Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations

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Abstract

Despite lack of paediatric labelling, contributions to the literature on paediatric applications of dexmedetomidine have increased over recent years. Dexmedetomidine possesses many properties that are advantageous for a sedative and anaesthetic; it has been reported to provide sedation that parallels natural sleep, anxiolysis, analgesia, sympatholysis, and an anaesthetic-sparing effect with minimal respiratory depression. In addition, there is increasing evidence supporting its organ-protective effects against ischaemic and hypoxic injury. These favourable physiological effects combined with a limited adverse effect profile make dexmedetomidine an attractive adjunct to anaesthesia (general and regional) for a variety of procedures in paediatric operating rooms. A comprehensive understanding of the pharmacological, pharmacokinetic, and pharmacodynamic effects of dexmedetomidine is critical to maximize its safe, efficacious, and efficient paediatric perioperative applications. This review focuses on the current paediatric perioperative and periprocedural applications of dexmedetomidine and its limitations, with a consideration for the future.

Key words: adverse events; anaesthesia; paediatric; pharmacology; sedation

Editor’s key points

• In this review, the authors describe the pharmacology of dexmedetomidine and review the background literature.
• They detail the applications in the paediatric perioperative context, outline the limitations of its use, and discuss the potential future applications.

The ideal anaesthetic for perioperative application would be fast in onset and offset, with limited lipid solubility, predictable in response, easy to titrate, reliable in achieving a targeted level of sedation, able to preserve airway tone, and sparing of respiratory effects. This ideal agent would be neuroprotective and exhibit minimal cardiovascular effects. Unfortunately, such an ideal agent does not exist. Dexmedetomidine (DEX, Precedex®; Hospira, Lake Forest, IL, USA; and Dexdor; Orion Corporation, Espoo, Finland) possesses some of the desirable properties mentioned. In rodents and humans, DEX, through action on α2-adrenergic receptors in the locus coeruleus, provides relatively fast onset of sedative properties paralleling natural sleep, with minimal respiratory depression.1–7

In some studies, DEX has been shown to be neuroprotective, reducing apoptosis in animals and humans.8–11 To date, DEX has no known active or toxic metabolites. Currently, it is United States Food and Drug Administration (FDA) approved in the USA for sedation via i.v. bolus and continuous infusion for up to 24 h on intubated adults and for adult procedural sedation in areas
outside the intensive care unit (ICU) and operating room setting. In Europe, it is approved for adults (intubated or non-intubated) in the ICU via continuous i.v. infusion, at higher doses than approved in the USA, and without a restriction on duration of administration. Currently, worldwide, there is no approval for administration to the paediatric population. Despite the lack of paediatric labelling, DEX for paediatric use has been described for almost a decade in the literature. The favourable physiological effects of DEX combined with its limited adverse effect profile have facilitated its introduction into the perioperative setting. The α₂-adrenergic effects of DEX, relative contraindications, and biphasic effect on blood pressure in both children and adults should be well understood by any provider who administers or cares for a patient receiving DEX.

This review focuses on the diverse and most recent applications of DEX in the perioperative period in the paediatric population. We will summarize its current use as a premedication for anxiolysis, as an adjunctive drug both during and after surgery, and as an adjunct to attenuate emergence agitation, postoperative pain, and shivering. We will also discuss the clinical limitations, challenges, and relative contraindications to its use.

A summary of the current paediatric perioperative and periprocedural applications of DEX and the varying dosing regimens, doses, and routes of administration are provided in Tables 1 and 2, respectively.

### Preoperative applications: anxiolysis

Anxiolysis before the induction of anaesthesia is an important aspect of paediatric perioperative planning. Currently, there is a growing interest in comparing efficacy, time to onset, and outcomes between the different available anxiolytics. As a premedication, administration of DEX has been described by i.m., intranasal, and buccal routes. Via the nasal and buccal routes, DEX bioavailability approximates 65% (35–93%) and 81.8% (72.6–92.1%), respectively. The bioavailability of DEX by the oral route is very poor (16%), and in the authors’ opinion, administration by such a route is unwarranted.

When used as a premedication in paediatric patients, intranasal DEX has been shown to confer an advantage over both buccal DEX (1 μg kg⁻¹) and oral midazolam (0.5 mg kg⁻¹). Higher intranasal doses of DEX (2 rather than 1 μg kg⁻¹) are more efficacious at producing sedation, anxiolysis, better acceptance to a mask inhalation induction, and less cardiovascular variability. Doses of 1 μg kg⁻¹ intranasal DEX produced a median onset of sedation of 25 min and median duration of 85 min in healthy children undergoing elective surgery. At a higher dose, intranasal DEX 2 μg kg⁻¹ (compared with oral midazolam 0.5 mg) produced faster onset of sedation without a demonstrable difference in conditions at induction, emergence, and recovery. In a prospective,

### Table 1 Current common perioperative and periprocedural applications of dexmedetomidine in children

<table>
<thead>
<tr>
<th>Application</th>
<th>Advantage</th>
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<tr>
<td>Preoperative applications</td>
<td>Easy and quick arousal from sedation</td>
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<tr>
<td>Anxiolysis</td>
<td>Minimal respiratory depression</td>
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<td>Attenuates sympathetic haemodynamic response</td>
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<td>Intraoperative applications</td>
<td>Obtunds airway reflexes while maintaining</td>
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<td>Stable haemodynamic and respiratory</td>
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<td>Profiles in spontaneously ventilating children</td>
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<tr>
<td>Airway procedures</td>
<td>Provides sedative properties paralleling natural sleep</td>
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<td>Rigid bronchoscopy</td>
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<td>Drug-induced sleep endoscopy</td>
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<td>Magnetic resonance imaging sleep studies</td>
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<td>Open thyroplasty</td>
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<td>Anterior mediastinal mass biopsy</td>
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<td>Difficult intubation</td>
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<td>Neurosurgical procedures</td>
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<td>Posterior spine fusions</td>
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<td>Brain tumour and epileptic seizure</td>
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<td>Foci resection</td>
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<td>Painful procedures</td>
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<td>Extracorporeal shock-wave lithotripsy</td>
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<td>Burn dressing change</td>
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<td>Lumbar puncture</td>
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<td>Bone marrow biopsy</td>
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<td>Central venous line placement</td>
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<td>Chest tube insertion</td>
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<td>Applications to benefit the recovery period</td>
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<tr>
<td>Adenotonsillectomy</td>
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<td>Postoperative shivering</td>
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<td>Postoperative emergence agitation</td>
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<tr>
<td>Cardiac surgery</td>
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<tr>
<td>Blunts sympathetic response, provides analgesia and sedation in the postoperative period, and expedites extubation</td>
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<tr>
<td>Painful procedures</td>
<td>Combining ketamine and dexmedetomidine in these procedures provides sedation, analgesia, amnesia, and haemodynamic stability</td>
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<tr>
<td>Extracorporeal shock-wave lithotripsy</td>
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randomized, open-label clinical trial, children were enrolled into one of three groups of premedication: midazolam 0.5 mg kg$^{-1}$ p. o., clonidine 4 µg kg$^{-1}$ p.o., or transmucosal DEX 1 µg kg$^{-1}$. All treatments produced similar anxiolysis, ease of separation from parents, recovery, and discharge time. Dexmedetomidine had advantages (compared with midazolam) with respect to analgesia and attenuation of the sympathetic haemodynamic response. A recent meta-analysis of 13 randomized controlled trials on non-i.v. (intranasal, sublingual, or oral) DEX vs midazolam was performed to examine the efficacy in improving perioperative sedation and analgesia and in reducing postoperative agitation when used as a pre-anaesthetic medication in 1033 children. The authors concluded that DEX as a premedication is superior to midazolam in ensuring satisfactory levels of sedation in children undergoing surgery, both at separation from parents and at emergence. This is in contrast with the findings of a recent meta-analysis that compared the use of DEX and midazolam as premedication in 829 children; this study did not show any superiority of DEX in ensuring satisfactory levels of sedation at induction of anaesthesia. The major limitations of both studies are the significant heterogeneity between studies in the scales and measures used for sedation and evaluation of children’s anxiety, differences in the anaesthesia protocols, and differences in the doses.

The future of using DEX as a premedication is not clear. Dexmedetomidine is characterized by an easy and quick arousal from sedation resembling natural sleep, which makes it theoretically a promising premedication. In contrast, its slow onset makes it an unsuitable substitute for oral midazolam. More prospectively randomized controlled trials are still required to identify the optimal doses and appropriate monitoring of DEX use for premedication.

**Table 2** Summary of various dosing regimens and routes of administration for perioperative dexmedetomidine

<table>
<thead>
<tr>
<th>Application</th>
<th>Route</th>
<th>Dose range</th>
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<tbody>
<tr>
<td><strong>Preoperative applications</strong></td>
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<tr>
<td>Anxiolysis</td>
<td>Buccal</td>
<td>1 µg kg$^{-1}$</td>
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<tr>
<td></td>
<td>Intranasal</td>
<td>0.5–2 µg kg$^{-1}$</td>
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<tr>
<td><strong>Intraoperative applications</strong></td>
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<td></td>
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<tr>
<td>Airway procedures</td>
<td>I.V.</td>
<td>Loading dose: 0.5–2 µg kg$^{-1}$ over 10 min followed by an infusion of 0.5–3 µg kg$^{-1}$ h$^{-1}$</td>
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<tr>
<td>Neurosurgical procedures</td>
<td>I.V.</td>
<td>0.1–0.5 µg kg$^{-1}$ h$^{-1}$ (a target plasma concentration of 0.4 ng ml$^{-1}$)</td>
</tr>
<tr>
<td>Posterior spine fusions</td>
<td>I.V.</td>
<td>0.1–0.5 µg kg$^{-1}$ h$^{-1}$</td>
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<tr>
<td>Brain tumour and epileptic seizure</td>
<td>I.V.</td>
<td>0.5 µg kg$^{-1}$ bolus and 0.5 µg kg$^{-1}$ h$^{-1}$ infusion</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>I.V.</td>
<td>0.5–1 µg kg$^{-1}$</td>
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<tr>
<td>Applications to benefit the recovery period</td>
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<tr>
<td>Adenotonsillectomy</td>
<td>I.V.</td>
<td>0.5–1 µg kg$^{-1}$</td>
</tr>
<tr>
<td>Postoperative shivering</td>
<td>I.V.</td>
<td>0.5 µg kg$^{-1}$</td>
</tr>
<tr>
<td>Postoperative emergence agitation</td>
<td>I.V.</td>
<td>0.2–1 µg kg$^{-1}$</td>
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**Intraoperative applications**

**Airway procedures**

Airway procedures, rigid bronchoscopy in particular, can be challenging because they often involve patients who are respiratory compromised, have apnoea (obstructive or central), may be an aspiration risk, and may require spontaneous ventilation for the benefit of the procedure and diagnosis. Total i.v. propofol anaesthesia, with or without remifentanil, is a common technique. Challenges with this technique include the ability to maintain spontaneous respiration, protect the airway (a particular concern in patients with aspiration risk), and prevent laryngospasm. Comparatively, DEX offers some advantages; in contrast to other agents, DEX converges on sleep pathways at the locus coeruleus and is associated with changes in neuronal activity similar to those seen in deeper stages of non-rapid eye movement sleep, without significant respiratory depression.

The ability to maintain spontaneous ventilation and airway tone makes DEX an attractive consideration, particularly for children with severe preoperative airway impairment. Previous reports have demonstrated that for rigid bronchoscopy, DEX offers advantages of obtunding airway reflexes while maintaining stable haemodynamic and respiratory profiles in spontaneously ventilating children. Even at higher than recommended doses (3 µg kg$^{-1}$ h$^{-1}$), DEX maintains airway patency and tone, even in children with obstructive sleep apnoea, making it an ideal choice for sleep endoscopy and dynamic airway imaging. Both sleep endoscopy and dynamic airway imaging favour techniques that mimic physiological sleep and avoid any airway interventions (including oral and nasal airways) that alter the child’s natural physiological and clinical condition.

Dexmedetomidine has also been described for other airway procedures, including open thyroplasty with vocal cord medialization, a treatment of dysphonia. To optimize surgical repair, the patients need to be awake or lightly sedated during the procedure. The anaesthesia challenges require that the non-intubated patient has adequate anxiolysis, sedation, and analgesia while maintaining the ability to phonate on command. Dexmedetomidine has also been shown to be a valuable aid for other airway procedures, during which it, in combination with local anaesthetic, has maintained spontaneous ventilation and patient cooperation during laryngoplasty. Incorporating and expanding the applications of DEX into appropriate paediatric airway surgeries will be invaluable, as it has already been successfully implemented for children at risk of airway collapse or a difficult airway. By maintaining spontaneous ventilation and avoiding respiratory depression, DEX has been useful for those at risk of suffering fatal cardiopulmonary, respiratory, and cardiovascular complications.
Neurosurgical procedures

Dexmedetomidine has been used as an adjunct to total i.v. anaesthesia in the perioperative regimen of posterior spine fusions, lowering the propofol and sevoflurane requirements and facilitating intraoperative wake-up tests.41 42 A target plasma concentration of DEX 0.4 ng ml−1 and propofol 2.5 μg ml−1 seems to have minimal effect on motor-evoked potentials. Higher plasma DEX concentrations, however, may attenuate the amplitude of motor-evoked potentials.15 Dexmedetomidine (0.2–0.7 μg kg−1 h−1) can also be used as an adjunct to establish and maintain controlled hypotension (mean arterial blood pressure of 55–65 mm Hg) during anterior spinal fusion.44 Its concomitant effect, when used for controlled hypotension, on cardiac function, cerebral blood flow, and cerebral perfusion pressure has not been carefully evaluated.

Brain mapping and neurophysiological testing have recently become an integral part of many neurosurgical techniques; in particular, brain tumour and epileptic seizure foci resection. The anaesthetic regimen requires anaesthesia during the craniotomy, followed by an awake, comfortable, and cooperative patient during lesion resection in order to provide near-instantaneous neurological feedback. The challenge is to achieve an adequate anaesthetic depth without untoward incidents of airway obstruction, respiratory depression, hyperventilation, coughing, or hypotension. Dexmedetomidine 0.1–0.3 μg kg−1 h−1 maintains respiratory drive and airway patency while still enabling the child to be awakened and responsive to verbal stimulation for functional brain mapping.45 Dexmedetomidine preserves epileptiform activity in children with seizure disorders, facilitating localization and identification of seizure foci.26 46 There is literature to suggest that in adults it may be neuroprotective, also decreasing cerebral blood flow in proportion to a decrease in cerebral metabolic rate.47

Cardiac surgery

α2-Adrenergic agonists have been used in the perioperative period for adult and paediatric cardiac surgery in order to blunt the sympathetic response, provide analgesia and sedation in the postoperative period, maximize neurocognitive function, and expedite extubation.48–50 A recent retrospective study suggests that perioperative DEX administration during cardiac surgery in adults (vs no DEX) was associated with a decrease in postoperative delirium and 1 yr mortality.51 In children (1–6 yr old) undergoing cardiac surgery, i.v. DEX (0.5 μg kg−1 bolus and 0.5 μg kg−1 h−1 infusion) attenuates the haemodynamic and neuroendocrine (epinephrine, norepinephrine, blood glucose, and plasma cortisol) responses at incision, sternotomy, and postbypass.52 Whether there is a long-term benefit in reducing delirium and mortality in the paediatric population has yet to be determined.

Dental procedures

Dexmedetomidine administered by different routes has been trialled for adult and paediatric dental sedation.53–59 Although the bioavailability of DEX is poor by the oral route, a prospective, triple-blind, randomized study compared the efficacy and safety of one of three doses of oral DEX (3, 4, and 5 μg kg−1) combined with ketamine (8 mg kg−1) for paediatric dental sedation. Children who received the combination with DEX 5 μg kg−1 had faster onset, superior intra- and postoperative analgesia and exhibited an anterograde amnesia.60

Regional anaesthesia

Clonidine, another α2-adrenergic agonist, has been administered with regional anaesthesia (epidural, intrathecal, and peripheral nerve block) for decades.61 Dexmedetomidine has recently been described with regional blocks in both adults and children. In adults, a meta-analysis of 16 randomized controlled trials including 1092 adults compared outcomes between DEX (intrathecal, epidural, or caudal) and bupivacaine or ropivacaine. Dexmedetomidine was found to decrease the pain and prolong the analgesia. Although there was an increased incidence of bradycardia in the DEX group, it was not associated with hypotension and did not warrant treatment.62 Likewise, the combination of caudal DEX and bupivacaine (1 μg kg−1 and 2.5 mg kg−1, respectively) in children has been shown to decrease the sevoflurane requirements, incidence of emergence agitation, and requirement for adjuvant postoperative analgesics and to increase the duration of postoperative pain relief compared with bupivacaine alone. The addition of caudal DEX to bupivacaine did not affect the haemodynamic response.63 Epidural DEX and clonidine produced similar analgesia, duration of action, and haemodynamic profile when used with bupivacaine (2.5 mg kg−1) for lower abdominal surgery in children.64 A recent meta-analysis concluded that the addition of DEX to a caudal anaesthetic provided an extended duration of postoperative pain relief in 328 paediatric patients. There was no statistically significant effect on haemodynamics and adverse events with the addition of DEX to the local anaesthetic. Subgroup analysis showed no advantage of caudal DEX at 2 μg kg−1 compared with 1 μg kg−1 in terms of analgesia.65

Administration of DEX by the neuraxial route is off label, and the safety has not been established in humans. In animal models, perineural administration of DEX attenuated inflammation in the sciatic nerve by reducing inflammatory cytokine concentrations.66 In rabbits, however, epidural DEX elicited what appeared to be a demyelination of oligodendrocytes in the white matter of the spinal cord.67 Future studies are warranted in order to support or dispel the concerns regarding neurotoxicity of DEX.

Caution should be exercised when DEX sedation is used in infants and neonates receiving epidural analgesia without support from external warming devices. Infants depend more on non-shivering thermogenesis than on shivering and vasocostriction. Dexmedetomidine interferes with non-shivering thermogenesis and can create the potential for development of hypothermia as a result of inhibition of lipolysis by postsynaptic α2 receptors. Recently, a 2–day-old neonate developed hypothermia (33°C axillary) and bradycardia that was unresponsive to atropine (75 beats min−1) in the postoperative period while being sedated with DEX and receiving epidural analgesia, without using external warming devices.68 The infant’s temperature was restored to 37.6°C within 3 h, without sequelae, after reducing DEX infusion and applying an external heat source.

Dexmedetomidine applications for ambulatory procedures

There is a paucity of literature describing DEX for ambulatory procedures, perhaps because its half-life and analgesic properties do not lend themselves to the fast pace (induction, emergence, and recovery) of most ambulatory schedules. Administration of DEX has been described for the pressure-equalizing myringotomy tube procedure, but without an advantage over the more common options of intranasal fentanyl or paracetamol.69 Likewise, when used for upper gastrointestinal endoscopy in children, DEX was not found to offer any advantages either alone or in combination with propofol.70
Dexmedetomidine for painful procedures

Although well described and successful for sedation for non-painful procedures, DEX has been largely unsuccessful in providing adequate analgesia when used alone for painful procedures.12-24 Dexmedetomidine i.v. with ketamine i.v. may be a successful combination, with relatively fast onset and amnesia, sedation, analgesia, and haemodynamic stability (Figs 1 and 2).75-76 This technique has been described in adults and children for extracorporeal shock-wave lithotripsy, lumbar puncture, bone marrow biopsy, burn dressing changes, chest tube insertion, and femoral cut-down for tunnelled central venous catheter placement.81 In the animal model, DEX has been shown to have beneficial effects on the mitochondrial membrane in ischaemic rats.82 If this quality extends to humans, DEX could offer advantages for use in children with mitochondrial disorders or those who require an i.v. technique because of risk of malignant hyperthermia.

Perioperative applications to benefit the recovery period

Emergence agitation, relatively common for paediatric ambulatory procedures, is associated with morbidity in the recovery period.83-86 A recent meta-analysis found that α2-agonists (clonidine or DEX) given by the oral, i.v., or caudal route had a prophylactic effect in preventing emergence agitation in children anaesthetized with sevoflurane or desflurane.85 Dexmedetomidine 0.25-1 μg kg⁻¹ can prevent and treat postoperative agitation in children.79-88 Perioperative infusion of 0.2 μg kg⁻¹ h⁻¹ decreases the incidence and frequency of postoperative agitation in children after sevoflurane without prolonging the time to extubation or discharge.87 Compared with placebo, DEX (0.5 and 1 μg kg⁻¹) decreases the incidence of emergence agitation from 47.6 to 4.8%, albeit with a slightly prolonged emergence and time to extubation.87-88 In comparison with fentanyl (1 μg kg⁻¹), intraoperative DEX (2 μg kg⁻¹ bolus followed by 0.7 μg kg⁻¹ h⁻¹) reduced the incidence of severe emergence agitation, the postoperative opioid requirements, and the episodes of desaturation in children with obstructive sleep apnoea after tonsillectomy and adenoidectomy.80 The optimal method (duration over which DEX should be administered and route of administration) and dosing of DEX for emergence agitation has not been determined in children. A rapid bolus may be preferable to a prolonged bolus over 10 min. Rapid DEX administration (<5 s) of 0.25-0.5 μg kg⁻¹ i.v. has been described in children undergoing cardiac catheterization without haemodynamic consequence.81 Whether this dosing, route, and rate of administration will be effective in treating emergence agitation without clinically significant haemodynamic effect warrants future investigation.

Dexmedetomidine has been successful to treat postoperative shivering. The exact mechanism of this effect is unknown. In a prospective, non-randomized open-label study in 24 children (7–16 yr old), DEX 0.5 μg kg⁻¹ i.v. permanently ablated postoperative shivering within 5 min.82 Although intraoperative DEX has been reported to reduce opioid consumption in children, the opioid-sparing effects of DEX in children are still not completely understood. In adults, intraoperative DEX has been shown in a recent meta-analysis to decrease postoperative pain scores and morphine consumption.83 A recent meta-analysis of 11 randomized controlled trials examined the effects of intraoperative DEX vs placebo or opioids on postoperative pain, analgesic consumption, and adverse events

Fig 1 In this study, 22 children (aged 5–17 yr) undergoing electrophysiological study and ablation for supraventricular tachycardia were enrolled. Changes in heart rate with dexmedetomidine and dexmedetomidine+ketamine administration were measured. The increase in mean arterial pressure was associated with a significant decrease in heart rate after dexmedetomidine (P<0.001), followed by a return towards baseline after co-administration of ketamine (1 mg kg⁻¹) followed by continuous infusion (1 mg kg⁻¹ h⁻¹; P=0.005). Haemodynamic and electrophysiological changes with dexmedetomidine and dexmedetomidine+ketamine administration were measured. Baseline denotes measurements obtained before administration of any study drug (time point 1), after dexmedetomidine denotes measurements obtained after dexmedetomidine administration (time point 2), and dexmedetomidine+ketamine denotes measurements obtained after dexmedetomidine and ketamine administration (time point 3). From Char and colleagues,75 with permission.

Fig 2 In this study, 22 children (aged 5–17 yr) undergoing electrophysiological study and ablation for supraventricular tachycardia were enrolled. Changes in mean arterial pressure (MAP) with dexmedetomidine and dexmedetomidine+ketamine administration were measured. A significant increase in MAP was seen compared with baseline after loading of dexmedetomidine (1 μg kg⁻¹) followed by continuous infusion of dexmedetomidine (0.7 μg kg⁻¹ h⁻¹; P<0.001). This returned to baseline 5 min after co-administration of ketamine (1 mg kg⁻¹) followed by continuous infusion (1 mg kg⁻¹ h⁻¹; P<0.001). Haemodynamic and electrophysiological changes with dexmedetomidine and dexmedetomidine+ketamine administration were measured. Baseline denotes measurements obtained before administration of any study drug (time point 1), after dexmedetomidine denotes measurements obtained after dexmedetomidine administration (time point 2), and dexmedetomidine+ketamine denotes measurements obtained after dexmedetomidine and ketamine administration (time point 3). From Char and colleagues,75 with permission.
in 434 children undergoing surgery. The study demonstrated that intraoperative use of DEX provided similar postoperative analgesia compared with intraoperative opioid use and better postoperative analgesia compared with placebo use. In a double-blind controlled trial, children who received high doses of DEX (2 and 4 μg kg\(^{-1}\) i.v.) immediately after tracheal intubation had a lower opioid requirement and longer opioid-free interval in recovery than the group that received a single i.v. dose of fentanyl (1 or 2 μg kg\(^{-1}\)). Dexametomidine may be an option to minimize intraoperative narcotic use, particularly for tonsillectomies. Dexametomidine 1 μg kg\(^{-1}\) and morphine 100 μg kg\(^{-1}\) i.v. have exhibited comparable morphine-sparing effects and time to discharge readiness after tonsillectomy and adenoidectomy. This opioid-sparing anesthetic and recovery profile of DEX in children after tonsillectomy and adenoidectomy may be particularly advantageous in those at risk of postoperative apnoea or respiratory compromise.

Precautions when using dexmedetomidine

Clinicians should be familiar with the varied haemodynamic responses to DEX. In children, the extent of these haemodynamic variations is related to the serum concentrations. At higher doses, with presumably higher serum concentrations, a biphasic response on blood pressure is observed. In general, at serum concentrations >1 μg litre\(^{-1}\), the blood pressure changes from a mild decrease from baseline to an elevation. Although decreases in heart rate and a biphasic effect on blood pressure are observed with increasing doses of DEX, the literature supports that concurrent haemodynamic collapse or need for pharmacological resuscitation does not occur. Rather, a recent publication suggests that immediate action to treat bradycardia associated with \(\alpha_2\)-adrenergic agonists in children is required only if concomitant vital signs are abnormal, if bradycardia is caused by a serious primary bradyarrhythmia, or both. The occurrence of hypotension can be attenuated by pretreatment with balanced salt solution boluses.

Bradycardia or a decrease in resting heart rate (up to a 30% decrease from baseline) is expected and should be considered as a predictable physiological response anticipated with DEX. The heart rate responses are rarely of clinical significance, and they do not usually warrant treatment. Extreme bradycardia can occur if DEX is administered to a patient receiving digoxin, and syncope, probably from a vasovagal response, has been cited in the literature and in the package insert. Although there are no absolute contraindications to DEX in the literature or package insert, the authors recommend that DEX be avoided or carefully considered before administration in children receiving digoxin, \(\beta\)-adrenergic blockers, calcium channel blockers, or other agents that predispose to bradycardia or hypotension.

Caution should be exercised when administering anticholinergics to treat isolated DEX-associated bradycardia in children, because i.v. glycopyrrolate has been shown to elicit immediate, significant hypertension. Electrocardiographic abnormalities as noted by R–R prolongation and junctional escape rhythms at 2 μg kg\(^{-1}\), administered as a single dose, have been reported with DEX use. The concomitant administration of DEX with medications that have negative chronotropic effects (propofol, pyridostigmine, succinylcholine, and remifentanil) may potentiate vagotonic or negative chronotropic effects. Sinus arrest has been shown in a young healthy adult volunteer 3.5 h after DEX administration. Asystole after atropine 0.5 mg to treat a heart rate in the 30s, was reported in a 52-yr-old woman receiving a DEX infusion during general anaesthesia (fentanyl, propofol, and sevoflurane). Clinicians should be familiar with the haemodynamic responses associated with rapid loading or bolus administration of DEX. Although the labelling recommends loads be administered over 10 min, rapid boluses in small doses (0.25 and 0.5 μg kg\(^{-1}\)) have been well tolerated in children undergoing cardiac catheterization with volatile anaesthetic after cardiac transplant. The denervation of the sinoatrial node, however, should be considered as a potential factor for the minimal observed response. A recent study examined the dose–response to a DEX bolus over 5 s administered to healthy children. The maximal elevation in mean arterial pressure was a 33% increase from baseline, and the maximal decrease in heart rate was 36% from baseline (Fig. 3). An ED\(_{50}\) (no haemodynamic response in half the subjects) of 0.49 μg kg\(^{-1}\) was extrapolated to avoid haemodynamic responses in half the subjects. Nevertheless, the authors do not condone off-label, rapid administration of DEX boluses until further literature is published to support the safety of this practice.

There is limited information regarding the effect of DEX on the pulmonary vasculature and pulmonary vascular resistance (PVR) in children with varying degrees of pulmonary hypertension. In an animal model, DEX (2 μg kg\(^{-1}\) over 1 min) transiently increased mean pulmonary artery pressure and PVR. Similar transient pulmonary haemodynamic changes have been shown in healthy adult volunteers subjected to increasing DEX infusions to a plasma concentration of 1.9 ng ml\(^{-1}\). After cardiac surgery, DEX doses as permitted by labelling had minimal effect on the pulmonary artery pressure, leaving ventricular function unchanged. The effect of DEX on infants and children with pulmonary hypertension can be variable. Children with...
pulmonary hypertension, compared with those without, both demonstrated no significant change in pulmonary vascular resistance, pulmonary artery pressure, and cardiac index in response to DEX bolus of up to 1 μg kg⁻¹ followed by a continuous infusion of 0.7 μg kg⁻¹ h⁻¹. In contrast, a recent FDA-monitored study evaluating the effect of DEX on PVR in children with pulmonary hypertension was terminated because of increased PVR in addition to premature ventricular complexes, bradycardia (<60 beats min⁻¹), and hypotension in one of the subjects (Table 3). Another prospective observational pilot study demonstrated that DEX after congenital cardiac surgery did not have a demonstrable effect on pulmonary artery pressure of children who did not have pulmonary hypertension. Given the potential impact of these findings on infants and children with pre-existing pulmonary hypertension, future studies are warranted before advocating routine use of DEX in this patient population.

End-organ effects of dexmedetomidine

Effect of dexmedetomidine on the kidney

Dexmedetomidine causes diuresis by reducing vasopressin secretion, enhancing renal blood flow and glomerular filtration, and increasing urine output. Recent animal studies showed that it can also protect against radiocontrast nephropathy by preserving outer medullary renal blood flow. One should also be aware of the potential development of polyuric syndrome when DEX is used. A recent case report in an adult patient who underwent posterior spinal fusion under general anaesthesia with isoflurane, and sufentanil, DEX, and lidocaine infusions showed that urine output increased from 150 to 950 ml h⁻¹. An increasing serum sodium, low urine specific gravity, and increased serum osmolarity occurred simultaneously with the polyuria. Within 2 h of discontinuing the DEX infusion, urine output greatly decreased, and all signs of the polyuric syndrome resolved spontaneously in 24 h.

Despite the diuretic effect of DEX in adults, the 74% increase in urinary output that has been seen for up to 4 h after cardiac surgery does not affect renal function when compared with placebo in a double-blind design. There are some data to support a renoprotective effect of DEX. A retrospective review of cardiac and thoracic surgeries in adults who received a DEX infusion of up to 0.6 μg kg⁻¹ h⁻¹ for up to 24 h after surgery revealed a decline in 30 day mortality and decrease in serum markers for acute kidney injury. Similar results were found in children who received i.v. iodine contrast for cardiac angiography. Compared with the control group, children 6 months to 6 yr of age had decreased elevation in plasma endothelin, renin, and markers of acute renal injury. Future studies are warranted to delineate the patient population, surgical procedures, and resultant effect of DEX on renal function.

Effect of dexmedetomidine on the brain

There is no literature to date that describes the effect of DEX on memory acquisition, recall, and amnesia in children. The challenges associated with designing and successfully implementing such a trial in children may have limited the conducting of such studies. In adults though, DEX dosing has been associated with the depth of sedation and specific aspects of memory acquisition. With increasing serum concentrations of DEX, there is a decrease in the Observer Assessment of Alertness/Sedation (OASS) scale and visual analog scale. With increasing plasma concentrations
of DEX administered to healthy adult volunteers, the correct recall or recognition of a picture decreased (Fig. 4).119

In adults, it has been suggested that on continuous-recognition tasks using photograph recognition to differentiate working from long-term memory, DEX impairs familiarity more than recognition.120 Whether a similar response is seen in children has been clarified, the authors suggest that synergistic administration of amnestic medications be administered if recall is impaired, and further studies are required. The adverse event profile of benzodiazepines, propofol, and opioids, alone and in combination, leaves a window of opportunity to consider alternative agents that may improve outcome and minimize risk. Particularly in patients with respiratory compromise, for whom the preservation of spontaneous ventilation and airway tone is preferable, or those for whom the preservation of neuromonitoring with or without patient responsiveness is the goal, DEX should be seriously considered. An in-depth understanding of the pharmacological, pharmacokinetic, and pharmacodynamic effects of DEX is critical to maximize its safe use in paediatric perioperative applications.

**Future considerations**

There has been growing interest and support, as evidenced in the burgeoning literature over the past few years, that DEX can be beneficial in the paediatric perioperative period. Recently, its potential as being organ protective, albeit mostly for animals and at the bench-top level, poses promise for future studies and for valuable clinical applications in humans.

One of the most interesting and valuable future directions of DEX research involves its potential for neuroprotection. Particularly in the paediatric population, the issue of anaesthetic-induced neurotoxicity has continued to gain attention and research support over the past decade, with some studies have suggested that inhalation and i.v. anaesthetics may both cause neurotoxicity.121–124 The laboratory and animal studies in the last decade indicate that DEX exhibits long-term effects on the brain, including neuroprotection through α2-adrenergic receptors.125 To date, only DEX and possibly xenon have been proposed to be ‘safe’.126 Further research is warranted to examine the existence of associations between early anaesthetic exposure to DEX and long-term neurocognitive function.

In conclusion, data regarding the perioperative ‘off-label’ use of DEX in the paediatric population are promising but still limited, and further studies are required. The adverse event profile of benzodiazepines, propofol, and opioids, alone and in combination, leaves a window of opportunity to consider alternative agents that may improve outcome and minimize risk. Particularly in patients with respiratory compromise, for whom the preservation of spontaneous ventilation and airway tone is preferable, or those for whom the preservation of neuromonitoring with or without patient responsiveness is the goal, DEX should be seriously considered. An in-depth understanding of the pharmacological, pharmacokinetic, and pharmacodynamic effects of DEX is critical to maximize its safe use in paediatric perioperative applications.

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Reviewing the relevant literature: M.M., K.M.

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**Declaration of interest**

None declared.

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