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Review

Common peripheral Nerve Block Adjuvants in Combination with Local Anaesthetics

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Abstract

Effective postoperative pain control is crucial. Various techniques are used for this purpose, including continuous nerve blocks, liposomal local anesthetics, and adjuvants added to local anesthetics. While continuous blocks offer advantages, they have challenges and failure rates. Liposomal local anesthetics also have limitations. Adjuvants, categorized as "old" and "new," can extend regional block duration. Epinephrine primarily prolongs local anesthetic effects through localized vasoconstriction. Sodium bicarbonate alkalization benefits specific peripheral nerve blocks but has varying outcomes. Alpha-2 adrenoreceptor agonists like clonidine and dexmedetomidine can extend analgesia but may lead to side effects through systemic absorption. Opioid agonists such as buprenorphine and tramadol yield variable results depending on the surgical type, with potential benefits through intravenous or intramuscular administration. The review further emphasizes the significance of adjuvants like corticosteroids and NMDA (N-Methyl-D-Aspartate) receptor antagonist magnesium sulfate in consistently prolonging analgesia when combined with local anesthetics. The comprehensive analysis of peripheral nerve block adjuvants provides valuable insights for healthcare practitioners to navigate this dynamic field and optimize pain management strategies. It underscores the evolving landscape and the necessity of considering patient-specific factors, surgical context, and available evidence in the selection of adjuvants. The call for further research highlights the ongoing efforts to refine the use of adjuvants for safe and effective postoperative pain management.

Keywords: *peripheral nerve blocks, adjuvants in nerve blocks, local anaesthetics, surgical pain management, extended analgesia*

Introduction

Peripheral nerve blocks (PNBs) have become increasingly integral in modern anesthesia and pain management, revolutionizing the way we provide surgical anesthesia and postoperative pain relief. By targeting specific nerves or nerve clusters, PNBs offer a localized, effective means of blocking pain signals, enabling patients to undergo various surgical procedures with minimal discomfort (1). This approach has gained prominence as an alternative to general anesthesia (GA) and neuraxial anesthesia, with several notable advantages, including improved pain control, reduced systemic side effects, and enhanced patient satisfaction (2). In recent years, the field of PNBs has witnessed a remarkable evolution driven by advancements in techniques and the introduction of adjuvants, which are adjunctive agents administered in combination with local anesthetics. These adjuvants play a pivotal role in extending the duration of analgesia, enhancing the quality of pain relief, and ultimately optimizing patient outcomes (3). Their application varies from traditional agents such as epinephrine and sodium bicarbonate to newer, more specialized compounds like dexamethasone, dexmedetomidine, buprenorphine, tramadol, and magnesium sulfate (4). The selection and use of these adjuvants have become crucial decision points for healthcare professionals performing PNBs. To navigate this evolving landscape effectively, a comprehensive understanding of the mechanisms of action, clinical effects, and safety profiles of these adjuvants is essential. This review aims to provide a thorough exploration and analysis of commonly employed peripheral nerve block adjuvants when combined with local anesthetics. By synthesizing the existing body of knowledge and research, we endeavor to equip healthcare practitioners with the knowledge and insights required to make informed decisions regarding the incorporation of adjuvants into their PNB protocols.

This review delves into the realm of common peripheral nerve block adjuvants when combined with local anesthetics, offering a comprehensive analysis of their roles, advantages, and considerations in contemporary anesthesia and pain management practices.

Methodology

This study is based on a comprehensive literature search conducted on November 8, 2023, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed common peripheral nerve block adjuvants in combination with local anesthetics. There were no restrictions on date, language, participant age, or type of publication.

Discussion

Typically, the duration of analgesia from a local anesthetic is limited to 12-16 hours, which may not cover the night hours when medical staffing is reduced (5). Ensuring optimal pain control, especially during the first postoperative day and night, is crucial. Therefore, various clinical techniques are employed to extend standard analgesia following the initial local anesthetic deposition. These methods encompass continuous nerve/plexus blocks with local anesthetic infusions, liposomal forms of local anesthetics, and the intravenous or perineural delivery of adjuvants (6).

While continuous peripheral nerve blocks offer many advantages, their routine use is hampered by factors such as organizational challenges and a significant rate of block failures (7). These failures can be attributed to primary factors related to difficulties during catheter implantation and secondary factors, which include catheter dislocation, spontaneous migration, or local anesthetic leaks (8). Secondary factors are the primary contributors to continuous block failures, with spontaneous migration or local anesthetic leakage occurring in 30-40% of properly implemented sets. Liposomal forms of local anesthetics face limitations in terms of registration,

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availability, and cost, making them less commonly used for prolonging peripheral blocks (9). Additionally, some of these formulations lack approval in certain regions. Another approach to extending regional block duration involves the use of adjuvants, classified as "old" or "new" based on their inclusion in the literature (10). "Old" adjuvants include adrenaline, sodium bicarbonate, clonidine, buprenorphine, tramadol, midazolam, and magnesium sulfate, while "new" adjuvants encompass dexamethasone and dexmedetomidine. These adjuvants can help prolong the effects of regional blocks, offering valuable options for pain management **(Table 1)**.

Table 1. Common peripheral nerve block adjuvants in combination with local anesthetics

Adjuvant Category	Examples	Mechanism of Action	Common Uses
Vasoconstrictors	Epinephrine	Localized vasoconstriction	Prolonging local anesthetic effects
Alkalizing Agents	Sodium Bicarbonate	Raises pH, enhances nerve block onset	Specific peripheral nerve blocks
Alpha-2 Agonists	Clonidine, Dexmedetomidine	Prolongs sensory blockade	Extending analgesia, reducing systemic effects
Opioid Agonists	Buprenorphine, Tramadol	Extends nerve block duration	Various surgical procedures
Corticosteroids	Dexamethasone	Prolongs blockade duration	Enhancing analgesia
NMDA (N-Methyl-D-Aspartate) Receptor Antagonist	Magnesium Sulfate	Blocks NMDA receptors	Potential enhancement of anesthesia
Benzodiazepines	Midazolam	Enhances local anesthetic effects	Limited exploration as peripheral adjuvant

NMDA: N-Methyl-D-Aspartate

Epinephrine

Epinephrine, commonly added at concentrations of 2.5-5 mg per mL of anesthetic injection, extends the duration of many local anesthetics. This is primarily attributed to localized vasoconstriction, which reduces anesthetic dissipation. While there is some suggestion of a direct effect on neural tissue, early studies with bilateral ulnar nerve blocks in volunteers demonstrated that epinephrine significantly prolonged analgesia for lidocaine and prilocaine, even with intradermal injections of bupivacaine, lidocaine, and prilocaine (11, 12). The primary mechanism appears to be localized vasoconstriction, rather than a direct effect on the anesthetic. Epinephrine decreases local blood flow and slows the clearance of the anesthetic, particularly in areas where epinephrine is present. However, the impact of epinephrine varies among different local anesthetics. For instance, it doesn't affect the duration of the sensory block when added to ropivacaine hydrochloride 0.5% (13). Epinephrine also delays the entry of local anesthetic into the bloodstream, allowing for the use of safer doses in vascular spaces. However, it can lead to unwanted side effects if systemically absorbed. Therefore, small amounts are often added to test doses to detect catheter placement errors. Regarding ropivacaine, recent studies challenge the notion that epinephrine has no significant effect on limiting systemic absorption, as it can reduce arterial ropivacaine levels and alter sensory block duration (14). Importantly, the addition of sodium bicarbonate to epinephrine-containing anesthetic solutions can rapidly degrade epinephrine, raising concerns about preparation timing (15). In summary, epinephrine primarily prolongs local anesthetic effects through localized vasoconstriction, but its impact varies depending on the specific anesthetic used. Clinicians should exercise caution regarding solution preparation and timing when using such combinations.

Sodium bicarbonate

Adding sodium bicarbonate to a local anesthetic solution raises its pH, promoting the un-ionized form of the anesthetic and potentially expediting nerve block onset (16). This approach is suitable for mepivacaine and lidocaine, with a common addition of 1 meq of sodium bicarbonate per 10 mL of local

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anesthetic. However, for bupivacaine, caution is required due to the risk of precipitation, limiting the use to small amounts, approximately 0.12 meq per 10 mL (17). Ropivacaine presents greater challenges, as even just 0.1 meq of sodium bicarbonate can lead to visible precipitation in a short time, making it unsuitable for alkalization at higher concentrations (0.75% and 1%) (18). The clinical outcomes of sodium bicarbonate alkalization vary. In interscalene brachial plexus blocks, alkalization of mepivacaine hydrochloride 1.4% with epinephrine 5 mg/mL accelerated sensory and motor block onset (19). However, it had no impact on lumbar plexus nerve blocks using bupivacaine hydrochloride 0.5%. In some instances, alkalization unexpectedly delayed the onset of lidocaine in femoral and sciatic nerve blocks (17). Consequently, the benefits of sodium bicarbonate alkalization for local anesthetics are uncertain and may be advisable only for specific peripheral nerve blocks. It is essential to note that the time from nerve block placement to surgical incision is typically much longer than the onset time of unalkalinized local anesthetics, potentially limiting the clinical impact of alkalization.

α-2 Adrenoreceptor agonists

Clonidine

Clonidine, an a2-selective adrenergic agonist, is commonly used to enhance nerve blocks (20, 21). A recent analysis of 20 trials found that perineural clonidine (typically 30-300 mg, with 150 mg common) extended pain relief time by about 2-2.5 hours (22) **(Table 2)**. It also prolonged sensory blockade for most local anesthetics, except mepivacaine. However, systemic absorption led to side effects like low blood pressure, sedation, bradycardia, and fainting. Some suggest smaller doses (0.5-1.0 mg/kg) to reduce these effects (22, 23).

Table 2. Advantages of peripheral nerve block adjuvants in combination with local anesthesia

Advantages	Description
Effective Pain Control	Highly effective pain relief for various procedures.
Localized Pain Management	Target specific nerves, minimizing systemic effects.
Reduced Systemic Side Effects	Decreased risk of nausea, vomiting, and CNS effects.
Prolonged Analgesia	Extended duration of pain relief.
Enhanced Block Quality	Improved quality of sensory and motor blockade.
Potential for Lower Anesthetic Doses	May allow for lower total local anesthetic doses.
Patient Satisfaction	Higher patient satisfaction and improved surgical experiences.
Reduced Opioid Use	Decreased opioid consumption, reducing opioid-related risks.
Flexibility in Pain Management	Tailor pain management strategies to patient needs.
Support for Enhanced Recovery After Surgery	Facilitates early mobilization and supports ERAS protocols.

Dexmedetomidine

Dexmedetomidine, a highly selective alpha-2 adrenoceptor agonist, provides sedative, hypnotic, and analgesic effects with a strong preference for alpha-2 receptors over alpha-1 receptors, making it seven times more specific than clonidine (24). It may induce hypotension and bradycardia as side effects. In general anesthesia, dexmedetomidine reduces the need for inhaled anesthetics and opioids (25). As a nerve block adjuvant, it has

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shown modest effects in human studies. For example, adding 100 mg of dexmedetomidine to 40 mL of levobupivacaine 0.5% during axillary brachial plexus block significantly delayed the need for additional analgesics (26). Similar results were observed when 1 mg/kg of dexmedetomidine was added to 10 mL of ropivacaine hydrochloride 0.5% for posterior tibial nerve blocks, significantly prolonging sensory block duration (27). However, perineural dexmedetomidine can lead to reductions in blood pressure and heart rate, necessitating careful patient selection.

Opioid agonists as adjuvants in peripheral nerve blocks

Buprenorphine

Buprenorphine, a potent mu-opioid receptor agonist, effectively extends nerve block duration when combined with local anesthetics (28). For example, in a study, adding buprenorphine 0.3 mg to a local anesthetic mixture tripled analgesia duration for a perivascular brachial plexus block without causing opioid-related side effects (29). In comparison, perineural buprenorphine significantly delayed pain onset in an axillary brachial plexus block, while intramuscular administration had intermediate effects, with no differences in opioid-related side effects. In foot or ankle surgery, perineural buprenorphine 0.3 mg with bupivacaine hydrochloride 0.5% delayed opioid use by six hours for a sciatic nerve block, with no significant opioid-related side effects and similar patient satisfaction (30). For rotator cuff repair under interscalene block, perineural buprenorphine 0.15 mg extended analgesia without significant respiratory depression or nausea/vomiting (31). Perineural buprenorphine (150–300 mg) effectively prolongs peripheral nerve block duration, potentially through the inhibition of voltage-gated sodium channels, similar to local anesthetics (32).

Tramadol

Tramadol, a versatile pain medication, extends analgesia when combined with local anesthetics for nerve blocks, but its effects vary by surgery type (33). In one study, adding tramadol hydrochloride 100 mg to levobupivacaine 0.5% for arthroscopic surgery nearly doubled analgesia duration (34). For hand or forearm surgeries, it didn't prolong nerve block duration. In studies with tramadol hydrochloride (40, 100, and 200 mg) and mepivacaine hydrochloride 1.5% for axillary brachial plexus block, sensory and motor block durations were similar to placebo, but fewer tramadol patients needed postoperative pain relief. Tramadol hydrochloride 200 mg with lidocaine hydrochloride 1.5% extended sensory block duration but delayed onset (35). Perineural tramadol had no effect on ropivacaine hydrochloride 0.75% nerve blocks. In a psoas compartment block with levobupivacaine, 0.5%, perineural and intravenous tramadol hydrochloride 1.5 mg/kg showed no significant differences in analgesia or block duration. Perineural tramadol hydrochloride 100 mg in axillary brachial plexus block with mepivacaine hydrochloride 1% significantly prolonged sensory and motor block durations compared to intravenous tramadol (36). Surgery type influences tramadol's effectiveness, and intravenous or intramuscular tramadol may offer benefits while minimizing concerns about neural toxicity.

Corticosteroids

Dexamethasone, a glucocorticoid, consistently extends analgesia duration when added to local anesthetics, although the ideal dose is uncertain. In one study, 8 mg of dexamethasone with mepivacaine 1.5% for supraclavicular brachial plexus block slightly delayed pain onset without complications (37). For interscalene blocks with ropivacaine 0.5% or bupivacaine 0.5%, 8 mg of dexamethasone prolonged the time to the first analgesic request significantly (38). Another study used 4 or 8 mg of dexamethasone with bupivacaine 0.5% for interscalene block extended time to moderate pain and reduced supplemental tablet requests. In axillary brachial plexus block with lidocaine 1.5%, 8 mg of dexamethasone more than doubled sensory and motor blockade durations without affecting onset times (39). The exact mechanism of dexamethasone's action in prolonging blockades remains unclear but may involve increased inhibitory potassium channel activity on nociceptive C fibers through glucocorticoid

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receptors (40). Studies have not reported adverse effects or neurotoxicity, but more research is necessary (41). Intravenous administration of dexamethasone offers a viable alternative to perineural use.

Ketamine

Ketamine, known for its anesthetic and analgesic properties, has shown potential as a peripheral nerve block adjuvant but lacks sufficient evidence for routine use (42, 43). In one study for hand or forearm surgery, adding ketamine 30 mg to ropivacaine 0.5% for an interscalene block did not significantly impact block duration or onset (44). Some patients experienced transient adverse effects, but no treatment was required. Another study used a high ketamine dose of 2 mg/kg with articaine 2% for an axillary brachial plexus block, extending anesthesia from 1.2 to 4.2 hours (45). However, concerns arose about systemic absorption due to the absence of a control group for other administration routes, and the frequency of adverse effects was unspecified. Intravenous regional anesthesia (Bier block) with ketamine 0.3% or 0.5% (0.6 mL/kg) provided comparable anesthesia to procaine without the latter's potential toxicity (46). However, volunteers found ketamine's psychotomimetic adverse effects unacceptable after tourniquet release. Currently, routine use of ketamine as a peripheral nerve block adjuvant cannot be recommended.

Midazolam

Midazolam, a water-soluble benzodiazepine, is known for enhancing the effects of local anesthetics via gamma-aminobutyric acid type A receptors, especially when used epidurally or intrathecally (47-49). Its potential as an additive for peripheral nerve blocks is less explored. Studies suggest that adding midazolam (50 mg/kg) to bupivacaine hydrochloride 0.5% for supraclavicular brachial plexus block can accelerate sensory blockade onset, extend duration, and reduce postoperative pain (50). A similar study produced comparable results but lacked blinding measures, introducing potential bias (51). Despite animal studies showing no neurotoxic effects, the safety of midazolam as a perineural adjunct remains uncertain (52, 53). Due to its modest impact on sensory blockade duration, its use in peripheral nerve blocks is not recommended without further safety data.

Magnesium

Magnesium, known for regulating neuronal calcium and blocking NMDA receptors, shows promise for enhancing anesthesia and analgesia through intravenous or intrathecal use (54). However, its role as an additive in peripheral nerve blocks needs more investigation. In one study, axillary brachial plexus blocks with prilocaine hydrochloride 2% combined with intravenous or perineural magnesium extended analgesia effectively (55). Another study added magnesium sulfate to interscalene block with bupivacaine hydrochloride 0.5%, prolonging nerve block duration and reducing pain scores (56). Similarly, magnesium sulfate with levobupivacaine 0.25% in femoral nerve blocks extended blockades while reducing opioid use (57). While promising, more comprehensive clinical data are needed to recommend routine use, considering concerns about potential neurotoxicity and unclear mechanisms (58). Established alternatives like ropivacaine hydrochloride 0.75% or levobupivacaine 0.5% offer longer-lasting effects (31).

Conclusion

PNBs have emerged as a pivotal component of modern anesthesia and pain management, offering localized pain relief for various surgical procedures. The integration of adjuvants with local anesthetics has further expanded the utility of PNBs, enhancing the duration and quality of analgesia. Adjuvants like epinephrine, sodium bicarbonate, α-2 adrenoreceptor agonists, opioid agonists, corticosteroids, and others have demonstrated their ability to optimize patient outcomes. However, their selection and use require careful consideration of specific patient needs and safety concerns. The field of PNBs continues to evolve, offering clinicians valuable options for pain relief, and ongoing studies will likely refine our understanding and practice in this area.

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There is no conflict of interest

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Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection, and final writing of the manuscript.

References

1. Crystal CS, Blankenship RB. Local anesthetics and peripheral nerve blocks in the emergency department. Emergency Medicine Clinics. 2005;23(2):477-502.

2. Hutton M, Brull R, Macfarlane A. Regional anaesthesia and outcomes. BJA education. 2018;18(2):52.

3. Nwosu ADG, Chukwu LC, Onwuasoigwe O, Nweze SO, Nwadike K. Redefining the Role of Analgesic Adjuvants in Pain Management: A Narrative Review. Indian Journal of Pain. 2023;37(2):65-73.

4. Emelife PI, Eng MR, Menard BL, Myers AS, Cornett EM, Urman RD, et al. Adjunct medications for peripheral and neuraxial anesthesia. Best Practice & Research Clinical Anaesthesiology. 2018;32(2):83-99.

5. Suresh S, Ecoffey C, Bosenberg A, Lonnqvist P-A, De Oliveira GS, de Leon Casasola O, et al. The European Society of Regional Anaesthesia and Pain Therapy/American Society of Regional Anesthesia and Pain Medicine recommendations on local anesthetics and adjuvants dosage in pediatric regional anesthesia. Regional Anesthesia & Pain Medicine. 2018;43(2):211-6.

6. Gola W, Zając M, Cugowski A. Adjuvants in peripheral nerve blocks–the current state of knowledge. Anaesthesiology Intensive Therapy. 2020;52(4):323-9.

7. Ilfeld BM. Continuous peripheral nerve blocks: a review of the published evidence. Anesthesia & Analgesia. 2011;113(4):904-25.

8. Russon K, Harrop-Griffiths W, Rice A, Justins D, Newton-John T, Howard R, et al. Continuous peripheral neural blockade for acute pain: Hodder Arnold London; 2008.

9. de Araujo DR, da Silva DC, Barbosa RM, Franz-Montan M, Cereda CM, Padula C, et al. Strategies for delivering local anesthetics to the skin: focus on liposomes, solid lipid nanoparticles, hydrogels and patches. Expert opinion on drug delivery. 2013;10(11):1551-63.

10. Cox JC, Coulter AR. Adjuvants—a classification and review of their modes of action. Vaccine. 1997;15(3):248-56.

11. Albért J, Löfström B. Bilateral ulnar nerve blocks for the evaluation of local anaesthetic agents. Acta Anaesthesiologica Scandinavica. 1961;5(3):99-105.

12. Swerdlow M, JONES R. The duration of action of bupivacaine, prilocaine and lignocaine. British journal of anaesthesia. 1970;42(4):335-9.

13. Weber A, Fournier R, Van Gessel E, Riand N, Gamulin Z. Epinephrine does not prolong the analgesia of 20 mL ropivacaine 0.5% or 0.2% in a femoral three-in-one block. Anesthesia & Analgesia. 2001;93(5):1327-31.

14. Lee BB, Kee WDN, Plummer JL, Karmakar MK, Wong AS. The effect of the addition of epinephrine on early systemic absorption of epidural ropivacaine in humans. Anesthesia & Analgesia. 2002;95(5):1402-7.

15. Bailard NS, Ortiz J, Flores RA. Additives to local anesthetics for peripheral nerve blocks: Evidence, limitations, and recommendations.

http://dx.doi.org/10.52533/JOHS.2023.31207

American Journal of Health-System Pharmacy. 2014;71(5):373-85.

16. Brandis K. Alkalinisation of local anaesthetic solutions. Australian Prescriber. 2011;34(6).

17. Capogna G, Celleno D, Laudano D. Which Block, Which Local Anesthetic? Regional anesthesia. 1995;20(5):369-77.

18. Fulling PD, Peterfreund RA. Alkalinization and precipitation characteristics of 0.2% ropivacaine. Regional Anesthesia & Pain Medicine. 2000;25(5):518-21.

19. Tetzlaff JE, Reaney J, Yoon HJ, Stein D, O'hara J, Grimes-Rice M. Alkalinization of mepivacaine accelerates onset of interscalene block for shoulder surgery. Regional Anesthesia and Pain Medicine. 1990;15(5):242-4.

20. Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. The Journal of the American Society of Anesthesiologists. 1991;74(3):581-605.

21. Eisenach JC, De Kock M, Klimscha W. α2-Adrenergic agonists for regional anesthesia: a clinical review of clonidine (1984-1995). The Journal of the American Society of Anesthesiologists. 1996;85(3):655-74.

22. Pöpping DM, Elia N, Marret E, Wenk M, Tramer MR, Warner DS, et al. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. The Journal of the American Society of Anesthesiologists. 2009;111(2):406-15.

23. Singelyn FJ, Gouverneur J-M, Robert A. A minimum dose of clonidine added to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. Anesthesia & Analgesia. 1996;83(5):1046-50.

24. Kamibayashi T, Maze M, Weiskopf RB, Weiskopf RB, Todd MM. Clinical uses of α2-adrenergic agonists. The Journal of the American Society of Anesthesiologists. 2000;93(5):1345-9.

25. Keniya VM, Ladi S, Naphade R. Dexmedetomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement. Indian journal of anaesthesia. 2011;55(4):352.

26. Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. Anesthesia & Analgesia. 2010;111(6):1548-51.

27. Rancourt M-PM, Albert NT, Côté M, Létourneau D-R, Bernard P-M. Posterior tibial nerve sensory blockade duration prolonged by adding dexmedetomidine to ropivacaine. Anesthesia & Analgesia. 2012;115(4):958-62.

28. Jonan AB, Kaye AD, Urman RD. Buprenorphine formulations: clinical best practice strategies recommendations for perioperative management of patients undergoing surgical or interventional pain procedures. Pain physician. 2018;21(1):E1.

29. Candido KD, Franco CD, Khan MA, Winnie AP, Raja DS. Buprenorphine added to the local anesthetic for brachial plexus block to provide postoperative analgesia in outpatients. Regional Anesthesia & Pain Medicine. 2001;26(4):352-6.

30. Candido KD, Hennes J, Gonzalez S, Mikat-Stevens M, Pinzur M, Vasic V, et al. Buprenorphine enhances and prolongs the postoperative analgesic effect of bupivacaine in patients receiving infragluteal sciatic nerve block. The Journal of the American Society of Anesthesiologists. 2010;113(6):1419-26.

31. Behr A, Freo U, Ori C, Westermann B, Alemanno F. Buprenorphine added to levobupivacaine enhances postoperative analgesia of middle interscalene brachial plexus block. Journal of anesthesia. 2012;26:746-51.

32. Leffler A, Frank G, Kistner K, Niedermirtl F, Koppert W, Reeh PW, et al. Local anesthetic-like inhibition of voltage-gated Na+ channels by the partial μ-opioid receptor agonist buprenorphine. The Journal of the American Society of Anesthesiologists. 2012;116(6):1335-46.

33. Haeseler G, Foadi N, Ahrens J, Dengler R, Hecker H, Leuwer M. Tramadol, fentanyl and

http://dx.doi.org/10.52533/JOHS.2023.31207

sufentanil but not morphine block voltage-operated sodium channels. Pain. 2006;126(1-3):234-44.

34. Alemanno F, Ghisi D, Fanelli A, Faliva A, Pergolotti B, Bizzarri F, et al. Tramadol and 0.5% levobupivacaine for single-shot interscalene block: effects on postoperative analgesia in patients undergoing shoulder arthroplasty. Minerva Anestesiol. 2012;78(3):291-6.

35. Kaabachi O, Ouezini R, Koubaa W, Ghrab B, Zargouni A, Abdelaziz AB. Tramadol as an adjuvant to lidocaine for axillary brachial plexus block. Anesthesia & Analgesia. 2009;108(1):367-70.

36. Kapral S, Gollmann G, Waltl B, Likar R, Sladen RN, Weinstabl C, et al. Tramadol added to mepivacaine prolongs the duration of an axillary brachial plexus blockade. Anesthesia & Analgesia. 1999;88(4):853-6.

37. Parrington SJ, O'Donnell D, Chan VW, Brown-Shreves D, Subramanyam R, Qu M, et al. Dexamethasone added to mepivacaine prolongs the duration of analgesia after supraclavicular brachial plexus blockade. Regional Anesthesia & Pain Medicine. 2010;35(5):422-6--6.

38. Cummings III KC, Napierkowski D, Parra-Sanchez I, Kurz A, Dalton J, Brems J, et al. Effect of dexamethasone on the duration of interscalene nerve blocks with ropivacaine or bupivacaine. British journal of anaesthesia. 2011;107(3):446-53.

39. Tandoc MN, Fan L, Kolesnikov S, Kruglov A, Nader ND. Adjuvant dexamethasone with bupivacaine prolongs the duration of interscalene block: a prospective randomized trial. Journal of anesthesia. 2011;25:704-9.

40. Attardi B, Takimoto K, Gealy R, Severns C, Levitan E. Glucocorticoid induced up-regulation of a pituitary K+ channel mRNA in vitro and in vivo. Receptors & channels. 1993;1(4):287-93.

41. Johansson A, Dahlin L, Kerns J. Long-term local corticosteroid application does not influence nerve transmission or structure. Acta Anaesthesiologica Scandinavica. 1995;39(3):364-9.

42. Dowdy EG, Kaya K, Gocho Y. Some pharmacologic similarities of ketamine, lidocaine, and procaine. Anesthesia & Analgesia. 1973;52(5):839-42.

43. Weber W, Jawalekar KS, Jawalekar S. The effect of ketamine on nerve conduction in isolated sciatic nerves of the toad. Neuroscience Letters. 1975;1(2):115-20.

44. Lee IO, Kim WK, Kong MH, Lee MK, Kim NS, Choi YS, et al. No enhancement of sensory and motor blockade by ketamine added to ropivacaine interscalene brachial plexus blockade. Acta Anaesthesiologica Scandinavica. 2002;46(7):821-6.

45. Noyan A. On effects of ketamine to axillary block in hand surgery. Journal of Reconstructive Microsurgery. 2002;18(03):197-8.

46. Durrani Z, Winnie AP, Zsigmond EK, Burnett ML. Ketamine for intravenous regional anesthesia. Anesthesia & Analgesia. 1989;68(3):328-32.

47. Kim M, Lee Y. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. British journal of anaesthesia. 2001;86(1):77-9.

48. Nishiyama T, Yokoyama T, Hanaoka K. Midazolam improves postoperative epidural analgesia with continuous infusion of local anaesthetics. Canadian journal of anaesthesia. 1998;45:551-5.

49. Edwards M, Serrao J, Gent J, Goodchild C. On the mechanism by which midazolam causes spinally mediated analgesia. Anesthesiology. 1990;73(2):273-7.

50. Jarbo K, Batra YK, Nidhi M, Panda B. Brachial plexus block with midazolam and bupivacaine improves analgesia. Canadian Journal of Anesthesia. 2005;52(8):822.

51. Laiq N, Khan MN, Arif M, Khan S. Midazolam with bupivacaine for improving analgesia quality in brachial plexus block for upper limb surgeries. J Coll Physicians Surg Pak. 2008;18(11):674-8.

http://dx.doi.org/10.52533/JOHS.2023.31207

52. Nishiyama T, Matsukawa T, Hanaoka K. Acute phase histopathological study of spinally administered midazolam in cats. Anesthesia & Analgesia. 1999;89(3):717.

53. Serrao J, MacKenzie J, Goodchild C, Gent J. Intrathecal midazolam in the rat: an investigation of possible neurotoxic effects. Eur J Anaesthesiol. 1990;7:115-22.

54. Koinig H, Wallner T, Marhofer P, Andel H, Horauf K, Mayer N. Magnesium sulfate reduces intra-and postoperative analgesic requirements. Anesthesia & Analgesia. 1998;87(1):206-10.

55. Gunduz A, Bilir A, Gulec S. Magnesium added to prilocaine prolongs the duration of axillary plexus block. Regional Anesthesia & Pain Medicine. 2006;31(3):233-6.

56. Lee AR, Yi H-w, Chung IS, Ko JS, Ahn HJ, Gwak MS, et al. Magnesium added to bupivacaine prolongs the duration of analgesia after interscalene nerve block. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2012;59(1):21-7.

57. Ekmekci P, Bengisun ZK, Akan B, Kazbek BK, Ozkan KS, Suer AH. The effect of magnesium added to levobupivacaine for femoral nerve block on postoperative analgesia in patients undergoing ACL reconstruction. Knee Surgery, Sports Traumatology, Arthroscopy. 2013;21:1119-24.

58. James MF. Clinical use of magnesium infusions in anesthesia. Anesthesia & Analgesia. 1992;74(1):129-36.

http://dx.doi.org/10.52533/JOHS.2023.31207