Original Article

# Comparison of the effects of dexmedetomidine-ketamine and sevoflurane-sufentanil anesthesia in children with obstructive sleep apnea after uvulopalatopharyngoplasty: An observational study

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## Abstract

**Background:** Children with obstructive sleep apnea (OSA) are particularly at risk under anesthesia after uvulopalatopharyngoplasty (UPPP). This prospective randomized double-blind study focused on the comparison of dexmedetomidine-ketamine and sevoflurane-sufentanil anesthesia on children with respect to safety, feasibility, and clinical effects.

**Materials and Methods:** A total of 60 children, aged 2-10 years, classified as American Society of Anesthesiologists (ASA) status I and II scheduled for UPPP were prospectively studied. Patients were randomly allocated to receive either dexmedetomidine-ketamine-based anesthesia (group DK, $n = 30$) or sevoflurane-sufentanil-based anesthesia (group SS, $n = 3$ 0). Heart rate (HR) and systolic blood pressure during the first 60 min of the procedure, Ramsay sedation score, the Pediatric Anesthesia Emergence Delirium (PAED) scale and a 5-point scale used to evaluate emergence agitation (EA) in postanesthesia care unit (PACU) and postoperative outcomes data were recorded.

**Results:** During the first 60 min of anesthesia, mean HR, and mean diastolic noninvasive arterial blood pressure (NIBP) were not statistically different in the two groups ($P > 0.05$) Compared with group SS, the patients in group DK had lower rescue tramadol requirement and lower pain score, PAED score, and EA score at 5, 10, 15, and 30 min in PACU; but had a higher Ramsay scale at 10, 15, 30, 45, and 60 min in PACU and the incidence of $SpO_2$ below 95%, also the time of first bowel movement and ambulation in group DK was shorter.

**Conclusions:** The dexmedetomidine-ketamine combination was not superior to a sevoflurane-sufentanil combination because of late awake time and a high potential for adverse respiratory events in PACU, the benefit of dexmedetomidine administration being a decreased incidence of EA and a lower recovery time of bowel movement and ambulation.

**Key words:** Dexmedetomidine, emergence agitation, sedation, sevoflurane, uvulopalatopharyngoplasty

## Introduction

Obstructive sleep apnea syndrome (OSAS), estimated to be 1%-3% of the children population[1] is becoming increasingly more prevalent in China. Uvulopalatopharyngoplasty (UPPP), one of the most common surgical procedures for the treatment of OSAS, was demonstrated to be effective and safe.[2] However, the postoperative period after UPPP is often challenging as children with OSA undergoing UPPP are at significant risk of respiratory and cardiovascular complications.[3] They also need to be adminstered effective and safe perioperative analgesia with effective prevention of emergence agitation (EA).[4]

Dexmedetomidine, as an adjunct to sevoflurane based anesthesia, has been confirmed for its efficacy and safety in sedation, analgesia, [5] and prevention of EA[6] in children with OSA after tonsillectomy and adenoidectomy. However, the coapplication of dexmedetomidine and ketamine for maintenance of anesthesia in children with OSA undergoing UPPP has not yet been reported, although its advantages of hemodynamic stability and protective properties had been suggested in coronary artery bypass grafting[7] and burn patients.[8]

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With this background, the primary objective was to compare the effect of dexmedetomidine-ketamine-based anesthesia with that of sevoflurane-sufentanil-based anesthesia on the safety, feasibility, and clinical effects in children with OSA undergoing UPPP.

## Materials and Methods

The study was successfully registered in www.hictr.rg (ChiCTR-TRC-12002388). After approval of the ethics committee of hospital and patients' written informed consent from the legal guardian and, when appropriate, assent from the child older than 7 years, a total of 60 patients, aged 2-10 years with American Society of Anesthesiologists (ASA) classification of I or II and characterized by a history of snoring or sleep-disordered breathing, were eligible for inclusion in the study. Clinical grading of OSAS was done by the surgeon on the basis of severity of symptoms. Exclusion criteria included a body mass index more than the 95$^{th}$ percentile for age, ASA classification III or more, and the presence of confirmed severe OSA by a polysomnograph test, respiratory tract infections, cardiovascular, liver and kidney dysfunction, and coagulation disorders, in particular, thrombocytopenia.

Patients were randomized into two treatment groups: dexmedetomidine-ketamine (DK) or sevoflurane-sufentanil (SS) group. All patients received a standardized anesthetic regimen that included premedication with oral midazolam 0.5 mg/kg (maximum of 10 mg), and induction with intravenous midazolam (0.1 mg/kg), etomidate (0.2 mg/kg), and rocuronium 0.6 mg/kg was used to facilitate tracheal intubation.

In group DK ($n$ = 30), patients received intravenous (IV) ketamine (2 mg/kg) before intubation, and a loading dose of dexmedetomidine(1 ug/kg ) over 10 min, followed by an infusion at the rate of 0.5-1 ug/kg/h.

Patients in group SS ($n$ = 30) received intravenous sufentanil (1 ug/kg) and were maintained with sevoflurane (1.0-1.5 minimal alveolar concentration (MAC) end-tidal) during the entire surgical procedure.

All patients were monitored by pulse oximetry, electrocardiogram, noninvasive arterial blood pressure (NIBP), end tidal $CO_2$ ($ETCO_2$), and a depth of anesthesia monitor, the bispectral index (BIS; Aspect Medical Systems, Natick, Massachusetts) which was maintained below 60 during the surgery. No additional opioid or propofol was used during the procedure except for acetaminophen (25 mg/kg) via rectum for postoperative pain control before surgery started. Intraoperative dexamethasone 0.2 mg/kg (maximum dose of 10 mg), IV antibiotics, and ondansetron 0.1 mg/kg (maximum of 4 mg) were administered per routine during intraoperative management.

At the end of surgery, atropine 20 ug/kg and neostigmine 50 ug/kg were used to antagonize the residual neuromuscular block. The trachea was extubated after recovery of adequate spontaneous ventilation. The time to awakening (TA), defined as spontaneous eye opening or on command from end of surgery, and the time to extubation (TE), defined as time from end of surgery to tracheal extubation, were recorded. After extubation, children were observed continuously in the postanesthesia care unit (PACU) for 60 min. Ramsay sedation score,[9] 5-point agitation scale[10] and Pediatric Anesthesia Emergence Delirium (PAED) scale[11] were measured and recorded on arrival in the PACU at 5, 10, and 15 min; and then every 15 min until the child was discharged. Patients in the PACU who were crying, restless, disoriented, unresponsive to the parent's voice, with nonpurposeful thrashing movements requiring additional personnel to prevent bodily harm, and inconsolable even after parental presence and rescue analgesia were considered to have EA.[10] Pain was evaluated using the objective pain score (OPS)[12] and tramadol (0.5-1 mg/kg) was given for pain (score 4) or severe agitation (score 4 or 5) lasting more than 5 min. Any desaturation episode with $SpO_2$ below 95% in PACU was noted. Postoperative outcomes data like the time to first sleepines, the time of first bowel movement and ambulation, and the length of hospital stay were also recorded.

The anesthesiologists in the operating room were not blinded because of the nature of the study and they were not involved in this study. The subjects, their parents, and observers in PACU and patient unit were blinded to treatment group.

Data were analyzed using Statistical Package for Social Sciences (SPSS) software (version 16, Chicago, Illinois), and expressed as either mean and standard deviation or numbers and percentages. Parametric data were analyzed with two-way repeated measures analysis of variance (RM ANOVA) and nonparametric data such as pain score, PAED score, and EA score on the Cole scale were compared between groups with Mann-Whitney U test. Fischer exact test was used for comparison of gender; percentage of patients in each group with a preoperative diagnosis of mild, moderate, or severe OSAS. $P < 0.05$ was considered statistically significant.

## Results

Results are presented for 57 patients. Sixty subjects were enrolled in this study; three subjects were eliminated from data

analysis for the following reasons: Two refused to participate after enrolling and one patient had an intraoperative complication.

The two groups were comparable in age, gender, weight, height, and diagnosis of OSAS [Table 1] and there were no significant difference between them. The age range of patients in the study was 2-10 years, more than 65% of patients were 2-3years-old.

Intraoperative data are presented in Table 2. There were no differences in duration of surgery, duration of anesthesia, time to extubate, and the dose of acetaminophen between the two groups besides the time to awakening ($P < 0.05$). During the first 60 min of anesthesia, mean HR and mean diastolic NIBP were not statistically different in the two groups [Figure 1a] ($P > 0.05$). None of the subjects needed glycopyrrolate for bradycardia or fluid bolus for hypotension in the operation room (OR). The variables measured in the PACU are also shown in Table 2, in group DK, four patients (14.3%) needed rescue tramadol in comparison with 13 (4 4.8%) in group SS ($P < 0.05$). Patients in group DK had a higher Ramsay scale at 10, 15, 30, 45, and 60 min in PACU ($P < 0.05$) [Figure 2a] and there was a statistically significant difference in the number of patients with $SpO_2$ below 95% between the two groups, 11 (46.4%) in group DK and 25 (17.2%) in group SS ($P < 0.01$). On the Cole scale (5-point scale), severe EA was defined as a score of 4 to 5. The score of EA is shown in Figure 2b. On arrival in the PACU, it was statistically lower, 2.25 ± 0.28 in group DK and 3.17 ± 0.41 in group SS ($P < 0.001$). At 5, 10, 15, and 30 min it was statistically lower in group DK ($P < 0.001$). After 30 min, there was no significant difference between them. Also the score of the PAED scale showed a statistical difference at first 30 min ($P < 0.001$) and the incidence of EA was 7.1

**Table 1: Demographic data**

| Parameters | Group DK ($n$ = 28) | Group SS ($n$ = 29) | *P*-value |
|---|---|---|---|
| Age (years) | 3.9 ± 1.2 | 4.4 ± 1.5 | >0.05 |
| 2-3, *N* (%) | 21 (75.0%) | 19 (65.5%) | >0.05 |
| Gender (F/M) | 13/15 | 11/18 | >0.05 |
| Weight (kg) | 18.9 ± 5.7 | 21.4 ± 7.6 | >0.05 |
| Height (cm) | 103.8 ± 16.5 | 112.4 ± 18.3 | >0.05 |
| OSAS (% patients) | | | |
| Mild | 30 | 26 | >0.05 |
| Moderate | 50 | 60 | |
| Severe | 20 | 14 | |

*F = Female, M = male, OSAS = obstructive sleep apnea syndrome, DK = dexmedetomidine-ketamine-based anesthesia, SS = sevoflurane-sufentanil-based anesthesia*

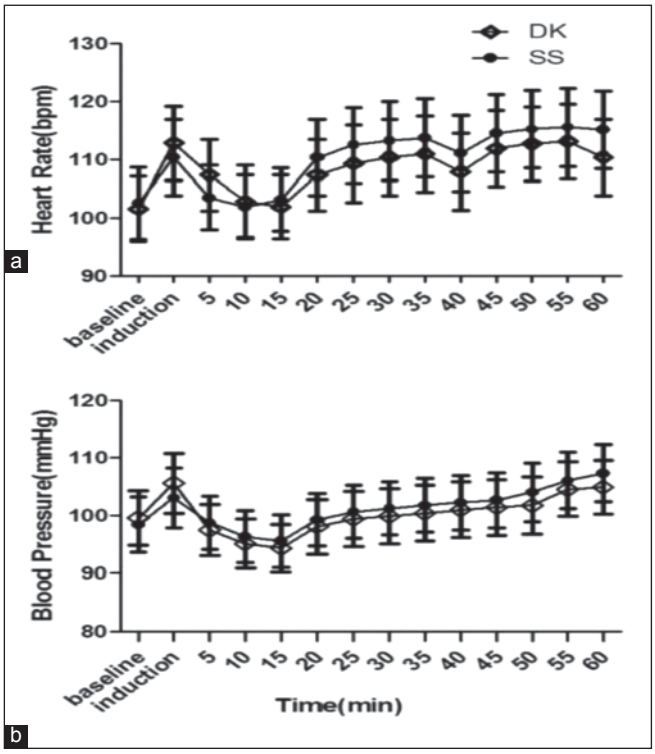


**Figure 1:** (a) Heart rate. (b) systolic blood pressure during the first 60 minutes of the procedure DK = Dexmedetomidine-Ketamine group SS = Sevoflurane-Sufentanil group

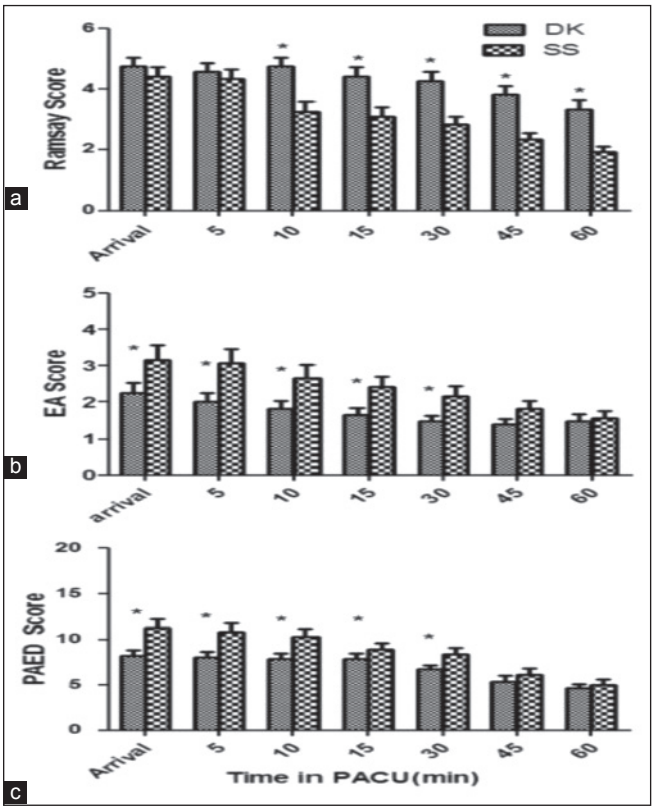


**Figure 2:** (a) Ramsay Score. (b) severe emergence agitation (EA) Score. (c) Pediatric Anesthesia Emergence Delirium (PAED) score In PACU.*indicates significant difference between two groups DK = Dexmedetomidine-Ketamine group SS = Sevoflurane-Sufentanil group

and 31.0%, respectively ($P < 0.05$). There was no statistical difference in the incidence of nausea and vomiting ($P > 0.05$).

Postoperative outcome data were shown in Table 3. In group DK, the mean time to first sleep was significant lower than group SS ($P < 0.001$) and the mean time to first bowel movement and first ambulation were also lower in group DK ($P < 0.05$). The mean length of hospital stay in group DK was 1.4 ± 0.5 day which was similar with group SS of 1.6 ± 0.6 day ($P > 0.05$).

## Discussion

Our primary result demonstrated that compared to sevoflurane-sufentanil-based anesthesia, an intraoperative infusion of dexmedetomidine combined with ketamine significantly increased sedation and the incidence of $SpO_2$ below 95% in the PACU, but the postoperative outcomes including better quality of sleep and lower recovery time of bowel movement and ambulation suggested that latter improved the late recovery.

Dexmedetomidine has been increasingly used as a component of general anesthesia due to its sedative/hypnotic and analgesic effects. The BIS monitor was used to ensure that patients in group DK had an adequate depth of anesthesia and the sevoflurane concentration was titrated to maintain equivalent depth of anesthesia in SS groups. In the DK group, non-significantly elevated incidences of hypertension and bradycardia after anesthesia induction were observed the cause of which could be a transient increase in vascular resistance caused by the stimulation of peripheral α1-adrenergic receptors.[13] In children, there is increasing data[14] indicating that OSAS could lead to pathological activation of the sympathetic nervous system and contribute to changes in heart rate (HR) responses and elevated blood pressure. In our study, the HR and systolic blood pressure were not significantly decreased between the two groups, because the inherent sympatholytic properties of dexmedetomidine on the cardiovascular system may be attenuated by sympathomimetic effects of ketamine.

The most serious risk for patients with OSA is loss of the airway owing to anesthetic, sedative, and opioid drugs; and increased risk of anesthesia. Providing satisfactory postoperative analgesia should be expected to be not complicated by sedative-induced upper airway obstruction. Optimal analgesia for children undergoing adenotonsillectomy for OSA was controversial. A study by Hullett *et al.*,[15] showed that tramadol was suitable drug for children undergoing adenotonsillectomy for OSA. We showed that intraoperative dexmedetomidine infusion decreased rescue tramadol requirement and also provided an analgesic sparing effect which was consistent with previous study.[16]

**Table 2: Intraoperative and recovery unit data**

| Parameters | Group DK ($n$ = 28) | Group SS ($n$ = 29) | *P*-value |
|---|---|---|---|
| Duration of surgery (min) | 31.2±8.9 | 28.9±8.4 | >0.05 |
| Duration of anesthesia (min) | 40.6±7.6 | 37.8±9.3 | >0.05 |
| Time to extubate (min) | 11.2±3.8 | 12.8±4.4 | >0.05 |
| Time to awake (min) | 16.4±5.2 | 13.8±3.7 | <0.01 |
| Acetaminophen dosage (mg/kg) | 31.5±4.8 | 29.7±6.5 | <0.05 |
| Rescue by tramadol, *n* (%) | 4 (14.3) | 13 (44.8) | <0.05 |
| Rescue tramadol (mg/kg) | 0.72±0.23 | 0.74±0.24 | >0.05 |
| Emergence agitation, *n* (%) | 2 (7.1) | 9 (31.0) | <0.05 |
| Nausea, *n* (%) | 2 (7.1) | 6 (20.7) | >0.05 |
| Vomiting, *n* (%) | 0 | 2 (6.9) | >0.05 |
| $SpO_2$ below 95%, *n* (%) | 13 (46.4) | 5 (17.2) | <0.05 |

*DK = Dexmedetomidine-ketamine-based anesthesia, SS = sevoflurane-sufentanil-based anesthesia*

**Table 3: Postoperative outcomes data**

| Parameters | Group DK ($n$ = 28) | Group SS ($n$ = 29) | *P*-value |
|---|---|---|---|
| Mean time to first sleep (min) | 6.8±2.2 | 19.6±6.7 | <0.001 |
| First bowel movement (h) | 5.2±1.7 | 7.5±2.4 | <0.05 |
| First ambulation (h) | 6.7±2.4 | 8.7±3.2 | <0.05 |
| Length of hospital stay (day) | 1.4±0.5 | 1.6±0.6 | >0.05 |

*DK = Dexmedetomidine-ketamine-based anesthesia, SS = sevoflurane-sufentanil-based anesthesia*

However, evaluation of postoperative pain in younger children is complicated. It is often difficult to distinguish between pain and EA, because pain itself can be the source of agitation.[17] Patel *et al.*,[6] found a positive correlation between agitation and pain. Our study showed group SS needed more rescue tramadol and had higher EA scores than did group DK. PAED scale[11] was a reliable and valid measure of emergence delirium in children. Results on the EA and PAED showed a very similar trend in both groups: Scores were highest on arrival in the PACU and decreased over time [Figures 2a-c] and a significantly lower score in group DK comparison with group SS until 45 min after entering into the PACU.

EA is complex because of its multifactorial etiology. The occurrence of EA in younger patients and otolaryngologic procedures is reported to be high, although the exact reason for this is not known.[4] Ninety percent of patients in our study were 6-years-old or younger, and more than 65% patients in each group were 2-3-years-old. Hyperactivity and attention deficit disorder are frequently seen in children with OSAS, possibly explaining or contributing to a high incidence of EA. Dexmedetomidine has been used

successfully to prevent or reduce emergence delirium in children as an infusion (0.2 μg/kg/h) or single dose at the end of surgery (0.5 μg/kg).[18,19] However, from our study and others, it remains difficult to discern whether the analgesic or sedative effects of α2 agonists are responsible for reducing EA in children. Meanwhile, it must be noted that sevoflurane anesthesia may contribute to higher incidence of EA in SS. Thus there was a lower incidence of EA in ketamine-dexmedetomidine-based anesthesia compared with sevoflurane-sufentanil-based anesthesia.

Patients with OSA are particularly at risk ascribe to upper airway obstruction. In the present study, one patient developed laryngospasm after extubation and was excluded from the study. In children, the half-life of dexmedetomidine is reported to be 1.8 h[20] and the duration of its sedative effects was longer after infusion. There was a statistically significant difference in the number of patients with $SpO_2$ below 95% in the PACU between the two groups, 13 in group DK and five in group SS. This could be related to the higher Ramsay scale until 60 min in the PACU in group DK. The residual effects on sedation of an intraoperative dexmedetomidine infusion may be responsible for higher incidence of $SpO_2$ below 95% in the PACU and is also a concern.

After PACU, in group DK, the mean time to first sleep was the lower recovery time of bowel movement and ambulation which may be related to the smaller requirement for tramadol in the PACU. As previously reported,[5] intraoperative infusion of dexmedetomidine did not significantly increase unanticipated hospital admission compared with the SS group.

In summary, for children with OSA after UPPP, the dexmedetomidine-ketamine combination was not superior to a sevoflurane-sufentanil combination because of sufficient sedation and a high potential for adverse respiratory events in PACU, the only benefit of dexmedetomidine administration was a decreased incidence of EA and a lower recovery time of bowel movement and ambulation, which may promote the late recovery time.

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