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ORIGINAL ARTICLE

The application of dexmedetomidine in children undergoing vitreoretinal surgery

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Abstract
Purpose Dexmedetomidine is a highly selective alpha-2 adrenergic agonist that has a sedative effect and has been shown to reduce anesthetic requirements. It also has a sympatholytic effect, which may prove useful when used to blunt the sympathetic surge during intubation and extubation. However, its effects on intraocular pressure, hemodynamic stability, attenuation of extubation response, and emergence agitation remain unclear for pediatric patients undergoing vitreoretinal surgery. We focused on these effects in this study.
Methods Sixty ASA I–II patients undergoing vitreoretinal surgery, were anesthetized with sevoflurane 1–2% end-tidal concentration in oxygen supplemented by remifentanil 0.2 μg/kg/min. Intraocular pressure was measured after inhalation of sevoflurane ($IOP_{Baseline}$) and 10 min after intravenous administration of dexmedetomidine 0.5 μg/kg or normal saline (IOP_{10min}), after induction of anesthesia. Blood pressure and heart rate were recorded every 5 min during surgery. The incidence and severity of coughing and emergence agitation and untoward airway events after extubation, for example breath holding, laryngospasm, bronchospasm, and oxygen desaturation, were assessed. Extubation time and emergence time were also documented.
Results There was no significant difference in intraocular pressure at the two time points between the groups ($p > 0.05$). In both groups mean arterial pressure and heart rate decreased from baseline after anesthetic induction ($p < 0.05$). The increase from intraoperative values in mean arterial pressure and heart rate associated with extubation was diminished in the dexmedetomidine group compared with the control group ($p < 0.05$). Coughing after extubation was less common (10 vs. 21) and less severe (3 moderate and 7 minimal; vs. 2 severe, 7 moderate and 12 minimal) in the dexmedetomidine group than in the control group ($p < 0.05$). There were no significant differences between the groups in time to emergence or extubation ($p > 0.05$). The dexmedetomidine group had a lower incidence of emergence agitation than the control group (10 vs. 43.3%, $p < 0.05$). The incidence of breath holding, laryngospasm, bronchospasm and oxygen desaturation was not significantly different between the groups ($p > 0.05$).
Conclusions Dexmedetomidine 0.5 μg/kg had no effect on intraoperative hemodynamics or intraocular pressure, but attenuated the hemodynamic response to extubation and diminished emergence agitation in pediatric patients undergoing vitreoretinal surgery.

Keywords Dexmedetomidine · Vitreoretinal surgery · Intraocular pressure · Emergence agitation

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Introduction

Providing an immobile and uncongested operative field without any major increase in intraocular pressure (IOP) is

the anesthetic objective for ophthalmic surgery. Sevoflurane is widely used in pediatric anesthesia because of fast and well tolerated inhaled induction, low hepatotoxicity, hemodynamic stability, and rapid emergence from anesthesia. However, its use is associated with incidence of emergence agitation of up to 80%. Different medications, for example analgesics, opioids, benzodiazepines, and clonidine, have been used for emergence delirium prophylaxis or treatment with variable success.

Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist with sedative, analgesic, anxiolytic, and sympatholytic effects without respiratory depression [1]. The objectives of this study were to determine if dexmedetomidine would prevent IOP elevation, maintain hemodynamic stability, and attenuate extubation response and emergence agitation in pediatric patients undergoing vitreoretinal surgery, and to assess the benefits of dexmedetomidine in ophthalmic surgery.

Materials and methods

This study was a prospective, randomized, double-blind trial. Our study was approved by the Local Research Ethics Committee and informed consent was obtained from the parents of the patients. Sixty ASA I–II patients aged 3–7 years undergoing vitreoretinal surgery participated in the study. We excluded patients with asthma, cardiovascular disease, abnormal renal or hepatic function, any known sensitivity to the study medications, previous sedative or analgesic medication use, and a history of past anesthesia. Patients received no anesthetic premedication. The patients were allocated randomly (by computer-generated random numbers) to receive an infusion of either dexmedetomidine or normal saline as placebo. The study drugs (dexmedetomidine and normal saline) were prepared by the hospital pharmacy in identical containers marked with the name of the project, the investigator's name, and consecutive numbers. Patients and investigators were unaware which was dexmedetomidine or normal saline (double-blind).

Anesthesia was induced with 8% sevoflurane in oxygen and spontaneous ventilation. After placement of an intravenous (IV) line, all patients received atropine 0.01 mg/kg IV. Subsequently dexmedetomidine 0.5 μg/kg diluted in normal saline to a volume of 10 mL (group D) or 10 mL of normal saline (group P) was administered intravenously over a period of 10 min. All patients then received propofol 2 mg/kg, remifentanil 0.5 μg/kg, and cisatracurium 0.15 mg/kg to facilitate endotracheal intubation and intermittent positive pressure ventilation. Anesthesia was maintained with an infusion of remifentanil 0.2 μg/kg/min and inhalation of sevoflurane (1–2% end-tidal concentration) in oxygen. Depth of anesthesia was maintained by adjusting the concentration of sevoflurane to achieve a bispectral index score of 40–60. Heart rate (HR), mean arterial pressure (MAP), respiratory rate, $ETCO_2$, and hemoglobin oxygen saturation (SpO_2) were recorded every 5 min. After bulbar conjunctiva closure, all anesthetic agents were discontinued and washed out with 100% O_2 at 5 L/min. Muscle relaxant reversal medications were not administered at the end of the surgery. The endotracheal tube was removed when patients were awake and breathing spontaneously.

Intraocular pressure was measured after inhalation of sevoflurane ($IOP_{Baseline}$) and again 10 min after the administration of dexmedetomidine or placebo (IOP_{10min}). The occurrence of coughing in the first 15 min after extubation was continuously observed. The incidence and severity of coughing was assessed by use of a previously reported 4-point scale: 1, no coughing; 2, minimal coughing (once or twice); 3, moderate coughing (3–4 times); 4, severe coughing (5 or more times) [2]. The incidence of untoward airway events after extubation, for example breath holding, laryngospasm, bronchospasm, and oxygen desaturation was recorded. The incidence and severity of emergence agitation was measured according to the pediatric anesthesia emergence agitation scale: 1, calm; 2, not calm but could be easily calmed; 3, not easily calmed, moderately agitated or restless; and 4, combative, excited, or disoriented [3]. For analysis, we considered grade 1 and 2 in the scale of behavior as indicating no agitation and grades 3 and 4 as indicative of agitation. Pain was evaluated on modified CHIPPS as 0 for no pain and 10 for severe pain [4]. Extubation time (defined as the time between discontinuation of anesthetic agents and extubation), and emergence time (between the discontinuation of anesthetic agents and verbal and motor responses to verbal stimuli) were recorded.

Statistical analysis

SPSS 12.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. The sample size was calculated to detect a 66% reduction of the incidence of agitation from 45% in control group with $\alpha = 0.05$ and $\beta = 0.80$. Numerical data including MAP, HR, IOP, extubation, and emergence time between groups were analyzed by Student's t test and intragroup numerical data were analyzed by repeated measures ANOVA. The nominal data including coughing and emergence agitation scores were analyzed by use of the χ^2 test. Statistical significance was accepted as $p < 0.05$.

Results

There were no significant differences in patient characteristics of between the two groups ($p > 0.05$) (Table 1). In both groups the IOP_{10min} was significantly lower than $IOP_{baseline}$ ($p < 0.01$). However, there was no significance difference in $IOP_{baseline}$ or IOP_{10min} between the two groups ($p > 0.05$) (Table 2). Similarly, in both groups MAP and HR were significantly lower after anesthetic induction than before induction ($p < 0.05$), but there was no significant difference between the groups. During extubation MAP and HR increased in the control group, but not the dexmedetomidine group ($p < 0.05$). Thus, MAP and HR during extubation were significantly lower in the dexmedetomidine group than in the control group ($p < 0.05$) (Figs. 1, 2). In the dexmedetomidine group, coughing after extubation was observed in ten patients (seven minimal and three moderate) compared with twenty-one (twelve minimal, seven moderate and two severe) in the control group ($p < 0.05$) (Table 3). There were no significant differences between the groups in time to emergence or extubation ($p > 0.05$). The incidence of emergence agitation was significantly lower in the dexmedetomidine group (3/30, 10%) than in the control group (13/30, 43.3%; $p < 0.05$) (Table 4). The incidence of breath holding, laryngospasm, bronchospasm, and oxygen

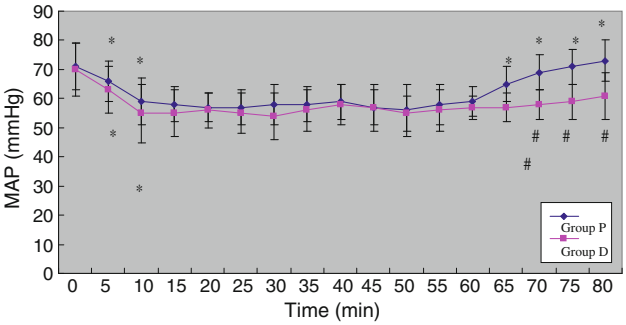

Fig. 1 Changes in mean arterial pressure (mean ± SD). *$p < 0.05$, different from the corresponding data point before anesthetic induction in both groups. *$p < 0.05$, different from the corresponding data point before extubation in group P. #$p < 0.05$ for comparison between groups. *x* axis is the duration of anesthesia

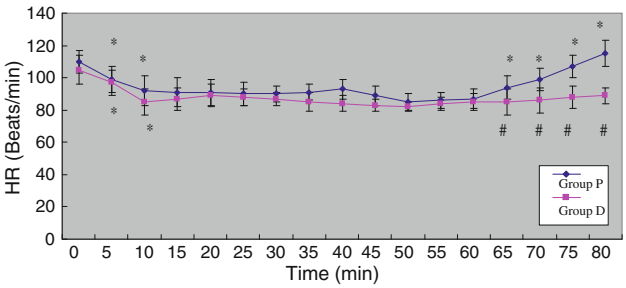

Fig. 2 Changes in heart rate (mean ± SD). *$p < 0.05$, different from the corresponding data point before anesthetic induction in both groups. *$p < 0.05$, different from the corresponding data point before extubation in group P. #$p < 0.05$ for comparison between groups. *x* axis is the duration of anesthesia

Table 1 Description of the two groups

	Group D ($n = 30$)	Group P ($n = 30$)	*p* value
Gender (male/female)	16/14	17/13	
Age (years)	5 ± 2	4 ± 1	0.647
Weight (kg)	20.5 ± 7.4	21.8 ± 6.2	0.532
ASA (I/II)	19/11	20/10	
Duration of surgery (min)	63 ± 12	65 ± 14	0.723

The was no statistically significant difference between these values. Mean ± SD are given for age, weight, and duration of surgery

Table 2 Intraocular pressure (IOP) data

	Group D ($n = 30$)	Group P ($n = 30$)	*p* value
$IOP_{Baseline}$, mean ± SD (mmHg)	19.36 ± 3.65	18.78 ± 4.01	0.218[a]
IOP_{10min}, mean ± SD (mmHg)	14.58 ± 4.39*	13.64 ± 3.31*	0.627[a]
p value	0.006[b]	0.005[b]	

* Statistically significant difference

[a] Differences between groups were analyzed by use of Student's *t* test

[b] Intragroup data were analyzed by use of repeated measures ANOVA

Table 3 Coughing scores data and extubation time and emergence time

	Group D ($n = 30$)	Group P ($n = 30$)	*p* value
1 point	20 (66.7%)*	9 (30.0%)	0.003
2 point	7 (23.3%)*	12 (40.0%)	0.028
3 point	3 (10.0%)*	7 (23.3%)	0.037
4 point	0 (0.0%)*	2 (6.7%)	0.046
Extubation time	5.78 ± 2.62	5.27 ± 3.08	0.757
Emergence time	12.35 ± 5.17	11.67 ± 4.12	0.462

* $p < 0.05$, statistically significant difference from group P

Table 4 Emergence agitation scores data

	Group D ($n = 30$)	Group P ($n = 30$)	*p* value
1 and 2 point	27 (90.0%)*	17 (56.7%)	0.024
3 and 4 point	3 (10.0%)*	13 (43.3%)	0.001
The incidence of emergence agitation	3/30 (10.0%)*	13/30 (43.3%)	0.001

* $p < 0.05$, statistically significant difference from group P

Table 5 Incidence of untoward airway events after extubation

	Group D ($n = 30$)	Group P ($n = 30$)	p value
Breath holding	5	6	0.084
Laryngospasm	0	1	0.061
Bronchospasm	0	0	0
Oxygen desaturation	4	5	0.075

There was no statistically significant difference between these values

desaturation was not significantly different between the groups ($p > 0.05$) (Table 5). In both groups the pain scores were less than 3 for all patients who were considered to have no emergence agitation.

Discussion

Our study showed that in pediatric patients undergoing vitreoretinal surgery dexmedetomidine 0.5 μg/kg had no effect on hemodynamics or IOP, but attenuated the extubation response and emergence agitation**.**

Virkkila et al. [5] previously found that dexmedetomidine could reduce IOP and BP. IOP mainly depends on the balance between the formation and drainage of aqueous humor. In addition to aqueous humor fluid dynamics, IOP during surgery is affected by changes in choroidal blood volume, vitreous volume, and extraocular muscle tone [6]. Although choroidal blood flow is autoregulated through a range of perfusion pressures, both choroidal blood flow and IOP drop when the MAP falls below 90 mmHg. We found no difference in IOP reduction in children between the dexmedetomidine and placebo groups when they were maintained at similar anesthetic levels, which suggested dexmedetomidine had no effect on IOP during induction. We suspect the reduction in IOP observed by Virkkila can be attributed to the effects of BP on IOP rather than to a direct effect of dexmedetomidine on the alpha-2 adrenoceptor. Moreover, Chhabra et al. [7] reported lens extrusion in open eye surgery when atropine was used to treat an episode of intraoperative bradycardia, resulting in a subsequent increase in heart rate and BP that was associated with spontaneous extrusion of the lens with vitreous prolapse. In consideration of the propensity of dexmedetomidine to induce bradycardia [8], we pretreated all study patients with atropine.

Dexmedetomidine is an alpha-2 adrenergic agonist, with a higher ratio of alpha-2/alpha-1 activity (1600:1) than clonidine (200:1). The hemodynamic effects of dexmedetomidine are similar to those of clonidine, but vary depending on dose, and rate and route of administration [12]. Dyck et al. [9] found that administration of dexmedetomidine 2 μg/kg over 5 min to volunteers had a biphasic response including an initial 22% increase in MAP and a 27% reduction in HR during the period of infusion, a subsequent stabilization of MAP at lower levels than baseline, and an unchanged HR. In contrast, Arain et al. [10] found that preoperative administration of 1 μg/kg in 10 min caused less than 20% reductions of HR and MAP in adults. Based on their experience with four cases from 10 weeks to 14 years of age, Tobias et al. [11] reported their use for sedation during mechanical ventilation for two patients. One a bolus dose of 0.50 μg/kg dexmedetomidine, diluted in normal saline to a volume of 10 ml and administered intravenously over a period of 10 min, reduced HR from 136 to 96 bpm and MAP from 158/108 to 126/66 mmHg. In contrast, administration of dexmedetomidine 0.60 μg/kg over 2 min to an 11-year-old patient did not cause obvious variations in HR and MAP. Thus, caution led us to choose 0.50 μg/kg administered over 10 min. As the duration of vitreoretinal surgery in pediatric patients is short (approx. 1 h) it is desirable to shorten extubation time and emergence time. This also affected our choice of a single bolus dose of 0.5 μg/kg without continuous infusion. In our study, the observed decreases in MAP and HR in both groups after anesthetic induction, that were assumed to be attributable to cardiovascular inhibition associated with anesthetic induction, indicated dexmedetomidine had no effect on MAP during anesthetic induction when anesthesia achieved a specific depth.

Although the mechanisms responsible for hemodynamic changes during extubation are unclear, wound pain, emergence from anesthesia, and tracheal irritation may be possible factors. Jin et al. [12] showed a moderate increase in blood pressure and heart rate for 5–15 min. Jaakola et al. [13] attenuated the increase in heart rate and arterial blood pressure during intubation by bolus injection of 0.6 μg/kg dexmedetomidine, which also reduced intra-operative IOP. Talke et al. [1] reported substantial attenuation of increases in blood pressure, heart rate, and plasma catecholamine concentrations during emergence for patients who had undergone vascular surgery, but postoperative blood pressure and heart rate were not affected. In that study, a dexmedetomidine infusion was given 20 min before the induction of anesthesia and continued for 48 h. Intraoperative use of anesthetics and post-operative use of analgesics were unaffected. Our single dose seems to have been as effective as infusion at extubation. Lawrence et al. [14] found that a single dose of dexmedetomidine before intubation reduced the need for both anesthetics and postoperative analgesics, and also attenuated the hemodynamic response to intubation and extubation. Because they used a large dose of dexmedetomidine before induction of anesthesia, hypotension and bradycardia were observed more frequently. Our study found that in the control group, MAP

and HR increased during extubation compared with before extubation. In contrast we found that dexmedetomidine attenuated the increases in blood pressure and heart rate during extubation because of a direct effect of dexmedetomidine on the alpha-2 adrenoceptor.

The presence of the endotracheal tube leads to reflex responses, the most common of which is coughing. Kim et al. [15] found a 76% incidence of coughing during emergence. Coughing can result in hypertension, tachycardia, increased intraocular and intracranial pressure, myocardial ischemia, bronchospasm, and surgical bleeding. Increases in IOP may also be associated with secondary glaucoma and irreversible damage of the optic nerve in intraocular surgery. Techniques used to minimize this problem include deep extubation and the use of a laryngeal mask. These techniques are inapplicable in non-fasted patients or those with gastroesophageal reflux disease. Intravenous opioids or lidocaine may diminish coughing, but may also delay emergence. Topical anesthesia applied before intubation is not effective. Our study found that a single bolus of dexmedetomidine 0.5 μg/kg facilitated tolerance of the endotracheal tube and significantly reduced coughing during extubation without affecting emergence time. This effect was possibly mediated by its sedative and analgesic properties.

Emergence agitation is a frequent side effect of inhalation anesthesia in children. Although there is no clinical evidence that the adverse effects affect long-term outcome, it is a source of dissatisfaction for parents and recovery room nurses. The etiology of agitation after sevoflurane anesthesia is uncertain and there is no well-established prophylaxis or treatment. Dexmedetomidine, because of its sedative and analgesic properties, might be also useful for management of emergence agitation. Ibacache et al. [16] studied the effect of dexmedetomidine 0.15 or 0.30 μg/kg compared with placebo controls on recovery characteristics for 90 children aged 1–10 year who underwent superficial lower abdominal and genital surgery. The time to eye opening and discharge from the postanesthesia care unit was similar in the 3 groups. The incidence of agitation was reduced from 37% (20–54%) in the control group, to 17% (4–30%) after 0.15 μg/kg dexmedetomidine and 10% (0–21%) after 0.30 μg/kg dexmedetomidine. In a placebo-controlled double-blinded trial involving 60 children (age 3–7 years) undergoing adenotonsillectomy, Guler et al. [17] found that a single dose of dexmedetomidine 0.5 μg/kg IV administered 5 min before the end of surgery reduced the incidence and severity of emergence agitation and postoperative pain after sevoflurane anesthesia. Isik et al. [18] found that prophylactic use of 1 μg/kg IV dexmedetomidine compared with placebo reduced the incidence of emergence agitation (EA) (from 47.6 to 4.8%) after sevoflurane-based anesthesia in 42 children (18 months to 10 years) undergoing magnetic resonance imaging (MRI). Although the times to LMA removal and eye opening to verbal stimuli were longer in the dexmedetomidine group, the recovery room and hospital discharge times were similar in the two groups.

In our study, we found that 0.5 μg/kg dexmedetomidine administered IV after induction, resulted in a reduction of postoperative agitation from 43.3% in the control group to 10%. Although this reduction is less than that reported for clonidine, described earlier, larger doses may have provided further protection from agitation. However, we would recommend a study of the potential increase in side effects before advocating use of a higher dose.

In conclusion, dexmedetomidine can be used without hemodynamic and IOP fluctuation. It can attenuate the extubation response and diminish emergence agitation in pediatric patients undergoing vitreoretinal surgery. The bolus administration of dexmedetomidine did not lead to an increased incidence of side effects. More studies are needed to determine whether larger doses would be more efficacious without increasing the risk of adverse effects, and to evaluate the suitability of this practice for other types of surgery.

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