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Adjuvant Drugs for Peripheral Nerve Blocks: The Role of Alpha-2 Agonists, Dexamethasone, Midazolam, and Non-steroidal Anti-inflammatory Drugs

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Abstract

Adjuvant drugs for peripheral nerve blocks are a promising solution to acute postoperative pain and the transition to chronic pain treatment. Peripheral nerve blocks (PNB) are used in the brachial plexus, lumbar plexus, femoral nerve, sciatic nerve, and many other anatomic locations for site-specific pain relief. However, the duration of action of a PNB is limited without an adjuvant drug. The use of non-opioid adjuvant drugs for single-shot peripheral nerve blocks (sPNB), such as alpha-2 agonists, dexamethasone, midazolam, and non-steroidal anti-inflammatory drugs, can extend the duration of local anesthetics and reduce the dose-dependent adverse effects of local anesthetics. Tramadol is a weak opioid that acts as a central analgesic. It can block voltage-dependent sodium and potassium channels, cause serotonin release, and inhibit norepinephrine reuptake and can also be used as an adjuvant in PNBs. However, tramadol's effectiveness and safety as an adjuvant to local anesthetic for PNB are inconsistent. The effects of the adjuvants on neurotoxicity must be further evaluated with further studies to delineate the safety in their use in PNB. Further research needs to be done. However, the use of adjuvants in PNB can be a way to help control postoperative pain.

Keywords: Peripheral Nerve Block, Postoperative Pain, Adjuvant Medications, Alpha-2 Agonists, NSAIDs, Dexamethasone, Midazolam

1. Introduction

Opioids are the most commonly prescribed analgesia in the postoperative period (1). The overreliance on opioids for pain management has resulted in the quadrupling of deaths from prescription opioids since 1999 (2). Although opioids are an effective treatment in the postoperative setting, the addictive potential makes it challenging to transition away from their use during chronic pain management. Alternative pain treatments are necessary because patients with chronic pain have a higher incidence of cognitive decline and early death (3). Furthermore, the estimated cost associated with chronic pain is $600 billion annually in the US alone (3). In an effort to reduce the reliance on opioid treatment and reduce the morbidity of chronic pain, adjuvant drugs for peripheral nerve blocks are a promising solution to acute postoperative pain and the transition to chronic pain treatment (4).

The pathophysiology of pain is complex and involves both peripheral and central nervous system sensitization, ascending and descending nervous system pathways, and overlapping regions within the brain (2). Current research targets numerous pathways within the complex physiological pathway of nociception. The likelihood of transitioning to chronic postsurgical pain has numerous risk fac-

tors, including age, gender, obesity, surgery duration, type of anesthesia, and psychological factors (2). Genetic mutations involving the COMT, OPRM1, GCH1, and other genes likely play a role in chronic postsurgical pain (2). Improvements in genetics, neurophysiological characterization of patients, and pharmacokinetics of drugs enable better individualized non-opioid treatments of acute and chronic pain (5). Individualized selection of adjuvant drugs used with peripheral nerve blocks (PNB) has the potential to improve patient outcomes.

Patient outcomes are further improved with advances in ultrasound technology that enables precision-guided techniques for peripheral nerve blocks (6). PNBs are used in the brachial plexus, lumbar plexus, femoral nerve, sciatic nerve, and many other anatomic locations for site-specific pain relief. However, the duration of action of a PNB is limited without an adjuvant drug. For example, the average duration of lidocaine and mepivacaine is two to three hours (6). Clonidine, an alpha-2 agonist, increases the duration of the nerve block by two hours in comparison to a local anesthetic alone (6). For longer-term pain control, continuous peripheral nerve blocks (CPNB) provide site-specific anesthesia and reduce or eliminate the use of opioids (7). Although CPNBs are effective for longer duration pain relief, the catheter is difficult to insert, it can dislodge, and there is an additional cost (8). For these aforementioned reasons, a single-shot peripheral nerve block with adjuvant drugs to extend the duration of action is commonly favored.

The use of adjuvant drugs for single-shot peripheral nerve blocks (sPNB), such as alpha-2 agonist, dexamethasone, midazolam, and non-steroidal anti-inflammatory drugs (NSAIDs), extends the duration of local anesthetics and reduces the dose-dependent adverse effects of local anesthetics (9). However, dose-dependent effects of local anesthetics are not eliminated with adjuvant drug use. Additionally, adjuvant drugs can also have dose-dependent neurotoxic effects. A severe adverse effect of local anesthetics is local anesthetic systemic toxicity (LAST). Additional risks of the PNB include hematoma, infection, and peripheral nerve injury (1). Despite these risks, sPNBs are a suitable option for patients who are at high risk of respiratory depression, opioid addiction, opioid-induced nausea, and vomiting or are not responsive to oral medications (6). Alpha-2 agonists, dexamethasone, midazolam, and non-steroidal anti-inflammatory drugs are efficacious adjuvant drugs that require additional research on their safety (10-14).

2. Alpha-2 Adrenergic Agonists (A2AA)

2.1. Clonidine

Clonidine is a commonly used alpha-2-adrenergic agonist in regional anesthesia (14). It has been used as a perineural adjunct to local anesthetics (LA) for peripheral nerve block (PNB) since 1991 to effectively prolong block duration and improve postoperative analgesia (15, 16).

The proposed mechanism for clonidine's action in PNB involves A-alpha (motor) and C (pain) fibers, which have cation currents that restore the resting potential after hyperpolarization to allow for the next action potential generation (17). Clonidine might inhibit these currents by increasing potassium conduction, thus blocking conduction of the pain fibers and prolonging the duration of the local anesthetic action (18, 19). It more strongly inhibits C fibers than A-alpha fibers, resulting in more sensory-specific effects than motor ones (17). Additionally, clonidine might also be delaying local anesthetic removal and enhancing its action by vasoconstriction (18, 19).

Pöpping et al.'s 2009 meta-analysis found that 30 - 300μg of clonidine used as a perineural adjunct with LA in PNB prolongs the duration of postoperative analgesia by about 2 hours; while this increase is independent of LA type, the relative gain was markedly higher with intermediate-acting LAs (56%) over long-acting LAs (18%) (16). The study found the motor and sensory blocks to be prolonged by 2.5 h and 1.25 h, respectively (16).

Clonidine can cause hemodynamic instability owing to its antihypertensive nature and result in bradycardia, arterial and orthostatic hypotension, sedation, rebound hypertension, and syncope (20-22). A controlled dosage of 0.5 μg/kg up to a maximum of 150 μg is recommended to prevent such side effects, but an optimal perineural clonidine dose is yet to be determined (17, 19). Clonidine is Federal Drug Administration (FDA)-approved for intrathecal and epidural uses, but its safety for PNB usage is considered to be "grandfathered" and generally accepted in anesthesia (23).

2.2. Dexmedetomidine

Dexmedetomidine is a newer alpha-2 agonist that has an eight-fold higher alpha-2 selectivity than clonidine, with an alpha-2: alpha-1 receptor specificity of 1,600:1 and a safer side effect profile (20, 24-26). Its sedative, anxiolytic, and analgesic properties suitably position DEX as a non-opioid adjuvant to local anesthetics (27-31).

The proposed mechanism for perineural dexmedetomidine in PNBs as first studied in rat models is similar to that of clonidine, which relies not on alpha-2 agonism mechanism, but instead blocks hyperpolarization-activated Ih cation currents and causes vasoconstriction

for prolonged analgesia (27-32). Perineural dexmedetomidine adjunct use is off-label, and proper risk-benefit analysis, especially in patients where bradycardia and hypotension would be concerning, would be necessary before even more widespread use of dexmedetomidine in PNBs can be expected (17, 33-35).

While both clonidine and dexmedetomidine could moderately prolong PNB, they both have the potential for causing hypotension and bradycardia at higher doses, warranting caution in their usage (13, 36). However, these two alpha-2-agonists could promise to be useful in multimodal perineural analgesia regimens (36, 37).

2.3. Dexamethasone

Dexamethasone is a glucocorticoid that is commonly used to decrease the body's inflammatory response. Doses of 1, 2, 4, and 8 mg have been used as an adjuvant in interscalene, supraclavicular, ankle, and brachial plexus blocks (6). However, when dexamethasone is used as an adjuvant in a PNB, the specific mechanism of action is unknown (38, 39). Dexamethasone may produce extended analgesia through vasoconstriction and reduced absorption of local anesthetic or through "direct action on the nerve cell to reduce neural discharge" (8).

Despite having an unknown mechanism, a Cochrane review of 35 trials of 2702 participants determined that perineural dexamethasone adjuvant increased sensory block 6.7 hours (95% confidence interval) in comparison to a placebo (8). Similarly, intravenous dexamethasone increased sensory block 6.2 hours in comparison to a placebo. The Cochrane review also determined that the cumulative 24-hour opioid consumption was significantly reduced for both the perineural and intravenous dexamethasone (19.25 mg reduction and 6.58 mg reduction, respectively) (8). Of note, De Oliveira's (2014) quantitative review determined that perineural dexamethasone decreased postoperative opioid consumption when bupivacaine or ropivacaine was used, but not when lidocaine was used (40). Although the Cochrane review demonstrated, perineural dexamethasone is superior to intravenous dexamethasone in extending the duration of a spinal block, Zhao (2017) determined (through a systemic review and meta-analysis of RCTs) that perineural dexamethasone can prolong the PNB effects only when epinephrine is co-administered (41). Epinephrine is a well-known adjuvant that increases the duration of local anesthetic through vasoconstriction. Zhao (2017) suggests that epinephrine and dexamethasone have a synergistic effect on extending perineural PNB duration. In terms of controlling late postoperative pain, most studies agree that the use of dexamethasone as an adjuvant has no significant effect on pain beyond 24 - 48 hours. The Cochrane review shows a significant decrease in pain with perineural administration at 12- and 24-hours post-surgery (no significant difference between placebo and dexamethasone adjuvant at the 48-hour mark) (8). In contrast, the De Oliveira review shows that a dexamethasone adjunct is ineffective, in comparison to the placebo, beyond 24 hours post-surgery (40).

Despite the relative agreement on the efficacy of dexamethasone, the safety profile has not been adequately studied. Gagne (2021) expands on the Cochrane review and examines nerve deficits beyond one month after surgery. The results of the Gagne (2021) study show that 62% of dexamethasone recipients had a nerve deficit, and 59% of the ropivacaine-only PNB patients had a nerve deficit at the two-week visit (42). At the six-month follow-up visit, 65% of the patients that had a nerve deficit in the dexamethasone group had not fully recovered, and 40% of the ropivacaine-only nerve deficit group had not recovered. The Gagne (2021) study shows "a 2-fold increased risk of delayed recovery when perineural dexamethasone was used as an adjunct" (42). Due to potential neurotoxicity and an inadequate understanding of the mechanism of action of dexamethasone, intravenous administration is preferable (43).

2.4. Midazolam

Midazolam is a short-acting benzodiazepine, chiefly used preoperatively as an anxiolytic agent and a sedative and also often employed in diagnostic and surgical procedures to induce sleep (12, 43, 44). The data for the use of midazolam as an adjunct to local anesthetics in peripheral nerve blocks are limited in the field's current literature landscape (45). Midazolam could be a promising adjuvant owing to its ability to maintain the patient's hemodynamics (unchanged blood pressure and heart rate), relatively low costs, rapid action onset, and metabolic clearance that is better than other benzodiazepines that could warrant its further characterization (46, 47).

The proposed mechanism for midazolam-induced nerve block involves it acting at the translocator protein (TPSO) (48). This has replaced the previous idea of midazolam acting on peripheral g-aminobutyric acid or GABA-A receptors, which are involved in producing midazolam's properties of sedation, anti-anxiety, and anterograde amnesia (44).

Midazolam has a weak interaction with the kappa opioid receptors, suggesting that it can play a part in pain control (49). Its action on the limbic system relieves negative emotions of anxiety and fear during surgery, and this reduction of the patient's psychological stress response, in turn, lowers the risk of cardiovascular and cerebrovascular accidents (44). Midazolam can be extremely useful in

upper extremity surgical procedures by helping block conduction of pain signals, prolong block duration, and particularly help with pain due to brachial plexus block (BPB) insufficiency through its analgesic and sedative properties (44). Midazolam usage as an adjuvant in PNB is discussed further in a later section.

3. Tramadol and Non-steroidal Anti-inflammatory Drugs (NSAIDs)

3.1. Tramadol

Tramadol is a weak opioid that acts as a central analgesic (50). It can block voltage-dependent sodium and potassium channels, cause serotonin release, and inhibit norepinephrine reuptake (36, 51). When administered parenterally or orally, tramadol effectively aids in managing acute postoperative pain in adults (52, 53). It can also produce a local anesthetic effect in blocking motor and nociceptive function or act as an adjuvant in peripheral nerve blocks to prolong sensory and motor block effects (36, 50). This analgesic can inhibit pain either through a μ-receptor-mediated opioid action or an α2-adrenergic and serotoninergic non-opioid action (52, 53). Tramadol usage as an adjuvant in PNB is discussed further in a later section.

3.2. NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used for many decades for their analgesic, anti-inflammatory, and antipyretic properties. They can be a better perioperative adjuvant choice than opiates for their ability to produce effective analgesia without causing respiratory depression (54, 55). NSAIDs block prostaglandins synthesis by inhibiting cyclooxygenase (COX) 1 and 2, thus limiting downstream cytokine release and reducing the inflammatory response (18, 56).

3.3. Parecoxib

Parecoxib sodium is a highly selective COX-2 inhibitor that is favored as an adjunct in acute postoperative management (55). It reduces postoperative pain, opioid consumption, and drug-related adverse reactions that all accelerate postoperative patient recovery (55). A 2019 study by Qiao et al. investigated intravenous parecoxib sodium in a transverse abdominis plane (TAP) block in patients who underwent hepatectomy for hepatocellular carcinoma (56). The use of parecoxib significantly lowered pain scores without significant adverse events, showing the safety of the drug and efficacy in managing acute postoperative pain when used as an adjuvant for TAP peripheral nerve block (56). It is important to note that parecoxib is not FDA approved for use in the USA. However, it is approved in Europe.

3.4. Ketorolac

Ketorolac prolongs local anesthesia action in regional anesthesia by inhibiting prostaglandin synthesis, and a dosage of 20 - 60 mg has been shown to benefit postoperative analgesia when used as a part of intravenous regional anesthesia (IVRA) (57, 58). Use of this drug with local anesthetic lidocaine in a peripheral nerve block for foot surgery increased analgesia duration and quality (59). However, ketorolac as an adjuvant in infraclavicular BPB could not prolong the duration of motor and sensory blocks and quicken their onset and dexmedetomidine (57). These results were consistent with the Budnyk et al. study, where ketorolac could not increase sensory and motor block duration when used as an adjuvant to bupivacaine in BPB (57).

Adjunct usage of NSAIDs is more widely explored in IVRA than in peripheral nerve blocks. In addition to ketorolac, paracetamol, and dexketaprofen added to lidocaine, prolonged motor and sensory blocks quickened their onset and reduced analgesic consumption (60). Similar benefits with adjunct use of NSAIDs like lornoxicam, tenoxicam, and lysine acetylsalicylate in IVRA have also been demonstrated (58). Perineural usage of NSAIDs in peripheral nerve blocks is not recommended until further research exploring their safety and efficacy and federal approval for this purpose (18, 36).

4. Clinical Studies: Safety and Efficacy

4.1. Dexmedetomidine

Evidence for dexmedetomidine as an adjunct for PNB is the strongest for BPB (61). As supported by a 2017 meta-analysis of 34 trials, perineural dexmedetomidine adjunct use in BPB effectively prolonged duration of analgesia by 4.5 h and motor and sensory blocks by 3 and 4 h, respectively, and decreased onset time of sensory block by 9 min and motor block by 8 min (62). A 2018 meta-analysis of 46 trials showed significant prolongation of postoperative analgesia by 5 h and motor blockade by 4 h in 25 to 150 μg perineural dexmedetomidine administration with long-acting LA in PNB (35).

Dexmedetomidine has been shown to prolong analgesia duration when added to bupivacaine, levobupivacaine, or ropivacaine for PNBs (63). A recent study investigated the efficacy of dexmedetomidine as an adjunct by comparing its use with ropivacaine in interscalene brachial plexus block (ISBs) versus only ISB for patients undergoing arthroscopic rotator cuff repair (63). The authors found the combination of dexmedetomidine and ISB significantly decreased postoperative visual analog scores (VAS) and significantly increased patient satisfaction scores (SAT) within the first 48 postoperative hours compared to the control

group (63). Additionally, dexmedetomidine also showed lower mean levels of interleukin 6 and 8 and delayed rebound pain (63). Given that ISB has a relatively short duration of effect, despite being one of the most powerful regional blocks for shoulder procedures, prolonged analgesia due to dexmedetomidine being an effective adjuvant to ropivacaine is highly beneficial in PNBs. A related study that compared dexmedetomidine with ropivacaine in a suprascapular nerve block (SSNB) and axillary nerve block (ANB) to only SSNB and ANB again found significantly lower VAS, higher SAT scores with the adjunct use, and delayed rebound pain (52). Given that SSNB is the most prevalent method for pain control in arthroscopic shoulder surgery, dexmedetomidine effectively enhancing the block as an adjuvant to LA in peripheral nerve blocks is promising (52).

The efficacy of dexmedetomidine as an adjuvant has also been evaluated in TAP block, where it has proved useful in enhancing block duration in many surgical procedures (64). 1μg/kg of dexmedetomidine with 20 mL of 0.125% bupivacaine in TAP in laparoscopic appendicectomy, compared to only bupivacaine, prolonged postoperative analgesia (7.33 vs. 4.8 h), and reduced the number of patients who needed rescue analgesics (56.7 vs. 80%).(66) Pain scores were significantly lower with dexmedetomidine at 2, 4, 6, and 24 h post-surgery (but comparable at 8 and 12 h timepoints) (64). The authors claimed that there is no difference in the safety profile of dexmedetomidine versus the control group and reported no additional risk of hemodynamic instability (64). Ultimately, the authors conclude dexmedetomidine to be a safe and effective adjuvant for TAP block. These results are consistent with a 2019 meta-analysis, which investigated the same in abdominal surgery patients and found dexmedetomidine to significantly reduce postoperative pain and opioid use and prolong sensory block in TAP block (65). It found no difference in the incidence of bradycardia, hypotension, postoperative nausea, and vomiting, etc (65).

The 2018 meta-analysis also showed up to three times higher risk of intraoperative hypotension and bradycardia with perineural dexmedetomidine over placebo, an association that should be evaluated cautiously owing to the low quality of evidence (35). The 2017 meta-analysis too reported transient and reversible side effects of bradycardia and hypotension (62). Neurotoxicity data for dexmedetomidine is inconsistent (19).

A dosage of 50 - 60 μg dexmedetomidine is recommended in BPB to maximize sensory block duration while minimizing hemodynamic side effects (61, 62). While a similarly strong recommendation for other PNBs is lacking and necessitating more dose-comparison studies, the literature consensus is 1 μg/kg dexmedetomidine to prolong peripheral nerve blockade by 200 min (36, 51). Meta-analyses suggest that dexmedetomidine is a stronger analgesic than clonidine but weaker than non-steroid inflammatory drugs; perineural dexmedetomidine is superior to clonidine but inferior to dexamethasone in terms of block characteristics indices and also has a greater risk of hypotension and sedation than dexamethasone (37, 66).

Any perineural applications of dexmedetomidine have been off-label, and special attention must be paid to the safety of the medication (67). FDA does not approve its peripheral administration (68). Adverse events, most commonly bradycardia and hypotension, have been mostly documented in adjuvant use of dexmedetomidine in BPB (67). Meta-analysis suggests that a dosage of more than 50 μg increases the risk for bradycardia (68). More large random controlled trials focusing on adverse events caused by dexmedetomidine as an adjuvant in PNBs are necessary to further characterize the safety of the drug.

4.2. Dexamethasone

Dexamethasone is one of the most studied and extensively used adjuvants administered to prolong peripheral nerve blockade duration with local anesthetics (69). It is believed to prolong PNB duration better than local anesthetics alone and increase sensory blockade (70, 71).

Perineural dexamethasone use in peripheral nerve block increases mean analgesia duration by about 1.5h and decreases opioid consumption by 7 mg at 24h and postoperative pain scores at 12h and 24h (19). It is most thoroughly evaluated for brachial plexus block in the literature, where 4mg of the additive has been reported to be the lowest sufficient dose in PNB (19, 69, 72).

As an adjuvant for supraclavicular brachial plexus, dexamethasone prolongs motor and sensory blockade with bupivacaine and levobupivacaine (72). A 2019 random controlled trial investigated 4 mg of dexamethasone with 3 mL of 0.56% ropivacaine found no beneficial effect in prolonging sensory block in a standard peripheral block, in either perineural or I.V. administration (69). At an 8 mg dose with 0.5% levobupivacaine for brachial plexus block in upper extremity surgery, it delayed requirement and time until rescue analgesia, quickened sensory and motor block onset, and prolonged sensory and motor blockade duration (72).

A 2021 meta-analysis of 6 RCTs found no significant difference amongst dexamethasone and dexmedetomidine for analgesia duration, sensory block onset, and motor and sensory block duration in PNB (73) However, when compared to dexmedetomidine, dexamethasone reduced fentanyl analgesic consumption by about 29 μg (73). A 2020 study showed that 1 μg/kg dexmedetomidine or 8 mg dexamethasone as an adjuvant to 0.5% ropivacaine in supraclavicular brachial plexus block significantly shortened

motor and sensory onset, prolonged motor and sensory block duration, and reduced 24h total analgesics, without any significant difference between the two (74). However, dexmedetomidine had better patient satisfaction owing to more sedation than with dexamethasone (75). Dexamethasone's ability to enhance analgesia duration by more than 6h is better than that achieved by adjuvants like clonidine (71). Its usage with levobupivacaine is most favorable as it does not produce side effects associated with adjuvants of clonidine, dexmedetomidine, or opioids (72). When compared to midazolam (2 mg) as an adjuvant for 0.5% bupivacaine in supraclavicular brachial plexus block, dexamethasone (4 mg) produced significantly faster onset of sensory and motor blocks, prolonged analgesia, sensory and motor blocks duration, and lower VAS scores (75). As Marhofer and colleagues highlight, despite several systematic reviews and meta-analyses to date, the efficacy of dexamethasone with local anesthetic in PNB is still uncertain due to low-quality evidence (as addressed by the authors of each themselves) and the high heterogeneity of the study designs (59).

Dexamethasone is still off-label for peripheral administration (73). The safety profile of dexamethasone remains open to debate (72). While some in-vitro studies show peripheral neurotoxicity produced by dexamethasone, others show it mitigating bupivacaine-induced neurotoxicity (69, 70). Large doses of dexamethasone (up to 133 μg/mL) can increase ropivacaine-induced neurotoxicity, but at clinically relevant concentrations, this combination did not increase neurotoxicity (76). While dexamethasone does not disrupt hemodynamic variables or produce any other adverse side effects, it could increase postoperative glucose concentration after perineural or intravenous administration (19, 75, 77). There are also concerns about localized nerve and muscle injury and inconsistent evidence for perineural versus systemic administration regarding dexamethasone use (19). Significantly higher rates of nerve injury might not be detected until sample sizes are much larger and conclusively show dexamethasone to be safe (78). In their 2021 review, Desai and colleagues recommend 0.1 - 0.2 mg/kg of dexamethasone administered via the systemic route for LA adjunct use in surgical procedures that can involve significant postoperative pain (19). More dose-finding studies are needed to determine the optimal dose of dexamethasone (73). Ultimately, it is a promising adjuvant candidate in peripheral nerve blocks and is likely the best option to prolong analgesia over other candidates like clonidine or midazolam (70).

4.3. Tramadol

Tramadol's effectiveness and safety as an adjuvant to LA for PNB are inconsistent (17, 19, 36, 51). Several studies and systematic reviews have investigated tramadol as an adjuvant in BPB but often yielded contradictory results (52, 79).

Reviews by Koyyalamudi et al. and Kirksey et al. investigate tramadol with different local anesthetics (like bupivacaine, levobupivacaine, mepivacaine, and ropivacaine) in various PNBs (interscalene, axillary brachial plexus) reveal the often contradictory nature of the results (19, 36). Recently, a 2019 RCT found that 100 mg tramadol with 0.5% ropivacaine for interscalene BPB lowered pain scores and cumulative morphine consumption 24h post-surgery (79). The authors claimed that the low incidence of complications suggests the safety of tramadol-ropivacaine combination to improve postoperative analgesia (79). Won Shin et al.'s 2017 meta-analysis of 16 RCTs reported 100 mg tramadol as prolonging sensory block, motor block and analgesia (high-quality evidence), and quickening sensory and motor block onsets for BPB in upper extremity surgeries (52). Tramadol also did not change adverse events incidence after BPB in their analysis (52). The findings for perineural versus systemic administration and the potential for neurotoxicity are still unclear (19, 36). While there have been no reports of nerve damage due to tramadol, its perineural administration is not FDA-approved and not recommended as an adjuvant in PNB (19, 51, 52).

4.4. Midazolam

A 2005 study by Jarbo and colleagues is primarily cited in support of efficacious perineural adjunct use of midazolam, where 50 μg/kg of the drug was used with 30 mL of 0.5% bupivacaine LA for a supraclavicular BPB (80). The authors reported enhanced onset of sensory and motor blockade, reduction of pain scores, and postoperative analgesia without any adverse effects (80). These results were replicated by a 2008 study, where once again 50 μg/kg midazolam with 30 mL of 0.5% bupivacaine for supraclavicular BPB increased onset speed of sensory and motor blocks, prolonged duration and quality of the blocks, and enhanced analgesia (lower pain scores and fewer rescue analgesics) (81). A 2020 study by Xu and colleagues strongly recommends adjuvant use of midazolam in BPB for upper limb surgery after finding benefits in its intravenous supplementation (44). However, the interactions of midazolam with the local anesthetic used in the procedures or the potential for midazolam neurotoxicity were not discussed in the study.

Besides in brachial plexus blocks, midazolam has also lately been explored as an adjuvant to bupivacaine for a TAP block. A 2019 prospective randomized control trial by El Kenany and colleagues of this purpose reported a reduction in 24h morphine use and prolongation of postoperative analgesia (47). They assuaged the concern of neurotoxicity through the use of the established dosage of 50 μg/kg

of midazolam (but with 20 mL of 0.25% bupivacaine) that has previously been proven to be safe (47). In their 2021 review, Desai et al. describe the results for perineural effectiveness of midazolam to be conflicting due to unclear evidence about its benefits over systemic administration (52). The authors ultimately did not recommend perineural use of midazolam (19).

The greatest concern about midazolam adjuvant use in PNB is its potential neurotoxicity (47). Multiple animal studies show intrathecal midazolam administration to be neurotoxic and midazolam's ability to significantly worsen neuronal cytotoxicity when combined with LA (36, 45). Currently, adjuvant use of midazolam is not FDA-approved and is strongly advised against being used perineurally with LA in PNB until more high-quality safety data is obtained (23, 36, 45, 51).

Interestingly, midazolam produces no in-vitro or in-vivo neurotoxicity when used with a combination of clonidine-buprenorphine-dexamethasone that lacks any LA (23). Additionally, a 2015 study proposes that midazolam-induced nerve block and its neurotoxicity are separatable, where selectively activating the translocator protein (TPSO) could minimize the potential for neurotoxicity (48). Until further research, midazolam as an adjuvant in PNB is currently limited to use at an established dosage with documented local anesthetics for this purpose.

5. Conclusions

Adjuvant drugs for peripheral nerve blocks are a promising solution to acute postoperative pain and the transition to chronic pain treatment. Many have shown in studies to increase the length of time the block is active and decrease the use of rescue pain medications in the postoperative period. Clonidine and dexmedetomidine are alpha-2 agonists that have been shown to prolong PNB. Dexamethasone has been shown to work better than both of the alpha-2 agonists. However, it shows no significant effect on pain beyond 24 - 48 hours. Others include midazolam, tramadol, and NSAIDs. Research on these adjuvants is not robust, and so many of them are not FDA approved as an adjuvant. The effects of the adjuvants on neurotoxicity must be reviewed with further studies to delineate the safety in their use in PNB. Their efficacy shows promise in recent studies. Further research needs to be done. However, the use of adjuvants in PNB can be a way help control postoperative pain.

Footnotes

Authors' Contribution: Study concept and design, SP, PI, AJK, EMC, ADK; Analysis and interpretation of data, ANE, GMH, HS, AJK; Drafting of the manuscript, ANE, GMH, PI, AJK, EMC, FI, KM, AMK, ADK; Critical revision of the manuscript for important intellectual content, ANE, PI, AJK, EMC, FI, KM, AMK, RDU, ADK; Statistical analysis, GMH, HS, SP.

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