

Original Article

Effects of different doses of dexmedetomidine in combination with sevoflurane for laryngeal mask airway placement in children during laparoscopic inguinal hernia repair

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Abstract: Objective: The aim of this study to investigate the effects of 2 µg/kg and 4 µg/kg of dexmedetomidine (Dex) pretreatment on the median effective concentration (EC₅₀) of sevoflurane for successful laryngeal mask airway (LMA) placement in children during laparoscopic inguinal hernia repair. Methods: 82 cases of children (aged from 2 to 6 years, and ASA at I or II grade) were recruited and randomly divided into 3 groups, including control (n=25), 2 µg/kg of Dex (n=28), and 4 µg/kg of Dex (n=29). After sublingual administration for 0.9% saline and Dex, probabilistic unit regression analysis was applied to calculate the EC₅₀ and the corresponding 95% confidence interval (95% CI) of sevoflurane in children for successful LMA placement. Results: The rates of parental separation satisfaction and mask acceptance satisfaction in the 4 µg/kg of Dex (100%, 89.66%) group were significantly higher than those in the control (8.0%, 0.0%) and 2 µg/kg of Dex (64.29%, 46.43%) groups. The positive rates of LMA placement among the control (48.0%), 2 µg/kg of Dex (46.43%), and 4 µg/kg of Dex (44.83%) groups had no significant difference. The EC₅₀ and 95% CI of sevoflurane in the 4 µg/kg of Dex group (1.55%, 1.42-1.66%) was remarkable lower than those in the control (2.02%, 1.89-2.14%) and 2 µg/kg of Dex (1.73%, 1.61-1.85%) groups. Compared with the control group, 2 µg/kg and 4 µg/kg of Dex could decrease the EC₅₀ of sevoflurane in children for successful LMA placement by 14.36% and 23.27%, respectively. Conclusion: Dex pretreatment effectively reduces the EC₅₀ of sevoflurane for successful LMA placement in children during laparoscopic inguinal hernia repair.

Keywords: Sevoflurane, dexmedetomidine, effects, LMA, pretreatment

Introduction

Laryngeal mask airway (LMA) placement is a common alternative to the endotracheal tube and face mask for insuring the respiratory tract in elective operation under general anesthesia in children [1, 2]. The forfeit of protective respiratory tract reflexes and blockade of the upper airway after general anesthesia can be life-threatening. LMA placement can offer a close against the glottis without changing the mucosal pressures, which also has a port for gastric drain tube to prohibit aspiration [3, 4]. Emerging evidences have suggested that sevoflurane is a useful and suitable inhalational drug for induction and preservation of anesthesia in children [5]. During LMA placement,

sevoflurane is applied as a prevalent induction drug based on the depressant effects for the airway reflexes. However, separating children from their parents before induction of anesthesia and receiving mask inhalation to induce LMA implantation is a major challenge for anesthesiologists worldwide.

Dexmedetomidine (Dex) is a highly selective α₂-adrenergic agonist, which shows analgesic and sedative effects with minimal respiratory depression [6, 7]. Recent studies have shown that Dex presents with a high bioavailability for drug administration [8]. On one hand, Dex is suitable for producing sedation before pediatric anesthesia, and its sedative effect is better than midazolam [7, 9]. On the other hand, Dex

as a general anesthetic agent can inhibit sympathetic activities, obviously reduce the stress responses during LMA placement, and decrease the dose required for general anesthesia [10]. For instance, Yoo et al [11] demonstrated that pretreatment with 1 µg/kg of Dex reduces the propofol requirement by 38% for boosting LMA placement without prolonged hemodynamic instability and respiratory depression. Nellore et al [12] suggested that Dex significantly reduces the induction doses of propofol for LMA placement.

To date, there is no dose-ranging study of Dex pretreatment on the median effective concentration (EC_{50}) of sevoflurane for successful LMA placement in children during laparoscopic inguinal hernia repair. Therefore, our study intended to refer the modified sequential method to determine the effects of 2 µg/kg and 4 µg/kg of Dex pretreatment on the EC_{50} of sevoflurane, and to provide references for the clinical application of Dex combined sevoflurane for insertion of LMA in children.

Materials and methods

Patients selection and experimental grouping

82 cases of children (aged from 2 to 6 years, ASA at I-II grade, and BMI at 18-25 kg/m²) who underwent laparoscopic inguinal hernia repair with elective general anesthesia were recruited and selected, and divided into three groups by random number method, including control (n=25), 2 µg/kg of Dex (n=28), and 4 µg/kg of Dex (n=29). Inclusion criteria: children underwent laparoscopic inguinal hernia. Exclusion criteria: bronchial asthma, history of upper respiratory tract infection within 2 weeks, allergy to Dex, arrhythmia, congenital heart disease, mental illness, and congenital and neurological disorders. This study was approved by the Ethics Committee of Longgang District People's Hospital of Shenzhen and registered at the China Clinical Trial Registration Center (No. ChiCTR-IOD-17011601). The parents of each child were informed of the risk and signed the informed consent form.

Anesthesia process

All children were banned from eating 6-8 h and drinking 2-3 h before surgery, and were established venous indwelling needles before sur-

gery. Non-invasive blood pressure (NIBP), electrocardiogram (ECG), and oxygen saturation (SpO_2) were monitored for 1 h before anesthesia. 2 and 4 µg/kg of Dex (No. 16062432; Jiangsu Hengrui Pharmaceutical Co., Ltd.) was used for sublingual administration. The children in control group were treated with equal amounts of 0.9% saline. After sublingual administration for 1 h, the children were separated from their parents and entered the operating room for sevoflurane treatment (No. 14112431; Shanghai Hengrui Pharmaceutical Co., Ltd.). After the concentration of sevoflurane reached 8%, the mask was applied to the nose and mouth of each child for inhalation induction. After the consciousness disappeared completely, the auxiliary-controlled breathing was adjusted. After maintaining the concentration for 10 min, the anesthesiologists were placed with a 1.5 type of LMA without using the muscle relaxant drugs or other intravenous anesthetic drugs. Then end-tidal concentration of sevoflurane was determined according to the modified sequential method [13]. The initial end-expiratory concentration of sevoflurane was 2%, and the next patient with end-tidal concentration of sevoflurane was determined according to the LMA placement reaction. When the patient's LMA placement reaction was positive, the end-tidal concentration of sevoflurane was increased by 0.2%; when the LMA placement reaction was negative, the end-expiratory concentration of sevoflurane was reduced by 0.2%. This process was repeated until the seventh exchange points appeared, and the experiment was completed to determine the sample sizes.

Observation indexes

Sedation scores, mask inhalation-induced acceptance and LMA placement reaction, and vital signs monitoring were conducted by another anesthesiologists. Sedation scoring criteria: crying and struggling counted as 1 point; awake and crying counted as 2 points; lethargy counted as 3 points; sleeping counted as 4 points. 1-2 points indicated dissatisfaction, and 3-4 points indicated satisfaction. Pediatric mask acceptance scoring criteria: aggressive and angry state did not accept a mask for 1 point; fear and not easy to accept a mask for 2 points; fear but easy to accept a mask for 3 points; quiet to accept a mask for 4

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Table 1. Comparison of general clinical indicators

Groups	Number of cases	Gender (man/female)	ASA grade (I/II)	Average ages (years)	BMI
Control	25	16/9	18/7	4.15 ± 1.78	20.33 ± 1.85
2 µg/kg of Dex	28	19/9	20/8	4.19 ± 1.54	21.82 ± 1.59
4 µg/kg of Dex	29	21/8	20/9	4.27 ± 1.80	20.94 ± 1.72
χ ² or F	-	0.44	0.07	0.52	1.61
P	-	0.80	0.97	0.77	0.34

points. 1-2 points indicated dissatisfaction, and 3-4 points indicated satisfaction. LMA placement reaction criteria: any one of cough, body movement, and throat or whole body conscious body movements within 1 min of LMA placement was positive; no response was negative. The heart rate (HR), systolic blood pressure (SBP) and blood oxygen saturation (SaO₂) were recorded before sublingual administration and every 5 min after sublingual administration. The incidence of adverse reactions such as hypotension, bradycardia, respiratory depression, nausea, and vomiting were observed. Clinical indicators before and after operation were also recorded, including operation time, hospitalization time, postoperative analgesic application, postoperative infection, recurrence of hernia, chronic pain, local discomfort, local hematoma, and urine retention.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 statistical software (SPSS, Chicago, IL, USA). Measurement data were expressed as the mean ± standard deviation (SD). One-way analysis of variance was used for comparing the differences between the three groups. Count data were expressed as percentages, and the differences were assessed by using chi-square (χ²) test. Probability unit regression analysis was applied to calculate the EC₅₀ and corresponding 95% CI of sevoflurane in children with successful LMA placement. Sequential test plots were drawn by using Microsoft Excel 2007 software (Microsoft Corp, Seattle, WA, USA). P<0.05 was considered statistically significant.

Results

General clinical indicators

A total of 82 cases of children were enrolled in the study, 25 cases of children were in the con-

trol group, 28 cases of children were in the 2 µg/kg of Dex group, and 29 cases were of children in the 4 µg/kg of Dex group. The constituent ratios of gender (man/female) in the control, 2 µg/kg of Dex, and 4 µg/kg of Dex groups were 16/9, 19/9, and 21/8, respectively. The constituent ratios of ASA grade (I/II) in the control, 2 µg/kg of Dex, and 4 µg/kg of Dex groups were 18/7, 20/8, and 20/9, respectively. The average ages in the control, 2 µg/kg of Dex, and 4 µg/kg of Dex groups were 4.15 ± 1.78, 4.19 ± 1.54, and 4.27 ± 1.80 years, respectively. The BMI in the control, 2 µg/kg of Dex, and 4 µg/kg of Dex groups was 20.33 ± 1.85, 21.82 ± 1.59, and 20.94 ± 1.72, respectively. There were no significant differences in constituent ratio of gender and ASA grade, average ages, and BMI among the control, 2 µg/kg of Dex, and 4 µg/kg of Dex groups (Table 1). All children were able to tolerate sublingual administration without significant discomfort. Before the induction of anesthesia, the SpO₂ was greater than 95% without significant respiratory depression. No adverse reactions such as bradycardia, hypotension, nausea and vomiting were observed. There was no significant difference in operation and hospitalization time among the three groups. All children had no postoperative infection, scrotal hematoma, scrotal effusion, and urinary retention. After 6 to 24 months of follow-up, all children had no obvious discomfort or foreign body sensation in the groin area, and no case recurred.

Dex pretreatment increases the rates of parental separation satisfaction and mask acceptance satisfaction

As shown in Table 2, the rates of parental separation satisfaction and mask acceptance satisfaction in the 4 µg/kg of Dex (100%, 89.66%) group were significantly higher than those in the control (8.0%, 0.0%) and 2 µg/kg of Dex (64.29%, 46.43%) groups (P<0.05). The

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Table 2. Comparison of the rates of parental separation satisfaction and mask acceptance satisfaction

Groups	Number of cases	Parental separation satisfaction (n, %)	Mask acceptance satisfaction (n, %)
Control	25	2 (8.0%)	0 (0.0%)
2 µg/kg of Dex	28	18 (64.29%)	13 (46.43%)
4 µg/kg of Dex	29	29 (100%)	26 (89.66%)
χ ²	-	47.62	43.29
P	-	<0.001	<0.001

4 µg/kg of Dex groups were 12/13, 13/15, and 13/16 (Figure 1). The positive rates of LMA placement among the control (48.0%), 2 µg/kg of Dex (46.43%), and 4 µg/kg of Dex (44.83%) groups had no significant difference.

Dex pretreatment decreases the EC₅₀ of sevoflurane for successful LMA placement in children

The EC₅₀ and 95% CI of sevoflurane in the 4 µg/kg of Dex group (1.55%, 1.42-1.66%) were markedly lower than those in the control (2.02%, 1.89-2.14%) and 2 µg/kg of Dex (1.73%, 1.61-1.85%) groups (Figure 2, P<0.05). Compared with the control group, 2 µg/kg and 4 µg/kg of Dex reduced the EC₅₀ of sevoflurane in children for successful LMA placement by 14.36% and 23.27%, respectively.

Discussion

Dex injection (pH at 4.5-7.0) contains no preservatives and chemical stabilizers, which is a colorless and odorless clear liquid and is suitable for oral and nasal administration [14]. Iriola et al [15] reported that oral administration of Dex in adult volunteers has a bioavailability of only 16% due to first-pass effects, while intranasal administration has 65% bioavailability and the bioavailability of sublingual administration is as high as 82%. Although partial swallowing may occur in the oral administration, the oral buccal mucosa absorbs Dex and can reach at an average of 56%, and it is more acceptable for

children than nasal administration [16]. In this study, we gave 57 cases of children with Dex by

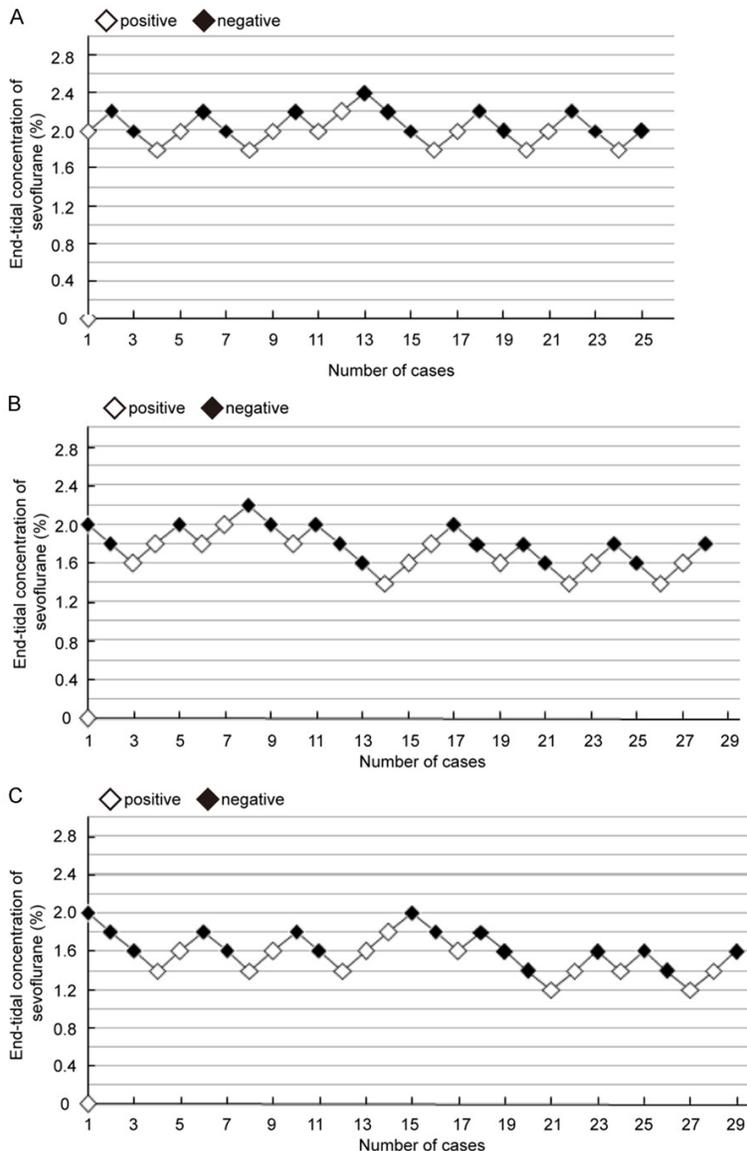


Figure 1. Sequential test charts of sevoflurane for inhibiting LMA placement in children. The number of positive/negative cases of LMA placement in the control (A), 2 µg/kg of Dex (B), and 4 µg/kg of Dex (C) groups were 12/13, 13/15, and 13/16.

numbers of positive/negative cases of LMA placement in the control, 2 µg/kg of Dex, and

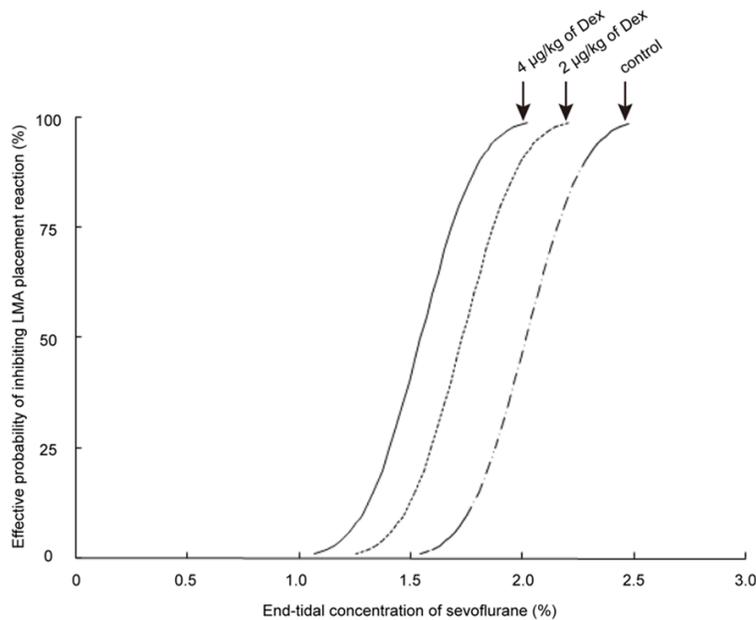


Figure 2. Concentration-effect curves of sevoflurane for inhibiting LMA placement in children. The EC₅₀ and 95% CI of sevoflurane in the 4 µg/kg of Dex group were markedly lower than those in the control and 2 µg/kg of Dex group.

sublingual administration, all children and their parents were easy to accept, suggesting that Dex is suitable for children sublingual administration before anesthesia.

Recent report by Sakurai et al [17] showed that 75% of children can achieve Ramsay sedation score of 5 points or more when 3-4 µg/kg of Dex was given 1 h before anesthesia. It was safe and effective to give 3-4 µg/kg of Dex 1 h before anesthesia, but the study did not evaluate the satisfaction of receiving a mask and LMA placement, and did not discuss the effects on the EC₅₀ of sevoflurane after Dex administration. Therefore, our study was divided into the control, 2 µg/kg, and 4 µg/kg of Dex groups, and the sedation scores, mask inhalation-induced acceptance, and LMA placement reaction, and vital signs monitoring among the three groups were evaluated 1 h before anesthesia. Our results revealed that the satisfaction rates of sedation and masks in the 4 µg/kg of Dex group were 100% and 89.7%, which were higher than those in the control (8.0%, 0.0%) and the 2 µg/kg (64.29%, 46.43%) of Dex groups, respectively. The positive rates of LMA placement in control (48.0%), 2 µg/kg of Dex (46.43%), and 4 µg/kg of Dex (44.83%) groups have no

statistical difference, indicating that 2 and 4 µg/kg of Dex have no effect on the positive reaction of mask placement. The possible reasons may be the following: 1) Dex has analgesic and sedative effects with minimal respiratory inhibition; 2) Dex can suppress sympathetic activities, and obviously reduce the stress responses during LMA placement; 3) Children are well tolerated with Dex; 4) Other factors. In addition, all children had no adverse reactions such as hypotension, bradycardia, and hypoxemia, indicating that Dex is absorbed into the blood through the oral mucosa, and it can achieve effective sedation and slow side effects.

Furthermore, we referred to Savla et al's report [18] to set

the initial end-tidal concentration of sevoflurane to 2% and the concentration gradient to 0.2%. The EC₅₀ of sevoflurane was determined by using a modified sequential method. The results showed that the inhalation of sevoflurane inhibited the LMA placement response of 2.02%, which was similar to that of He et al study [19] (2.01%), but higher than Aantaa et al's research [20]. Aantaa et al reported that the EC₅₀ of sevoflurane satisfied for LMA placement was 1.57% in children aged 4 to 12 years old. The main reason might be the difference in ages, in addition to the research methods and criteria for evaluating the LMA placement reaction [21, 22]. Here, we found that 2 µg/kg of Dex and 4 µg/kg inhibited the LMA placement reaction with the EC₅₀ of sevoflurane of 1.73% and 1.55%, respectively, which were 14.36% and 23.27% lower than that of the control group. These data indicated that Dex enhances the sedative effects of sevoflurane and significantly inhibits the stress response during LMA placement, thereby reducing the end-tidal concentration of sevoflurane.

In clinical application, some children did not cooperate, and spat out the drug solution immediately after administration, which affect-

ed the sedative effect and should be noticed. In this study, we recommended a small amount (0.1-0.3 ml) of 50% glucose injection mixed with Dex injection for sublingual administration, so the children are more likely to receive without increasing the amounts of the drug and causing swallowing. At the same time, we should also notice clearly that this study only explored the dose-effects relationship of Dex combined with sevoflurane in the inhibition of LMA placement in children, and the dose-effects in other ages need further study.

In summary, our study demonstrated that Dex pretreatment effectively reduces the EC_{50} of sevoflurane for successful LMA placement in children, indicating that Dex combined with sevoflurane is the suitable induction agent of choice for insertion of LMA.

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Disclosure of conflict of interest

None.

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References

- [1] Xu R, Lian Y and Li WX. Airway complications during and after general anesthesia: a comparison, systematic review and meta-analysis of using flexible laryngeal mask airways and endotracheal tubes. *PLoS One* 2016; 11: e0158137.
- [2] van Esch BF, Stegeman I and Smit AL. Comparison of laryngeal mask airway vs tracheal intubation: a systematic review on airway complications. *J Clin Anesth* 2017; 36: 142-150.
- [3] Bansal SC, Caoci S, Dempsey E, Trevisanuto D and Roehr CC. The laryngeal mask airway and its use in neonatal resuscitation: a critical review of where we are in 2017/2018. *Neonatology* 2018; 113: 152-161.
- [4] Pourciau DC, Hotard D 3rd, Hayley S, Hayley K, Sutton C, McWhorter AJ and Fink DS. Safety and efficacy of laryngeal mask airway ventilation in obese patients with airway stenosis. *Laryngoscope* 2017; 127: 2582-2584.
- [5] Kim EH, Song IK, Lee JH, Kim HS, Kim HC, Yoon SH, Jang YE and Kim JT. Desflurane versus sevoflurane in pediatric anesthesia with a laryngeal mask airway: a randomized controlled trial. *Medicine (Baltimore)* 2017; 96: e7977.
- [6] Mahmoud M and Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. *Br J Anaesth* 2015; 115: 171-182.
- [7] Barends CR, Absalom A, van Minnen B, Vissink A and Visser A. Dexmedetomidine versus midazolam in procedural sedation. A systematic review of efficacy and safety. *PLoS One* 2017; 12: e0169525.
- [8] Venkatraman R, Hungerford JL, Hall MW, Moore-Clingenpeel M and Tobias JD. Dexmedetomidine for sedation during noninvasive ventilation in pediatric patients. *Pediatr Crit Care Med* 2017; 18: 831-837.
- [9] Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR and Takala J. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012; 307: 1151-1160.
- [10] Ramaswamy AH and Shaikh SI. Comparison of dexmedetomidine-propofol versus fentanyl-propofol for insertion of laryngeal mask airway. *J Anaesthesiol Clin Pharmacol* 2015; 31: 217-220.
- [11] Yoo JY, Kwak HJ, Kim YB, Park CK, Lee SY and Kim JY. The effect of dexmedetomidine pretreatment on the median effective bolus dose of propofol for facilitating laryngeal mask airway insertion. *J Anesth* 2017; 31: 11-17.
- [12] Nellore SS, Waychal AD and Rustagi PS. Comparison of dexmedetomidine-propofol versus fentanyl-propofol on insertion conditions of proSeal laryngeal mask airway. *J Clin Diagn Res* 2016; 10: UC06-UC09.
- [13] Lee JM, Bahk JH, Lim YJ, Lee J and Lim L. The EC_{90} of remifentanyl for blunting cardiovascular responses to head fixation for neurosurgery under total intravenous anesthesia with propofol and remifentanyl based on bispectral index monitoring: estimation with the biased coin up-and-down sequential method. *BMC Anesthesiol* 2017; 17: 136.
- [14] Marhofer P and Brummett CM. Safety and efficiency of dexmedetomidine as adjuvant to local anesthetics. *Curr Opin Anaesthesiol* 2016; 29: 632-637.
- [15] Iirola T, Vilo S, Manner T, Aantaa R, Lahtinen M, Scheinin M and Olkkola KT. Bioavailability of

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- dexmedetomidine after intranasal administration. *Eur J Clin Pharmacol* 2011; 67: 825-831.
- [16] Tomita S, Yamazaki S, Togami K, Tada H and Kawaai H. The effect of dexmedetomidine on oral mucosal blood flow and the absorption of lidocaine. *Anesth Prog* 2018; 65: 168-176.
- [17] Sakurai Y, Obata T, Odaka A, Terui K, Tamura M and Miyao H. Buccal administration of dexmedetomidine as a preanesthetic in children. *J Anesth* 2010; 24: 49-53.
- [18] Savla JR, Ghai B, Bansal D and Wig J. Effect of intranasal dexmedetomidine or oral midazolam premedication on sevoflurane EC50 for successful laryngeal mask airway placement in children: a randomized, double-blind, placebo-controlled trial. *Paediatr Anaesth* 2014; 24: 433-439.
- [19] He J, Zhang XP, Yang MY, Yuan YH, Zhou X, Zhao WJ and Xiao ZH. Application of dexmedetomidine in children with agitation during ventilator weaning. *Zhongguo Dang Dai Er Ke Za Zhi* 2019; 21: 522-527.
- [20] Aantaa R, Jaakola ML, Kallio A and Kanto J. Reduction of the minimum alveolar concentration of isoflurane by dexmedetomidine. *Anesthesiology* 1997; 86: 1055-1060.
- [21] Kim JS, Park WK, Lee MH, Hwang KH, Kim HS and Lee JR. Caudal analgesia reduces the sevoflurane requirement for LMA removal in anesthetized children. *Korean J Anesthesiol* 2010; 58: 527-531.
- [22] Singh A, Sinha R, Aravindan A, Kumar KR and Datta PK. Comparison of low-fresh gas flow technique to standard technique of sevoflurane induction in children-a randomized controlled trial. *Paediatr Anaesth* 2019; 29: 304-309.