Journal of Dental Sciences 19 (2024) 285–291

Available online at www.sciencedirect.com

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journal homepage: www.e-jds.com

Original Article

Dexmedetomidine versus midazolam as intranasal premedication for intravenous deep sedation in pediatric dental treatment

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Received 21 March 2023; Final revision received 11 April 2023
Available online 26 April 2023

KEYWORDS
Children;
Deep intravenous sedation;
Dental treatment;
Dexmedetomidine;
Premedication

Abstract *Background/purpose:* Optimal sedation management for pediatric dental treatment demands special focus as it's tubeless and shares a same oral space. The study was to evaluate dexmedetomidine compared to midazolam for intranasal premedication in pediatric dental treatment under intravenous deep sedation.
Materials and methods: A hundred children aged 3–7 years scheduled for elective dental treatment under intravenous deep sedation anesthesia were enrolled, of whom 50 children (Group D) were intranasally premedicated with 2.0 μg/kg dexmedetomidine and the remaining 50 children (Group M) received traditional 0.2 mg/kg midazolam. Acceptance rate of venipuncture was regarded as the primary endpoint.
Results: The acceptance rate of venipuncture in Group D and Group M were 76% versus 52%, respectively ($P = 0.021$). More children in Group M complained about bitter/sour taste than Group D (62% vs. 8%, $P < 0.001$). Intraoperatively, children in Group M were found to have more choking cough than Group D (30% vs. 9%, $P = 0.003$), and patients in Group M required more suction (18 [36%] in Group M vs. 4 [8%] in Group D, $P = 0.001$). There were no significant differences between the groups in the incidences of temporal hypoxemia ($SpO_2 \leq 90\%$), however, two children in Group M experienced hypoxemia over 10 s.
Conclusion: Compared to the 0.2 mg/kg midazolam, children premedicated with 2.0 μg/kg intranasal dexmedetomidine showed superior venipuncture acceptance, had less

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https://doi.org/10.1016/j.jds.2023.04.009

intraoperative choking cough and required fewer suction. It seems to be a good alternative to midazolam as premedication for deep sedation in pediatric dental treatment.

Introduction

Optimal anesthesia management is crucial for pediatric dental treatment. Unlike adults, children are commonly present with behavior management problems during clinical procedures due to fear or anxiety, especially those preschool-aged or with intellectual disabilities. For such uncooperative children, forceful treatment with protective stabilization, tubeless sedation or general anesthesia with endotracheal intubation are common methods.[1,2] Intravenous deep sedation is a state of tubeless anesthesia during which patients are not easily aroused but could respond to repeated or painful stimulation. It has the advantages of rapid onset, effective, controllable, comfortable, easy titration.[3,4]

Premedication followed by intravenous propofol infusion is a most commonly used method in deep sedation. The route of intranasal drug administration has been highlighted for its better acceptance, higher safety and superior bioavailability compared with oral administration.[5] Midazolam is the most commonly used premedication drug. However, side effects, including stronger nasal irritation, respiratory depression and cognitive impairment, limit its availability.[6–8] Dexmedetomidine has been extensively investigated in the pediatric population with increasing evidence supporting its use, including as premedication before dental treatment under general anesthesia.[8,9] However, the comparison of nasal route dexmedetomidine and midazolam in children undergoing intravenous deep sedation dental treatment has not been explored. Influence of these two premedications to the intraoperative management of deep sedation also remains unclear. Thus, our randomized clinical trial (RCT) was to evaluate the efficacy and safety of intranasal administered dexmedetomidine compared to intranasal midazolam for premedication in pediatric dental treatment under deep intravenous sedation.

Materials and methods

Ethical approval for the present RCT was provided by the Peking University Hospital of Stomatology Ethics Committee (No. PKUSSIRB-202056077). The study was registered at ClinicalTrials.gov (No. NCT04509414).

Participants

Potential study participants were assessed based on the inclusion criteria at their arrival. The RCT included pediatric patients behaving uncooperatively during outpatient dental treatment, in need of deep sedation, aged 3–7 years, with anticipated operation time between 60 and 120 min. Patients were excluded according to the following criteria: (1) any known medical records with neural, mental disorder or severe systemic disease; (2) any known allergic history of dexmedetomidine, midazolam or propofol; (3) morbid obesity, history of obstructive sleep apnea hypopnea or acute respiratory infection in two weeks.

Randomization

Randomization was conducted via SAS software in blocks of 4 and placed in sealed envelopes by a statistician with no relationship to the study. Following randomization, patients were assigned to intranasal premedication with either dexmedetomidine or midazolam. Patients in the Group D were premedicated with 2.0 μg/kg dexmedetomidine (Yangtze River Pharmaceutical (Group) Co., Ltd., Taizhou, China),[10–12] while Group M patients were given 0.2 mg/kg (up to a maximum 5 mg) midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd., Xuzhou, China).[13–15] 0.9% saline was added to make a final volume of one ml in a 1 ml syringe.

Perioperative management

The uncooperative children scheduled for dental treatment under intravenous deep sedation arrived over 30 min before induction for the assessment of eligibility. After informed consent obtained, the intranasal premedication was administrated in a recumbent position according to randomization. Then, 5% compound lidocaine cream (Beijing Unisplendour Pharmaceutical Co., Ltd., Beijing, China) was applied to the potential venipuncture site.

Before dental treatment, intravenous cannulation was attempted by the nurse and the sedated level was assessed by modified observer's assessment of alert/sedation score (MOAA/S).[16] Anesthesia induction was conducted by propofol. For those children with strong physically resistance to venipuncture, failed in inserting the catheter or catheter disengaged, the remedial mask inhalation induction would be done with sevoflurane. Once the patient was induced to deep-sedation, a proper position of the patient was confirmed to keep airway patency before operation.

During dental procedure, the depth of anesthesia was maintained by intravenous propofol. Standard vital signs were closely monitored and recorded. Administration of oxygen (O_2) was initiated via a dual nasal cannula (Flexicare Medical Limited, Mountain Ash, UK), through which the end-tidal carbon dioxide ($EtCO_2$) was monitored in real time. Spontaneous breathing should be maintained, however, additional assistance would be conducted upon signs of airway obstruction or respiratory suppression. Once necessary, the clinicians would improve the respiration by

suspending the treatment, lightning the sedation depth, jaw-lifting, suction, mask ventilation or even intubation.

At the end of dental procedure and anesthesia, the patient was transferred to the recovery room for medical/dental supervision until discharge. Emergence agitation (EA) was assessed with pediatric anesthesia emergence delirium scale (PAED).[17] The discharge criteria were in accordance with the guideline recommendation of the American Academy of Pediatrics (AAP) and the American Academy of Pediatric Dentistry (AAPD).[1] Further adverse event was interviewed 24 h after the treatment through a telephone follow-up, and behavior change was assessed with the gold-standard postoperative hospital behavioral questionnaire (PHBQ).[18] The follow-up feedback information was acquired from questionnaires completed by parents.

Definitions of outcomes

The primary endpoint was the venipuncture acceptance, defined as the children accept venipuncture before induction without strong physical resistance, no matter the patients were awake or asleep. Secondary endpoints included: (1) Venipuncture success rate, defined as the IV was successfully started before induction; (2) The sedated level of children during the attempt to start IV; (3) Remedial mask acceptance; (4) The success rate, complete rate and adverse effects of intranasal premedication; (5) The requirement of intraoperative airway assisted maneuvers; (6) Intraoperative body movement, which was in need of temporary treatment interruption; (7) Vital sign parameters during the treatment; (8) EA (PAED $\geq$ 10); (9) Recovery time. Other endpoints included the intraoperative drug dosages, postoperative adverse event and behavior change.

Hypothesis statement and calculation of sample size

The primary hypothesis was that the acceptance rate of venipuncture without strong resistance of the patients differs significantly between dexmedetomidine and midazolam. In the previous studies using 0.2 mg/kg intranasal midazolam or 2.0 μg/kg dexmedetomidine, the success rate of venipuncture without strong resistance were 54% and 81%, respectively.[12,14] With a significance level of 0.05 and a power of 0.8, the calculated sample size was 44. Considering a drop-out rate of about 10%, we planned to include 50 patients in each group. Sample calculation was performed using PASS 11.0 software (NCSS Statistical Software, East Kaysville, UT, USA).

Statistical analysis

Normally distributed quantitative data were expressed as mean ± standard deviation, and quantitative data with abnormal distribution were represented using the median and interquartile range. Categorical data were presented as a percentage. The independent samples t-test was used for comparison of normally distributed variables among groups. A comparison of numeric data with abnormal distribution was made using the Mann–Whitney U test. Qualitative variables were compared using either the chi-square or Fisher's exact tests. For all statistical tests, two-sided $P < 0.05$ was regarded as statistically significant. All statistics were using intention-to-treat analysis with the SPSS 26.0 software (IBM, Armonk, NY, USA).

Results

The present RCT was conducted between August 2020 to April 2022 and included 100 subjects, 50 in the dexmedetomidine group (Group D), and 50 in the midazolam group (Group M). A flow diagram of the trial is presented in Fig. 1.

There were no significant differences in the baseline and preoperative characteristics of patients in the two groups (Table 1). For the primary endpoint, acceptance rates of venipuncture were 76% versus 52% for patients in Group D and Group M, respectively ($P = 0.021$).

Intranasal premedication was successfully administrated in all children. The premedication complete rate was 98% for Group D and 94% for Group M, but with no significant difference ($P = 0.617$). Time from premedication to venipuncture was comparable between the two groups, whereas patients in Group D were more sedated compared with Group M ($P < 0.001$). As to adverse effects of the premedication, more children in Group M complained about bitter/sour taste than Group D ($P < 0.001$) (Table 2).

Intraoperative drug dosages and vital sign parameters were not significantly different between the two groups. However, 20 children experienced temporal hypoxemia, among which six in Group D and 14 in Group M, and 2 patients in Group M experienced a hypoxemia of over 10 s. Patients in Group M were found to have more choking cough during the dental procedure than in Group D ($P = 0.003$), in the meantime, patients in the Group M required more suction ($P = 0.001$). No unpredicted intubation occurred during the study and other remedial airway management was not significantly different between the groups (Table 3, Table 4).

As regards postoperative events, the recovery time between groups were comparable. Two patients in Group D and five in Group M experienced EA ($P = 0.436$). Furthermore, the occurrence rates of behavioral changes, nightmare, and nasal obstruction were not significantly different between the two groups (Table 5).

Discussion

Intravenous deep sedation in pediatric dental treatment with the advantages of noninvasive, reliable, titratable and lower air pollution. The sedation management demands special focus as it is tubeless and shares a same oral space. Several studies have explored the ideal premedication method including the choice of drug, administration route, and better dosage in different situations.[8,19,20] An ideal premedication could calm the children preoperatively in some degree, therefore provide clinicians with a better condition for venipuncture and induction, reduce intraoperative drug dosage and improve clinical safety as well.[16] Our results suggest that compared to 0.2 mg/kg nasal midazolam, in pediatric intravenous deep sedation dental patients, a premedication of 2.0 μg/kg nasal

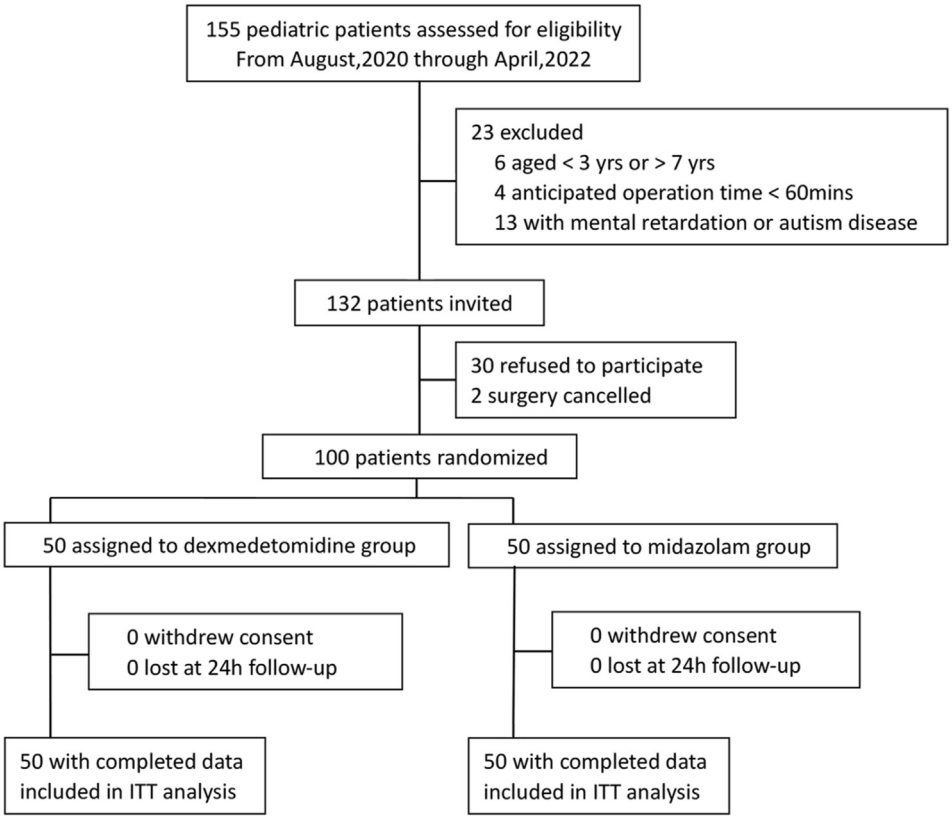

Figure 1 Flow diagram.

Table 1 Baseline characteristics and preoperative conditions.

	Group D (n = 50)	Group M (n = 50)	*P* value
Age (yrs)	5 (4, 5)	4 (4, 5)	0.765
Sex			
Male	36 (72.0%)	34 (68.0%)	0.828
Female	14 (28.0%)	16 (32.0%)	
Height (cm)	112.3 ± 9.1	113.7 ± 9.1	0.458
Weight (kg)	18.3 (16.4, 22.0)	19.0 (16.8, 23.4)	0.490
Clinical behavior score[a]			
1	44 (88.0%)	43 (86.0%)	0.900
2	2 (4.0%)	3 (6.0%)	
3	4 (8.0%)	4 (8.0%)	
4	0 (0.0%)	0 (0.0%)	
Medical conditions			
History of general anesthesia	3 (6.0%)	2 (4.0%)	>0.999
Upper airway disorders[b]	6 (12.0%)	9 (18.0%)	0.577

Data are expressed as mean ± SD, median (interquartile range), or number of patients (percentage).

[a] Behavior of children during clinical dental examination scored by Flankl Behavior Score.

[b] Including upper airway infection in last 4 weeks, rhinitis, adenoidal hypertrophy, antiadoncus.

dexmedetomidine could provide a better acceptance and success rate of venipuncture, few adverse effects and reduce intraoperative secretion as well.

In the process of deep sedation management, venipuncture stands as an essential procedure.[4] However, children presenting to us — the anesthesiology department — are frequently exceptional. Most of these children have distinctive fear, anxiety, and refuse any invasive operation especially venipuncture, which leads to difficulty of the whole treatment. Traditional strategies include physical restriction, mask inhalation induction and oral premedication, but all with shortcomings. Physical restriction is concerned of causing psychological impairment.[2] Mask inhalation induction with sevoflurane is an acceptable choice, however, the problem of air pollution could hardly be ignored, not to mention its increased incidence of nausea and emergence agitation.[21,22] In terms of oral premedication, the main holdback is its poor bioavailability due to the first pass hepatic effect.[19,23,24] It also increases probability of reflux and aspiration, especially during tubeless anesthesia. In recent years, clinicians pointed out that, most of the children could accept the intranasal instillation of the drugs with minimum discomfort.[25] Articles demonstrated its high bioavailability and better safety as well.[24] Therefore, we considered nasal route as the better way of premedication.

As for the premedication drug, midazolam is the most commonly used one with the advantages of rapid onset of action, anxiolytic and anterograde amnesia effects.[14,26,27] Previous investigators have used 0.2—0.5 mg/kg intranasal

Table 2 Premedication effect and induction acceptance before dental treatment.

	Group D (n = 50)	Group M (n = 50)	*P* value
Adverse effect	6 (12.0%)	36 (72.0%)	<0.001
Bitter or sour taste	4 (8.0%)	31 (62.0%)	<0.001
Pain	0 (0.0%)	3 (6.0%)	0.242
Nasal irritation	3 (6.0%)	5 (10.0%)	0.715
Nausea	1 (2.0%)	2 (4.0%)	>0.999
HR ≤ 60bpm	0 (0.0%)	0 (0.0%)	/
SpO_2 ≤ 90%	0 (0.0%)	0 (0.0%)	/
Sedated level before venipuncture			
Alert (MOAA/S = 6)	2 (4.0%)	13 (26.0%)	<0.001
Clam (MOAA/S = 5)	16 (32.0%)	28 (56.0%)	
Drowsy or asleep (MOAA/S ≤ 4)	32 (64.0%)	9 (18.0%)	
Time to venipuncture attempt	30 (30, 35)	30 (25, 40)	0.900
Venipuncture acceptance[a]	38 (76.0%)	26 (52.0%)	0.021
Venipuncture success	35 (70.0%)	24 (48.0%)	0.041
Remedial mask acceptance[b]	8 (53.3%) (n = 15)	13 (48.1%) (n = 27)	>0.999

Data are expressed as mean ± SD, median (interquartile range), or number of patients (percentage).
HR heart rate, MOAA/S modified observer's assessment of alert/sedation score, SpO_2 pulse oxygen saturation.
[a] Defined as no strong resistance occurred during venipuncture attempt.
[b] Defined as no strong resistance occurred during mask inhalation induction.

Table 3 Drugs, complications and remedial airway management during dental treatment.

	Group D (n = 50)	Group M (n = 50)	*P* value
Intraoperative drugs			
Total propofol dose (mg)	250.9 ± 91.6	285.5 ± 92.0	0.062
Flurbiprofen (mg)	20 (15, 25)	20 (20, 25)	0.563
Vital signs			
HR ≤ 60 bpm	0 (0.0%)	0 (0.0%)	/
SpO_2 ≤ 90%	6 (12.0%)	14 (28.0%)	0.078
SpO_2 ≤ 85%	3 (6.0%)	4 (8.0%)	0.500
$EtCO_2$ ≥ 55 mmHg	4 (8.0%)	7 (14.0%)	0.525
Heightest BIS	65 ± 8	66 ± 8	0.573
Lowest BIS	42 ± 9	41 ± 8	0.201
Choking cough	3 (9.0%)	15 (30.0%)	0.003
Airway management remedy			
Jaw lifting	9 (18.0%)	15 (30.0%)	0.241
Suction	4 (8.0%)	18 (36.0%)	0.001
Mask ventilation	0 (0.0%)	2 (4.0%)	0.495
Intubation	0 (0.0%)	0 (0.0%)	/

Data are expressed as mean ± SD, median (interquartile range), or number of patients (percentage).
BIS bispectral index, $EtCO_2$ end-tidal carbon dioxide, HR heart rate, SpO_2 pulse oxygen saturation.

midazolam for pediatric patients.[28] Whereas 0.2 mg/kg is the most widely used dosage when it comes to premedication combined with subsequent sedatives.[13–15,29] Studies demonstrated that 0.2 mg/kg midazolam could provide similar sedation effect as 0.3 mg/kg.[30,31] In the meantime, the higher 0.3 mg/kg dosage has been noted with severe respiratory depression without obvious other advantages.[32] As a classic premedication, however, side effects, including stronger nasal irritation, respiratory depression and postoperative cognitive impairment, limit the availability of midazolam in pediatric dental treatment.[6–8] Meanwhile, the bitter taste made it less preferred. Dexmedetomidine is a relatively new alpha-2 adrenoceptor agonist with sedative, anxiolytic, sympatholytic and analgesic-sparing effects, as well as minimal depression of respiratory function.[24] Previous studies showed that 1.0 μg/kg or 2.0 μg/kg intranasal dexmedetomidine could be used safely and effectively to induce a state of moderate conscious sedation and to facilitate IV cannulation.[33–35] However, A. Akin et al. found that 1.0 μg/kg might be inadequate when it comes to mask induction.[36] Other researchers demonstrated that the dose of 2.0 μg/kg resulted in a shorter onset time and a higher proportion of satisfactory sedation in children aged over 4.[20] Combined with our clinical experiences, we also made the option of 2.0 μg/kg in Group D. In our study, for patients in either Group M or Group D, the duration from premedication administration to venipuncture attempt were adequate and the same.[37,38] Children premedicated with dexmedetomidine were significantly better sedated and venipuncture acceptance in Group D was significantly higher than that in midazolam group. According to our results, the anti-anxiety and sedation effect of 2.0 μg/kg intranasal dexmedetomidine was better than 0.2 mg/kg midazolam for pediatric dental patients in need of deep intravenous sedation anesthesia.

As is highly accepted, nasal premedication may also cause adverse effect, including unpleasant taste, pain, nasal irritation and nausea. In our study, much more

Table 4 Details of the dental treatment.

	Group D (n = 50)	Group M (n = 50)	*P* value
Types			
Resin restoration	50 (100.0%)	49 (98.0%)	>0.999
Pulp treatment	36 (72.0%)	40 (80.0%)	0.483
Stainless steel crow	20 (40.0%)	26 (52.0%)	0.316
Pit and fissure sealant	4 (8.0%)	1 (2.0%)	0.362
Tooth extraction	7 (14.0%)	8 (16.0%)	>0.999
Tooth position			
Maxillary anterior tooth	24 (48.0%)	23 (23.0%)	>0.999
Maxillary posterior tooth	48 (96.0%)	49 (98.0%)	>0.999
Mandibular anterior tooth	7 (14.0%)	7 (14.0%)	>0.999
Mandibular posterior tooth	48 (96.0%)	49 (98.0%)	>0.999
Duration of operation (min)	73 ± 18	74 ± 20	0.760
Number of treated teeth	8 (7, 9)	8 (7, 9)	0.444

Data are expressed as mean ± SD, median (interquartile range), or number of patients (percentage).

Table 5 Recovery time and postoperative complications.

	Group D (n = 50)	Group M (n = 50)	*P* value
Recovery time (MOAA/S $\geq$ 4)	35 $\pm$ 14	32 $\pm$ 14	0.588
Pain	2 (4.0%)	0 (0.0%)	0.495
PONV	0 (0.0%)	0 (0.0%)	/
Discharge delayed[a]	3 (6.0%)	2 (4.0%)	>0.999
24 h follow-up			
NPOBCs[b]	2 (4.0%)	4 (8.0%)	0.678
Nightmare	3 (6.0%)	4 (8.0%)	>0.999

Data are expressed as mean $\pm$ SD, median (interquartile range), or number of patients (percentage).
MOAA/S modified observer's assessment of alert/sedation score, NPOBCs negative postoperative behavioral changes, PONV postoperative nausea and vomiting.
[a] Defined as discharge time over 60 min.
[b] When 7 or more negative behavioral changes were present on the PHBQ, the child was considered to be NPOBC.

children in midazolam group complained about bitter/sour taste. Even though the premedication were completely accepted by most children in our study, we have to take a long-term thinking. The current unpleasant experience may lead to strong resistance the next time. And that will increase our difficulty to do nasal premedication. Our result suggested dexmedetomidine to be the superior option providing better experience.

Since premedication can influence intraoperative anesthesia management or even postoperative recovery, its safety and side effects during intravenous deep sedation must also be considered. Our results also revealed the intraoperative advantages of intranasal dexmedetomidine.

Dexmedetomidine induced sedation resembles natural sleep because its action site is not cerebral cortex but locus coeruleus. Therefore, it is considered to lead less hypoxemia during anesthesia. In our study, two patients experienced a hypoxemia of $SpO_2 \leq 90\%$ over 10 s, and they were both in midazolam group. Although there wasn't obvious statistical difference, children in dexmedetomidine group trended to have better intraoperative oxygen saturation. Previous retrospective study revealed that the duration of treatment was independent risk factor of intraoperative desaturation, while choking cough and suction were significantly associated with it.[4] We also found that the children in dexmedetomidine group had less choking cough and required less suction. The effect of dexmedetomidine to reduce catecholamine and gland secretions may play an important role in this aspect.[39]

As for adverse effect, bradycardia as well as delayed discharge are of great concern while administrating high dose dexmedetomidine. In our result, none of the participants experienced bradycardia. The avoidance of opioids and a relatively lower dose might contribute to it. The occurrence rates of delayed discharge were also comparable in the two groups. Therefore, we think dexmedetomidine would not increase adverse effects in pediatric dental treatment under tubeless anesthesia.

There are several limitations in this study. First, children included in our study were not attend for a same single dental problem, however, the types of treatment were comparable between groups. Second, patients with mental disorders were not included in our study, therefore the conclusion requires more research in these patients. Last, the present data were collected following procedures conducted in a single institution. Therefore, the replicability of the current findings should be assessed in other institutions and environments.

Declaration of competing interest

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Acknowledgments

The authors thank the nursing staff of department of pediatric dentistry involved with the project for their hard work and cooperation.

References

1. Cote CJ, Wilson S, American Academy of Pediatrics, et al. Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures. *Pediatrics* 2019;143:e20191000.
2. Karibe H, Umezu Y, Hasegawa Y, et al. Factors affecting the use of protective stabilization in dental patients with cognitive disabilities. *Spec Care Dent* 2008;28:214—20.
3. Ahmed SS, Hicks SR, Slaven JE, et al. Deep sedation for pediatric dental procedures: is this a Safe and Effective Option? *J Clin Pediatr Dent* 2016;40:156—60.
4. Wu XR, Liu Y, Li B, et al. Safety of deep intravenous propofol sedation in the dental treatment of children in the outpatient department. *J Dent Sci* 2023;18:1073—8.
5. Jun JH, Kim KN, Kim JY, et al. The effects of intranasal dexmedetomidine premedication in children: a systematic review and meta-analysis. *Can J Anaesth* 2017;64:947—61.
6. Mcgraw T, Kendrick A. Oral midazolam premedication and postoperative behaviour in children. *Paediatr Anaesth* 1998;8:117—21.
7. Kanegaye JT, Favela JL, Acosta M, et al. High-dose rectal midazolam for pediatric procedures: a randomized trial of sedative efficacy and agitation. *Pediatr Emerg Care* 2003;19:329—36.
8. Sun Y, Lu Y, Huang Y, et al. Is dexmedetomidine superior to midazolam as a premedication in children? A meta-analysis of randomized controlled trials. *Paediatr Anaesth* 2014;24:863—74.
9. Sheta SA, Al-Sarheed MA, Abdelhalim AA. Intranasal dexmedetomidine vs midazolam for premedication in children undergoing complete dental rehabilitation: a double-blinded randomized controlled trial. *Paediatr Anaesth* 2014;24:181—9.
10. Talon MD, Woodson LC, Sherwood ER, et al. Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. *J Burn Care Res* 2009;30:599—605.
11. Wang SS, Zhang MZ, Sun Y, et al. The sedative effects and the attenuation of cardiovascular and arousal responses during anesthesia induction and intubation in pediatric patients: a randomized comparison between two different doses of preoperative intranasal dexmedetomidine. *Paediatr Anaesth* 2014;24:275—81.
12. Gyanesh P, Haldar R, Srivastava D, et al. Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI:

a double-blind, randomized, placebo-controlled trial. *J Anesth* 2014;28:12—8.
13. Gupta A, Dalvi NP, Tendolkar BA. Comparison between intranasal dexmedetomidine and intranasal midazolam as premedication for brain magnetic resonance imaging in pediatric patients: a prospective randomized double blind trial. *J Anaesthesiol Clin Pharmacol* 2017;33:236—40.
14. Narendra PL, Naphade RW, Nallamilli S, et al. A comparison of intranasal ketamine and intranasal midazolam for pediatric premedication. *Anesth Essays Res* 2015;9:213—8.
15. Shanmugaavel AK, Asokan S, Baby JJ, et al. Comparison of behavior and dental anxiety during intranasal and sublingual midazolam sedation - a randomized controlled trial. *J Clin Pediatr Dent* 2016;40:81—7.
16. Khatavkar SS, Bakhshi RG. Comparison of nasal midazolam with ketamine versus nasal midazolam as a premedication in children. *Saudi J Anaesth* 2014;8:17—21.
17. Wang HY, Chen TY, Li DJ, et al. Association of pharmacological prophylaxis with the risk of pediatric emergence delirium after sevoflurane anesthesia: an updated network meta-analysis. *J Clin Anesth* 2021;75:110488.
18. Vernon DT, Schulman JL, Foley JM. Changes in children's behavior after hospitalization. Some dimensions of response and their correlates. *Am J Dis Child* 1966;111:581—93.
19. Malinovsky JM, Populaire C, Cozian A, et al. Premedication with midazolam in children. Effect of intranasal, rectal and oral routes on plasma midazolam concentrations. *Anaesthesia* 1995;50:351—4.
20. Yuen VM, Hui TW, Irwin MG, et al. A randomised comparison of two intranasal dexmedetomidine doses for premedication in children. *Anaesthesia* 2012;67:1210—6.
21. Picard V, Dumont L, Pellegrini M. Quality of recovery in children: sevoflurane versus propofol. *Acta Anaesthesiol Scand* 2000;44:307—10.
22. Dashfield AK, Birt DJ, Thurlow J, et al. Recovery characteristics using single-breath 8% sevoflurane or propofol for induction of anaesthesia in day-case arthroscopy patients. *Anaesthesia* 1998;53:1062—6.
23. Allonen H, Ziegler G, Klotz U. Midazolam kinetics. *Clin Pharmacol Ther* 1981;30:653—61.
24. Iirola T, Vilo S, Manner T, et al. Bioavailability of dexmedetomidine after intranasal administration. *Eur J Clin Pharmacol* 2011;67:825—31.
25. Yuen VM, Irwin MG, Hui TW, et al. A double-blind, crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. *Anesth Analg* 2007;105:374—80.
26. Mehdi I, Parveen S, Choubey S, et al. Comparative study of oral midazolam syrup and intranasal midazolam spray for sedative premedication in pediatric surgeries. *Anesth Essays Res* 2019;13:370—5.
27. Kain ZN, Hofstadter MB, Mayes LC, et al. Midazolam: effects on amnesia and anxiety in children. *Anesthesiology* 2000;93:676—84.
28. Greaves A. The use of midazolam as an intranasal sedative in dentistry. *SAAD Dig* 2016;32:46—9.
29. Wilton NC, Leigh J, Rosen DR, et al. Preanesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology* 1988;69:972—5.
30. Davis PJ, Tome JA, Mcgowan JR FX, et al. Preanesthetic medication with intranasal midazolam for brief pediatric surgical procedures. Effect on recovery and hospital discharge times. *Anesthesiology* 1995;82:2—5.
31. Fuks AB, Kaufman E, Ram D, et al. Assessment of two doses of intranasal midazolam for sedation of young pediatric dental patients. *Pediatr Dent* 1994;16:301—5.
32. Fukuta O, Braham RL, Yanase H, et al. Intranasal administration of midazolam: pharmacokinetic and pharmacodynamic properties and sedative potential. *ASDC (Am Soc Dent Child) J Dent Child* 1997;64:89—98.
33. Yuen VM, Hui TW, Irwin MG, et al. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. *Anesth Analg* 2008;106:1715—21.
34. Wang SS, Zhang MZ, Sun Y, et al. The sedative effects and the attenuation of cardiovascular and arousal responses during anesthesia induction and intubation in pediatric patients: a randomized comparison between two different doses of preoperative intranasal dexmedetomidine. *Paediatr Anaesth* 2014;24:275—81.
35. Kim HJ, Shin WJ, Park S, et al. The sedative effects of the intranasal administration of dexmedetomidine in children undergoing surgeries compared to other sedation methods: a systematic review and meta-analysis. *J Clin Anesth* 2017;38:33—9.
36. Akin A, Bayram A, Esmaoglu A, et al. Dexmedetomidine vs midazolam for premedication of pediatric patients undergoing anesthesia. *Paediatr Anaesth* 2012;22:871—6.
37. Yuen VM, Hui TW, Irwin MG, et al. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. *Anaesthesia* 2010;65:922—9.
38. Kogan A, Katz J, Efrat R, et al. Premedication with midazolam in young children: a comparison of four routes of administration. *Paediatr Anaesth* 2002;12:685—9.
39. Bhana N, Goa KL, Mcclellan KJ. Dexmedetomidine. *Drugs* 2000;59:263—8. discussion 9—70.