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OTHER PAIN (AD KAYE AND N VADIVELU, SECTION EDITORS)

Dexmedetomidine in Enhanced Recovery After Surgery (ERAS) Protocols for Postoperative Pain

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Abstract

Purpose of Review Effective acute pain management has evolved considerably in recent years and is a primary area of focus in attempts to defend against the opioid epidemic. Persistent postsurgical pain (PPP) has an incidence of up to 30–50% and has negative outcome of quality of life and negative burden on individuals, family, and society. The 2016 American Society of Anesthesiologists (ASA) guidelines states that enhanced recovery after surgery (ERAS) forms an integral part of Perioperative Surgical Home (PSH) and is now recommended to use a multimodal opioid-sparing approach for management of postoperative pain. As such, dexmedetomidine is now being used as part of ERAS protocols along with regional nerve blocks and other medications, to create a satisfactory postoperative outcome with reduced opioid consumption in the Post anesthesia care unit (PACU).

Recent Findings Dexmedetomidine, a selective alpha$_2$ agonist, possesses analgesic effects and has a different mechanism of action when compared with opioids. When dexmedetomidine is initiated at the end of a procedure, it has a better hemodynamic stability and pain response than ropivacaine. Dexmedetomidine can be used as an adjuvant in epidurals with local anesthetic sparing effects. Its use during nerve blocks results in reduced postoperative pain. Also, local infiltration of IV dexmedetomidine is associated with earlier discharge from PACU.

Summary Perioperative use of dexmedetomidine has significantly improved postoperative outcomes when used as part of ERAS protocols. An in-depth review of the use of dexmedetomidine in ERAS protocols is presented for clinical anesthesiologists.

Keywords Chronic pain · Alpha 2 antagonists · ERAS · Clonidine · Dexmedetomidine

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Introduction

Enhanced recovery after surgery (ERAS) protocols are a series of perioperative care protocols that promote early postsurgical recovery [1]. The main aspects of ERAS involve decreasing postoperative stress and protecting organ function, perioperatively. This is accomplished via pre and post-operative counseling, enhanced nutritional support, early mobilization and standard utilization of anesthetics and analgesics.

The significance of ERAS protocols is evident through a review of the literature, which demonstrates that they improve patient outcomes and have advanced patient care. As such, ERAS protocols have a distinct place in modern medical care, which has added to the continued implementation of such protocols nationwide. And while the role of ERAS protocols have been demonstrated, a significant area of improvement with context to postoperative pain management needs to be addressed, so that patients can benefit postoperatively through implementation of these protocols. Doing so would maximize the benefits for patients that are receiving care through the implementation of ERAS protocols [2]. Enhancing the management of persistent perioperative pain would translate into decreased time in the postanesthesia recovery unit (PACU), reduced opioid consumption, earlier hospital discharge, and improvement in patient satisfaction.

A key strategy for enhancing persistent perioperative pain management and reducing PACU time includes incorporating a multimodal analgesia approach and reducing opioid use [3••, 4••]. Dexmedetomidine, therefore, is a crucial component of the multimodal analgesia approach. A large collection of studies have demonstrated the efficacy of dexmedetomidine to be superior to other agents in the perioperative setting [5–8, 9••, 10, 11••, 12–16]. For example, dexmedetomidine has superior pain control in several types of laparoscopic procedures, such as bariatric and gynecological procedures, and open-surgery approaches, such as colorectal, major spine, and abdominal hysterectomy surgeries. Patients report higher satisfaction scores after dexmedetomidine, which is likely related to decreased pain and decreased postoperative nausea and vomiting (PONV). For these reasons, many providers opt for using dexmedetomidine as part of multimodal therapy.

This manuscript will comprehensively discuss dexmedetomidine with regards to postoperative pain management, ERAS protocols, pharmacokinetics, pharmacodynamics, cardiovascular and respiratory effects, toxicity, drug interactions, abuse and dependence. This review will also include a discussion of clinical considerations, incorporating an extensive review of the positive and negative studies, will follow the reporting of drug formulation, and dosing regimens.

Pharmacokinetics and Pharmacodynamics of Dexmedetomidine

Dexmedetomidine is a potent, versatile, and highly selective short-acting alpha-2 agonist with sedative, anxiolytic, perioperative sympatholytic, and hypnotic effects [14]. Dexmedetomidine is highly selective alpha-2 agonist similar to clonidine. With regards to alpha2:alpha1 receptor specificity; Clonidine has alpha2:alpha1 specificity of 220:1; where as dexmedetomidine has specificity of 1620:1. In 2008, the FDA approved dexmedetomidine use for procedural sedation and for sedation in non-intubated patients. It also has analgesic, anesthetic-sparing, and sympatholytic properties [15]. Dexmedetomidine has the ideal characteristics of a sedative for ICU use, with predictable sedation and hemodynamic stability and is easy to titrate [16].

Formulation and Dosing

In the USA, dexmedetomidine is available as dexmedetomidine hydrochloride, equivalent to 100 μgm/ml. This formulation needs to be diluted 4 to 8 μgm/ml. Prediluted solutions containing 4 μgm/ml in sodium chloride 0.9% are also available. For ICU sedation, a loading dose of 1 μgm/ml over 10 min is infused followed by maintenance dose of 0.2 to 0.7 μgm/h; adjusted to desired level of sedation and avoiding any hypotensive effects. Similar dosing regimen of 1 μgm/ml over 10 min is infused followed by maintenance dose of 0.6 μgm/h for procedural sedation [14].

Mechanism of Action

Dexmedetomidine is highly selective for alpha-2: alpha-1 in ratio of 1620:1 [14]. As previously mentioned, it is a potent alpha-2 adrenergic receptor agonist, yet the molecular mechanism is not fully clear. It is likely due to activation of inhibitory G proteins and the nitric oxide cGMP pathway. Dexmedetomidine produces an agonist affect after binding to G protein-coupled receptors which have three subtypes (alpha-2A, alpha-2B, and alpha-2C). Alpha-2A and alpha2c receptors are primarily found on CNS and alpha-2B are found on vascular smooth vessels.

Dexmedetomidine binds selectively to alpha-2A receptors via all three receptors, which inhibits adenyl cyclase reducing levels of adenosine monophosphate and leading to hyperpolarization of noradrenergic neurons. This leads to the suppression of nerve conduction by inhibiting calcium entry required for neurotransmitter vesicle fusion. This negative feedback back loop leads to attenuation of sympathetic response and decreases both heart rate and blood pressure [16]. At the alpha-2 receptor, dexmedetomidine, causes inhibition of norepinephrine release from presynaptic neurons, produces centrally induced sedation via alpha-2 receptors in the locus ceruleus and centrally mediated pain modification via the dorsal horn [16].

Pharmacokinetics

Dexmedetomidine is a highly lipophilic drug and follows the two-compartment model, following rapid distribution and redistribution. The volume of distribution and clearance seems to be affected by patient BMI, hepatic function, plasma albumin binding, and cardiac output. Although it was initially approved for only IV use, it is now also available in both intranasal and oral preparations. Dexmedetomidine is well absorbed via intranasal and buccal route and these routes could be used for uncooperative pediatric or adult patients.

Following intravenous administration, dexmedetomidine undergoes rapid distribution with distribution half time (T1/2) of 6 min followed by terminal half-time (T1/2) of 2 h. The onset of action after an IV loading dose is usually 5–10 min and it peaks effect in 15 to 30 min. Intranasal route has onset of action in 45 min with peak effect in 90 to100 min. There is no difference in the pharmacokinetic profile of either males or females, and both have similar protein binding [14]. After the oral administration, dexmedetomidine undergoes extensive first pass metabolism and has a poor bioavailability of only 16% [14, 15].

Distribution

Dexmedetomidine is highly protein-bound. Almost 94% is bound to albumin and alpha-1-glycoprotein with a wide volume of distribution and is known to readily cross blood brain and placental barriers. Adult volume of distribution is around 1.3 to 2.4 L/kg. Infant and children less than 2 years of age and patients with low albumin have larger volume of distribution [14].

Metabolism

Biotransformation is the primary route of elimination for dexmedetomidine with less than 1% excreted unchanged (of which 95% is excreted really and 5% via stool).

Dexmedetomidine has hepatic extraction ratio of 0.7 [17]. Uridine 5′-diphospho-glucuronosyltransferase also known as UGT2B10 and UGT1A4 are responsible for metabolizing dexmedetomidine. Up to 5% of metabolism is via hydroxylation by CYP2A6 in the liver microsomes [17]. Large volume of distribution and increased elimination half-life was seen in patients with hepatic impairment, due to higher unbound fraction. It is recommended to reduce the dose of dexmedetomidine in patients with deteriorated liver function. Renal impairment does not affect the dexmedetomidine dosing, but sedative effects may last longer. This could be due to higher unbound drug [17].

Elimination

Dexmedetomidine clearance ranges from 0.6 to 0.7 L/min in healthy adults [17]. Low albumin levels, especially in the ICU patients, can have an effect on clearance. However, the effect of low albumin could be marginal, since for compounds with high extraction ratios, blood flow and not plasma protein effects the clearance of drug. Decreased cardiac output also has impact and leads to reduced dexmedetomidine clearance [17]. Nevertheless, low albumin levels, end organ failure, and hemodynamic changes all are factors to be considered in an ICU patient that can affect the pharmacokinetics of dexmedetomidine. Alpha-2 receptor polymorphisms and ethnicity are other factors that can affect the pharmacokinetics of the drug [17].

To achieve a specific blood plasma concentration, a target-controlling infusion protocol has also been suggested to maintain the Richmond Agitation-sedation scale between zero and minus three (− 3). Factors like height, total body weight, and serum albumin levels can affect achieving the steady-state concentration. Dexmedetomidine exhibits linear kinetics between the dose range of 0.2 to 0.7 μg/kg/h and it is 94% bound in steady state [15]. The context sensitive half time (T1/2) of dexmedetomidine can range from 4 min after a 10-min infusion [15]. Context sensitive time half time (T1/2) can be over 4 h after a prolonged 8-h infusion. Clearance of dexmedetomidine matures with age reaching maturity at 1 year of age and is reduced by 27% after a cardiac surgery [18].

Pharmacodynamics

As mentioned, dexmedetomidine exerts its sedative and hypnotic effects by action on central presynaptic and postsynaptic alpha-2 receptors. These effects are concentration-dependent between 0.2 and 0.3 ng/ml. Postsynaptic alpha-2 binding in locus cereus and spinal cord leads to sedation and analgesia. Its affinity to alpha-2 receptor leads to vagolytic effects leading to bradycardia and vasodilation [15]. Dexmedetomidine is known to mimic natural sleep while maintaining a normal physiological sleep and wake cycle. The patient remains arousable which decreases the risk of delirium. Respiratory depression is rare when used in dosages between 0.2 and 0.7 μg/kg/h. Dexmedetomidine suppresses pain transmission, likely through inhibiting the release of neurotransmitters such as substance P, which may alter the perception of pain [17].

ICU Sedation

Dexmedetomidine is approved for only 24 h of ICU use. Studies have shown an acceptable safety profile for use up to 30 days in the ICU patients. Dexmedetomidine also reduces mechanical ventilation and length of ICU stay by 22% and 14%, respectively [17].

Side Effects

The most frequently observed side effects include hemodynamic alterations such as hypertension, bradycardia, and hypotension due to postsynaptic alpha-2 receptor activation. Others include bradycardia, dry mouth, and nausea. Additional reported side effects include fever, muscle weakness, bronchospasm (especially in asthmatic patients), respiratory depression, conduction abnormalities, arrhythmia, A-V block, tachycardia, syncope, neuropathy, paresthesia, potassium abnormality with EKG changes, lactic acidosis, and elevated glucose levels [15]. Tachyphylaxis can also occur if given more than 24 h as intravenous infusion.

Cardiovascular Effects

Dexmedetomidine has a biphasic hemodynamic response. A bolus of high-dose dexmedetomidine can result in tachycardia and elevated blood pressure, whereas a low-dose bolus can decrease blood pressure and decrease cardiac output but preserve stroke output. This is due to alpha-2-mediated vasoconstriction, which eventually leads to baroreceptor-mediated bradycardia and increased vagal activity, resulting in hypotension. Dexmedetomidine also results in a reduction of circulating catecholamines, due to its sympatholytic effects [17].

Dexmedetomidine loses its alpha-2 receptor agonism if infused as bolus via rapid infusion, leading to increase in blood pressure and low heart rate that eventually normalizes in 15 min. This effect is primarily mediated via central alpha-2A receptors. Hypertension can also be observed because of activation of alpha-2b receptors. Therefore, extreme care must be taken when using dexmedetomidine in patients who are volume-depleted and have underlying cardiac issues. High doses of dexmedetomidine can result in pulmonary hypertension and can be a limiting factor for its use in patients with underlying cardiac disease.

Respiratory Effects

At low plasma concentrations of 2.4 ng/ml, respiratory drive and the ventilatory response of CO2 are preserved. With increasing doses, there is a slight fall in tidal volume. Even at supra-therapeutic concentrations of 14.9 ng/ml, respiratory drive is unaffected [17]. Hypercapnic ventilatory response has been observed with dexmedetomidine use and this decreases with age but can lead to respiratory depression, especially in the elderly population in conjunction with other hypnotics or opioids that depresses respiratory drive. Therefore, it has been approved for ICU sedation only, with continuous cardiac and respiratory monitoring. However, the overall effects of dexmedetomidine on the respiratory system when combined with other anesthetic drugs are minimal. Dexmedetomidine also demonstrates protective effects by attenuating oxidative stress from acute lung injury by inhibiting the generation of ROS (reactive oxidative species). This is in part due to its activation of alpha-2 adrenoreceptor effects, which promotes cell survival and proliferation of lung alveolar epithelial cell in acute lung injury (ALI). Therefore, dexmedetomidine has established itself as sedative of choice in patients with ALI [19].

Elderly

Side effects in the elderly can be more pronounced, especially hemodynamic side effects. Hypotension can result if a loading dose of more than 0.7 μm/kg is used. It is recommended to be cautious when using dexmedetomidine in the elderly due to a higher incidence of hypotension and bradycardia, as they often have numerous comorbidities [17]. Therefore, a continuous monitoring of pulse oximetry and EKG is recommended for continuous infusion, especially in patients with cardiac ejection fraction less than 30%, or with other underlying cardiac comorbidity.

Obese

Monitoring respiration in an obese patient is important. They are more likely to have obstructive sleep apnea and when dexmedetomidine is used in conjunction with other opioids, this may compound the problem. Beneficial effects with use of dexmedetomidine include less use of volatile gas, less opioids requirements with better pain control, and less antiemetic requirements.

Abuse and Dependence

No human studies are available with use of dexmedetomidine and drug dependence, but clonidine-like withdrawal symptoms have been noticed. Animal studies following abrupt withdrawal of dexmedetomidine have shown symptoms of nervousness, headache, and agitation. Elevation of blood pressure and catecholamine levels along with elevated plasma catecholamines is also seen. A recent study showed that use of dexmedetomidine in patients with substance abuse had shorter ICU and ventilator-dependent days [20]. The patients with substance abuse also had beneficial effect from anxiolytic and analgesic effects of dexmedetomidine without respiratory depression. Hence, it may be a sedative of choice in patients with substance abuse.

Although the mechanism of dexmedetomidine in attenuating withdrawal symptom of opioids is poorly understood, it is hypothesized that use of strong opioids like heroin leads to a hyperadrenergic state. Thus, use of alpha-2 agonists decreases the sympathetic outflow and counteracts the physiological effects, but the clear mechanism of dexmedetomidine effects is still unclear. Further studies may be warranted in formulation

of ICU treatment protocol for dexmedetomidine for use as part of substance abuse withdrawal regimen protocol [21].

Precautions, Limitations to Use, and Contraindications

When dexmedetomidine is used in co-administration with other anesthetics, sedatives, and opioids, this may synergistically enhance their effects. Similarly, caution must be exercised when using vasodilators or negative Chronotropic agents, since dexmedetomidine may enhance cardiodepressant side effects. Vigilance should be used in patients who have greater than 30% decrease in heart rate from their baseline, because these patients are predisposed to severe bradycardia that could progress to pulseless electrical activity [22]. A rapid bolus could result in fatality; therefore, caution must be exercised even in healthy adults with high vagal tones. No meaningful side effects are seen when dexmedetomidine is used with neuromuscular blocking agents.

Caution should also be exercised in patients receiving dexmedetomidine beyond 24 h as this has been associated with both tachyphylaxis and tolerance. There are no studies involving dexmedetomidine and pregnancy. Nevertheless, it has been suggested that a lactating woman who received dexmedetomidine may pump and discard breast milk for next 12 h.

Toxicity

Dexmedetomidine can cause significant nerve damage in diabetic rats when used for local nerve blocks [23]. Although this produced significant motor and sensory blockade but also warranting the caution to be used in patients with peripheral neuropathy while using precedes in combination with local anesthetics [23]. Similarly, in another study when dexmedetomidine was used as an adjuvant for a nerve block, it not only prolonged nerve block duration but increased systemic side effects [24]. Overdosage of dexmedetomidine primary leads to cardiodepressant side effects that may require supportive therapy.

Pediatric Considerations

Dexmedetomidine has been extensively studied in pediatric intensive care patients, pediatric cardiac, and general surgery patients. Its sympatholytic effects are generally beneficial for patients undergoing cardiac procedures [16]. The recommended adult dose may also be given in children, given as a loading dose of 0.25 to 6 μg/kg/h over 10 min and a maintenance does of 0.2 to 1.4 μg/kg/h to achieve a cook scale between 7 and 14 points [14]. Dexmedetomidine clearance is about 50% in newborns that eventually matures to adult levels by the end of new neonatal age. Neonates have larger volume of distribution with increased elimination half-life due to liver immaturity and lower albumin levels [14]. Also, a higher concentration of dexmedetomidine is found in neonatal brains due to immature blood-brain barrier. At lower doses, no cardiopulmonary side effects occur but hypothermia and bradycardia have been reported with use of dexmedetomidine in neonates [14]. In older children, dexmedetomidine is well tolerated and efficacy similar to that seen in adults. Analgesia with non-opioids analgesics like dexmedetomidine are being used as part of an ERAS protocol intraoperatively, along with regional nerve blocks to attain a satisfactory postoperative outcome with reduced requirements of opioids in PACU in the pediatric population. With more requests for procedural sedation for diagnostics procedures like MRI, ambulatory center procedures, dexmedetomidine has become an attractive option for non-IV route of sedation especially buccal administration at least 45 min before the elected time in a dose 2 to 3 μg/kg. This provides adequate sedation in approximately 80% of patients with a failure rate of 20% requiring other modes of sedation [25].

Emergence Delirium

Delirium is an acute confusional state wherein the patient's cognitive functioning is impaired with inability to process awareness of environment and attention. Most patients transition to normal consciousness smoothly, after the anesthetic agents are disconnected at the end of a surgical procedure. A select few patients may end up having emergence delirium with the risk being higher in pediatric age groups and the elderly population. The incidence has been reported up to 80% in pediatric age group and this can increase risk of postoperative respiratory depression and airway obstruction [26].

Amongst the numerous agents available, dexmedetomidine has found to be beneficial, especially in sevoflurane-induced emergence delirium. At a dose of 0.5 μg/kg, dexmedetomidine is beneficial in reducing the incidence of emergence delirium and negative postoperative behavioral changes (NPOBC). Caution must be exercised with vigilant cardiopulmonary monitoring when dexmedetomidine is administrated after induction of anesthesia. The data on negative postoperative behavioral changes is limited, but up to 50% children undergoing surgical procedures under general anesthesia manifest some kind of behavioral symptoms including but not limited to inconsolable crying, irritability, feeding and sleeping issues, temper tantrums, and nightmares that could manifest anywhere from postoperative day to 1 to a week or later after discharge. Such symptoms have been prone to be decreased and limited by the use of dexmedetomidine when quantified by Pediatric Anesthesia Emergence Delirium (PAED) scale [26].

Although the incidence of emergence agitation is not as high as emergence delirium in the pediatric age group, it has been found to be in ranges of ~ 35% when using sevoflurane alone versus when dexmedetomidine is used in addition to sevoflurane with incidence of only 13% when quantified on Riker sedation agitation scale. Although a recent published study did show that with dexmedetomidine, infusion leads to decreased norepinephrine and epinephrine, suggesting that dexmedetomidine's effects are primarily by reducing catecholamines and not via anti-inflammatory effects [27]. Dexmedetomidine can also decrease the occurrence of emergence delirium, especially in the pediatric population. It has been found that patients treated with dexmedetomidine had reduced incidence of emergence delirium when compared with midazolam. Even with lorazepam, dexmedetomidine had lower incidence of emergence delirium. Therefore, dexmedetomidine could be used prophylactically or in an emergent setting for the prevention or control of emergence delirium [16]. For patients at risk, a dose of 0.25 mcg/kg of dexmedetomidine may be slowly injected intravenously and to treat patients emergently, a dose of 0.5 mcg/kg of dexmedetomidine may be used [16].

Reversal Agents Atipamezole

Atipamezole is highly selective alpha-2 antagonist approved only for use in veterinary medicine. Further research and clinical studies are warranted before it is approved for use in humans. Atipamezole rapidly reverses both sedative and sympathetic effects of dexmedetomidine. Higher doses of atipamezole 15–150 μg/kg can quickly reverse side effects of IV dexmedetomidine.

Perioperative Dexmedetomidine Use for Postoperative Pain

Numerous meta-analyses demonstrate the effectiveness of dexmedetomidine for postoperative pain control [9••, 28–32, 33••, 34••, 35]. In a 2012 meta-analysis of 1792 patients, dexmedetomidine reduced opioid consumption by 30% at 24 h postoperatively [28]. Dexmedetomidine has a stronger analgesic effect than clonidine and acetaminophen, but weaker than ketamine or non-steroidal anti-inflammatory drugs [28]. This not only makes dexmedetomidine an attractive agent for ERAS, but also for chronic pain patients [36]. In a 2015 meta-analysis, although dexmedetomidine reduced pain intensity, opioid consumption, and postoperative nausea and vomiting (PONV), it had no effect on recovery time [29]. Notably, in a Cochrane review of dexmedetomidine use in abdominal surgery, there was too much heterogeneity of the data for meta-analysis [37]. Dexmedetomidine is an effective analgesic for pediatric patients and has the added benefits of reducing anxiety and emergence agitation [9••, 38–40].

There is variability in the timing of dexmedetomidine administration without consensus on the optimal time for administration. When given preoperatively, a single 1 mcg/kg dose of dexmedetomidine given 10 min prior to induction has been shown to reduce postoperative opioid use [41]. Multiple studies demonstrate the effectiveness of intraoperative dexmedetomidine and it has also been shown to be superior to intraoperative remifentanil, providing better postoperative analgesia with fewer side effects [42–46]. In two recent meta-analyses, patients that received postoperative dexmedetomidine infusion and IV opioid patient-controlled analgesia (PCA) had lower postoperative pain scores and lower opioid consumption in the first 24 h postoperatively with decreased PONV and pruritis compared with those with PCA alone [47, 48]. One randomized controlled trial comparing dexmedetomidine PCA with fentanyl PCA for postoperative pain control found that although there was no significant difference in VAS pain score at 6 h postoperatively, the patients with the dexmedetomidine PCA had higher patient satisfaction with pain control, faster return of bsowel function, and a lower incidence of PONV [8]. As most ERAS pathways do not utilize IV opioid PCAs, there may be a limited role for dexmedetomidine PCA. However, it may be an attractive alternative to opioid PCA in patients that require PCA despite other multimodal analgesics.

Another potential use for dexmedetomidine perioperatively for postoperative pain is as an adjunct for regional anesthesia [49, 50]. Regional anesthesia is an important modality for minimizing opioid use as part of an ERAS multimodal analgesic regimen. The addition of dexmedetomidine to neuraxial analgesia, IV regional anesthesia, and peripheral nerve blocks [51, 52] can hasten block onset, prolongs duration, and reduces opioid use [50, 53]. In a 2017 meta-analysis of over 2000 patients, the addition of dexmedetomidine to brachial plexus blocks led to faster block onset, longer block duration, improved analgesia, and reduced postoperative morphine requirements by 10.2 mg [52]. While dexmedetomidine is effective as an adjunct to regional anesthesia, it is not as effective as dexamethasone and carries a higher risk of hypotension and sedation compared with dexamethasone [54]. This may limit its widespread use as an adjunct to regional anesthetic ERAS pathways and may support its preferential use as an intravenous infusion.

Drug Formulations and Dosing Regimens

The vast majority of dexmedetomidine studies for postoperative pain control report intravenous administration of dexmedetomidine; however, there is heterogeneity of the doses given and the optimal dose is unknown. Table 1 lists

Table 1 Dosing regimens for various routes of dexmedetomidine administration

Route of administration	Bolus	Infusion	Notes
IV (adults) [9••, 35, 44, 48, 49, 51–53, 55, 56]	0.25–1 mcg/kg or 75–150 mcg	0.2–1 mcg/kg/h or 60–120 mcg/h	
IV (pediatrics) [10, 44]	0.15–4 mcg/kg	0.2–0.7 mcg/kg/h	
IV PCA (with opioid) [53, 54]	2.5–10 mcg or 0.1 mcg/kg	0.02–0.6 mcg/kg/h basal rate or 2.5–10 mcg/h	10–15-min lockout
IV PCA (as sole agent) [9••]	0.25 mcg	0.5 mcg/kg/h	15-min lockout
Oral [57]	4 mcg/kg		
Intranasal [45, 58]	1–2 mcg/kg		
Buccal [59]	2.5 mcg/kg		
Intramuscular [59]	2.5 mcg/kg		

IV, intravenous; *PCA*, patient-controlled analgesia; *min*, minute

dexmedetomidine doses which have been described in the literature for various routes of administration [8, 9••, 29, 40, 42, 43, 45, 48, 50, 60]. Of note, a loading dose of IV dexmedetomidine may not be necessary. In two recent randomized studies, there was no difference in 24-h opioid consumption between those who received a loading dose of 1 mcg/kg dexmedetomidine immediately before induction, followed by 0.4 mcg/kg/h infusion and those who only received dexmedetomidine infusion [45, 60]. A bolus of ≥ 0.5 mcg/kg/h in pediatric patients is sufficient to decrease postoperative pain scores and opioid requirements, even without a continuous infusion [9••].

While intravenous administration is the most widely used, other routes of administration of dexmedetomidine have been described, including transdermal, intramuscular, oral, buccal, and intranasal, not to mention its use as an adjunct for regional anesthesia [55]. These alternate routes of administration could potentially be important particularly for patients with limited or difficult IV access, including pediatric and autistic patients, and could be ideal for chronic pain patients to use on an outpatient basis. The bioavailability and onset of action can differ significantly depending on the route of administration. The mean absolute bioavailability for oral, intranasal, buccal, and intramuscular administration is 16%, 65–82% [61, 62], 82%, and 73–104% respectively [61–63]. There is high interindividual variability in dexmedetomidine pharmacokinetics, which is influenced by body size, liver function, cardiac output, and albumin levels [14].

Given the low bioavailability of oral dexmedetomidine, it is not surprising that oral dexmedetomidine (4 mcg/kg) provides inferior pain relief to oral ketamine (5 mcg/kg) in burn patients [64]. A newly developed orally disintegrating tablet has 95.28% release of the drug after 5 min, which has potential for postoperative ERAS use [56]. With 1–1.5 mcg/kg intranasal or transmucosal dexmedetomidine, patients have a similar sedation and anxiolytic effect as midazolam, but less postoperative pain and less sympathetic stimulation [38]. This route has a slower onset than intravenous with a peak plasma concentration is reached by 38 min [62]. Although buccal dexmedetomidine (2.5 mcg/kg) and intramuscular dexmedetomidine (2.5 mcg/kg) provide equal sedation and anxiolysis, buccal dexmedetomidine results in better analgesia than intramuscular [65]. After intramuscular dexmedetomidine, there is a large range in time to peak concentration ranging from 2 min to as high as 1.7 h, and an elimination half-life of 1.6–2.4 h [66, 67].

The addition of dexmedetomidine has been described as an adjunct for neuraxial analgesia, IV regional anesthesia, and peripheral nerve blockade [53]. One mcg/kg dose of dexmedetomidine has been described for lumbar epidural and caudal analgesia; 5 mcg dose has been described for intrathecal use. As an adjunct for peripheral nerve blockade, most studies use 1 mcg/kg dexmedetomidine in peripheral nerve blockade [49]. Although in a meta-analysis of dexmedetomidine use in brachial plexus blockade, 50−60 mcg was recommended to maximize sensory block duration while minimizing risk of bradycardia and hypotension [52]. There seems to be little evidence of adverse events with alternate routes of dexmedetomidine administration; however, there is evidence of neurotoxicity with 6 mcg/kg epidurally in an animal model [68].

Clinical Considerations

As mentioned, dexmedetomidine has gained popularity in large part related to its ability to reduce reliance on opioids in postsurgical analgesia. Shariffuddin et al. demonstrated in a double-blinded, randomized controlled study that a single preoperative dose of dexmedetomedine 0.5 μg kg^{-1} in patients undergoing either ureteroscopy or ureteric stenting resulted in a clinically significant reduction of anesthetic and opioid use both intraoperatively and postoperatively. They reported a reduction of the MAC of sevoflurane (0.6 (0.2) vs. 0.9 (0.1), $p =$

0.037) needed to achieve adequate sedation, as well as a 60% reduction of pain immediately postop with further reduction lasting until POD 3 [69]. Panchgar et al. had similar results in laparoscopic surgeries with a loading dose of 1 μg/kg body weight and then a maintenance dose of 0.5 μg/kg/h for the remainder of the procedure. Time to rescue analgesia postoperatively was 50 min in the control group vs. 360 min in the dexmedetomidine group. The total 24-h analgesic need was also significantly less for the dexmedetomidine group (90 mg) vs. the NS control group (195 mg) [70].

A recent meta-analysis involving 18 studies and 1284 patients showed that dexmedetomidine used in conjunction with opioids in patient-controlled analgesia resulted in lower overall opioid utilization with no increase in adverse reactions [48]. Dexmedetomidine has been paired with propofol to achieve opioid-free total intravenous anesthesia in gynecologic laparoscopy. It demonstrated improved pain scores, delayed rescue analgesia, and decreased total rescue analgesic dose [59].

The effects of dexmedetomidine on local anesthetic and nerve blocks have also been studied. Dexmedetomidine significantly prolonged postoperative analgesia in children undergoing ilioinguinal/iliohypogastic nerve block for hernia repair [71]. It had better analgesia and fewer adverse reactions than fentanyl when added to bupivacaine for epidural anesthesia [72]. It similarly outperformed fentanyl when combined with ropivacaine administered intraperitoneally to control pain following laparoscopic cholecystectomy [73].

Other studies have shown that dexmedetomidine can significantly reduce the incidence of postoperative nausea [8]. Song et al. demonstrated that within a high-risk group, dexmedetomidine administered 30 min before the completion of surgery reduced the frequency and severity of nausea [57]. Postoperative delirium is another complication that could potentially benefit from the addition of dexmedetomidine. One study showed that there was a reduction in both the incidence and severity of delirium in POD 1–7 in patients undergoing pulmonary resection due to lung carcinoma [58]. Other trials demonstrated that dexmedetomidine may decrease negative postoperative behavioral changes and agitation in pediatric patients without excessive sedation or other negative side effects [26, 74].

The major side effect noted in many of these studies was hemodynamic instability in the form of bradycardia and hypotension [69, 70, 74]. These changes, although statistically significant, were well tolerated by most of study participants. Some studies suggest that this is beneficial in that it curtails hemodynamic stress response generated by the trauma of surgery [69]. Still other studies did not find dexmedetomidine to be superior to other drugs. One such study found that fentanyl provided longer postoperative analgesia than dexmedetomidine when added to lidocaine in women undergoing spinal epidural during elective c-section, although it did have a higher incidence of nausea and vomiting [75] (see Table 2).

Conclusion

Enhanced recovery after surgery is an approach to patient care that focuses on optimizing the postoperative period. This includes implementing protocols meant to reduce postoperative complications, patient discomfort, and length of hospital stay. Dexmedetomidine is a highly selective a2-adrenergic agonist, which has become a valuable addition to the multimodal approach to anesthesia. Its sedative, anxiolytic, and analgesic properties are useful in potentiating postoperative analgesia. These features make it a useful adjuvant to the anesthesia protocol, especially in the context of enhanced recovery after surgery.

Dexmedetomidine acts in the locus ceruleus and spinal cord, inhibiting presynaptic release of norepinephrine. This results in sedation, analgesia, and a centrally mediated sympatholytic effect [70]. Use of dexmedetomidine has been shown to reduce the anesthetic and opioid requirements both intraoperatively and postoperatively. Dexmedetomidine has also been shown to reduce the incidence of postoperative nausea, vomiting, delirium, and agitation with minimal effect on respiratory drive [78]. These features make it a valuable tool in achieving the goals of enhanced recovery after surgery. Many of its on and off label uses have been studied. It has been used for sedation in the ICU, as an adjuvant for epidural and peripheral nerve block, and for preprocedure anxiolysis [79]. More research is warranted to better understand dexmedetomidine's far reaching applications.

The main adverse event healthcare workers should be cautious of when administering dexmedetomidine is hemodynamic instability, namely bradycardia, hypotension, and hypertension. Song et al. found that patients who received dexmedetomidine intraoperatively had almost a 2-fold increase in bradycardia compared with the control group [57]. Meanwhile, Shariffudin et al. found a significant decrease in the systolic blood pressure at the 15-min mark after infusion. This phenomena disappeared by the 20-min mark and did not return for the remainder of the case [69]. It appears that these episodes of hemodynamic disturbance are associated with the use of a loading dose or fast initial infusion rates. One way to mitigate this is to forgo a loading bolus and instead utilize a slower basal infusion rate. Although these hemodynamic changes do not cause issue for the majority of patients, healthcare providers should use caution when administering dexmedetomidine to patients who are less able to tolerate bradycardia. These might include patients with cardiac conduction abnormalities, those taking medications that alter cardiac conduction, and the elderly [80]. Additionally, care should be taken to adjust the dosing in patients with hepatic impairment,

Table 2 Studies on the applications and efficacy of dexmedetomidine in surgery and recovery from surgery

Reference	Study design	Application	Dosage	Outcomes	Hemodynamic changes
[69]	Double blind, randomized, controlled	Postoperative recovery	Single preinduction dose of 0.5 μg kg^{-1} DEX via IV vs. normal saline	-60% reduction in postop pain -Reduction in MAC (0.6 (0.2) vs. 0.9 (0.1), $p = 0.037$)	At 15 min, $p < 0.05$ -Lower SBP 104.3 (12.8) vs.114.2 (21.2) -Lower DBP 62.3 (11.8) vs.72.2 (19.2) -Lower HR 62.6 (10.5) vs. 69.7 (12.1)
[70]	Double blind, randomized, controlled	Controlling stress response during surgery	1 μg/kg bolus over 10 min and 0.5 μg/kg/h intraoperatively as maintenance vs. normal saline	-Time to rescue analgesia: DEX group (360 min) vs. control group (50 min) -24-h analgesic need: DEX group (90 mg) vs. the NS control group (195 mg)	MAP in DEX group was significantly less after 10 min of drug infusion and after laryngoscopy, tracheal intubation, pneumoperitoneum, and extubation
[59]	Prospective, comparative, randomized, controlled	Opioid-free total intravenous anesthesia	DEX (0.6 μg/kg loading and 0.2 μg/kg/h maintenance) with propofol vs. fentanyl (1 μg/kg loading and 0.5 μg/kg/h maintenance) with propofol	-8.5% improvement in quality of recovery score at 24 h (from 175 to 190) -Time to first analgesic dose (min): DEX 40.5 (8.25) vs. opioid 35.6 (6.7) $p < 0.004$	Significant fall in HR and BP
[71]	Double blind, randomized, control	Ilioinguinal-iliohypogastric nerve blocks for hernia repair in children	0.2 ml/kg ropivacaine 0.2% vs. ropivacaine 0.2% with adjunct DEX 1 μg/kg	-Postop analgesia duration: DEX+ropivacaine (970.23 ± 46.71 min) vs. control (419.56 ± 60.6 min) -DEX+ropivacaine had decreased CHIIPPS score vs. control	Decreased HR at 5 min in the DEX group
[72]	Prospective, randomized double blinded	Epidural anesthesia	15 ml bupivacaine 0.20% + 50 μg of DEX vs. 15 ml bupivacaine 0.20% + 50 μg fentanyl	-Increased time to first analgesic: DEX 392.7 ± 34.8 min vs. control 296.9 ± 24.5 min ($p < 0.001$) -Decreased opioid requirement: DEX 18.9 ± 3.4 vs. control 23.3 ± 3.2 ($p < 0.001$)	Incidence of bradycardia and hypotension was significantly higher in DEX group vs. control ($p = 0.003$, 0.012, respectively)
[73]	Comparative, Randomized	Intraperitoneal local anesthetic	30 ml of 0.2% ropivacaine + 1 μg/kg DEX vs. 30 ml of 0.2% ropivacaine + with 1 μg/kg fentanyl	-VAS pain score decreased: (DEX 1.68 ± 0.46 vs. control 4.47 ± 0.94) -Time to first analgesia (min): (DEX 122.7 ± 24.5 vs. control 89.3 ± 13.2) -Total analgesic consumption (mg): (DEX 95.3 ± 15.6 vs. control 135.7 ± 75.1)	None reported
[8]	Consort-prospective, randomized, controlled	PCA after surgery	DEX 0.25 μg/kg/h diluted to 100 ml in 0.9% saline vs. fentanyl 20 μg/kg diluted to 100 ml in 0.9% saline	-VAS pain score postop was not significantly different between the groups ($p > 0.05$) -10% of DEX group experienced PONV vs. 31.2% of fentanyl group -Decreased time to first flatus and bowel movement	No significant differences

Table 2 (continued)

Reference	Study design	Application	Dosage	Outcomes	Hemodynamic changes
[57]	Randomized, controlled	PCA after surgery	DEX 0.5 μg kg^{-1} IV vs. 0.9% normal saline 30 min before completion of surgery	-DEX group experienced less nausea 1 to 3 h postoperatively ($p = 0.019$) -DEX group had lower incidence of severe nausea ($p < 0.003$)	DEX group experienced higher incidences of hypotension and bradycardia, however not statistically significant
[58]	Double blind, randomized, controlled	Prevention of postoperative delirium	DEX (0.5 μg/kg) 20 min preop followed by continuous intravenous infusion of 0.1 μg/kg/h intraop vs. normal saline	-Dex group experienced lower incidence and severity of delirium from POD 1 to POD 5	-Bradycardia: DEX (10.4%) vs. control (7.5%) -Hypotension: DEX (6.9%) vs. control (5.2%)
[26]	Double blind, randomized, controlled	Prevention of emergence delirium in pediatric patients	DEX 0.5 μg/kg vs. normal saline over 10 min intraoperatively	DEX decreased the incidence of emergence delirium (31.1% vs 53.3%; $p = 0.033$)	HR and SBP were significantly decreased in the DEX group at the 15-min mark and at extubation, but did not require intervention
[74]	Prospective, randomized, controlled	Postop recovery after pediatric tonsillectomy	DEX 1 μg/kg vs. volume-matched saline 10 min before anesthesia	DEX group agitation score was 9.37 ± 1.33; median 9.5 vs. 13.84 ± 1.39; median 14 in control ($p < 0.001$)	Significant decrease in HR and MBP in DEX group without bradycardia or hypotension
[76]	Randomized, controlled	DEX for prevention of postop anxiety in pediatrics	DEX 0.5 μg/kg vs. midazolam 0.08 mg/kg in 20 ml of NS 10 min preop	DEX group had lower anxiety at 2 h (mean difference [95% CI], 1.89 [0.52–3.26]; $p = 0.01$) and 4 h (mean difference [95% CI], 3.32 [1.98–4.66], $p < 0.001$)	Decrease in SBP, DBP, and HR in DEX group, all p values $p < 0.001$
[77]	Randomized, controlled	DEX for sedation during ankle surgery under spinal anesthesia	DEX group receiving loading dose of 1 mcg kg^{-1} over 10 min, maintenance dose of 0.2–0.7 μg kg^{-1} h^{-1} vs. propofol group receiving effective site concentration of 0.5–2.0 μg ml^{-1}	Less postop morphine requirement in DEX group 14.5 mg (0.75–31.75 mg) compared with 48.0 mg (31.5–92.5 mg) in the propofol group (median difference, 33.2 mg; 95% confidence interval, 21.0–54.8 mg; $p < 0.001$).	Higher incidence of bradycardia in DEX group (31.8%) vs. (4.8%) in the propofol group, $p = 0.046$
[75]	Randomized, controlled	DEX as adjuvant to lidocaine in spinal anesthesia	0.5 μg/kg DEX vs. 25 μg fentanyl added to lidocaine 5%	-Shorter postop analgesia in DEX group (h) 1.2 ± 57.3 vs. 4.40 ± 1.4 ($p = 0.01$) -More opioid requirement in DEX group (mg) 148.26 ± 8.3 vs. 119.04 ± 23.3 ($p = 0.01$)	No significant difference in HR or BP both after spinal anesthesia or in recovery

DEX, dexmedetomidine

as dexmedetomidine is predominantly metabolized in the liver [14].

Although dexmedetomidine has proven to be a relatively safe drug, the lack of a reversal agent is an issue. Atipamezole is a synthetic a2-antagonist that has been shown to reverse the actions of dexmedetomidine; however, it is currently only approved for use in dogs. More studies are needed to assess the effectiveness and safety of atipamezole in humans. Gaining approval for human use would make dexmedetomidine an even more attractive option [14]. There is currently a paucity of data addressing the potential neuroprotective, cardioprotective, and renoprotective effects of

dexmedetomidine. The trials that have been conducted are mostly animal models, but have been encouraging enough to merit future research in humans [79].

Compliance with Ethical Standards

Conflict of Interest David Chernobylsky, Pankaj Thakur, Harish Siddaiah, Rachel Kaye, Lauren Eng, Monica Harbell, Jared Lajaunie, and Elyse Cornett declare no conflict of interest.

Alan Kaye is a Section Editor for *Current Headache and Pain Reports*. He has not been involved in the editorial handling of this manuscript. Dr. Kaye is also a speaker for Merck.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Melnyk M, Casey RG, Black P, Koupparis AJ. Enhanced recovery after surgery (ERAS) protocols: time to change practice?. Can Urol Assoc J. 2011;5(5):342–8. https://doi.org/10.5489/cuaj.11002.
2. Weng-Ingersoll E, Greene A. ASRA news - review of dexmedetomidine (Precedex) for acute pain and analgesia - American Society of Regional Anesthesia and Pain Medicine [Internet]. ASRA News. 2018 [cited 2019 Aug 14]. p. 1. Available from: https://www.asra.com/asra-news/article/104/review-of-dexmedetomidine-precedex-for-a. Accessed 14 Aug 2019.
3. •• Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol [Internet]. 2009 [cited 2019 Aug 14];22:588–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19606021. Accessed 14 Aug 2019. **Excellent review of dexmedetomidine.**
4. •• Helander EM, Billeaud CB, Kline RJ, Emelife PI, Harmon CM, Prabhakar A, et al. Multimodal approaches to analgesia in enhanced recovery after surgery pathways. Int Anesthesiol Clin [Internet]. 2017 [cited 2017 Nov 15];55:51–69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28901981. Accessed 14 Aug 2019. **Excellent review of multimodal approach to ERAS).**
5. Paris A, Tonner PH. Dexmedetomidine in anaesthesia. Curr Opin Anaesthesiol [Internet]. 2005 [cited 2019 Aug 14];18:412–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16534267. Accessed 14 Aug 2019.
6. Rajan S, Hutcherson MT, Sessler DI, Kurz A, Yang D, Ghobrial M, et al. The effects of dexmedetomidine and remifentanil on hemodynamic stability and analgesic requirement after craniotomy. J Neurosurg Anesthesiol [Internet]. 2016 [cited 2019 Aug 14];28:282–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26325514. Accessed 14 Aug 2019.
7. Naik BI, Nemergut EC, Kazemi A, Fernández L, Cederholm SK, McMurry TL, et al. The effect of dexmedetomidine on postoperative opioid consumption and pain after major spine surgery. Anesth Analg [Internet]. 2016 [cited 2019 Aug 14];122:1646–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27003917. Accessed 14 Aug 2019.
8. Wang X, Liu W, Xu Z, Wang F, Zhang C, Wang B, et al. Effect of dexmedetomidine alone for intravenous patient-controlled analgesia after gynecological laparoscopic surgery. Medicine (Baltimore). 2016;95:e3639.
9. •• Bellon M, Le Bot A, Michelet D, Hilly J, Maesani M, Brasher C, et al. Efficacy of intraoperative dexmedetomidine compared with placebo for postoperative pain management: a meta-analysis of published studies. Pain Ther. 2016;5:63–80. **Excellent study of dexmedetomidine compared with placebo for postoperative pain management.**
10. Hwang W, Lee J, Park J, Joo J. Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: a randomized controlled study. BMC Anesthesiol [Internet]. 2015 [cited 2019 Aug 14];15:21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25750586. Accessed 14 Aug 2019.
11. Abdallah FW, Brull R. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth. The Author(s). 2013;110:915–25.
12. Grewal A. Dexmedetomidine: new avenues. J Anaesthesiol Clin Pharmacol [Internet]. Medknow Publications and Media Pvt. Ltd.; 2011 [cited 2019 Aug 14];27:297. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21897496. Accessed 14 Aug 2019.
13. Tufanogullari B, White PF, Peixoto MP, Kianpour D, Lacour T, Griffin J, et al. Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. Anesth Analg [Internet]. 2008 [cited 2019 Aug 14];106:1741–8. Available from: https://insights.ovid.com/crossref?an=00000539-200806000-00021. Accessed 14 Aug 2019.
14. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet Springer. 2017;56:893–913.
15. Naaz S, Ozair E. Dexmedetomidine in current anaesthesia practice-a review. J Clin Diagn Res [Internet]. JCDR Research & Publications Private Limited; 2014 [cited 2019 Aug 16];8:GE01–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25478365. Accessed 14 Aug 2019.
16. Giovannitti JA, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. Anesth Prog. 2015.
17. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical Pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet [Internet]. 2017 [cited 2019 Aug 16];56:893–913. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28105598. Accessed 14 Aug 2019.
18. Haenecour AS, Seto W, Urbain CM, Stephens D, Laussen PC, Balit CR. Prolonged dexmedetomidine infusion and drug withdrawal in critically ill children. J Pediatr Pharmacol Ther. 2017;22(6)453–60. https://doi.org/10.5863/1551-6776-22.6.453.
19. Cui J, Zhao H, Wang C, Sun JJ, Lu K, Ma D. Dexmedetomidine attenuates oxidative stress induced lung alveolar epithelial cell apoptosis *in vitro*. Oxid Med Cell Longev [Internet]. Hindawi; 2015 [cited 2019 Aug 15];2015:1–11. Available from: http://www.hindawi.com/journals/omcl/2015/358396/. Accessed 14 Aug 2019.
20. Mohammed A, Maheshwari A, Manns S. Dexmedetomidine: sedative of choice in substance abuse. Chest [Internet]. Elsevier; 2016 [cited 2019 Aug 16];150:225A. Available from: https://linkinghub.elsevier.com/retrieve/pii/S001236921656437X. Accessed 14 Aug 2019.
21. Upadhyay S, Elmatite W, Taqi S, Jagia M, Mallick P. Dexmedetomidine infusion to facilitate opioid detoxification and withdrawal in a patient with chronic opioid abuse. Indian J Palliat Care [Internet]. 2011 [cited 2019 Aug 16];17:251. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/22346054. Accessed 14 Aug 2019.
22. Gerlach AT, Murphy C V. Dexmedetomidine-associated bradycardia progressing to pulseless electrical activity: case report and review of the literature. Pharmacotherapy [Internet]. 2009 [cited 2019 Aug 15];29:1492–1492. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19947809. Accessed 14 Aug 2019.
23. Yu ZY, Geng J, Li ZQ, Sun YB, Wang SL, Masters J, et al. Dexmedetomidine enhances ropivacaine-induced sciatic nerve injury in diabetic rats. Br J Anaesth [Internet]. 2019 [cited 2019 Aug 15];122:141–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30579393. Accessed 14 Aug 2019.
24. Rwei AY, Sherburne RT, Zurakowski D, Wang B, Kohane DS. Prolonged duration local anesthesia using liposomal bupivacaine combined with liposomal dexamethasone and dexmedetomidine. Anesth Analg [Internet]. 2018 [cited 2019 Aug 15];126:1170–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29239940. Accessed 14 Aug 2019.
25. Boriosi JP, Eickhoff JC, Hollman GA. Safety and efficacy of buccal dexmedetomidine for MRI sedation in school-aged children. Hosp Pediatr [Internet]. 2019 [cited 2019 Aug 15];9:348–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30971402. Accessed 14 Aug 2019.
26. Shi M, Miao S, Gu T, Wang D, Zhang H, Liu J. Dexmedetomidine for the prevention of emergence delirium and postoperative behavioral changes in pediatric patients with sevoflurane anesthesia: a double-blind, randomized trial. Drug Des Dev Ther Dove Press. 2019;13:897–905.
27. Kim JA, Ahn HJ, Yang M, Lee SH, Jeong H, Seong BG. Intraoperative use of dexmedetomidine for the prevention of emergence agitation and postoperative delirium in thoracic surgery: a randomized-controlled trial. Can J Anesth Can d'anesthésie [Internet]. 2019 [cited 2019 Aug 15];66:371–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30710258. Accessed 14 Aug 2019.
28. Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology. 2012;116:1312–22.
29. Le Bot A, Michelet D, Hilly J, Maesani M, Dilly MP, Brasher C, et al. Efficacy of intraoperative dexmedetomidine compared with placebo for surgery in adults: a meta-analysis of published studies. Minerva Anestesiol. 2015;81:1105–17.
30. Wang L, Shen J, Ge L, Arango MF, Tang X, Moodie J, et al. Dexmedetomidine for craniotomy under general anesthesia: a systematic review and meta-analysis of randomized clinical trials. J Clin Anesth. 2019;54:114–25.
31. Singh PM, Panwar R, Borle A, Mulier JP, Sinha A, Goudra B. Perioperative analgesic profile of dexmedetomidine infusions in morbidly obese undergoing bariatric surgery: a meta-analysis and trial sequential analysis. Surg Obes Relat Dis. 2017;13:1434–46.
32. Tsaousi GG, Pourzitaki C, Aloisio S, Bilotta F. Dexmedetomidine as a sedative and analgesic adjuvant in spine surgery: a systematic review and meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. 2018;74:1377–89.
33.•• Liu Y, Liang F, Liu X, Shao X, Jiang N, Gan X. Dexmedetomidine reduces perioperative opioid consumption and postoperative pain intensity in neurosurgery. J Neurosurg Anesthesiol. 2017;30:1. **Excellent study of dexmedetomidine reducing opioid comsumption postoperatively.**
34.•• Li C, Qu J. Efficacy of dexmedetomidine for pain management in knee arthroscopy. Medicine (Baltimore). 2017;96:e7938. **Excellent study of dexmedetomidine reducing opioid comsumption postoperatively.**
35. Wang X, Liu N, Chen J, Xu Z, Wang F, Ding C. Effect of intravenous dexmedetomidine during general anesthesia on acute postoperative pain in adults. Clin J Pain. 2018;34:1.
36. Tumber PS. Optimizing perioperative analgesia for the complex pain patient: medical and interventional strategies. Can J Anesth. 2014;61:131–40.
37. Jessen Lundorf L, Korvenius Nedergaard H, Møller AM. Perioperative dexmedetomidine for acute pain after abdominal surgery in adults. Cochrane Database Syst Rev. 2016;2:CD010358.
38. Schmidt AP, Valinetti EA, Bandeira D, Bertacchi MF, Simões CM, Auler JOC. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. Pediatr Anesth. 2007;17:667–74.
39. Ni J, Wei J, Yao Y, Jiang X, Luo L, Luo D. Effect of dexmedetomidine on preventing postoperative agitation in children: a meta-analysis. Gemma M, editor. PLoS One. 2015;10:e0128450.
40. Zhu A, Benzon HA, Anderson TA. Evidence for the efficacy of systemic opioid-sparing analgesics in pediatric surgical populations. Anesth Analg. 2017;125:1569–87.
41. Unlugenc H, Gunduz M, Guler T, Yagmur O, Isik G. The effect of pre-anaesthetic administration of intravenous dexmedetomidine on postoperative pain in patients receiving patient-controlled morphine. Eur J Anaesthesiol. 2005;22:386–91.
42. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anesth. 2006;53:646–52.
43. Xu S-Q, Li Y-H, Wang S-B, Hu S-H, Ju X, Xiao J-B. Effects of intravenous lidocaine, dexmedetomidine and their combination on postoperative pain and bowel function recovery after abdominal hysterectomy. Minerva Anestesiol. 2017;83:685–94.
44. Wang K, Zhang X, Zhang T, Yue H, Sun S, Zhao H, et al. The efficacy of ultrasound-guided type II pectoral nerve blocks in perioperative pain management for immediate reconstruction after modified radical mastectomy. A prospective, randomized study. Clin J Pain. 2017;34:1.
45. Fan W, Yang H, Sun Y, Zhang J, Li G, Zheng Y, et al. Comparison of the pro-postoperative analgesia of intraoperative dexmedetomidine with and without loading dose following general anesthesia. Medicine (Baltimore). 2017;96:e6106.
46. Grape S, Kirkham KR, Frauenknecht J, Albrecht E. Intra-operative analgesia with remifentanil vs. dexmedetomidine: a systematic review and meta-analysis with trial sequential analysis. Anaesthesia. 2019;74:793–800.
47. Feng M, Chen X, Liu T, Zhang C, Wan L, Yao W. Dexmedetomidine and sufentanil combination versus sufentanil alone for postoperative intravenous patient-controlled analgesia: a systematic review and meta-analysis of randomized controlled trials. BMC Anesthesiol. 2019;19:81.
48. Peng K, Zhang J, Meng X-W, Liu H-Y, Ji F-H. Optimization of postoperative intravenous patient-controlled analgesia with opioid-dexmedetomidine combinations: an updated meta-analysis with trial sequential analysis of randomized controlled trials. Pain Physician. 2017;20:569–96.
49. Koyyalamudi V, Sen S, Patil S, Creel JB, Cornett EM, Fox CJ, et al. Adjuvant agents in regional anesthesia in the ambulatory setting. Curr Pain Headache Rep [Internet]. 2017 [cited 2018 Jun 7];21:6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28210917. Accessed 14 Aug 2019.
50. Tang C, Xia Z. Dexmedetomidine in perioperative acute pain management: a non-opioid adjuvant analgesic. J Pain Res Dove Press. 2017;10:1899.
51. Sun Q, Liu S, Wu H, Ma H, Liu W, Fang M, et al. Dexmedetomidine as an adjuvant to local anesthetics in transversus abdominis plane block. Clin J Pain. 2019;35:375–84.
52. Vorobeichik L, Brull R, Abdallah FW. Evidence basis for using perineural dexmedetomidine to enhance the quality of brachial plexus nerve blocks: a systematic review and meta-analysis of randomized controlled trials. Br J Anaesth. 2017;118:167–81.

53. Zhang X, Wang D, Shi M, Luo Y. Efficacy and safety of dexmedetomidine as an adjuvant in epidural analgesia and anesthesia: a systematic review and meta-analysis of randomized controlled trials. Clin Drug Investig. 2017;37:343–54.
54. Albrecht E, Vorobeichik L, Jacot-Guillarmod A, Fournier N, Abdallah FW. Dexamethasone is superior to dexmedetomidine as a perineural adjunct for supraclavicular brachial plexus block. Anesth Analg. 2019;128:543–54.
55. Liu S, Wang Y, Zhu Y, Yu T, Zhao H. Safety and sedative effect of intranasal dexmedetomidine in mandibular third molar surgery: a systematic review and meta-analysis. Drug Des Dev Ther. 2019;13:1301–10.
56. Soroush H, Ghorbani-Bidkorbeh F, Mortazavi SA, Mehramizi A. Formulation optimization and assessment of dexamethasone orally disintegrating tablets using Box-Behnken design. Iran J Pharm Res. 2018;17:1150–63.
57. Song Y, Shim J-K, Song J-W, Kim E-K, Kwak Y-L. Dexmedetomidine added to an opioid-based analgesic regimen for the prevention of postoperative nausea and vomiting in highly susceptible patients: a randomised controlled trial. Eur J Anaesthesiol. 2016;33:75–83.
58. Huyan T, Hu X, Peng H, Zhu Z, Li Q, Zhang W. Perioperative dexmedetomidine reduces delirium in elderly patients after lung cancer surgery. Psychiatr Danub. 2019;31:95–101.
59. Hakim KYK, WZB W. Opioid-free total intravenous anesthesia improves postoperative quality of recovery after ambulatory gynecologic laparoscopy. Anesth Essays Res Wolters Kluwer – Medknow Publications. 2019;13:199–203.
60. Zhao J-N, Kong M, Qi B, Ge D-J. Comparison of the morphine-sparing effect of intraoperative dexmedetomidine with and without loading dose following general anesthesia in multiple-fracture patients. Medicine (Baltimore). 2016;95:e4576.
61. Yoo H, Iirola T, Vilo S, Manner T, Aantaa R, Lahtinen M, et al. Mechanism-based population pharmacokinetic and pharmacodynamic modeling of intravenous and intranasal dexmedetomidine in healthy subjects. Eur J Clin Pharmacol. 2015;71:1197–207.
62. Iirola T, Vilo S, Manner T, Aantaa R, Lahtinen M, Scheinin M, et al. Bioavailability of dexmedetomidine after intranasal administration. Eur J Clin Pharmacol. 2011;67:825–31.
63. Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. Br J Clin Pharmacol. 2003;56:691–3.
64. Kundra P, Velayudhan S, Krishnamachari S, Gupta SL. Oral ketamine and dexmedetomidine in adults' burns wound dressing–a randomized double blind cross over study. Burns. 2013;39:1150–6.
65. Karaaslan D, Peker TT, Alaca A, Ozmen S, Kirdemir P, Yorgancigil H, et al. Comparison of buccal and intramuscular dexmedetomidine premedication for arthroscopic knee surgery. J Clin Anesth. 2006;18:589–93.
66. Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology. 1993;78:813–20.
67. Scheinin H, Karhuvaara S, Olkkola KT, Kallio A, Anttila M, Vuorilehto L, et al. Pharmacodynamics and pharmacokinetics of intramuscular dexmedetomidine. Clin Pharmacol Ther. 1992;52:537–46.
68. Sun S, Wang J, Bao N, Chen Y, Wang J. Comparison of dexmedetomidine and fentanyl as local anesthetic adjuvants in spinal anesthesia: a systematic review and meta-analysis of randomized controlled trials. Drug Des Dev Ther. 2017;11:3413–24.
69. Shariffuddin II, Teoh WH, Wahab S, Wang CY. Effect of single-dose dexmedetomidine on postoperative recovery after ambulatory ureteroscopy and ureteric stenting: a double blind randomized controlled study. BMC Anesthesiol BioMed Central. 2018;18:3.
70. Panchgar V, Shetti AN, Sunitha HB, Dhulkhed VK, Nadkarni AV. The effectiveness of intravenous dexmedetomidine on perioperative hemodynamics, analgesic requirement, and side effects profile in patients undergoing laparoscopic surgery under general anesthesia. Anesth Essays Res Wolters Kluwer – Medknow Publications. 2017;11:72–7.
71. Karan D, Swaro S, Mahapatra PR, Banerjee A. Effect of dexmedetomidine as an adjuvant to ropivacaine in ilioinguinal-iliohypogastric nerve blocks for inguinal hernia repair in pediatric patients: a randomized, double-blind, control trial. Anesth Essays Res. 12:924–9.
72. Alansary AM, Elbeialy MAK. Dexmedetomidine versus fentanyl added to bupivacaine for epidural analgesia in combination with general anesthesia for elective lumbar disc operations: a prospective, randomized double-blinded study. Saudi J Anaesth. 2019;13(2):119–25. https://doi.org/10.4103/sja.SJA_600_18.
73. Lakshmi Praveena B, Bharathi B, Sahana VR. Intraperitoneal ropivacaine with dexmedetomidine or fentanyl for postoperative analgesia following laparoscopic cholecystectomy: a comparative randomized trial. Anesth Essays Res. 2019;13(1):169–73. https://doi.org/10.4103/aer.AER_191_18.
74. Sharma K, Kumar M, Gandhi R. Effect of single-dose dexmedetomidine on intraoperative hemodynamics and postoperative recovery during pediatric adenotonsillectomy. Anesth Essays Res. 2019;13:63.
75. Kamali A, Azadfar R, Pazuki S, Shokrpour M. Comparison of dexmedetomidine and fentanyl as an adjuvant to lidocaine 5% for spinal anesthesia in women candidate for elective caesarean. Open access. Maced J Med Sci ID Design Press. 2018;6:1862–7.
76. Du Z, Zhang X, Qu S, Song Z, Wei S, Xiang Z, et al. The comparison of dexmedetomidine and midazolam premedication on postoperative anxiety in children for hernia repair surgery: a randomized controlled trial. Cravero J, editor. Pediatr Anesth. 2019;pan.13667.
77. Kim D, Jeong JS, Park H, Sung K-S, Choi SJ, Gwak MS, et al. Postoperative pain control after the use of dexmedetomidine and propofol to sedate patients undergoing ankle surgery under spinal anesthesia: a randomized controlled trial. J Pain Res Dove Press. 2019;12:1479–87.
78. Davy A, Fessler J, Fischler M, LE Guen M. Dexmedetomidine and general anesthesia: a narrative literature review of its major indications for use in adults undergoing non-cardiac surgery. Minerva Anestesiol. 2017;83:1294–308.
79. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015;115(2):171–82. https://doi.org/10.1093/bja/aev226.
80. Lee S. Dexmedetomidine: present and future directions. Korean J Anesthesiol. 2019.