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ORIGINAL ARTICLE

Buccal administration of dexmedetomidine as a preanesthetic in children

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Abstract
Purpose The objective of this study was to evaluate the efficacy and safety of buccal dexmedetomidine as a preanesthetic in children, to compare it with diazepam, and to investigate the optimal dosage for buccal dexmedetomidine administration by measuring its serum concentration.
Methods We performed a prospective study with 40 children who were assigned to two groups. The patients underwent an operation for inguinal or umbilical hernia. Twenty children received dexmedetomidine buccally at 3–4 μg/kg (Dex Group) and 20 received a diazepam suppository at 0.7 mg/kg (Diazepam Group) as preanesthetics 1 h before the operation. Heart rate, systolic blood pressure, SpO_2, and respiratory rate were measured 1 h after premedication in all children. Sedation level was preoperatively evaluated, and compared with the Ramsay score, in the ward, at the entrance to the main operating rooms, and at anesthesia induction between the two groups. To investigate the optimal dosage of buccal dexmedetomidine, we compared the mean serum concentration of dexmedetomidine at induction between patients with a Ramsay score of 5 or greater and those with a Ramsay score less than 5. The Mann–Whitney *U* test was used for statistical analysis.
Results There was no significant difference between the two groups in age or body weight. Furthermore, there was no significant difference between the two groups in heart rate, systolic blood pressure, SpO_2, or respiratory rate after administration of either medication. The Ramsay score of the Dex Group was significantly higher than that of the Diazepam Group at all times. The mean serum dexmedetomidine concentration at induction in patients with a Ramsay score of 5 or greater (75 ± 50 pg/ml) was significantly higher than in those with a Ramsay score less than 5 (34 ± 36 pg/ml, $P < 0.05$).
Conclusion These results suggest that the buccal administration of dexmedetomidine (3–4 μg/kg) 1 h before the operation can be safely and effectively applied as a preanesthetic in children.

Keywords Dexmedetomidine · Premedication · Child · Alpha-2 agonist

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Introduction

Dexmedetomidine is a selective α_2-receptor agonist with sedative and analgesic properties that produces less respiratory suppression [1, 2]. Dexmedetomidine has been administered intravenously for sedation in the ICU and for procedures such as computed tomography (CT),

electroencephalography (EEG), and magnetic resonance imaging (MRI) in children [3–6]. Dexmedetomidine has also been used intramuscularly as a preanesthetic in adults [7]. Because children prefer a noninvasive approach for procedural sedation and anesthetic premedication, a nonIV delivery route of midazolam, chloral hydrate, and fentanyl has previously been used in children. However, there are few studies on sedation with dexmedetomidine via a nonIV route, especially buccal administration, and there are no published data on the plasma concentration of dexmedetomidine when it is administered through a nonIV route in children. The objective of this study was to evaluate the efficacy and safety of buccal dexmedetomidine as a preanesthetic in children, compare it with diazepam, and to investigate the optimal buccal dosage of dexmedetomidine by measuring its serum concentration.

Subjects and methods

Anesthetic premedication protocol

This prospective study was approved by the institutional review board of our hospital, and we received informed consent from each family for enrollment in this study. Forty children with ASA physical status 1 were assigned to two groups:

1 Dex Group: 3–4 μg/kg dexmedetomidine was administered buccally 60 min before the operation. We administered dexmedetomidine buccally using the undiluted IV drug because the volume was so small that it could be more easily absorbed buccally.
2 Diazepam Group: a diazepam suppository (0.7 mg/kg) was administered rectally 60 min before the operation.

All patients were continuously monitored using a pulse oximeter during the perioperative period. Heart rate, systolic blood pressure, SpO_2, and respiratory rate were recorded 1 h after administration of the preanesthetics. In the operating room the children were anesthetized by slow induction via a mask with nitrous oxide (4 L/min), oxygen (2 L/min), and Sevoflurane (5%). Anesthesia was maintained during the operation through a laryngeal mask with nitrous oxide (4 L/min), oxygen (2 L/min), and Sevoflurane (2%). The children underwent the operation for inguinal or umbilical hernia. All extubations were performed during deep sleep. The Ramsay score sedation level was preoperatively compared between the two groups in the ward, at the entrance to the main operating rooms, and when anesthesia was induced. Blood samples were taken from the Dex Group during the induction to measure the serum concentration of dexmedetomidine, which was analyzed by liquid chromatography–mass spectrometry (Q-Trap; Applied Biosystems; Foster City, CA, USA). The measurement method is described in detail elsewhere [8]. To investigate the ideal dosage of buccal dexmedetomidine, we compared the mean serum concentration of dexmedetomidine at induction between patients with a Ramsay score of 5 or greater and those with a Ramsay score less than 5.

Table 1 Summary of the demography of the subjects

	Diazepam Group	Dex Group	*P* value
Number	20	20	
Age (y.o.)	3.1 ± 1.7 (1–6)	3.2 ± 2.0 (1–7)	NS
Body weight (kg)	13.9 ± 3.2 (9–20)	15.3 ± 4.4 (9–28)	NS

Dex dexmedetomidine, *NS* not significant

Values are mean ± standard deviation (SD)

Ramsay scale for scoring sedation

1. Anxious or agitated and restless, or both
2. Cooperative, orientated, and tranquil
3. Drowsy, but responds to commands
4. Asleep, brisk response to light glabellar tap or loud auditory stimulus
5. Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6. Asleep and unarousable

Statistical analysis

Age, body weight, heart rate, SpO_2, blood pressure, respiratory rate, and the serum concentration of dexmedetomidine are expressed as the mean and standard deviation (SD). Ramsay score is expressed as the median.

The Mann–Whitney *U* test was used for statistical analysis, and was performed by use of the SPSS software package (version 13.0; SPSS, Chicago, IL, USA). Two-tailed $P < 0.05$ values were considered statistically significant.

Results

Forty children were enrolled in the study. There were no significant differences in age or body weight between the two groups (Table 1; mean age, 3.2 ± 2.0 years in the Dex Group vs. 3.1 ± 1.7 years in the Diazepam Group; mean body weight, 15.3 ± 4.4 kg in the Dex Group vs. 13.9 ± 3.2 kg in the Diazepam Group). There were no significant differences in heart rate, systolic blood pressure, SpO_2, or the respiratory rate between the two groups 1 h after administering the anesthetic premedications (Table 2). The Ramsay score in the Dex Group was significantly higher

Table 2 Comparison of the vital signs between the Dex and Diazepam groups after preanesthetic administration

Vital sign	Dex Group	Diazepam Group	*P* value
HR (beat/min)	100 ± 18 (78–132)	103 ± 16 (78–126)	NS
sBP (mmHg)	105 ± 8 (94–120)	98 ± 10 (86–116)	NS
SpO_2 (%)	99.0 ± 1.6 (96–100)	99.5 ± 1.1 (96–100)	NS
RR (rate/min)	26 ± 5 (20–36)	24 ± 6 (18–36)	NS

HR heart rate, *sBP* systolic blood pressure, *SpO_2* saturation of peripheral oxygen, *RR* respiration rate

Values are mean ± SD (range)

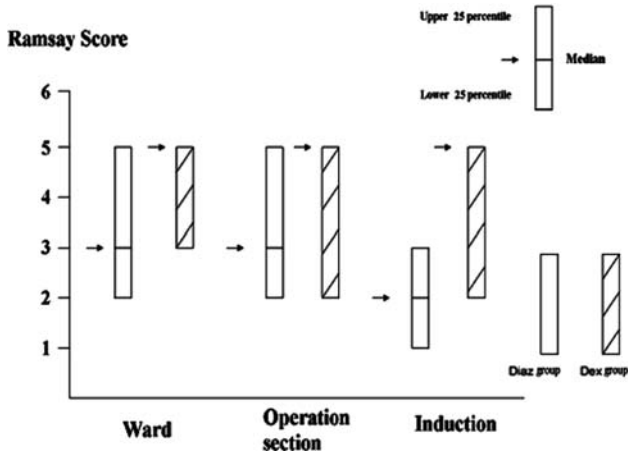

Fig. 1 Comparison of the Ramsay score between Dex and Diazepam groups

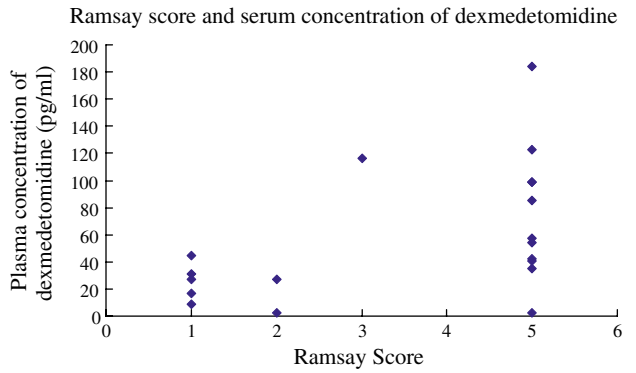

Fig. 2 The relationship between Ramsay score and serum concentration of dexmedetomidine

than that in the Diazepam Group at different times (Fig. 1). The mean serum concentration of dexmedetomidine in patients with a Ramsay score of 5 or greater at induction (75 ± 50 pg/ml) was significantly higher than that in patients with a Ramsay score less than 5 (34 ± 36 pg/ml, $P < 0.05$) (Fig. 2).

Discussion

Dexmedetomidine has a high ratio of specificity for the α_2 versus the α_1 receptor (1600:1) [1]. The signal results in reducing noradrenergic neuronal activity in the locus ceruleus causing sedation and analgesia [9]. An advantage of dexmedetomidine is that it results in less respiratory suppression than other sedatives [2], which could be beneficial for children.

Several studies have evaluated the efficacy of dexmedetomidine for child sedation. Mason et al. [10] prospectively evaluated pediatric sedation in a dexmedetomidine pilot program for CT imaging studies. Sixty-two children received dexmedetomidine intravenously as a 2 μg/kg loading dose over 10 min, followed by repeat boluses of a 2 μg/kg loading dose over 10 min until a target Ramsay score of 4 was achieved. Patients were then maintained on 1 μg/kg/h infusion until imaging was completed; there were no significant changes in the respiratory rate or end-tidal CO_2. Compared with pre-sedation values, the heart rate and mean BP decreased by an average of 15% during bolus, infusion, and recovery; however, the decreases were still clinically acceptable for this pediatric population. Berkenbosch et al. [11] investigated the efficacy of dexmedetomidine for noninvasive procedural sedation in children after failed sedation with chloral hydrate and/or midazolam. Fifteen children received dexmedetomidine intravenously with a bolus of 0.5–1 μg/kg followed by an infusion of 0.5–1.0 μg/kg/h for MRI, EEG, or nuclear medicine. All procedures were completed, and vital signs remained within normal limits for their ages. Both studies demonstrated that IV dexmedetomidine could be safely and effectively used for noninvasive procedural sedation in children. However, dexmedetomidine has caused potentially life-threatening cardiovascular complications in some adults and children [12, 13]. When dexmedetomidine is administered for child sedation, vital signs should be carefully monitored during sedation. Rosen et al. [14] reported the safe and effective administration of dexmedetomidine to a 3-year-old male who received intranasal dexmedetomidine at 4 μg/kg as a preanesthetic after failed sedation with oral midazolam (0.5 mg/kg). Yuen et al. [15] reported on a double-blind crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine in adults. Both 1 and 1.5 μg/kg of intranasally administered dexmedetomidine produced equal and significant sedation. Yuen et al. [16] also reported on a double-blind randomized controlled trial to compare intranasal dexmedetomidine with oral midazolam as a preanesthetic in pediatric patients. Patients who received 1 μg/kg dexmedetomidine intranasally were significantly more sedated at induction than patients who were administered 0.5 mg/kg oral midazolam; however, their plasma dexmedetomidine concentration was not measured. Zub

et al. [17] conducted a retrospective study to investigate the efficacy of buccal dexmedetomidine as a procedural and anesthetic premedication. Thirteen children received buccal dexmedetomidine at 1.0–4.2 μg/kg, and effective sedation was achieved in 11 of 13. However, there have been no prospective reports regarding buccal dexmedetomidine as a preanesthetic in children. We therefore performed this prospective study.

Although bradycardia of less than 60 has often been indicated as an adverse effect of dexmedetomidine, there were no cases with bradycardia less than 60 in the Dex Group. Because we found no differences in vital signs between the two groups after administering dexmedetomidine, the safety of buccal dexmedetomidine could be comparable with that of diazepam, which has been used as a preanesthetic in children for some time in Japan. The Ramsay score in the Dex Group was significantly higher than that of the Diazepam Group, suggesting that buccal dexmedetomidine may be more effective than diazepam for anesthetic sedation in children. The children with a Ramsay score less than 5 often woke up during induction. Although 75% of the children in the Dex Group showed a Ramsay score of 5 or greater at the entrance to the main operating rooms, the ratio decreased to 55% at induction. We speculate that 3–4 μg/kg of buccal dexmedetomidine might be less than the optimal dosage of preanesthetics. The serum dexmedetomidine concentration for children with a Ramsay score of 5 or greater was 75 ± 50 pg/ml. The optimal plasma concentration for sedation in the adult ICU shown in the data from the pharmaceutical company (Abbott) is more than 300 pg/ml. Because the mean serum concentration following administration of 3–4 μg/kg buccal dexmedetomidine was 58 ± 48 pg/ml, it may be possible to increase the dosage of buccal dexmedetomidine in children.

The bioavailability of buccal dexmedetomidine is an important issue. Anttila et al. [18] reported that dexmedetomidine bioavailability after extravascular doses in healthy human adults was 82%. After buccal administration, peak plasma concentration is achieved at 1.5 h after a lag time of 0.13 h. We tried the buccal administration of dexmedetomidine using the undiluted IV drug, which was such a small volume that it could be more easily absorbed buccally. Because we obtained the blood samples 1–1.5 h after administration, the measured concentration may have been similar to the maximal concentration.

There were some limitations to this study. First, this was not a randomized study, so there are some biases. Second, one anesthetist evaluated the sedation state; therefore, personal biases may have affected our evaluation. Finally, the bioavailability of buccal dexmedetomidine is based on the adult data [18]. We need to decide the timing of the buccal administration as a preanesthetic based on the data in children. Therefore, the bioavailability of buccal dexmedetomidine should be elucidated in children.

In conclusion, buccal administration of dexmedetomidine can be applied safely and effectively as a preanesthetic in children. The optimal buccal dosage of dexmedetomidine as a preanesthetic could be more than 3–4 μg/kg.

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