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ORIGINAL ARTICLE

Intranasal dexmedetomidine premedication reduces minimum alveolar concentration of sevoflurane for laryngeal mask airway insertion and emergence delirium in children: a prospective, randomized, double-blind, placebo-controlled trial

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What is already known

- Intranasal dexmedetomidine is an effective sedative for premedication in children. It minimizes distress for children in the operating room environment and facilitates a smooth induction of anesthesia.

What this article adds

- Dexmedetomidine premedication produces a dose-dependent reduction in the minimum alveolar concentration for laryngeal mask airway insertion of sevoflurane, diminishes the incidence of emergence delirium without delaying PACU discharge, and improves parental satisfaction.

Implications for translation

- Dexmedetomidine premedication may be beneficial for sevoflurane induction and maintenance of anesthesia protocols in children.

Keywords
inhaled agents; depth of anesthesia; emergence delirium; postanesthesia care unit; child

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Summary

Background: We conducted a prospective, randomized, double-blind, placebo-controlled study to verify the hypothesis that intranasal dexmedetomidine premedication can reduce the minimum alveolar concentration of sevoflurane for laryngeal mask airway insertion in children.
Methods: Ninety American Society of Anesthesiologists (ASA) physical status I subjects, aged 3–7 years, were randomized to three equal groups to receive saline (Group S), dexmedetomidine 1 $\mu g \cdot kg^{-1}$ (Group D_1), or dexmedetomidine 2 $\mu g \cdot kg^{-1}$ (Group D_2) approximately 45 min before anesthesia. The minimum alveolar concentration for laryngeal mask airway insertion of sevoflurane was determined according to the Dixon's up-and-down method. Emergence delirium was evaluated using the Pediatric Anesthesia Emergence Delirium (PAED) scale in the postanesthesia care unit (PACU).
Results: Dexmedetomidine premedication of 1 and 2 $\mu g \cdot kg^{-1}$ was associated with reduction in sevoflurane from 1.92% to 1.53% and 1.23%, corresponding to decrease of 20% and 36%, respectively. The peak PAED scores (median [IQR]) were 9 [8–11.5], 5 [3–5.3], and 3 [2–4] in Group S, Group D_1, and Group D_2, respectively. The incidence of emergence delirium (defined as peak PAED score ≥10) was significantly lower in Groups D_1 and D_2 than in Group S ($P < 0.001$). Simultaneously, the induction qualities and the parent's

satisfaction scores were significantly higher in Groups D_1 and D_2 than in Group S ($P < 0.001$).
Conclusion: Intranasal dexmedetomidine premedication produces a dose-dependent decrease in the minimum alveolar concentration for laryngeal mask airway insertion of sevoflurane and emergence delirium in the PACU.

Introduction

Volatile induction and maintenance of anesthesia is a valid choice for pediatric day-care minor surgery (1). Sevoflurane is widely employed for pediatric anesthesia because of its beneficial pharmacological characteristics (2). However, the excitatory phenomenon is one of the main disadvantages during the inhalation induction and emergence, particularly in preschool children. Inhalation induction with high alveolar sevoflurane concentration may also be associated with an epileptiform electroencephalogram (3,4).

Laryngeal mask airway has been established as a useful device for pediatric anesthesia, which allows patients spontaneous respiration during general anesthesia with sevoflurane for minor surgery (5). However, airway complications (e.g., laryngospasm and cough), sometimes life-threatening, are commonly encountered during laryngeal mask airway placement in children, but the laryngeal mask airway can be smoothly inserted by deepening anesthesia.

Dexmedetomidine, a potent selective α_2-adrenergic agonist, possesses sedative, anesthetic-sparing, analgesic, sympatholytic, and hemodynamic-stabilizing properties and lacks respiratory depression, making it a useful and safe adjunct in diverse clinical applications (6). There is now increasing evidence to support the use of dexmedetomidine as a preanaesthetic medication in children (7,8). Premedication reduces anesthetic requirements, deepens the level of anesthesia and facilitates smooth inhalation induction (9). However, the dose-related effects of dexmedetomidine premedication on the minimum alveolar concentration of sevoflurane for laryngeal mask airway insertion remain undetermined in children. Therefore, we conducted this prospective, randomized, double-blind study to verify the hypothesis that intranasal dexmedetomidine might decrease the minimum alveolar concentration for laryngeal mask airway insertion of sevoflurane. The doses of 1 and 2 $\mu g \cdot kg^{-1}$ were chosen based on pediatric literature (10,11) and our pilot study.

Materials and methods

The study protocol was approved by the Institutional Ethics Committee of Fujian Provincial Hospital (Ref: FJSL 20130326) and registered at http://www.anzctr.org.au (ID ACTRN12613000462785) on April 23, 2013. This study was performed in line with the Declaration of Helsinki. Written informed consent was obtained from the parent or legal guardian before randomization. We enrolled 90 ASA physical status I children, aged 3–7 years, who underwent elective unilateral strabismus surgery from May 2013 to January 2014 at Fujian Provincial Hospital, Fuzhou, China. Subjects with potentially difficult airway, reactive airway malformation, any sign of upper respiratory infection, or asthma were excluded.

The enrolled subjects were randomly allocated to one of the three groups to receive premedication of 0.9% saline (Group S), dexmedetomidine 1 $\mu g \cdot kg^{-1}$ (Group D_1), or dexmedetomidine 2 $\mu g \cdot kg^{-1}$ (Group D_2) in a double-blinded fashion according to random number sequences generated using the SPSS 19.0 (SPSS Inc., Chicago, IL, USA) statistical software. The allocation ratio was 1 : 1 for the three groups. Group allocation concealment was ensured using numbered sealed opaque envelopes. The parent, investigator, attending anesthesiologist, and the person who performed the statistical analysis were blinded to group assignment.

Children received intranasal saline or dexmedetomidine at approximately 45 min before sevoflurane induction in the preoperative holding area. Dexmedetomidine 100 $\mu g \cdot ml^{-1}$ (Jiangsu Xinchen Pharmaceutical Co., Ltd, Lianyungang, China) was prepared in a 1-ml tuberculin syringe. The total final volume of administered solution was 0.02 $ml \cdot kg^{-1}$. Prior to the procedure, all subjects fasted for 6 h. Standard monitoring, including electrocardiogram, noninvasive blood pressure, pulse oximetry, and rectal temperature, was used in all children. Body temperature was maintained at 36.8 ± 0.4°C using a warming device (Bair Hugger; Augustine Medical Inc., Eden Praire, MN, USA). Inhaled and exhaled concentrations of sevoflurane and endtidal carbon dioxide partial pressure ($P_{ET}CO_2$) were continuously monitored (Cardiocap/5; Datex-Ohmeda, Louisville, CO, USA).

Anesthesia was induced with 5% sevoflurane in oxygen. The fresh gas flow was set at 6 $l \cdot min^{-1}$. Initially, subjects breathed spontaneously, and then ventilation was gently manually assisted, targeting $P_{ET}CO_2$ at 35–45 mmHg. Induction quality was assessed by a single attending anesthesiologist using a 4-point scale: 1 = crying, needs restraint; 2 = moderate fear and reassured

with difficulty; 3 = slight fear but can be reassured easily; and 4 = asleep or awake but co-operative, accepting the mask (12).

The minimum alveolar concentration for laryngeal mask airway insertion of sevoflurane was determined according to the modified Dixon's 'up-and-down' approach (13). The initial endtidal sevoflurane concentration was arbitrarily set at 2.0%, 1.5%, or 1.0% in the Group S, Group D_1, and Group D_2, respectively. The step size of the sevoflurane concentration was 0.2%. The ratio of predetermined endtidal to inspiratory concentration was maintained at 0.95–1.00 for at least 15 min to ensure equilibration between the brain, arterial blood and alveolar gas tension before a laryngeal mask airway (flexible Laryngeal Mask Airway™; The Laryngeal Mask Company Limited, Singapore) insertion was attempted. A single experienced anesthesiologist, who performed all laryngeal mask airway insertions in the study, was blinded to the nature of the premedication and sevoflurane concentration. Patient's responses to laryngeal mask airway insertion were classified by 'movement' or 'no movement'. Movement was defined as the presence of purposeful movement of extremities, coughing, or bucking within 1 min of laryngeal mask airway insertion. All responses to laryngeal mask airway insertion were assessed by two nurses who were blinded to the anesthetic concentration. If laryngeal mask airway insertion failed because of the patient's movement or upper-airway reactivity (coughing or bucking), anesthesia was immediately deepened by increasing inspired sevoflurane concentration; meanwhile, propofol 2 $mg{\cdot}kg^{-1}$ was used to facilitate laryngeal mask airway insertion. Thus, a single measurement was obtained from each subject.

After laryngeal mask airway insertion but before operation, the subjects received 15 $mg{\cdot}kg^{-1}$ intravenous paracetamol to control postoperative pain. Anesthesia was maintained with sevoflurane, supplemented by 60% nitrous oxide in oxygen. All subjects received topical anesthesia with two drops of 0.4% oxybuprocaine before and after the operation. The laryngeal mask airway was removed whenever the child resumed adequate spontaneous breathing. Delirium was assessed after removal of the laryngeal mask airway, and continuously thereafter until all children were clam. Emergence delirium was evaluated by the Pediatric Anesthesia Emergence Delirium (PAED) scale (14), and the peak value was recorded. Emergence delirium is defined as the PAED scale ≥10. Immediately before discharge, the parent's satisfaction was evaluated with a 10-point numerical rating scale: 10 = excellent, 1 = bad.

The primary outcome of our study was the minimum alveolar concentration for laryngeal mask airway insertion of sevoflurane. The secondary outcomes included the incidence of emergence delirium, the induction quality, the time of emergence, duration of postanesthesia care unit (PACU) stay, the parent's satisfaction, and the incidence of adverse effects such as bradycardia and hypotension.

Statistical analysis

Our sample size estimation was based on the minimum alveolar concentration for laryngeal mask airway insertion of sevoflurane in children is approximately 2.0% (15,16). Twenty-eight patients were required in each group to detect a 20% difference in the MAC (from 2.0% to 1.6%) between the groups at a power of 0.8 and a type I error of 5%. Allowing for incomplete follow-up or dropout, the total number of included patients was increased to 30 per group.

Statistical analyses were performed using the SPSS 19.0 for Windows (SPSS Inc.). Parametric data were described as means and standard deviations (SD); nonparametric data were described as medians and interquartile ranges (IQR). EC_{50} values were obtained by calculating the midpoint concentration of all independent response crossovers in which a 'movement' response to a 'no movement' response. The up-and-down sequences data were also analyzed using probit regression to obtain the endtidal sevoflurane concentration wherein 50% (EC_{50}) and 95% (EC_{95}) of the laryngeal mask airway insertion attempts were successful. The induction quality, delirium scores, and the parent's satisfaction were analyzed by Students–Newman–Keuls (SNK), Kruskal–Wallis, and Mann–Whitney *U*-tests, where appropriate. A *P*-value < 0.05 was considered statistically significant.

Results

A total of 123 subjects were screened for eligibility to participate in the study, and 90 subjects were subsequently enrolled. No subject cried, required restraint, or complained of discomfort with intranasal dexmedetomidine administration in our study. One subject in Group S was excluded due to administration of additional bolus injections of sufentanil 0.05 $\mu g{\cdot}kg^{-1}$ as rescue analgesia during the operation. Consolidated Standards of Reporting Trials (CONSORT) flow diagram (17) is shown in Figure 1. Subjects were comparable with respect to demographic characteristics, duration of surgery, and duration of anesthesia among the three groups (Table 1).

Dose–response data obtained with the up-and-down method are shown in Figure 2. The minimum alveolar concentration for laryngeal mask airway insertion of

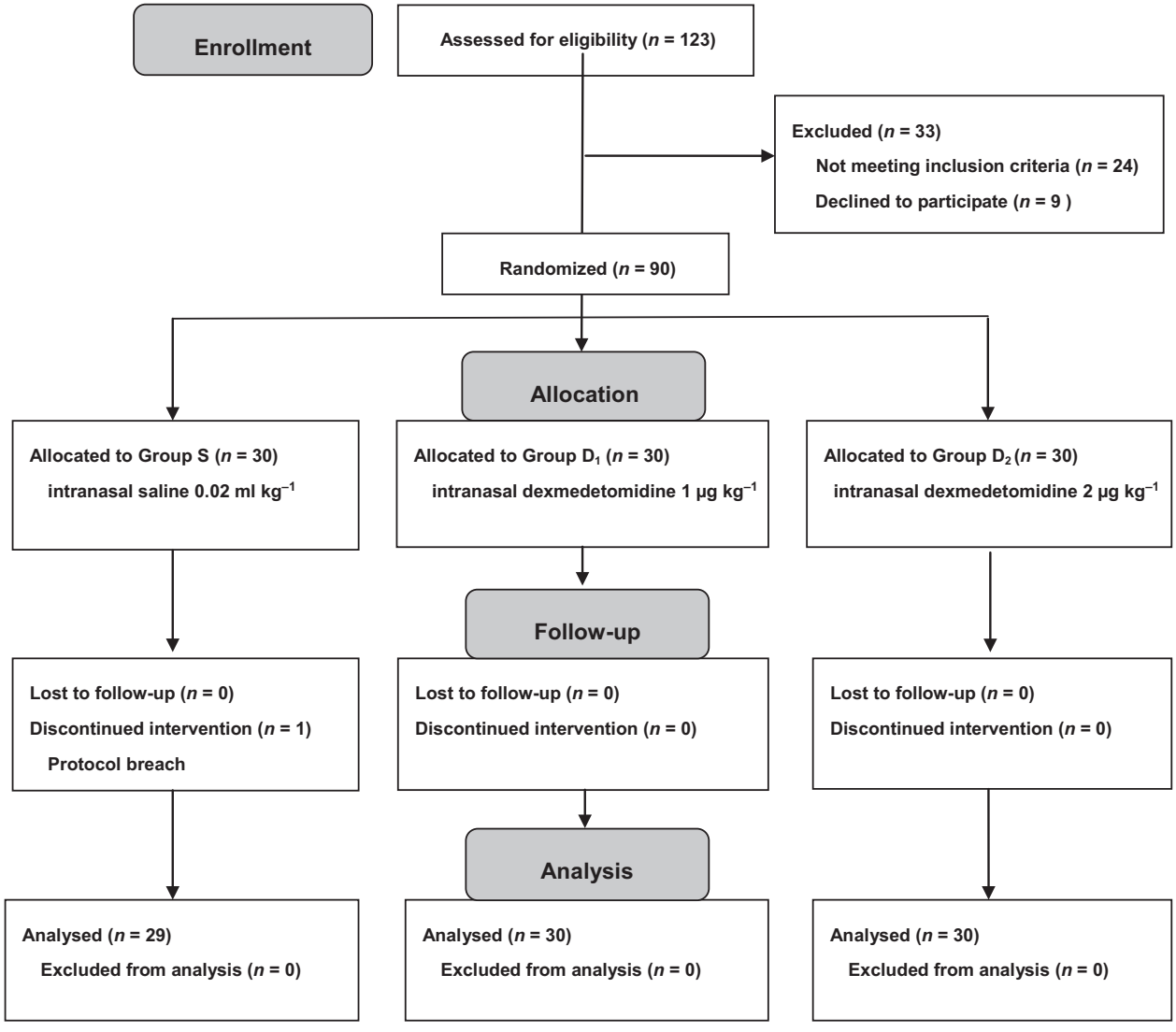

Figure 1 Consort flow diagram.

Table 1 Patient characteristics

	Saline (n = 30)	DEX 1 μg·kg^{-1} (n = 30)	DEX 2 μg·kg^{-1} (n = 30)	P-value
Age (year)	4.7 ± 0.9	4.5 ± 0.8	4.4 ± 0.8	0.242
Gender (M/F)	18/12	19/11	17/13	0.553
Weight (kg)	17.8 ± 2.0	18.3 ± 2.4	17.9 ± 2.9	0.491
Height (cm)	103.4 ± 8.7	105.2 ± 6.1	103.1 ± 9.9	0.399
Duration of anesthesia (min)	81.1 ± 5.9	78.4 ± 5.6	80.5 ± 5.4	0.167
Duration of surgery (min)	39.0 ± 6.0	37.6 ± 5.1	39.5 ± 5.8	0.415

Values are presented as mean ± SD or number of patients.

sevoflurane was 1.92 ± 0.16%, 1.53 ± 0.14%, and 1.23 ± 0.14% in Group S, Group D_1 and Group D_2, respectively. EC_{50} and EC_{95} values of sevoflurane for laryngeal mask airway insertion by probit regression analysis were 1.99% (95% CI, 1.87–2.12%) and 2.28% (95% CI, 2.15–2.92%) in Group S, 1.59% (95% CI, 1.51–1.67%) and 1.78% (95% CI, 1.69–2.09%) in Group D_1, and 1.29% (95% CI, 1.21–1.38%) and 1.48% (95% CI, 1.39–1.83%) in Group D_2. EC_{50} values calculated by probit regression were

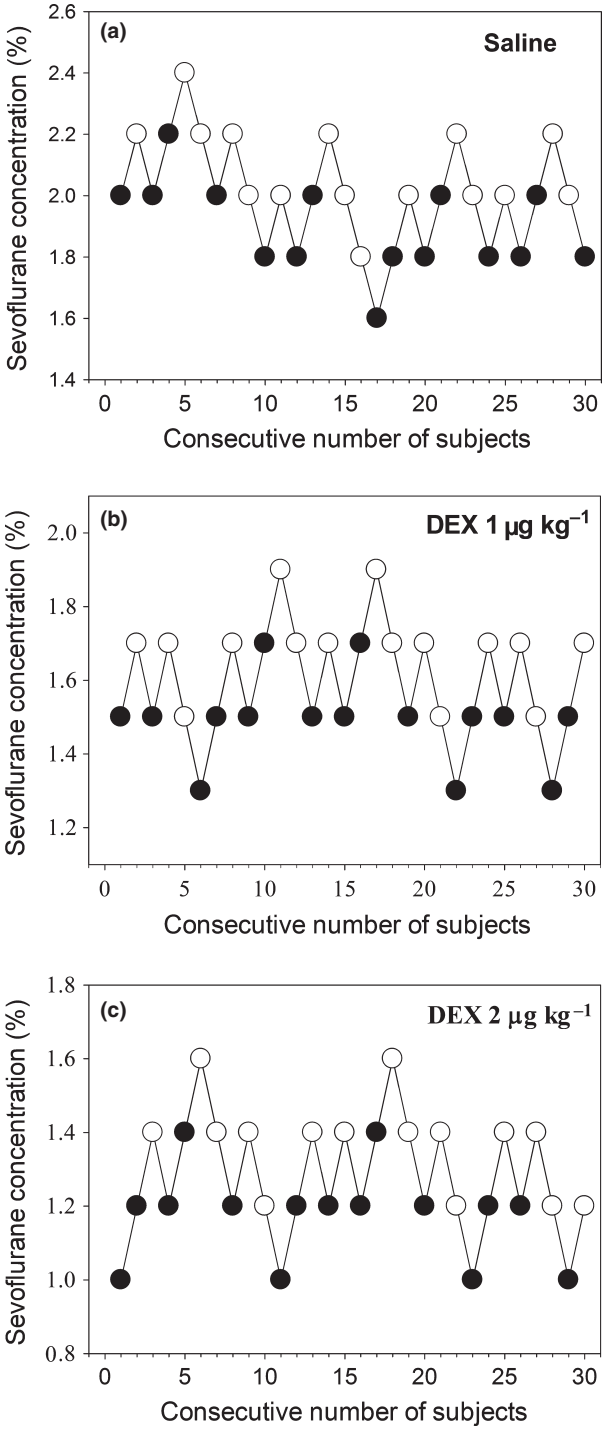

Figure 2 The end-tidal sevoflurane concentrations at which patients did (●) or did not (○) move in response to laryngeal mask airway insertion. (a) The responses of 30 consecutive saline premedicated children. (b) The responses of 30 consecutive dexmedetomidine 1 $\mu g \cdot kg^{-1}$ premedicated children. (c) The responses of 30 consecutive dexmedetomidine 2 $\mu g \cdot kg^{-1}$ premedicated children.

comparable with those determined by up-and-down methodology.

As shown in Table 2, the peak agitation scores (median [IQR]) were 9 [8–11.5] in Group S, 5 [3–5.3] in Group D_1, and 3 [2–4] in Group D_2. The percentage of patients with a score of 10 and above for the PAED were significantly lower in Groups D_1 and D_2 than in Group S ($P < 0.001$). Simultaneously, the parent's satisfaction scores were significantly higher in Groups D_1 and D_2 than in Group S ($P < 0.001$).

The induction quality scores (median [IQR]) were 2.5 [2–3], 3 [3–4], and 4 [3–4] in Group S, Group D_1, and Group D_2, respectively. The induction qualities of Groups D_1 and D_2 were significantly higher than Group S during sevoflurane induction ($P < 0.001$). The time for awakening of Groups D_1 and D_2 was comparable ($P = 0.121$) and significantly longer than that of Group S ($P < 0.001$). However, there was no statistical difference in PACU stay duration among groups ($P = 0.292$).

Changes in heart rate (HR) and systolic blood pressure (SBP) are shown in Figure 3. The maximum mean reductions in HR were 13.8% and 17.5% for Groups D_1 and D_2, respectively. The maximum mean reductions in SBP were 12.7% and 16.1% for Groups D_1 and D_2, respectively. No patient developed bradycardia (HR <60 bpm), hypotension (SBP <70 mmHg), or hypoxemia (oxygen saturation <95%) during the observation period.

Discussion

This prospective double-blind randomized study demonstrated that intranasal dexmedetomidine premedication of 1 and 2 $\mu g \cdot kg^{-1}$ was associated with dose-dependent reduction in sevoflurane from 1.92% to 1.53% and 1.23%, corresponding to decrease of 20% and 36%, respectively. Moreover, we found that intranasal dexmedetomidine premedication diminishes emergence delirium without delaying PACU discharge in children undergoing elective unilateral strabismus surgery.

Sevoflurane induction has proved to be an appropriate procedure for laryngeal mask airway insertion in children. The minimum alveolar concentration for laryngeal mask airway insertion of sevoflurane is in the range of 1.57–2.0% in children (18,19). In this present study, we revealed an analogous minimum alveolar concentration for laryngeal mask airway insertion (1.92% in Group S). The small difference in minimum alveolar concentration for laryngeal mask airway insertions among studies may be explained in part by several methodological differences. Dexmedetomidine has been shown to reduce the requirement of volatile anesthetics

Table 2 Characteristics of the recovery phase in the PACU

	Saline (n = 29)	DEX 1 μg·kg^{-1} (n = 30)	DEX 2 μg·kg^{-1} (n = 30)	P-value
Peak PAED score	9 (8–11.5)	5 (3–5.3)*	3 (2–4)*,†	<0.001
PAED score ≥10, n (%)	14/29 (48.3%)	5/30 (16.7%)*	1/30 (3.3%)*,†	<0.001
Emergence time (min)	16.6 ± 2.9	22.3 ± 4.0*	24.5 ± 4.2*	<0.001
Duration of PACU stay(min)	33.1 ± 4.0	32.6 ± 4.2	34.3 ± 4.6	0.292
Parents satisfaction	6.1 ± 1.3	7.6 ± 1.4*	8.5 ± 1.1*,†	<0.001

PACU, postanesthesia care unit; DEX, dexmedetomidine; PAED, Pediatric Anesthesia Emergence Delirium.
Data are presented as median (interquartile range), or numbers (percent), or mean ± standard deviation (SD).
*P < 0.05, vs the control group.
†P < 0.05, vs the dexmedetomidine 1 μg·kg^{-1} group.

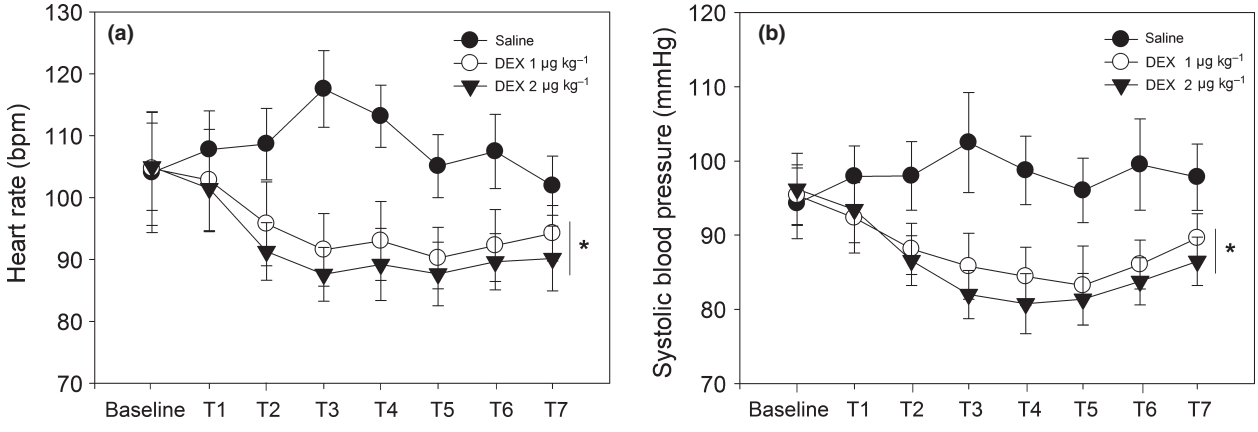

Figure 3 Changes in heart rate (HR) and systolic blood pressure (SBP) during observation period. Overall, both hemodynamic variables were statistically lower in the dexmedetomidine group (*P < 0.05). Values are means ± SD. Measurement points: baseline = before premedication, T1 = 15 min after premedication, T2 = 30 min after premedication, T3 = 45 min after premedication, T4 = before laryngeal mask airway intubation, T5 = before operation, T6 = before laryngeal mask airway extubation, T7 = before discharge from (postanesthesia care unit [PACU]).

in clinical studies (20,21). In our study, the extent of reduction of minimum alveolar concentration for laryngeal mask airway insertion of sevoflurane by intranasal dexmedetomidine 2 μg·kg^{-1} premedication was approximately 36%, which was comparable with the previous study (15).

The clinical implications of the current study are several. Intranasal administration is an effective and noninvasive route. The absorption is very rapid due to the large surface area and vascularity of the nasal mucosa. Dexmedetomidine premedication may produce satisfactory sedation by activating of the locus ceruleus. It facilitates a smooth induction of general anesthesia and deepen anesthesia with minimum the emotional trauma.

Another important finding of this study was the beneficial effect of dexmedetomidine premedication on the quality of recovery profile. Emergence delirium occurs frequently in children during recovery from sevoflurane anesthesia. Emergence delirium carries the risks of self-injury and the stress caused to both caregivers and families. Dexmedetomidine has been used for the management of emergence delirium due to its sedative and analgesic effects (22). In our study, intranasal dexmedetomidine premedication of 1 and 2 μg·kg^{-1} resulted in a reduction of postoperative delirium (defined as peak PAED score ≥10) from 48.3% in the control group to 16.7% and 3.3%, respectively. In addition, our data indicated that dexmedetomidine premedication may improve parent satisfaction. The improved recovery profile in the dexmedetomidine group was associated with a significantly longer awakening time (6–8 min) compared with the saline group. However, this statistically significant difference is not clinically significant. Moreover, the delayed emergence from anesthesia did not delay PACU discharge.

The current study revealed that intranasal dexmedetomidine (1 or 2 μg·kg^{-1}) produces a dose-dependent reduction in HR and SBP, which may be attributed to a decrease in central sympathetic tone and an increase in vagal activity. However, we only observed a modest reduction (within 20% of baseline values) of hemodynamic variables, and these effects were clinically insignificant; at least in this setting, no intervention was required.

There are some limitations to the present study that require consideration when interpreting the results. First, there are no pharmacokinetic data available following administration of intranasal dexmedetomidine in children. Furthermore, we did not measure the actual serum concentrations of dexmedetomidine. Therefore, intranasal dexmedetomidine premedication may not reach its peak effect before laryngeal mask airway insertion. However, Yuen *et al*. (23) reported that the median time of onset of sedation was 25–45 min. To fit our clinical practice, the premedication period was 45 min in this study. Second, our preliminary results indicated no subjects need rescue analgesics and all subjects were expected to experience a similar slight pain in this study, and we did not evaluate the degree of postoperative pain, which is likely to affect the incidence of agitation. Third, we did not measure glucose levels in the children studied. Ghimire *et al*. (24) reported that dexmedetomidine decreased plasma insulin concentration and may cause hyperglycemia in healthy fasting individuals. Therefore, further studies are required to address these limitations and verify our findings.

In conclusion, intranasal premedication dexmedetomidine produces a dose-dependent reduction in the minimum alveolar concentration for laryngeal mask airway insertion of sevoflurane, diminishes the incidence of emergence delirium in the PACU, and improves parental satisfaction.

Acknowledgements

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Conflict of interest

No conflicts of interest declared.

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