidine also acts to block conduction of A and C pain fibers by increasing potassium conduction and subsequently enhancing the duration of action of the local anesthetic [11,12]. Clonidine may also result in vasoconstriction of the surrounding vasculature which can prolong the anesthetic effect of the local anesthetic by slowing its elimination from the intended site of action [12,13]. One meta-analysis noted a 2 h increase in duration of intermediate and long acting local anesthetics when used in conjunction with clonidine [13]. Another systematic review performed by McCartney et al. showed prolonged analgesia with clonidine when used with intermediate acting local anesthetics [14]. Both studies utilized doses of 0.50–150 μg to avoid unwanted systemic side effects such as arterial hypotension, orthostatic hypotension, and bradycardia.

Dexmedetomidine is a alpha 2 agonist with both analgesic and sedative properties that is seven times more selective than clonidine [15,16]. Intravenous dexmedetomidine is frequently used as a sedative in the ICU or perioperative setting, particularly when the goal is to limit respiratory depression. More research has also looked at its potential role in regional anesthetics. A recent prospective double blinded RCT done by Liu et al. looked at dexmedetomidine use with bupivacaine in spinal anesthesia. They compared a treatment group receiving intrathecal bupivacaine with 5 μg adjuvant dexmedetomidine to a control group without the adjuvant dexmedetomidine. Findings were relevant for increases in duration of analgesia in the treatment group without observation of significant adverse effects [17]. A meta-analysis reviewed 14 clinical studies with 848 patients to compare perineural dexmedetomidine versus clonidine when added to local anesthetic in supraclavicular brachial plexus blocks. It was found that dexmedetomidine prolonged duration of sensory and motor block by an estimate of 1.2 ($p < .00001$) [18,19]. Another study by Andersen et al. compared perineural

administration to intravenous. Although both routes of dexmedetomidine were found to prolong the duration of ropivacaine, perineural was found to be more effective than systemic [19].

Safety considerations for dexmedetomidine use include the potential for hypotension and or bradycardia [2]. There is also some debate whether perineural dexmedetomidine may be neurotoxic in patients with diabetic neuropathy however much more research needs to be done prior to establishing true causation [20].

Midazolam

Midazolam is a short acting benzodiazepine that acts as a GABA A receptor agonist in the CNS. While there is evidence that the GABA A receptor is located outside the CNS, the exact mechanism of action of benzodiazepines in the peripheral nervous system is not well understood. The peripheral target is believed to be translocator protein (TSPO), formerly known as the peripheral benzodiazepine receptor [21]. TSPO is found throughout the body where it functions as a cholesterol binding protein in the outer mitochondrial membrane for steroid production. It has also been found to have a protective role in microglial cells after nerve damage [22].

A double blind, prospective, randomized study looked at the use of midazolam as an adjuvant in brachial plexus blocks with bupivacaine in 50 patients. Patients were administered either 0.5% bupivacaine 30 mL injection with 2 mL normal saline or 0.5% bupivacaine 30 mL injection with 0.05 mg/kg of midazolam. While limited by a small sample size, findings were significant for an increased mean duration of pain relief and better pain relief scores at 12 h post injection in those who received adjuvant midazolam. The only adverse reaction from the midazolam adjuvant group was a decreased respiratory rate from baseline 10–30 min after administration. This decrease did not require any intervention other than the addition of supplemental oxygen delivered via face mask [23].

A recent article examined the effectiveness of midazolam as an adjuvant in peribulbar blocks for cataract surgery. Midazolam, in concentrations of 50 ug/ml and 100 ug/ml, was combined with lidocaine and hyaluronidase and compared to a control. The mean onset of sensory block, but not motor, was significantly reduced among the midazolam groups. The overall duration of motor and sensory anesthesia was also prolonged in the groups that received midazolam [24].

The safety of midazolam as an adjuvant in regional anesthesia is still under investigation primarily due to a lack of sufficient in vivo studies. Some in vitro studies have suggested potential neurotoxicity of perineural midazolam however this has not been proven in vivo [25]. More research with larger randomized control studies is needed before perineural midazolam is routinely used as a regional adjuvant.

Anti-inflammatory agents

Non-steroidal anti-inflammatory drugs (NSAIDs) act by inhibition of COX-1, COX-2, or both to help limit downstream cytokine release. Thus far, limited research has been performed to ascertain their use in regional anesthesia. Animal models have yielded conflicting findings on whether or not NSAIDs are neurotoxic [26,27]. Human trials for NSAIDs or acetaminophen use in regional are sparse. A small study combined the use of lidocaine with dexketoprofen or paracetamol as an adjuvant in intravenous regional anesthesia. They found that both combinations reduced time of onset and prolonged the duration of sensory and motor blockade when compared to control groups. There was no significant difference between dexketoprofen and paracetamol. This study was limited by sample size and also the potential systemic crossover analgesic effect of these medications via the intravenous route [28]. Too many questions remain about the efficacy and safety of NSAIDs in regional anesthesia before their use can be recommended.

Buprenorphine

Buprenorphine is a semisynthetic partial opioid agonist at the mu opioid receptor and an antagonist at the kappa opioid receptor [29]. All opioid receptors are G-protein coupled and activate a downstream inhibitory cascade. The most important pharmacologic aspect of the opioid receptor is their

ability to modulate calcium and potassium channels. By blocking inward rectifying potassium channels, the cell hyperpolarizes and inhibits continued neuronal excitability. Calcium conductance is also inhibited by preventing voltage activation of the calcium channel [30]. Buprenorphine has a higher affinity for the mu receptor compared to a full agonist like morphine [31,32]. This property allows it to displace more potent opioids from the mu receptor and is the basis for buprenorphine therapy for patients with opioid use disorder. The pharmacokinetics of buprenorphine are not changed by renal dysfunction or advanced age [33]. Buprenorphine's analgesic effect does not exhibit a ceiling effect, but there is a ceiling effect for respiratory depression, reducing the likelihood of this potentially fatal adverse effect. It's effects can be completely reversed by naloxone [34].

Buprenorphine has been used as an adjuvant for a variety of regional techniques such as neuraxial, intravenous, and peripheral nerve blocks [35]. Several studies have shown that buprenorphine can help to significantly prolong the median time of duration of analgesia for both upper and lower extremity nerve blocks. Candido et al. have published several studies which show a 1.5–3 fold increase in time of analgesia with the addition of buprenorphine for subclavian, axillary, and sciatic nerve blocks [36–38]. Data thus far has shown promise however larger studies are needed for further validation. Buprenorphine is a relatively safe medication to use however several studies have shown an increased incidence of nausea and vomiting after administration.

NMDA antagonists

NMDA (N-methyl-D-aspartate) receptors are glutamate-gated cation channels with high calcium permeability that have many important roles throughout the body [39]. They are critical for the development of the central nervous system, initiation of the respiratory drive, acute and chronic pain physiology, and the processes underlying memory, learning, and neuroplasticity. Two types of NMDA receptor antagonists include ketamine and magnesium.

Ketamine has clinical applications for acute pain management, palliative care, and chronic neuropathic pain conditions. As an adjuvant, lower doses can be used for postoperative analgesia or for reduction of exogenous opioid induced hyperalgesia. The combination of ketamine with opioids has been shown to greatly reduce pain scores, total morphine consumption, and postoperative desaturation in patients undergoing thoracic surgery.

Intravenous ketamine infusions can also be used to treat intractable neuropathic pain conditions such as complex regional pain syndrome, postherpetic neuralgia, traumatic spinal cord injury, and phantom limb pain [40]. So far, there has been very limited data pertaining to perineural ketamine use for regional anesthesia. Adverse effects of ketamine include hallucinations, memory defects, panic attacks, nausea, vomiting, somnolence, sympathetic stimulation, and cardiac depression [41]. Many psychologic effects can be mitigated by preemptive benzodiazepine administration.

Magnesium is another NMDA antagonist that has potential merit as an adjuvant. The blockade of the NMDA receptor channel by magnesium administration helps to decrease peripheral nerve excitability while also helping local anesthetics to increase the threshold for pain fiber excitation. Several studies have shown that the addition of magnesium can prolong analgesia in femoral, interscalene, and axillary blocks [42]. Magnesium has been shown to be safe at therapeutic doses and generally has a wide margin of safety. Renal function needs to be considered prior to administration to avoid toxicity due to lack of adequate excretion. Potential adverse effects include flushing, hypotension, vasodilation, and somnolence. Data also suggests that doses greater than 150 mg may be associated with a higher risk for nausea and vomiting. More studies looking at potential neurotoxicity need to be done prior to recommending routine perineural administration.

Neostigmine

Neostigmine inhibits the breakdown of acetylcholine. In the spinal cord acetylcholine is the primary neurotransmitter involved in spinal analgesia. Neostigmine inhibits afferent pain impulses to lamina 1, 2, and 3 of the dorsal horn through M1 and M2 muscarinic receptors and is also thought to potentiate analgesia by releasing nitric oxide in the spinal cord [43,44]. Intrathecal neostigmine has dose-

dependent complications, such as nausea, vomiting, sedation, muscle weakness, and sometimes temporary reduction of tendon reflexes.

Spinal neostigmine alone produces analgesia in humans and animals at doses larger than 100 μg but dose-related associated nausea and vomiting have limited its use [45–48]. Nausea associated with the neuraxial administration of neostigmine is thought to be linked to the diffusion through the cerebrospinal fluid toward the brainstem and does not respond to standard antiemetic drugs [47]. The use of intrathecal neostigmine has shown potentiating effects on opioid-induced analgesia [49]. The intrathecal doses of neostigmine used in multimodal pain therapy causing nausea and vomiting have been 10 μg or higher. A small study showed that the combination of 1, 2.5 or 5 μg neostigmine and morphine resulted in 8 h of analgesia, demonstrating the potentiation of the analgesic effect of morphine, with no increase in the incidence of adverse effects [50]. Recently, enhanced analgesia after 1 μg intrathecal neostigmine combined with fentanyl and bupivacaine in total knee replacement surgery was demonstrated [51]. Neostigmine intrathecally in low doses might have an opioid-enhancing analgesic effect but larger randomized controlled trials would be warranted to assess the benefit and frequency of cholinergic side effects.

Two studies have evaluated the effects of epidural neostigmine alone. Only 10% of neostigmine penetrates the dura and hence large doses of neostigmine are necessary to produce an effect. This analgesic effect is accompanied by adverse effects like nausea and vomiting [52]. The use of neostigmine in combination with other drugs like local anesthetics, opioids and ketamine were found to significantly enhance analgesia [53]. There were no significant differences in side effects between the groups. In children undergoing inguinal hernia or hypospadia surgery neostigmine 2 μg/kg was added to caudal ropivacaine undergoing inguinal hernia or hypospadia surgery prolonging the time to rescue analgesic compared to the control group [54]. There was a non-significant trend towards more postoperative nausea and vomiting in the neostigmine group. In obstetric anesthesia a recent meta-analysis concluded that epidural (and intrathecal but with significantly increased maternal nausea and vomiting) administration of neostigmine significantly reduces local anesthetic consumption without serious adverse side effects to the mother or fetus [55].

Acetylcholine receptor activation in peripheral nerves is associated with analgesia and intra-articular neostigmine (500 mcg) seems to relieve pain after knee arthroplasty [56]. Neostigmine addition to intravenous anesthesia for upper limb surgery has shown a benefit with shortened block onset times, prolonged sensory and motor block, and prolonged time to first postoperative rescue analgesic [57]. Postoperative bradycardia was more apparent when neostigmine had been given. Few studies have looked at the effect of neostigmine on peripheral nerve blocks. Neostigmine was found to be less effective than dexamethasone and midazolam as an adjunct to brachial plexus blocks [58,59].

Sodium bicarbonate

Sodium bicarbonate is an adjuvant theorized to help hasten the onset of regional anesthesia and increase the depth of blockade of a variety of local anesthetics. It is proposed that sodium bicarbonate alkalinizes the local anesthetic solution, which allows more of the local anesthetic to exist in its un-ionized form. In the un-ionized state, the drug crosses the lipid cell membrane more readily, blocking neuron depolarization. Unfortunately, the evidence is not consistent in proving this theory [60]. The pH of a local anesthetic solution is variable depending on how it is manufactured, and it has not been determined how much alkalization is needed to produce the desired result [61]. Also some local anesthetics, such as bupivacaine and ropivacaine, can precipitate with the addition of sodium bicarbonate. With other local anesthetics, such as lidocaine, the presence or absence of epinephrine can alter the effect of sodium bicarbonate within the solution causing a possible reduction in onset time but also may decrease degree and duration of analgesia according to Sinnott et al. [62]. Furthermore, sodium bicarbonate has not been approved for clinical use as an alkalinizing agent for local anesthetics, thus its use should be done with caution.

Epinephrine

Epinephrine is the most widely used adjunct for local anesthetics in regional anesthesia. It is used to reduce local anesthetic systemic toxicity, prolong the duration of sensory and motor blockade, detect intravascular injection, and increase block density [63,64]. As a vasoconstrictor, epinephrine helps to reduce systemic reabsorption of several local anesthetics, allowing more time for the local anesthetic effect at the nerve site. Typically, a dose of 2.5–5 μg per milliliter of epinephrine hydrochloride is added to a local anesthetic to produce these results. The addition of epinephrine 5 mcg/ml to 1% lidocaine hydrochloride was demonstrated to increase the duration of an ulnar nerve block five-fold and also double the ulnar block analgesia duration of 1% prilocaine hydrochloride. Prolongation of sensory and motor blockade has also been demonstrated with an axillary nerve block with lidocaine and brachial plexus block with mepivacaine and bupivacaine [65,66]. However, epinephrine does not alter the duration or onset of ropivacaine. When epinephrine is used as an additive, caution must be used as hypertension, tachycardia, and or arrhythmias may occur.

Conclusion

Practitioners taking care of patients in the perioperative, acute, or chronic pain setting need to be familiar with regional anesthetic techniques and the medications administered for them. Regional anesthesia will only continue to grow in the coming years as ultrasound technology continues to improve and techniques continue to evolve. In the present investigation, we have reviewed the most commonly utilized adjuvants for regional anesthesia. Some adjuvants clearly need more evidence-based data before recommending regular use. However, as this manuscript has demonstrated, many adjuvants have been studied extensively at present with good data to support their supplementation to local anesthetics. The addition of adjuvants can help to improve patient safety, increase patient satisfaction, and enhance clinical efficacy. Future studies and best practice techniques will ultimately help standardize the role of regional anesthesia adjuvants in the delivery of nerve blocks in clinical practice.

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