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Master thesis | Original study

Dexmedetomidine as premedication in children: a narrative review

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Abstract

Background: **Emergence delirium is a frequent complication in children during recovery after general anesthesia. Dexmedetomidine, an α2-adrenergic receptor agonist, has significant sedative and analgetic actions, but there is still little evidence for the effects of premedication in the pediatric population.**
Objectives: **This study aimed to assess the effects of dexmedetomidine as a premedication drug in children.**
Methods: **A literature search was conducted for articles published in English that matched the keywords 'dexmedetomidine', 'premedication' and 'children' in PubMed, Embase and the Web of Science database to identify important literature such as randomized controlled trials (RCT), meta-analyses and systematic reviews regarding this issue. Additional papers were identified from the references of the retrieved literature.**
Results: **The results suggested positive effects on anxiety, emergence delirium, anesthetic requirements, pain, and a small positive effect on postoperative nausea and vomiting. Caution is advised because of the possible development of bradycardia and hypotension after bolus administration intravenously. However, dexmedetomidine did not cause any clinically significant cardiorespiratory events when administered intranasally. An important disadvantage of dexmedetomidine was a delay in extubation and emergence time. Nevertheless, preoperatively administered dexmedetomidine had no significant effects on the discharge from PACU and the hospital discharge.**
Conclusions: **Dexmedetomidine as premedication in children is valuable and safe. No severe adverse events were reported.**

Keywords: **Dexmedetomidine, premedication, children.**

Introduction

Every year worldwide, millions of children undergo surgery and require anesthesia. Premedication in children is favorable for separating them from their parents and reducing their anxiety and stress1. This facilitates the induction of anesthesia and could prevent emergence agitation. The ideal drug for premedication should have a minor effect on either hemodynamics or respiratory function and promote early recovery and hospital discharge. Several drugs have been investigated to achieve this goal in the past few years. Intravenous administration is not a standard premedication route because cannulation is painful and will frighten the child, and could lead to refusing any further contact with healthcare providers. Hence, several alternative drugs and administration routes were studied; for example, orally administered midazolam, today considered the gold standard drug for premedication by many anesthesiologists.

Dexmedetomidine (DEX), a highly selective α2-adrenergic receptor agonist, has sedative and analgesic actions via the locus coeruleus and the spinal cord and has minimal effects on respiratory rate or tidal volume[2,3]. The EEG activity is similar to natural sleep[4]. DEX is a shorter-acting drug than clonidine, and it is eight times more specific for α2- than for α1-receptors, particularly for the 2A-subtype, which causes to be more sedative than clonidine[5]. DEX has several sites of action. Firstly, a reduction of the sympathetic nervous system activity from the locus coeruleus and a decrease in catecholamine release follows when central α2A-receptors are activated[6]. Figure 1 shows a schematic overview of the most important site of action in the

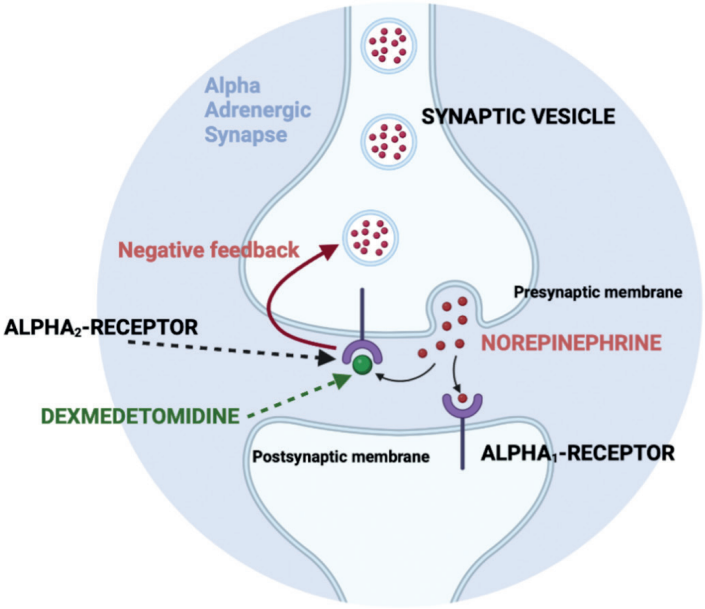

Fig. 1 — Schematic overview of the action of Dexmedetomidine on the alpha-adrenergic synapse in the central nervous system. The binding of DEX to the presynaptic α2-adrenergic receptor inhibits the release of norepinephrine, which inhibits sympathetic activity and modulates consciousness. This figure was made using Biorender.com with K.U. Leuven institutional access.

central nervous system. Secondly, the inhibition of the release of substance P and the activation of α2B-receptors at the dorsal horn of the spinal cord may be responsible for the analgesic effects of DEX6. Furthermore, DEX also stimulates peripheral α2-receptors in sympathetic nerve endings[7]. This leads to reduced opioid requirements. Amnestic properties are also reported[8]. For that reason, the use of DEX could be beneficial for surgical procedures in the outpatient setting[9].

The use of DEX is well described in adults, but there still needs to be more known about the pharmacological effects in the pediatric population. We performed this literature review regarding our interest in using DEX as premedication in children. In particular, we were interested in its anxiolytic effects, efficacy on parental separation, tolerance to the mask, the ability to prevent emergence agitation, effects on pain and postoperative nausea and vomiting events, possible side effects, and the effects on PACU and hospital discharge time.

Methods

Even though this is a narrative review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to search the literature (Figure 2) systematically[10]. We set up a literature search in PubMed, Embase, and the Web of Science database with the Medical Subject Heading (MeSH) search terms ("Dexmedetomidine") AND ("Premedication") AND ("Children"). This search strategy was developed in consultation with the KU Leuven Libraries. We identified more relevant studies by cross-referencing. The final update of this literature search was performed on the 23rd of March, 2022.

The search strategy yielded 815 articles. After deduplication, 594 articles remained. The final number of effectively analyzed reports we included was 70.

Exclusion criteria were observational studies, case reports, retrospective studies, nonoperating room use (e.g., treatment of delirium, sedation in the ICU), in vitro-studies, animal studies, studies in languages other than English, and articles older than 2003.

Results

Pharmacokinetics of dexmedetomidine

Pharmacokinetically, the intravenous administration of DEX in children has been well analyzed[11–15]. Even if noninvasive administration routes are well-described in children, the pharmacokinetics remain unclear. Some studies concluded that the bioavailability of DEX appears oral at 16%, but buccal at 82%, intranasal at 83,8%, and intramuscular at nearly 100% in a healthy adult population, due to avoiding first pass metabolism[9,16,17]. DEX is a highly lipophilic drug with wide-ranging tissue distribution. 94% of DEX in the blood is bound to plasma proteins, mainly albumin and α1-acid glycoprotein[17]. In healthy children, the half-life of

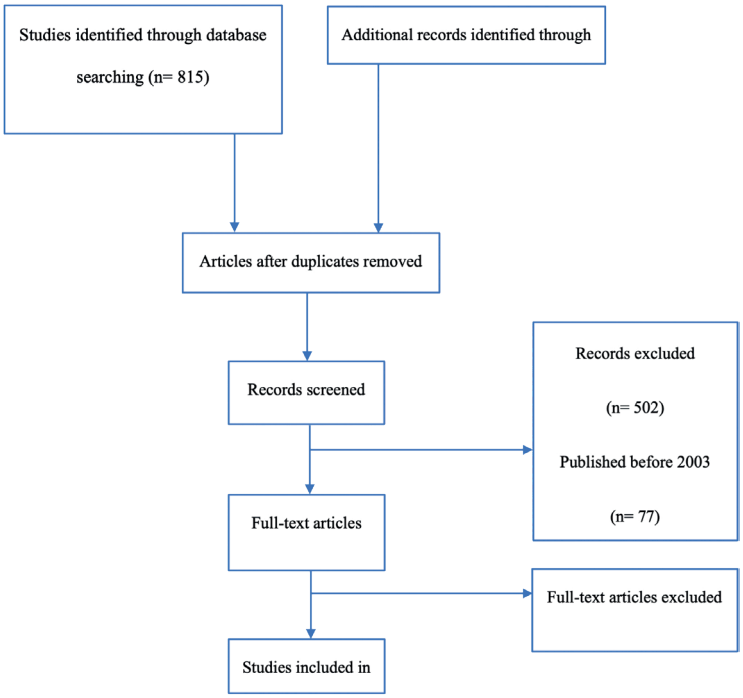

Fig. 2 — Flowchart of selection of studies for inclusion in this literature review. Adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria.

rapid (α) phase redistribution is approximately seven minutes; clearance is approx. 15 mL kg-1 min-1, and the terminal (β) elimination half-life is approx. two hours[11,18]. DEX is nearly completely biotransformed by the hepatic enzymes (uridine 5'-diphospho-glucuronosyl-transferase and cytochrome P4502A6) to inactive metabolites, which are excreted in bile and through renal pathways[9]. Only a tiny part of DEX will be eliminated unaffected in urine and feces[9]. Sex, environmental, and genetic factors could affect the metabolic activity of CYP2A6[9]. The best model to predict the effects of DEX is a two-compartment model with first-order elimination from the central compartment[11].

Pharmacodynamics of dexmedetomidine

Anxiolytic effects of dexmedetomidine

An important meta-analysis revealed that DEX enhanced preoperative sedation and at least similar anxiolysis as midazolam[19]. Other studies showed that DEX, used as premedication in children, effectively produces sedation and reduces anxiety, resulting in better parent separation and better acceptance of mask inhalation induction[1,20–23]. Additionally, premedication with DEX showed promising results in smoothly obtaining intravenous cannulation[19]. A recent systematic review suggests that intranasal DEX provides more profound sedation than conventional sedatives (e.g. oral midazolam)[24]. Linares et al. used the m-YPAS to delineate better the sedative effects of DEX from the anxiolytic effects[25]. They concluded that intranasally administered DEX was superior to oral midazolam in reducing preoperative anxiety in preschool-aged children[25].

Effects of dexmedetomidine on emergence agitation

A recent meta-analysis showed that α2-adrenergic receptor agonists (clonidine or DEX) significantly prevent emergence agitation in children anesthetized with sevoflurane or desflurane[26]. Moreover, Lin et al. reported that premedication with intranasal DEX diminished the incidence of emergence agitation in children anesthetized with sevoflurane for cataract surgery[27]. A recently published RCT learned that emergence agitation was lower in patients who received intranasal DEX than those who were given oral midazolam[28].

Analgesic effects of dexmedetomidine

Several studies support pain relief in children when treated with DEX in a dose-dependent manner[29–32]. Furthermore, DEX decreased the need for pain medication in the PACU[33]. A systematic review by Jong et al. reported a reduced need for rescue analgesics after DEX compared to oral midazolam or intranasal clonidine[1].

Effects of dexmedetomidine on anaesthesia requirements

Several authors published a dose-dependent anesthesia-sparing effect in children who received DEX[29,31,34–39]. A randomized controlled trial demonstrated that premedication with intranasal

DEX at 1 µg kg-1 and 2 µg kg-1 could reduce the end-tidal concentration of sevoflurane required for smooth tracheal intubation by 20% and 35%, respectively[34]. No complications were observed. Preoperatively administered DEX also reduces the propofol dose required for sedation, induction, and maintenance of anaesthesia[36].

Hemodynamic effects of dexmedetomidine

As described above, DEX tends to activate central α2A-adrenergic receptors, which leads to a decrease in catecholamine release, especially norepinephrine. If peripheral α2B-adrenergic receptors are activated, will this induce vasoconstriction[11]. This decrease in the sympathetic outflow from the CNS and the peripheral vasoconstriction leads to a reflex response at the sinus node, which causes a decrease in heart rate[9]. A biphasic response in mean arterial pressure (MAP) has been reported, especially after bolus administration of DEX[13]. Inhaled anesthetics could accentuate a decreased MAP by DEX due to their vasodilatory effects.

Respiratory effects of dexmedetomidine

A randomized controlled trial (RCT) of 90 children, aged between 2 and 9, who were anesthetized for an elective adenotonsillectomy, were randomly allocated to receive a preoperative bolus of intranasal DEX or midazolam[40]. The DEX group significantly reduced laryngospasm compared with the midazolam group. Moreover, the results of an RCT published by Yanmei et al. learned that premedication with DEX, compared to saline, reduces coughing, breath-holding and laryngospasm during foreign body removal by bronchoscopy[41].

Neuroprotective effects of dexmedetomidine

There is limited literature about the neuroprotective effects in children treated with DEX. Intranasally administered DEX in children does not alter the seizure threshold or influence spike-wave activity during electroencephalogram tracings[42].

Effects of dexmedetomidine on postoperative nausea and vomiting

Some older studies showed no significant difference in postoperative nausea and vomiting (PONV) in children who received DEX[7,36,43,44]. In contrast, a recent meta-analysis reported that the incidence of PONV was significantly lower in children treated with DEX than in children under saline administration[45].

Effects of dexmedetomidine on Post Anesthesia Care Unit (PACU) and hospital discharge time

Most studies showed an increased extubation time when children were treated with DEX[35,37,45,46]. Due to the elimination half-life of DEX, approximately two hours, children in the DEX group needed more time to regain consciousness (emergence time) compared with children in the control group[38,45,47]. In contrast, most studies showed no significant differences in time to discharge from the PACU between DEX and other sedative agents[19,30,47–49]. Furthermore, an RCT that included 100 children between 1 and 7 years old compared intranasal DEX with placebo, midazolam, or intranasal fentanyl. There were no significant differences in total time in the PACU or hospital discharge between the four groups[50]. In addition, Isik et al. reported no differences between intravenous DEX vs placebo in the discharge time to the recovery room and the hospital discharge time after sevoflurane anesthesia without surgery (anesthesia for MRI imaging)[51].

Effects of dexmedetomidine on thermal regulation

DEX intervenes with temperature management by reducing vasoconstriction, shivering and nonshivering thermogenesis[52]. Along with these effects, stimulation of hypothalamic α2-adrenergic receptors declines centrally mediated heat production[52]. Additionally, DEX suppresses lipolysis through postsynaptic α2-adrenergic receptors, which hinders nonshivering thermogenesis in infants, generating the possibility of developing hypothermia[52].

Routes of administration

The most widely used route for all drugs is the oral one. On the one hand, DEX is an odorless, colorless, and tasteless drug. On the other hand, oral administration results in low bioavailability[19]. Transmucosal administration, such as buccal, sublingual, or intranasal (IN), is successful due to the high mucosal blood supply and due to a bypass of the first-pass metabolism[19]. There is evidence that intranasally administered DEX could also produce effects by direct nose-to-brain action, probably via the olfactory and trigeminal nerves, thus bypassing the blood-brain barrier[22]. Studies showed that premedication with intranasal midazolam could cause nasal irritation, but children given IN DEX did not show any nasal discomfort[53].

Intranasal DEX could be administered by drops or a mucosal atomizer device (MAD, figure 3). The pharmacokinetics of both administration routes are comparable, with no important difference in bioavailability, median onset time, and duration of sedation[2]. Xie et al. reported a reduced pain perception during venous cannulation using a MAD[54]. Presumably, the MAD avails of the nasal cavity's rich vascular supply and large mucosal surface area. In children, they reported a median

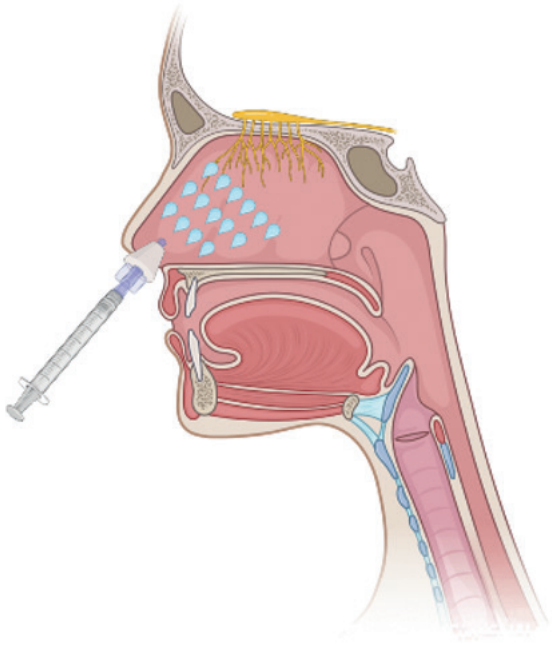

Fig. 3 — Schematic overview of the working mechanism of the mucosal atomizer device (MAD). This figure was made using Biorender.com with KU. Leuven institutional access.

onset and duration of sedation of 25 (25–30) and 85 (55–100) minutes, respectively[4]. Even though higher peak plasma concentrations were obtained by intravenous administration, the sedation depth is similar once it occurs[2].

Comparison with other sedatives

A few papers reported intranasal DEX, compared with per os or intranasal midazolam, to be more effective44,53. In most literature, DEX had similar sedative effects as intranasal ketamine32, intranasal fentanyl50, benzodiazepines40,55, and chloral hydrate56–58. In addition, a recently published meta-analysis reported that transmucosal administration of one µg kg-1 DEX administered 45 minutes preoperatively provided similar anxiolysis and comparable depth of sedation as 0.5 mg kg-1 oral midazolam, administered 30 minutes preoperatively[59]. Recovery and time of discharge were similar between the groups[59]. The major referred disadvantage of DEX was the slower onset of action[60].

Recommended dosages

The optimal dosing of DEX as premedication is not well known. Literature showed that the dose of 0.5 µg kg-1 of intranasal DEX was inadequate for effective sedation[44]. Although larger doses were investigated for procedural sedation, intranasal DEX at two µg kg-1 could only reduce anxiety but failed to achieve profound sedation to perform a procedure[22,61]. Furthermore, Yuen et al. compared two intranasal doses of DEX for premedication in children[62]. They concluded that intranasal drops of DEX in doses of 1 and 2 µg kg-1 produced comparable satisfactory sedation in children aged 1-4[62]. A two µg kg-1 dose had a higher rate of adequate sedation in children aged 5-8. They did not report a higher rate of adverse effects[62].

Need of monitoring

Most studies showed a very low incidence of adverse effects in children after receiving premedication[19,21,22,44,63–67]. In a survey by Yuen et al., no child had a reduced oxygen saturation below 95% during the monitoring time after premedication[44]. A recent meta-analysis reported mild bradycardia and hypotension after administration of intranasal DEX. However, none of the subjects needed treatment[64]. In contrast, a case report has been published about a healthy pediatric patient with symptomatic bradycardia after the administration of intranasal DEX[68].

Discussion

In the last decade, the perioperative use of DEX in children has been a scorching topic of publications. Most results come from Asia because the drug still needs to be approved in Europe and the USA for noninvasive administration in children. The main reason to develop knowledge about DEX is that no technique or premedication drug has been entirely satisfactory in children. In search for a sedative agent with a high success rate, well accepted by children, that is easy to use, and with a good safety

profile, we conducted a literature search on DEX as premedication in children. The found literature, mostly RCTs and systematic reviews, investigated the safety and efficacy of DEX, especially when administered intranasally.

Untreated anxiety could result in a problematic induction of anesthesia, higher anesthetic requirements, increased postoperative pain, emergence agitation, and even postoperative behavioral issues. In this context, DEX is known to have very potent sympatholytic properties[63]. DEX effectively reduces anxiety resulting in better mask acceptance and parental separation. Furthermore, the primary pharmacological aspects of DEX, such as the sedative effects that mimic the natural sleep cycle, the ability to reduce the anesthetic requirements, and the relief of pain, may decrease causative factors for emergence agitation.

Administration of intranasal DEX showed a lower incidence of respiratory depression and hemodynamic instability than intravenous use because of intranasal DEX's slower and more gradual onset time compared to intravenous administration[69]. Evidence suggests that possible adverse cardiorespiratory events were self-resolving because no resuscitative procedures were described. Nevertheless, the American Academy of Pediatrics has recommended at least pulse oximetry as monitoring when sedating children[70]. In that case, we suggest not administrating DEX on the ward before transport to the OR but only where monitoring is available. Most carefully, we recommend limiting intranasal DEX to children without severe bradycardia, irregular cardiac conduction, hypotension, or use of other sympatholytic agents[24]. Furthermore, DEX interferes with thermoregulation in children by negative effects on shivering and vasoconstriction. Stimulation of hypothalamic α2-adrenergic receptors declines centrally mediated heat production[52]. In this case, it could be recommended to use external heating devices for all children premedicated with DEX, especially neonates and infants. More research could increase our knowledge about adverse events.

Due to its relatively easy way to deliver, intranasal administration of DEX is the most likely administration route, with a high bioavailability due to avoiding first-pass metabolism. It does not require patient collaboration and is well tolerated because it provides no unpleasant sensation.

However, an ideal dose of intranasal DEX was not identified. Less than 1 μg kg-1 of IN administered DEX was inadequate to produce effective sedation in children aged 1-4. A two μg kg-1 dose produced a higher rate of adequate sedation in children between 5 and 8 years old. These findings support the conclusion that increasing age requires a higher dose of DEX. The onset time of intranasally administered DEX may be influenced by age and dose, but more studies regarding pharmacokinetics in children are needed. The sedative effectiveness of DEX has been determined compared with other sedative drugs like midazolam, ketamine, chloral hydrate, and fentanyl. Mainly, studies reported good results, but only in a few cases greater efficacy[1,19,21,23,28]. One possible explanation for the eventual superiority of intranasal DEX above oral midazolam in preventing emergence agitation could be the shorter time of action of midazolam that wears off before the end of an operation, while DEX still works. Another limitation of this review is that it is challenging to compare articles that used different rating scales, to describe perioperative agitation or anxiety. The overall superiority of DEX over other drugs could not be concluded. More extensive and methodologically accurate trials are needed before standard implementation.

Most of the studies reported an increase in extubation and emergence time. Nevertheless, none of them could demonstrate, compared with other sedative drugs, a significant difference in time to discharge from the PACU or hospital because DEX offers good analgesia, prolonged sedation and prevents unusual behavior and restlessness45. These findings make DEX a valuable drug in the outpatient clinic with a high turnover. However, the slower onset time might delay patient flow in the morning hours.

The opioid-sparing analgesic properties of DEX in children could be notably beneficial in children at risk for respiratory depression[37]. Thanks to this lower need for rescue opioids and reduced perioperative distress, the incidence of PONV in children treated with DEX was significantly lower than in children under saline administration.

There was essential heterogeneity between study types, methods, interventions, and conclusions because of the small number of patients in subgroups and wide age range. Future large and more homogenous studies are needed regarding specific indications, optimal dosing, and administration time.

Conclusion

This literature review investigated the effects of DEX as a drug to premedicate children undergoing general anesthesia. DEX is a suitable drug to premedicate children because it has anxiolytic effects, prevents emergence agitation, lowers the anesthesia requirements and rescue analgesics, decreases postoperative nausea and vomiting, and has no respiratory depressant effects. Furthermore,

it could be considered a safe and equivalent drug compared to other sedatives. The existing literature describes primarily beneficial effects, but we must be thoughtful because of possible cardiovascular side effects such as bradycardia and hypotension. Another weakness of DEX is the negative effect on emergence and extubation time, but it had no significant impact on the discharge from PACU and the hospital discharge. In conclusion, given the small sample sizes and heterogeneity between the studies, evidence for the overall superiority of DEX over other premedication drugs needs to be more convincing. Large and more homogenous studies are required to evaluate further the specific indications, optimal dosing, safety profile, and timing of administration as well as the effects on clinical outcomes.

Declaration of conflicting interest: The author(s) confirm that no conflict of interest occurred.

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