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Review article

Dexmedetomidine: perioperative applications in children

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Summary

Dexmedetomidine is a highly specific and selective alpha-2-adrenergic agonist with sedative, anxiolytic, and organ protective effects. Its clinical applications in children include premedication, prevention of emergence delirium, as part of multimodal anesthetic regimen and sedation in the pediatric intensive care unit. Its role in neuroprotection in children undergoing anesthesia should be explored. In this review, various uses of dexmedetomidine are discussed in detail.

Keywords: dexmedetomidine; pediatric anesthesia; perioperative applications

Introduction

Dexmedetomidine is a highly specific and selective alpha-2-adrenergic agonist with sedative, anxiolytic, and analgesic effects (1). The sedative state produced by dexmedetomidine is unique in a number of ways and is dose dependent (2). At low doses, it produces sedation wherein the patient is drowsy but remains arousable and cooperative. When the dose is large enough, it produces deep sedation or even general anesthesia. Minimal respiratory depression is observed even when large doses are used (2,3). The sedative effect mimics natural stage 2 nonrapid eye movement sleep, which is evident from the electroencephalograph (4,5). Because it has minimal respiratory depressant effect and only modest cardiovascular effects in the majority of patients, the safety margin of this drug is favorable compared to gamma-aminobutyric acid receptor agonists such as propofol and benzodiazepines.

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Recently, dexmedetomidine has been investigated extensively in the pediatric population and there is now increasing evidence to support the use of this drug as sedative and anesthetic adjunct in children. In this review, the perioperative application of dexmedetomidine in children is discussed. However, although we have good clinical data in children, it is currently only approved by the US FDA for continuous infusion of up to 24 h in the adult intensive care unit. Hence, the uses of dexmedetomidine in children described in this review are 'off-label'.

Premedication

Perioperative anxiety is a common phenomenon, especially in children of preschool age. It occurs in at least 60% of children in one report (6). Anesthetic induction has been shown to be the most stressful period for children who have undergone previous surgery (6,7). Premedication with the short acting benzodiazepine, midazolam, has been shown to alleviate preoperative anxiety and distress at induction of anesthesia (8–11). Midazolam is the most commonly used premedication in children in the

United States (12,13). However, it is relatively contraindicated in children with high impulsivity (14) and may be less effective in younger children who are more emotional and anxious at baseline (15). Clonidine, an alpha-2-adrenergic agonist, has been investigated as an alternative premedicaton. When compared with benzodiazepines, α_2-adrenergic agonists produce anxiolysis, sedation, analgesia, antisialogogue activity, reduced gastric secretions, sympatholytic effects, and reduced postoperative nausea and vomiting (16). They also attenuate the catecholamine release and hemodynamic response secondary to endotracheal intubation (17–20) and surgical stimulation (21,22). Clonidine, however, has a number of limitations when used for premedication. The elimination half-life is 12.5 h, and the onset of action is slow when it is given orally, intranasally, or rectally (23). In children, the peak plasma concentration occurs 60–90 min after oral administration, so this agent should be given at least 1 h prior to induction of anesthesia (24).

Compared to clonidine, dexmedetomidine is a more selective alpha-2-adrenoceptor agonist with a shorter elimination half-life. Hence, it should possess a more favorable pharmacologic profile than clonidine when it is used for premedication.

Although currently formulated for intravenous administration, there are reports of the successful use of dexmedetomidine administered before noninvasive procedures orally (25) and intranasally (26) in children with neurobehavioral disorders and in children with extreme anxiety.

Anttila *et al.* (27) have shown in healthy volunteers that the bioavailability of oral dexmedetomidine is approximately 15%. When it is administrated transmucosally via the buccal mucosa, the bioavailability is above 80%. Yuen *et al.* (28) reported a clinically significant sedative effect when dexmedetomidine was given to healthy adult volunteers intranasally. The doses used in this double-blind crossover evaluation were 1 and 1.5 $\mu g \cdot kg^{-1}$. In another double-blind randomized controlled trial of 96 children aged between 2 and 12 , intranasal dexmedetomidine at 1 $\mu g \cdot kg^{-1}$ was shown to be an effective sedative when compared with 0.5 $mg \cdot kg^{-1}$ oral midazolam (29). In this report, satisfactory sedation was achieved in 21.9%, 59.4%, and 75% of the children who received 0.5 $mg \cdot kg^{-1}$ oral midazolam, 0.5 $\mu g \cdot kg^{-1}$ intranasal dexmedetomidine, and 1 $\mu g \cdot kg^{-1}$ intranasal dexmedetomidine, respectively, at separation from parents. At induction of anesthesia, 18.8%, 40.6%, and 53.1% of the children who received 0.5 $mg \cdot kg^{-1}$ oral midazolam, 0.5 $\mu g \cdot kg^{-1}$ intranasal dexmedetomidine, and 1 $\mu g \cdot kg^{-1}$ intranasal dexmedetomidine, respectively, remained sedated. Modest hemodynamic effects were observed after intranasal dexmedetomidine in children; however, these effects were clinically insignificant, and no intervention was required. Maximum reduction of systolic blood pressure and heart rate after 1 $\mu g \cdot kg^{-1}$ of intranasal dexmedetomidine was 14.1% and 16.4%, respectively. Moreover, intranasal dexmedetomidine was well tolerated by children as it produced no unpleasant sensation when it was administered intranasally. Effective sedation may be achieved with intranasal dexmedetomidine in children who are anxious and noncompliant to oral medication. In another prospective double-blind, randomized controlled trial by the same group of authors, intranasal dexmedetomidine at 1 $\mu g \cdot kg^{-1}$ was compared with placebo as premedication in children aged 1–12 (V.M.Y. Yuen, T.W. Hui, M.G. Irwin, T.J. Yao, G.L. Wong, M.K. Yuen, personal communication). Hundred children were enrolled and 79 children received intranasal dexmedetomidine whereas 21 children received placebo. Satisfactory sedation was produced in 62% of the children when intravenous cannulation was attempted under the effect of topical local anesthetic. The median time of onset of sedation was 25 min (95% CI: 25–30 min) and, by 45 min, 91% (95% CI: 85–98) of the subjects who had 1 $\mu g \cdot kg^{-1}$ intranasal dexmedetomidine were satisfactorily sedated. The median duration of sedation was 85 min (95% CI: 55–100 min). As it can be difficult to accurately coordinate premedication with time of surgery, this trial suggests that 1 $\mu g \cdot kg^{-1}$ of intranasal dexmedetomidine provides some flexibility as long as it is given at least 30 and preferably 45 min in advance.

Schmidt *et al.* (22) have used transmucosal dexmedetomidine as premedication in children. In a recent prospective study, intranasal dexmedetomidine at 2 $\mu g \cdot kg^{-1}$ was more effective at inducing sleep when compared with 0.5 $mg \cdot kg^{-1}$ oral midazolam (30). Future research should be directed at the optimal dosage and timing of transmucosal route of administration of dexmedetomidine in children and its application in clinical settings. To date, we

have pharmacokinetic information on intravenous administration of dexmedetomidine in children (31,32) and on transmucosal administration in adults (27). Pharmacokinetic information on various ways of transmucosal administration of dexmedetomidine in the pediatric population is lacking but will be valuable to the understanding of this route of administration in children.

Emergence delirium

Another important perioperative application of dexmedetomidine is its role in prevention of emergence delirium. Emergence delirium or agitation is a common phenomenon. Its incidence is related to child temperament, preoperative anxiety level, and anesthetic technique. To date, at least six prospective clinical trials have shown that dexmedetomidine significantly reduced the incidence of emergence delirium when it was given to children prior to recovery from sevoflurane or desflurane anesthesia (33–38). The dose of dexmedetomidine used ranged from 0.15 to 1 $\mu g \cdot kg^{-1}$, given as either an intravenous bolus or an infusion prior to completion of surgery. The incidence of emergence delirium was shown to be decreased by three- to 10-fold. In one study, dexmedetomidine was given via the caudal epidural route in a dose of 1 $\mu g \cdot kg^{-1}$ and was shown to reduce incidence of emergence delirium from 27% in the placebo group to 7% in the study group (38). Although these are all small studies, they have consistently shown a significant effect of dexmedetomidine on reducing the incidence of emergence delirium, which in turn facilitates smooth recovery from general anesthesia in children.

Analgesic effects

The use of dexmedetomidine as a sedative in the immediate postoperative period may extend to children who have major, painful surgical procedures. Dexmedetomidine has analgesic properties and it exerts its analgesic effect at the spinal cord and supra-spinal level. There is controversy with respect to the analgesic effect of dexmedetomidine. Early studies suggested that the analgesic effect may be mediated by the affective-motivational component of pain (39). In experiment studies, its analgesic effect varies with different pain models. Ebert *et al.* (2) demonstrated a dose-dependent analgesic effect of intravenous dexmedetomidine to the cold pressor test with no ceiling effect. The range of plasma concentration evaluated in this study was wide and included targeted plasma concentration of 0.5–8.0 $\eta g \cdot ml^{-1}$. In this study, increasing doses led to linearly decreasing pain sensation to cold pressor test. A mild to moderate analgesic effect was shown in another study using the same experimental pain model (3). When dexmedetomidine was used as an analgesic in an ischemic pain model in healthy volunteers, the ceiling effect was noted at dose of 0.5 $\mu g \cdot kg^{-1}$ (40). However, dexmedetomidine lacks analgesic activity in other experimental pain models, including heat–pain stimulation (41), heat and electrical pain tolerance and threshold (42), and pain pressure threshold (28). Not only is there variation in analgesic effect of dexmedetomidine in different kind of pain model, recently Kohli *et al.* (43) have shown that variation in the human α2A- and α2C-adrenoceptor genes may contribute to inter-individual variability in pain perception and response to dexmedetomidine.

Dexmedetomidine was shown to be an effective analgesic in adult patients who underwent laparoscopic tubal ligation (44). When it was used in adult patients who had major abdominal or orthopedic procedures, patients who were given dexmedetomidine before the end of surgery required less morphine in the immediate postoperative period when compared to patients who were given morphine during surgery (45). Dexmedetomidine given for intraoperative sedation in adult patients undergoing surgical procedures with regional anesthesia was associated with lower postoperative morphine consumption when compared with propofol sedation (46). When dexmedetomidine was as a substitute for fentanyl during bariatric surgery, it provided more effective pain relief in the postanesthesia care unit (47). Unlugenc *et al.* (48) have shown that a single dose of dexmedetomidine (1 $\mu g \cdot kg^{-1}$) given before induction of anesthesia significantly reduced morphine consumption in the first 24 h. In another two prospective studies, adjunctive use of an intraoperative dexmedetomidine infusion was shown to reduce postoperative opioid requirement in the first 24 h (49,50).

Dexmedetomidine was also examined in the postoperative setting. When it was given intravenously

as an adjunct to epidural analgesia in patients who had underwent thoracic surgery, it decreased opioid requirement (51). More recently, Lin *et al*. (52) have examined the analgesic effect of adding dexmedetomidine to intravenous patient-controlled morphine analgesia total abdominal hysterectomy. When 5 μg of dexmedetomidine was added to 1 mg of morphine, morphine consumption in the first 24 h was significantly reduced with improved pain control. Moreover, the opioid sparing effect was shown to be associated with a reduced incidence of postoperative nausea and vomiting in three investigations (49,50,52).

Clinical data demonstrating the analgesic effect of dexmedetomidine in children are lacking. Olutoye *et al*. (53) reported their preliminary experience of using dexmedetomidine as analgesic in children underwent tonsillectomy and adenoidectomy. In this study, dexmedetomidine 0.5 $\mu g \cdot kg^{-1}$ was compared with morphine 50 $\mu g \cdot kg^{-1}$, postoperative pain scores and morphine requirement were not different between the two groups. In another prospective study, dexmedetomidine administered caudally with bupivacaine was associated with an extended duration of postoperative pain relief and reduced requirement of postoperative analgesic drugs (38).

Although further evidence is needed, dexmedetomidine may be a useful agent in multimodal analgesic regimens, especially in patients who have undergone major and painful surgery. When it is used in children who have undergone major procedures, they may benefit from its analgesic and opioid sparing effect, as well as its sedative effect during the immediate postoperative period.

Anesthesia for the challenging patients

Dexmedetomidine has been used as a sole agent to produce general anesthetic in infants. Shurky *et al*. (54) have described the use of dexmedetomidine as the sole anesthetic for four infants requiring general anesthesia for direct laryngoscopy and bronchoscopy with spontaneous ventilation. The doses described in this report were 2–5 $\mu g \cdot kg^{-1}$. In this report, no untoward hemodynamic effect was seen when such high dose was used.

A few anecdotal reports have described the use of dexmedetomidine with ketamine to produce deep sedation and general anesthesia in children with challenging medical conditions. General anesthesia is often required for infants and toddlers undergoing the most simple but invasive procedure such as central line insertion or cardiac catherization. However, in children with marginal cardiac or respiratory reserve, general anesthesia is associated with high risk of morbidity and mortality. Because dexmedetomidine has a favorable safety margin, there are reports of its use as a sedative agent in children with critical and marginal cardiovascular status or respiratory status undergoing invasive procedures. Bozdogan *et al*. (55) have reported the uses of dexmedetomidine combined with ketamine as sedative agents in three infants with acute viral bronchiolitis and congenital cardiac abnormalities. They underwent repair of incarcerated hernia under caudal anesthesia. Sedation with dexmedetomidine and ketamine allowed caudal anesthesia and a surgical procedure to be performed with the infants breathing spontaneously. Both ventilatory and hemodynamic changes were within normal limits during the procedure. Mohmoud *et al*. (56) have used dexmedetomidine and ketamine to provide general anesthesia for a child with a large anterior mediastinal mass who underwent ultrasound-guided needle biopsy of the lesion. This child had respiratory symptoms because of compression of the trachea by the large tumor. Moreover, he was symptomatic for superior vena caval obstruction. General anesthesia was induced with midazolam, dexmedetomidine, and ketamine. Dexmedetomidine bolus of 2 $\mu g \cdot kg^{-1}$ infused over 10 min followed by infusion of 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was given. In addition, ketamine and midazolam boluses were titrated to allow the diagnostic procedure to take place. Spontaneous respiration and hemodynamic stability was preserved throughout the diagnostic procedure.

Barton *et al*. (57) have also reported a series of six infants and toddlers with complex cyanotic heart disease underwent invasive procedure with dexmedetomidine and ketamine as the main sedative agents. The dose of dexmedetomidine used in this series ranged from 1 to 3 $\mu g \cdot kg^{-1}$ and ketamine used ranged from 0 to 1.5 $mg \cdot kg^{-1}$. The procedures performed included cut-down for central line insertion, chest tube insertion, and fiberoptic bronchoscopy. Maintaining respiration under sedation in these children with complex cyanotic heart disease offers a major advantage because this would avoid

tracheal intubation and positive pressure ventilation in these infants and children who have marginal cardiorespiratory reserve. Nathan *et al.* (58) reported using dexmedetomidine as the main sedative in an adolescent with severe pulmonary hypertension, pneumonia, and impending cardiorespiratory failure. This patient was successfully sedated with dexmedetomidine and ketamine. Endotracheal intubation and positive pressure ventilation were avoided. Dexmedetomidine combined with ketamine for fiberoptic intubation in a child with Treacher Collins syndrome was described (59). Dexmedetomidine 1 $\mu g \cdot kg^{-1}$ as a loading dose followed by 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ as continuous infusion. A total of five boluses of ketamine each at 0.25 $mg \cdot kg^{-1}$ were given intermittently to allow the procedure to be completed in excellent conditions, including secretion-free airway with no episodes of coughing, apnea, and oxygenation desaturation.

There are a number of advantages to combine dexmedetomidine and ketamine to produce sedation and analgesia for children undergoing invasive and painful procedures. Both drugs have minimal effect on respiration. Moreover, dexmedetomidine was reported to attenuate the cardiostimulatory effects and postoperative delirium of ketamine (60). Therefore, the sympathomimetic and tachycardia effect of ketamine are attenuated by dexmedetomidine premedication. While ketamine use is associated with an increase in salivation, dexmedetomidine has an antisialogogue effect. Dexmedetomidine is a sedative with sympatholytic and mild analgesic effects, whereas ketamine is a more potent analgesic with sympathomimetic and amnesic properties. Combining them seems to be a sensible choice of sedation regimen in children undergoing painful procedures. However, more investigation is warranted to examine the appropriate dose range, possible synergism, and clinical application of combining these two drugs in children.

Other perioperative uses

Apart from its sedative and analgesic effects, dexmedetomidine possesses other properties that render it a useful adjunct in perioperative care in children.

α_2-Agonists are known to have antiemetic properties. Previous investigation has shown that clonidine premedication is associated with a reduction in postoperative nausea and vomiting (61). Dexmedetomidine has been used successfully to treat cyclical vomiting in children (62,63), and the opioid sparing effect of dexmedetomidine was also associated with a reduced incidence of postoperative nausea and vomiting (49,50,52).

In a number of prospective studies, dexmedetomidine was reported to reduce intraocular pressure in adults. The earliest investigation was performed by Jaakola and colleagues (64). In this prospective study comparing intravenous dexmedetomidine with placebo, dexmedetomidine 0.6 $\mu g \cdot kg^{-1}$ i.v. given prior to induction of anesthesia was associated with a 34% decrease in intraocular pressure and 62% decrease in plasma norepinephrine concentrations. Mowafi *et al.* (65) have shown that dexmedetomidine blunted the suxamethonium-associated rise in intraocular pressure in adult patients with open globe injuries. In another double-blind prospective and placebo-controlled trial, low dose of intravenous infusion of dexmedetomidine decreased intraocular pressure by approximately 20% during ophthalmic surgery under local anesthesia (66). Yavascaoglu *et al.* (67) have reported that a single intravenous bolus of dexmedetomidine at 0.5 $\mu g \cdot kg^{-1}$ was more effective than esmolol for attenuation of the hemodynamic and intraocular pressure responses to tracheal intubation. However, in another prospective study, it was reported that dexmedetomidine had no effect on intraocular pressure (68). The absence of effect on intraocular pressure in this study may have been related to atropine premedication. With its sedative, analgesic, and antiemetic properties and its effect on intraocular pressure, dexmedetomidine may be a useful anesthetic adjunct in ophthalmic surgery in children. This warrants further investigation.

The use of dexmedetomidine as a sedative during awake craniotomy has also been described in adolescents (69,70). Low dose dexmedetomidine infusion, ranging from 0.1 to 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$, was used to facilitate intraoperative direct brain stimulation mapping, preservation of critical and important cortical and subcortical function and resection of brain lesion such as epileptogenic foci.

Dexmedetomidine is also a potentially useful adjunct in children undergoing other neurosurgery and corrective spinal surgery when neurophysiological monitoring is required. In animal studies,

dexmedetomidine has no effect on cortical somatosensory-evoked potentials (71) and myogenic motor-evoked potentials (72). In two retrospective reviews, it was suggested that combining dexmedetomidine with opioid–propofol-based total intravenous anesthesia has no effect on neurophysiological monitoring in adolescents; therefore, both somatosensory-evoked potential and motor-evoked potential were preserved. The concomitant use of dexmedetomidine reduced the dose of propofol by approximately 30% (73); this may reduce the side effects and risks associated with prolonged propofol infusion in children.

Neuroprotection

There is increasing evidence that dexmedetomidine has a number of organ protective effects, including renal, cardiac, and neurologic (74). There is increasing and compelling evidence that most general anesthetic agents, including the commonly used inhalation agents, benzodiazepines, and N-methyl-d-aspartate receptor antagonists, are associated with neuroapotosis and neurodengeneration in animal models (75). Clinical evidence is still limited because this phenomenon is difficult to study in human subjects. Nevertheless, a recent retrospective cohort study has suggested that multiple exposure to anesthesia before the age of 4 year was a significant risk factor for the later development of learning difficulties in children (76). Because this was a retrospective study, it is not certain whether this association reflects causal relationship between anesthesia in early childhood and learning difficulties. As we are searching for more evidence on how the commonly used anesthetic and sedative agents affect the developing human brain, we are also seeking alternative agents to provide anesthesia and sedation in children without adverse neurodevelopmental effects. Dexmedetomidine has been shown to exert a neuroprotective effect *in vitro* and *in vivo* animal models (74). More importantly, its use has been shown to attenuate isoflurane-induced neurocognitive impairment in neonatal rats (77). Kakinohana *et al*. have also demonstrated that intravenous infusion of dexmedetomidine can prevent the degeneration of spinal ventral neurons induced by intrathecal morphine after spinal cord ischemia in rats (78). Therefore, there are preclinical data from animal studies to support that dexmedetomidine may exert its neuroprotective effect in infants and young children who are exposed to commonly used anesthetic and sedative agents.

Adverse effects and contraindications

With appropriate monitoring, dexmedetomidine be used safely in the pediatric population. It typically causes a reduction in heart rate and blood pressure, commensurate with the reduction in plasma catecholamine levels (79). Hemodynamic parameters usually return to baseline within an hour of stopping the infusion. There is one report of severe bradycardia observed in a 5-week-old infant during sedation with dexmedetomidine, who was treated with digoxin (80). Recently, in a study of cardiac electrophysiology on 12 children, Hammer *et al.* (81) have demonstrated that dexmedetomidine significantly depressed sinus and atrioventricular nodal function. The dosing regimen used in this investigation consisted of a loading dose of 1 $\mu g \cdot kg^{-1}$ over 10 min, followed by 10 min continuous infusion of 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$. As a result, the authors suggested that the use of dexmedetomidine may not be desirable in patients at risk for bradycardia or atrioventricular nodal block. Dexmedetomidine should be avoided in patients with a compromised cardiovascular state, hypovolemia, atrioventricular nodal block, or taking concurrent medications that increase vagal tone or delay atrial–ventricular conduction. When pronounced hypotension or bradycardia occurs, treatment includes cessation of drug administration, volume expansion, vasopressor infusions and/or administration of anticholinergic agents.

Conclusion

Dexmedetomidine is a drug with diverse utility. There is increasing clinical evidence of various applications in children during the perioperative period and clinical data to show that this is a drug with a favorable safety profile. One important potential clinical application to explore would be its neuroprotective effect in the developing brain. Clinicians should exploit the preclinical data of its neurologic and other organ protective effects in animal models and translate them to human studies.

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