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Research Article

Effect of intranasal dexmedetomidine or intranasal midazolam on prevention of emergence agitation in pediatric strabismus surgery: A randomized controlled study

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KEYWORDS

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Abstract *Background:* Following strabismus surgery under sevoflurane anesthesia children often experience emergence agitation (EA) and postoperative vomiting (POV). This study compared the effects of premedication with intranasal dexmedetomidine, midazolam, and placebo on postoperative EA and POV.

Methods: 105 children (aged 1–7 years) undergoing elective strabismus surgery under sevoflurane anesthesia were randomly assigned to one of three groups ($n = 35$ each). Preoperatively, group D received intranasal (IN) dexmedetomidine (1 μg/kg), group M received IN midazolam (0.1 mg/kg), and group C received (1 ml) IN normal saline. Agitation scores (Pediatric Anesthesia Emergence Delirium [PAED] scale) and POV were assessed in post-anesthesia care unit (PACU). The incidence of intraoperative Oculocardiac Reflex OCR events, Time to spontaneous eye opening, Postoperative pain score, total consumption of rescue analgesia and time to discharge from PACU were also assessed.

Results: 98 children completed the study. Incidence of agitation (defined as PAED score $\geqslant 10$) was significantly higher in the control group and the midazolam group than in the dexmedetomidine group ($P = 0.014$), and the number of patients who developed severe agitation requiring fentanyl (PAED score $\geqslant 15$) was also higher in the control group ($P = 0.042$).

There was no significant difference between the incidence of POV in the PACU between the control group (28%) and the midazolam group (21%); however, the incidence was significantly lower in the dexmedetomidine group (15%). The number of intraoperative OCR events was significantly higher in the control group (39%) than in the dexmedetomidine (0%; $P = 0.006$) and in the midazolam group the incidence was higher than the dexmedetomidine (9%; 3 events) but did not reach statistical significance.

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Conclusion: Administration of intranasal dexmedetomidine to children undergoing strabismus surgery under sevoflurane anesthesia resulted in a reduced incidence of EA compared with intranasal midazolam or placebo. The incidence of POV and intraoperative OCR was also significantly lower with dexmedetomidine.

1. Introduction

Emergence agitation (EA) is a complex behavioral disturbance characterized by psychomotor agitation, perceptual disturbances, delusions, and disorientation during recovery from general anesthesia [1]. The incidence of EA in children is higher than in adults ranging from ten to eighty percent [2].

Agitated behavior associated with EA can delay discharge from the post-anesthesia care unit (PACU), decrease parent and caregiver satisfaction, and increase the overall cost to the institution [3]. Risk factors for development of EA include preschool age, previous surgery, ophthalmology or otorhinolaryngology procedures, and inhalation agents associated with fast emergence [4].

Strabismus surgery is one of the most common eye operations in children and it may be associated with significant postoperative pain [5]. Pain can cause distress, anxiety and agitation in children [6]. The oculocardiac reflex (OCR) is another major complication of pediatric strabismus surgery when the heart rate drops to 20% of the resting rate [7]. The incidence of OCR during strabismus surgery has been variously reported between 14% and 90%, depending on premedication and the anesthetic agent used [8,9]. Strabismus surgery is also associated with significant postoperative vomiting (POV) with an incidence of approximately 30% [10], and this contributes significantly to the postoperative distress observed in these children and subsequently limits the use of opioids for pain management after strabismus surgery [11,12].

Sevoflurane is frequently used for pediatric anesthesia because it has low pungency and rapid onset and offset of action [13,14]. The reported incidence of emergence agitation (EA) following sevoflurane anesthesia varies from 10% to 80% between studies, suggesting that EA may depend on numerous factors.

Midazolam is an anxiolytic, sedative, hypnotic, and amnesic drug and is used for premedication in children via several routes [15–19]. Previous studies have shown that intranasal administration of midazolam is easy, effective, and noninvasive, but may cause nasal irritation [20]. Other adverse effects of midazolam include postoperative behavioral changes, cognitive impairment, and respiratory depression [21].

Dexmedetomidine is a potent, highly selective, and specific α2 adrenoreceptor agonist that has both sedative and analgesic effects. Unlike traditional gabaminergic sedative drugs, the primary site of action of dexmedetomidine is the locus coeruleus rather than the cerebral cortex [22]. Therefore, its induced sedation is characterized by an easy and quick arousal from sedation resembling natural sleep [23].

There is evidence that dexmedetomidine decreases the incidence of EA after sevoflurane anesthesia in children undergoing different surgical procedures [24]. It has also been reported that dexmedetomidine can lower the incidence of POV, and decrease the occurrence of OCR during strabismus surgery [25].

The present study was undertaken to investigate the relative benefits of using intranasal dexmedetomidine or midazolam premedication in sevoflurane anesthetized children undergoing strabismus surgery. The primary objective of this study was to compare the effects of intranasal dexmedetomidine and intranasal midazolam on the incidence of EA after sevoflurane anesthesia in children undergoing strabismus surgery. We hypothesized that the incidence of EA would be lower with dexmedetomidine due to its sedative, anxiolytic, and analgesic effects. The secondary objective was to estimate the effects of the two drugs on POV and the incidence of OCR.

2. Methodology

The study was conducted in Magrabi specialist eye hospital between September 2013 and April 2015. Approval by the local Institutional Review Board (IRB), and parental written informed consent were obtained. Children aged between 1 and 7 years of American Society of Anesthesiologists (ASA) physical status I or II undergoing strabismus surgeries were included in this double blind, prospective, randomized study. Primary exclusion criteria included ASA III and IV children, children with developmental delays, any neurological disease associated with symptoms of agitation. Secondary exclusion criteria included parental refusal of consent and allergy to any of the study medications. Of 123 children screened, 105 patients were found eligible and enrolled in the study.

All children were fasted from solid foods for 6 h before the procedure; clear liquids were permitted until 2 h prior to admission to the OR. Before entrance to the OR, Patients were allocated randomly to one of three groups using computer-generated random numbers which were obtained and kept in opaque sealed envelopes that were opened by an independent anesthesiologist not involved in the study: group D, included patients who received intranasal (IN) dexmedetomidine (1 μg/kg), group M included patients who received IN midazolam (0.1 mg/kg), and group C included patients who received IN normal saline. All study drugs were prepared by an anesthesiologist who was blinded to the details of the study.

Parental presence was facilitated during induction of anesthesia. An observer blinded to the group evaluated the modified Yale Preoperative Anxiety Scale (m-YPAS) [26] in the preoperative holding area. Routine monitoring of electrocardiography (ECG), noninvasive blood pressure (NIBP), and Oxygen Saturation (SpO2), were attached before induction of anesthesia and continued during surgery. Anesthesia was induced with 8% sevoflurane in 50% nitrous oxide, and

oxygen and an appropriate sized laryngeal mask airway was inserted for maintenance of airway. After the fixation of the laryngeal mask airway, anesthesia was maintained with 50% nitrous oxide in oxygen and sevoflurane with spontaneous breathing. All children received 15 mg/kg intravenous acetaminophen for analgesia. All patients received topical anesthesia with two conjunctival drops of 0.4% oxybuprocaine on four occasions: before washing the eye at the beginning of the operation, before incision of the conjunctiva, before closure, and after closure of the conjunctiva.

The minimal heart rate during this procedure was recorded during traction of extraocular muscles. Oculocardiac reflex (OCR) was defined as an acute reduction in heart rate of $\geqslant$20% associated with traction on an eye muscle. Atropine (0.01 mg/kg IV) was given in cases where the heart rate did not return to baseline after release of the extraocular muscle or if the reflex recurred. The number of OCR events was recorded. After the end of surgery, at the time of dressing, children were administered 100% oxygen and the laryngeal mask airway was removed. Sevoflurane was turned off after laryngeal mask airway removal.

The independent investigator blinded to the study continuously monitored the patient in the PACU and recorded the maximum value of each variable of the Pediatric Anesthesia Emergence Delirium (PAED) scale [27] at arrival, 5 min later then every 15 min for the first hour starting from time of awakening. Patients who were asleep during these intervals were given zero score in PAED scale.

Postoperative pain was assessed by using face, legs, activity, cry and consolability (FLACC) pain scale [28,29] in all patients every 15 min for 1 h.

Blinded study personnel recorded the number of episodes of vomiting or retching occurring in the PACU. For the purpose of the current study, vomiting was defined as the forceful oral expulsion of liquid or solid gastric contents. Both vomiting and retching were considered as vomiting events. Patients requesting an antiemetic were treated with ondansetron 0.1 mg/kg^{-1}. If the vomiting remained uncontrolled, repeat administrations of ondansetron were given up to a maximum total dose of 4 mg. The total consumption of antiemetic was recorded.

The need for rescue analgesia in the form of IV acetaminophen was noted in the PACU. Time to spontaneous eye opening and time to discharge from PACU were also noted. Children were discharged when they were calm, had no pain and had a modified Aldrete [30] score >9.

The PAED scale contains five items (eye contact, purposefulness of actions, awareness of surroundings, restlessness and consolability), each scored on a 0 to 4 scale, for a maximum of 20 points. A perfectly calm child scores 0 and extreme agitation corresponds to 20 points. The peak EA score was recorded. Agitation scores <10 were interpreted as an absence of agitation, scores $\geqslant$10 were regarded as presence of agitation, and scores $\geqslant$15 were regarded as severe agitation.

For patients with a total PAED score of >10 or a FLACC scale >4 in the PACU, the first measure was to facilitate parental contact and when this failed intravenous fentanyl 0.5 μg/kg was administered as rescue medication and repeated after 10 min if the agitation did not subside. Patients who received intravenous fentanyl were removed from the analysis after the administration of fentanyl.

2.1. Sample size calculation

We performed a pilot study of 10 patients and analyzed the results by power calculation to determine the number of patients required in each group. We wished to detect a minimum clinically important difference of 30% decrease in the primary end point (PAED score) between the three groups. The sample size was calculated based on the assumptions of standard deviation of PAED score values of up to 4, with α of 0.05 (two tailed) and type II error of 0.2. Therefore, 30 patients were required in each group and we decided to include 35 patients per group to compensate any possible dropouts. The primary outcome measured was the PAED scale at different time intervals in each group. The secondary outcomes measured were the incidence of emergence delirium, intraoperative OCR events, and postoperative vomiting.

2.2. Statistical analysis

Data were statistically described in terms of median and range, mean $\pm$ standard deviation ($\pm$SD), frequencies and percentages when appropriate. Comparison of quantitative variables between the study groups was done using one way ANOVA for independent samples in comparing three groups when normally distributed and Kruskal Wallis for independent samples when not normally distributed. For comparing categorical data, Chi square test was performed. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2010 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results

105 subjects were initially enrolled in the study. 7 subjects were subsequently excluded from the analysis, of these, 6 were excluded because they received fentanyl (3 in the control group, two in the midazolam group, and one in the dexmedetomidine group), and one subject in the dexmedetomidine group was lost to follow-up. 98 subjects completed the study. The subjects in the three groups were comparable with respect to age, body weight, sex, m-YPAS scale, duration of surgery, and mean time to eye opening (Table 1). The duration of stay in the PACU and the number of patients requiring rescue analgesia were also comparable in the three study groups. There were no significant between-group differences in the pain scores, measured as maximal FLACC scores in the PACU (Table 1).

The incidence of agitation (defined as PAED score $\geqslant$ 10) was significantly higher in the control group and the midazolam group than in the dexmedetomidine group (P = 0.014), and the number of patients who developed severe agitation requiring fentanyl (PAED score $\geqslant$ 15) was also higher in the control group than in the dexmedetomidine group (P = 0.042). The incidence of severe agitation was significantly higher in the control group than the midazolam group (P = 0.017); however, there was no statistically significant difference between the dexmedetomidine group and the midazolam group in this regard (Table 2).

Table 1 Demographic data, Preoperative Anxiety Scale, surgery duration, time to eye opening, pain scale, duration of stay in PACU, in control, dexmedetomidine, and midazolam groups.

	Group C $N = 32$	Group D $N = 33$	Group M $N = 33$
ASA Status (I/II)	31/1	32/1	33/0
Age (year)	2.78 ± 1.67	2.68 ± 1.54	2.48 ± 1.17
Weight (kg)	11.4 ± 3.3	12 ± 3.9	11.8 ± 3.7
Gender (male/female)	18/14	17/16	17/16
Surgery duration (min)	42.27 ± 3.507	45.93 ± 3.378	46.27 ± 3.608
Time to eye opening (min)	3.23 ± 1.270	2.14 ± 0 .170	3.23 ± 1.270
Patients requiring rescue analgesia *n* (%)	6 (18%)	3(9%)	4(12%)
FLACC scale	3 (0–9)	3.5 (0–9)	3 (0–9)
m-YPAS scale	36 (24–61)	34 (25–61)	35 (26–58)
Duration of PACU stay (min)	43.68 ± 2.032	44.39 ± 3.432	45.78 ± 3.032

PACU, Post-anesthesia care unit; FLACC scale, Face, Legs, Activity, Cry and Consolability Scale; m-YPAS, modified Yale Preoperative Anxiety Scale in the preoperative holding area. Values are expressed as mean ± SD or median (range).

Table 2 Incidence of emergence agitation (PAED ⩾ 10), severe emergence agitation (PAED ⩾ 15), postoperative vomiting (POV), and intraoperative Oculocardiac reflex in the control, dexmedetomidine, and midazolam groups.

	Group C $N = 32$	Group D $N = 33$	Group M $N = 33$
PAED score ⩾ 10, *n* (%)	15 (47%)	4 (12%)[*,†]	7 (21%)[*]
PAED score ⩾ 15, *n* (%)	8 (25%)	2 (6%)[*]	3 (9%)[*]
POV (one episode), *n* (%)	9 (28%)	5 (15%)[*,†]	7 (21%)
POV (two or more episodes), *n* (%)	7 (22%)	1 (3%)[*,†]	6 (18%)
Oculocardiac reflex requiring atropine, *n* (%)	13 (39%)	0 (0%)[*]	3 (9%)[*]
Nasal irritation, *n* (%)	0 (0%)	0 (0%)[†]	7 (21%)

PAED = Pediatric Anesthesia Emergence Delirium scale (scale 0–20); POV = postoperative vomiting.
[*] $P < 0.05$ for dexmedetomidine or midazolam group versus control group.
[†] $P < 0.05$ for dexmedetomidine versus midazolam group.

There was no statistically significant difference between the incidence of POV occurring in the PACU between the control group (28%) and the midazolam group (21%); however, the incidence was significantly lower in the dexmedetomidine group (15%) than both the control and the midazolam group. Severe vomiting (two or more episodes, requiring administration of antiemetic medication) was observed in 7 subjects in the control group, 6 subjects in the midazolam group, and 1 subject in the dexmedetomidine group, and the difference was statistically significant between the dexmedetomidine group and both the control and the midazolam groups (Table 2).

The number of intraoperative OCR events was significantly higher in the control group (13; 39%) than the dexmedetomidine (0%; $P = 0.006$) and the midazolam group. In the midazolam group the incidence was higher (9%; 3 events) than the dexmedetomidine group; however, the difference did not reach statistical significance. Thirteen subjects in the control group and three subjects in the midazolam group required atropine for persistent bradycardia (Table 2).

The PAED scale scores were significantly lower in the dexmedetomidine and midazolam groups than in the control group. There was also a statistically significant difference in PAED scale scores between the dexmedetomidine group and midazolam group in favor of the dexmedetomidine group. These differences were evident at admission to the PACU, 5 min, 15 min, and 30 min later. There were, however, no differences between the 3 groups at 45 min and 60 min from admission to the PACU (Table 3).

4. Discussion

The results of this study showed that IN dexmedetomidine premedication for children undergoing strabismus surgery under sevoflurane anesthesia reduces the incidence of emergence delirium when compared with intranasal midazolam or placebo. The study also showed that the incidence of OCR occurring intraoperatively and the incidence of postoperative vomiting were also lower in children receiving intranasal dexmedetomidine premedication.

Strabismus surgery is performed commonly in children to restore binocular vision as well as for cosmetic reasons. Undesired effects, including EA [31], POV [32], and postoperative pain [33] are major causes of distress after recovery from general anesthesia.

In the current study the intranasal route for drug administration was chosen as a relatively quick, simple method showing benefits over other routes which require more patient cooperation. The Intranasal administration of midazolam has previously been shown to be an effective premedication agent for children. However, the sensation of burning and nasal irritation can be considered as disadvantages of this route [34,35]. In this study 7 out of 33 children showed signs

Table 3 Pediatric Anesthesia Emergence Delirium (PAED) scale in control, dexmedetomidine, and midazolam groups at different time intervals in PACU.

	Group C $N = 32$	Group D $N = 33$	Group M $N = 33$
Arrival – Median (range)	9 (0–18)	4 (0–16)*,†	7 (0–16)*
5 min – Median (range)	9 (0–15)	4 (0–15)*,†	6 (0–15)*
15 min – Median (range)	7 (0–15)	4 (0–9)*,†	6 (0–10)*
30 min – Median (range)	5 (0–17)	0 (0–5)*,†	3 (0–15)*
45 min – Median (range)	2 (0–17)	0 (0–5)	2 (0–15)
60 min – Median (range)	2 (0–17)	0 (0)	0 (0–2)

PAED scale at arrival to PACU, and 5, 15, 30, 45 and 60 min later. Data are expressed as median and range. Between-group analysis using one way ANOVA.

* $P > 0.05$ for dexmedetomidine or midazolam group vs. control group.

† $P > 0.05$ for dexmedetomidine vs. midazolam group.

of nasal irritation with intranasal midazolam premedication. On the other hand, this sign was not seen in any of the children when intranasal dexmedetomidine was used. Similar observations were previously reported by Yuen et al. In their study, the authors showed that 1 μg/kg intranasal dexmedetomidine was an effective technique for producing sedation in children and it caused no discomfort during administration [36].

Emergence agitation is a common side effect of sevoflurane in pediatric anesthesia, yet there is no clinical evidence that agitation affects long term outcome. As the mechanism of agitation after sevoflurane anesthesia is not clear, there is no well-known prophylaxis or treatment, although the incidence of this excitatory behavior seems to be reduced by the perioperative use of sedative and analgesic drugs [37].

In the current study, the PAED scale scores were significantly lower in the dexmedetomidine and midazolam groups than in the control group and there was also a statistically significant difference between the dexmedetomidine group and midazolam group in favor of the dexmedetomidine group. Furthermore, the incidence of emergence delirium and severe emergence delirium was also significantly lower in the dexmedetomidine group compared to both the midazolam and the control groups. No previous studies were done to compare the effect of the nasal administration of these drugs on the incidence of emergence delirium following recovery from pediatric strabismus surgery; however, other studies obtained comparable results in different types of pediatric surgery and using different routes. Sun et al. conducted a meta-analysis of randomized controlled trials to compare dexmedetomidine with midazolam as premedication in children undergoing different types of surgery. Their pooled data analysis revealed that dexmedetomidine premedication effectively lowered the incidence of agitation or delirium following the operations (RR: 0.59; 95% CI: 0.40, 0.88; I2 = 25%; NNT: 8.4). The authors concluded that dexmedetomidine premedication was superior to midazolam premedication in terms of reducing emergence agitation or delirium [38].

Sheta et al. compared premedication with intranasal midazolam or intranasal dexmedetomidine in children undergoing complete dental rehab and found a significantly lower incidence of postoperative agitation (agitation score of 3, 4) in the dexmedetomidine group compared to midazolam group (11.1% vs. 30.6%, respectively, CI 0.01–0.37, $P = 0.036$) [39].

Ming et al. compared two different doses of dexmedetomidine and placebo in children undergoing adenotonsilectomy under sevoflurane anesthesia and obtained significantly lower agitation scores in both groups receiving dexmedetomidine [40].

On the other hand, Asaad et al. compared the effectiveness of fentanyl and dexmedetomidine administered by the intravenous route in decreasing emergence agitation in children undergoing different surgeries under general anesthesia and caudal block. They found a significant difference when comparing the two groups to placebo but no significant difference was found when comparing fentanyl and dexmedetomidine [41]. The discrepancy between these results and our own may be due to the different types of surgery and anesthetic techniques used which may have been provided for confounding variables. Similarly, Akin et al. compared intranasal dexmedetomidine and intranasal midazolam in children undergoing adenotonsilectomy under sevoflurane anesthesia and found comparable incidences of emergence delirium in both study groups [42].

Our secondary endpoints were the incidence of POV and the incidence of OCR. Strabismus surgery is often associated with a remarkable high rate of PONV [43]. The reasons for the fairly high rates of PONV are not, as yet, understood. Van den Berg et al. suggested in a previous study that an "oculo-emetic reflex" may be responsible for the high incidence of PONV following strabismus surgery [44]. Intraoperative recession and manipulation cause traction on eye muscle spindles; thus, *via* vagal and trigeminal afferents may activate the vomiting system. Another hypothesis is based on an optokinetic imbalance and disturbance of visual axes [45]. Recent analyses have demonstrated convincingly, that in the pediatric population strabismus surgery is clearly a risk factor that needs to be taken into account when the risk for POV should be assessed in children [46].

Our study found a favorable effect of dexmedetomidine on the incidence of POV. The incidence of POV was significantly lower with dexmedetomidine than with midazolam, or placebo. The antiemetic effect of dexmedetomidine may be explained by the alpha 2 adrenoceptor agonist effect of dexmedetomidine which, similar to clonidine, decreases the noradrenergic activity as a result of binding to the alpha 2 presynaptic inhibitory receptors in the locus coeruleus an inhibition that probably results in an antiemetic effect [47].

In other studies, dexmedetomidine has been shown to be effective in the treatment of cyclical vomiting [48,49]. It has also been shown to reduce the requirement for postoperative opioids, and thereby lower the risk of opioid-induced nausea and vomiting [50,51]. These antiemetic properties of dexmedetomidine further support its use as an adjunct for general anesthesia in children.

Our results are consistent with the results obtained by Suga et al. who compared the effect of 2 different doses of dexmedetomidine or placebo on the incidence of postoperative nausea and vomiting in 97 children undergoing ear reconstructive surgery. The authors found that the intraoperative infusion of dexmedetomidine had an opioid sparing effect and reduced incidence of PONV in a "dose-dependent" manner [52].

Again similar results were obtained by Chen et al. who compared the incidence of POV in children undergoing strabismus surgery under sevoflurane anesthesia. The patients were assigned to intraoperatively receive placebo, dexmedetomidine, or ketamine. The authors found that the incidence of POV was similar with ketamine and placebo, but less with dexmedetomidine [25].

OCR is another complication that often occurs during strabismus surgery. It is defined as a fall of heart rate of more than 20% and is caused by traction on the extraocular muscles. In the current study there were no significant differences in the incidence of oculocardiac reflex between the dexmedetomidine and the midazolam groups; however, the incidence of OCR was significantly higher in the control group. Similar results were obtained by Mizrak et al. who found a significant reduction in the incidence of OCR in children undergoing strabismus surgery under ketamine anesthesia when dexmedetomidine was added as premedication [53]. On the other hand, conflicting results were obtained by Kim et al. [54] who found no difference in the incidence of OCR events when comparing low-dose infusion of dexmedetomidine or placebo in children undergoing strabismus surgery. This may be due to the fact that, in their study, Kim et al. administered fentanyl (1 μg/kg IV) to all children after induction of anesthesia.

In conclusion, the administration of intranasal dexmedetomidine to children undergoing strabismus surgery under sevoflurane anesthesia resulted in a reduced incidence of EA compared with midazolam or placebo. The incidence of POV was significantly lower with dexmedetomidine than with midazolam or placebo. These findings suggest that intranasal dexmedetomidine with sevoflurane may form an effective combination for anesthesia in children undergoing strabismus surgery.

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Conflict of interests

None to declare.

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