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Original Article

The Comparison of the Efficacy of Early versus Late Administration of Dexmedetomidine on Postoperative Emergence Agitation in Children Undergoing Oral Surgeries: A Randomized Clinical Trial

Afsaneh Sadeghi[1], MD; Seyed Sajad Razavi[1], MD; Ahmad Eghbali[1], MD; Seyed Alireza Mahdavi[1], MD; Fereshteh Kimia[1], MD; Ashkan Panah[2], MD

[1]Anesthesia Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
[2]Anesthesiology and Critical Care Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence:
Ashkan Panah, MD;
Department of Anesthesiology, Namazi Hospital, Zand Ave., Shiraz, Iran
Tel: +98 71 32337636
Fax: +98 71 32318072
Email: panah@sums.ac.ir
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Abstract

Background: Emergence Agitation (EA) is a dissociated state of consciousness characterized by irritability, uncompromising stance, and inconsolability. The etiology of EA is not completely understood. Dexmedetomidine is a highly selective α_2-adrenoreceptor agonist with sedative and analgesic properties, which has been used to reduce the incidence of EA. We aimed to assess the efficacy of early versus late administration of dexmedetomidine on EA in children undergoing oral surgery.

Methods: A randomized, parallel, double-blind clinical trial was conducted at Mofid Children's Hospital affiliated to Shahid Beheshti University of Medical Sciences (Tehran, Iran) from November 2016 to March 2017. A total of 81 children, who underwent adenotonsillectomy or cleft palate repair surgery were enrolled in the study. Based on simple randomization, the children were assigned to two groups, namely early (group A, n=41) and late (group B, n=40) administration of dexmedetomidine. Intra-operative and postoperative hemodynamic variables, extubation time, post-anesthesia care unit (PACU) length of stay, and the scores on Ramsay sedation scale and FLACC pain scale were measured and compared. The data were analyzed using SPSS software (version 20.0), and $P<0.05$ were considered statistically significant.

Results: The mean FLACC score was lower in the late group than in the early group (2.0±1.5 vs. 4.2±1.6, $P<0.001$). The mean Ramsay sedation score was higher in the late group than in the early group (3.5±1.4 vs. 1.8±0.8, $P<0.001$).

Conclusion: Late administration of dexmedetomidine 1 µg/kg reduced the incidence of EA and PACU length of stay and improved postoperative pain management.

Trial registration number: IRCT 2016122031497N1.

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Keywords ● Delayed emergence from anesthesia ● Emergence delirium ● Dexmedetomidine ● Cleft palate ● Tonsillectomy

What's Known

- The etiology of emergence agitation (EA) in children is not exactly known.
- The risk factors associated with EA are age, pre-operative anxiety, inhaled anesthetics, anesthetic technique, type of surgery, and postoperative pain.

What's New

- EA is a preventable side effect of inhalational anesthetics. Anesthesiologists should choose the most appropriate technique or drug to reduce the incidence of EA toward smooth recovery from anesthesia.
- Dexmedetomidine is a safe and effective choice due to its sedative and analgesic properties.

Introduction

Emergence agitation (EA) in children is a dissociated state of consciousness characterized by irritability, uncompromising stance, and inconsolability. It is commonly exhibited as

incoherence, prolonged crying, kicking, or thrashing.[1] The incidence of EA is not exactly known but has been reported to vary from 2% to 80%.[2, 3] EA usually occurs within 30 minutes after termination of general anesthesia in the post-anesthesia care unit (PACU). Although it is usually short-lived, it may harm the child, since an agitated child may pull out indwelling catheters or cause bleeding at the surgical site. Not only will these be disturbing sights for the parents, but will also necessitate additional nursing care.[2] The etiology of EA is not completely understood, but reported risk factors are age, pre-operative anxiety, inhaled anesthetics, anesthetic technique, type of surgery (head and neck), and postoperative pain.[2]

Sevoflurane is an inhalational anesthetic for both the induction and maintenance of anesthesia in children. It provides rapid induction and emergence from anesthesia, due to its low blood solubility, and has desirable properties such as agreeable odor, less airway irritation, and stable hemodynamic profile. However, sevoflurane is associated with increased EA in children,[3] particularly in adenotonsillectomy and cleft palate repair surgery. Adenotonsillectomy is the first-line treatment for obstructive sleep apnea. It is a common procedure with an estimated prevalence rate of 15% in those under the age of 15.[4, 5] Cleft palate is the most common congenital anomaly of the gastrointestinal tract representing 15% of all congenital anomalies.[6] These surgeries are common in children and associated with increased EA after sevoflurane anesthesia due to severe pain, upper airway narrowing, tongue swelling, and a sense of suffocation.[7]

Pediatric anesthesiologists should always consider adjuvant drugs to reduce EA. Several drugs such as benzodiazepines, opioids, ketamine, and propofol have been used to reduce EA. However, the main concern is their side effects such as pain, postoperative nausea and vomiting, and respiratory depression.[8] Dexmedetomidine is a potent α_2-adrenoreceptor agonist with sedative and analgesic properties.[9] It has been used as an adjuvant to local anesthetics to prolong the duration of neuraxial blocks[10] and is shown to reduce bleeding during neurosurgical operations.[11] Various studies have investigated the efficacy of dexmedetomidine toward EA prevention compared to other drugs or placebo.[12-14] However, to the best of our knowledge, no studies have investigated the effect of dexmedetomidine administration at different time points during surgery. Hence, we assessed the efficacy of dexmedetomidine infusion on EA at two-time points, namely during the first and last 10 minutes of adenotonsillectomy and cleft palate repair surgery. In addition, we assessed the pain score, sedation score, extubation time, PACU length of stay, and hemodynamic changes in pediatric patients undergoing these surgeries.

Patients and Methods

A randomized, parallel, double-blind clinical trial was conducted at Mofid Children's Hospital affiliated to Shahid Beheshti University of Medical Sciences (Tehran, Iran) from November 2016 to March 2017. The study protocol was approved by both the Institutional Review Board and Medical Ethics Committee of the University (number: IR.SBMU.MSP.95.281). The trial was registered at the Iranian Registry of Clinical Trials (registration number: IRCT 2016122031497N1).

The sample size was calculated using the below formula.[14] Considering a dropout rate of 20%, alpha level probability=0.05, and power=0.80, a sample size of 80 participants (40 per group) was required.

$$N = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left(P_1(1-P_1) + P_2(1-P_2)\right)}{(P_1 - P_2)^2}$$

where: α=0.05, β=0.2, Z_1=1.96, P_1=0.30, P_2=0.61

Accordingly, a total of 81 children, who underwent adenotonsillectomy or cleft palate repair surgery were enrolled in the study. The inclusion criteria were children aged nine months to nine years and those with American Society of Anesthesiologists (ASA) physical status class 1. The exclusion criteria were children with a history of congenital cardiac disorder, mental retardation, liver disease, renal disease, allergy to any drugs used in this study, and a history of acute upper respiratory infection. Written informed consent was obtained from the parents of the eligible children.

The basic method of simple randomization was used to assign the children to two groups, namely early (group A, n=41) and late (group B, n=40) administration of dexmedetomidine. Randomization was carried out by a nurse anesthetist (not involved in the study), using computer-generated random numbers in sealed envelopes. The same nurse also prepared and labeled sets of two 10 mL syringes of the same shape and size. The syringe labeled A contained dexmedetomidine (Precedex®, Hospira Inc., Lake Forest, USA) at a concentration of 10 mcg/kg and the syringe labeled B contained physiologic saline solution (Darou Pakhsh Pharma Chem, Tehran, Iran).

All children orally received midazolam 0.5 mg/kg (Caspian Tamin Pharmaceutical Co., Iran)

30 minutes before entering the operating room. Standard monitoring of all patients included non-invasive monitoring of arterial blood pressure, heart rate, oxygen saturation, electrocardiogram, and capnography. Anesthesia was induced by inhalation of sevoflurane 8% (Baxter, USA) through a face mask and decreased gradually to 1 MAC (minimum alveolar concentration) after the loss of consciousness. Then, an IV catheter (SUPA, Iran) was inserted followed by intravenous administration of fentanyl 1 µg/kg and atracurium 0.5 mg/kg (both from Aburaihan pharmaceutical Co., Iran). After three minutes, patients were intubated and administered a mixture of 50% nitrous oxide (Shomal Co., Iran), oxygen, and 1 MAC sevoflurane for maintenance of anesthesia. All patients received Ringer's solution (Samen pharmaceutical CO., Iran) for maintenance fluid therapy. Vital signs were recorded every five minutes, and in the case of hemodynamic changes >20% above the baseline, the patient was treated and excluded from the analysis. After intubation, children in the early group were administered dexmedetomidine infusion (syringe labeled A) during the first 10 minutes and saline solution (syringe labeled B) during the last 10 minutes of surgery. The reverse applied to children in the late group, i.e., they were injected with the syringe labeled B during the first 10 minutes and with the syringe labeled A during the last 10 minutes of surgery. At the end of the surgery, all anesthetics were discontinued and the patients ventilated with 100% oxygen. Upon reaching optimal general conditions, patients were extubated and transferred to the PACU.

As the primary outcome, the sedation level of children was measured using the Ramsay sedation scale (table 1). The scale is scored from one to six, where higher scores indicate a higher level of sedation.[15] Secondary outcomes were the time from discontinuation of anesthetic drugs to extubation, arterial blood pressure and heart rate (recorded every 10 minutes by a trained nurse blinded to grouping), and the level of postoperative pain (measured using the FLACC scale). The FLACC (face, legs, activity, cry, consolability) scale is used to assess pain based on five criteria and scored in the range of 0-10 (table 2).[16, 17] Children with pain scores >4 were given fentanyl 0.5 µg/kg for rescue analgesia. As soon as the discharge criteria were fulfilled, the children were transferred to the appropriate ward and the PACU length of stay was noted.

Statistical Analysis

The data were analyzed using SPSS software (version 20.0). Quantitative and qualitative variables were presented as mean±SD and frequency and percentages, respectively. Quantitative variables between groups were compared using an independent *t* test. Qualitative variables between groups were

Table 1: Levels of sedation according to the Ramsay sedation scale.

Level	Characteristics
1	Patient awake, anxious, agitated, or restless
2	Patient awake, cooperative, orientated, and tranquil
3	Patient drowsy, with response to commands
4	Patient asleep, brisk response to glabella tap or loud auditory stimulus
5	Patient asleep, sluggish response to stimulus
6	Patient has no response to firm nail-bed pressure or other noxious stimuli

Table 2: The criteria for the FLACC behavioral pain scale. Each of the five categories (F) face, (L) legs, (A) activity, (C) cry, (C) consolability is scored from 0-2, resulting in a total score between zero and ten

Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested, sad, appears worried	Frequency to the constant quivering chin, clenched jaw, distressed looking face, expression of fright/panic
Legs	Normal position or relaxed; usual tone and motion to limbs	Uneasy, restless, tense, occasional tremors	Kicking or legs drawn up, marked increase in spasticity, constant tremors, jerking
Activity	Lying quietly, normal position, moves easily, regular, rhythmic respiration	Squirming, shifting back and forth, tense/guarded movements, mildly agitated, shallow/splinting respirations, intermittent sighs	Arched, rigid, or jerking; severe agitation, head-banging, shivering, breath-holding, gasping, severe splinting
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint, occasional verbal outbursts, constant grunting	Crying steadily, screams or sobs, frequent complaints, repeated outbursts, constant grunting
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort, pushing caregiver away, resisting care or comfort measures

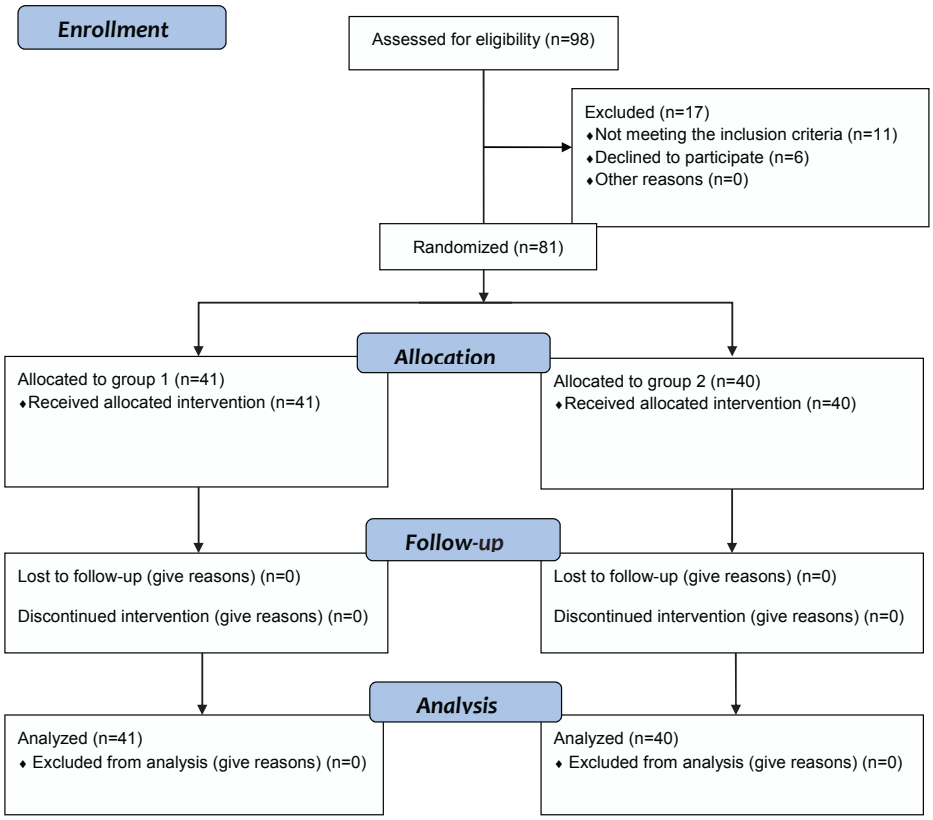

Figure 1: The CONSORT diagram shows the allocation process throughout the trial.

compared using Fisher's exact *t* test and Chi squared test. Using 95% confidence interval, P values less than 0.05 were considered statistically significant.

Results

From a total of 98 eligible children scheduled for an adenotonsillectomy or cleft palate repair surgery, 17 were excluded due to allergy or asthma (n=7), congenital heart disease (n=4), and parental objection to participation (n=6). Eventually, 81 children were enrolled in the study and randomly assigned to two groups (figure 1).

There was no significant difference between the early and the late groups concerning the patients' demographic data such as age, weight, female/male ratio, the total time of anesthesia, operative time, and PACU length of stay. However, extubation time in the early group was significantly shorter than late group (9.59±3.15 vs. 15.43±8.40 min, P<0.001) (table 3).

Table 4 shows the mean arterial pressure (MAP) and heart rate during surgery and in the PACU. There was a statistically significant difference between the early and late groups with respect to the intra-operative MAP (P=0.001) and heart rate (P=0.005). These two variables were similar in the PACU. The early group had higher pain (FLACC) and lower sedation scores than the late group (P<0.001).

Discussion

The etiology of EA in children is still unknown, but reported risk factors are anesthetic technique,

Table 3: Demographic data of children in both groups of early (A) and late (B) administration of dexmedetomidine

		Group A (early)	Group B (late)	P value
Age (months)		59.81±29.43	69.42±36.60	0.195*
Weight (kg)		18.76±6.60	18.94±6.23	0.959*
Sex (n, %)	Male	25 (61)	21 (52.2)	0.505#
	Female	16 (39)	19(47.5)	
Total time of anesthesia (minutes)		89.27±31.26	83.38±26.25	0.373*
Surgical time (minutes)		60.24±27.68	52.25±23.23	0.164*
Extubation time (minutes)		9.59±3.15	15.43±8.40	<0.001*
PACU length of stay (minutes)		24.72±10.25	28.21±9.70	0.135*

*Independent sample *t* test; #Chi square test

Table 4: Arterial blood pressure and heart rate (during surgery and while in the PACU) and the scores of Ramsay sedation and FLACC scales in both groups of early (A) and late (B) administration of dexmedetomidine

Variable	Group A (early)	Group B (late)	P value
MAP mmHg	69.10±9.84	76.12±8.96	0.001*
Heart rate BPM	94.82±19.20	106.10±15.32	0.005*
MAP mmHg while in the PACU	11.15±78.92	76.84±11.21	0.402*
Heart rate while in the PACU	103.89±19.01	95.54±12.69	0.057*
FLACC score	4.21±1.64	2.01±1.46	<0.001*
RSS score	1.83±0.84	3.49±1.42	<0.001*

*Independent sample *t* test; MAP: Mean arterial pressure; PACU: Post-anesthesia care unit; FLACC: Face, legs, activity, cry, consolability scale; RSS: Ramsay sedation scale

postoperative pain, age, head and neck surgeries, and pre-operative anxiety.[2] Several drugs have been used to prevent or reduce EA.[18] The results of a meta-analysis showed that anesthetic adjuncts such as propofol, ketamine, and fentanyl are effective in preventing EA.[12]

Complications associated with tonsillectomy or cleft palate repair surgery pose a challenge during the recovery period. Severe pain, tongue swelling, respiratory complications due to temporary narrowing of the airway, and other airway complications create a sense of suffocation, which may lead to severe EA. It is therefore important to accelerate airway management to control EA.[19, 20] To prevent EA, anesthesiologists favor drugs that cause the least respiratory depression. Dexmedetomidine is a highly selective α_2-adrenoreceptor agonist with sedative and analgesic properties. In clinical doses, it does not cause respiratory depression. In a meta-analysis, Zhu and colleagues showed the positive effects of dexmedetomidine on EA and postoperative recovery profiles compared to placebo.[21] We found that in children anesthetized with sevoflurane, the late administration of dexmedetomidine 1 µg/kg (during the last 10 minutes of surgery) provided better sedation and analgesia than the early administration (during the first 10 minutes of surgery). To the best of our knowledge, no studies have investigated the effect of dexmedetomidine administration on EA at two different time points during surgery. However, several studies reported the positive effects of dexmedetomidine on EA as a premedication, i.e., at the beginning of surgery.

Boku and colleagues investigated the effectiveness of dexmedetomidine on EA in infants undergoing palatoplasty with sevoflurane anesthesia. They showed that administration of dexmedetomidine 6 µg/kg/h during the first 10 minutes of cleft palate surgery followed by 4 mg/kg/h until five minutes after extubation is more effective than placebo.[22] Hauber and colleagues compared rapid intravenous bolus of 4 µg/mL dexmedetomidine at a dose of 0.5 µg/kg with placebo in pediatric ENT surgeries and found that dexmedetomidine reduced the incidence of EA.[14] Cao and colleagues compared the effect of intra-operative infusion of dexmedetomidine with placebo on EA in pediatric patients, who underwent tonsillectomy using propofol and remifentanil anesthetics. In contrast to our findings, they reported no significant difference between the groups in terms of the effect on the incidence of EA.[13] This may be in part due to the use of propofol for maintenance of anesthesia, which is suggested to reduce EA.[23] Liu and colleagues compared administration of dexmedetomidine 0.5 µg/kg with placebo five minutes before the start of orthopedic surgery in children with cerebral palsy. They found that dexmedetomidine reduced the incidence and severity of EA.[24] In comparison with our study, due to the lack of a placebo group, we could not assess the effect of early administration of dexmedetomidine in reducing the incidence of EA.

Another finding of our study was lower FLACC scores in the late group than the early group. This could be due to the continued analgesic properties of dexmedetomidine during the recovery period resulting from its late administration. Moreover, the short distribution half-life of dexmedetomidine could have resulted in reduced analgesia in the early group. We believe that the same mechanism resulted in more sedation and a higher Ramsay sedation scale score in the late group. In line with our finding, Boku and colleagues reported that the administration of dexmedetomidine during the last minutes of cleft palate surgery reduced EA and pain scores compared to placebo.[22] Kim and colleagues studied the effects of continuous infusion of low-dose dexmedetomidine 0.2 µ/kg/h compared to placebo in children undergoing strabismus surgery and found its effectiveness in reducing the incidence of EA.[25] Patel and colleagues compared the continuous infusion of dexmedetomidine with fentanyl and showed that dexmedetomidine provided better analgesia.[26]

Longer extubation time in the late group was another finding of the present study. This was in line with a meta-analysis by Zhu and colleagues reporting that the infusion and late administration

of dexmedetomidine compared to placebo increased extubation time.[21] Again, this could be due to the sedative effects of dexmedetomidine.

One of the main concerns about prescribing dexmedetomidine is its hemodynamic effects (typically bradycardia). However, this usually occurs in doses over 10 mcg/kg/h.[27] In addition, treatment of bradycardia is indicated, if there is an association with hemodynamic changes, early serious bradyarrhythmia, or both.[28] In our study, intra-operative mean heart rate and mean arterial blood pressure were significantly higher in the late group than the early group. This could be due to shorter intra-operative exposure to analgesic and hemodynamic depressant effects of dexmedetomidine resulting from late administration.

Recovery time was similar in both the early and late groups. However, in the absence of a placebo group, we could not compare the effect of dexmedetomidine on the recovery time. Nonetheless, a previous study reported a longer recovery time, due to dexmedetomidine than placebo.[21]

There are some notable limitations in the present study. First, the inclusion of patients spanning a wide age range due to the inclusion of two different types of surgery with a high incidence of EA. It is recommended that future studies narrow down the age range. Second, it would have been advantageous to use the pediatric emergence agitation scale (PAED), which is a more sensitive measure of EA than the Ramsay sedation scale. Third, contrary to our study design, the inclusion of a placebo group as a baseline is recommended to compare the effect of early administration of dexmedetomidine. Fourth, clinical signs were used to assess the depth of anesthesia and extubation time. Instead, the use of the bispectral index and nerve stimulator is recommended to determine the exact time of extubation.

Conclusion

EA is a preventable side effect of inhalational anesthetics. Anesthesiologists should choose the most appropriate anesthetic technique and drug to reduce the incidence of EA toward a smooth recovery from anesthesia. Dexmedetomidine is a safe and effective choice due to its sedative and analgesic properties. It is recommended that pediatric anesthesiologists use an early administration of dexmedetomidine infusion to control blood pressure during head and neck surgery. Late administration of dexmedetomidine infusion is recommended to reduce the incidence of EA.

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Conflict of Interests: None declared.

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