SCIENTIFIC ARTICLE

Effectiveness of dexmedetomidine for emergence agitation in infants undergoing palatoplasty: a randomized controlled trial

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Abstract
Objectives: In infants, there is a high incidence of emergence agitation (EA) after sevoflurane (Sev) anesthesia. This study aimed to test the hypothesis that dexmedetomidine (Dex) administration would reduce the incidence and severity of EA after Sev-based anesthesia in infants undergoing palatoplasty.
Methods: A prospective randomized clinical trial was conducted with 70 patients undergoing palatoplasty, aged 10–14 months. Infants were randomly allocated into two groups: Dex ($n = 35$) and saline ($n = 35$). In the Dex group, Dex ($6\,\mu g/kg/h$) was administered approximately 10 min before the end of the surgery for 10 min, followed by $0.4\,\mu g/kg/h$ until 5 min after extubation. In the saline group, an equivalent amount of saline was administered in a similar manner. After the surgery, patients were transferred to the postanesthetic care unit (PACU). The infant's behavior and pain were assessed with scoring system for EA (5-point rating scale) and pain scale (PS; 10-point rating scale), respectively. EA and PS were estimated at six time points (after extubation, leaving the operating room, 0, 30, 60, and 120 min after arrival in PACU).
Results: EA and PS scores were significantly lower in the Dex group than in the saline group from extubation to 120 min after arrival in PACU.
Conclusions: Dex administration has the advantage of a reduced EA and PS without any adverse effects. Dex provided satisfactory recovery in infants undergoing palatoplasty.
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Eficácia de dexmedetomidina para o surgimento de agitação em lactentes submetidos à palatoplastia: estudo clínico randomizado

Resumo

Objetivos: Em crianças, é elevada a incidência de surgimento de agitação (SA) em seguida à anestesia com sevoflurano (Sev). Este estudo teve como objetivo testar a hipótese de que a administração de dexmedetomidina (Dex) reduziria a incidência e gravidade do SA após anestesia com Sev em lactentes submetidos à palatoplastia.

Métodos: Estudo clínico prospectivo randomizado, realizado com 70 pacientes submetidos a uma palatoplastia, com idades entre 10-14 meses. As crianças foram divididas randomicamente em dois grupos: Dex (n = 35) e solução salina (n = 35). No grupo de Dex, Dex (6 μg/kg/h) foi administrada cerca de 10 minutos antes do final da cirurgia durante 10 min, seguida de 0,4 μg/kg/h até 5 minutos após a extubação. No grupo de solução salina, uma quantidade equivalente de salina foi administrada com o mesmo esquema de dosagem. Após a cirurgia, os pacientes foram transferidos para a unidade de cuidados pós-anestésicos (UCPA). O comportamento e a dor dos bebês foram avaliados com um sistema de pontuação para SA (escala de classificação de 5 pontos) e com uma escala de dor (ED; escala de classificação de 10 pontos), respectivamente. SA e ED foram estimados em seis pontos cronológicos (após a extubação, ao deixar a sala de cirurgia, e 0, 30, 60 e 120 minutos após a chegada à UCPA).

Resultados: Os escores SA e ED foram significativamente menores no grupo Dex versus grupo salina, desde a extubação até 120 min após a chegada à UCPA.

Conclusões: A administração de Dex tem a vantagem de uma redução no SA e na ED, sem quaisquer efeitos adversos. Dex proporcionou uma recuperação satisfatória em lactentes submetidos à palatoplastia.

Introduction

Sevoflurane (Sev) is a popular inhalational anesthetic in children. It is characterized by a more rapid onset and offset because of a lower blood/gas partition coefficient, a less pungent and irritation to the airway, and a less cardiodepressive effect when compared with other potent inhaled anesthetics.[1,2] However, the incidence of emergence agitation (EA) after Sev anesthesia is high in infants,[3,4] and the etiology for the higher incidence of EA in infants is unknown. EA is not only a major source of dissatisfaction for parents and caregivers postoperatively, but it also may lead to some complications such as increased bleeding from operative sites and pulling out an intravenous catheter. Possible etiological factors for EA include a rapid recovery, psychological immaturity, otolaryngology procedures, anesthesia time, and concurrent medications.[5–8] Pediatric anesthesiologists should consider methods to reduce the risk of EA after Sev anesthesia.

In the present study, we focused on EA in specific patients aged approximately 1 year (10–14 months) and undergoing palatoplasty for more reliable results because the incidence and severity of EA depends on patient's age and procedure.[9] Otolaryngology procedures such as tonsillectomy and adenoidectomy as well as children are risk factors for EA.[10] A sense of suffocation in airway procedures is considered a major cause of the high incidence of EA.

The immediate postoperative period after palatoplasty is difficult because this surgery has specific complications associated with the surgical procedure. Severe pain is suspected and narrowing of the upper respiratory tract may result in transient worsening of obstructive symptoms and hypoxemia. Because EA after palatoplasty is a mild complication in comparison with lingual swelling and other airway-related complications,[11] rapid emergence from anesthesia may be desirable to allow for full airway control after extubation. Therefore, it is important that prophylaxis or treatment for EA after palatoplasty should not have an unfavorable impact on airway.

Various medications, including benzodiazepines, ketamine, and propofol, were used to reduce the incidence of EA.[12] However, there is no well-established prophylaxis or treatment for EA. Although supplemental opioids and/or sedatives are often used to reduce the incidence and severity of EA, anesthesiologists should always consider the risk of postoperative respiratory complications.

Dexmedetomidine (Dex), a potent α_2-adrenoceptor agonist, has sedative, analgesic, and anxiolytic properties without respiratory depression.[13] Some studies have shown the effectiveness of Dex in postoperative recovery in a pediatric population undergoing tonsillectomy and adenoidectomy.[14,15] However, the effectiveness of Dex in younger infants undergoing palatoplasty has not yet been well established.

The objective of this study was to test the hypothesis that the administration of Dex would reduce the incidence and severity of EA after Sev-based anesthesia in infants undergoing palatoplasty.

Materials and methods

This randomized and double-blind study was approved by the Institutional Ethical Committee of Osaka University Dental Hospital, Suita, Japan (Chairperson Prof. S. Wakisaka) on August 23, 2011 and the protocol number is H23-E9. Registration for this study (UMIN 000009869) can be found at http://upload.umin.ac.jp. Patient's parents were advised about the risk and benefits of participation and written informed consent was obtained.

Patients

Seventy patients undergoing palatoplasty were enrolled in this study. Participants were required to be ASA physical status class I, aged 10–14 months old, weight between 7 and 10 kg. Exclusion criteria included lack of consent, ASA class > II, cardiovascular disease, or a history of airway obstruction. Randomization was performed using a computer-generated random number table. Five anesthesiologists participated in this study, and each had over 7 years' experience. The patient's parents and the attending anesthesiologist were blinded to the group allocation. Patients were randomly allocated into two groups: Dex (n = 35) and saline (n = 35).

Anesthesia protocol

After standard monitoring (including pulse oximetry, electrocardiogram, noninvasive arterial blood pressure) in the operating room, anesthesia was induced with Sev (4%). After induction, endotracheal intubation was facilitated with 0.6 mg/kg rocuronium. Anesthesia was maintained with 1%–2% end-tidal Sev and 66% nitrous oxide in oxygen. Fentanyl (20 μg) was administered as a bolus to patients in both groups, and local anesthetics (1% lidocaine containing adrenalin: 2 ml) was also injected into the operative site. In the Dex group, Dex (6 μg/kg/h) was continuously administered approximately 10 min before the end of the surgery for 10 min, followed by 0.4 μg/kg/h until 5 min after the extubation. In the saline group, an equivalent amount of saline was administered in a similar manner. At the end of the surgery, anesthetic gases were discontinued. The trachea was extubated when patients were awake. Patients were then transferred to the postanesthetic care unit (PACU), and both groups received rectal acetaminophen (200 mg). In PACU, parents were allowed to be with their child. Supplemental oxygen was administered when SpO_2 decreased to less than 95%.

Table 1 Scoring system for emergence agitation.

Score	Behavior
1	Sleeping
2	Awake, Calm
3	Irritable, crying
4	Inconsolable crying
5	Severe restlessness, disorientation

We evaluated time to extubation (TE), which was defined as the time from discontinuation of Sev and nitrous oxide to extubation. Heart rate (HR), mean arterial blood pressure (MAP), and SpO_2 were documented before, undergoing, and after the administration of Dex or saline. To assess the EA and pain scale (PS) score, the scoring system for EA and PS score were used. EA was assessed with a 5-point scale (Table 1).[5] PS score was assessed by Face, Legs, Activity, Cry, Consolability (FLACC) Scale (Table 2).[16] This pain assessment scale was used for nonverbal patients. Each scale has three categories. We added each scale and expressed it as total points. EA and PS score were estimated at six time points (after extubation, leaving the operating room, 0, 30, 60, and 120 min after arrival in PACU). Data for each patient were obtained by the blinded anesthesiologist.

Statistical analysis

Before initiating the study, a power analysis suggested that a sample size of 35 patients in each groups are required to show that the administration of Dex would decrease the incidence of severe EA (point 4 or 5) after the surgery by 40% with 80% power (α = 0.05) in comparison with the control group.

Data are presented as number (n), mean (SD), or median (IQR) as appropriate. Student's t-test was used for height, weight, age, anesthesia time, surgery time, and TE. Chi-square for independence test 2×2 contingency table was used for sex. Two-factor repeated-measures ANOVA and multiple comparison was used for HR and MAP. EA and PS score were compared between groups with Mann–Whitney's U-test. p-values of <0.05 were considered statistically significant.

Results

Eighty infants presenting with palatoplasty under general anesthesia were assessed for eligibility from August 2011 to July 2012. Fig. 1 shows the CONSORT flow chart detailing

Table 2 Scoring system for pain scale.

Category	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace	Frequent to constant frown
Legs	Normal position	Uneasy, restless	Kicking or legs drawn up
Activity	Lying quietly, moves easily	Squirming, shifting back	Arched rigid
Cry	No crying	Moans or whimpers	Crying steadily, screams
Consolability	Content, relaxed	Reassured by occasional touching, hugging	Difficult to console

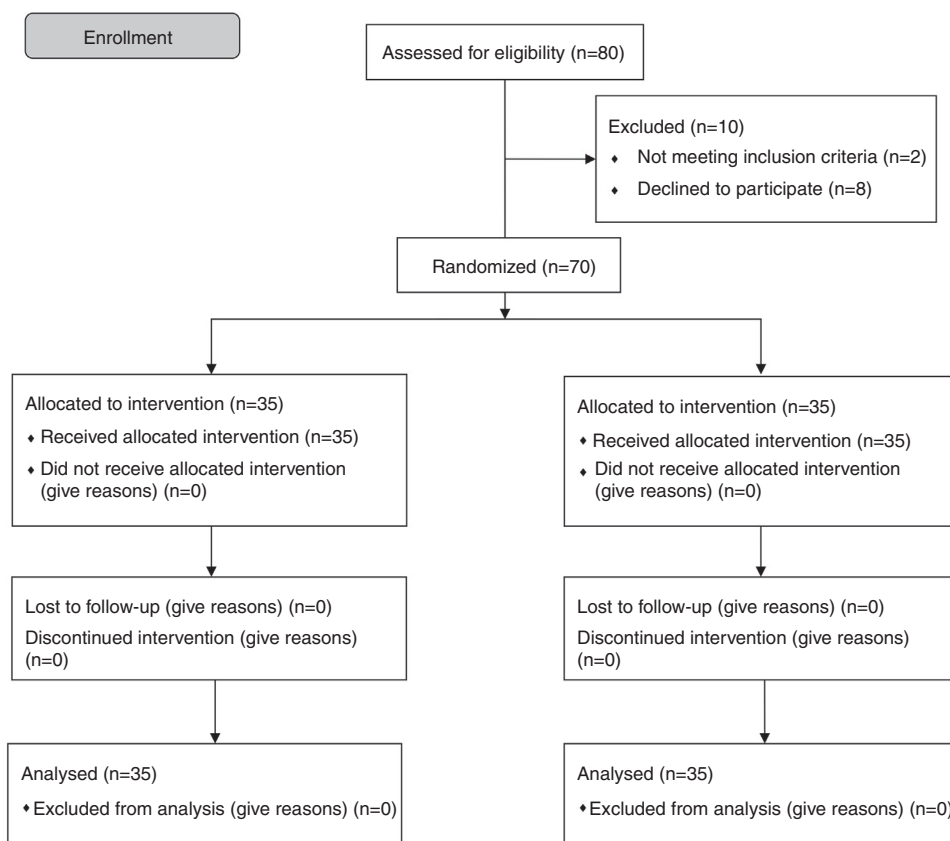Each scale was added and expressed as a total points.

Figure 1   Consolidated Standards of Reporting Trials (CONSORT) recommended description of patient recruitment.

patient recruitment. Data analysis was performed on two groups (Dex group, $n = 35$; saline group, $n = 35$).

Details of demographic characteristics are summarized in Table 3. There were no differences between the two groups in patient demographics, surgery time, and anesthesia time. Total dosage of Dex was 11.5 (2.5) μg. TE was significantly longer in the Dex group [8.1 (2.9) min] than in the saline group [6.4 (1.9) min]. Tables 4 and 5 demonstrated the scoring system for EA and PS score. EA and PS scores were significantly lower in the Dex group than in the saline group during the observation period.

Two patients in each group required supplemental oxygen because of reduced SpO_2 (Table 6); however, none of these patients exhibited any signs of airway obstruction and prolonged oxygen requirement.

MAP and HR after extubation (after administration of Dex) were significantly lower in the Dex group [59.7 (5.3) mmHg, 128.1 (9.8) beats/min, respectively] than in the saline group [67.3 (6.6) mmHg, 142.5 (9.7) beats/min, respectively]. Hemodynamic instability did not occur in any of the patients, and vital signs remained within 20% of baseline in all patients (Figs. 2 and 3).

Table 3   Demographic data.

	Dex ($n = 35$)	Saline ($n = 35$)	p value
Patient characteristics			
Age (month)	12.2 (1.5)	11.9 (1.6)	0.44 NS
Male/Female	14/22	16/19	0.21 NS
Height (cm)	74.9 (3.1)	74.0 (3.8)	0.23 NS
Weight (kg)	8.8 (1.0)	8.9 (1.2)	0.32 NS
Surgery characteristics			
Surgery time (min)	76.5 (22.2)	74.5 (15.1)	0.18 NS
Anesthesia time (min)	148.5 (19.8)	143.0 (25.0)	0.39 NS
TE (min)[a]	8.1 (2.9)	6.4 (1.9)	0.01
Total amount of Dex (μg)	11.5 (2.5)		

Data are expressed by mean (SD); NS, not significant.
[a] $p < 0.05$; Dex vs. saline.

Table 4 The scoring system for emergence agitation at six points of time.

After extubation	Leaving the operating room	Time from arrival in the postanesthetic care unit (min)			
		0	30	60	120
Saline					
3	3	3	3	3	2
(3–4)	(3–4)	(3–3.5)	(3–3)	(2–3)	(1–3)
Dex					
3[a]	1[a]	1[a]	1.5[a]	1[a]	1[a]
(2–3)	(1–2)	(1–2)	(1–2)	(1–2)	(1–2)

Data are expressed as median (IQR).
[a] p < 0.05; Dex vs. saline.

Table 5 The scoring system for pain scale at six points of time.

After extubation	Leaving the operating room	Time from arrival in the postanesthetic care unit (min)			
		0	30	60	120
Saline					
9	8	8	6	5	5
(8–9)	(7–9)	(6–9)	(5–8)	(3.5–6)	(3.5–6)
Dex					
7[a]	1[a]	1.5[a]	2[a]	1[a]	0[a]
(2.75–9)	(0–4.25)	(0–4)	(0–3.25)	(0–2.25)	(0–2)

Data are expressed as median (IQR).
[a] p < 0.05; Dex vs. saline.

Table 6 Desaturation episode with SpO_2 below 95% after extubation.

Saline	2/35
Dexmedetomidine	2/36

Discussion

The results of this study show that Dex has the advantage of a reduced EA and PS score without any adverse effects after Sev anesthesia in infants undergoing palatoplasty. The effects on EA and PS score lasted for more than 2 h after the surgery.

Dex is a potent α_2-adrenoceptor agonist and primarily used as a postoperative sedative in ICU.[17] Recently, Dex is increasingly used for procedural sedation during awake fiberoptic intubation,[18] colonoscopy,[19] and magnetic resonance imaging (MRI) for young children.[20–22] Dex is also extremely useful as a sedative for children undergoing tonsillectomy and adenoidectomy.[10] These reports suggest a possible beneficial effect of Dex for postoperative management after palatoplasty. The present study clearly
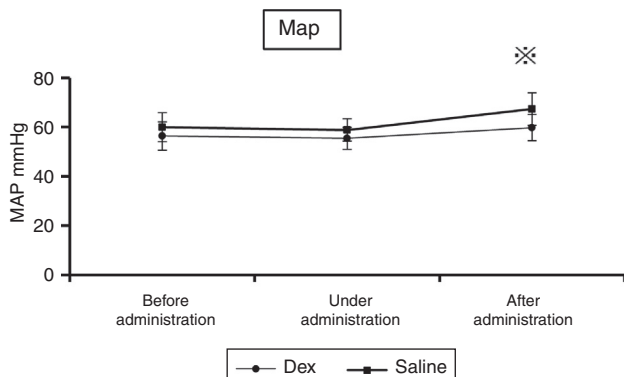

Figure 2 Mean arterial blood pressure (MAP) responses at the time of before, undergoing, after administration of dexmedetomidine (Dex) or saline. Data are mean (SD). *p < 0.05 versus before administration.
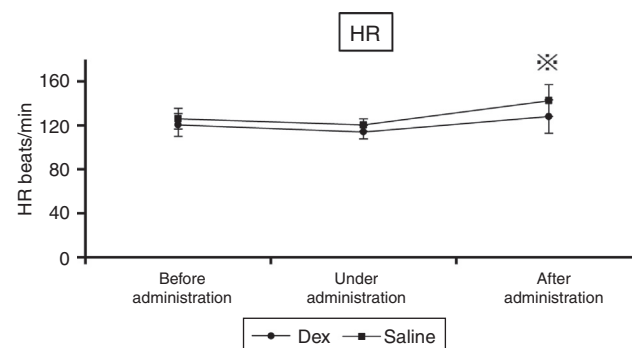

Figure 3 Heart rate (HR) responses at the time of before, undergoing, and after administration of dexmedetomidine (Dex) or saline. Data are mean (SD). *p < 0.05 versus before administration.

demonstrated the effectiveness of Dex on the reduction in EA score.

Pain is a major factor increasing the severity and frequency of agitation, and sufficient analgesia leads to the reduction in agitation.[23,24] Dex is beneficial for pain treatment. Dex demonstrates peripheral and centrally mediated antinociception via receptor activation in the dorsal horn and the locus coeruleus.[25,26] Dex administered before the end of surgery reduced morphine requirement in the immediate postoperative period in adult patients undergoing major abdominal or orthopedic procedures.[27] Patel et al.[14] also reported that an intraoperative infusion of Dex significantly reduced the postoperative opioid requirement in children. Our PS score results indicate that Dex provides considerable analgesia following palatoplasty.

Some studies have demonstrated that opioids are effective to relieve EA after Sev anesthesia.[28] However, in the postoperative period following palatoplasty, effective analgesia with opioid alone would be difficult to provide without any effects on airway. In contrast, there are evidences that even pain-free children with caudal block or undergoing MRI become agitated during emergence from anesthesia.[29,30] EA often occurs even after adequate pain treatment or after procedures that are not associated with pain. Because Dex has both sedative and analgesic properties, it is beneficial even in such situations.

Dex can lead to dose-dependent bradycardia, hypo- or hypertension in children, when Dex is applied as a sole agent for sedation.[31,32] Bloor et al.[33] reported that after the administration of Dex, there is a decrease in the HR and biphasic blood pressure response with a short initial increase, followed by a prolonged decrease of the blood pressure. The decrease in blood pressure and HR are the result of the stimulation of central presynaptic α_{2a}-adrenergic receptor.[31,33]

In this study, Dex was administered at an intraoperative initial loading dose of $6\,\mu g/kg/h$, followed by an infusion at $0.4\,\mu g/kg/h$. HR and MAP after extubation were significantly lower in the Dex group than in the saline group, but no serious circulatory depression was observed after the administration of Dex. A recent meta-analysis revealed a lower risk for EA following Dex in comparison with placebo.[34] However, there were large differences in Dex regimen (low dose: $0.15\,\mu g/kg$, high dose: $4\,\mu g/kg$) between studies. Shurky et al.[35] also reported that Dex was used successfully as a continuous infusion ($0.2\,\mu g/kg/h$) for 15 min in the postoperative period to prevent or reduce EA in children. On the other hand, Guler et al.[10] and Ibacache et al.[36] reported that a single dose of Dex ($0.5\,\mu g/kg$) 5 min before the end of surgery and $0.3\,\mu g/kg$ after induction of anesthesia reduced EA without significant hemodynamic effects, respectively. Thus, the administration of Dex at a slow rate may contribute to hemodynamic stability.

In our study, two patients in each group required supplemental oxygen because of reduced SpO_2 after extubation; however, none of these patients exhibited signs of airway obstruction and prolonged oxygen requirement.

There are some limitations in our study. First, although pain is definitely a major reason for EA, screaming as a result of pain should be distinguished from EA. However, it is impossible to distinguish between them in children in the preverbal stage of development. Furthermore, there are some difficulties in interpreting behavior with other influencing factors such as hunger or fear of strangers. Although it is uncertain whether postoperative rectal acetaminophen provided the expected level of analgesia, the analgesic and sedative effects of Dex would to be advantageous to this situation in infants.

Second, we used the scoring system for EA and PS score.[5,16] Five anesthesiologists participated to assess EA and PS score in our study. Although the method we used is well accepted and has been validated in other studies,[5,30] there may be a difference in an evaluation of EA and PS score due to experimenter's bias. If we use another criterion, different results may be obtained.

Third, it is important to note that we studied relatively healthy infants and excluded infants with a history of airway problems because Dex required in the study protocol may subject these infants to unacceptably greater risks for postoperative airway complications. In the absence of such a study, we would urge caution in the use of Dex in infants with documented airway obstruction. Further studies focusing on obstructive airway complications due to Dex in infants with Robin sequence and/or Treacher Collins syndrome are needed.

In conclusion, although our sample size is small, it seems that the use of Dex reduced EA and PS score without any adverse effects and provided satisfactory recovery with stable hemodynamics in infants undergoing palatoplasty.

Funding

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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