Journal of Pain Research

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REVIEW

Dexmedetomidine in perioperative acute pain management: a non-opioid adjuvant analgesic

This article was published in the following Dove Press journal:
Journal of Pain Research
11 August 2017
Number of times this article has been viewed

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Abstract: Many nociceptive, inflammatory, and neuropathic pathways contribute to perioperative pain. Although opioids have long been a mainstay for perioperative analgesia, other non-opioid therapies, and dexmedetomidine, in particular, have been increasingly used as part of a multimodal analgesic regimen to provide improved pain control while minimizing opioid-related side effects. This article reviews the evidence supporting the preoperative, intraoperative, and postoperative efficacy of dexmedetomidine as an adjuvant, and the efficacy of intravenous, spinal canal, and nerve block analgesia with dexmedetomidine for perioperative acute pain treatment. While there have not been any large-scale clinical trials conducted, the current body of evidence suggests that dexmedetomidine is suitable for use as an adjuvant analgesic at all perioperative stages. However, there are potential adverse effects, such as hypotension and bradycardia, which must be taken into consideration by clinicians.

Keywords: dexmedetomidine, analgesia, perioperative pain, non-opioid, adjuvant

Introduction

The poor control of perioperative pain levels may lead to increased morbidity and complications, including nausea, ileus, delayed mobilization, prolonged hospital stays, and the development of chronic pain syndromes.[1,2] Effective pain control may contribute to improved surgical outcomes, shorter hospital stays, and a decreased risk of developing chronic pain.[3] Opioids have traditionally been used for perioperative analgesia, but are associated with potential short- and long-term side effects.[4,5] Therefore, there has been much investigation into the use of non-opioid analgesics, to provide improved pain control while minimizing opioid-related side effects. The alpha-2 adrenergic receptor agonist dexmedetomidine has sedative, analgesic, and anti-sympathetic effects, and is now widely used as an adjuvant in general anesthesia, spinal canal anesthesia, nerve block anesthesia, topical anesthesia, and postoperative analgesia.[6] This paper reviews the recent advances in the use of dexmedetomidine for perioperative analgesia, to provide a reference for perioperative analgesic medication. Detailed descriptions of the interventions and comparators are available in Table 1.

The analgesic mechanism of dexmedetomidine

Dexmedetomidine is an alpha-2 adrenergic receptor agonist that can be directly applied to the peripheral nervous system, causing a dose-dependent inhibition of C-fibers and Aα-fibers. Alpha-2 adrenergic receptors act on the locus ceruleus area, inhibiting nociceptive neurotransmission through the posterior horn of the spinal cord.[7]

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http://dx.doi.org/10.2147/JPR.S139387

Table 1 Conclusions from the full texts of included systematic reviews which are grouped according to the analyzed interventions

Route of administration	Sample size	Comparators	Efficacy	Safety	Reduce adverse events
Preoperative dexmedetomidine					
Buccal[15]	75	Intramuscular and 0.9% NaCl	Sedation and anxiolytics, equal; analgesia, positive	Positive	Mild hypotension and bradycardia
Intramuscular[16]	40	Midazolam	Positive	Positive	Similar
Intranasal[22]	60	0.9% NaCl	Positive	Positive	No opinion
Intraoperative dexmedetomidine					
Intravenous[26]	94	0.9% NaCl	Positive	Positive	Similar
Spinal[32]	60	Clonidine	Positive	Positive	Similar
Intrathecal[33]	60	Placebo	Positive	Positive	Similar
Caudal[34]	100	0.9% NaCl	Positive	Positive	Similar
Saphenous nerve block[35]	21	0.9% NaCl	Positive	Positive	Numbness
Posterior tibial nerve block[36]	14	Placebo	Positive	Positive	Hypotension
Femoral nerve block[37]	60	0.9% NaCl	Positive	Positive	Hypotension
Femoral-sciatic nerve block[38]	60	Placebo	Positive	Positive	Bradycardia
Interscalene brachial plexus block[39]	62	Placebo	Positive, more research is needed	Positive	Similar
Lumbar plexus and sciatic nerve block[40]	1	None, case report	Positive, more research is needed	More research is needed	None
Thoracic paravertebral block[41]	60	Placebo	Positive	Positive	Similar
Transversus abdominis plane block[42]	50	0.9% NaCl	Positive	Positive	Similar
Superficial cervical plexus block[43]	60	Placebo	Positive	Positive	Similar
Postoperative dexmedetomidine					
Intravenous[44]	84	Placebo	Positive	Positive	Advantageous
Epidural[45]	60	Placebo and neostigmine	Positive	Positive	Advantageous
Intrathecal[46]	80	Midazolam	Positive	Positive	Similar
Interscalene block[47]	105	Placebo and clonidine	Positive	Positive	Similar, more research is needed
Transversus abdominis plane block[48]	60	0.9% NaCl	Positive	Positive	Similar
Intra-articular injection[49]	46	Placebo	Positive	Positive	Similar
Intraperitoneal instillation[50]	100	Placebo	Positive	Positive	Advantageous

Alpha-2 adrenergic receptors also act on the presynaptic membrane, inhibiting the release of norepinephrine, which in turn induces hyperpolarization and inhibits the pain signals to the brain.[8,9] Moreover, dexmedetomidine promotes the release of acetylcholine from spinal interneurons; the resulting increased synthesis and release of nitric oxide could be involved in the regulation of analgesia.[10]

Effect of preoperative dexmedetomidine on perioperative pain

Dexmedetomidine can be administered intravenously, intramuscularly, orally, buccally, and intranasally.[11–16] The buccal and intranasal administrations of dexmedetomidine with a high bioavailability are more easily tolerated by patients because of its noninvasiveness, making it an especially good choice for preoperative medication in children.[12,14,17] Intranasal 1 μg/kg dexmedetomidine and 0.2 mg/kg midazolam approximately 45–60 min before the induction of pediatric tonsillectomy and complete dental rehabilitation resulted in the same sedation, but dexmedetomidine markedly reduced the required dosage of postoperative analgesia drugs, suggesting that preoperative dexmedetomidine reduces early postoperative pain in children and has a relatively prolonged duration of adjuvant analgesic.[18,19] Another study compared the sedative and analgesic effects of intranasal 2 μg/kg fentanyl, and 1 μg/kg and 2 μg/kg dexmedetomidine during myringotomy and pressure-equalizing tube placement in children, and found that dexmedetomidine reduced the need for additional analgesics, as well as perioperative pain levels. However, increasing the intranasal dose of dexmedetomidine to 2 μg/kg led to a prolonged postoperative recovery time. Thus, the dose of intranasal dexmedetomidine should not be more than 2 μg/kg during short procedures in children.[20] In a placebo-controlled study involving intranasal 1 μg/kg dexmedetomidine administered approximately 45 min before the induction of local anesthesia 30 patients undergoing unilateral third molar surgery were more deeply sedated perioperatively with better postoperative pain relief after 1–12 h at rest and during mouth opening.[21] In another study, intranasal 1.5 μg/kg

dexmedetomidine was administered approximately 1 h before the induction of local anesthesia in 30 patients undergoing functional endoscopic sinus surgery. These patients required less local anesthesia and experienced better postoperative comfort with hemostatic stuffing and analgesia.[22]

Effect of intraoperative dexmedetomidine on perioperative pain

A large number of clinical studies have shown that intraoperative dexmedetomidine can significantly reduce postoperative pain intensity and opioid use, and the incidence of opioid-related adverse events.[23]

Progress of intravenous analgesia with dexmedetomidine

High doses of opioids such as remifentanil which is a special opioid unlike alfentanil or fentanyl can induce hyperalgesia, which presents as a decreased mechanical hyperalgesia threshold, enhanced pain intensity, a shorter time to first postoperative analgesic requirement, and greater opioid consumption. An initial intravenous dose of 1.0 μg/kg dexmedetomidine for 10 min, followed by a continuous infusion of 0.7 μg/kg/h approximately 15 min before the induction of general anesthesia, may be a novel and effective treatment option for preventing or attenuating opioid-induced hyperalgesia.[24] One study reported that dexmedetomidine led to a decreased requirement for opioid analgesics and inhaled anesthetics, and lessened the incidence of severe changes of circulation during traumatic phases of surgeries.[25] Forty-six thoracic surgery patients given dexmedetomidine at a loading dose of 1 μg/kg for 10 min, followed by continuous infusion at 0.5 μg/kg/h until 30 min before the end of surgery, exhibited reduced resting and coughing numerical rating scale scores and a sufentanil-sparing effect during the first 24 h.[26] Premedication with a single intravenous dose of 0.5 μg/kg dexmedetomidine decreased the intraoperative propofol and postoperative analgesic requirements, and increased the postoperative satisfaction and Ramsay sedation scale scores considerably in patients undergoing direct laryngoscopic biopsy under total intravenous anesthesia.[27] In an analysis of 364 patients from seven intermediate- to high-quality randomized controlled trials, it was found that sensory block duration was prolonged by at least 34%, motor block duration was prolonged by at least 17%, and time to first analgesic request was increased by at least 53% when intravenous dexmedetomidine was administered with spinal anesthesia. Further, the use of dexmedetomidine was associated with a 3.7-fold increase in transient reversible bradycardia.[28] In a study involving 99 patients, intravenous dexmedetomidine with a single-injection interscalene brachial plexus block for outpatient shoulder surgery reduced the pain and opioid consumption for up to 8 h postoperatively, without prolonging motor blockade. The authors suggested that this may be related to the central sedative and analgesic effects, and sensitization of the nervous system produced by the excited alpha-2 adrenergic receptor.[29] A prospective, randomized, double-blind, multicenter trial reported that dexmedetomidine is an effective baseline anesthetic adjuvant for patients undergoing local anesthesia for a broad range of surgical procedures, providing better patient satisfaction, lower opioid requirements, and less respiratory depression than placebo rescued with midazolam and fentanyl. Further, common adverse events associated with dexmedetomidine, such as bradycardia and hypotension, were predominately mild to moderate in severity.[30]

Progress of spinal analgesia with dexmedetomidine

Twenty patients undergoing lower limb vascular surgery under lumbar epidural anesthesia received 15 mL of levobupivacaine with 0.5 μg/kg dexmedetomidine and exhibited a longer time to two-segment regression and total regression, compared to patients who received levobupivacaine and racemic bupivacaine. Nevertheless, dexmedetomidine caused significant bradycardia that required treatment.[31] Epidural administration of 15 mL of 0.5% isobaric bupivacaine with 1 μg/kg dexmedetomidine provided superior early onset of analgesia, superior intraoperative analgesia, stable cardiorespiratory parameters, prolonged postoperative analgesia, and increased patient comfort, compared to 15 mL of 0.5% isobaric bupivacaine with 2 μg/kg clonidine in patients undergoing lower limb orthopedic surgery.[32] Some scholars reported that intrathecal administration of 15 mg of 0.5% isobaric bupivacaine with 5 μg of dexmedetomidine provided earlier onset of sensory and motor block with longer duration of analgesia and hemodynamic stability, compared to bupivacaine alone, in patients undergoing infraumbilical surgeries.[33] A study administered 1 μg/kg dexmedetomidine as an adjuvant to 1 mL/kg of 0.25% bupivacaine in caudal analgesia in 50 pediatric patients, aged 2–10 years, undergoing infraumbilical surgeries, and found an increased duration of caudal analgesia and improved hemodynamic stability without an increase in adverse effects.[34]

Progress of nerve block analgesia with dexmedetomidine

A randomized, paired, triple-blind trial in 21 healthy volunteers who received bilateral saphenous nerve blocks with 20 mL of 0.5% ropivacaine and 1 mL of 100 μg/ml dexmedetomidine in one thigh, and 20 mL of 0.5% ropivacaine and 1 mL of saline in the contralateral thigh showed that dexmedetomidine prolonged the saphenous nerve block by a peripheral mechanism, but not necessarily to a clinically relevant extent.[35] In another prospective, randomized, controlled, double-blind, crossover trial, 14 healthy volunteers received an ultrasound-guided tibial nerve block with a 10 mL solution containing 0.5% ropivacaine with 1 μg/kg dexmedetomidine. The added dexmedetomidine prolonged the duration of sensory blockade without affecting onset time.[36] Forty-five patients undergoing arthroscopic knee surgery received ultrasound-guided femoral nerve block with 25 mL of 0.5% bupivacaine combined with 25 μg, 50 μg, or 75 μg of dexmedetomidine before the induction of general anesthesia. The addition of 50 μg and 75 μg of dexmedetomidine reduced the onset time, extended the duration of block, prolonged the time to the first postoperative request for rescue analgesia, and reduced postoperative morphine requirements. The 75 μg dose had the best analgesic profile, but was associated with an increased risk of hypotension.[37] A study using dexmedetomidine 100 μg as an adjuvant to 0.5% bupivacaine in ultrasound-guided combined femoral-sciatic nerve block in 30 patients undergoing below-knee surgery found a prolonged duration of analgesia. However, these patients also experienced significant bradycardia.[38] In another study of 31 patients undergoing elective shoulder surgery under general anesthesia with an interscalene block, adding 150 μg dexmedetomidine to 0.5% ropivacaine increased the duration of the nerve block and improved postoperative pain. However, dexmedetomidine lowered the heart rate without influencing the blood pressure.[39] A 79-year-old man with multiple cerebral infarcts, congestive heart failure, atrial flutter, and syncope was treated with an above-knee amputation under lumbar plexus and sciatic nerve block with the addition of 1 μg dexmedetomidine to 0.33% ropivacaine. Complete nerve block was maintained for the full duration of the surgery, and analgesia was maintained for 26 h with hemodynamic stability and moderate sedation. The patient did not complain of pain or require any supplementary analgesics postoperatively; this suggests that dexmedetomidine with ropivacaine for lumbar plexus and sciatic nerve block may be a feasible and safe technique for high-risk patients undergoing lower limb surgery.[40] Thirty patients undergoing modified radical mastectomy received ultrasound-guided thoracic paravertebral blocks with the addition of 1 μg/kg dexmedetomidine to 0.25% bupivacaine, and exhibited an improved quality and duration of analgesia, as well as an analgesic sparing effect with no serious side effects.[41] Some scholars reported that 0.5 μg/kg dexmedetomidine with 0.25% bupivacaine for transversus abdominis plane block in 50 patients undergoing abdominal hysterectomy led to better local anesthesia and better pain control postoperatively without any major side effects.[42] In a double-blinded study, 60 adults undergoing thyroid surgeries received bilateral superficial cervical plexus block with the addition of 0.5 μg/kg dexmedetomidine to 0.5% ropivacaine, and exhibited a significantly prolonged and better quality of postoperative analgesia and patient satisfaction.[43]

Effect of postoperative dexmedetomidine on perioperative pain

A prospective, randomized, double-blind, controlled trial reported that the combination of 50 mg oxycodone and 0.5 μg/kg/h dexmedetomidine for patient-controlled analgesia after video-assisted thoracoscopic lobectomy reduced oxycodone consumption, improved patient satisfaction, and provided better analgesia with fewer side effects (nausea and vomiting), compared with patient-controlled analgesia with oxycodone alone.[44] Another study adding 0.5 μg/kg dexmedetomidine and 1 μg/kg of neostigmine to 0.25% bupivacaine for epidural anesthesia in 20 patients undergoing orthopedic surgeries found synergism in the analgesic action and a decreased incidence of drug-related side effects. However, there was also an increased requirement of fluids to maintain blood pressure.[45] Forty patients undergoing vaginal hysterectomies received intrathecal administration of 3 mL of 0.5% hyperbaric bupivacaine with 5 μg dexmedetomidine in 0.5 mL of normal saline, exhibited a significantly longer duration of sensory block, and reduced doses of postoperative analgesic agents with comparable side effects when compared to the intrathecal administration of 3 mL of 0.5% hyperbaric bupivacaine with 2 mg midazolam in 0.4 mL and 0.1 mL normal saline.[46] Adding 1 μg/kg dexmedetomidine to 0.75% ropivacaine in 35 patients undergoing arthroscopic shoulder surgery with ultrasound-guided single-dose interscalene block prolonged the interscalene block, and provided better postoperative pain control during the first 24 h, compared to that produced by clonidine.[47] The addition of 2 mL of 0.5 μg/kg dexmedetomidine to 20 mL of 0.3% ropivacaine

for ultrasound-guided bilateral transversus abdominis plane block for postoperative analgesia after abdominal hysterectomy surgery potentiated the analgesic properties of ropivacaine, reduced sufentanil consumption, and provided better pain control.[48] Intra-articular injection of 1 μg/kg dexmedetomidine at the end of arthroscopic knee surgery was reported to alleviate pain, reduce the postoperative need for narcotics as analgesics, and increase the time to first analgesic request after surgery.[49] A prospective double-blinded study of 100 patients found that intraperitoneal instillations of 50 mL of 0.25% bupivacaine and 1 μg/kg dexmedetomidine led to a prolonged duration of postoperative analgesia and a decreased requirement for postoperative rescue analgesics, compared to that with bupivacaine alone.[50]

Conclusion

In summary, dexmedetomidine plays its analgesic and adjuvant analgesic roles through multiple mechanisms in each stage of the perioperative period. The addition of dexmedetomidine to local anesthetics is a promising new avenue to enhance their effectiveness. However, dexmedetomidine also has potential adverse effects such as hypotension and bradycardia that must be taken into consideration when administered. Therefore, clinical trials are needed to establish the safe optimal doses that provide the maximum benefit with minimum side effects. In addition, the successful application of epidural and subarachnoid analgesia suggests that dexmedetomidine has the potential to be used for the treatment of chronic pain and neuropathic pain, which is another potential avenue of study.

Acknowledgment

This study was supported by the National Natural Science Foundation of China (Grant No. 81671891).

Disclosure

The authors report no conflicts of interest in this work.

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