

ORIGINAL RESEARCH

PEDIATRIC ANESTHESIA

Use of self-made midazolam mixtures in preoperative sedation of children undergoing oral surgery under general anesthesia: a prospective, randomized, control study

Zhijun Xin, Huaizhou Wang, Changhui Li, Qing Wan, Ning Wang

Author affiliation:

Department of Surgical Anesthesiology, Yantai Stomatology Hospital, Yantai, Shandong Province, China

Correspondence: Ning Wang; E-mail: zhijun1711@126.com; Phone: 13963865993

Abstract

Objective: Pediatric patients have high tendency of anxiety and tension before going to operating room and till they are anesthetized. So they usually need to be well-sedated before shifting to the operating room. We investigated the use of self-made midazolam mixture for preoperative sedation in children before oral treatment under general anesthesia.

Methods: A total of 64 children who received intra-oral surgery under general anesthesia from January 2021 to June 2021 in the Department of Pediatric Stomatology of Yantai Stomatology Hospital were randomly divided into two groups; Group A (n = 32) received 0.5 mg/kg midazolam solution mixed with 50% glucose injection. Group B (n = 32) received 0.5 mg/kg midazolam solution mixed with jasmine honey tea. Both solutions were 10 ml mixture and the children were instructed to take it. After 30 min, Ramsay score, oral drug compliance score, oral drug success rate, any adverse reactions, PSAS score, and venipuncture compliance score were noted. Adverse reactions were also recorded at 24 h post-operatively in both groups.

Results: Oral success rate (87.5%) in Group A was higher compared to Group B (65.6%) and the difference was statistically significant ($P < 0.05$). Children in Group A had higher drug oral compliance compared with Group B ($P < 0.05$). The number of children in Group B had more bitter mouth and nausea after oral medication than in Group A, and the difference was statistically significant ($P < 0.05$). There were no significant differences in Ramsay scores, PSAS scores, venipuncture compliance scores, and postoperative adverse effects in the two groups ($P > 0.05$).

Conclusion: The mixed solution of midazolam and 50% glucose injection (Group A) was associated with a higher oral success rate, good oral compliance and venipuncture compliance, and less adverse reactions after oral administration. The Ramsay score, PSAS score and postoperative adverse reactions of children were equivalent to those of oral midazolam injection, which could provide reference for clinical use.

Key words: Administration, Oral; Child; Humans; Hypnotics and Sedatives / administration & dosage; Oral surgery; Midazolam / administration & dosage; Preanesthetic Medication; Anesthesia, General;

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1. Introduction

With the rapid progress of socioeconomic status the people paid more attention to oral health, and the health

of children's teeth attracted more and more attention from the parents. However, due to the low level of awareness and willingness of parents towards children's early dental

Rating	Description
0.	Total cooperation, best possible working conditions, no crying or physical protest
1.	Mild, soft verbal protest or (quite) crying as a signal of discomfort, but does not obstruct progress. Appropriate behavior for procedure
2.	Protest more prominent. Both crying and hand signals. May move head around making it hard to administer treatment. Protest more distracting and troublesome. However, child still complies with request to cooperate
3.	Protest presents real problem to dentist. Complies with demands reluctantly, requiring extra effort by dentist. Body movement
4.	Protest disrupts procedure, requires that all of the dentist attention be directed toward the child behavior. Compliance eventually achieved after considerable effort by dentist, but without much actual physical restraints. More prominent body movement
5.	General protest, no compliance or cooperation. Physical restraint is required

treatment, it is very common to see children with multiple tooth caries. So, the treatment of children's teeth under general anesthesia has emerged.¹ It is usually performed as day-case surgery. Children are often hospitalized in the morning on the day of the surgery, and venous access cannot be timely established in the ward. Many children are too young, are very anxious and cry when being separated from their parents or entering the operating room. In the operating room, they don't cooperate with the nurses to allow them establish the venous access, Forced induction of inhalation anesthesia may also cause adverse psychological effects on the children.² Moreover, crying children have increased airway secretions, increasing the risk of laryngospasm and bronchospasm during tracheal intubation, and difficult anesthesia management. Therefore, it is essential to gain the trust of the children before surgery and reduce their anxiety and fear. Midazolam is a good sedative, with high safety and few adverse reactions. It can provide anterograde amnesic effects and is widely used in children for preoperative sedation.^{3,4} However, the taste of midazolam is bitter, and there is no oral midazolam preparation in China. Domestic studies or guidelines often use midazolam plus 50% glucose solution for oral administration in children to improve taste, but there are still many children with poor oral compliance and cannot achieve the desired sedation effect. Some scholars at China and abroad, have added various sweeteners such as sodium citrate, honey, pomegranate juice, grapefruit juice, and alike to improve the bitter taste of midazolam, and drew different conclusions.^{5,6} Some sweeteners such as single syrup taste better. Marin et al. prepared midazolam and single syrup in a 1:2 ratio for the children, which showed good taste and stability.⁷ Nevertheless, the availability of single syrup is a problem. There is a lack of midazolam oral ingredients that can be prepared quickly and can be

used alone. Jasmine honey tea is a regular drink in supermarkets and stores. It tastes sweet and slightly fragrant with the fragrance of tea, which can relieve the bitter taste of midazolam. This study was designed to explore the compliance and sedation effects of midazolam mixture with 50% glucose solution and jasmine tea in oral administration before general anesthesia in children.

2. Methodology

2.1. Patients

64 children, scheduled for intraoral surgery under general anesthesia from January 2021 to June 2021, in the Department of Pediatric Stomatology, Yantai Stomatology Hospital, were selected under convenient sampling. All the children were randomized into two groups: A and B. Group A (n = 32) included 17 male and 15 female children. Group B (n = 32) included 14 male and 18 female children. The mean age of the children in Group A was 3.68 ± 0.91 y, with an average height of 102.97 ± 8.29 cm, and a mean weight of 17.54 ± 3.50 kg. The mean age of the children in Group B was 3.91 ± 1.06 y, with an average height of 106.50 ± 7.01 cm, and a mean weight of 17.85 ± 2.36 kg.

Inclusion criteria were; children who needed intraoral therapy under general anesthesia, ASA I, with Venham behavioral rating 4 or 5,⁷ (poor coordination, unable to communicate effectively, and prone to crying emotions after separation from their parents); and parents informed consent to preoperative oral sedation.

Children with an upper respiratory tract infection within the last 2 weeks, children fasted for less than 6 h and who drank within 2 h, a history of severe respiratory, circulatory, digestive, and neurological disease, allergy to study drugs or beverages and children who refused

preoperative sedation or venipuncture procedures, were excluded.

2.2. Procedure

The child was hospitalized on the day of the surgery, and his/her weight was measured. The anesthesiologist screened the children with Venham behavioral rating 4 or 5 at 30 min before surgery, explained the preoperative sedation risks and precautions after communication with their parents, and instructed the parents to sign and confirm the preoperative sedation in the anesthetic informed consent form. The oral dosage of midazolam injection (2 ml = 10 mg, Chinese medicine quasi-word H20067041, Yichang Renfu Pharmaceutical Co., Ltd.) was 0.5 mg/kg, and the maximum total dose not to exceed 15 mg.

Group A - midazolam injection was mixed with 50% glucose injection. Group B - mixed the midazolam injection with jasmine honey tea (Master Kong Ltd.: 500 ml). Both groups of drugs were mixed to make 10 ml mixture, and the children were instructed to take them. After taking the medicines, parents were instructed to take good care of the children, do not do strenuous activities to prevent falls, and protect the children's necks. After 30 min, the anesthesiologist evaluated the sedation state of the child, and checked with the surgical nurse that the child's information was correct, and then carried the child into the operating room. After entering the operating room, standard monitoring was established. One surgical nurse performed intravenous puncture, and the other nurse restrained the puncture limb. The anesthesiologist determined the compliance of venipuncture. After the establishment of venous access, anesthesia was induced by the same anesthesiologist. The administration of anesthesia in both groups was as follows: inj. fentanyl 4 µg/kg, propofol 2 mg/kg, cisatracurium besylate 2 mg/kg, dexamethasone 0.1 mg/kg, and ondansetron 0.1 mg/kg IV. Sevoflurane 2% inhalation was used for maintenance. After the operation, the tracheal tube was removed when the child was fully awake and the reflexes recovered. When the Steward score reached 6, the child was sent out of the operating room. 24 h after the operation, the child was followed up by telephone to inquire about the adverse reactions after treatment.

2.3. Observational indicators

The same anesthesiologist observed the indices of the children after 30 min of administration of the solution, including Ramsay score, oral drug compliance score, number of successful oral drugs, adverse reactions, Parental Separation Anxiety Scale (PSAS) score, venipuncture compliance score and adverse reactions after 24 h of follow-up treatment. Ramsay sedation scores at 2 - 4 indicated good sedation.⁸

The oral drug compliance score criteria were as follows: Point 0 represented complete compliance: children could drink the medicine under the guidance of the doctor or parents, 1 point represented part of compliance: Children needed parental verbal and behavioral induction to take drugs, 2 points represented compulsory compliance: Children needed to be ordered or forcibly fed by their parents to take the drug. 3 points represented total non-compliance: the child refused to take medication completely, or vomited it out after oral medication.⁹

Success determination criteria for oral medication: The configured drugs were all drunk by the children.

PSAS score criteria:¹⁰

- 1 - The child was easily separated from his parents when entering the operating room,
- 2 - The child sobbed and cried, but could still be separated.
- 3 - The child cried, but did not hold his parents tightly.
- 4 - The child cried and hugged his parents tightly, and was difficult to be separated. PSAS score of 1~2 points showed that children were easy to be separated from their parents.

The criteria for venipuncture compliance score¹¹ was as follows:

- 1 - The child cooperated in the puncture process, and there might be crying but no resistance;
- 2 - The child cried and resisted during the puncture, but not violently.
- 3 - The child cried and resisted violently during the puncture and did not cooperate with the puncture.

2.4. Statistical analysis

All statistical analyses were conducted with SPSS 17.0. Measurement data are expressed as mean ± SD, that used t-test, χ^2 test or Fisher's exact test were used for counting data. The ranked data that did not obey the normal distribution were expressed by rank mean; and Mann-Whitney test was used. $P < 0.05$ were considered statistically significant.

3. Results

3.1. The success rates

The results showed that the oral success rate of children in Group A was higher than that in Group B, and the difference was statistically significant ($P < 0.05$), as detailed in Table 2.

3.2. Comparison of Scores

The oral drug compliance scores, Ramsay scores, PSAS

Table 2: Comparison of success rates of oral midazolam mixture in the two groups

Success rate	Group A (n = 32)	Group B (n = 32)	χ^2 values	P value
Success	28 (87.5)	21 (65.6)	4.267	0.037
Failure	4 (12.5)	11 (34.4)		

Data presented as n (%)

Table 3: Comparative test scores in the two groups

Comparative test scores	Group A (n = 28)	Group B (n = 21)	Z values	P values
Oral drug compliance scores	21.54	29.62	-2.125	0.039
Ramsay scores	25.43	24.43	-0.378	0.819
PSAS scores	25.21	24.71	-0.292	1.000
Venipuncture compliance scores	25.41	24.45	-0.264	0.900

Table 4: Comparison of adverse reactions after oral midazolam mixture in the two groups

Adverse reactions	Group A (n = 32)	Group B (n = 32)	χ^2 values	P values
Bitter mouth	1 (3.6)	10 (47.6)	13.373	0.000
Dry mouth	0 (0.0)	1 (4.8)	1.361	0.429
Nausea	1 (3.6)	7 (33.3)	5.755	0.015
Hiccup	0 (0.0)	1 (4.8)	1.361	0.429

Data presented as n (%)

scores, and venipuncture compliance scores were compared. The oral drug compliance scores of children in Group A were higher than that in the Group B, and the difference was statistically significant ($P < 0.05$). The Ramsay scores, PSAS scores and venipuncture compliance scores of children in the two groups were roughly the same ($P > 0.05$), as shown in Table 3.

3.3. Adverse reactions

The number of children in Group B had more bitter mouth and nausea after oral medication than in Group A, which was statistically significant ($P < 0.05$), as shown in Table 4. There was no significant difference in the adverse reactions after the 24 h postoperative return visit between the two groups ($P > 0.05$).

4. Discussion

This study showed that the preoperative oral administration of 0.5 mg/kg midazolam made the

children easily separated from the parents and they showed good compliance with venipuncture. It indicated that oral administration of midazolam for preoperative sedation could significantly reduce the anxiety and fear of children entering the operating room and the pain of venipuncture.¹²

Midazolam is a benzodiazepine drug, which has the effects of sedation, hypnosis, anti-anxiety and anterograde amnesia.¹³ It can significantly alleviate the fear and anxiety of the children,¹⁴ and reduce the preoperative psychological trauma to them. However, its bitter taste affects the oral compliance of children. Clinically, midazolam is often added to sweeteners such as 50% glucose, fruit juice and honey to

improve the taste of drugs, but many children still have poor oral drug compliance and cannot achieve the due sedative effect.¹⁵ Some scholars added various sweeteners, such as sodium citrate, honey, pomegranate juice, grapefruit juice, flavor syrup, single syrup and other sweeteners to improve the bitter taste of midazolam, and drew different conclusions.^{16,17} Some sweeteners, such as single syrup, taste better. For example, in the study of Marin et al., midazolam and single syrup were prepared into a 5 mg/ml mixture in the ratio of 1:2 for oral treatment of dental phobia in children, which had good taste and stability.¹⁸ However, the single syrup is not available commercially, and its preparation is inconvenient. In this study, jasmine honey tea and 50% glucose injection were mixed with midazolam, respectively. The results showed that the success rate of oral drug in the dextrose group was 87.5%, which was higher than that in the high jasmine honey tea group. The children's oral drug compliance was also better, and there were fewer adverse reactions

after oral drugs, It shows that the mixture of 50% dextrose or jasmine honey tea and midazolam can significantly improve the bitter taste of midazolam. Jasmine honey tea is a regular drink in major supermarkets and stores, the main ingredients are honey, sodium citrate, jasmine tea, its taste is fragrant, sweet, children like to drink. Some scholars have shown that the oral administration of the mixture of midazolam and honey or sodium citrate can be easily accepted by children without obvious adverse reactions.¹⁹⁻²⁰ According to traditional Chinese medicine, jasmine tea has the effect of eliminating boredom and quenching thirst, treating food accumulation, halitosis and sore throat.²¹ Min, Xiaoyan used jasmine tea for oral care, which could significantly eliminate halitosis and oral odor. It had a fragrance and was easy for patients to accept. It also showed the important role of jasmine tea in improving taste and removing odor. Therefore, the oral administration of the mixture of midazolam and jasmine honey tea for pediatric patients can be used as an effective means of preoperative sedation.

5. Limitations

There were also shortcomings in this study. First of all, we did not measure the pH of jasmine honey tea. Some studies have shown that pH affects the stability of midazolam; the addition of sweeteners to midazolam may alter its pH and thus affect its absorption. Secondly, the oral absorption rate of midazolam is 15% - 49%. There are great individual differences in drug absorption, and the sedation state achieved at the same time may be different. Finally, the midazolam mixture was based on the weight configuration of the child, so the concentration of the mixture was not uniform, which could not determine the best ratio scheme of the mixture. So further research without these shortcomings is still needed.

6. Conclusion

To sum up, children who underwent intraoral surgery under general anesthesia took midazolam plus 50% dextrose, before operation had a high success rate, were easy to separate from their parents, had good oral drug compliance and venipuncture compliance, less adverse reactions as compared to a mixture of midazolam plus jasmine honey tea. However, jasmine honey tea is easily available commercially, which makes its use more convenient.

7. Conflict of interest

None declared by the authors.

8. Authors' contribution

ZX: Conduction of the study work, manuscript editing

HW: Research design, subject guidance

NW: Study design, data collection, and data collation.

CL, QW: Participated in study design, data collection

9. Reference

- Liu Y, Wu XR, Yang XD, et al. A retrospective analysis of intravenous deep sedation for uncooperative pediatric patients undergoing oral treatment in outpatient clinic. *Chinese J Anesthesiol.* 2019;39(10):1212-1215. DOI: [10.3760/cma.j.issn.0254-1416.2019.10.016](https://doi.org/10.3760/cma.j.issn.0254-1416.2019.10.016)
- Wang L, Huang LL, Peng W. Application of dexmedetomidine with midazolam in preoperative sedation in pediatric dental patients. *Oral Med Res.* 2020;36(10):953-956.
- Wang RY, Zhang FC, Du B, et al. Prior intravenous administration of midazolam on postoperative adverse behavior changes in children with general anesthesia surgery. *Shandong Medi.* 2021;61(18):65-68.
- Chen L. Oral midazolam combined behavioral intervention improves preoperative anxiety in children. *Wenzhou Med College.* 2009:1-37.
- Pearce JI, Brousseau DC, Yan K, et al. Behavioral changes in children after emergency department procedural sedation. *Acad Emerg Med.* 2018;25(3):267-274. [PubMed] DOI: [10.1111/acem.13332](https://doi.org/10.1111/acem.13332)
- Ma L, Zhang J, Hou XY, et al. The clinical effect of oral midazolam compound laughing gas sedation on dental phobia in children. *J Chinese Acad Med Sci.* 2019;41(1):106-110.
- Venham LL, Gaulin-Kremer E, Munster E, Bengston-Audia D, Cohan J. *Interval rating scales for children's dental anxiety and uncooperative behavior.* *Pediatr Dent.* 1980;2:195-202. [Google Scholar]
- Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *Br Med J.* 1974 Jun 22;2(5920):656-9. [PubMed] DOI: [10.1136/bmj.2.5920.656](https://doi.org/10.1136/bmj.2.5920.656)
- Niu J, Chen CC, Xie J, et al. Comparison of clinical efficacy of oral and midazolam sedation in children with dental anxiety. *Oral Med Res.* 2021;37(2):148-152.
- Carol J, Dashiff, Michael, Weaver. Development and testing of a scale to measure separation anxiety of parents of adolescents. *J Nurs Meas.* 2008;16(1):61-80. [PubMed] DOI: [10.1891/1061-3749.16.1.61](https://doi.org/10.1891/1061-3749.16.1.61)
- Pei Y. The influence of family participation fun games on the compliance and subjective feelings of children with school-age intravenous welling needle infusion. *Int Med Health Guide.* 2019;25(20):3482-3484.
- Wu JH, Li WX, Lv PP, et al. Analysis of the effects of oral and intravenous midazolam used for pediatric preoperative sedation. *Int J Anesth Recovery.* 2021;42(5):487-490.
- Zhao Y, Chang QF, Ye Y, et al. Effects of different midazolam administration methods on sedation effects in children with dental fear. *Graduate J Med.* 2020;33(5):504-508.
- Long Y, Zhang CC, Tan C, et al. Comparison of the effect of midazolam for oral administration in children: meta-analysis. *Chinese J Anesthesiol.* 2020;40(2):195-198.
- Hou XY. Study on the stability of the midazolam syrup mixture.

- Chinese Academy of Medical Sciences, Peking Union Medical College. 2017:1-40.
16. Isik B, Baygin O, Bodur H. Effect of drinks that are added as flavoring in oral midazolam premedication on sedation success. *Paediatr Anaesth.* 2008 Jun;18(6):494-500. [PubMed] DOI: [10.1111/j.1460-9592.2008.02462.x](https://doi.org/10.1111/j.1460-9592.2008.02462.x)
 17. Ma L, Zhang J, Hou XY, et al. Clinical effect of oral midazolam compound laughing gas sedation on dental phobia in children. *J Chinese Acad Med Sci.* 2019;41(1):106-110.
 18. Jain K, Ghai B, Saxena AK, Saini D, Khandelwal N. Efficacy of two oral premedicants: midazolam or a low-dose combination of midazolam-ketamine for reducing stress during intravenous cannulation in children undergoing CT imaging. *Paediatr Anaesth.* 2010 Apr;20(4):330-7. [PubMed] DOI: [10.1111/j.1460-9592.2010.03279.x](https://doi.org/10.1111/j.1460-9592.2010.03279.x)
 19. Tian RH, Xie ZW. The second volume of the Practical Traditional Chinese Medicine Dictionary. The People's Health Press. 2005;5(1):1292.
 20. Min XY, Wu SQ, Lin XA. Application of jasmine tea in the oral care of ICU patients. *Strait Pharm.* 2009;21(2):105-107.
 21. Zhu L, Feng L, Li WW. Comparison of dexmedetomidine nose with midazolam oral administration in pediatric strabismus surgery. *Chinese J Antropia Ped Ophthalmol.* 2020;28(3):22-24.