Drug Design, Development and Therapy

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REVIEW

Dexmedetomidine as an Adjuvant in Peripheral Nerve Block

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Abstract: Peripheral nerve block technology is important to balanced anesthesia technology. It can effectively reduce opioid usage. It is the key to enhance clinical rehabilitation as an important part of the multimodal analgesia scheme. The emergence of ultrasound technology has accelerated peripheral nerve block technology development. It can directly observe the nerve shape, surrounding tissue, and diffusion path of drugs. It can also reduce the dosage of local anesthetics by improving positioning accuracy while enhancing the block's efficacy. Dexmedetomidine is a highly selective drug α_2-adrenergic receptor agonist. Dexmedetomidine has the characteristics of sedation, analgesia, anti-anxiety, inhibition of sympathetic activity, mild respiratory inhibition, and stable hemodynamics. Numerous studies have revealed that dexmedetomidine in peripheral nerve blocks can shorten the onset time of anesthesia and prolong the time of sensory and motor nerve blocks. Although dexmedetomidine was approved by the European Drug Administration for sedation and analgesia in 2017, it has not yet been approved by the US Food and Drug Administration (FDA). It is used as a non-label drug as an adjuvant. Therefore, the risk-benefit ratio must be evaluated when using these drugs as adjuvants. This review explains the pharmacology and mechanism of dexmedetomidine, the effect of dexmedetomidine on various peripheral nerve block as an adjuvant, and compare it with other types of adjuvants. We summarized and reviewed the application progress of dexmedetomidine as an adjuvant in nerve block and look forward to its future research direction.

Keywords: dexmedetomidine, alpha-2 agonists, adjuvant, peripheral nerve block, anesthesia, analgesic

Introduction

In 1885, William Stewart Halsted discovered that injecting cocaine into specific parts of the nerve (around the plexus and nerve trunk) can block the sensory conduction of human nerves through self-experiment. Therefore, he invented nerve block anesthesia and pioneered regional nerve block.[1] Numerous traditional regional anesthesia technologies have realized visualization with the help of ultrasound with the continuous development of ultrasound technology. Peripheral nerve blocks (PNB) technology is increasingly significant in perioperative analgesia and clinical anesthesia. PNB or PNB combined with general anesthesia (GA) can reduce persistent incision and visceral pain, reduce opioid usage, shorten hospital stay, and reduce the recurrence rate of some cancers compared to GA, consistent with the concept of enhanced recovery after surgery (ERAS) advocated by modern medicine.[2,3] PNB is now well-established as an integral part of a balanced anesthetic technique and constitutes a vital component of a multimodal analgesic regimen that enhances ERAS.

PNB has become the cornerstone of perioperative pain management in modern surgical practice. The finite duration of single injection techniques is one of the greatest limitations of PNB in acute pain management. Continuous catheter techniques are widely employed to prolong regional analgesia; however, they have several drawbacks, such as the difficulty of catheter removal and the increased risk of infection.[4,5] Single-injection PNB is an attractive option because it is technically easier and can be performed quickly. Therefore, there is a growing demand to identify a reliable solution for prolonging analgesia duration from PNB.

Different agents have been combined with local anesthetics (LA) over the years to prolong the duration of action, with varying degrees of success. Analgesic adjuvants include opioids, epinephrine, sodium bicarbonate, magnesium sulfate, dexamethasone, ketorolac, ketamine, neostigmine, midazolam, cortisol, and α2-adrenergic receptor (α_2-AR) agonists.[6–8]

Received: 31 January 2023
Accepted: 5 May 2023
Published: 17 May 2023

The existing randomized controlled studies (RCTs) and meta-analysis exhibit that adding LA adjuvant to peripheral nerve block helps to prolong the analgesic time,[9] can significantly improve the quality of PNB,[7,8] and has a synergistic analgesic effect with LA. Most adjuvants are safe; neurotoxicity and tissue damage are rare. Although these drugs synergize when used as an adjuvant with LA, several studies have reported systemic adverse reactions, such as itching, nausea, and vomiting caused by opioids, including fentanyl and buprenorphine.[10,11] Dexamethasone excessively prolonged the analgesic time, resulting in the slow recovery of postoperative walking ability.[12] Neostigmine can increase the analgesic effect by increasing the secretion of acetylcholine in nerve endings, but it can also increase the adverse reactions in the gastrointestinal tract. Ketamine can cause various adverse reactions, including hallucinations, nausea, and drowsiness.[13] Therefore, adjuvants may have side effects that should be considered.[14]

Dexmedetomidine has certain advantages over other adjuvants. Dexmedetomidine is a highly selective drug α_2-adrenergic receptor agonist with characteristics including sedation, analgesia, anti-anxiety, inhibition of sympathetic activity, mild respiratory inhibition, and stable hemodynamics.[15] Numerous studies have discovered that applying dexmedetomidine in peripheral nerve blocks can shorten the onset time of anesthesia, prolong the time of sensory and motor nerve block, and achieve a satisfactory sedative effect. However, dexmedetomidine can lead to adverse reactions, such as bradycardia, hypotension, and excessive sedation.[16,17] The dosage and safety of a drug should be considered during clinical application.

This review discusses the pharmacological characteristics of dexmedetomidine, its application progress and reasonable dose as an adjuvant in peripheral nerve block, the performance of dexmedetomidine in analgesic time and intensity, and its future application in peripheral nerve block.

Materials and Methods

The medical subject heading (MeSH) and text words related to dexmedetomidine, medetomidine, and clonidine were sought as interventions to avoid omitting the potentially relevant articles. The results were combined using the Boolean operator "AND" with Mesh and text words, including PNB, local anesthesia, infiltration anesthesia, "anesthetics", local [MeSH], "nerve block" [MeSH], "adjuvants", pharmaceutic [MeSH], adjuvant and regional anesthesia. The search included RCTs, meta-analysis, and a literature review. There was no restriction regarding the publication language.

Pharmacological Characteristics of Dexmedetomidine

Pharmacological and Physiological Effects of Dexmedetomidine

Dexmedetomidine is an imidazole compound. It is a right-handed isomer of medetomidine and a highly selective membrane-bound G-protein coupling α_2-adrenergic receptor agonist discovered by Segal in the 1980s, with sedative and hypnosis effect.[18] In 1999, it was approved by the US Food and Drug Administration (FDA) for short-term sedation of mechanical ventilation patients in an adult intensive care unit (ICU).[19] It was approved for procedural sedation with many off-label indications to employ it in perioperative medicine. Moreover, it was approved by the European Medicines Agency for sedation and analgesia in 2017. The α_2-adrenergic receptor is a G-protein coupled receptor with seven transmembranes. It is widely distributed in the periphery, central nervous system, and autonomic ganglion. It has the highest density in locus coeruleus, pontine nucleus, pontine tegmental reticular nucleus, parahippocampal gyrus, and cingulate gyrus. The α_2-adrenergic receptors can be divided into α_{2A}, α_{2B}, and α_{2c}. Previous studies have demonstrated that α_{2A} receptors primarily control the exocytosis of adrenergic neurons. The absence of the α_{2A} receptor can lead to increased blood pressure and faster heart rate; the α_{2A} receptor can activate α_{2A} receptor agonists, plays the role of sedation and analgesia; α_{2B} receptors are mainly distributed in peripheral vascular smooth muscle, and transient blood pressure rise can occur after transient activation;[20] and α_{2C} receptors are primarily distributed in the hippocampus, basal ganglia, and cerebral cortex to regulate memory system and behavioral function.[21]

Highly selective activation of the dexmedetomidine α_{2A} receptor is sedative and hypnotic by acting on the locus coeruleus nucleus.[22] It also activates the dorsal horn by acting on the nucleus coeruleus α_{2C} and α_{2A} receptor, reducing the secretion of anterior pain transmission molecules, substance P, glutamate, and the hyperpolarization of interneurons, to inhibit pain transmission and produce an analgesic effect directly.[23,24] When dexmedetomidine was administered,

blood pressure could demonstrate a dose-dependent biphasic response. When administered in small doses, it primarily reduces vascular resistance, heart rate, and blood pressure through selective α_2 function. When administered in large doses or rapidly, it loses its selectivity α_2, increasing blood pressure and decreasing heart rate, and gradually recovers over time (Figure 1).[20]

Mechanism of Dexmedetomidine in Peripheral Nerve Block

The mechanism by which dexmedetomidine as an adjuvant to local anesthetics enhances their effect is a multifactorial theory still being debated. Several possible mechanisms have been suggested.

Peripheral Level

Peripheral action is the widely accepted mechanism by which dexmedetomidine enhances the blocking effect as an adjuvant. When dexmedetomidine was used alone in healthy volunteers, its blood concentration reached 1.23 ng/mL, but it did not have a sufficient analgesic effect on thermal or electrical stimulation.[25] When the same dose of dexmedetomidine was used in PNB combined with LA, the perineural injection had a stronger analgesic effect than systemic application or subcutaneous injection. This indicated that the peripheral effect was the primary mechanism by which dexmedetomidine could be used as an adjuvant for local anesthetics to enhance their effect.[26,27] Brummett et al[28] compared dexmedetomidine combined with ropivacaine alone; the analgesic time could be effectively prolonged, while the analgesic effect of dexmedetomidine could not be reversed when α_2 receptor antagonist was given, proving that dexmedetomidine extended analgesia through local action. Hypothalamic paraventricular nucleus (PVN) neurons are in direct contact with noradrenergic synapses and are controlled by the hyperpolarization-activated currents called I_h (H current).[29] I_h is also called the pacemaker current because it is believed to play a significant role in cell excitability.[30] Dexmedetomidine can maintain the hyperpolarized state of cells by inhibiting the activation of the I_h current, inhibit the next action potential by inhibiting the potassium channel, maintain the depolarization of cells, and increase the inhibition of the sodium channel, thereby enhancing the effect of LA.[28,31–35] This inhibitory effect is more obvious in unmyelinated C fibers (pain fibers) and small myelinated A-δ fibers (temperature sensation and rapid pain sensation) than in large myelinated motor fibers; consequently, the effect of dexmedetomidine on the sensory block is more obvious than on the motor block.[36–38] Dexmedetomidine may exert its peripheral effect by activating α_2 adrenoceptors in peripheral blood

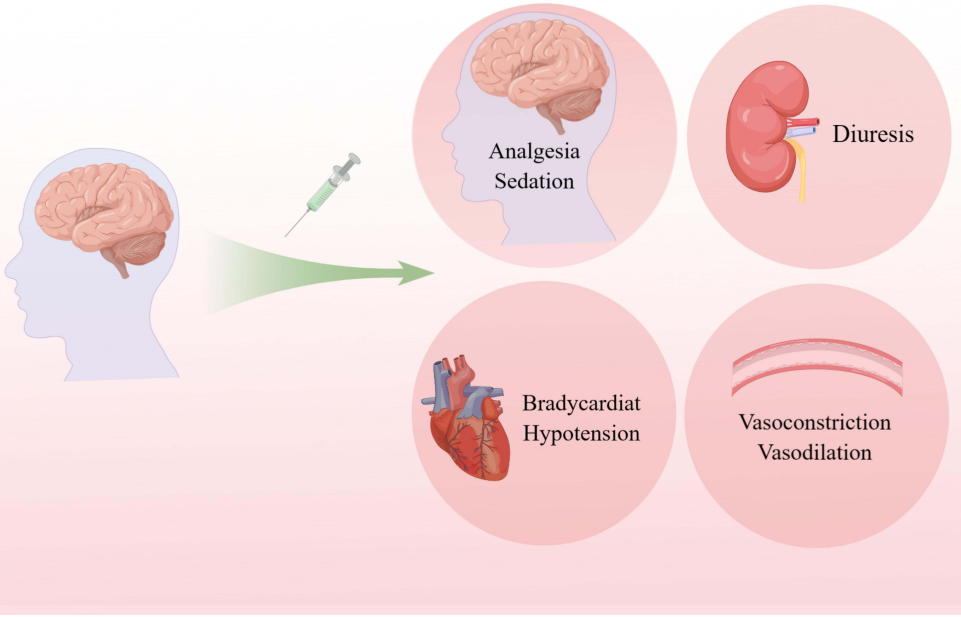

Figure 1 Multiple sites of action of dexmedetomidine (peripherally and centrally).

vessels, constricting blood vessels around the injection site, delaying the absorption of local anesthetics, and prolonging their block time.[39]

Spinal Cord Level

Dexmedetomidine can reduce the release and reuptake of excitatory neurotransmitters, such as glutamate and substance P, by binding to α_2 receptors in the spinal dorsal horn after systemic absorption or local diffusion.[23,24,40] Hyperpolarized interneurons inhibit the ascending spinal pathway related to nociceptive sensation, producing analgesia.[41]

Supraspinal Level

Although dexmedetomidine is ideally injected peripherally, few studies have discovered that it may have a certain systemic absorption so that it may have peripheral and central effects. It can spread to the cerebrospinal fluid via systemic absorption after perineural injection or intradural application, act on α_{2A} and α_{2C} adrenergic receptors in the brainstem, inhibit the descending noradrenergic pathway in the medulla or reduce sympathetic nerve signals, and achieve analgesic effect from the central level.[36,41–44] However, the mechanism must be confirmed through further studies. El Sherif et al[45] discovered that systemic absorption of dexmedetomidine administered in TAP block is common. Dexmedetomidine, in addition to its local effects, may cause direct central effects on locus coeruleus by systemic absorption, thus affecting the analgesic and hemodynamic effects of TAP. This was similar to a previous study in which dexmedetomidine had the same effect as intravenous injection, despite being administered around the nerve.[46] Dexmedetomidine as an adjuvant for nerve block can also have a certain sedative effect on the center.[43,44] All of the above evidence indicates that dexmedetomidine exists in different degrees of systemic absorption.

Existing studies have demonstrated that the analgesic mechanism of dexmedetomidine can be summarized as central analgesia and peripheral analgesia (Table 1).

Application of Dexmedetomidine in Peripheral Nerve Block

Dexmedetomidine, as an adjuvant, can affect nerve blocks to different degrees (Table 2).

Brachial Plexus Block (BPB)

Brachial plexus nerves are composed primarily of anterior branches of C_{5-8} and T1 spinal nerves, frequently with the participation of anterior branches of C_4 and T_2 spinal nerves. These nerves dominate the whole upper limb movement and most of the upper limb sensation. Anesthesia in upper limb surgery can block the nerve trunk, nerve bundle, and branches of brachial plexus nerves separately and have been well-applied.[47]

Biswas et al[44] divided 60 patients into control and experimental groups equally. The experimental group was given 35 mL of levobupivacaine and 1 mL (100 μg) of dexmedetomidine, while the control group was given 35 mL of levobupivacaine and 1 mL of normal saline. The results revealed that the control group had a longer duration of sensory block, motor block, and the first time of salvage analgesia, and adding levobupivacaine to supraclavicular brachial nerve block could prolong the duration of block and postoperative analgesia time. However, ultrasound-guided localization was not used. Therefore, Bharti et al[48] adjusted the above deficiencies in the trial in 2015 and added the onset time of sensory

Table 1 Analgesic Mechanism of Dexmedetomidine

Classification of Analgesia	Mechanism
Spinal level	Act on the presynaptic of the posterior horn of the spinal, the postsynaptic membrane of intermediate neurons, and the locus coeruleus of the brain stem α_2 receptor, changing action potential in spinal and supraspinal[157] Inhibit the release of excitatory neurotransmitters, such as glutamate and substance P, in the spinal[23,24]
Peripheral level	Inhibit δ and C fibers[158] Act on the α_2 receptors in peripheral vascular smooth muscle cells to constrict the peripheral blood vessels, reduce the absorption of local anesthetics, and prolong the block time Inhibit Ih current for pain control (Na^+ and K^+ based inward mixed cation current generated by activation of cell membrane hyperpolarization of cyclic-nucleotide gated channel) to reduce pain[26]

Table 2 Characteristics of Included Randomised Controlled Trial

	Nerve Block Location	Guiding Technique	Surgery	Dose
Biswas et al[44]	Supraclavicular brachial plexus block	NS	Orthopaedic surgery of forearm and hand	100μg
Bharti et al[48]	Supraclavicular brachial plexus block	US	Upper limb and hand surgeries	1μg/kg
Nazir et al[49]	Supraclavicular brachial plexus block	US	Upper limb surgeries	1μg/kg
Reddy et al[50]	Supraclavicular brachial plexus block	US	Upper limb surgeries	1μg/kg
Venkatraman et al[53]	Supraclavicular brachial plexus block	US	Upper extremity surgeries	50μg
Sane et al[51]	Supraclavicular brachial plexus block	US	Upper extremity orthopedic surgery	0.75μg/kg
Jung et al[52]	Interscalene brachial plexus block	US	Arthroscopic shoulder surgery	1, 1.5, 2μg/kg
Samar et al[56]	Supraclavicular brachial plexus block	NS	Upper limb orthopaedic surgery	1μg/kg
Somsunder et al[57]	Supraclavicular brachial plexus block	NS	Upper limb surgeries	1μg/kg
Yang et al[159]	Children axillary brachial plexus block	US	Children polydactyly surgery	0.25, 0.5, 0.75μg/kg
Helal et al[62]	Femoral-sciatic nerve block	US	Below knee surgery	100μg
Chaudhary et al[63]	Femoral-sciatic nerve block	US	Below knee orthopaedic surgeries	0.5μg/kg
Jin et al[64]	Femoral-sciatic nerve block	US+NS	TKA	0.5μg/kg
Yu et al[65]	Lumbar plexus-sciatic nerve block	NS	Ankle surgery	1, 1.5, 2μg/kg
Hu et al[67]	Popliteal sciatic nerve blockade along with femoral and obturator nerve blocks	US	Varicose saphenous vein resection	50μg
Sharma et al[68]	Femoral nerve block	US (catheter)	Unilateral total knee replacement	1.5μg/kg
Goel et al[73]	Femoral nerve block	US	Hip surgeries	50μg
Packiasabapathy et al[69]	Femoral nerve block	NS	Total knee replacement	1, 2μg/kg
Abdulatif et al[70]	Femoral nerve block	US	Arthroscopic knee surgery	25,50,75μg
Li et al[71]	Femoral nerve block	NS (catheter)	TKA	1μg/kg
Xiao et al[72]	Femoral nerve block and femoral-sciatic nerve block	US+NS	TKA	0.6μg/kg
Ding et al[76]	Paravertebral block	US	Thoracoscopic lobectomy	1μg/kg
Abdulatif et al[70]	Paravertebral block	LM	Elective modified radical mastectomy with axillary dissection	1μg/kg
Mohta et al[77]	Paravertebral block	LM	Breast cancer surgery	1μg/kg
Zha et al[79]	Thoracic paravertebral block	US	Video-assisted thoracoscopic lobectomy	1μg/kg
Guo et al[80]	Thoracic paravertebral block	US	Breast cancer surgery	1μg/kg
Bicer et al[81]	Paravertebral block	US	Thoracotomy	100μg
Yang et al[83]	Transversus abdominis plane block	US	Renal transplantation	1μg/kg
Qian et al[84]	Transversus abdominis plane block	US	Caesarian section	0.5μg/kg
Joseph et al[85]	Transversus abdominis plane block	US	Caesarian section	25μg
Singla et al[160]	Transversus abdominis plane block	US	Caesarean section	1μg/kg
Varshney et al[86]	Transversus abdominis plane block	US	Cesarean delivery	1μg/kg
Madangopal et al[87]	Transversus abdominis plane block	US	Unilateral inguinal hernioplasty	0.5,0.25μg/kg
Zeng et al[88]	Transversus abdominis plane block	US	Laparotomy for gynecologic malignancies	0.5, 1, 2μg/kg
Chapman et al[161]	Transversus abdominis plane block	US	Colorectal surgery	25μg
Karasu et al[89]	Transversus abdominis plane block	US	Laparoscopic cholecystectomy	1μg/kg
Mostafa et al[90]	Transversus abdominis plane block	US	Laparoscopic surgery in children	0.5μg/kg
El Sherif et al[45]	Transversus abdominis plane block	US	Lower abdominal cancer surgery	1μg/kg
Santosh et al[94]	Bilateral superficial cervical plexus block	/	Thyroid surgery	0.5μg/kg
Lin et al[95]	Cervical plexus block	LM	Thyroid surgery	1μg/kg

(*Continued*)

Table 2 (Continued).

	Nerve Block Location	Guiding Technique	Surgery	Dose
Elmaddawy et al[96]	Bilateral superficial cervical plexus block	US	Thyroid surgery	1μg/kg
Zhang et al[98]	Intercostal nerve block (six intercostal)	Under thoracoscopic direct vision	Thoracoscopic pneumonectomy	1μg/kg
Yao et al[99]	Intercostal nerve block (T2 to T6 intercostal)	LM	Lumpectomy	0.5μg/kg
Abdallah et al[101]	Serratus anterior plane block	US	Video-assisted thoracic surgery	1μg/kg
Wu et al[162]	Deep serratus anterior plane block	US	Modified radical mastectomy	1μg/kg
Li et al[163]	Continuous serratus anterior plane block	US	Thoracotomy	0.5,1μg/kg
Goyal et al[103]	Adductor canal block	US	Bilateral total knee replacement	0.25,0.5μg/kg
Wang et al[105]	Adductor canal block	US	TKA	1μg/kg
Thapa et al[106]	Adductor canal block	US	Anterior cruciate ligament reconstruction surgery	0.5μg/kg
Wang et al[110]	Erector spinae plane block	US	Thoracotomy	0.5μg/kg
Wang et al[111]	Erector spinae plane block	US	Modified radical mastectomy	1μg/kg
Gao et al[112]	Erector spinae plane block	US	VATS	1μg/kg
Gao et al[164]	Erector spinae plane block	US	VATS	0.1, 0.5, 1μg/kg
Manzoor et al[115]	Pectoral nerve block I,II	US	Breast surgery	1μg/kg
Kaur et al[116]	Pectoral nerve block I,II	US	Oncological breast surgery	1μg/kg
Alansary et al[121]	Quadratus lumborum block	US	Open renal surgery	1μg/kg
Thapa et al[124]	Stellate ganglion block	US	Upper limb surgery	0.5μg/kg
Andersen et al[165]	Aphenous nerve blocks	US	/	100μg/mL
Sivakumar et al [166]	Fascia iliaca compartment block	US	Femur surgeries	1μg/kg
Varsha et al[167]	Ilioinguinal-iliohypogastric block	US	Pediatric inguinal hernia surgeries	1μg/kg

Abbreviations: NS, Nerve stimulator; US, Ultrasound; LM, Landmark; TKA, Total knee replacement; VATS, Video-assisted thoracic surgery.

and motor blocks in the result records to observe and record the hemodynamic changes of patients and the number of postoperative analgesics. However, 1 μg/kg dexmedetomidine was administered to the experimental group. The results presented that adding dexmedetomidine to the ropivacaine-lidocaine mixture can significantly prolong the duration of the block, improve postoperative analgesia, and reduce the need for emergency analgesics in patients undergoing upper limb surgery. Consistent with the results of Nazir et al[49] the experimental group was also established using the standard of 1 μg/kg. Moreover, Nazir also included a sedation score in the evaluation, and the results suggested that dexmedetomidine could increase the postoperative sedation effect. Reddy et al[50] compared the intravenous infusion of dexmedetomidine with the adjuvant of 0.5% lebupivacaine (1 μg/kg) in suclavicular brachial nerve block. The results revealed that sensory and motor blocks acted more quickly in the perineural group, with longer duration and analgesia than intravenous dexmedetomidine. Sane et al[51] employed 39 mL bupivacaine (0.25%) + 0.75 μg/kg dexmedetomidine as the test group. The results also confirmed that dexmedetomidine combined with bupivacaine reduced the onset time of sensory and motor block and increased the duration of numbness and immobility. Jung et al[52] compared the addition of dexmedetomidine in local anesthetics with the simple control and established dexmedetomidine experimental groups with various concentrations (1, 1.5, and 2 μg/kg). The results demonstrated that 2 μg/kg dexmedetomidine could provide sufficient analgesic duration, indicating that Dexmedetomidine 2 μg/kg may be the best dose for brachial plexus block during arthroscopic shoulder surgery. Venkatraman et al[53] compared quantitative morphine (5 mg), dexmedetomidine (50 μg), and dexamethasone (8 mg) for supraclavicular brachial Plexus block (SBPB). The results presented that dexmedetomidine had the shortest onset time of the sensory and motor blocks, but dexamethasone had the best duration of postoperative analgesia.

Therefore, dexmedetomidine, as an adjuvant of LA in BPB, has certain advantages in sedation, analgesia, and onset time, despite the specific concentration of dexmedetomidine or quantitative dexmedetomidine. Similar conclusions have

been reached in a series of recent meta-analyses.[54,55] However, the selection of different dexmedetomidine concentrations lacks a unified conclusion. The comparison between intravenous infusion and perineural use of dexmedetomidine was also inconsistent. Sehmbi et al[55] showed that intravenous dexmedetomidine infusion did not prolong the sensation, motor, or pain relief duration. Samar et al[56] revealed that intravenous dexmedetomidine could produce sensory block earlier, with a longer sensory and motor block and analgesia duration. Regarding the onset and duration of block and duration of analgesia, Somsunder et al[57] discovered that intravenous dexmedetomidine was equally effective as epineural dexmedetomidine, but the hemodynamic fluctuation was larger. However, additional research indicates that intravenous dexmedetomidine can prolong the analgesic time and reduce opioid consumption to a certain extent, and perineural application has a more pronounced effect.[46,50]

Sciatic Nerve Block (SNB)

Due to the sciatic nerve is the longest human body is the most massive peripheral nerve (by multilayer membrane package), mainly by the former branch of $L_{4–5}$ and $S_{1–3}$ nerve, compared to the smaller nerve, local anesthetics to penetrate or dispersion to target sodium channels need longer effective time.[58]

Currently, Brummett et al[59] discovered that bupivacaine combined with high-dose dexmedetomidine intranasal administration significantly prolonged the duration of sensory and motor blocks in animal experiments. Other basic studies also demonstrated that dexmedetomidine combined with LA could prolong peripheral nerve block analgesic time in rats.[60,61]

Clinical studies frequently combine sciatic nerve blocks with other nerve blocks. It usually includes a femoral-sciatic nerve block and a lumbar plexus-sciatic nerve block.

Femoral-Sciatic Nerve Block

Helal et al[62] used 0.5% bupivacaine to perform nerve block on 60 patients undergoing knee surgery and found that adding 100 μg dexmedetomidine to bupivacaine for femoral sciatic nerve block shortened the pre-operative time of sensory and motor block by 20%. Sensory and motor block durations were 45% and 40% longer, respectively, but blood pressure and heart rate decreased 10 to 90 min after the block. Chaudhary et al[63] used dexmedetomidine (0.5 μg/kg) with a combined quantitative dose of 0.125% levobupivaine to perform femoral-sciatic nerve blocks on patients undergoing knee surgery, and the results demonstrated that dexmedetomidine could prolong the block time. Jin et al[64] compared the intravenous and systemic administration of dexmedetomidine (0.5 μg/kg) combined with 0.25% ropivacaine (0.25% Rop 40 mL) in total knee arthroplasty (TKA) patients. The results revealed that intranasal dexmedetomidine could significantly prolong the time interval between the onset of pain after TKA, reduce postoperative pain, reduce postoperative opioid dosage, and improve postoperative sleep quality and pain management satisfaction.

Lumbar Plexus-Sciatic Nerve Block (LSB)

Yu et al[65] added 1 μg/kg, 1.5 μg/kg, and 2 μg/kg of dexmedetomidine to 30 mL 0.5% ropivacaine (ROP) in 80 patients undergoing LSB lower ankle surgery. The results suggested that the peripheral nerve administration of dexmedetomidine (2 μg/kg) was consistent with ropivacaine, which can most significantly prolong the duration of sensory and motor block. Wang et al[66] demonstrated that an LSB block and 0.33% ropivacaine combined with dexmedetomidine (1 μg/kg) in a 79-year-old man with multiple cerebral infarctions and congestive heart failure who underwent knee amputation due to ischemic necrosis of the left lower limb could also prolong the analgesic time to 26 h and maintain hemodynamic stability. Hu et al[67] performed a popliteal sciatic nerve block combined with femoral nerve and obturator nerve block in 60 patients with great saphenous vein varicose. The results indicated that 0.5 mL (50 μg) dexmedetomidine could also prolong the block time.

Femoral Nerve Block (FNB)

The femoral nerve (lumbar 2~4) is the largest branch of the lumbar plexus. It descends between the psoas major and the iliac muscles and supplies this muscle with branches. It enters the thigh through the deep surface of the midpoint of the inguinal ligament and is divided into several branches.

Sharma et al[68] performed femoral nerve block in 50 patients with unilateral total knee replacement (TKR). The results demonstrated that adding 0.2% dexmedetomidine to ropivacaine could improve the quality and prolong the postoperative analgesia time. Subsequently, Packiasabapathy et al[69] proposed different concentrations of dexmedetomidine, with 1 μg/kg and 2 μg/kg dexmedetomidine + 20 mL (0.25%) bupivacaine used in the experimental group, respectively. The results revealed that dexmedetomidine at 2 μg/kg in FNB was better than 1 μg/kg. Compared to bupivacaine alone, it can prolong the analgesic time and reduce the use of opioids after the operation.

Abdulatif et al[70] conducted a quantitative study of dexmedetomidine combined with bupivacaine and added 25 μg, 50 μg, and 75 μg multiple doses of dexmedetomidine to 0.5% bupivacaine solution, compared to the blank control group. In comparison to the addition of 25 μg dexmedetomidine, the addition of 50 μg and 75 μg dexmedetomidine could shorten the onset time of the sensory and motor block, prolong the duration of sensory and motor block, reduce the time of postoperative first remedial analgesia and the use of postoperative analgesic morphine. These advantages are more evident with the increase in dexmedetomidine dose, but the risk of adverse reactions also increases.

Additionally, Li et al[71] discovered that ropivacaine combined with dexmedetomidine for femoral nerve block could inhibit the local inflammatory response. For patients requiring TKR, 20 mL of 0.5% ropivacaine with 1 μg/kg dexmedetomidine was used for the femoral nerve block. The results indicated that the VAS score, knee circumference, IL-6 concentration in joint fluid, and prostaglandin E-2 concentration in the experimental group were lower than in the control group 12~ 8 h after the operation. After the femoral nerve block, adding 1 μg/kg dexmedetomidine to ropivacaine can significantly inhibit the local inflammatory response. Moreover, ropivacaine with dexmedetomidine has a better postoperative analgesic effect on TKA than ropivacaine alone.

Xiao et al[72] compared the difference between femoral and sciatic nerve blocks. The results indicated that the analgesic effect of dexmedetomidine combined with femoral nerve block in TKA was similar to that of femoral-sciatic nerve block. Goel et al[73] compared the effects of peripheral and systemic dexmedetomidine. The results displayed that peripheral (39.5 mL 0.25% bupivacaine + 0.5 mL 50 μg dexmedetomidine) or systemic dexmedetomidine did not prolong the duration of analgesia compared to femoral nerve block using bupivacaine alone.

Paravertebral Blockade (PVB)

Paravertebral blockade (PVB) is a technique used to block the conduction of somatosensory and motor nerves by injecting local anesthetics into the spinal nerve in paravertebral space to pass through the lateral spinal nerve formed by the foraminal foramen to relieve chest and abdominal surgery-related pain.[74] Previous thoracic epidural analgesia is the gold standard for postoperative analgesia after thoracic surgery, but it is associated with risks, such as hypotension. Studies have demonstrated that the analgesic effect of PVB is comparable to thoracic epidural analgesia (TEA) after chest surgery with fewer adverse reactions, so PVB is widely used in clinical practice.[75]

Ding et al[76] applied PVB or TEA in 113 patients requiring video-assisted surgery. The results revealed that 0.5% ropivacaine combined with 1 μg/kg dexmedetomidine perineural administration in PVB could prolong the analgesic time and reduce postoperative pain score compared to 0.5% ropivacaine alone. It can effectively reduce postoperative adverse reactions compared to 0.5% ropivacaine TEA. Mohamed et al[77] performed PVB on patients undergoing radical mastectomy for breast cancer. Compared to 20 mL of 0.25% ropivacaine alone, ropivacaine combined with 1 μg/kg dexmedetomidine could effectively improve postoperative analgesia, prolong analgesia time, and reduce the use of postoperative opioids. This is consistent with the results of Mohta et al[78] except Mohta used 0.5% bupivacaine combined with 1 μg/kg dexmedetomidine. The results displayed that complications, such as hypotension and arrhythmia, could be effectively avoided. However, the latest results of Zha et al[79] discovered that 0.5% ropivacaine combined with 1 μg/kg dexmedetomidine perineural application did not reduce the complications of hypotension and arrhythmia, despite producing a longer analgesic effect, reducing postoperative opioid consumption, and reducing the incidence of side effects, such as nausea and vomiting. Guo et al[80] studied the effect of dexmedetomidine as a PVB adjuvant on the effective concentration (EC_{50}) of propofol successfully placed in the laryngeal mask. The results demonstrated that 0.3 mL/kg of 0.5% ropivacaine combined with 1 μg/kg dexmedetomidine could reduce the TCI concentration of propofol, making it easier for female patients to place the laryngeal mask. Biçer et al[81] conducted a study of dexmedetomidine in PVB in 93 patients requiring thoracotomy. The results revealed a paravertebral block with 20 mL

0.5% bupivacaine + 1 mL dexmedetomidine (100 μg) reduced postoperative pain scores and morphine consumption. However, the perineural administration of dexmedetomidine did not affect hemodynamics.

Transversus Abdominis Plane Block (TAPB)

Transversus abdominis plane block (TAPB) is also known as transversal fascia block. The abdominal muscles can be divided into external oblique, internal oblique, and transverse abdominis, with the fascia layer between them, and the plane between the internal oblique and transverse abdominis is called TAP.[82] TAPB has an excellent analgesic effect on skin, muscle, and parietal peritoneum of the anterior abdominal wall.

Yang et al[83] compared the analgesic effect of TAPB on kidney transplant recipients with or without dexmedetomidine. The results disclosed that 30 mL of 0.33% ropivacaine combined with 1 μg/kg dexmedetomidine reduced morphine consumption in the first 24 h after kidney transplantation. Dexmedetomidine as an adjuvant provided more effective analgesia. Qian et al[84] performed TAPB on 70 patients requiring cesarean section. The experimental group used bilateral 20 mL 0.3% ropivacaine combined with 0.5 μg/kg dexmedetomidine TAPB. The results indicated that adding 0.5 μg/kg dexmedetomidine to 0.3%, ropivacaine can prolong the painless duration and reduce the VAS score. It can also reduce the number of patients who require emergency analgesia, extendthe duration of initial analgesia, and improve patient satisfaction without serious side effects. This result was consistent with Joseph et al.[85] He discovered that 20 mL of 0.5% ropivacaine combined with 25 μg fentanyl or 25 μg dexmedetomidine effectively prolonged analgesia and reduced total analgesic consumption. Varshney et al[86] and others have also proved this point of view.

In addition to kidney transplantation and Caesarean section, dexmedetomidine has been successfully applied as an adjuvant in hernia repair Madangopal et al[87] open treatment of gynecological malignant tumor,[88] minimally invasive colorectal surgery,[161] laparoscopic cholecystectomy,[89] laparoscopic bile duct exploration in children[90] and other operations. It has obvious advantages in postoperative analgesia.

Cervical Plexus Block (CPB)

The cervical plexus comprises the anterior branches from the first to fourth cervical nerves, and the cervical plexus block can be divided into deep and shallow cervical plexus blocks.[91] It is effective in thyroid surgery, transcatheter aortic valve implantation (TAVI), clavicular surgery, carotid endarterectomy, and chest surgery with spontaneous breathing preservation.[92,93]

Santosh et al[94] performed CPB on 60 patients requiring thyroid surgery. The results showed that compared to 0.5% ropivacaine alone, 20 mL of 0.5% ropivacaine combined with 0.5 μg/kg dexmedetomidine significantly prolonged postoperative analgesia and patient satisfaction, and patient satisfaction was higher. However, it did not improve hemodynamic stability and sedation and swallowing pain, consistent with Lin et al[95] previous results. Lin administrated 0.375% ropivacaine to 40 patients undergoing thyroid surgery to receive CPB, and the experimental group additionally administrated 1 μg/kg dexmedetomidine around the nerve. The results confirmed that the experimental group could shorten the sensory block's onset time and prolong the analgesia's duration. The patient remained sedated and could be awakened at any time during the operation, but the mean arterial pressure and heart rate decreased after the procedure, requiring the anesthesiologist to pay close attention to hemodynamic changes during the operation. Elmaddawy et al[96] mixed bupivacaine, epinephrine, and dexmedetomidine in thyroid surgery for bilateral CPB. The results demonstrated that applying 1 μg/kg dexmedetomidine around the cervical plexus prolonged the analgesic time during and after surgery, reduced the demand for opioids, and reduced the heart rate. Postoperative complications and mean arterial pressure did not differ.

Intercostal Nerve Block (INB)

The intercostal nerve runs from the inside of the rib angle (6–8 cm from the midline) between the pleura and the intercostal fascia. Intercostal nerve block has been used for various chronic and acute pain conditions, including rib fracture, herpes zoster, postoperative thoracotomy pain syndrome, and intercostal neuralgia.[97]

Zhang et al[98] performed INB on 80 patients who underwent thoracoscopic pneumonectomy. The experimental group received 10 mg dexamethasone 2 mL or 2mL 1 μg/kg dexmedetomidine based on 28 mL 0.5% ropivacaine + 2 mL

normal saline, respectively, injected into six intercostal spaces with 5 mL injection in each space. The results presented that perineural application of dexmedetomidine or dexamethasone could effectively prolong the analgesic time and reduce the use of postoperative remedial analgesics, but could not reduce the incidence of postoperative complications. Yao et al[99] compared the effect of intravenous or perineural dexmedetomidine combined with ropivacaine on mass resection and proved that 0.5 μg/kg dexmedetomidine combined with 0.5% ropivacaine for intercostal nerve block could prolong the duration of postoperative analgesia. The analgesia duration via the nerve route is longer than that via the venous route. However, the sedation scores did not differ.

Serratus Anterior Plane Block (SAPB)

Serratus anterior plane block (SAPB) is a newly proposed thoracic nerve block method that primarily blocks the lateral cutaneous branch of the thoracic intercostal nerve, providing anterolateral and partial posterior thoracic regional analgesia that can be used for postoperative analgesia of breast surgery, rib fracture, and thoracotomy.[100]

Abdallah et al[163] evaluated the postoperative analgesic efficiency of SAPB with dexmedetomidine as an adjuvant of levobupivacaine for thoracic surgery and proposed that levobupivacaine plus dexmedetomidine continuous SAPB can be used as an analgesic program after thoracic surgery, and combined with acetaminophen can provide sufficient sedation and analgesic effect. Li et al[101] performed SAPB on 80 patients undergoing video-assisted thoracic surgery (VATS), and the experimental group received 20 mL of 0.5% ropivacaine + 0.5 μg/kg or 1 μg/kg dexmedetomidine. The results revealed that 1 μg/kg dexmedetomidine was the most beneficial adjuvant for prolonging the analgesic time and effect.

Adductor Canal Block (ACB)

Femoral nerve block (FNB) is an effective analgesic method. However, the application of FNB is limited in minimally invasive arthroscopic knee surgery because FNB reduces the muscle strength of the quadriceps femoris, leads to lower limb immobility, and increases the risk of falling. However, adductor Canal block (ACB) can reduce postoperative opioid dosage and has little effect on muscle strength, attracting increased attention.[102]

Goyal et al[103] proved that adding dexmedetomidine to ropivacaine in Total Knee arthroplasty (TKA) can prolong the analgesic time after adductor canal block. On this basis, Herman et al[104] proposed that an adjuvant combination of dexmedetomidine and dexamethasone (DEX-DEX) can be used in TKA, and their synergistic effect can prolong the analgesic time. Further, Wang et al[105] recently demonstrated that peripheral application of dexmedetomidine 1 μg/kg in TKA reduced the median effective concentration of ropivacaine for adduction block (from 0.38% to 0.29%). In addition to TKA, FNB with dexmedetomidine as an adjuvant was also used in Achilles tendon repair and anterior cruciate ligament reconstruction surgeries.[106]

Erector Spinae Plane Block (ESPB)

The erector spinae (ES) is the longest and largest of the deep dorsal muscles. It is located in the sulcus on each side of the spine, rising from the dorsal side of the sacrum and posterior to the iliac crest and terminating in the vertebrae and ribs. Ultrasonics-guided Erector Spinae plane block (ESPB) is a novel interfascial plane block technique first proposed by Forero et al[107] in 2016 and successfully applied in treating severe acute postoperative and neuropathic pain. Several studies have validated that ESPB and PVB may have the same effect in breast cancer surgery and thoracoscopic surgery, and the ESPB is more effective than INB.[108,109]

Wang et al[110] demonstrated that 28 mL 0.5% ropivacaine combined with 2 mL of 0.5 μg/kg dexmedetomidine in treating ESPB after thoracotomy could effectively prolong postoperative analgesia time and reduce opioid consumption without increasing the incidence of additional adverse reactions. Wang et al[111] also demonstrated this point by using ESPB in modified radical mastectomy, with the difference that 30 mL dexmedetomidine + 0.33% ropivacaine was used in the experimentalgroup. Additionally, Gao et al[112] reached the same conclusion in thoracoscopic lobectomy and discovered that 1 μg/kg dexmedetomidine was better than 10 mg dexamethasone as an adjuvant.

Pectoral Nerve Block (PECS)

PECS includes PECS-I and PECS-II, followed by PECS-I combined with PECS-II, widely used in clinics. Since PECS, ESPB, INB, and PVB have similar effects, they have been frequently compared recently, and PECS has certain advantages in breast cancer.[97,113,114]

Manzoor et al[115] reported that PECS with 1 μg/kg dexmedetomidine as an adjuvant of bupivacaine could prolong the duration of postoperative analgesia and improve the quality of postoperative analgesia without serious side effects. Kaur et al[116] focused on pain and stress, presenting that dexmedetomidine at 1 μg/kg in PECS provided better analgesia and greater inhibition of stress hormone levels (cortisol and prolactin) without serious side effects. Zusman et al[117] examined the synergistic effect of dexmedetomidine and dexamethasone (DEX-DEX) as adjuvants in analgesia, consistent with Herman et al.[104]

Quadratus Lumborum Block (QLB)

Quadratus Lumborum block (QLB) has been developed for over a decade since it was first proposed in 2007. QLB suits auxiliary anesthesia and perioperative analgesia in abdominal, hip, and lower limb surgeries.[118,119] Currently, four common approaches, including lateral QLB, posterior QLB, anterior QLB, and intramuscular QLB, are used for quadratus lumborum block in clinical practice.[120]

Alansary et al[121] performed QLB on 80 patients undergoing open kidney surgery. The experimental group received 30 mL of 0.25% bupivacaine + 1 μg/kg dexmedetomidine. Compared to bupivacaine alone, the amount of postoperative morphine was significantly reduced, the duration of initial analgesia was prolonged, and sufficient sedation was achieved. Moreover, it can effectively reduce the incidence of adverse reactions, but the average blood pressure and heart rate have a certain decrease.

Stellate Ganglion Block (SGB)

Stellate ganglion block is a method in which a local anesthetic is injected into the surface of the stellate ganglion so that it is infiltrated with the drug fluid, thereby blocking sympathetic activity in the area dominated.[122] General indications for stellate ganglion block include postherpetic neuralgia of the face, chest, back, and upper limbs, trigeminal neuralgia, and migraine.[123]

Thapa et al[124] evaluated the effect of dexmedetomidine as an adjuvant in SGB. In upper limb surgery, 3 mL 2% lidocaine + 0.5 μg/kg dexmedetomidine for SGB can reduce the use of tramadol within 24 h after surgery, prolong postoperative analgesia time, and has more advantages than intravenous dexmedetomidine. Shrestha et al[125] recently proposed ultrasound-guided SGB with dexmedetomidine as an adjuvant for treating Complex Regional Pain Syndrome (CRPS). This case report exposed that dexmedetomidine as an adjuvant of LA in SGB did not cause significant side effects.

Neurotoxicity of Dexmedetomidine in Peripheral Nerve Block

A series of animal experiments were conducted to evaluate the possible neurotoxicity of dexmedetomidine during PNB. The sciatic nerve block was performed with a high dose of dexmedetomidine (20–40 mg/kg) combined with bupivacaine and ropivacaine, respectively. Neurotoxicity, axon, or myelin sheath damage were not observed 24 h and 14 d after injection.[123,126,127] Meanwhile, dexmedetomidine attenuated bupivacaine-induced neurotoxicity by regulating mast cell degranulation.[128] It is suggested that the neuroprotective effect of dexmedetomidine makes it suitable for peripheral nerve block as a combined local anesthetic. However, Yu et al[129] recently discovered that 0.5% ropivacaine caused significant sciatic nerve injury in diabetic rats. A large dose of dexmedetomidine was significantly enhanced, although 20 μg/kg dexmedetomidine was higher than the clinical dose. However, ropivacaine (alone and combined with dexmedetomidine) for peripheral nerve block in diabetic patients must be studied further. Wang et al[130] studied the dose-dependent neurotoxicity of dexmedetomidine and discovered that the lowest dose of dexmedetomidine (1 and 2 μg/mL) combined with 0.25% ropivacaine was used for continuous femoral nerve block without neurotoxic damage, whereas a higher dose (3 μg/mL) could lead to neurotoxic damage in the experimental rabbit model. Xue et al[131] also proposed that adding dexmedetomidine in ropivacaine to sciatic nerve block in rats prolonged the duration of sciatic nerve sensory and motor block and significantly alleviated the neurotoxicity induced by ropivacaine by reducing caspase-

3-dependent sciatic nerve cell apoptosis. Studies have demonstrated that 20 μg/kg of dexmedetomidine is more effective than 6 μg/kg. Therefore, most current studies are animal and in vitro neural experiments. There is still insufficient strong evidence of whether human peripheral nerve fiber toxicity has a clinical application.

Comparative Studies of Dexmedetomidine with Other Drugs

In several studies, we compared dexmedetomidine and some other drugs as adjuvants (Table 3).

Table 3 Comparative Studies of Dexmedetomidine with Other Drugs as Adjuvants

Comparative Agents	Purpose	Outcome	Reference
Dexmedetomidine vs clonidine	Compare clonidine and dexmedetomidine in supraclavicular BPB	When added to local anesthetic in the supraclavicular BPB, Dexmedetomidine enhanced the duration of sensory and motor block and analgesia. The time for rescue analgesia was prolonged in patients receiving dexmedetomidine. It also enhanced the quality of the block as compared with clonidine	[132]
Dexmedetomidine vs clonidine	Compare dexmedetomidine or clonidine could improve the analgesic profile of levobupivacaine to the same extent during TAPB	Adding dexmedetomidine to levobupivacaine can extend the time of analgesia and reduce the use of postoperative backup analgesics with minimal sedation effects when used in TAPB in pediatrics undergoing laparoscopic orchiopexy. Clonidine can be used as an alternative adjuvant to local anesthetics with good postoperative analgesic profiles	[90]
Dexmedetomidine vs clonidine	Compare dexmedetomidine and clonidine added to bupivacaine in infraclavicular BPB	Dexmedetomidine provides a quicker and prolonged analgesic action without major adverse effects	[133]
Dexmedetomidine vs clonidine	Review the efficacy and safety of dexmedetomidine and clonidine as perineural or systemic adjuvants for BPB	Alpha2-receptor agonists used as adjuvants for BPB lead to a prolonged duration of analgesia, with dexmedetomidine as the most efficient. Alpha2-receptor agonists were associated with an increased risk of cardiovascular adverse events	[54]
Dexmedetomidine vs nalbuphine	Compare dexmedetomidine and nalbuphine in BPB	Compared with dexmedetomidine, nalbuphine had significantly shorter sensory and motor block onset time, longer block duration, less analgesic need, and fewer side effects	[135]
Dexmedetomidine vs nalbuphine	Compare nalbuphine and dexmedetomidine for ESPB in VATS	Nalbuphine and dexmedetomidine are comparable in terms of the associated analgesia, sensory block duration, need for rescue analgesia, and incidence of chronic pain in patients after VATS in ESPB	[136]
Dexmedetomidine vs nalbuphine	Compare dexmedetomidine and nalbuphine in TVPB in breast cancer surgeries	Adding nalbuphine to TPVB improved the block's quality and decreased postoperative analgesic requirements. Adding dexmedetomidine to bupivacaine increased the time to the first analgesic request and more sedation than bupivacaine and bupivacaine with nalbuphine	[134]
Dexmedetomidine vs dexamethasone	Compare dexmedetomidine and dexamethasone in supraclavicular BPB	Both dexmedetomidine and dexamethasone, when used as adjuvants to ropivacaine for supraclavicular BPB, block onset time and prolong block duration.	[17]
Dexmedetomidine vs morphine and dexamethasone	Compare morphine, dexmedetomidine, and dexamethasone in ultrasound-guided supraclavicular BPB	Dexamethasone is an ideal adjuvant to ropivacaine in BPB to prolong postoperative analgesia and is devoid of adverse effects. Dexmedetomidine has a quicker onset of sensory and motor blockade	[53]

(*Continued*)

Table 3 (Continued).

Comparative Agents	Purpose	Outcome	Reference
Dexmedetomidine vs dexamethasone	Compare dexamethasone and dexmedetomidine for the infraclavicular BPB in patients undergoing forearm fracture surgery	There was no significant difference in postoperative pain intensity between dexamethasone and dexmedetomidine groups, although dexmedetomidine demonstrated a longer sensory block duration in comparison with dexamethasone as a lidocaine adjuvant in infraclavicular BPB	[138]
Dexmedetomidine vs dexamethasone	Compares dexamethasone and dexmedetomidine on postoperative analgesia	Dexamethasone and dexmedetomidine have equivalent analgesic effects in peripheral nerve blocks	[137]
Dexmedetomidine vs magnesium sulfate	Compare dexmedetomidine and $MgSO_4$ in supraclavicular BPB	Dexmedetomidine provides earlier onset of the sensory and motor block and a prolonged duration of sensory and motor blocks, the duration of analgesia is longer, and postoperative rescue analgesia is less compared to patients receiving $MgSO_4$. The incidence of hypotension and bradycardia and sedation score was higher with dexmedetomidine	[139]
Dexmedetomidine vs magnesium sulfate	Compare magnesium sulfate and dexmedetomidine in infraclavicular BPB	Dexmedetomidine provided quicker onset, longer duration of analgesia with lesser consumption of postoperative rescue analgesia. It showed a higher incidence of intraoperative hypotension and bradycardia than magnesium sulfate	[140]
Dexmedetomidine vs sufentanil	Compare dexmedetomidine and sufentanil as adjuvants for bupivacaine in BPB	Sufentanil is a fairly better choice than dexmedetomidine as an adjuvant for bupivacaine and can provide preferable sensory and motor blocks	[141]
Dexmedetomidine vs fentanyl	Compare dexmedetomidine and fentanyl under ultrasound guidance in supraclavicular BPB	Dexmedetomidine prolongs the duration of sensory and motor block and postoperative analgesia as compared to fentanyl when used as an adjuvant to ropivacaine in supraclavicular BPB and is not associated with any major adverse events	[122]
Dexmedetomidine vs epinephrine	Compare dexmedetomidine and epinephrine in infraclavicular BPB.	Perineural 1 μg/kg of dexmedetomidine similarly prolonged nerve block duration compared to 200 μg of epinephrine but slowed heart rate	[13]
Dexmedetomidine vs ketorolac	Examine dexmedetomidine and ketorolac as local anesthetic adjuvants in infraclavicular BPB	Dexmedetomidine had better effects on sensory and motor block duration and onset than ketorolac, as lidocaine adjuvants in infraclavicular BPB were present in both protocols. The first time to an analgesic request by ketorolac was longer than dexmedetomidine	[143]

Abbreviations: BPB, Brachial plexus block; TAPB, Transversus abdominis plane block; ESPB, Erector spinae plane block; VATS, Video-assisted thoracic surgery; TPVB, thoracic paravertebral block.

Dexmedetomidine vs Clonidine

Clonidine, similar to dexmedetomidine, has received great attention. When 1 μg/kg Dexmedetomidine was added to local anesthetic in the supraclavicular brachial plexus block, it enhanced the sensory and motor block and analgesia duration compared to 1 μg/kg Clonidine. The time for rescue analgesia was prolonged in patients receiving dexmedetomidine. It also enhanced the quality of the block compared to clonidine.[132] This suggests that dexmedetomidine may have a better analgesic effect and longer analgesic time as an adjuvant. Another study on the brachial plexus block also proves this view, although it is not the supraclavicular brachial plexus block but the axial plexus block. The results indicate that adding dexmedetomidine to the axial plexus block increases the sensor and motor block duration and time to first acute

use while decreasing total acute use without side effects. The results were consistent when dexmedetomidine was used as an adjuvant in the subclavian brachial plexus block. Compared to 1 μg/kg clonidine, 1 μg/kg dexmedetomidine provides a quicker and prolonged analgesic action without major adverse effects.[133] More systematic meta-analysis also identified that α_2-adrenergic receptor agonists used as adjustments for BPBs lead to a prolonged analysis period, with dexmedetomidine as the most effective. However, α_2-adrenergic receptor agonists were associated with an increased risk of cardiovascular adverse events.[54] When used in TAPB in pediatrics undergoing laparoscopic orchiopexy, adding dexmedetomidine to levobupivacaine can extend the time of analgesia and reduce the use of postoperative backup analgesics with minimal sedation effects. Clonidine can be an alternative adjuvant to local anesthetics with good postoperative analgesic profiles. However, considering the price of these two drugs, clonidine can be the best choice in developing countries and regions.[90]

Dexmedetomidine vs Nalbuphine

Nalbuphine is a recently developed and powerful analgesic. Nalbuphine and μ, κ, and δ receptor binding, but not with σ receptor binding, nalbuphine is κ receptor agonist/μ receptor partially antagonistic analgesic. A new study exhibits that adding nalbuphine 10 mg as an adjuvant to bupivacaine local anesthetic in PVB improved the quality of the block and decreased postoperative analgesic requirements than the bupivacaine only group and dexmedetomidine and bupivacaine group. Although nalbuphine has more advantages in analgesic quality, dexmedetomidine can prolong the analgesic time and provide stronger sedation.[134] This is not completely consistent with Jiang's results, indicating that 10 mg nalbuphine has significantly shorter sensory and motor block onset time, longer block duration, less analgesic need, and fewer side effects than 0.75 μg/kg dexmedetomidine.[135] Rao et al[136] results are also different from the above. As an adjuvant to ropivacaine in ESPB, 20 mg nalbuphine and 1 μg/kg dexmedetomidine are comparable in terms of the associated analgesia, sensory block duration, need for rescue analgesia, and incidence of chronic pain.

Therefore, the results of nalbuphine and dexmedetomidine as adjuvants are inconsistent, likely due to the type of nerve block and the concentration of the two drugs, as we discovered that most comparisons were produced at different doses.

Dexmedetomidine vs Dexamethasone

Singh et al[17] discovered that 1 μg/kg dexmedetomidine and 8 mg dexamethasone when used as adjuvants to ropivacaine for SCBP block, delay onset time and prolong block duration. In the comparative meta-analysis of the two drugs, Song et al[137] concluded that the analgesic effects of dexamethasone and dexmedetomidine in peripheral nerve blocks are equivalent. Venkatraman's research results present different views. In brachial plexus block, 8 mg dexamethasone is an ideal adjuvant to ropivacaine to prolong postoperative analgesia without adverse effects. However, 50 μg dexmedetomidine has a quicker sensory and motor blockade onset.[53] Yaghoobi et al[138] discovered no significant difference in postoperative pain intensity between the 8 mg Dexamethasone and 1 μg/kg dexmedetomidine. However, dexmedetomidine demonstrated a longer sensory block duration than dexamethasone as a lidocaine adjuvant in the infraclavicular block. We consider that the dose may be the most important factor affecting the results.

Dexmedetomidine vs $MgSO_4$

The comparison results of Shukla et al[139,140] and Elyazed et al[140] on dexmedetomidine and magnesium sulfate are similar. The results proved that dexmedetomidine provides earlier onset of the sensory and motor block and prolonged duration of sensory and motor blocks and duration of analgesia is longer, and postoperative rescue analgesia is less compared to patients receiving $MgSO_4$. However, the incidence of hypotension and bradycardia was higher with dexmedetomidine.

Dexmedetomidine vs Others

Ghasemifa et al[141] identified that 5 μg/mL sufentanil is superior to 100 μg/mL dexmedetomidine in analgesia, contrary to Dharmarao et al.[122] The most likely explanation is the difference between concentration and dose. Additionally, the efficacy of sufentanil and fentanyl differs.

Song et al[142] identified that perineural 1 μg/kg dexmedetomidine prolonged nerve block duration similarly to 200 μg epinephrine but slowed heart rate. Mirkheshti et al[143] found that dexmedetomidine had better effects on sensory and motor block duration and onset than ketorolac, as lidocaine adjuvants in infraclavicular brachial plexus block were present in both protocols.

Recommendations for Peripheral Nerve Blocks

The optimal dose of dexmedetomidine as an adjuvant in peripheral nerve block depends on the dose, the block location, the concentration and dose of the local anesthetic drug, surgical method, population, and other factors. Additionally, the choice of dose varies according to the investigator's purpose.

Based on numerous meta-analyses and clinical studies results, we revealed that a dexmedetomidine dose greater than 50 μg has great potential for clinicians who want to accelerate the onset of action and prolong the duration of peripheral nerve anesthesia.[144,145] The peripheral effect of dexmedetomidine is dose-dependent, and 100 μg dexmedetomidine has more advantages in prolonging the block time.[145]

Many studies have established that the maximum safe dose of dexmedetomidine is 2 μg/kg, and the duration of continuous analgesia is the longest, but the incidence of hypotension is higher in 1.5–2 μg/kg dexmedetomidine.[145] Thus, a dose of dexmedetomidine of 1 μg/kg provides an optimal balance between adequate postoperative analgesia and the adverse effects of peripheral nerve block.[50,146]

Summarize

As early as 1902, American neurosurgeon Cushing proposed the definition of "local anesthesia" and the technology of combined application of local anesthesia and general anesthesia to control perioperative stress response, reduce drug dosage of general anesthesia, and control postoperative pain. Recently, the popularization of ERAS and Multimodal Analgesia (MMA) has raised higher requirements for perioperative management. Therefore, PNB technology has been widely used in clinical practice. Anesthesiologists have focused on applying PNB as an adjuvant of LA around nerves to increase the analgesic effect and duration of PNB.

Currently, the advantages and limitations of adjuvants have been widely discussed.[147] Adjuvants are widely used in clinical practice to prolong the duration of anesthesia/analgesia, stabilize hemodynamics, reduce postoperative pain, and reduce postoperative complications. However, their clinical use in most cases has not been ethically reviewed and demonstrated, with the unclear definition of possible neurotoxicity and systemic adverse effects. Therefore, any anesthesiologist should obtain the patient's informed consent before adding adjuvants and assess the risks and benefits adequately.

A recent meta-analysis of dexmedetomidine as an adjuvant demonstrated that it had achieved good clinical efficacy in PNB. It can reduce the use of LA and analgesic drugs. Simultaneously, it can improve the effect of analgesia, extend the time of analgesia, and improve the quality of anesthesia and patient satisfaction.[148,149] However, it is undeniable that many studies support the possible hypotension, bradycardia, and excessive sedation caused by dexmedetomidine as an adjuvant, so the risks and benefits of adding dexmedetomidine should be carefully weighed.[150,151]

As previously stated, sufficient evidence presents that dexmedetomidine as an adjuvant has apparent advantages in brachial plexus block, paravertebral block, and transverse abdominis plane block, manifesting as prolonged analgesia time. These studies were mainly based on adult patients. We discovered a few clinical studies on nerve block in children with dexmedetomidine as an adjuvant, including transversus abdominis plane block,[152,153] greater palatine nerve block,[154] retrobulbar nerve block,[155] and caudal blockade.[156] Based on the results, dexmedetomidine as a local anesthetic adjuvant for other nerve blocks in children is also worth trying and promoting.

However, the optimal dose of dexmedetomidine for clinical applications needs further study. Although possible neurotoxicity is rarely reported in clinical practice, neurotoxicity in animal studies requires further research and consideration. Finally, intravenous versus perineural administration of dexmedetomidine is controversial; therefore, additional clinical studies and evidence-based medical evidence are needed.

Ethical Approval

No ethical approval was required for the review.

Acknowledgments

We thank Figdraw (www.figdraw.com) for expert assistance in Figure 1.

Funding

The present study was supported by grants from 2021 Shandong Medical Association Clinical Research Fund-Qilu Special Project YXH2022ZX02079.

Disclosure

The authors report no conflicts of interest in this work.

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