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EDITORIAL

Adjuvants to local anesthetics: Current understanding and future trends

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Abstract

Although beneficial in acute and chronic pain management, the use of local anaesthetics is limited by its duration of action and the dose dependent adverse effects on the cardiac and central nervous system. Adjuvants or additives are often used with local anaesthetics for its synergistic effect by prolonging the duration of sensory-motor block and limiting the cumulative dose requirement of local anaesthetics. The armamentarium of local anesthetic adjuvants have evolved over time from classical opioids to a wide array of drugs spanning several groups and varying mechanisms of action. A large array of opioids ranging from morphine, fentanyl and sufentanyl to hydromorphone, buprenorphine and tramadol has been used with varying success. However, their use has been limited by their adverse effect like respiratory depression, nausea, vomiting and pruritus, especially with its neuraxial use. Epinephrine potentiates the local anesthetics by its antinociceptive properties mediated by alpha-2 adrenoreceptor activation along with its vasoconstrictive properties limiting the systemic absorption of local anesthetics. Alpha 2 adrenoreceptor antagonists like clonidine and dexmedetomidine are one of the most widely used class of local anesthetic adjuvants. Other drugs like steroids (dexamethasone), anti-inflammatory agents (parecoxib and lornoxicam), midazolam, ketamine, magnesium sulfate and neostigmine have also been used with mixed success. The concern regarding the safety profile of these adjuvants is due to its potential neurotoxicity and neurological complications which necessitate further research in this direction. Current research is directed towards a search for agents and techniques which would prolong local anaesthetic action without its deleterious effects. This includes novel approaches like use of charged molecules to produce local anaesthetic action (tonicaine and n butyl tetracaine), new age delivery mechanisms for prolonged bioavailability (liposomal, microspheres and cyclodextrin systems) and further studies with other drugs (adenosine, neuromuscular blockers, dextrans).

Key words: Local anesthetics; Adjuvants; Neurotoxicity; Opioids; Ketamine; Midazolam; Alpha-2 adrenoreceptor antagonists

Core tip: The use of local anaesthetics in acute and chronic pain is limited by its duration of action and the dose dependent adverse effects. Adjuvants or additives are often used with local anaesthetics for its synergistic effect by prolonging the duration of sensory-motor block and limiting its cumulative dose requirement. Various drugs like opioids, epinephrine, alpha-2 adrenergic antagonists, steroids, anti-inflammatory drugs, midazolam, ketamine, magnesium sulfate and neostigmine have been used to potentiate the effect of local anesthetics. Due its potential adverse effects, current research is exploring newer drugs and delivery mechanisms to prolong the duration of action of local anesthetics.

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INTRODUCTION

From time immemorial, alleviation of acute and chronic pain has continued to perplex medical professionals. The early success of pharmacologic endeavors in pain mitigation involved extensive use of opioids. Although reasonably successful, it was often associated with systemic complications like nausea, vomiting, respiratory depression, sedation, delayed recovery of bowel functions and hyperalgesia. In an effort to reduce the need and adverse effects of systemic opioids, the perineural (intrathecal, epidural or peripheral nerve blocks) use of local anesthetics have gradually evolved over time.

Although beneficial in acute and chronic pain management, local anaesthetics do have the potential to produce deleterious effects like cardiac arrhythmias, central nervous system depression, seizures, respiratory depression, hypertension and allergic reactions[1-4]. By prolonging the duration of sensory-motor block and limiting the cumulative dose requirement of local anaesthetics, co-administration of adjuvants has the potential to improve efficacy of perineural blocks and decrease local anaesthetic toxicity. The terms, local anaesthetic "adjuvants" or "additives", have often been used interchangeably. They contribute in their own special manner to potentiate the analgesic effect of the local anaesthetics[5]. The armamentarium of local anesthetic adjuvants have evolved over time from classical opioids to a wide array of drugs spanning several groups and varying mechanisms of action.

The aim of this editorial is to have a comprehensive look at the various local anesthetic adjuvants which have been studied till date, ascertain the evidence for their safety and efficacy in perineural use, discuss various novel approaches in local anesthetic usage and highlight the present lacuna in knowledge for directing future research on the subject.

DISCUSSION

Opioid

Opioids are the most frequently used local anesthetic adjuvants and their use in neuraxial blocks have evolved over the last 50 years[6]. The opioids potentiate antinociception of local anesthetics by G protein coupled receptor mechanisms by causing hyperpolarisation of the afferent sensory neurons[7]. The dose, site of injection, lipophilicity and the acid-base milieu of the site of drug deposition determine the extent of efficacy of the block[8,9].

Morphine: Use of preservative free morphine with or without local anesthetics has been used extensively in neuraxial blocks across all age groups[10,11]. Intrathecal Morphine in the dose range of 100-200 μg has exhibited good analgesic efficacy, especially in obstetric and orthopedic subsets[12,13]. Similarly epidural morphine has also been used over a wide dose range (1-5 mg) and has exhibited efficacy in diverse population subsets[14-17]. The hydrophilic nature of neuraxial Morphine results in cephalad spread, thereby increasing the area of analgesia. However the adverse effect of its use in neuraxial blocks includes respiratory depression (early and late), nausea, vomiting, pruritus and urinary retention. Specifically, there is evidence to suggest that intrathecal morphine administration of doses lower than 100 μg results in lesser adverse effects in elderly patients[13]. The use of Morphine in peripheral nerve blocks is presently not recommended as studies have failed to show any advantage over intravenous (Ⅳ) and intramuscular (IM) routes. Their adverse effects persist irrespective of the route of administration[18-22].

Fentanyl: Intrathecal fentanyl in the dose range of 10-25 μg has also been shown to prolong the duration and extent of sensory block with a favorable adverse effect profile in comparison to morphine[23-25]. However, epidural fentanyl does not necessarily follow the same pattern and a higher incidence of adverse effects have been observed with its use[26]. The addition of epinephrine 2 μg/mL to neuraxial local anesthetic-fentanyl mixtures has also been investigated. However, it was demonstrated that thoracic neuraxial instillation resulted in lesser nausea but its lumbar neuraxial administration didn't reduce any opioid related adverse effects[27-29]. Numerous studies have however failed

to conclusively prove the efficacy of fentanyl as an adjuvant in peripheral nerve blocks[30-35].

Sufentanyl: Intrathecal sufentanyl in the dose of 5 μg as an adjuvant to local anesthetics has shown good efficacy, however, for lesser adverse effects, the dose range needs to be lower (around 1.5 μg)[36,37]. The epidural dose of sufentanyl is 0.75-1 μg/mL and has been shown to be strikingly effective in ameliorating pain in various patient subsets[38-40].

Other opioids: Hydromorphone and Buprenorphine: Hydromorphone has been shown be an efficacious adjuvant in both intrathecal and epidural routes at the dosages of 100 μg and 500-600 μg respectively[41,42]. It is preferred in patients with renal insufficiency and had a better adverse effect profile when compared to morphine[43,44].

Buprenorphine has also been used in intrathecal (75-150 μg) and epidural routes (150-300 μg) with reasonable efficacy[5,45]. Additionally, it has also shown good efficacy when used in a dose of 0.3 mg as an adjuvant to peripheral nerve blocks[46-48].

Tramadol: Tramadol is a weak opioid agonist having sodium and potassium channel blocking actions as well as ancillary actions such as blockage of uptake of norepinephrine and serotonin[49-51]. Intrathecal tramadol in doses ranging from 10-50 mg has been in used different subsets with varying success[52-57].

Epidural tramadol in doses of 1-2 mg/kg presented itself as an attractive alternative to morphine for postoperative analgesia without any respiratory depressant effect[58]. Epidural tramadol has given good results for amelioration of pain in various patient subsets ranging from obstetric patients and abdominal surgeries to pediatric patients for lower abdominal procedures[59-63].

The incidence of nausea and vomiting remains a concern. However, incidence was less with lower doses. Other adverse effects like itching and sedation are less frequent[58,62]. Tramadol when used as an adjuvant in peripheral nerve blocks has shown conflicting and contradictory results with an unknown safety profile[64-67]. A couple of studies have shown Tramadol to increase the analgesic efficacy[64,66]. However, there have been other studies which have shown limited or no benefit of Tramadol when used as an adjuvant to local anesthetics for peripheral nerve blocks[65,68-72]. Hence, except for postoperative epidural infusions, present day anesthesia practice does not recommend routine use of Tramadol as a local anesthetic adjuvant.

Adverse effects of neuraxial opioids: The troublesome adverse effects of neuraxial opioids include pruritus, nausea, vomiting and respiratory failure, especially in elderly patients. This has prompted studies to determine the upper safe limit of administration of these drugs. The effects are more profound when the drug is deposited in the intrathecal space resulting in recommendations to reduce intrathecal dosage to avoid respiratory depression[73]. The pruritus produced by neuraxial opioids is dose dependent and responds well to Naloxone 200 μg and Ondansetron 4-8 mg[24,37,74].

Epinephrine

Epinephrine is one of the oldest additives to local anesthetic solutions with a recommended dosing of 0.5-1.0 μg/kg in a concentration of 5-10 μg/mL[75,76]. In addition to its vasoconstrictive actions, it also seems to have intrinsic antinociceptive properties mediated by alpha-2 adrenoreceptor activation[77]. A matter of concern with the use of continuous infusion of neuraxial epinephrine has been the association of severe neurologic complications as well as evidence of intrinsic neurotoxicity attributed to epinephrine[78-82]. Its use in neuraxial anesthesia is limited to being used as an additive to caudal Bupivacaine administration and for the detection of inadvertent intra vascular placement of epidural and other perineural catheters[83,84]. In peripheral nerve blocks, Epinephrine has shown certain analgesic benefits with short and intermediate acting local anesthetic such as lidocaine, but similar effects have not been observed with long acting local anesthetic such as Bupivacaine and Ropivacaine[85,86]. The effect of Epinephrine in peripheral blocks seems to be largely dependent on its vasoconstrictive action as perineural Epinephrine alone doesn't seem to cause any sensory or motor block[82,87,88].

Epinephrine has however had a significant role in preventing inadvertent intravascular administration of local anesthetic solutions; however the recent surge in routine use of ultrasonography in nerve blocks has made such use largely redundant. There is significant evidence indicating potential neurotoxicity with the perineural use of Epinephrine, especially in patients with diabetes mellitus, hypertension and in smokers[80,87]. Current recommendations allow use of epinephrine in peripheral blocks only when ultrasonography is not available or where needle tip and local anesthetic spread are not visualized[85].

Alpha 2 adrenoreceptor antagonists

Alpha 2 adrenoreceptor antagonists (Clonidine, Dexmedetomidine) are one of the most widely used class of local anesthetic adjuvants which give satisfactory effect in neuraxial and peripheral blocks.

Clonidine: Clonidine is an imidazole derivative with selective partial agonist properties which inhibits nociceptive impulses by activation of postjunctional alpha-2 adrenoreceptor in the dorsal horn of spinal cord[89]. In neuraxial blocks, it has a local effect on blockage of sympathetic outflow while in peripheral nerve blocks it prolongs duration of analgesia by

hyperpolarisation of cyclic nucleotide gated cation channels[87,90].

Clonidine was first used in 1984 in epidural blocks[91]. Epidural clonidine in doses of 25-50 μg/h has been found to have beneficial effects in various study populations like spine instrumentation and orthopedic procedures[92-96]. Caudal administration of clonidine in pediatric age groups has also exhibited significant prolongation of the duration of analgesia with minimal cardiorespiratory perturbations[97-99]. Intrathecal administration of clonidine has evolved in terms of dosing from the initial phases of higher doses (150 μg) to routine use of lesser doses (15-40 μg) in present day practice to avoid its cardiovascular adverse effects. Intrathecal Clonidine supplementation of local anesthetic solutions result in increased segmental spread of sensory block, delayed regression of such blocks and decrease the failure rate and analgesic supplementation required in various surgical subsets[100-103]. It has also peculiarly shown benefits in alcoholics undergoing surgery by preventing postoperative alcohol withdrawal symptoms[104]. Use of clonidine in neuraxial blocks had been plagued by the adverse effects like sedation, bradycardia and hypotension, thus necessitating a gradual evolution to present day recommendations of lower dosages[93,105,106].

There have been a plethora of studies investigating efficacy of Clonidine as a local anesthetic adjuvant and results have shown varying outcomes[107-112]. A meta analysis by Pöpping *et al*[113] demonstrated prolongation of peripheral nerve block duration by 2 h when clonidine was used as an adjuvant. McCartney *et al*[114] analyzed 27 well designed studies (15 positive, 12 negative) and found that clonidine prolonged peripheral nerve blockade best in amalgamation with intermediate acting local anesthetics such as mepivacaine and lidocaine. Lesser potentiation was observed with bupivacaine and levobupivacaine while ropivacaine produced the most disappointing results. Interestingly upper extremity blocks fared better in comparison to the lower extremity blocks when clonidine was used as an adjuvant[114]. The extensive studies by McCartney and Pöpping presented convincing evidence suggesting significant association of increased doses with hemodynamic manifestations such as hypotension and bradycardia. Hence a dose of 0.5 μg/kg with a maximum of 150 μg is the recommended maximum dose of clonidine for use as an adjuvant in peripheral blocks[113,114]. Subsequently there has been evidence suggesting that clonidine as an adjuvant is beneficial in popliteal sciatic block and in specific circumstances such as axillary blocks in patients with chronic renal failure and patients undergoing paronychia surgery (analgesia in infected tissue)[115,116]. The heterogeneity of results, especially in routine brachial plexus blocks, suggest that until further well directed research shows unequivocal evidence to advocate the use of Clonidine as an adjuvant to local anesthetic, it cannot be routinely recommended for perineural use[117-120].

Dexmedetomidine: Dexmedetomidine is a 7 times more selective alpha-2 receptor agonist in comparison to clonidine and has a similar mechanism of blocking hyperpolarisation activated cation channels[121,122].

Intrathecal (5-10 μg) and epidural dexmedetomidine (1 μg/kg) as an adjuvant to isobaric bupivacaine or in combination with commonly used local anaesthetics (like ropivacaine) have been investigated for its analgesic efficacy in various patient subsets[123-129]. A meta-analysis on intrathecal dexmedetomidine has shown that its use has been associated with prolonged duration of block and improved post-operative analgesia without any associated hypotension or other adverse events, especially when used at doses less than 5 μg[130]. A qualitative review and meta-analysis on the role of dexmedetomidine in neuraxial blocks had concluded that it is a favorable local anesthetic adjuvant providing prolonged anesthesia and analgesia and decrease the need for rescue analgesics; however, it is often associated with a higher incidence of bradycardia[131]. Comparative evaluation of dexmedetomidine and clonidine has revealed the superiority of dexmedetomidine when used as an adjuvant for epidural or intrathecal administration[132,133].

Since 2004, when it was first used as a local anaesthetic adjuvant in Ⅳ regional anaesthesia, the use of dexmedetomidine in peripheral nerve blocks have evolved with burgeoning evidence of considerable utility in such situations[134]. There have been multiple studies claiming increased effectiveness of use of dexmedetomidine and this has been consolidated in a meta-analysis examining the effectiveness of dexmedetomidine as a peripheral nerve block adjuvant[135].

The meta-analysis examined primarily brachial plexus blocks at doses of 0.75 μg/kg, 1.0 μg/kg, 30 μg and 100 μg and found significant prolongation of motor block and reduced requirement of rescue analgesics[135]. The studies in this review did not reveal any increase in the incidence of hypotension as a significant adverse effect. However, reversible bradycardia was observed in less than 10% of the patients. Sensory block prolongation was not statistically significant[135].

Subsequently, there have been studies in supraclavicular, interscalene, cervical plexus and ulnar nerve blocks where dexmedetomidine has been shown to increase quality and duration of analgesia of commonly used local anaesthetics like ropivacaine and bupivacaine[136-141]. An interesting study found that dexmedetomidine fared significantly better than clonidine when used as a adjuvant in supraclavicular blocks[142]. Neuro-toxicity of dexmedetomidine, especially when used in perineural spaces is a valid

concern. Surprisingly, preliminary evidence seems to suggest that dexmedetomidine has potential for neuroprotection, especially when compared with lidocaine and bupivacaine[143,144].

Hence current evidence seems to suggest that dexmedetomidine is effective when used as an adjuvant in peripheral nerve blocks in doses of 1 μg/kg. The adverse affect profile seems to be acceptable with known complications such as hypotension and bradycardia which are responsive to conventional therapies[145].

Steroids

Dexamethasone: Dexamethasone is a potent anti-inflammatory agent which has been investigated in the last decade for its role as an adjuvant to local anaesthetics in neuraxial as well as peripheral nerve blocks.

The mechanisms by which steroids potentiate the analgesic effects seem to be different from its intrinsic anti-inflammatory mechanism[146,147]. There is also evidence to show that the local action on nerve fibres and systemic effects, both potentiate dexamethasone's analgesic properties[148,149].

A study examined the effect of intrathecal dexamethasone in a dose of 8 mg (preservative free) with standard doses of hyperbaric bupivacaine 0.5% in orthopedic surgeries. It was shown to significantly prolong the duration of sensory block in spinal anaesthesia without any significant adverse effects[150].

Epidural dexamethasone in dose range of 4-8 mg has also been investigated for its analgesic efficacy and a recent meta-analysis has looked at its effectiveness[151]. The meta-analysis showed the advantages of the use of dexamethasone as an adjuvant to epidural local anaesthetics. However, it also highlighted the need of further well powered studies to establish its safety in terms of neurological complications[151].

Dexamethasone in a dose range of 1, 2, 4 and 8 mg has largely shown to be efficacious as a local anaesthetic adjuvant in a variety of blocks such as supraclavicular and inter-scalene brachial plexus block, ankle block and TAP block[152-155]. In fact, a meta-analysis exploring the use of dexamethasone as an adjuvant in brachial plexus block has found it to significantly prolong the duration of block of conventional local anaesthetic solutions[156]. A recent study by Liu *et al*[157] demonstrated that perineural dexamethasone (1, 2 and 4 mg) prolonged the duration of analgesia and motor blockade of bupivacaine in patients receiving supraclavicular brachial plexus nerve block for ambulatory shoulder surgery. This effect was despite the fact that most patients in the study population as well as control group received intravenous dexamethasone as well, hence refuting the assumption that perineural dexamethasone produced analgesia because of systemic absorption[157]. However, in some studies the use of perineural dexamethasone has not produced desirable results and it continues to be debated whether the analgesia produced by dexamethasone is related to its systemic effects[158-160].

Other anti-inflammatory agents

Other than dexamethasone, there have been very few studies on anti-inflammatory agents as perineural local anesthetic adjuvants. Neurotoxicity of neuraxial or perineural non-steroidal anti-inflammatory drugs (NSAIDs) as adjuvants has been a major concern. Although there are studies showing prolongation of the effect of local anaesthetics with epidural instillation of Parecoxib and Lornoxicam[161,162], the use of epidural Lornoxicam has also shown "histopathological signs of neurotoxicity". There is very little research evidence available on the use of anti-inflammatory medications in peripheral nerve blocks and further studies are warranted. Until new evidence comes up, their use cannot be recommended for neuraxial and peripheral nerve blocks.

Other drugs

Midazolam: Neuraxial midazolam acts on the benzodiazepine receptors on the gray matter of the spinal cord, the highest concentration of which is found on the lamina Ⅱ of the dorsal horn. The analgesic effect of neuraxial midazolam is caused by the spinal suppression of sensory functions and its anti-nociceptive effect mediated by GABAergic and opioid receptor mechanisms[163-168].

Intrathecal midazolam in a dose of 1-2.5 mg has been shown to be effective in providing prolonged post-operative analgesia without significant adverse effects in adults undergoing orthopedic, urological and lower abdominal surgeries, parturients undergoing caesarean sections and children undergoing urologic procedures[169-178]. Prochazka reported the safe use of intrathecal midazolam as a useful adjuvant for prolongation of analgesia in 775 patients over a period of 10 years[179].

Studies have found that epidural midazolam in doses of 50 μg/kg potentiates the effect of bupivacaine in patients undergoing upper abdominal surgery[180]. Similarly, it has also been found to potentiate the effect of caudal epidural bupivacaine by increasing the time to first analgesic requirement and decreasing the need for post-operative analgesia in children undergoing inguinal herniotomy[181].

Neurotoxicity of intrathecal and epidural midazolam in animal models has been a concern[182-184]. However, its use in a cohort study in 1100 patients by Tucker *et al*[185] conclusively proved that neuraxial midazolam is not associated with any adverse neurological or bladder-bowel symptoms in conventional therapeutic doses. Midazolam is not currently recommended for use in peripheral nerve blocks[145].

Neostigmine: Intrathecal neostigmine has been found

to cause analgesia by muscarinic receptor mediated mechanisms[186-188]. Studies have reported its usage in the dose of 5-10 μg to as high as 50-150 μg in the intrathecal route with increased doses showing greater association with nausea and vomiting, bradycardia, agitation and restlessness[189-196].

Epidural neostigmine in the doses of 1 μg, 2 μg and 4 μg have also been investigated and have been found to be efficacious local anaesthetic adjuvants[197,198]. Studies on the use of neostigmine as a peripheral nerve block adjuvant have been very few and have exhibited very little clinical prolongation of anaesthesia and have shown to be associated with troublesome gastrointestinal adverse effects. Currently its use in peripheral nerve blocks is not recommended[199].

Neurotoxicity of perineural neostigmine remains a concern, especially because animal studies have shown mixed results and human studies have essentially found the adverse effect to be related to its dose, with doses less than 50 μg not being associated with any adverse effects[200-203].

Ketamine: Ketamine, a NMDA receptor antagonist has been explored for its local anesthetic properties[204]. Preservative free forms of ketamine are recommended for neuraxial use because of the evidence of neurotoxicity due to its preservative[205]. Ketamine has been shown to exert analgesic effects by epidural, caudal and spinal routes by a multitude of mechanisms involving N-methyl-D-aspartate (NMDA), Cholinergic, adrenergic and 5-hydroxytryptamine receptors or 5-HT receptors[206-213].

Intrathecal and epidural ketamine has been studied most commonly in patients undergoing caesarean section, prostate surgeries and orthopedic procedures. It has been found to potentiate the effect of local anaesthetics by shortening the onset of sensory and motor block, but simultaneously decreasing the duration and extent of motor block[214-219]. This effect profile of intrathecal ketamine (early onset and decreased duration of action) has led to its use in day care surgeries wherein the early return of full motor power could be advantageous[220].

Caudal ketamine in a dose of 0.5 mg/kg has been studied in children undergoing lower abdominal surgeries and has prolonged the duration of analgesia without significant adverse effects[221]. A systematic review of caudal ketamine use concluded that though efficacious, there are uncertainties related to its neurotoxicity[222]. The association of neuraxial ketamine use with troublesome adverse effects which seems to be a dose dependant phenomenon with lower doses associated with lesser systemic effects[219,223].

Use of ketamine in peripheral nerve blocks has shown it to be associated with unacceptably high incidence of adverse affects such as psychotomimetic sequelae (hallucinations, drowsiness, nausea) without any increase of block duration. Currently, ketamine is not recommended for use in peripheral nerve blocks[224].

Magnesium sulfate: Magnesium sulfate is an NMDA receptor antagonist and inhibitor of voltage gated calcium channel. It had been investigated for its analgesic properties in a variety of clinical scenarios and routes of administration[225]. It had been shown to reduce the postoperative analgesic requirements in a variety of cases.

Intrathecal administration of magnesium sulfate has been shown to suppress nociceptive impulses in neuropathic pain and potentiates opioid anti-nociception in animal studies[226,227]. In humans, profound motor and sensory block for up to 3-27 h was reported in orthopedic, general surgery and gynecological procedures[228]. The duration of spinal opioid analgesia in patients requesting analgesia for labor was significantly prolonged by co-administration of magnesium sulfate with no effect on motor block, sensory block or the incidence of adverse effects like pruritus[229]. Magnesium sulfate has been used in doses of 25-100 mg along with opioids (fentanyl/sufentanyl) with or without local anaesthetic agents (lidocaine, bupivacaine, levobupivacaine and ropivacaine)[225].

A rapid onset of sensory block has been reported with epidural administration of magnesium sulfate as an adjuvant to local anaesthetic agents in thoracic and orthopedic surgeries with a lower incidence of post-operative shivering, nausea and vomiting[230-232]. A faster onset of action, longer duration of actions and reduced breakthrough pain with no change in adverse effects or fetal outcome was observed when magnesium sulfate was used as an adjuvant in labor analgesia[233].

Magnesium sulfate has been used as an adjuvant to local anaesthetics in interscalene and supraclavicular brachial plexus block, axillary block, femoral nerve block and popliteal nerve block. It has shown to increase the duration of analgesia without any adverse effects[234-237].

The adverse effects of neuraxial use of magnesium sulfate has been reported in isolated cases and are restricted to bradycardia, hypotension, sedation, headache, disorientation or periumbilical burning pain[238,239].

Animal studies were the first to report neurological complications and pain at injection site in a dose dependant manner, especially at dose more than 2-3 mg/kg[240]. Although neurodegenerative changes on intrathecal administration of magnesium sulfate into the rat spine have been reported[241], histological evidence of direct neuronal injury is lacking in canine models, thus suggesting that the neurological injury associated with the use of magnesium sulfate in neuraxial blocks may be species specific[242,243]. The

lack of well defined neurotoxicity studies for the use of magnesium sulfate precludes any recommendation for its use as an adjuvant to local anaesthetic agents[145].

FUTURE TRENDS

There has been an ongoing search for agents and techniques which would prolong local anaesthetic action without its deleterious effects, primarily systemic toxicity and neurotoxicity. Butyl-amino-benzoate is an ester local anaesthetic agent, which though not strictly an adjuvant, has shown to provide pain relief for up-to 14 wk by novel mechanisms such as blockade of sodium and potassium channels[244-247].

Another novel approach has been to use charged molecules to produce local anaesthetic action, as with tonicaine and n butyl tetracaine[248-251]. Although onset is slow because of the time required to penetrate neuronal membranes, the duration of action is prolonged because of charge properties. However, more human trials are required before these novel local anesthetics can be used in routine clinical practice.

Recent advancement in the world of perineural local anaesthetic use has been the progress in new age delivery mechanisms such as liposomal, microspheres and cyclodextrin systems. Liposomes are microscopic lipid vesicles ranging in size from 0.02-40 μm which have the advantage of acting as a reservoir of drug with low bioavailability resulting in prolonged analgesic effects without systemic toxicity[252-254]. Liposomal local anesthetics have been used in multiple routes[255,256] and had shown prolonged analgesia with less motor block in various populations[257-259]. However there are concerns about their potential toxicity because of the compounds, their metabolites and breakdown of the liposomal core[260]. Microspheres and cyclodextrins are also alternatives drug delivery systems which have shown initial promises in animal models[149,261-264].

Among other adjuvants, adenosine showed initial promise because of its analgesia mediated at the spinal adenosine receptors and inherent anti-inflammatory actions without any neurotoxicity in initial animal studies[265-267]. However human studies using intrathecal adenosine (0.5-1.0 mg) as well as its use as an adjuvant to local anaesthetic solutions in peripheral nerve blocks have shown no additional benefit[268-270]. Dextrans, a complex branched polysaccharides derived from sucrose, had been hypothesized to form water soluble complexes with local anesthetics and thereby prolonging the duration of analgesia by sustained action at the store of its deposition, as well as by altering the local pH favorably[271,272]. Human studies on the use of dextrans as a local anaesthetic adjuvant have been mixed, some showing advantage and others being inconclusive and there remains a need for further high powered studies[273-276].

Neuromuscular blocking drugs have also been explored as local anaesthetic adjuncts and have shown promising results in peri-bulbar blocks and intravenous regional anaesthesia with good results[277-281]. However there have been concerns of such use being associated with local anesthetic toxicity and prolonged motor blockade[282].

A summary of commonly used local anaesthetic adjuvants is given in Table 1.

CONCLUSION

Adjuvant to local anesthetics is an evolving and exciting field of anesthesia practice with new technology promising to improve patient satisfaction and safety. While opioids continue to be the most commonly used local anesthetic adjuvant in clinical practice, alpha-2 receptor antagonists, especially dexmedetomidine, has been shown to potentiate the effect of local anaesthetics with an acceptable safety profile. Use of adjuvants to local anesthetic should take into consideration the available evidence and the advocated safe dose ranges, its effective routes of administration, the adverse effect profile of use of such adjuncts as well as preparedness to manage life threatening complications such as Local Anesthesia Systemic Toxicity (LAST). Its users should be aware of its neurotoxicity potential following perineural use and watch for its clinical implications. Search for newer molecules and techniques allowing for lesser perineural doses of local anesthetic, enhanced analgesic effect and improved safety profile are expected to guide further studies in future to fill up the present lacuna in evidence about the use of adjuvant for local anaesthetics.

Table 1 Summary of the commonly used local anaesthetic adjuvants

Name of drug	Routes and dosages	Adverse effects	Recommendations for use	Mechanism of action
Morphine[12,22]	Intrathecal: 100-200 μg Epidural: 1-5 mg Peripheral nerve block: 75-100 μg/kg	Pruritus Nausea vomiting Respiratory failure	Useful in neuraxial blocks Not recommended for peripheral nerve blocks	
Fentanyl[23-26,30-35]	Intrathecal: 10-25 μg Epidural: 2-4 μg/mL Peripheral nerve block	Same adverse effects as morphine Adverse effect profile slightly favourable in neuraxial use Increased sedation, bradycardia and hypotension	Useful in neuraxial blocks Not recommended in neuraxial blocks due to inconsistent results	Spinal opioid receptor
Sufentanyl[36-40]	Intrathecal: 1.5-5 μg Epidural: 0.75-1.0 μg/mL Not used in peripheral nerve blocks		Efficacious in neuraxial blocks	Local action in peripheral nerve blocks
Hydromorphone[41-44]	Intrathecal: 100 μg Epidural: 500-600 μg Not used in peripheral nerve blocks	Better adverse effect profile than Morphine	Useful in neuraxial blocks	
Buprenorphine[5,45-48]	Intrathecal: 75-150 μg Epidural: 150-300 μg Peripheral nerve block: 300 μg		Good efficacy in neuraxial and peripheral nerve block routes	
Tramadol[49-72]	Intrathecal: 10-50 mg Epidural: 1-2 mg/kg Peripheral nerve block: 1-5 mg/kg	Nausea and vomiting	Present evidence supports use in epidural infusions Poor evidence in peripheral nerve block studies	Weak opioid agonist actions Sodium/potassium channel blocking actions Blockade of norepinephrine and serotonin uptake
Clonidine[89-121]	Intrathecal: 15-40 μg Epidural: 25-50 μg Peripheral nerve block: 0.5-5 μg/kg (150 μg is the maximum allowed dose in PNB)	Sedation Bradycardia Hypertension Adverse effects show association with dose	Good quality evidence to support use in neuraxial blocks especially at lower dosages In PNB prolongs block with Bupivacaine but poor efficacy with Ropivacaine and levobupivacaine Additional benefit in Alcohol withdrawal	Activation of post junctional alpha-2 receptors in dorsal horn of spinal cord
Dexmeditomidine[122-147]	Intrathecal: 5-10 μg Epidural: 1 μg/kg Peripheral nerve block: 20-150 μg	Sedation Bradycardia Hypertension Adverse effects show association with dose	Prolongation of neuraxial and peripheral nerve blocks with good efficacy of use	Mechanism similar to Clonidine
Dexamethasone[148-161]	Intrathecal: 8 mg Epidural: 4-8 mg Peripheral nerve block: 1-8 mg	Adverse effects minimal Advantageous to prevent ponv Troublesome paresthesias with PNB use	Efficacious in neuraxial blocks, however better studies required Prolongs nerve blockade in PNB	Local action on nerve fibers
Midazolam[164-184]	Intrathecal: 1-2.5 mg Epidural: 50 μg/kg diluted in 10 mL of saline	Sedation Respiratory depression	Neurotoxicity is a major concern in neuraxial and peripheral nerve routes Not recommended for routine neuraxial and PNB use	GABAergic and opioid receptor mechanisms
Neostigmine[185-202]	Intrathecal: 5-10 μg to 50-150 μg Epidural: 1, 2 and 4 μg Peripheral nerve block-not investigated	Neuraxial use associated with bradycardia, restlessness PNB use associated with gastrointestinal adverse effects	Lower dosages recommended for neuraxial use Not recommended for PNB use (neurotoxicity in animal models)	Enhancement of endogenous acetylcholine at nerve terminal

Ketamine[203-223]		Neuraxial use associated with nausea, vomiting and hallucinations	Neuraxial use-shortens onset and duration of anesthesia	NMDA receptor antagonists shown to have local anesthetic properties
		PNB use associated with psychomimetic sequelae	Not recommended for PNB use	Cholinergic, adrenergic and 5HT mechanisms
Magnesium[224-238]	Intrathecal: 25-100 mg	Headache	Prolongs analgesia and quality of block by all perineural routes	NMDA receptor antagonism
	Epidural: 50-100 mg	Cardiovascular disturbances	However more studies required to determine minimal effective doses	Voltage gated calcium channel blockade
		Nausea vomiting	Not recommended for routine use	

PNB: Peripheral nerve block; NMDA: N-methyl-D-aspartate; 5HT: % hydroxyl-tryptamine.

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