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Adjuvant Drugs for Peripheral Nerve Blocks: The Role of NMDA Antagonists, Neostigmine, Epinephrine, and Sodium Bicarbonate

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Abstract

The potential for misuse, overdose, and chronic use has led researchers to look for other methods to decrease opioid consumption in patients with acute and chronic pain states. The use of peripheral nerve blocks for surgery has gained increasing popularity as it minimizes peripheral pain signals from the nociceptors of local tissue sustaining trauma and inflammation from surgery. The individualization of peripheral nerve blocks using adjuvant drugs has the potential to improve patient outcomes and reduce chronic pain. The major limitations of peripheral nerve blocks are their limited duration of action and dose-dependent adverse effects. Adjuvant drugs for peripheral nerve blocks show increasing potential as a solution for postoperative and chronic pain with their synergistic effects to increase the duration of action and decrease the required dosage of local anesthetic. N-methyl-d-aspartate (NMDA) receptor antagonists are a viable option for patients with opioid resistance and neuropathic pain due to their affinity to the neurotransmitter glutamate, which is released when patients experience a noxious stimulus. Neostigmine is a cholinesterase inhibitor that exerts its effect by competitively binding at the active site of acetylcholinesterase, which prevents the hydrolysis of acetylcholine and subsequently retaining acetylcholine at the nerve terminal. Epinephrine, also known as adrenaline, can potentially be used as an adjuvant to accelerate and prolong analgesic effects in digital nerve blocks. The theorized role of sodium bicarbonate in local anesthetic preparations is to increase the pH of the anesthetic. The resulting alkaline solution enables the anesthetic to more readily exist in its un-ionized form, which more efficiently crosses lipid membranes of peripheral nerves. However, more research is needed to show the efficacy of these adjuvants for nerve block prolongation as studies have been either mixed or have small sample sizes.

Keywords: Peripheral Nerve Blocks, NMDA Antagonists, Adjuvants, Neostigmine, Bicarbonate, Epinephrine

1. Context

Much attention has been brought to the use of opioids for both acute and chronic pain in recent years. The overuse of opioids for pain control has quadrupled the prescription opioid deaths since 1999 (1). Although opioids can be beneficial in controlling both acute and chronic pain, the risk for dependence and overuse and numerous side effects, including urinary retention, constipation, sedation, and other adverse effects, make the reliance on opioids problematic (2, 3).

The pathophysiology of pain is multi-faceted and involves components of peripheral and central nervous systems. As surgery is noted to be one of the most common causes of chronic pain (22.5% of chronic pain), the transition from acute postoperative pain to chronic pain is the focus of increasing research (1). Risk factors for the transition to chronic pain include younger age, female gender, obesity, surgical technique, anesthetic type, and other psychosocial factors (4). Other potential risk factors for

chronic postoperative pain include genetic mutations in COMT, OPRM1, GCH1, and others (1). The complexity of chronic pain necessitates the individualization of genetic, physiologic, and pharmacokinetic properties of nonopioid pain treatments (5).

To decrease the morbidity and mortality due to opioid use, peripheral nerve blocks are a promising answer for acute pain and the transition to chronic pain management. The use of peripheral nerve blocks for surgery has gained wide acceptance as it minimizes peripheral pain signals from the nociceptors of local tissue sustaining trauma and inflammation from surgery.

Peripheral nerve blocks have gained popularity as improvements in ultrasound technology enable safe, precise techniques for local anesthetic injection. Despite improvements in technique, peripheral nerve blocks are limited by the duration of action (6). Continuous peripheral nerve blocks (CPNB) provide long-term pain control via the transcutaneous insertion of a catheter to the targeted nerve or plexus through which local anesthetic can be infused (7). Although CPNB provides an effective alternative for long-term pain management, disadvantages of cost, difficulty in insertion, and morbidity with catheter-associated infections and incidental dislodgement often outweigh its advantages (8). Due to these concerns, the use of an adjuvant drug that extends the duration of action of the local anesthetic, which can be given in a single injection, is more favorable (9).

Dose-dependent adverse effects of peripheral nerve blocks are reduced by adjuvant drugs but not entirely eliminated. Local anesthetic systemic toxicity (LAST) is one of the most concerning adverse effects of peripheral nerve blocks due to its systemic effects and long duration of neurologic complications. Other adverse effects include vascular puncture, hemorrhage, peripheral nerve injury, and infection (10). Despite these complications, peripheral nerve blocks are an effective alternative in postoperative and chronic pain management, especially in patients who are at high risk of opioid abuse or side effects of respiratory depression, urinary retention, and cognitive impairment (2). NMDA antagonists, neostigmine, epinephrine, and sodium bicarbonate play an important role as potential adjuvants for local anesthetics.

2. NMDA Antagonists

N-methyl-d-aspartate (NMDA) receptor antagonists are a viable option for patients with opioid resistance and neuropathic pain due to their affinity to the neurotransmitter glutamate, which is released when patients experience a noxious stimulus (11). There are several NMDA receptor antagonists, each with unique levels of activity on a specific receptor, with some such as ketamine having adverse central nervous system (CNS) side effects that include hallucinations, confusion, a dreamlike state, and irrational behavior (12). However, when utilized as an adjuvant with opioids, ketamine can improve postoperative analgesia and reduce total morphine consumption in patients undergoing thoracic and abdominal surgeries (13, 14). Memantine, amantadine, and dextromethorphan do not have the same extensive list of adverse side effects compared to ketamine and methadone, but they also do not show linear long-term reduction of pain (15-17).

Although ketamine demonstrates more neurotoxicity when used as an adjuvant for local anesthesia, it also directly inhibits Na^+ channels where action potentials and pain are initially created and maintained (4). In patients with chronic regional pain syndrome (CRPS), ketamine, when administered with a local anesthetic, demonstrate sympatholytic traits against heat allodynia without adverse side effects in the CNS when injected at 0.5 mg/kg (18).

While these NMDA receptors collectively prevent the development of opioid tolerance, reduce pain scores, and decrease pain medication consumption, it is understood that more randomized clinical trials must be done to isolate NMDA's physiological activation from its pathological activation to minimize or eliminate CNS adverse effects on patients (19). Furthermore, additional studies must be done to pinpoint the exact concentration for these adjuvants to be effective in managing pain across the board (20). Caution must be practiced when administering local anesthesia in pediatric patients due to the risk of compartment syndrome, inhibition of motor functions, and an increase in plasma levels (21). For safety, adjuvants like epinephrine, clonidine, and ketamine without preservatives should be administered because the potential of adverse side effects associated with these drugs are low in children (21). Furthermore, location techniques such as electrocardiogram guidance, stimulating catheters, and ultrasonography should be utilized when placing catheters and administering blockade in children to assure children's comfort (21).

2.1. Neostigmine

Neostigmine is a cholinesterase inhibitor that increases acetylcholine levels at nerve terminals (22). It exerts this effect by competitively binding at the active site of acetylcholinesterase, which prevents the hydrolysis of acetylcholine and subsequently retaining acetylcholine at the nerve terminal (23). Cholinesterase inhibitors are commonly used in anesthesia to reverse the effects of nondepolarizing muscle relaxants, which competitively inhibit acetylcholine receptors at the motor endplate. The increased level of acetylcholine in the synaptic cleft com-

petes for the binding of acetylcholine receptors and facilitates the degradation of the muscle relaxant. With newer, shorter-acting muscle relaxants and the development of specific reversal agents such as sugammadex for rocuronium and vecuronium, however, cholinesterase inhibitors have become less common in anesthesia in recent years (22). The potential of cholinesterase inhibitors as adjuvants for local anesthetics has yet to be fully determined.

It is thought that the potential of neostigmine as an adjuvant is not through its action on endplates containing nicotinic receptors but through its action to increase acetylcholine at muscarinic junctions of peripheral nerves (24). Cholinesterase inhibitors activate intrinsic ascending and descending cholinergic pathways to exhibit a dose-dependent effect (25). The use of neostigmine as a central nerve anesthetic and adjuvant has been shown to be effective but of limited use. As a postoperative analgesic, neostigmine has been shown to be an effective intrathecal alternative to opioids following lower limb orthopedic surgeries (25, 26). Activation of the parasympathetic nervous system produces numerous side effects, however, such as nausea, vomiting, diarrhea, and diaphoresis, so the use of neostigmine as an intrathecal analgesic is limited (23). As an adjuvant for epidural anesthesia, it showed efficacy at postoperative analgesia with minimal risk of nausea and vomiting, but it increased the risk of sedation (27, 28). Due to its numerous side effects, it has limited use as a centrally acting agent.

The use of neostigmine in peripheral nerve blocks has shown mixed results in studies. Bone et al. found that 500 mcg of neostigmine used as an adjuvant to 500 mg of mepivacaine in an axillary brachial plexus block resulted in significantly lower pain ratings and decreased the use of analgesics in the first 24 hours postoperatively compared to placebo with no incidence of adverse effects (29). Two other studies, however, showed no improvement in postoperative analgesia (30, 31). Van Elstraete et al. found that 500 mcg of neostigmine as an adjuvant to an axillary brachial plexus block consisting of 450 mg of 1.5% lidocaine and 5 mcg of epinephrine demonstrated no significant difference in duration of analgesia, the need for supplemental analgesia, or in pain ratings compared to placebo. Side effects were not significantly different in the experimental group compared to control (30). Bouaziz et al. compared the use of 500 mcg of neostigmine as an adjuvant to mepivacaine in axillary plexus block through injection of neostigmine either subcutaneously or directly in the block compared to placebo. They found no significant difference in duration of the sensory block between the three groups and a slight decrease in duration of motor block in the subcutaneous neostigmine group compared to the other two groups ($P = 0.045$). In addition, they found significant gastrointestinal side effects in 30% of patients in both neostigmine groups, with no side effects in the placebo group (31). The use of neostigmine as an adjuvant drug for peripheral nerve blocks is not recommended at this time due to limited evidence of an increase in the duration of postoperative analgesia and a significant increase in gastrointestinal side effects (32).

2.2. Epinephrine

Epinephrine, also known as adrenaline, can potentially be used as a local adjuvant to nerve blocks to accelerate and prolong analgesic effects in neuraxial and peripheral nerve blocks (33, 34). However, epinephrine causes vasoconstriction and is often taught to healthcare professionals to not be used in digital nerve blocks (DNB) due to the theoretical risk of digital ischemia and necrosis (33). There is an increased concern when handling patients with compromised circulation in diseases such as peripheral vascular disease (PVD) (33). However, epinephrine is often paired as an adjunct drug to increase the efficiency of additional nerve blocks such as lidocaine, although effects and mechanisms are not always clear (35-37).

In a 2015 systematic review looking at 39 studies, researchers aimed to identify the safety of epinephrine in healthy individuals and those with poor peripheral circulation at a concentration of 1: 100,000 - 200,000 (33). Of the studies examined, one identified complication in healthy individuals, which included hypertensive crisis and infection (38). However, these complications did not occur at an increased rate compared to the control group, who did not receive epinephrine (38). No complications were reported in thousands of DNBs (33). The review concluded that not only was epinephrine safe for healthy individuals but that it also accelerated and prolonged anesthesia and analgesia, decreasing the need for additional local injections (33). Unfortunately, those with poor peripheral circulation are often excluded from research involving DNBs with epinephrine. Therefore the overall evidence is lacking (33). However, in those studies that have included DNBs in individuals with poor peripheral circulation, no complications have been reported (33). If ischemia does appear to occur during the use of epinephrine with DNB, phentolamine can be used to reverse the effects (33).

Additionally, epinephrine can be combined as an adjunct with another peripheral nerve block for increased effectiveness (35-37). For example, the addition of epinephrine to tetrodotoxin (TTX) plus chemical permeation enhancers (CPEs) greatly increases the duration of sciatic nerve block in rats compared to any combination of two of the nerve blocks alone (35). The use of epinephrine reduces the risk of systemic adverse reactions, including mortality associated with TTX (35). This

is believed to potentially be due to the vasoconstriction effects of epinephrine causing retention of local drug concentration, restricting systemic drug distribution (35).

Similar results have been found with the use of epinephrine with lidocaine. Multiple studies have found that the use of epinephrine increases the amplitude and duration of analgesic effects of lidocaine as a peripheral nerve block (36, 37). In rats, epinephrine can prolong the effects of lidocaine in the sciatic nerve by a magnitude of 4-fold (36). Similarly, epinephrine and lidocaine combinations have been used in horses with forefoot lameness to determine safety and efficiency (37). A dilution of 1: 200,000 epinephrine with 1% lidocaine had increased efficacy and duration as a PNB compared to the 1 and 2% lidocaine treatments alone with no adverse reactions (37). In conclusion, epinephrine is a safe adjunct in peripheral nerve blocks that can increase the amplitude and duration of analgesic effects for healthy individuals and those with compromised circulation at a dilution of 1: 100,000 - 200,000.

2.3. Sodium Bicarbonate

The theorized role of sodium bicarbonate in local anesthetic preparations is to increase the pH of the anesthetic. The resulting alkaline solution enables the anesthetic to more readily exist in its un-ionized form. The un-ionized anesthetic more efficiently crosses lipid membranes of peripheral nerves, which theoretically increases the effects of the nerve blockade and results in a more rapid onset of action (32). The amount of sodium bicarbonate needed to produce an effect is variable due to differences in solution pH between individual anesthetics and between manufacturers. For example, mepivacaine and lidocaine are two anesthetics that will readily alkalinize with sodium bicarbonate and can be used with minimal risk of adverse effects. However, with some anesthetic solutions, such as bupivacaine or ropivacaine, sodium bicarbonate must be used in much smaller quantities for this purpose because the anesthetic will more readily precipitate into an insoluble base with even slight increases in pH (39). Because the extent of pH increase remains unknown, the potential of sodium bicarbonate as an adjuvant to peripheral nerve blocks has yet to be fully determined.

Several studies have investigated the use of bicarbonate in peripheral nerve blocks, but the results are inconsistent. In rat models, Yung et al. found that adding sodium bicarbonate to chloroprocaine shortened the onset of action but decreased the duration of the blockade, and adding both bicarbonate and epinephrine to chloroprocaine shortened the onset of action and increased the duration of blockade (40). Human studies have shown conflicting results, and clinical significance remains an issue. In oral peripheral nerve blocks, Shurtz et al. found no significant difference in onset of action, depth of blockade, or pain of injection between buffered and nonbuffered articaine (41). With bupivacaine in oral nerve blocks, Shyamala et al. observed significantly decreased onset of action and pain of injection with the addition of sodium bicarbonate, with no differences in duration of action (42). Other studies showed no significant effect on duration or onset of action with the addition of sodium bicarbonate to peripheral nerve blocks, such as with lidocaine in brachial plexus blocks and with bupivacaine in lumbar plexus blocks (43, 44). Capogna et al. observed significantly shorter onset of action with alkalinized lidocaine and bupivacaine for epidural blocks, alkalinized lidocaine for brachial plexus block, and alkalinized mepivacaine for sciatic and femoral nerve blocks, suggesting that the site of peripheral nerve block may play a role in these inconsistencies (45).

It is difficult to determine the utility of sodium bicarbonate as an adjuvant to peripheral nerve blocks due to conflicting results in studies. Theoretically, sodium bicarbonate could be an effective adjuvant in select peripheral nerve blocks, but more studies may be necessary to fully determine its potential. In addition, current statistically significant findings show decreased onset of action only, but the clinical significance of this is unclear (46). Shyamala et al. observed that the addition of bicarbonate shortened local anesthetic onset of action by one minute, and Tetzlaff et al. observed that sodium bicarbonate shortened the mean onset of action from 2.7 minutes to 1.0 minute (42, 47). These observed differences in onset of action are likely not clinically significant in the perioperative setting, as peripheral nerve blocks are often performed before the patient is taken to the operating room, making a difference of one to two minutes inconsequential (39). Furthermore, the addition of sodium bicarbonate to local anesthetics has not been approved for clinical use, so its use in this role should be performed with caution (13).

3. Clinical Studies: Safety and Efficacy

A prospective, randomized, double-blind study looked at the addition of neostigmine to enhance an axillary brachial plexus nerve block where 34 participants were assigned to 2 groups (29). The treatment group was given 500 μg of neostigmine (1 mL) plus 500 mg of mepivacaine (50 mL), while the control group was given 500 mg of mepivacaine (50 mL) plus saline (0.9%, 1 mL).(48) The study found no difference between the two groups in the time the block took effect and the total duration of the block. However, there was a lower reported pain

rating on a visual analog scale (VAS: 14.7 ± 9.9 vs. 32.4 ± 23.5; P < 0.05) in the neostigmine plus mepivacaine group 24 hours post-surgery (48). In addition, this group required fewer additional analgesics in the first 24 hours post-surgery (P < 0.05) possibly due to the long duration of anti-inflammatory effects. While there were no reported side effects and all cardiovascular functions remained stable with the addition of neostigmine, the sample size of this study was small. The authors concluded that neostigmine was an effective adjuvant anesthetic at relieving postoperative pain with axillary brachial plexus blocks (29).

Another study examined the combined effect of hyaluronidase and lidocaine with epinephrine during inferior alveolar nerve blocks (IAN) (48). This prospective, double-blinded study randomized 30 participants into two groups that received an IAN block at two appointments that were at least one week apart. One group was assigned 24 mg buffered lidocaine plus 12 μg epinephrine into a 1.2 mL volume of solution. The second group was assigned 24 mg buffered lidocaine plus 12 μg epinephrine into a 1.8 mL volume of solution that was buffered with 0.33 mEq/mL of sodium bicarbonate with the addition of hyaluronidase solution (150 USP units) (48). The addition of hyaluronidase did not improve the number of participants who experienced anesthetic success (P < 0.05). Nor did it improve participant's discomfort ratings as measured on a 0 to 3 scale (P < 0.05) but in fact, the lidocaine with hyaluronidase group had an increase in postoperative pain (P < 0.05) than compared to the lidocaine plus epinephrine group. The researchers concluded that hyaluronidase should not be added to anesthetic during an IAN block as there was no additional benefit and a potential to harm healthy tissue (48). Another prospective, double-blinded study that looked at an IAN block examined buffered versus non-buffered lidocaine with epinephrine in patients with symptomatic irreversible pulpitis (48). There was no significant difference in the success of the block as measured by having no or mild pain on a VAS between one group that received 2% lidocaine with 1: 80,000 epinephrine buffered with 8.4% sodium bicarbonate and a second group that received only 2% lidocaine with 1: 80,000 epinephrine (buffered group: 62.5%; non-buffered group: 47.5%; P > 0.05) (49). The same author completed another prospective, randomized, double-blinded study to examine if the same buffered solution was effective as a buccal infiltration during an IAN also in patients with symptomatic irreversible pulpitis (50). One hundred patients were placed into the same two groups as above with a successful block measured as having no or mild pain on a VAS. There was a statistically higher success rate using the buffered solution using a buccal infiltration (buffered group: 78%; non-buffered group: 44%; P < 0.05) (50).

Dexmedetomidine is a highly selective alpha-2 agonist, and has been used as an adjuvant to local anesthetics in many central and peripheral nerve blocks (51-57). Another study looked at adding either dexmedetomidine or epinephrine to 1% mepivacaine during a brachial plexus block (58). Thirty patients aged 18 - 65 years were randomly assigned to 3 groups; one group was given 40 mL of 1% mepivacaine as a control, the second group was given 40 mL of 1% mepivacaine plus an adjuvant of 200 μg of epinephrine, and the third group was given 40 mL of 1% mepivacaine plus an adjuvant of 1 μg/kg of dexmedetomidine. Both groups that had an adjuvant drug added to the anesthetic showed an increase in motor block duration (min) (epinephrine: 334.3 ± 46.5, dexmedetomidine: 349 ± 28.2; P < 0.05) and an increase in sensory block duration (min) (epinephrine: 353.5 ± 53.4, dexmedetomidine: 367.9 ± 35.8; P < 0.05) with no statistical difference between the two adjuvant groups (58). There was also an increased time when first onset of pain, measured in minutes, was felt as compared to the control group (epinephrine: 349.3 ± 50.5, dexmedetomidine: 358.0 ± 36.2; P < 0.05), however, there was no difference between the three groups in onset time to complete block or to mean VAS for the first sensation of pain (P < 0.05) (58). There was a difference in participants affected heart rate as the mepivacaine plus epinephrine group had an increase in heart rate compared to baseline at 10 to 40 min post drug administration (P < 0.05), while the mepivacaine plus dexmedetomidine group had a decrease in heart rate compared to the group with epinephrine at 20 to 40 min (P < 0.05) (58).

Another study evaluated the addition of clonidine at two different potency levels compared to tramadol during a brachial plexus block (59). Ninety patients were randomized with a single-blind investigation into three groups; one group received lidocaine plus 1 μg/kg clonidine, the second group received lidocaine plus a larger dose of 1.5 μg/kg clonidine, and a third group received lidocaine plus 1 mg/kg tramadol. The time to rescue analgesia (min) was significantly shorter with tramadol as an adjuvant as compared to both groups of clonidine and between the two groups of clonidine (tramadol: 313.3 ± 21.4; 1 μg clonidine: 470.7 ± 38.6; 1.5 μg clonidine: 491.8 ± 33.9; P < 0.001) (59). A significantly faster onset to sensory block (seconds) was seen with both groups of clonidine as compared to tramadol (tramadol: 293.6 ± 19.1; 1 μg clonidine: 259.0 ± 39; 1.5 μg clonidine: 241.0 ± 4.3; P < 0.001) and a significantly faster onset to motor block (s) (tramadol: 674.0 ± 180.8; 1 μg clonidine: 462.0 ± 83.6; 1.5 μg clonidine: 396.0 ± 0.2; P < 0.001) (59). When the mean duration of sensory and motor blockade (min) was compared, there was a statistically longer duration between both groups of clonidine and tra-

madol but not between the 2 groups of clonidine (sensory tramadol: 247.2 ± 25.2; 1 μg clonidine: 301.3 ± 34; 1.5 μg clonidine: 315.7 ± 6.9; P < 0.001) (motor tramadol: 186.0 ± 20; 1 μg clonidine: 237.0 ± 18.2; 1.5 μg clonidine: 235.0 ± 2.4; P < 0.001). Both groups with clonidine as an adjuvant remained hemodynamically stable with no major side effects reported. There was additionally less nausea reported with the adjuvant use of clonidine than with tramadol (59).

Another study looked into epinephrine as an adjuvant in digital nerve blocks. This study looked at the use of bupivacaine versus lidocaine with epinephrine in digital nerve blocks to compare pain at the injection site, time of onset, and duration of the block. Twelve patients were randomized in this prospective, double-blinded study into two groups. One group received 1% lidocaine with epinephrine, versus the other group received 0.5% bupivacaine. There was no difference between the median time onset of anesthetic between the two groups (lidocaine + epi: 3.45 min (3 - 8); bupivacaine: 3.30 min (3 - 8); P = 0.84). However, the lidocaine plus epinephrine group did have significantly less pain at the site of anesthetic injection as measured by a 0 - 100mm VAS (median 26.00 mm (4-52) vs. 40.50 mm (10 - 71); P < 0.05). This group also showed a shorter duration of anesthetic (lidocaine + epi: 321 min (228 - 463); bupivacaine: 701 min (24 - 913); P < 0.05) which the authors concluded should still be sufficient to allow the use of lidocaine plus epinephrine use in an emergency room (60).

The effect of epinephrine on potentially affecting perfusion and blood flow was assessed in a randomized controlled trial of supraclavicular brachial plexus blocks. Eighty-two patients were placed in 2 groups where one group received 12.5 mL of 2% lidocaine, 12.5 mL of 0.75% ropivacaine, and 0.1 mL of normal saline in the non-epinephrine group while the other group received 12.5 mL of 2% lidocaine, 12.5 mL of 0.75% ropivacaine, and 5mcg/mL of epinephrine in the epinephrine group. Using a pulse oximeter to assess the perfusion index, the study found the addition of epinephrine did not affect the perfusion index or perfusion index ratio during the block (P = 0.894 and P = 0.079, respectively) (61). All clinical studies are summarized below in Table 1.

3.1. Ketamine as Adjunct to Nerve Block

A three-arm, randomized control trial was conducted to observe effects of mixing ketamine with local anesthetics during ACL reconstruction. The study utilized 87 patients undergoing ACL reconstruction, all with similar demographics and surgery duration. Patients were randomized into three groups which received either a single perineural 40 mL dose of 0.375% ropivacaine, a 40 mL dose of ketamine 40 mg and 0.375% ropivacaine mixture, or a 40 mL dose of 0.375% ropivacaine preoperatively in addition to 40 mg of ketamine intravenously during the operation. Anesthesiologists and patients were blinded to group allocation. Efficacy was assessed using AUC scores based on pain scores from a numerical rating scale at rest and with movement, which was assessed from 4 hours to 48 hours postoperatively. The study also included duration of the sensory block, time to first request for pain medicine, and time to full motor block to find significant differences. No significance was found between the three groups for time to motor block, but the group with the mixture of ketamine and ropivacaine displayed significance reduced post-op pain, more time to first request for analgesics, and longer sensory block. IV-administered ketamine during operation did not produce the same effects as preoperative administration (62).

A case series was published describing the effects of ketamine on three patients with complex regional pain syndrome (CRPS) after gunshot wounds. Patients ranged from 28 - 45 years old and exhibited typical allodynia of CRPS Type II and vicarious pain. Patients first received traditional treatments including pharmacological treatments for nerve pain or satellite ganglion blocks such as bupivacaine with lidocaine, clonidine, or morphine. Patients used a VAS to report temporary relief of their pain, but no lasting relief of other symptoms such as heat allodynia and vicarious symptoms. Patients were then treated with nerve blocks using ketamine as an adjunct with a treatment regimen of 0.5 mg/kg/day. All three patients reported dramatic and lasting relief of all symptoms after this treatment (18).

Another double-blinded clinical trial was conducted to observe the effects of ketamine versus fentanyl as an adjunct to lidocaine for axillary nerve block in 60 patients undergoing upper extremity surgery for fractures. Patients were divided into equal groups to receive either a 1% lidocaine and 50 microgram fentanyl or 1% lidocaine with 30 mg ketamine. Study measures were duration of analgesia after operation, time to first request for pain medication, and amount of pain medicine received over 24 hours. This study found a significant difference in the severity of pain and that there was an increased time to first request for analgesics for the group who received fentanyl as opposed to ketamine. The study concluded that fentanyl may be a better adjunct for axillary nerve block than ketamine but did note that it would be beneficial for higher doses of ketamine to be used in future trials (63).

4. Conclusions

Local anesthetics are often limited in their motor and sensory block durations and the potential for negative side effects in the cardiac and central nervous systems. Some

Table 1. Clinical Efficacy and Safety - Adjuvant Drugs for Peripheral Nerve Blocks

Author (y)	Groups Studied and Interventions	Results and Findings	Conclusions
Bone et al. (1999) (29)	Patients between 18 to 75 y of age, ASA I or II scheduled for an elective upper extremity surgery with an axillary plexus block. Exclusion criteria included the use of analgesics 24 hrs before surgery, pregnancy, history of asthma or arrhythmias, and allergy to anesthesia.	No difference between the two groups in the onset for nerve block and the total duration of the block. Lower reported pain rating on a visual analog scale (VAS: 14.7 ± 9.9 vs. 32.4 ± 23.5; P < .05) in the neostigmine plus mepivacaine group 24 hours post-surgery and they required less additional analgesics in the first 24 hours post-surgery (P < 0.05).	Neostigmine was an effective adjuvant anesthetic at relieving postoperative pain with axillary brachial plexus blocks.
Ridenour et al. (2001) (48)	Healthy subjects not taking medications that alter pain perception. Teeth were free of caries, periodontal disease, large restorations, or trauma.	No improvement in anesthetic success (P < 0.05) with hyaluronidase. lidocaine with hyaluronidase group had an increase in postoperative pain (P < 0.05).	Hyaluronidase should not be added to anesthetic during an IAN block.
Saatchi et al. (2015) (49)	Healthy patients over 18 with active pain in a mandibular posterior tooth. Exclusion criteria included significant medical conditions, allergies to local anesthetics, active areas of disease at the injection site, or taking medications to affect anesthetic assessment.	Was no significant difference in anesthetic success between group using sodium bicarbonate buffered lidocaine with epinephrine vs. non-buffered lidocaine with epinephrine (P > 0.05).	The success of an IAN block in mandibular molars with irreversible pulpitis was not improved with buffering a lidocaine with epi solution with sodium bicarbonate.
Saatchi et al. (2016) (50)	Healthy patients over 18 with active moderate to severe pain in vital mandibular first molar.	Statistically higher success rate using the sodium bicarbonate buffered lidocaine with epinephrine solution vs. non buffered lidocaine with epinephrine using a buccal infiltration (P < 0.05).	The efficacy of an IAN block in mandibular first molars with irreversible pulpitis was improved with sodium bicarbonate buccal infiltration.
Song et al. (2014) (58)	Patients 18 - 65 years of age, ASA I or II scheduled for upper extremity surgery and brachial plexus block. Exclusion criteria included BMI > 35, pregnancy, liver or kidney disorder, diabetic neuropathy, arrythmia, or α-2 adrenergic drug within 2 weeks.	Increase in motor and sensory block duration and an increased time when first onset of pain with epinephrine and dexmedetomidine (P < 0.05). No difference in onset time to complete block as compared to mepivacaine (P < 0.05).	Duration of block and post-op control of pain with dexmedetomidine is similar to epinephrine.
Kelika et al. (2017) (59)	Patients 18 - 50 years of age, ASA I or II with routine or emergency forearm and hand surgery, surgery performed under tourniquet. Patients with cardiovascular, respiratory, CNS, liver, or kidney disease and bleeding disorders were excluded.	Increase in sensory, and motor onset as well increased duration of sensory and motor block, and longer time until rescue analgesic needed with both groups of clonidine as compared to tramadol (P < 0.001).	Clonidine provides a quicker onset and longer-lasting level of a brachial plexus block.
Alhelail et al. (2009) (60)	Patients over 18 years of age without a hx of cardiovascular, liver, diabetes, peripheral vascular disease, or hand conditions.	Less pain at the injection site and shorter duration of anesthetic seen in lidocaine plus epinephrine group (P < 0.05).	Lidocaine plus epinephrine was sufficient to use for emergency room procedures.
Kim et al. (2020) (61)	Patients between 19 and 76 years of age ASA I or II with unilateral upper extremity surgery.	There was no significant difference in the perfusion index or ratio when using epinephrine as an adjuvant drug (P = 0.894 and P = 0.079, respectively).	The PI and PI ratio were not affected with the use of epinephrine.
Zhu et al. (2020) (62)	Patients aged 25 - 45, ASA I or II undergoing elective ACL repair.	No difference in onset of motor block between groups. Decreased post op pain, longer onset for rescue analgesic, and longer duration of sensory block see in ketamine and ropivacaine group.	Ketamine given preoperatively improved patient satisfaction and patients experienced less postoperative pain.
Sunder et al. (2008) (18)	3 case reports of patients aged 28 - 45 years old with gunshot wounds with CRPS Type II.	Dramatic and long-lasting relief of heat allodynia seen with ketamine.	Ketamine impact on central pain pathway showed positive response on heat allodynia symptoms.
Akhondzadeh et al. (2019) (63)	Patients aged 18 to 75 years of age, ASA I or II undergoing upper extremity surgery due to fracture.	The fentanyl group showed less pain 9, 12, and 24 hours post-surgery compared to ketamine group.	Fentanyl may be a better adjuvant for axillary blocks compared to ketamine.

adjuvant drugs have been well studied to recommend use in various environments such as perioperative, acute, or chronic use setting with no reported adverse side effects. The use of adjuvants such as NMDA antagonists, neostigmine, epinephrine, and sodium bicarbonate have shown safety and efficacy in increasing the duration of a peripheral nerve block, increasing the onset of action, improving pain post-op with need for rescue analgesics, or limiting

the required needed dose. However, more research should go into showing the efficacy of these adjuvants for nerve block prolongation as studies have been either mixed or have small sample sizes.

Footnotes

Authors' Contribution: Study concept and design, JGR, SEM, SGM, AJK, EMC, ADK; Analysis and interpretation of data, ANE, JSFG, KAAH, AJK; Drafting of the manuscript, ANE, JSFG, SGM, AJK, EMC, FI, SHK, AMK, ADK; Critical revision of the manuscript for important intellectual content, ANE, SGM, AJK, EMC, FI, SHK, AMK, RDU, ADK; Statistical analysis, JSFG, KAAH, JGR, SEM

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