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Efficacy of Intranasal Dexmedetomidine as a Preoperative Anxiolytic in Children: A Systematic Review

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Abstract

Preoperative anxiety is a common problem in pediatric patients that can have many negative effects; oral premedications (eg, midazolam) are often used to reduce anxiety and improve compliance. Dexmedetomidine (DEX) is an alpha-2 receptor agonist that can be given intranasally to children as a premedication and may be useful as an anxiolytic. In this systematic review of the PubMed, CINAHL, Ovid, and Cochrane Library databases, the efficacy of intranasal dexmedetomidine (IN DEX) was compared with that of oral midazolam for relieving preoperative anxiety among pediatric surgical patients. Three trials were assessed: 2 of these trials concluded that IN DEX was a superior anxiolytic for use in children; the third showed that there was no significant difference. More rigorous research that includes a larger sample size and an objective measurement tool is needed before drawing conclusions.

INTRODUCTION

Preoperative anxiety and fear affect up to 60% of pediatric patients and can lead to enuresis and delayed recovery from surgery.[1,2] Ten percent of children with high preoperative anxiety go on to experience emergence delirium in the recovery room.[2] Moreover, anxiety can increase stress for patients and their families and can delay the induction of anesthesia and the start of surgery.[2] Of those children who experience preoperative anxiety, 50% will continue to exhibit negative behavior changes at 2 weeks after surgery.[1,2] Negative behavior changes continue in 20% of children at 6 months and in 7.5% of children at 1 year.[1,2] The most common negative behavior responses include separation anxiety, eating problems, nightmares, aggression toward authority, and temper tantrums.[1,2] Problems with eating and sleeping may be attributable to the fact that children with increased preoperative anxiety often experience a more painful and slower recovery than those with low anxiety levels.[2] Predictors of preoperative anxiety include increased parental anxiety, a low activity level, a less sociable temperament, and a history of poor-quality medical encounters.[1] It is important to identify these at-risk children so that anesthesia providers can mitigate the negative effects by reducing or preventing preoperative anxiety.

Anesthesia providers commonly administer preoperative sedatives that help to reduce anxiety for the child and expedite anesthesia induction and surgery.[3-5] Midazolam, a benzodiazepine receptor agonist that causes sedation and amnesia, is the most common premedication for children,[4-7] and its benefits include a short duration of action and a reduction in the incidence of postoperative vomiting.[7] Midazolam is most commonly delivered to children by the oral route, but this method has several disadvantages, including restlessness, cognitive impairment, and respiratory depression.[6,8] Use of midazolam is hampered by low bioavailability that results in a slow onset and a bitter aftertaste that can reduce compliance to as low as 45%.[9] Ketamine is another popular premedication that causes dissociative anesthesia, sedation, and analgesia in children.[4,5,10] Side effects of ketamine include nausea and vomiting, excessive salivation, nystagmus, and psychological disturbances such as emergence delirium.[10]

Dexmedetomidine (DEX) is a highly selective alpha-2 adrenergic agonist that produces sedation, analgesia, and anxiolysis without causing respiratory depression.[11] Other benefits of DEX include its ability to increase glomerular filtration and

to decrease salivation, intraocular pressure, and the shivering threshold.[12] Preliminary studies report that DEX is effective for the prevention and treatment of postoperative emergence delirium,[13-15] and there is a growing trend among anesthesia providers to deliver DEX by the intranasal (IN) route. The bioavailability of intranasal dexmedetomidine (IN DEX) is high (65%), and it does not cause discomfort when administered by this route.[12,16] The nasal mucosa offers better absorption, faster onset, and better compliance without gastric stimulation, painful needle sticks, or a high risk of aspiration.[10,17] IN DEX has shown promise as an alternative to oral agents for premedication in children.

The purpose of this systematic review was to identify whether there was a difference in anxiety levels among pediatric patients who received IN DEX or oral anxiolytics as premedication.

METHODS

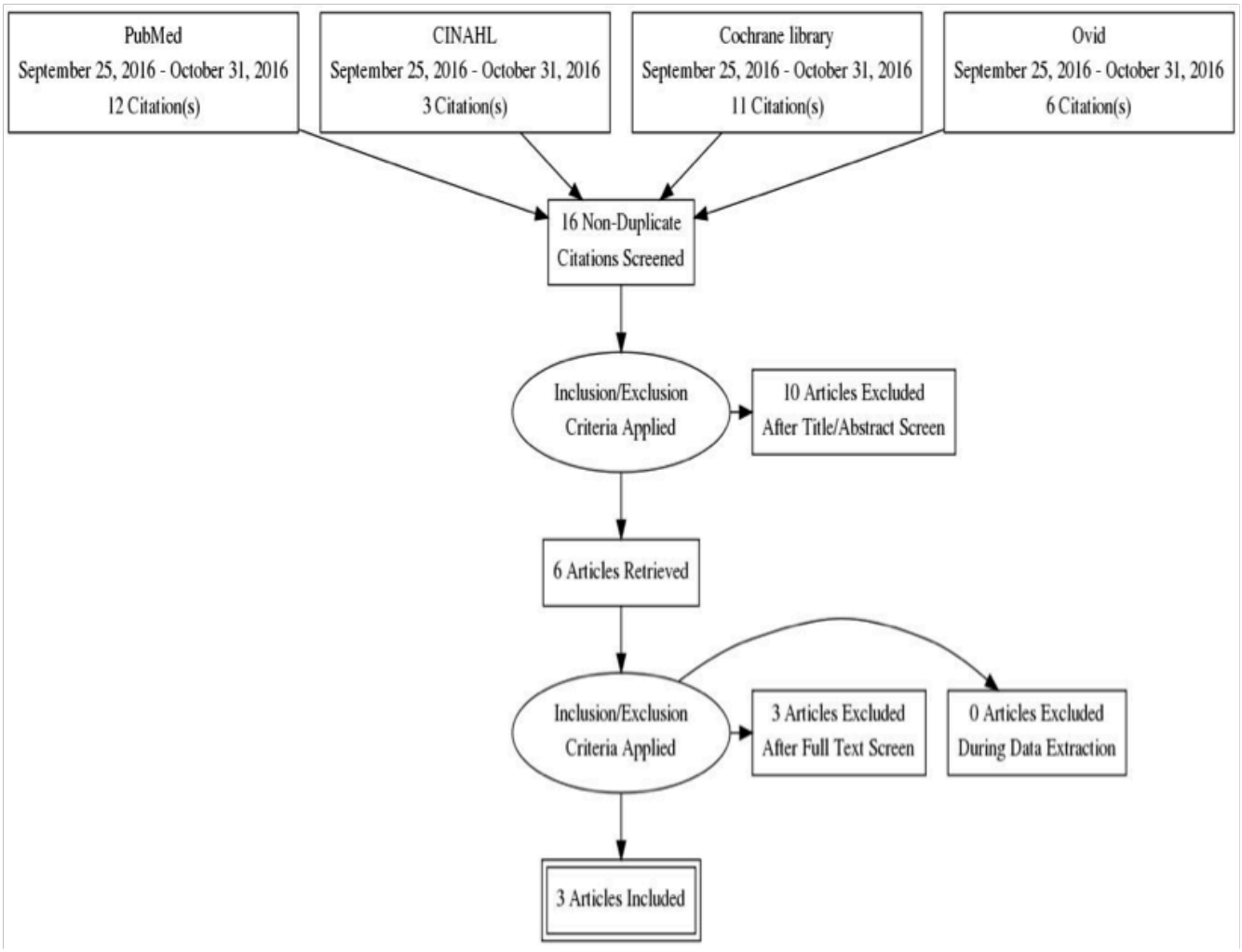
Search strategy and trial selection

The following databases were searched during the period from September 25, 2016, to October 31, 2016: PubMed (National Library of Medicine), CINAHL (EBSCO), Cochrane Database of Systematic Reviews (The Cochrane Collaboration), and Ovid. The Medical Subject Headings (MeSH) terms used in the search strategy were as follows: dexmedetomidine, premedication, anxiety, intranasal, and children. All searches were initially performed without restrictions. The results were then moved to RefWorks (ProQuest) and checked for duplications, which were removed. Titles and abstracts of randomized controlled trials (RCTs) were screened for historical significance. As premedication via the intranasal route is a relatively new technique, the results were restricted to articles published within the past 5 years.

Inclusion and exclusion criteria

Articles were required to meet the following inclusion criteria: (1) have an RCT design, (2) be original research comparing premedication with IN DEX to a single oral premedication, (3) report anxiety or behavior before induction of anesthesia as a primary outcome, and (4) examine pediatric patients aged 2 to 12 years with an American Society of Anesthesiologists physical status of I to II[18] and who were undergoing elective surgery. Studies were excluded if they examined children with mental or physical deficiencies, chronic pain, or any condition that placed them in a physical status category above II. Titles and abstracts were screened for the inclusion and exclusion criteria. Full texts were then retrieved for any publication that met the defined criteria. A flow diagram of the study search algorithm is shown in **Figure 1**.

Figure 1. Search Algorithm



RESULTS

Description of the included studies

Three studies were included in the final analysis. The characteristics of the studies by Yuen et al,[19] Ghali et al,[20] and Linares Segovia et al[21] are summarized in **Table 1**. All studies compared premedication with IN DEX to premedication with oral midazolam and used preoperative anxiety at the time of transferring the child from the parent to the operating room as the primary outcome. In the studies by Yuen et al and Linares Segovia et al, the participants were given a premedication 60 min before the induction of general anesthesia.[19,21] However, in the trial by Ghali et al, one group of participants was given IN DEX 60 min before the induction of general anesthesia, whereas another group of participants was given oral midazolam 30 min before the induction of general anesthesia.[20]

Measurement of anxiety

Anxiety was measured differently in the studies. In an older study by Yuen et al, the participants were given premedication 60 min before the induction of general anesthesia; the authors measured anxiety by evaluating behavior at parental separation by using a 4-point Likert-type behavior scale (a score of 1 indicated "calm and cooperative" and a score of 4 indicated "crying or resisting").[19] By contrast, both Ghali et al and Linares Segovia et al utilized the validated modified Yale Preoperative Anxiety Scale (mYPAS) to evaluate anxiety at the time of transfer to the operating room.[20-22] The mYPAS, which can be performed by an observer in less than 1 min,[20] contains 22 items within 5 categories.[20,21] The categories include activity, emotional expressivity, state of arousal, vocalization, and use of adults.[20,21] Scores range from 23 to 100, with an increased score indicating an increased anxiety state.[20]

Primary conclusions

At the time of parental separation, Yuen et al found no significant difference in behavior scores between the oral midazolam group and the 2 IN DEX dose groups ($P = 0.771$).[19] In contrast, Ghali et al and Linares Segovia et al found that the patients in the IN DEX group had significantly lower anxiety levels than did patients in the oral midazolam group ($P = 0.029$ and $P = 0.036$, respectively).[20,21] Similarly, Linares Segovia et al found that at 60 min after receiving premedication, anxiety was significantly lower among children who received IN DEX than among those who received oral midazolam ($P = 0.001$).[21] A risk analysis also showed that IN DEX reduced the risk of anxiety by 28% at 60 min.[21]

Table 1. Characteristics of the included studies

Study	Design	Intervention	No.	Age, y (mean)	Sex (M/F)	PS
Linares Segovia et al[21]	Prospective, randomized, double-blind controlled trial	a. DEX 1 mcg/kg IN 60 min before induction b. Midazolam 0.5 mg/kg PO 60 min before induction	a. 52 b. 56	a. 4 b. 4	a. 24/28 b. 32/24	I
Ghali et al[20]	Prospective, randomized, double-blind controlled trial	a. DEX 1 mcg/kg IN 60 min before induction b. Midazolam 0.5 mg/kg PO 30 min before induction	a. 60 b. 60	a. 8.2 b. 8.1	a. 34/26 b. 28/32	I
Yuen et al[19]	Prospective, randomized, double-blind controlled trial	a. DEX 1 mcg/kg IN 60 min before induction b. DEX 0.5 mcg/kg IN 60 min before induction c. Midazolam 0.5 mg/kg 30 min before induction	a. 32 b. 32 c. 32	a. 6.1 b. 6.8 c. 6.4	a. 30/2 b. 29/3 c. 30/2	I or II

Abbreviations: DEX, dexmedetomidine; IN, intranasal; PO, by mouth; PS, American Society of Anesthesiologists physical status.

Additional outcome measures

Two of the studies measured anxiety at the time of induction as an additional primary outcome.[20,21] In the study by Yuen et al, there was no significant difference in behavior scores at induction of general anesthesia among the 3 groups ($P = 0.148$).[19] The results of the study by Linares Segovia et al differed with those of the Yuen et al study, concluding that patients who received IN DEX experienced significantly less anxiety at induction of anesthesia than did those who received oral midazolam ($P = 0.04$).[21]

In addition to these primary outcomes, all 3 studies also examined the hemodynamic effects of the premedications as secondary outcomes.[19-21] The methods of hemodynamic assessment and the statistically significant findings of each study are shown in **Table 2**. Although all studies found that IN DEX produced statistically significant hemodynamic changes, there were no clinically significant adverse effects.

Risk of bias

In all of the studies, the authors implemented random selection methods to ensure a low risk of selection bias.[19-21] Although the participants understood that they were undergoing a minor surgical procedure, researchers in all of the studies used double-blinding to minimize the risks of both performance bias and detection bias.[19-21] Ghali et al and Linares Segovia et al used the validated mYPAS to assess anxiety,[20,21] whereas Yuen et al used a Likert-type scale.[19] The scale did not include a midpoint, which can force a biased response (positive or negative).[19,23] Yuen et al and Ghali et al performed a power analysis and met their sample goal.[19,20] Linares Segovia et al performed a power analysis and calculated that a sample of 75 participants was needed per group (n = 150); however, the researchers were only able to enroll 108 patients.[21] Thus, sampling bias limited our ability to draw useful conclusions from the results of that study.

Table 2. Significant hemodynamic findings

Study	Method	spO_2	HR	BP
Linares Segovia et al[21]	HR, SpO_2, and BP were measured at baseline and every 15 min after drug administration	SpO2 decreased 1.5% at 30 min in the DEX group ($P = 0.001$) SpO_2 decreased 1.2% at 15 min in the midazolam group ($P = 0.001$)	HR decreased by 8 bpm at 45 min in the DEX group ($P = 0.001$)	MAP decreased by an average of 5 mm Hg at 30 min in the DEX group ($P = 0.005$)
Ghali et al[20]	HR, SpO_2, and BP were measured at baseline and every 10 min after drug administration	No statistically significant findings	At transfer to OR, HR was significantly less in the DEX group (85 bpm) than in the midazolam group (96 bpm) ($P = 0.036$)	At transfer to OR, SBP was significantly less in the DEX group (92 mm Hg) than in the midazolam group (105 mm Hg) ($P = 0.032$)
Yuen et al[19]	HR, SpO_2, and BP were measured at baseline and every 15 min after drug administration	No statistically significant findings	HR decreased by 11.1% and 16.4% from baseline in group D0.5 and group D1 at 60 min, respectively	SBP decreased by 14.1% at 60 min in group D1

Abbreviations: BP, blood pressure; bpm, beats per minute; D0.5, 0.5 mcg/kg IN DEX; D1, 1 mcg/kg IN DEX; DEX, dexmedetomidine; HR, heart rate; IN, intranasal; MAP, mean arterial pressure; OR, operating room; SBP, systolic BP; SpO_2, oxygen saturation.

DISCUSSION AND LIMITATIONS

There was no consensus among the 3 studies regarding the superiority of IN DEX over oral midazolam as a preoperative anxiolytic.[19-21] All of the studies measured anxiety with subjective scales, which increased the likelihood of inconsistency. Whereas Yuen et al utilized a 4-point behavior scale to assess anxiety, the other studies used the mYPAS.[19] Ideally, all of the studies would have utilized the same validated scale. Nevertheless, it is noteworthy that the study by Yuen et al, which found no significant differences between therapies, used a simplistic 4-point behavior scale to assess anxiety.[19] Moreover, the outcomes in that study were simply reported as "satisfactory" or "unsatisfactory" without either term being defined, and with no mean behavior scores being documented.[19] We think it is fair to say that this method was less rigorous,[19] and that the trials by Ghali et al and Linares Segovia et al were more reliable as demonstrated by their reproducibility with similar methods.[20,21]

None of the studies evaluated the onset time or peak effect of the administered drugs. In all of the studies, IN DEX was administered 60 min before induction of general anesthesia.[19-21] The average time a pediatric patient spends in the preoperative holding area is less than 50 min.[24,25] Ideally, the authors would have given the medication within this average time (ie, 30–45 min before induction).

Although there is a great deal of clinical data concerning the use of DEX in children, its use has not been approved for premedication, which is still an off-label indication. Anesthesia providers must always consider the risks and benefits when selecting a medication, and this should be no different in the case of IN DEX. However, the results of this analysis indicate that IN DEX was safe and may be especially useful when an anesthesia provider is concerned about emergence delirium, analgesia, or compliance.

In conclusion, this systematic review was performed to compare the efficacy of IN DEX with that of oral midazolam as a preoperative anxiolytic in children. Three RCTs were selected and critically reviewed, but the results were inconclusive. Because the studies by Ghali et al and Linares Segovia et al were more reliable and used similar methods,[20,21] we think it is fair to conclude that the evidence favors IN DEX having beneficial effects. An ideal study would be one with a large sample size and an objective measurement tool in which IN DEX is administered 30 to 45 min before induction of general anesthesia. While IN DEX appears to be a safe and effective alternative to oral midazolam, additional rigorous studies are needed before any practice recommendations can be made.

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