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Narrative Review

Research Status of Different Adjuvants on Nerve Block's Effect

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Background: Acute postoperative pain is one of the most common challenges faced by patients who undergo surgery. Multimodal analgesia has been recommended in recent years to effectively control this condition. Nerve blocks are an important part of multimodal analgesia; a single peripheral nerve block is widely used in clinical practice. To prolong the analgesic duration of a single nerve block, adjuvants with different mechanisms, dosages, or administration routes are added to local anesthetics; however, it is not clear which adjuvant or combination is better.

Objectives: This study aimed to provide a comprehensive review of the current utilization of diverse adjuvants in single peripheral nerve block analgesia and to recommend optimal adjuvants for single peripheral nerve blocks based on current literature.

Study Design: A narrative review.

Methods: PubMed was searched using the terms "postoperative analgesia," "nerve block," "adjuvant," "epinephrine," "clonidine," "dexmedetomidine," "dexamethasone," "buprenorphine," "morphine," "magnesium sulfate," and "ketamine." The mechanisms of action of different adjuvants were investigated and clinical trials of different adjuvants for postoperative analgesia were determined and reviewed.

Results: According to current literature, there are 4 main types of adjuvants added to local anesthetics to prolong analgesic effects: adrenergic receptor agonists, anti-inflammatory agents, opioids, and N-methyl-D-aspartic acid (NMDA) receptor antagonists. As a single adjuvant, adrenergic agonists, dexmedetomidine, and anti-inflammatory agents are more effective than opioids and NMDA receptor antagonists. When added to local anesthetics, intravenous dexamethasone (10 mg) had an effect similar to that of perineural dexamethasone (8 mg). However, considering the side effects of perineural dexamethasone, intravenous injection of dexamethasone is preferable.

Magnesium sulfate is a suitable NMDA receptor antagonist for peripheral nerve blocks. The combination of adjuvants with different mechanisms can further prolong local anesthetic duration. When more than one adjuvant was used, the combination of dexmedetomidine and dexamethasone was determined to be excellent.

Limitations: Additional compatibility tests with different adjuvants are required to completely determine the curative effect and optimal dosage parameters.

Conclusion: Adjuvants with diverse mechanisms of action can variably extend the duration of local anesthetic effects. When utilizing adjuvants in conjunction with local anesthetics, perineural dexmedetomidine (1 μg/kg) or intravenous dexamethasone (10 mg) may be preferable, considering their efficacy and side effects. Current research suggests that the combination of perineural dexmedetomidine (1 μg/kg) and intravenous dexamethasone (10 mg) is more effective than either dexmedetomidine or dexamethasone alone.

Key words: Adjuvant, local anesthetic, nerve block, postoperative analgesia, duration of action, pain management, dexmedetomidine, analgesia

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Acute postoperative pain includes incisional, visceral, and neuroinflammatory pain (1). It affects postoperative recovery and a patient's prognosis. Therefore, it is of great clinical importance to actively and effectively manage acute postoperative pain.

In recent years, multimodal analgesia (2) has been recommended to achieve optimal analgesic effect with minimal side effects. A single peripheral nerve block is an important part of multimodal analgesia. However, its main disadvantage is its short duration of action (3). Though this can be extended by increasing the dose and concentration of local anesthetics, doing so increases the risk of local anesthetic toxicity. Therefore, clinicians are seeking safer ways to prolong the duration of action of single peripheral nerve blocks (4).

One approach involves the addition of different adjuvants to local anesthetics, including α2-adrenergic agonists, anti-inflammatory agents, opioids, N-methyl-D-aspartic acid (NMDA) receptor antagonists, among others. Although many researchers have reported the advantages and disadvantages of using a single adjuvant, a systematic and comprehensive evaluation is required to determine the best option. This article reviews the effects of different adjuvants on nerve block duration and their compatibility in order to provide guidance for adjuvant selection for nerve blocks.

Methods

PubMed was searched using the following terms: "postoperative analgesia," "nerve block," "adjuvant," "epinephrine," "clonidine," "dexmedetomidine," "dexamethasone," "buprenorphine," "morphine," "magnesium sulfate," and "ketamine". The mechanisms of action of different adjuvants were investigated and clinical trials of different adjuvants for postoperative analgesia were determined and reviewed from January 1989 to May 2023.

Results

The Mechanism of Action of Different Adjuvants

Adrenergic Receptor Agonists

Adrenergic receptor agonists are often used as adjuvants for peripheral nerve blocks. Their main mechanism of action is thought to be constriction of blood vessels and delay in the systemic absorption of local anesthetics (5).

The mechanism by which clonidine prolongs block duration is not well understood. Many studies have shown that in addition to local vasoconstriction, clonidine may have a direct effect on nerves, reducing the systemic absorption of local anesthetics at the block site, thereby increasing the duration of its effect (6).

Dexmedetomidine exhibits a 7-times higher affinity as an α2-adrenergic agonist than clonidine (7,8). When administered intravenously, its mechanism of action may involve the activation of α2-adrenergic receptors in the locus coeruleus. In addition, it may also inhibit the descending medullary-spinal cord norepinephrine pathway, reducing norepinephrine release and producing an inhibitory effect on pain.

When acting on peripheral nerves, dexmedetomidine demonstrates a dose-dependent inhibition of C-fibers and Aα-fibers (9) or directly activates vascular ATP potassium channels through the Kir6.0 subunit, resulting in blood vessel constriction (10) and an extended duration of local anesthesia. Additionally, Li, et al (11) found that dexmedetomidine significantly inhibits the local inflammatory response to femoral nerve blocks. Previous studies have shown that dexmedetomidine is a suitable adjuvant for peripheral nerve blocks.

Anti-inflammatory Agent: Dexamethasone

Dexamethasone, a glucocorticoid (12), has been proved to prolong the analgesic duration of nerve blocks when administered either perineurally or intravenously (13-17). Perineural administration prolongs the duration of local anesthesia by stimulating glucocorticoid receptors on the nerve cell membrane, augmenting the expression of suppressed potassium channels, and reducing the excitability of unmyelinated C fibers (18). It may also exert its effects by inducing local vasoconstriction or by causing a systemic anti-inflammatory response after absorption into the bloodstream.

The mechanism by which intravenous dexamethasone extends the duration of local anesthesia may involve its anti-inflammatory properties, inhibiting the synthesis of cyclooxygenase-2 (COX-2) in peripheral tissues and the central nervous system. This action reduces the production of prostaglandins associated with inflammation and pain (19). Experiments by Hewson, et al (20) confirmed its anti-inflammatory effects. Therefore, regardless of whether it is administered intravenously or perineurally, the mechanism of dexamethasone prolonging the analgesic duration of nerve blocks is primarily anti-inflammatory. However, perineural

administration may also induce vasoconstriction, which requires further confirmation.

Opioids

Opioids are well known for their strong analgesic effects and long duration of action (21). The mechanism by which morphine enhances the duration of a nerve block remains unclear. This may be related to the presence of opioid receptors on peripheral nerves, central effects after absorption, and impaired sodium and potassium conduction on nerves (22).

Among opioids, buprenorphine has the strongest affinity for μ-opioid receptors (23). Peripherally, it acts through μ-opioid receptors located on C-fiber axons and blocks sodium channels in a concentration-dependent manner, exhibiting local anesthetic effects (24).

NMDA Receptor Antagonists

NMDA receptors play a key role in neuronal plasticity leading to central sensitization and increased pain sensitivity to sensory stimuli (25). The blockade of NMDA receptors can prevent central sensitization. NMDA receptors blockade is dose-dependent. At low concentrations, analgesic properties are evident, whereas at high concentrations, anesthetic properties are evident (26).

Clinical research has shown that using magnesium sulfate as an auxiliary drug to local anesthetics (27) is effective in relieving acute postoperative pain (8,28); however, its mechanism is not well understood. Magnesium exerts analgesic effects by blocking calcium influx and NMDA receptors (29,30). This may enhance the effects of local anesthetics and extend the block's duration.

Ketamine may relieve pain by preventing postoperative hyperalgesia.

Magnesium sulfate may be superior to ketamine in enhancing the effects of local anesthetics owing to its calcium channel blocker and NMDA receptor antagonist properties; however, further research is needed.

The above outlines the mechanisms of commonly used adjuvants in clinical practice (Fig. 1). However, the specific mechanisms related to prolonged analgesic duration remain uncertain and require further research. In addition, some researchers have reported adjuvants with alternative mechanisms of action, such as midazolam, tramadol, and neostigmine. Nevertheless, there are limited studies on their effectiveness and side effects; therefore, some researchers do not recommend their use in peripheral nerve blocks, so these adjuvants are not discussed in this review.

Research on Adjuvants

Adrenergic Receptor Agonists

Epinephrine

When used as an adjuvant, epinephrine prolongs the duration of peripheral nerve block. In Song's (31) study, the co-administration of 200 μg of adrenaline with 40 mL 1% mepivacaine during brachial plexus block lengthened the motor block duration by approximately 45 minutes and the sensory block by approximately 60 minutes (Table 1).

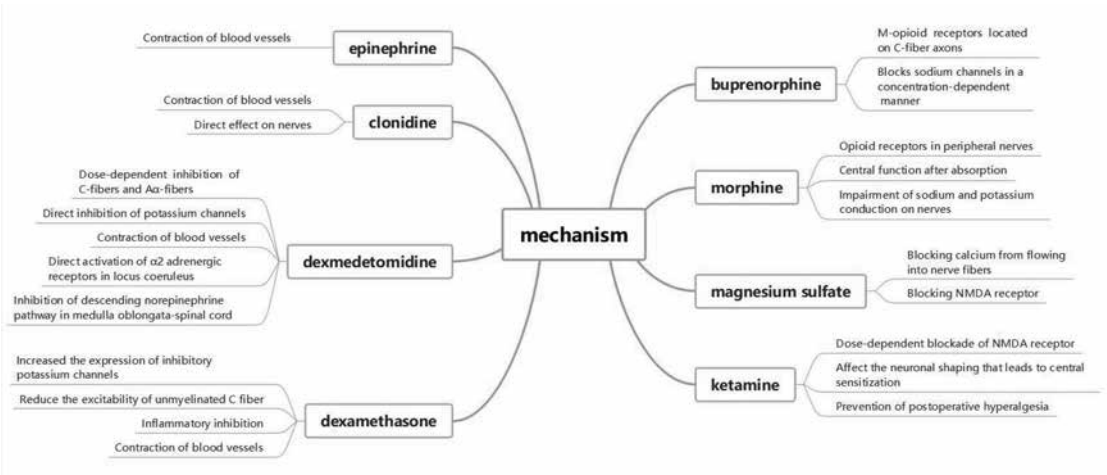

Fig. 1. *Mechanism of action of different adjuvants.*

Table 1. *Single adjuvant combined with a local anesthetic.*

Study	Adjuvant	Administration route/Dose	Local Anesthetic	Site	Onset time of sensory block (min)	Onset time of motor block (min)	Duration of sensory block (min)	Duration of motor block (min)	Duration of analgesia (min)	Side effects
Song et al 2014 (31)	epinephrine	PN 200 μg	1% Mepivacaine (20 mL)	BPB (31)	/	/	353.5 ± 53.4 vs 289.7 ± 52.9	334.3 ± 46.5 vs 283.7 ± 43.7	349.3 ± 50.5 vs 295.7 ± 52.1	None
Lee et al 2012 (77)	epinephrine	PN 1:200,000	0.5% Bupivacaine (20 mL)	ISB (75)	13.2 (2.6)	15.7 (2.6)	518 (174)	296 (132)	653 ± 155 /	/
Nasir et al 2017 (36)	clonidine	PN 100 μg	Ropivacaine (25 mL)	SCB (36)	/	/	/	/	265.8 ± 137.4 vs 238.8 ± 154.8	Bradycardia 25%, Hypotension 5%, PONV 10%
Sardar et al 2017 (78)	clonidine	PO 4 μg/kg	4% Bupivacaine 0.25 mL/kg	ilioinguinal/ iliohypogastric block (76)	/	/	/	/	169.8 ± 120.6 vs 238.8 ± 154.8	Bradycardia 20%, Hypotension 10%, PONV 10%
Song et al 2014 (31)	dexmedetomidine	PN 1 μg/kg	1% Mepivacaine (20 mL)	BPB (31)	/	/	367.9 ± 35.8 vs 289.7 ± 52.9	349.9 ± 28.2 vs 283.7 ± 43.7	358.9 ± 36.2 vs 295.7 ± 52.1	All bradycardia, sedative effects
Wang et al 2021 (45)	dexmedetomidine	PN 0.5 μg·kg-1	0.5% Ropivacaine (28 mL)	ESP (45)	/	/	/	/	505.1 ± 113.9 vs 323.2 ± 75.4	nausea 10%, vomiting 3.33%, dizzy 6.67%
Bisui et al 2017 (85)	dexmedetomidine	PN 0.75 μg·kg-1	0.5% Levobupivacaine (28 mL)	BPB (84)	12.03 ± 0.85 vs 14.32 ± 1.15	13.58 ± 0.97 vs 15 ± 0.98	563.94 ± 15.60 vs 368.53 ± 9.89	495.15 ± 10.34 vs 321.47 ± 7.84	672.12 ± 11.39 vs 506.47 ± 9.497	None
Shuklau et al 2020 (47)	dexmedetomidine	PN 100 μg	0.5% Ropivacaine (29 mL)	SCB (47)	5.6 ± 1.27 vs 16.10 ± 2.07	8.95 ± 1.31 vs 21.90 ± 3.95	917.40 ± 103.17 vs 339.75 ± 30.67	827.55 ± 86.81 vs 282.25 ± 23.7	1018.85 ± 96.84 vs 406.40 ± 48.69	bradycardia 10%, nausea 10%, hypotension 20%, calm 25%
Shahtaheri et al 2020 (79)	dexmedetomidine	PN 0.5 μg·kg-1	1.5% lidocaine (35 mL)	axillary plexus (77)	1.07 ± 4.90 vs 1.16 ± 6.12	1.39 ± 4.00 vs 1.80 ± 6.06	/	322.14 ± 20.30 vs 148.22 ± 22.52	/	None
Zhang et al 2019 (80)	dexmedetomidine	PN 1 μg·kg-1	0.5% Ropivacaine (28 mL)	ICB (78)	/	/	/	/	602.5 ± 108.5 vs 440.0 ± 109.6	nausea 10%, dizzy 5%
Zaman et al 2017 (59)	dexamethasone	PN 8mg	1% lidocaine (38 mL)	axillary brachial plexus (58)	5.65 ± 2.48 vs 5 ± 1.09	12.26 ± 1.34 vs 12.69 ± 1.66	174.42 ± 13.06 vs 106.15 ± 7.91	194.26 ± 13.68 vs 123.26 ± 8.82	/	/

Table 1 cont. *Single adjuvant combined with a local anesthetic.*

Study	Adjuvant	Administration route/Dose	Local Anesthetic	Site	Onset time of sensory block (min)	Onset time of motor block (min)	Duration of sensory block (min)	Duration of motor block (min)	Duration of analgesia (min)	Side effects
Zhang et al 2019 (80)	dexamethasone	PN 10 mg	0.5% Ropivacaine (28 mL)	ICB (78)	/	/	/	/	611.5 ± 133.0 vs 440.0 ± 109.6	nausea 5%, vomiting 10%, dizzy 5%
Siddeshwara et al 2019 (81)	dexamethasone	PN 4 mg	0.25% Levobupivacaine (24 mL)	pectoral nerve (79)	/	/	/	/	474.1 ±84.93 /	itch 5%, nausea 5%
Siddeshwara et al 2019 (81)	dexamethasone	PN 4mg	0.25% Levobupivacaine (24 mL)	TPVB (79)	/	/	/	/	371.5 ± 51.53 /	hypotension 5%, calm 5%
Kumar et al 2014 (82)	dexamethasone	PN 8 mg	0.5% Ropivacaine (30 mL)	BPB (80)	3.35 ± 0.86 vs 3.62 ± 0.79	4.92 ± 0.81 vs 5.23 ± 0.69	1179.4 ± 108.6 vs 557.25 ± 58.99	1091 ±106.74 vs 465.62 ± 54.29	/	None
Movafegh et al 2006 (83)	dexamethasone	PN 8 mg	1.5% lidocaine (34 mL)	axillary brachial plexus block (81)	14 ± 5 vs 11 ± 4	26 ± 7 vs 22 ± 8	242 ± 76 vs 98 ± 33	310 ± 81 vs 130 ± 31	/	/
Desmet et al 2013 (86)	dexamethasone	PN 10 mg	0.5% ropivacaine (28 mL)	ISB (85)	/	/	/	/	1405 (1015–1710) vs 757 (635-910)	
Desmet et al 2013 (86)	dexamethasone	IV 10 mg	0.5% ropivacaine (30 mL)	ISB (85)	/	/	/	/	1275 (1095-2035) vs 757 (635-910)	
shahtaheri et al 2020 (79)	magnesium sulfate	PN 100 mg	1.5% lidocaine (35 mL)	axillary brachial plexus block (77)	2.23 ± 3.93 vs 1.16 ± 6.12	1.82 ± 3.42 vs 1.80 ± 6.06	/	207 ± 19.64 vs 148.22 ± 22.52	/	None
Shuklau et al 2020 (47)	magnesium sulfate	PN 250 mg	0.5% Ropivacaine (29 mL)	SCB (47)	7.65 ± 1.69 vs 16.10 ± 2.07	11.35 ± 2.13 vs 21.90 ± 3.95	584.50 ± 71.57 vs 339.75 ± 30.67	543.3 ± 69.01 vs 282.25 ± 23.7	635.4 ± 59.98 vs 406.40 ± 48.69	nausea 5.3%
Zaman et al 2017 (59)	ketamine	PN 50 mg	1% lidocaine	axillary brachial plexus block (58)	5.32 ± 1.06 vs 5 ± 1.09	12.3 ± 1.64 vs 12.69 ± 1.66	114.8 ± 12.53 vs 106.15 ± 7.91	138.36 ± 17.08 vs 123.26 ± 8.82	/	nystagmus 26.9%
Behr et al 2012 (50)	buprenorphine	PN 0.15 mg	0.75 % Levobupivacaine (29.5 mL)	ISB (50)	/	/	856.1 ± 215.2 vs 488.3 ± 137.6	/	1,049.7 ± 242.2 vs 637.5 ± 72.1	None
Behr et al 2012 (50)	buprenorphine	IM 0.15 mg	0.75 % Levobupivacaine (29.5 mL)	ISB (50)	/	/	693.6 ± 143.4 vs 488.3 ± 137.6	/	820.3 ± 335.3 vs 637.5 ± 72.1	None

PN, perineural nerve; IV, intravenous; IM, intramuscular injection; PO, by mouth; BPB, brachial plexus block; ISB, interscalene block; TAP, transversus abdominis plane; ACB, inner adductor canal block; SCB, supraclavicular block; ESP, erector spinae plane block; ICB, intercostal nerve block; TPVB, thoracic paravertebral block; PONV, postoperative nausea and vomiting

Clonidine

Whether clonidine prolongs the duration of the peripheral block remains controversial.

Sruthi, et al (32) added 75 μg and 150 μg of clonidine to 0.25% levobupivacaine for lower abdominal surgery. They reported an enhanced analgesic effect in transversus abdominis plane (TAP) block. Mohamed, et al (33) demonstrated that adding 150 μg-250 μg of clonidine to 0.5% bupivacaine for postmastectomy pain prolonged the analgesic duration by 360 minutes (6 hours)–720 minutes (12 hours). In contrast, Nath, et al (34) reported that clonidine combined with ropivacaine for TAP block does not extend the analgesic duration of ropivacaine. However, other researchers have reported that adding clonidine to ropivacaine for adductor canal block (35) and supraclavicular brachial plexus block (36) prolongs the duration of analgesia significantly .

Dexmedetomidine

Numerous studies have demonstrated that combining dexmedetomidine with local anesthetics accelerates the onset and prolongs the duration of a nerve block (37-41). In a study involving 57patients undergoing elective posterior lumbar fusion, Li, et al (42) added 1 μg/kg dexmedetomidine to 0.5%ropivacaine for incisional skin infiltration and observed a significant delay in the time to first postoperative sedation and pain medication. Gao, et al(43) added 1 μg/kg dexmedetomidine to 0.5% ropivacaine in erector spinae plane block, resulting in a prolonged duration of sensory block to 1,080 minutes (18 hours) and an extended time to first pain rescue medication to 1,620 minutes (27 hours).

Similar conclusions were reached by Wang, et al (44). They found that adding 1 μg/kg dexmedetomidine to 0.33% ropivacaine in erector spinae plane block (44,45) provided superior postoperative analgesia compared to ropivacaine alone.

Dexmedetomidine also lowers blood pressure, causes perioperative sympathetic nerve lysis, and improves the anesthetic effects of other anesthetics (46). Shukla, et al (47) reported that when 100 μg dexmedetomidine was used as an adjuvant with 0.5% ropivacaine in supraclavicular brachial plexus block, it prolonged the block duration by approximately 1018.85 minutes (≈17 hours) ± 96.84 minutes (≈1.5 hours).

The duration of nerve block prolonged by epinephrine is relatively short; clonidine's effect lasts longer. Therefore, when compared with epinephrine and clonidine, dexmedetomidine emerges as a more suitable choice for peripheral nerve blocks combined with local anesthetics.

Anti-inflammatory Agent: Dexamethasone

Dexamethasone can be administered either intravenously or perineurally; both routes of administration can prolong the a nerve block's duration. A study by Albrecht, et al (14) showed that dexamethasone administered perineurally at doses of 1–4 mg increased the brachial plexus block's duration in a dose-dependent manner: 1 mg prolonged the block duration to 835 minutes (≈14 hours); 2 mg to 904 minutes (≈15 hours); 3 mg to 965 minutes (≈16 hours); and 4mg to 1,023 minutes (≈17 hours). Desmet, et al (15) showed that a 10 mg intravenous injection of dexamethasone with 0.5% ropivacaine could prolong the analgesic duration of a single brachial plexus block. However, in a further meta-analysis, Teshome, et al (48) found that only an intravenous administration of 10 mg of dexamethasone significantly prolonged the analgesic duration of peripheral nerve blocks, whereas doses of 4 mg and 8 mg did not. A study by Byung-Gun Kim,et al (16) showed similar results.

Regarding whether dexamethasone should be administered perineurally or intravenously, Abdallah,et al (17) reported that in a single supraclavicular brachial plexus block, intravenous dexamethasone was more effective than perineural dexamethasone injection and produced similar durations of analgesia when combined with long-acting local anesthetics.

Regardless of whether dexamethasone was administered intravenously or perineurally, the blockade's duration increased in a dose-dependent manner. Intravenous administration of 10 mg and perineural administration of 8 mg maximized the duration. Therefore, intravenous administration of dexamethasone combined with a local anesthetic for peripheral nerve block may be more beneficial to patients. It should be noted that currently, although dexamethasone is added to local anesthetics for peripheral nerve block in clinical practice, it is not included in the therapeutic indications for dexamethasone.

Opioids

Buprenorphine

A meta-analysis by Schnabel, et al (49) showed that combining buprenorphine with most local anesthetic (bupivacaine ,lidocaine, levobupivacaine, mepivacaine, ropivacaine) could prolong postoperative analgesic du-

ration by approximately 8 hours (480 minutes) in peripheral nerve block. Perineural injection of buprenorphine prolonged the effect by approximately 200 minutes when compared with levobupivacaine alone (50).

However, in another study (51), combining buprenorphine with 0.75% bupivacaine significantly prolonged nerve block's duration but shortened the duration of anesthesia when combined with 2% lidocaine. Careful consideration should be given to the choice and concentration of local anesthetic.

Morphine

Previous studies have reported different results regarding the effects of morphine on peripheral nerve blockade. Some studies have reported prolonged analgesia (22), while others have reported no benefit (52). Bazin, et al (22) found that in patients undergoing upper limb orthopedic surgery, adding morphine to bupivacaine and lidocaine for supraclavicular nerve block prolonged the average duration from 690 minutes (11.5 hours) to 1,260 minutes (21 hours). Keskinbora, et al (53) studied the effect of morphine combined with bupivacaine vs bupivacaine alone in patients with chronic ischemic lower extremity pain and found that morphine prolonged the analgesic duration by approximately 180 minutes (3 hours). Since the effect of morphine on nerve blockade remains controversial, it is rarely used clinically.

NMDA Receptor Antagonists

Magnesium Sulfate

Zeng, et al (54) reported that when magnesium sulfate is used as an adjuvant in combination with local anesthetics for nerve blocks, it can enhance the anesthetic effect of the local anesthetics and improve the postoperative analgesic effect post block. Abd-Elsalam, et al (55) obtained similar results. They reported that combining 20 mL of 0.25% bupivacaine with 2 mL of 10% magnesium sulfate per side in a TAP block significantly reduced postoperative opioid requirements and prolonged analgesic duration (940.2 minutes [≈16.67 hours] ± 362.4 minutes [≈6 hours]). Abdelfatah, et al (56) found that adding magnesium sulfate to lidocaine significantly prolonged the duration of analgesia.

Shukla, et al (47) also reported that 250 mg of magnesium sulfate used as an adjuvant to 0.5% ropivacaine for supraclavicular brachial plexus block prolonged the block duration by approximately 635.40 minutes (≈10.6 hours) ± 59.98 minutes (≈one hour).

Ketamine

Using ketamine for peripheral nerve block remains controversial. Zhu, et al (57) reported that ketamine prolongs the duration of peripheral nerve blocks and enhances the effects of local anesthetics on peripheral nerves. Abdel-Ghaffar, et al (58) reported that in 40 patients undergoing hand or forearm surgery, 50 mg of ketamine combined with 3 mg/kg of lidocaine (diluted to 40 mL) for peripheral nerve block significantly reduced intraoperative and postoperative sedation and pain requirements, thereby improving patient satisfaction. Zaman, et al (59) reached similar conclusions when 50 mg of ketamine was added to 38 mL of 1% lidocaine for nerve blockade. However, Lee et al (60) reported that combining 30 mg of ketamine with 30 mL of 0.5% ropivacaine did not improve the onset time or duration of brachial plexus blockade.

Magnesium sulfate alone combined with local anesthetics is effective for nerve block; the effect of ketamine combined with local anesthetics on prolonging nerve block duration remains controversial and may be related to dose. Therefore, compared with ketamine, magnesium sulfate is more suitable for peripheral nerve blocks; the optimal dosage may be 200 mg.

Side Effects and Precautions of Different Adjuvants

Adrenergic Receptor Agonists

Epinephrine

Häfner, et al (61) reported that adding epinephrine at a concentration of 1:200,000 to lidocaine for local anesthesia temporarily reduced extremity blood flow by 55%; however, this change was reversible after 40 minutes. Bernardset, al (62) believed that epinephrine could increase the toxicity of bupivacaine, causing seizures, arrhythmias, and an increase in heart rate. Myers, et al (63) reported that epinephrine can reduce in-nerve blood flow and increase neurotoxicity, particularly in animal models of diabetes mellitus. Therefore, it is not recommended to use epinephrine in combination with lidocaine in patients with diabetic peripheral neuropathy (7).

Clonidine

In patients undergoing surgery who have chronic renal failure, combining 150 μg of clonidine with 40 mL of 1% lidocaine for axillary block resulted in decreased arterial pressure and heart rate, accompanied by in-

creased sedation. Even at low doses (2 μg/kg), similar effects were observed. However, when used at a high dose (300 μg), it significantly prolonged analgesic duration but also led to a higher incidence of bradycardia and sedation (34).

These adverse effects should be considered when using clonidine in patients with bradycardia. In addition to these systemic effects, Williams, et al (64) found that when clonidine was combined with ropivacaine for peripheral nerve blocks, it exhibited neurotoxic effects around the nerves. The neurotoxic effects last longer in a rat model of diabetes (65).

Dexmedetomidine

Adverse effects of dexmedetomidine include hypotension, bradycardia, and sedation.

A meta-analysis by Hussain, et al (66) revealed a significant increase in the incidence of bradycardia when dexmedetomidine was administered perineurally at doses > 50 μg.

However, the neurotoxicity of dexmedetomidine has not been extensively documented to date. In a study by Brummett, et al (67), adding a large dose (28-40 μg/kg) of 0.005% dexmedetomidine to 0.5% bupivacaine (total volume, 2 mL) demonstrated not only a neuroprotective effect but also a reduction in acute peripheral inflammation in rats.

Conversely, in an in vivo study by Yu, et al (68) coadministration with 0.5% ropivacaine showed that a large dose (20 μg/kg) of dexmedetomidine increased toxicity in rats. Therefore, clinical trials are needed to determine the safe and optimal dose (69) to provide maximum analgesic effects and minimum side effects. Dexmedetomidine combined with local anesthetic was administered to the peripheral nerves. Although neuroprotective, dexmedetomidine may not produce the same protective effects in patients with diabetes mellitus (70). While dexmedetomidine has shown no obvious neurotoxicity, its adverse reactions are more prevalent in older adults, and the relevant side effects should be considered when administering it.

Anti-inflammatory Agent: Dexamethasone

The side effects of dexamethasone are influenced by its route of administration. Some studies have shown that administering dexamethasone around the nerve can enhance the cytotoxicity of ropivacaine at high doses (0.5%) (71). Although dexamethasone has been administered perineurally for decades and there are hardly any reports of neurological harm, compared to the "off-label" use and potential neurotoxicity of perineurally administered dexamethasone, intravenous administration may be more appropriate for peripheral nerve blocks (12).

Opioids

Buprenorphine

Compared with local anesthetics alone for peripheral nerve block, the main adverse events associated with combining buprenorphine with local anesthetics are a higher risk of vomiting, nausea, and neurotoxicity to isolated sensory neurons, but these only occur at high concentrations (0.3 mg) (49). This should be carefully considered in clinical practice.

Morphine

Keskinbora, et al (53) reported that although morphine prolonged the duration of analgesia, patients experienced significant side effects (nausea and lethargy). Therefore, the combination of morphine with a local anesthetic is not recommended for routine use.

Opioids can be used as adjuvants to prolong the duration of a peripheral nerve block; however, the incidence of side effects (e.g., nausea and vomiting) is high. Therefore, the routine use of opioids as adjuvants in peripheral nerve blocks is not recommended.

NMDA Receptor Antagonists

Magnesium Sulfate

According to Vissers et al (72), theoretically, when the serum magnesium concentrations exceed 2 mmol/L, minor side effects such as flushing, nausea, and headache may occur. However, when serum magnesium concentrations surpass 5 mmol/L, potentially life-threatening complications, primarily involving cardiovascular and neuromuscular systems, may arise. Currently, there is insufficient evidence demonstrating the toxic side effects of magnesium sulfate as an adjuvant. Therefore, magnesium sulfate is a promising adjuvant.

Ketamine

The incidence of ketamine side effects is correlated with its administration route and dosage, with relatively high occurrences noted for both intravenous and intramuscular injections. The primary side effects were mental symptoms (hallucinations or cognitive impairment) (73).

However, data on ketamine's peripheral neurotoxicity are limited. In a study by Lee, et al (60), combining 30 mg ketamine with 30 mL of 0.5% ropivacaine did not enhance the onset time or duration of brachial plexus blockade; the incidence of adverse reactions was approximately 44%, whereas intravenous administration of 30 mg ketamine resulted in an incidence of adverse reactions as high as 94%.

Therefore, ketamine is not recommended for routine use as an adjuvant in peripheral nerve blocks due to its toxic side effects. However, whether esketamine, a dextro isomer of ketamine, has the same side effects when combined with local anesthetics for peripheral nerve blocks has not been extensively studied and requires further research.

Combination of Different Types of Adjuvants

Because of the different mechanisms of drug action, many researchers are currently conducting compatibility tests between different adjuvants (Table 2) to obtain the best combination.

α2-Adrenergic Agonist Combined with an Anti-inflammatory Agent

Aliste, et al (74) demonstrated that combining 2 mg of dexamethasone with 50 μg of dexmedetomidine was more effective than when using 2 mg of dexamethasone alone combined with a local anesthetic (1% lidocaine - 0.5% bupivacaine) for subclavian brachial plexus block. It provided a longer duration of motor block (1,290 minutes [21.5 hours] vs 1,020 minutes [17 hours]), sensory block (1,296 minutes [21.6 hours] vs 1,032 minutes [17.2 hours]), and postoperative analgesia (1,530 minutes [25.5 hours] vs 1,410 minutes [23.5 hours]).

Zhao, et al (75) demonstrated that the effects of perineural and intravenous dexamethasone on analgesic duration were equivalent when epinephrine was not added; however, when epinephrine was added, compared with intravenous dexamethasone, the duration of analgesia was prolonged. Therefore, epinephrine and dexamethasone (administered perineurally) were considered synergistic in pro-

Table 2. *The two adjuvants are applied to local anesthetics in combination with each other.*

Study	Adjuvant	Local Anesthetic/ Dose	Site	Duration of sensory block (min)	Duration of motor block (min)	Duration of analgesia (min)	Side effects
Bazin et al 1997 (22)	buprenorphine 3 μg·kg-1 + 1:200,000 epinephrine	0.5% Bupivacaine 1 mg·kg-1 + 1% lidocaine 2 mg·kg-1	BPB (22)	/	/	1,200 (840-2,040)	itch 5%, nausea 30%, vomiting 20%
Bazin et al 1997 (22)	morphine 75 μg·kg-1 + 1:200,000 Epinephrine	0.5% Bupivacaine 1 mg·kg-1 + 1% lidocaine 2 mg·kg-1	BPB (22)	/	/	1,260 (480-1,620)	/
Nasir et al 2017 (36)	clonidine100 μg + dexamethasone 4 mg	0.5% Ropivacaine (25 mL)	SCB (36)	1128 ± 372 vs 804 ± 360	1092 ± 342 vs 720 ± 300	/	/
Abdelfatah et al 2014 (56)	magnesium sulfate 500 mg + 1:200,000 epinephrine	2% lidocaine (20 mL)	ISB (55)	442.3 ± 40.5	244.3 ± 27.1	/	PONV6.7%
Lee et al 2012 (77)	Magnesium sulfate 200 mg + 1:200,000 Epinephrine	0.5% Bupivacaine (20 mL)	ISB (75)	636 (239)	636 (239)	664 ± 188	None
Zhang et al 2019 (80)	dexmedetomidine 1 μg·kg-1 + dexamethasone 10 mg	0.5% Ropivacaine (28 mL)	ICB (78)	/	/	824.2 ± 150.1 vs 440.0 ± 109.6	nausea 10%, vomiting 5%
Berger et al 2022 (84)	dexmedetomidine 25 mg + dexamethasone 5 mg	0.2% Ropivacaine (20 mL)	ISB (82)	/	/	4,752 vs 720	Persistent bradycardia, hypotension and nausea 5.3%
Bagade et al 2021 (51)	buprenorphine 0.03 mg + 1:80,000 Epinephrine	2% lidocaine	Inferior Alveolar /Lingual/ Long Buccal (83)	/	/	3,396 vs 204	/

BPB, brachial plexus block; ISB, interscalene block; SCB, supraclavicular block; ICB, intercostal nerve block; PONV, postoperative nausea and vomiting

longing the duration of peripheral nerve blockade. Nasir, et al (36) also observed that the duration of sensory and motor blockade induced by combining 4 mg dexamethasone and 100 μg clonidine with 25 mL of 0.5% ropivacaine (1,128 minutes [≈18.8 hours] ± 372 minutes [≈6.2 hours] and 1,092 minutes [≈18.2 hours] ± 342 minutes [≈5.7 hours], respectively) was significantly longer than that of ropivacaine alone (804 minutes [≈13.4 hours] ± 360 minutes [6 hours] and 720 minutes [12 hours] ± 300 minutes [5 hours], respectively).

Combining 1:200,000 epinephrine or 1 μg/kg dexmedetomidine and dexamethasone (10 mg intravenously or 4 mg perineurally) is the most widely used and effective method in clinical practice for peripheral nerve block. However, the optimal administration method for dexamethasone and the optimal compatible dose of the drugs require further investigation.

α2- Adrenergic Agonists Combined With Opioid Receptor Agonists

Bazin, et al (22) reported that adding morphine (77 μg/kg) or buprenorphine (3 μg/kg) to a mixture of 0.5% bupivacaine and 1% lidocaine with 1:200,000 epinephrine can prolong analgesic duration to 1,260 minutes (21 hours) and 1,200 minutes (20 hours), respectively, which is approximately 600 minutes (10 hours) longer than the analgesic duration (690 minutes [11.5 hours]) of the mixture alone.

Opioids have side effects (nausea, vomiting, pruritus, and drowsiness) that should be carefully considered when adding them to local anesthetics for peripheral nerve blocks in combination with other adjuvants.

α2-Adrenergic Agonists Combined With Others

Abdelfatah, et al (56) reported that when adding 500 mg of 10% magnesium sulfate to a 20 mL mixture of 2% lidocaine and 1:200,000 epinephrine for interscalene brachial plexus block, it prolonged sensory block duration to 442.3 minutes (≈7.37 hours) ± 40.5 minutes and motor block duration to 244.3 minutes (≈4 hours) ± 27.1 minutes.

Magnesium sulfate is a promising adjuvant. According to the currently available literature, when used perineurally in combination with other adjuvants, the usual dose is 200 mg. No obvious magnesium-related side effects were observed; however, the optimal dose of the drug requires further research.

The results of these experiments are exciting. These findings show that combining adjuvants with different mechanisms and local anesthetics can prolong the analgesic duration of peripheral nerve blocks to different degrees (76-86). However, the optimal combination and dose of different adjuvants still lacks experimental support and requires further research.

Conclusion

Prolonging the duration of a single peripheral nerve block with minimal side effects and toxicity is a current clinical concern. The use of adjuvants in combination with local anesthetics is a growing field in anesthesia practice. Current studies have shown that different adjuvants have different mechanisms and effects and that there are interactions between different types of adjuvants. However, the specific dosage or combination that is most effective remains controversial.

Based on the available literature and considering the effects and side effects of each adjuvant, we recommend the following: when using a single adjuvant with a local anesthetic, perineural dexmedetomidine at 1 μg/kg or intravenous dexamethasone at 10 mg is preferable.

The combination of perineural dexmedetomidine at 1 μg/kg or intravenous dexamethasone at 10mg with a local anesthetic appears to be more effective than other combinations.

However, it remains unclear if there is a superior alternative. Further research is needed to address this question. It is essential to emphasize that, when exploring new applications for adjuvants, researchers bear an ethical responsibility to thoroughly consider all potential side effects.

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