

Comparison of Oral and Buccal Midazolam for Pediatric Dental Sedation: A Randomized, Cross-Over, Clinical Trial for Efficacy, Acceptance and Safety

Sara Tavassoli-Hojjati, DDS, MSc; Majid Mehran, DDS, MSc; Roza Haghgoo, DDS, MSc;
Monireh Tohid-Rahbari, DDS, MSc; Rahil Ahmadi*, DDS, MSc

Pediatric Dentistry Department, Dental School, Shahed University, Tehran, Iran

Received: Jun 13, 2013; Accepted: Feb 03, 2014; First Online Available: Apr 01, 2014

Abstract

Objective: Providing a safe and efficient dental treatment for a young patient is a challenge for the dentist and the child. The purpose of this study was to investigate the effectiveness, safety and acceptability of buccal midazolam in dental pediatric patients and to compare it with oral Midazolam.

Methods: Eighteen uncooperative healthy children aged 2.5-6 years were randomized to each of buccal midazolam (0.3mg/kg) or oral midazolam (0.5mg/kg) at the first visit, the alternative has been used at the second visit in a cross-over manner. The study took place at pediatric dentistry clinic of Shahed University, Tehran, from November 2011 to June 2012. The patients' vital signs and behavioral scores were recorded. The patient, the operator and the observer were blinded to the applied medication. Post operatively, patients' and parents' satisfaction were assessed by Visual Analogue Score and a questionnaire respectively. The P-value was set at 0.05 for significance level.

Findings: There were no significant differences in physiologic factors in the medication groups at time 0, 10, 20, 30 minutes and discharge. There was also no significant difference between the two groups in behavioral parameters. The majority of parents rated both sedative agents as "effective" or "very effective" and their children mostly were without anxiety or with minor anxiety.

Conclusion: Buccal midazolam may be safely and efficiently used in sedation of pediatric dental patients.

Iranian Journal of Pediatrics, Volume 24 (Number 2), April 2014, Pages: 198-206

Key Words: Sedation; Midazolam; Pediatric Dentistry; Clinical Trial; Treatment Efficacy

Introduction

Dental treatment in young children between 15 months and 6 years of age may be a challenge for both the child and the dentist^[1]. Some current behavior management techniques may help to reduce resistant negative behaviors and facilitate the acceptance of the treatment by the child^[2]. Although such techniques are effective in some patients, those with mental, physical or

communicational underdevelopment will not be able to benefit from the management techniques^[1,3]. In such cases to avoid a substandard and unsafe dental treatment, a combination of behavior modification and pharmacologic methods are advised^[1,4].

Conscious sedation as a pharmacologic anxiety control technique in pediatric dentistry is a way to make a cooperative yet conscious condition in an uncooperative dental patient^[1,3]. As defined by

* Corresponding Author;

Address: Pediatric Dentistry Department, Dental School, Shahed University, Tehran, Iran

E-mail: rahilsh@yahoo.com

© 2014 by Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, All rights reserved.

American Academy of Pediatric Dentistry (AAPD) conscious sedation is a controlled drug-induced state, with a minimally depressed consciousness during which patients are able to maintain ventilatory function and respond to verbal or physical stimulations^[5]. Drugs and dosages in conscious sedation have a margin of safety to preclude unconsciousness and maintain the reflexes intact^[1,3].

In the past decades introduction of benzodiazepines in particular midazolam has decreased the use of other sedative agents with less efficiency or more adverse effects^[3,6-8]. Midazolam, as a water soluble benzodiazepine with no active metabolites and mild side effects, demonstrates anxiolytic, sedative, hypnotic and amnesic effects^[9,10]. The most common way of administration for this drug is via oral route, although other routes of administration, such as intramuscular, transmucosal and intravenous, have also been defined^[1,4,9-13].

Nevertheless, the oral route has demonstrated less predictable results compared to other routes. Children undergoing sedation by the oral midazolam have to starve for 4-6 hours before the dental treatment and they will have postoperative nausea and vomiting more frequently^[1,10,14].

Recently transmucosal sedation has received attention in conscious sedation procedures^[9,12,15]. Rapid onset of action, ease of administration, higher bio-availability, absence of nausea, vomiting and respiratory side effects make this way more effective in emergency dental practice of young children unable to fast^[1,9,12,16,17].

Intranasal (IN) and buccal are two possible routes of midazolam transmucosal sedation. However, the IN sedation, although widely used, may be uncomfortable to the young patients due to the mucosal irritation during its administration^[15,18]. Because of the advantages of the buccal midazolam in management of status epilepticus, interest has focused on this route in medical circumstances, yet its application in dentistry is currently not common^[15,19-21].

It has been suggested that oral administration of midazolam is a safe and acceptable form of sedation in pediatric dentistry^[4,22], however, despite of numerous superior advantages of the buccal Midazolam, its application has been limited and to date there is no literature comparing these two methods. Thus, the aim of this study was to

investigate the effectiveness, safety and acceptability of buccal midazolam in dental pediatric patients and to compare it with oral Midazolam.

Subjects and Methods

The study was designed as a prospective randomized, crossover, clinical trial and approved by Shahed University Ethics Committee. It was preregistered in Iranian Registry of Clinical Trials with code IRCT2013020312350N1.

The study took place at pediatric dentistry clinic of Shahed University, Tehran, from November 2011 to June 2012. Out of 34 patients referred for dental treatment, 18 uncooperative healthy American society of Anesthesiology I (ASA I) patients between 2.5 and 6 years, were recruited (Fig. 1). Eligible participants were those who needed bilateral and identical restorative and pulp treatment requiring 2 or more dental visits and were unable to tolerate the dental procedure with behavior management techniques. Those with known hypersensitivity to the drug, acute narrow-angle glaucoma, renal or hepatic impairment, upper respiratory tract infection and tonsillar hypertrophy were excluded. A full written and verbal explanation of the study was given to the parents and an informed consent obtained. Children were assigned to one of the 2 groups (1 or 2) according to their medication in their first appointment by simple randomization procedures using a random number table. Group 1 received 0.5 mg/kg oral midazolam syrup (Amsed, 2.5 mg/ml, Dales Pharmaceutical, England) 30-45 minutes before treatment, while group 2 was given 0.3 mg/kg buccal midazolam (Epistatus, 10mg/ml, Special Product Ltd, England), 15-30 minutes prior to dental procedure. The other regimen was used at the second appointment. All the dental treatments were carried out by an experienced pediatric dentist assisted by a trained dental sedation nurse and both of them were blinded to the applied sedation method.

A sedationist administered the medication, recorded patients' weight before the first appointment and monitored pulse rate and oxygen saturation by a pulse oximeter, every 10 minutes

during treatment and at recovery in each session. The sedation procedure and dental treatment was performed in an eligible ambulatory setting. All patients were instructed to refrain from liquids and solid foods for 2 and 4 hours.

The sedationist placed the drug in the mandibular buccal sulcus in both quadrants using a unique syringe in children receiving buccal sedation. Patients were encouraged trying not to swallow the sedative medication for a few moments to permit transmucosal absorption. The oral midazolam was administered by a needleless syringe and the sedation nurse made sure that the child has swallowed the whole drug.

Once the child demonstrated adequate level of sedation, dental treatment was initiated. A proper level of sedation was achieved when the child appeared relaxed or exhibited slurring of speech, mild ptosis and took a distant gaze^[1,3,12]. Benzocaine 2% as a topical anesthetic was applied on the dried mucosa for 2 minutes followed by lidocaine 2% with 1:80000 epinephrine local analgesics in a standard technique. After achieving a total analgesia, the dental treatment was performed.

Behavior of each patient during the 2 appointments was recorded by a camera and evaluated by an experienced pediatric dentist who was also blinded to the groups, according to the four categories of the Houpt behavior rating scale^[23].

Postoperatively the acceptability of each method for children and their parents was assessed by a 5 point visual analogue scale (VAS) and a 3 point questionnaire, respectively^[2,24]. VSA evaluated the anxiety level of the child during the treatment. This self-report measurement

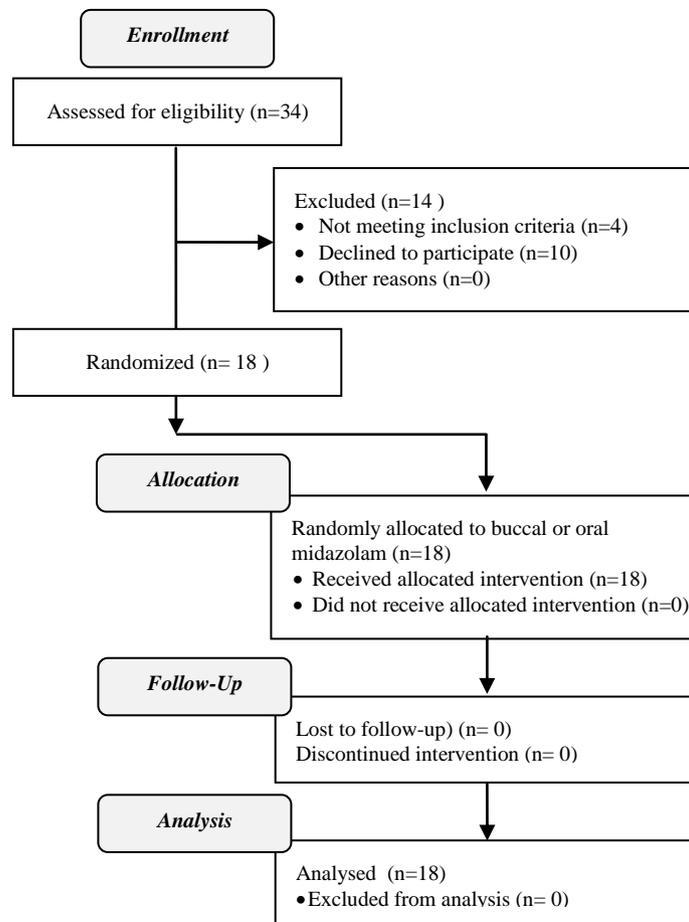


Fig. 1: Participant flow chart

instrument comprised of 5 cartoon-type faces, numbered 1-5 and from left to right: 1 represented “calm” and 5 displayed “very high anxiety”. Children were asked to put a mark on the faces according to the intensity of their anxiety. The questionnaire also as a self-report assessment tool, asked the parents how they found the efficacy of each method (ineffective to very effective). At the end of each session patients were transferred to recovery room and supervised by their parents and the sedation nurse. Finally the standard criteria for discharge were used^[3,12].

Data were analyzed using SPSS 10.0 for windows (SPSS Inc, Chicago, IL). A nonparametric Wilcoxon sign rank test was utilized to compare the ordinal parameters of the two medications. Quantitative data were examined by the Paired t-test. The *P*-value was set at 0.05 for significance level.

Table 1: Heart rate (bpm) recorded during buccal and oral midazolam sedation

Groups/ time	HR ^a bpm ^b mean (range)	P value
Group 1, t=0	119.2 (94-155)	0.3
Group 2, t=0	114.8 (94-146)	
Group 1, t=10	139.5 (111-170)	0.2
Group 2, t=10	131.1(99-166)	
Group 1, t=20	138.7 (113-170)	0.9
Group2, t=20	139.0 (98-168)	
Group 1, t=30	138.0 (105-165)	0.9
Group 2, t=30	138.7 (98-175)	
Group 1, discharge	135.2 (115-160)	0.5
Group 2, discharge	131.7(98-165)	

a: HR indicates Heart rate ; b: bpm indicates beats per minute.

Findings

Thirty four children were assessed for inclusion in the study. The parents of 10 children were unwilling to take part, 4 patients were assigned to ASA class III and two showed tonsillar hypertrophy, leaving 18 patients (9 boys and 9 girls) who completed both sessions (Fig. 1). The mean weight was 16.8 kg (range 12-25 kg) and the mean age was 41.48 months (range 16-60 months).

Physiologic parameters: As demonstrated in Tables 1 and 2, there were no significant differences in oxygen saturation and pulse rate between the 2 methods at the time (t) = 10, 20, 30 minutes and at discharge ($P>0.05$). The lowest pulse rate of 94 beats per minutes (bpm) was observed at t=0 in both sedation methods, whereas the highest pulse rate (175 bpm) was seen in a patient sedated by buccal route. The lowest and the highest oxygen saturation levels at both sedation sessions were 94% and 100%.

Behavior evaluation: We found no significant difference in behavior assessments between the 2 groups at either dental appointments ($P>0.05$).

Behavior parameters during the first 20 minutes of the treatment: During this treatment phase the majority of patients in both sessions were fully awake. More than half of the patients did not cry or move at all (Tables 3-5). Overall behavior evaluation revealed a success rate (code 1-3) of 88.9% in oral midazolam and 83.4% in buccal Midazolam sedation (Table 6).

Behavior parameters during the last 20 minutes of the treatment: In the second phase, there was no significant difference in the behavior factors between the two medication groups, when using Houpt classifications ($P>0.05$)^[23]. According to Table 2, most of the subjects remained awake, yet drowsy. The majority of the children were rated as "not moving" in both groups. The overall success rate for both medication groups was high (Tables 4 and 6).

Table 2: Peripheral oxygen saturation (%) recorded during buccal and oral midazolam sedation

Groups/ time	POS ^a mean % (range)	P. value
Group 1, t=0	97.8 (96-99)	0.4
Group 2, t=0	98.0 (97-99)	
Group 1, t=10	97.2 (96-99)	0.5
Group 2, t=10	97.4 (94-100)	
Group 1, t=20	97.1 (95-98)	0.08
Group2, t=20	97.7 (96-99)	
Group 1, t=30	97.1 (95-99)	0.2
Group 2, t=30	97.5 (96-99)	
Group 1, discharge	97.7 (97-99)	1.0
Group 2, discharge	97.7 (96-99)	

^a POS: Peripheral oxygen saturation

Table 3: Rating for sleep during the sedation procedure

Drug route	Phase	Fully awake n (%)	Drowsy n (%)	Asleep n (%)	Total n (%)
Buccal	First Phase*	13 (72.2)	5 (27.8)	0 (0)	18 (100)
	Second phase**	12 (66.7)	3 (16.7)	3 (16.7)	18 (100)
Oral	First Phase*	15 (83.3)	2 (11.1)	1 (5.6)	18 (100)
	Second phase**	14 (77.8)	3 (16.7)	1 (5.6)	18 (100)

* Insignificant difference for the first phase of the treatment between the 2 medications for sleep scores. ($P= 0.6$)

** Insignificant difference for the second phase of the treatment between the 2 medications for sleep scores. ($P= 0.2$)

Acceptability of the methods: The parents' and patients' view of the treatment is illustrated in Fig 2 and 3. All the parents in both groups found the sedation process successful, regardless of the applied sedation method ($P>0.05$). According to the visual analogue scale more than half of the children expressed their feelings during treatment as "not anxious". Due to the young age, 3 patients were unable to rate their perception about the sedation procedure.

Discussion

In the last decades sedation with midazolam has acted as an alternative to general anesthesia in severe behavior management problems^[22]. An optimal sedation method for children should be efficient, safe and easy to use and acceptable for patients^[24]. Present study compared the safety, efficacy and patients' and parents' satisfaction of the oral and buccal midazolam sedation.

Table 4: Rating for movement during the sedation procedure

Drug route	Phase	No movement n (%)	Controllable movement n (%)	Continues movement n (%)	Violent movement n (%)	Total n (%)
Buccal	First Phase*	11 (61.1)	4 (22.2)	3 (16.7)	0 (0)	18 (100)
	Second phase**	11 (61.1)	7 (38.9)	0 (0)	0 (0)	18 (100)
Oral	First Phase*	13 (72.2)	3 (16.7)	0 (0)	2 (11.2)	18 (100)
	Second phase**	16 (88.9)	1 (5.6)	0 (0)	1 (5.6)	18 (100)

* Insignificant difference for the first phase of the treatment between the 2 medications for movement scores ($P= 0.7$)

** Insignificant difference for the second phase of the treatment between the 2 medications for movement scores ($P= 0.4$)

In the present investigation 0.5 mg/kg oral midazolam and 0.3 mg/kg buccal midazolam was administrated. Although some researches indicate that oral midazolam at the range of 0.25-1 mg/kg is safe and no difference was found in sedative effects of 0.5 mg/kg, 0.75 mg/kg and 1 mg/kg of oral midazolam^[3,22,25-27], others have reported adverse effects in children receiving 1 mg/kg^[4]. Some studies suggested 0.5 mg/kg of oral

midazolam as safe and efficient in sedating children^[22,26].

Johnson et al found no significant difference between the physiologic and behavioral impacts of 0.5 mg/kg oral midazolam and 0.3 mg/kg transmucosal midazolam^[9]. Due to the successful results of investigations implementing 0.3 mg/kg transmucosal midazolam, we have chosen this dose of midazolam for buccal sedation^[1,9].

Table 5: Rating for crying during the sedation procedure

Drug route	Phase	No crying n (%)	mild crying n (%)	Continues crying n (%)	Hysterical crying n (%)	Total n (%)
Buccal	First Phase*	10 (55.6)	7 (38.9)	1 (5.6)	0 (0)	18 (100)
	Second phase**	9 (50)	9 (50)	0 (0)	0 (0)	18 (100)
Oral	First Phase*	11 (61.1)	5 (27.8)	2 (11.2)	0 (0)	18 (100)
	Second phase**	12 (66.7)	5 (27.8)	0 (0)	1 (5.6)	18 (100)

* Insignificant difference for the first phase of the treatment between the 2 medications for crying scores. ($P= 1.0$)

** Insignificant difference for the second phase of the treatment between the 2 medications for crying scores ($P= 0.7$)

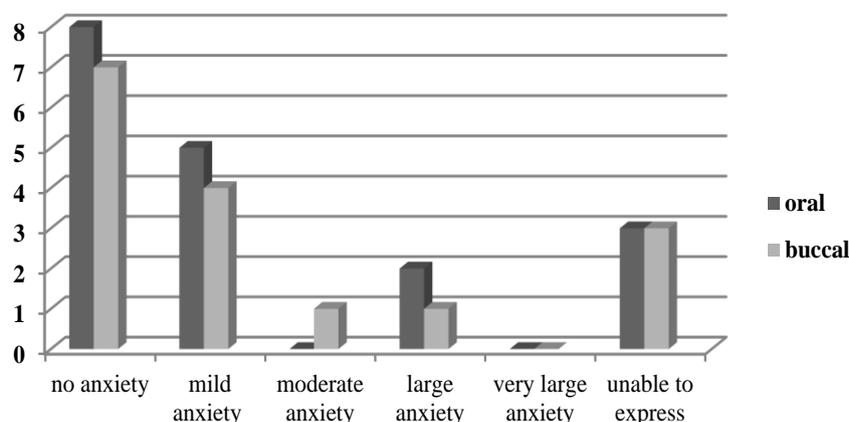


Fig. 2: Feelings experienced by patients during the treatment. No significant difference was found between the 2 groups ($P= 0.1$)

In the present research an onset time of 30-45 minutes for oral midazolam and 10-15 minutes for buccal midazolam was applied before the dental treatment. Selecting the time interval was based on the fact that the peak plasma level of oral midazolam occurs approximately 30 minutes after

drug administration and is comparable to the peak plasma concentration of buccal midazolam after 10 minutes^[28].

Our findings support the hypothesis that both types of sedation methods are safe. The highest pulse rate was 175 bpm observed in one patient,

Table 6: Rating for overall behavior during the sedation procedure

Drug route	Phase	Excellent(1) n (%)	Very good (2) n (%)	Good(3) n (%)	Fair(4) n (%)	Poor(5) n (%)	Aborted(6) n (%)	Total n (%)
Buccal	First*	5 (27.8)	5 (27.8)	5 (27.8)	2 (11.1)	1 (5.6)	0 (0)	18 (100)
	Second**	6 (33.6)	6 (33.6)	5 (27.8)	0 (0)	1 (5.6)	0 (0)	18 (100)
Oral	First*	5 (27.8)	8 (44.4)	3 (16.7)	2 (11.1)	0 (0)	0 (0)	18 (100)
	Second**	5 (27.8)	6 (33.6)	5 (27.8)	2 (11.1)	0 (0)	0 (0)	18 (100)

* Insignificant difference for the first phase of the treatment between the 2 medications for overall behavior ($P= 0.4$)

**Insignificant difference for the second phase of the treatment between the 2 medications for overall behavior ($P= 0.5$)

exceeding the normal rate of 130 bpm. This result should be considered in light of the fact that the normal heart rate in physiologic condition may

pass 170 bpm during crying, which is not life threatening and only persistent tachycardia would require close monitoring^[29]. Similar to the heart

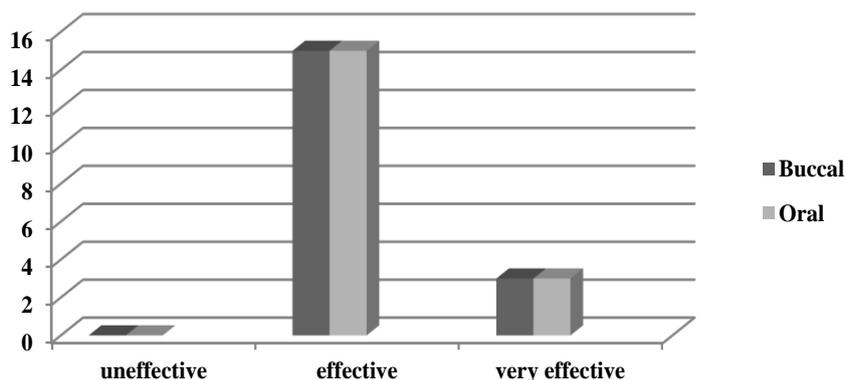


Fig. 3: Parents' opinions of sedation. No significant difference was found between the 2 groups ($P= 1.0$)

rate, the arterial oxygen saturation levels were clinically comparable in both medication regimens and did not surpass the critical levels^[22,23]. The lowest oxygen saturation level of 94% in this study was comparable to the findings of Wilson et al with the same minimum oxygen saturation, in which a lower dose of buccal midazolam [0.2 mg/kg) was administered. This may indicate that based on the arterial oxygen saturation, the 0.3mg/kg dose of the buccal midazolam is as safe as 0.2mg/kg^[12]. However, despite the similarities between the two studies, caution should be exercised when comparing the findings, as differences such as study design and age group of patients may affect the data. Oxygen de-saturation was also observed by Johnson et al when using 0.5mg/kg oral midazolam or 0.3 mg/kg intranasal midazolam. However, such de-saturation was reported to be false and attributable to the violent movements and hysterical crying of the patient, rather than the direct effect of the drug^[9].

According to the observer's evaluation based on the Houpt behavior classification for "sleep", "movement", "crying" and "general behavior" there was no significant difference between the two sedation methods. In both methods the majority of the subjects remained calm, with no or little movement and crying in the first and last phase of the dental treatment, showing that midazolam in both forms may successfully reduce the unwanted movements and crying reactions of the uncooperative patient.

During the sedation procedure most of patients were fully awake. Shapira et al reported a greater proportion of patients asleep or drowsy compared to our study when a combination of midazolam and hydroxyzine was administered. They concluded that combination of sedative drugs should be approached with a great caution due to their additive adverse effects^[30].

In the present study, 94.4% and 88.9% of the subjects were rated with a score of 3 and less for oral and buccal route respectively. Lima et al reported a relatively lower success rate for midazolam. Nevertheless, they declared that the value of reported success rate was limited as the behavior assessments were carried out every 15 minutes and a more comprehensive evaluation of the whole session was not possible by this method^[29]. To overcome this bias we have filmed the entire treatment sessions and divided this into

2 phases (the first and the last 20 minutes). This was especially helpful as the serum concentration of the drug may vary by the time, thus probably resulting in various behavioral reactions^[31].

Parents did not prefer one regimen over the other, and were overall satisfied with both of the methods. Most of the patients experienced no or mild anxiety during the treatment. One of the factors influencing the acceptability of the sedative agent through oral route is its taste. The vials of intravenous midazolam, which are widely used in oral midazolam sedation, have a bitter taste, which may be not tolerable for young patients^[22]. To solve this problem usually extemporaneous formulations with unidentified bioavailability are used^[32]. As we have used syrup of oral midazolam with a palatable taste; this was not the case in our study. Neither buccal midazolam nor oral midazolam resulted in any paradoxical or disinhibition reactions in our subjects and this was in agreement with the findings of Wilson et al^[12].

This study was designed in a cross-over manner, reducing the impact of individual variants throughout the study, as each patient serves as his or her own control^[33]. To minimize the bias of the evaluations, a blinded observer confirmed the ratings and an operator completed the dental procedures.

There were some limitations to the present study. First, the parents' opinion regarding their child's treatment is a subjective and very individual measure. Although self-report assessments are widely used to attain qualitative information on the acceptability of the sedation procedures, however, a more detailed questionnaire may help to overcome this shortcoming^[4]. Second, the fluidity and bitter taste of buccal midazolam resulted in increased salivation and difficulty in retaining the medication in buccal sulcus, thus a minute amount of the buccal midazolam may be swallowed and not buccally absorbed. Therefore we recommend production of midazolam in a gel form, avoiding oral ingestion and allowing maximum transmucosal absorption.

This study was primarily intended to investigate the safety, efficacy and acceptability of buccal midazolam as a sedative agent for dental treatment, however, we suggest a similar survey focusing on the recovery characteristics of this

medication after the completion of sedation procedure.

Conclusion

Both 0.3 mg/kg buccal midazolam and 0.5 mg/kg oral midazolam resulted in similar efficient sedation outcomes. We did not observe any arterial oxygen de-saturation or abnormal heart rate in subjects receiving either of the 2 methods. Both medication regimens received high acceptability among sedated children and their parents.

Acknowledgment

The research described in this article was financially supported by Shahed University, Tehran, Iran. This study was registered in Iranian Registry of Clinical Trials with code: IRCT2013020312350N1.

Authors' Contribution

Concept/design: S. Tavassoli-Hojjati, M. Tohid-Rahbari
Acquisition of data, data analysis/interpretation: S. Tavassoli-Hojjati, M. Mehran
Drafting of the manuscript: R. Ahmadi
Critical revision of the manuscript: R. Haghgoo
All authors approved final version of the paper.

Conflict of Interest: None

References

- Al-Rakaf H, Bello LL, Turkustani A, et al. Intra-nasal midazolam in conscious sedation of young paediatric dental patients. *Int J Paediatr Dent* 2001; 11(1):33-40.
- Howard KE, Freeman R. An evaluation of the PALS after treatment modeling intervention to reduce dental anxiety in child dental patients. *Int J Paediatr Dent* 2009;19(4):233-42.
- Dean JA, Avery DA, Mc Donald RE. *Dentistry for Child and Adolescent*. 9th ed. Indiana: Mosby Elsevier. 2011; Pp: 30-31, 253 and 270.
- Somri M, Parisinos CA, Kharouba J, et al. Optimizing the dose of oral midazolam sedation for dental procedures in children: a prospective, randomized, and controlled study. *Int J Paediatr Dent* 2012; 22(4):271-9.
- American Academy of Pediatrics; American Academy of Pediatric Dentistry, Coté CJ, Wilson S. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. *Pediatrics* 2006;118(6):2587-602.
- Haupt M. Project USAP 2000-use of sedative agents by pediatric dentists: a 15-year follow-up survey. *Pediatr Dent* 2002;24(4):289-94.
- Wilson S, Farrell K, Griffen A, et al. Conscious sedation experiences in graduate pediatric dentistry programs. *Pediatr Dent* 2001;23(4):307-14.
- Haas DA, Nenniger SA, Yacobi R, et al. A pilot study of the efficacy of oral midazolam for sedation in pediatric dental patients. *Anesth Prog* 1996;43(1):1-8.
- Johnson E, Briskie D, Majewski R, et al. The physiologic and behavioral effects of oral and intranasal midazolam in pediatric dental patients. *Pediatr Dent* 2010;32(3):229-38.
- Lam C, Udin RD, Malamed SF, et al. Midazolam premedication in children: a pilot study comparing intramuscular and intranasal administration. *Anesth Prog* 2005;52(2):56-61.
- Saint-Maurice C, Meistelman C, Rey E, et al. The pharmacokinetics of rectal midazolam for premedication in children. *Anesthesiology* 1986; 65(5):536-8.
- Wilson KE, Welbury RR, Girdler NM. Comparison of transmucosal midazolam with inhalation sedation for dental extractions in children. A randomized, cross-over, clinical trial. *Acta Anaesthesiol Scand* 2007;51(8):1062-7.
- Mireskandari SM; Akhvirad SAM; Darabi ME; Alizadeh R. A comparative study on the efficacy of rectal diazepam and midazolam for reduction of pre-operative anxiety in pediatric patients. *Iran J Pediatr* 2007;17(2):157-62.
- Tolksdorf W, Eick C. Rectal, oral and nasal premedication using midazolam in children aged 1-6 years. A comparative clinical study. *Anaesthesist* 1991;40(12):661-7.
- Hosey MT, Asbury AJ, Bowman AW, et al. The effect of transmucosal 0.2 mg/kg midazolam premedication on dental anxiety, anaesthetic induction and psychological morbidity in children undergoing general anaesthesia for tooth extraction. *Br Dent J* 2009;207(1):E2; discussion 32-3.
- Pandit UA, Collier PJ, Malviya S, et al. Oral transmucosal midazolam premedication for preschool children. *Can J Anaesth* 2001;48(2):191-5.
- Chopra R, Marwaha M. Assessment of buccal aerosolized midazolam for pediatric conscious sedation. *J Investig Clin Dent* 2013;5:1-5.
- Moss ML, Buongiorno PA, Clancy VA. Intranasal midazolam for claustrophobia in MRI. *J Comput Assist Tomogr* 1993;17(6):991-2.
- Armijo JA, Herranz JL, Pena Pardo MA, et al. Intranasal and buccal midazolam in the treatment of acute seizures. *Rev Neurol* 2004;38(5):458-68.

20. Tonekaboni SH, Mahvelati Shamsabadi F, Anvari SS, et al. A Comparison of Buccal Midazolam and Intravenous Diazepam for the Acute Treatment of Seizures in Children. *Iran J Pediatr* 2012;22(3):303-8.
21. Anderson M. Buccal midazolam for pediatric convulsive seizures: efficacy, safety, and patient acceptability. *Patient Prefer Adherence* 2013;7:27-34.
22. Wilson KE, Welbury RR, Girdler NM. A randomised, controlled, crossover trial of oral midazolam and nitrous oxide for paediatric dental sedation. *Anaesthesia* 2002;57(9):860-7.
23. Houpt MI, Weiss NJ, Koenigsberg SR, et al. Comparison of chloral hydrate with and without promethazine in the sedation of young children. *Pediatr Dent* 1985;7(1):41-6.
24. Uldum B, Hallonsten AL, Poulsen S. Midazolam conscious sedation in a large Danish municipal dental service for children and adolescents. *Int J Paediatr Dent* 2008;18(4):256-61.
25. Piscalchaiyong T, Trairatvorakul C, Jirakijja J, et al. Comparison of the effectiveness of oral diazepam and midazolam for the sedation of autistic patients during dental treatment. *Pediatr Dent* 2005;27(3):198-206.
26. Davies FC, Waters M. Oral midazolam for conscious sedation of children during minor procedures. *J Accid Emerg Med* 1998;15(4):244-8.
27. McMillan CO, Spahr-Schopfer IA, Sikich N, et al. Premedication of children with oral midazolam. *Can J Anaesth* 1992;39(6):545-50.
28. Weldon BC, Watcha MF, White PF. Oral midazolam in children: effect of time and adjunctive therapy. *Anesth Analg* 1992;75(1):51-5.
29. Lima AR, da Costa LR, da Costa PS. A randomized, controlled, crossover trial of oral midazolam and hydroxyzine for pediatric dental sedation. *Pesqui Odontol Bras* 2003;17(3):206-11.
30. Shapira J, Kupietzky A, Kadari A, et al. Comparison of oral midazolam with and without hydroxyzine in the sedation of pediatric dental patients. *Pediatr Dent* 2004;26(6):492-6.
31. Burstein AH, Modica R, Hatton M, et al. Intranasal midazolam plasma concentration profile and its effect on anxiety associated with dental procedures. *Anesth Prog* 1996;43(2):52-7.
32. Côté CJ, Cohen IT, Suresh S, et al. A comparison of three doses of a commercially prepared oral midazolam syrup in children. *Anesth Analg* 2002;94(1):37-43.
33. Mills EJ, Chan AW, Wu P, et al. Design, analysis, and presentation of crossover trials. *Trials* 2009;10:27.