Original Article

http://dx.doi.org/10.3349/ymj.2014.55.1.209
pISSN: 0513-5796, eISSN: 1976-2437

Yonsei Med J 55(1):209-215, 2014

YMJ

Effect of Dexmedetomidine on Sevoflurane Requirements and Emergence Agitation in Children Undergoing Ambulatory Surgery

Na Young Kim,[1,2] So Yeon Kim,[1,2] Hye Jin Yoon,[1] and Hae Keum Kil[1,2]

[1]Department of Anesthesiology and Pain Medicine, [2]Anesthesia and Pain Research Institute, Yonsei University College of Medicine, Seoul, Korea.

Received: January 17, 2013
Revised: May 7, 2013
Accepted: May 23, 2013
Corresponding author: Dr. Hae Keum Kil, Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea.
Tel: 82-2-2228-2420, Fax: 82-2-2227-7897
E-mail: hkkil@yuhs.ac

This study was presented in ASA 2012.

· The authors have no financial conflicts of interest.

Purpose: Dexmedetomidine, a potent selective α2-adrenergic agonist, produces sedation and analgesia. This study was conducted to assess the effect of dexmedetomidine infusion on sevoflurane requirements, recovery profiles, and emergence agitation in children undergoing ambulatory surgery. **Materials and Methods:** Forty children undergoing ambulatory hernioplasty or orchiopexy were randomized into two groups. The dexmedetomidine group (Group D, n=20) received dexmedetomidine 1 μg/kg, followed by 0.1 μg/kg/h until the end of surgery, whereas the saline group (Group S, n=20) received volume-matched normal saline. Sevoflurane was used for induction and maintenance of anesthesia and caudal block was performed in all children. End-tidal sevoflurane concentration (ET-sevo), the incidence of emergence agitation, pain scores, and sedation scores were recorded. Hemodynamic changes and other adverse effects were assessed in the perioperative period. **Results:** ET-sevo of Group D was significantly reduced in 23.8-67% compared to Group S during surgery. The incidence of emergence agitation was lower in Group D than in Group S (5% vs. 55%, p=0.001). Postoperative pain was comparable, and discharge time was not different between the groups. Mean arterial pressure and heart rate were significantly lower in Group D during surgery. **Conclusion:** Intraoperative infusion of dexmedetomidine reduced sevoflurane requirements and decreased emergence agitation without delaying discharge in children undergoing ambulatory surgery. However, caution should be taken in regard to bradycardia and hypotension.

Key Words: Agitation, ambulatory surgery, dexmedetomidine, emergence, sevoflurane

INTRODUCTION

Dexmedetomidine, a potent selective α_2-adrenergic agonist, is frequently used off-label in children because of its efficacy and lack of respiratory depression.[1,2] Because dexmedetomidine has sedative, hypnotic and analgesic properties, it can reduce the dose of hypnotics, opioids, analgesics, and anesthetics required to be concomitantly administered.[3] Intraoperative administration of dexmedetomidine

reduced sevoflurane requirements in children undergoing various surgeries.[4-6]

Emergence agitation (EA) occurs frequently in children during recovery from anesthesia. The etiology of EA includes multiple factors, such as pain, anxiety, surgical type, personal character, rapid awakening, and anesthetic type, and sevoflurane has been considered to cause a higher incidence of EA than other anesthetics in pediatric patients.[7-9] The incidence of EA under sevoflurane anesthesia varies from 10 to 70% depending on the definition of EA.[4,10-13] Several preventative strategies have been investigated for EA under sevoflurane anesthesia in children.[14-16] Also, intraoperative administration of dexmedetomidine has shown to effectively reduce EA in children because of its anxiolytic and analgesic properties without respiratory depression.[4,12,13,17,18]

In this randomized double blind study, we hypothesized that intraoperative use of dexmedetomidine would reduce sevoflurane requirements in children undergoing ambulatory surgery. Furthermore, we evaluated the effects of dexmedetomidine on recovery profiles and EA.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of Severance Hospital (IRB number: 4-2011-0430) and registered to the www.ClinicalTrials.gov (NCT01691001). After obtaining written informed consent from parents, 40 children, ASA 1, aged 1-5 years (≤20 kg) who were undergoing ambulatory hernioplasty or orchiopexy were enrolled in this study. Children with mental retardation, developmental delay, neurological or psychiatric illnesses that may be associated with agitation, coagulation disorder, spinal anomalies, or bilateral procedures were excluded.

The patients were randomly assigned to two groups; those who received dexmedetomidine (Group D, n=20) or saline (Group S, n=20) using a computer-generated randomization. Drugs used in the study were prepared in an anesthesia preparation room and coded as A or B by a nurse who was blinded to the study. For Group D, dexmedetomidine (Precedex™, Hospira Worldwide, Lake Forest, IL, USA) was mixed in normal saline to make 1 μg/mL in a 50 mL syringe. For Group S, normal saline was also prepared in a 50 mL syringe, and no premedication was given. To reduce preoperative anxiety, the children were moved to the operating room while watching an animated movie with their parents, and the parents remained next to the children until the children lost consciousness. Anesthesia was induced via a facemask with 6-7% sevoflurane in oxygen at a gas flow of 4 L/min. The induction scale was assessed based upon mask acceptance (1=accept mask readily; 2=slight fear of mask, easily calmed; 3=not calmed with reassurance; 4=terrified, crying, agitated).[19] A scale score of 1 or 2 was considered to be satisfactory induction. After the loss of consciousness, intravenous access was achieved. The coded drug was accordingly given to each group by the blinded anesthetic practitioner. The drug of 1 μg/kg was administered intravenously over 10 min using a syringe pump, followed by a 0.1 μg/kg/h infusion until the end of surgery in both groups. In Group S, the same amount of saline was administered in an identical sequence. When the bispectral index (BIS) score reached 40, the laryngeal mask airway (LMA) was inserted. A caudal block was then performed with 1.3 mL/kg of 0.2% ropivacaine (maximum volume, 20 mL) in both groups. Successful drug injection within the caudal space was routinely confirmed with ultrasound. As soon as caudal block was done, the operation was started. Anesthesia was maintained by adjusting the end-tidal concentration of sevoflurane (ET-sevo) to achieve a BIS score of 45-50 during surgery. During operation, no additional analgesics were given. Respiration was maintained spontaneously throughout the operation. When skin suture was started, sevoflurane and dexmedetomidine or saline administrations were discontinued. All patients were kept breathing spontaneously throughout the surgery. The LMA was removed when the patients opened their eyes spontaneously or moved when their chins were lifted. Time to LMA removal was defined as the time interval from 'end of operation' to 'LMA removal' and regarded as the time to awake.

ET-sevo, mean arterial pressure (MAP), and heart rate (HR) were recorded just before dexmedetomidine administration (T0, baseline), just after dexmedetomidine loading of 1 μg/kg (T1), 10 min after dexmedetomidine loading (T2), start of operation (T3), 10, 20, 30 min after the start of operation (T4, T5, T6), and at the end of operation (T7). Atropine 0.01 mg/kg was administered during the procedure when the HR decreased >30% of baseline value (T0). The patients were monitored in the post-anesthetic care unit (PACU) by a nurse and their parents, both of whom were blinded to the child's group allocation. Because most of the EA episodes occurred within 30 min of PACU arrival,[13,18,20] EA was assessed at arrival and every 5 min for up to 30 min in PACU. EA was rated using a four-point scale modified by Watcha, et al.[21] (1=calm, 2=crying, but can be consoled, 3=crying and

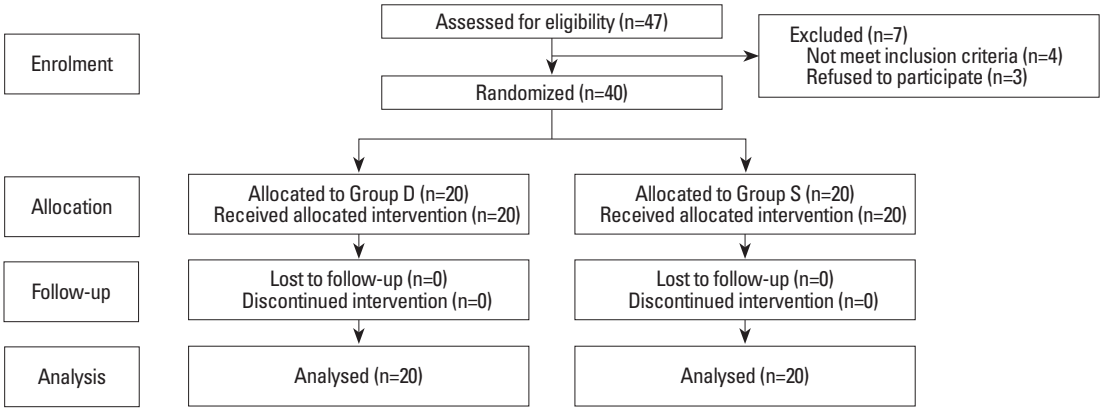

Fig. 1. Flow chart representing patient assignment to study groups (randomized) and treatment protocols.

cannot be consoled, 4=agitated and thrashing around). If a child fell asleep, this was defined as a score of 0. Children with scores of 3 or 4 were considered to have had an EA episode. Postoperative pain was assessed with the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)[22] and the Face, Legs, Activity, Cry, Consolability scale (FLACC)[23] upon PACU arrival, at 30 min, 60 min, and 120 min postoperatively. When children showed CHEOPS or FLACC scores ≥4, 0.5 μg/kg of fentanyl was administered. Sedation level was assessed with the Ramsay's sedation scale (1= anxious and agitated or restless, or both; 2=co-operative, oriented, and calm; 3=responsive to commands only; 4= exhibiting brisk response to light glabellar tap or loud auditory stimulus; 5=exhibiting a sluggish response to light glabellar tap or loud auditory stimulus; and 6=unresponsive).[24] The first oral intake time and discharge time were recorded, and adverse events were also noted.

Statistical analysis

Sample size calculation was based on previous studies.[4,25] In these studies, ET-sevo was decreased 33.1% and 41.6% in patients who received dexmedetomidine.[4,25] If dexmedetomidine infusion can reduce 35% of the ET-sevo, the difference of the means of ET-sevo would be 1.0%, and SD would be estimated as 1.0%. For an α=0.05 and a power of 80%, 17 patients were required per group. Therefore, 20 patients were included in each group to allow for possible drop-outs.

Data were analyzed using IBM SPSS Statistics 19™ (SPSS Inc., Chicago, IL, USA). The normality of distribution was assessed with a Q-Q plot and the Shapiro-Wilk test. Parametric data were analysed with the independent t-test, and non-parametric data were analyzed using the Mann-Whitney U test. Categorical data were analyzed using the χ^2-test or Fisher exact tests when appropriate. A repeated measures analysis of variance was performed to compare repeated measure variables (ET-sevo, MAP, and HR) with a Bonferroni correction for multiple comparisons. Data are presented as mean±SD, median (range) and number. A p-value <0.05 was considered statistically significant.

Table 1. Demographic and Anesthetic Characteristics

	Group D (n=20)	Group S (n=20)
Age (months)	17 (8-35)	16.5 (6-53)
Weight (kg)	11.7 (7.4-15.5)	11.9 (6.6-16.8)
Height (cm)	85 (63-100)	83.5 (62.8-108)
Satisfactory induction	16	15
Operation time (min)	39±20	44±24
Anesthesia time (min)	64±20	67±22
Time to LMA removal (min)	4 (0-8)	3 (0-9)

D, dexmedetomidine; S, saline; LMA, laryngeal mask airway.
Data are presented as mean±SD, median (range) or number.

RESULTS

Of a total of 47 patients assessed for eligibility, 40 subjects received dexmedetomidine or saline after randomization and none were eliminated from the data collection (Fig. 1).

No differences were seen in demographics and anesthetic characteristics between the two groups (Table 1). As shown in Fig. 2, ET-sevo was significantly lower in Group D than in Group S after dexmedetomidine administration; ET-sevo reduced by 60% (±10) in Group D compared to Group S.

The incidence of EA was lower in Group D than in Group S (5% vs. 55%, p=0.001) and agitation scores were significantly lower in Group D than in Group S during the first 20 min after PACU arrival (Table 2).

Pain scores were comparable in the two groups except at

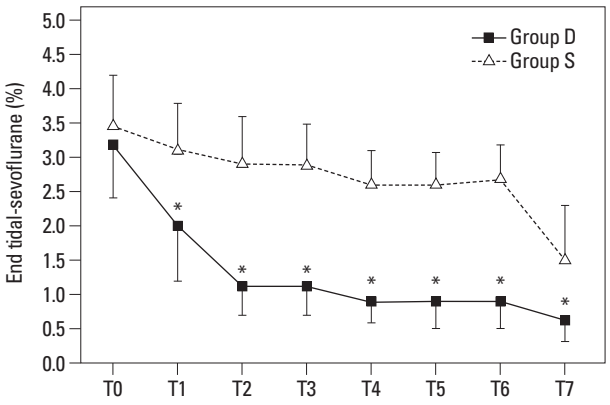

Fig. 2. End tidal-sevoflurane concentration during operation: Values are presented as mean±SD. *p<0.05 compared with Group S (Bonferroni-corrected). D, dexmedetomidine; S, saline; T0, just before dexmedetomidine administration; T1, just after dexmedetomidine loading; T2, 10 min after dexmedetomidine loading; T3, start of operation; T4, 10 min after the start of operation; T5, 20 min after the start of operation; T6, 30 min after the start of operation; T7, at the end of operation.

Table 2. Incidence and Scores of Emergence Agitation in the Post-Anesthetic Care Unit

	Group D (n=20)	Group S (n=20)
Emergence agitation	1*	11
Agitation scores		
PACU arrival	0 (0-2)*	0 (0-4)
5 min in PACU	0 (0-2)*	1 (0-4)
10 min in PACU	2 (0-3)*	3 (0-4)
15 min in PACU	1 (0-3)*	3 (0-3)
20 min in PACU	1 (1-2)*	2 (1-3)
25 min in PACU	1 (1-2)	1 (1-2)
30 min in PACU	1 (1-2)	1 (1-1)

PACU, post-anesthetic care unit; D, dexmedetomidine; S, saline.
Data are presented as median (range) or number. Emergence agitation is defined as an agitation score ≥3 during the period of arrival to 30 min in PACU. Agitation score: 0=asleep, 1=calm, 2=crying, but can be consoled, 3=crying and cannot be consoled, 4=agitated and thrashing around. Emergence agitation means agitation scores of 3 or 4.
*p<0.05 compared with Group S.

30 min in PACU. Fentanyl was given in 2 patients of Group S for pain control in the PACU (Table 3). Sedation scores were significantly higher in Group D than in Group S at the time of arrival in the PACU and at 30 min (Table 4).

The hemodynamic changes are shown in Fig. 3. MAP and HR were significantly lower in Group D than in Group S; MAP and HR decreased by 22-28% and 18-21% respectively in Group D than Group S. Atropine was administered to 6 patients of Group D who showed bradycardia with or without hypotension (p=0.020), during the dexmedetomidine load.

First oral intake and discharge time were not different between the groups. There were no significant adverse effects

Table 3. Postoperative Pain Scales

	Group D (n=20)	Group S (n=20)
CHEOPS		
PACU arrival	1 (1-4)	1 (1-5)
Postoperative 30 min	1 (1-4)*	2 (1-4)
Postoperative 60 min	1 (0-2)	1 (0-2)
Postoperative 120 min	1 (0-2)	1 (0-2)
FLACC		
PACU arrival	0 (0-8)	0 (0-6)
Postoperative 30 min	0 (0-8)*	3 (0-7)
Postoperative 60 min	0 (0-2)	0 (0-4)
Postoperative 120 min	0 (0-2)	0 (0-2)
Analgesic administraion	0	2

CHEOPS, Children's Hospital of Eastern Ontario Pain Scale (appendix 1); FLACC, Face, Legs, Activity, Cry, Consolability scale (appendix 2); PACU, post-anesthetic care unit; D, dexmedetomidine; S, saline.
Data are presented as median (range) or number.
*p<0.05 compared with Group S.

Table 4. Postoperative Sedation Scales and Other Recovery Profiles

	Group D (n=20)	Group S (n=20)
Ramsay's sedation scale		
PACU arrival	5 (1-6)*	3 (1-6)
Postoperative 30 min	2 (1-4)*	2 (1-3)
Postoperative 60 min	2 (1-4)	2 (1-3)
Postoperative 120 min	2 (1-3)	2 (1-3)
Oral intake time (min)	103.5 (43-190)	70 (45-164)
Discharge time (min)	201 (180-270)	207 (150-480)

PACU, post-anesthetic care unit; D, dexmedetomidine; S, saline.
Data are presented as median (range) or number. Ramsay's sedation scale: 1=anxious and agitated or restless, or both; 2=co-operative, oriented, and calm; 3=responsive to commands only; 4=exhibiting brisk response to light glabellar tap or loud auditory stimulus; 5=exhibiting a sluggish response to light glabellar tap or loud auditory stimulus; and 6=unresponsive.
*p<0.05 compared with Group S.

related to the anesthesia such as nausea, vomiting, or urinary retention (Table 4).

DISCUSSION

The results of this prospective double-blinded randomized study suggest that intraoperative dexmedetomidine infusion reduced anesthetic requirements and decreased emergence agitation without delaying discharge in children undergoing ambulatory surgery.

Dexmedetomidine is a potent α_2-adrenoceptors agonist, and presynaptic activation of α_2-adrenoceptors in the locus ceruleus is responsible for both analgesic and sedative effect.[3,26] Therefore, dexmedetomidine may be an effective

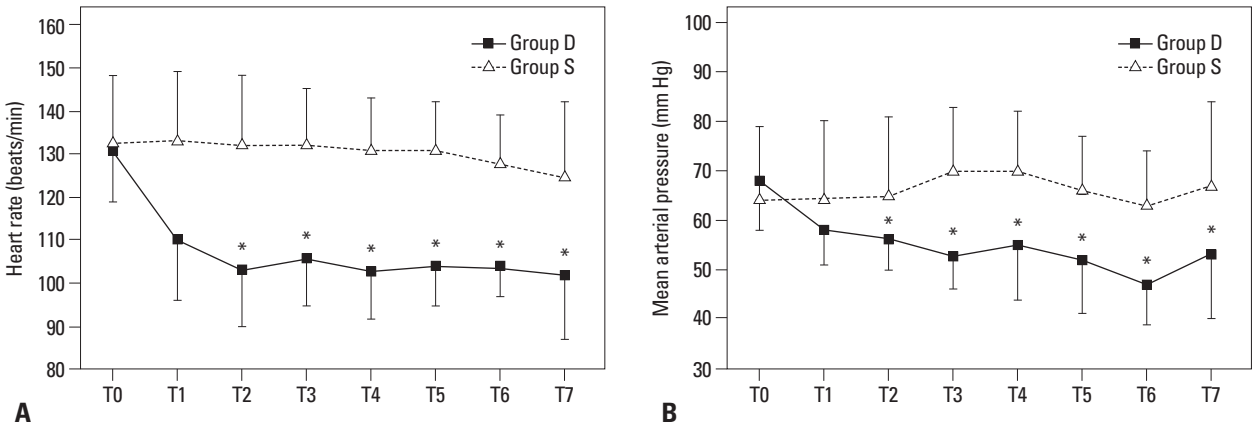

Fig. 3. Hemodynamic changes during operation. (A) Mean arterial pressure. (B) Heart rate. Values are presented as mean±SD. *p<0.05 compared with Group S (Bonferroni-corrected). D, dexmedetomidine; S, saline; T0, just before dexmedetomidine administration; T1, just after dexmedetomidine loading; T2, 10 min after dexmedetomidine loading; T3, start of operation; T4, 10 min after the start of operation; T5, 20 min after the start of operation; T6, 30 min after the start of operation; T7, at the end of operation.

adjuvant during general anesthesia by decreasing the doses of anesthetics and analgesics.[27-29] The primary end-point of this study was the reduction of ET-sevo to maintain a BIS score of 45-50 during surgery. To provide adequate anesthetic depth, the BIS was kept within 45-50 range in both groups. Although it is considered that BIS has low sensitivity and specificity to assess the anesthetic depth and it may be dependent on anesthetics used, it is usual to maintain BIS values less than 50 during anesthesia in children.[30]

In several studies performed on adults undergoing abdominal surgery, ET-sevo was decreased by 27.3-33% with a dexmedetomidine 1 μg/kg bolus and a 0.4-0.6 μg/kg/h infusion.[25,29,31] In pediatric tonsillectomy patients, the ET-sevo can be reduced up to 41.6% with a dexmedetomidine 2 μg/kg bolus, followed by 0.7 μg/kg/h infusion when compared with intraoperative fentanyl bolus.[4] The analgesic-sparing effect of dexmedetomidine can be enhanced when using N_2O.[32] Supplemental drugs such as dexamethasone and acetaminophen may affect the additive analgesic interactions of dexmedetomidine and sevoflurane.[4] In our study, no supplemental drugs or N_2O were given during surgery, and the ET-sevo of Group D was reduced by 23.8-67% compared to Group S, despite the low dose of dexmedetomidine (1 μg/kg bolus, followed by 0.1 μg/kg/h infusion).

In previous studies in children, dexmedetomidine infusion rate varied (0.2-0.7 μg/kg/h) under sevoflurane anesthesia.[1,4,12,17,29] We selected a low infusion rate of dexmedetomidine (0.1 μg/kg/h), because the children were undergoing minor urological surgery and supplemental caudal block. Inguinal hernioplasty or orchiopexy produce less surgical stimulation than other procedures, such as tonsillectomy. The anesthetic-sparing effects of dexmedetomidine may differ according to the type of surgery in addition to dexmedetomidine dose, different age of patients and combined effects of anesthetics or analgesics.[3,20,27,28,32,33]

EA is not a new phenomenon, though its prevalence has increased with the introduction of sevoflurane, especially in pre-school aged children. EA is self-limiting and resolves spontaneously, but restless recoveries can result in patient injury, surgical site damage and dissatisfaction for patients and parents. This characteristic of EA has been attributed to several factors such as patient-related (age, anxiety, and temperament), anesthesia-related (rapid emergence, and anesthetics), and surgery-related (pain and surgery type).[9] In the current study, we tried to exclude several possible factors of EA such as preoperative anxiety, surgical type, and postoperative pain. The incidence of EA has been reported up to 70% in sevoflurane anesthesia.[11] Sevoflurane even causes a high incidence of EA in the absence of surgery.[9,18] The reason for frequent EA after sevoflurane is not clearly understood. Nevertheless, sevoflurane in any particular situation may exert an irritating effect on the central nervous system,[34,35] although it was suggested that the type of inhalation agent may not be directly correlated with the incidence of EA.[36]

In the current study, we found that dexmedetomidine administration reduced EA significantly without delaying discharge. A single dose or continuous infusion of dexmedetomidine reduces EA after sevoflurane in children.[4,12,13] The reason for reducing EA is yet unclear, however, the analgesic and sedative effects of dexmedetomidine may provide a protective effect against EA.[4,12,13,18] However, in a recent meta-analysis that evaluated prevention of EA, analgesic properties did not seem to play a role in preventing EA.[37] A recent study also suggested that lower incidence of EA could be

related to the lower concentration of sevoflurane.[14] The combined effects of reduction of sevoflurane and dexmedetomidine administration might have reduced the incidence of EA in our study.

Time to LMA removal which is also regarded as the time to awake was not different between the two groups. Furthermore, the LMA removal time of Group D was short compared to other studies.[4,12,38] These different results may be due to the low infusion rate of dexmedetomidine and the type of surgery (minor urological surgery).

Dexmedetomidine can also cause a variety of hemodynamic changes in children.[1,2,39] The most common hemodynamic effects of dexmedetomidine are bradycardia and hypotension, which are attributed to central α_2-agonist properties.[1] Transient hypertension can also be result from peripheral α-receptor stimulation.[1] In the current study, Group D showed significantly lower MAP and HR during operation than Group S. Although the hemodynamic changes varied according to dose and surgical type, hemodynamic instability may occur frequently in minor surgery even if low doses of dexmedetomidine are used.[1,2,4,12]

The limitation of this study is uncertainty about whether we used a proper scoring tool for EA. The pediatric anesthesia emergence delirum scale developed by Sikich and Lerman[40] is a valid and reliable rating scale, but it may not be applicable to children who are asleep in the PACU. Therefore, we used a scale by Watcha, et al.,[21] which includes a consolability component. Although there is a risk of mis-scaling due to pain, we excluded the possibility of pain because we confirmed successful drug injection within the caudal space using ultrasound. In addition, since sample size calculation was based on ET-sevo, sample size may not be enough to check emergence agitation. Therefore, emergence agitation observed in Group D may be underpowered.

In conclusion, intraoperative dexmedetomidine 1 μg/kg bolus, followed by 0.1 μg/kg/h infusion, significantly reduced anesthetic requirements and also decreased the incidence of EA during recovery without delaying discharge in children undergoing ambulatory surgery. However, caution should be taken because of the side effects including hypotension and bradycardia.

REFERENCES

1. Su F, Hammer GB. Dexmedetomidine: pediatric pharmacology, clinical uses and safety. Expert Opin Drug Saf 2011;10:55-66.
2. Mason KP, Lerman J. Review article: dexmedetomidine in children: current knowledge and future applications. Anesth Analg 2011;113:1129-42.
3. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg 2000;90:699-705.
4. Patel A, Davidson M, Tran MC, Quraishi H, Schoenberg C, Sant M, et al. Dexmedetomidine infusion for analgesia and prevention of emergence agitation in children with obstructive sleep apnea syndrome undergoing tonsillectomy and adenoidectomy. Anesth Analg 2010;111:1004-10.
5. Al-Zaben KR, Qudaisat IY, Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Oweidi AS, et al. Intraoperative administration of dexmedetomidine reduces the analgesic requirements for children undergoing hypospadius surgery. Eur J Anaesthesiol 2010;27:247-52.
6. Lili X, Jianjun S, Haiyan Z. The application of dexmedetomidine in children undergoing vitreoretinal surgery. J Anesth 2012;26:556-61.
7. Lerman J, Davis PJ, Welborn LG, Orr RJ, Rabb M, Carpenter R, et al. Induction, recovery, and safety characteristics of sevoflurane in children undergoing ambulatory surgery. A comparison with halothane. Anesthesiology 1996;84:1332-40.
8. Bock M, Kunz P, Schreckenberger R, Graf BM, Martin E, Motsch J. Comparison of caudal and intravenous clonidine in the prevention of agitation after sevoflurane in children. Br J Anaesth 2002;88:790-6.
9. Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. Paediatr Anaesth 2000;10:419-24.
10. Moore JK, Moore EW, Elliott RA, St Leger AS, Payne K, Kerr J. Propofol and halothane versus sevoflurane in paediatric day-case surgery: induction and recovery characteristics. Br J Anaesth 2003;90:461-6.
11. Guler G, Akin A, Tosun Z, Ors S, Esmaoglu A, Boyaci A. Single-dose dexmedetomidine reduces agitation and provides smooth extubation after pediatric adenotonsillectomy. Paediatr Anaesth 2005;15:762-6.
12. Shukry M, Clyde MC, Kalarickal PL, Ramadhyani U. Does dexmedetomidine prevent emergence delirium in children after sevoflurane-based general anesthesia? Paediatr Anaesth 2005;15:1098-104.
13. Sato M, Shirakami G, Tazuke-Nishimura M, Matsuura S, Tanimoto K, Fukuda K. Effect of single-dose dexmedetomidine on emergence agitation and recovery profiles after sevoflurane anesthesia in pediatric ambulatory surgery. J Anesth 2010;24:675-82.
14. Na HS, Song IA, Hwang JW, Do SH, Oh AY. Emergence agitation in children undergoing adenotonsillectomy: a comparison of sevoflurane vs. sevoflurane-remifentanil administration. Acta Anaesthesiol Scand 2013;57:100-5.
15. Aouad MT, Yazbeck-Karam VG, Nasr VG, El-Khatib MF, Kanazi GE, Bleik JH. A single dose of propofol at the end of surgery for the prevention of emergence agitation in children undergoing strabismus surgery during sevoflurane anesthesia. Anesthesiology 2007;107:733-8.
16. Cohen IT, Finkel JC, Hannallah RS, Hummer KA, Patel KM. The effect of fentanyl on the emergence characteristics after desflurane or sevoflurane anesthesia in children. Anesth Analg 2002;94:1178-81.
17. Meng QT, Xia ZY, Luo T, Wu Y, Tang LH, Zhao B, et al. Dexme-

detomidine reduces emergence agitation after tonsillectomy in children by sevoflurane anesthesia: a case-control study. Int J Pediatr Otorhinolaryngol 2012;76:1036-41.
18. Isik B, Arslan M, Tunga AD, Kurtipek O. Dexmedetomidine decreases emergence agitation in pediatric patients after sevoflurane anesthesia without surgery. Paediatr Anaesth 2006;16:748-53.
19. Weldon BC, Watcha MF, White PF. Oral midazolam in children: effect of time and adjunctive therapy. Anesth Analg 1992;75:51-5.
20. Weldon BC, Bell M, Craddock T. The effect of caudal analgesia on emergence agitation in children after sevoflurane versus halothane anesthesia. Anesth Analg 2004;98:321-6.
21. Watcha MF, Ramirez-Ruiz M, White PF, Jones MB, Lagueruela RG, Terkonda RP. Perioperative effects of oral ketorolac and acetaminophen in children undergoing bilateral myringotomy. Can J Anaesth 1992;39:649-54.
22. McGrath PJ, Johnson G, Schillinger JT. The Children of Eastern Ontario Pain Scale CHEOPS: a behavioral scale for rating postoperative pain in children. In: Fields HL, Dubner R, Cervero F, editors. Advances in Pain Research and Therapy, Volume 9: Proceedings of the Fourth World Congress on Pain. New York: Raven Press; 1985. p.395-402.
23. Voepel-Lewis T, Zanotti J, Dammeyer JA, Merkel S. Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients. Am J Crit Care 2010;19:55-61.
24. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2:656-9.
25. Magalhães E, Govêia CS, Ladeira LC, Espíndola BV. [Relationship between dexmedetomidine continuous infusion and end-tidal sevoflurane concentration, monitored by bispectral analysis.]. Rev Bras Anestesiol 2004;54:303-10.
26. Guo TZ, Jiang JY, Buttermann AE, Maze M. Dexmedetomidine injection into the locus ceruleus produces antinociception. Anesthesiology 1996;84:873-81.
27. Tufanogullari B, White PF, Peixoto MP, Kianpour D, Lacour T, Griffin J, et al. Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. Anesth Analg 2008;106:1741-8.
28. Fragen RJ, Fitzgerald PC. Effect of dexmedetomidine on the minimum alveolar concentration (MAC) of sevoflurane in adults age 55 to 70 years. J Clin Anesth 1999;11:466-70.
29. Ohtani N, Kida K, Shoji K, Yasui Y, Masaki E. Recovery profiles from dexmedetomidine as a general anesthetic adjuvant in patients undergoing lower abdominal surgery. Anesth Analg 2008;107:1871-4.
30. Drummond JC. Monitoring depth of anesthesia: with emphasis on the application of the bispectral index and the middle latency auditory evoked response to the prevention of recall. Anesthesiology 2000;93:876-82.
31. Nunes RR, Cavalcante SL. Influence of dexmedetomidine upon sevoflurane end-expiratory concentration. Evaluation by bispectral index, suppression rate and electroencephalographic power spectral analysis. Rev Bras Anestesiol 2002;52:133-45.
32. Dawson C, Ma D, Chow A, Maze M. Dexmedetomidine enhances analgesic action of nitrous oxide: mechanisms of action. Anesthesiology 2004;100:894-904.
33. Aantaa R, Jaakola ML, Kallio A, Kanto J. Reduction of the minimum alveolar concentration of isoflurane by dexmedetomidine. Anesthesiology 1997;86:1055-60.
34. Komatsu H, Taie S, Endo S, Fukuda K, Ueki M, Nogaya J, et al. Electrical seizures during sevoflurane anesthesia in two pediatric patients with epilepsy. Anesthesiology 1994;81:1535-7.
35. Woodforth IJ, Hicks RG, Crawford MR, Stephen JP, Burke DJ. Electroencephalographic evidence of seizure activity under deep sevoflurane anesthesia in a nonepileptic patient. Anesthesiology 1997;87:1579-82.
36. Kim JM, Lee JH, Lee HJ, Koo BN. Comparison of emergence time in children undergoing minor surgery according to anesthetic: desflurane and sevoflurane. Yonsei Med J 2013;54:732-8.
37. Dahmani S, Stany I, Brasher C, Lejeune C, Bruneau B, Wood C, et al. Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. Br J Anaesth 2010;104:216-23.
38. Pestieau SR, Quezado ZM, Johnson YJ, Anderson JL, Cheng YI, McCarter RJ, et al. High-dose dexmedetomidine increases the opioid-free interval and decreases opioid requirement after tonsillectomy in children. Can J Anaesth 2011;58:540-50.
39. Hammer GB, Drover DR, Cao H, Jackson E, Williams GD, Ramamoorthy C, et al. The effects of dexmedetomidine on cardiac electrophysiology in children. Anesth Analg 2008;106:79-83.
40. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology 2004;100:1138-45.