Comparative Evaluation of Intranasal, Buccal and Oral Midazolam for Procedural Sedation in Pediatric Dental Patients

[1]Dr. Malika Agarwal, [2]Dr. Neerja Singh, [3]Dr. Bibhav Dubey

[1]MDS, [2]PhD, MDS, Professor, [3]MDS PG student
Babu banarasi das college of dental sciences

Abstract

Objectives: The objective of this study was to evaluate the safety and efficacy of Midazolam administered through intranasal, buccal and oral routes for procedural sedation in pediatric dental patients.

Study Design: 90 children aged 3-11 years with Frankel behavior rating I and II were randomly divided into three groups for Midazolam administration through different routes (intranasal and buccal 0.3mg/kg, oral 0.5mg/kg respectively). During sedation session, children were evaluated for behavior response. Acceptance of drug, onset of sedation, peak sedation time, level of sedation, ease of treatment completion, recovery time, discharge time and post-operative complications were evaluated.

Results: Both oral and intranasal routes produced minimal to moderate level of sedation. Intranasal route showed rapid onset time, early peak sedation time and better level of sedation. Buccal midazolam was not found to be effective and provided only minimal sedation in some patients. Oral and buccal groups exhibited better acceptance of drug. No post operative complications were found with any of these three routes. Faster recovery and discharge time with intranasal and buccal routes were found in comparison to oral group.

Conclusions: Midazolam in the dose of 0.3mg/kg for intranasal route and 0.5 mg/kg for oral route was found to be effective but 0.3 mg/kg for buccal route was not found to be effective. All three routes were safe, none of them reported any intraoperative and postoperative complications.

Keywords: Midazolam, Procedural sedation, Intranasal, Buccal, Oral

Introduction

Procedural sedation refers to the technique of administering drugs or dissociative agents to reduce anxiety and pain associated with unpleasant procedures in children. It induces a state that allows patient to tolerate painful or uncomfortable procedures while maintaining the cardiorespiratory function. It benefits clinicians in managing painful or unpleasant diagnostic or therapeutic procedures. Due to physiological, financial and logistical considerations, it may be preferred over general anaesthesia. Sedative drugs can be administered through various routes such as oral, inhalational, intranasal, intramuscular, subcutaneous, and intravenous routes.

There are a variety of drugs available that can be used for procedural sedation in dental office. Benzodiazepines are a class of drugs primarily used for treating anxiety. They facilitate the ability for the inhibitory neurotransmitter GABA to bind to various GABA receptors throughout the CNS. Some of the most commonly used benzodiazepines are Alprazolam, diazepam, lorazepam and midazolam. Midazolam is a 1, 4-benzodiazepine derivative and has a unique chemical structure. It is short acting and efficacious with anxiolytic, sedative, and hypnotic properties. Midazolam causes minimal hemodynamic effects, good cardiovascular stability, amnesia, and rapid onset of sedation. Midazolam is the commonly used agent for anxiolysis in children and has a good track record of use for minimal and moderate sedation [1]. It is an effective, reliable and safe sedative that could be used in routine practice, benefitting a wide range of patients.

Midazolam can be administered by almost all routes of drug administration. Non-invasive techniques of drug administration are more convenient for apprehensive children. Oral route is the oldest, most convenient, and most economical route of drug administration with almost universal acceptability. In addition, no needles, syringes, or equipment's are required but it has disadvantage of first pass metabolism which decreases the predictability of the sedative effect. Transmucosal routes like intranasal, buccal, sublingual routes can be used in apprehensive children as it avoids first pass metabolism as well as pain and discomfort associated with invasive routes. The mucosal lining of buccal cavity and nasal passage has rich blood supply and is also relatively permeable which helps in rapid absorption of administered drug [1]. Use of buccal/nasal mucosa for administration of midazolam has advantages like ease of administration, more acceptable to children, faster onset of action, rapid recovery and absence of first pass metabolism [1,2]. Delivery of drug by these routes is relatively convenient, inexpensive, and easily rendered with a minimal training. Hence, this study was conducted to assess the safety and efficacy of midazolam in behavior management of un-cooperative children through various non-invasive routes (oral, intra-nasal and buccal) for procedural sedation in pediatric dental patients.

Materials and Method

The study protocol (figure 1) was analyzed and approved by the institutional ethical committee of BBD university, Lucknow. This randomized controlled trial was carried out in the Department of Pediatric and preventive Dentistry, BBDCODS between January 2020 and March 2022. Fearful and anxious children of both the genders who were uncooperative towards dental treatment and were difficult to be managed by basic behavior guidance techniques were included in study. Children satisfying criteria of ASA-I

classification for physical status evaluation and Brodsky's classification (0 and +1) of tonsils for airway obstruction were included in the study.

Eligible Participants were randomly assigned to one of the 3 treatment groups, using a permuted block randomization method in a ratio of 1:1:1. The allocation method was followed until the participants in each group was 30. It was a double blinded study, parents and those assessing outcomes was blinded whereas the care provider was not blinded.

The procedure was explained to parents/guardian including the benefits and risks involved. A written consent from the parents/guardians was obtained. The children were physically examined by the anesthesiologist for sedation fitness. The parents were instructed to ensure fasting of their children as instructed (AAPD sedation guidelines 2019) [3]. Sample size was calculated with type I error 5% and power of test 80% was 90 with 30 participants in each group. On the day of sedation, the children were administered sedation as per their assigned group. Group 1 (intranasal 0.3 mg/ kg) or Group 2 (buccal 0.3mg/kg) or Group 3 (oral 0.5 mg/kg).

Midazolam spray 5mg/ml bottle with a dispenser of 0.1 ml per puff (Medistat, marketed in India by Alteus Biogenics) was used for intranasal and buccal routes. Midazolam vial 1mg/1ml (Mezolam, manufactured in India by Neon Pharmaceuticals) was used for oral route. For intranasal route the required amount of drug according to the body weight of the patient in two divided doses was sprayed into each nostril with the patient in semi reclined position. For buccal route the drug was sprayed in two divided doses on both sides in buccal vestibule. For oral route drug was mixed with sweetened juice and was given to the patient to drink.

All the required procedures like extraction, pulpectomy, pulpotomy, restoration were done by a single operator who was blinded to the route of drug administration. During sedation session, the children were evaluated for the behavior response for acceptance of drug during administration, onset of sedation, peak of sedation, ease of completion of treatment, recovery from sedation and side effects of drug. The vital signs (Pulse rate, Blood pressure and Oxygen saturation) were noted down before the administration of the drug and at every 5 min interval after the administration of the drug till the completion of the procedure. Post-operatively vital signs were noted at every 10 mins till the discharge of the patient. The Ohio State Behavioral Rating Scale (OSBRS) [4] was selected for the patient's drug acceptance. The onset time of sedation was noted when the level of sedation of the patient was relatable to score 2 according to the sedation rating scale according to AAPD guidelines 2019 [3]. Similarly, the peak of sedation was noted when the level of sedation of the patient was relatable to score 3 according to the sedation rating scale.

The children were evaluated every ten minutes using Post Anesthetic Aldrette Recovery Score [5] for discharge which assessed the patient's airway, color, respiration, movement and the level of consciousness (each scale of 0-2). When the score was greater than 9 the children were discharged.

Statistical Analysis

The results were tabulated and analysed statistically using SPSS version 19.0 (SPSS Inc., IBM, USA) with a 5% significance level ($p<0.05$). The mentioned p in the text indicates the following: $p>0.05$- Not significant (ns), $p<0.05$- Significant (*), $p<0.01$- Highly significant (**) The chi-square (χ^2) test was used to compare the categorical data. ANOVA test was used for intergroup comparison and after performing ANOVA, Tukey's HSD post hoc test was used for intra group comparison. Values with different letters indicate statistically significant difference.

Results

Table 1 shows Demographic characteristics of all three groups. Table 2 shows comparison of acceptance of drug between three groups. Significant difference was found between the groups with group 3 showing better acceptance followed by group 2. Table 3 shows level of sedation significant difference was found between groups with group 1 showing better level of sedation followed by group 3. Table 4 shows ease of treatment completion between the groups. Significant difference was found between group 1 and group 3. Table 5 shows comparison of onset, peak sedation, recovery and discharge between the groups. Significant differences were found between the groups.

Flow chart for study protocol

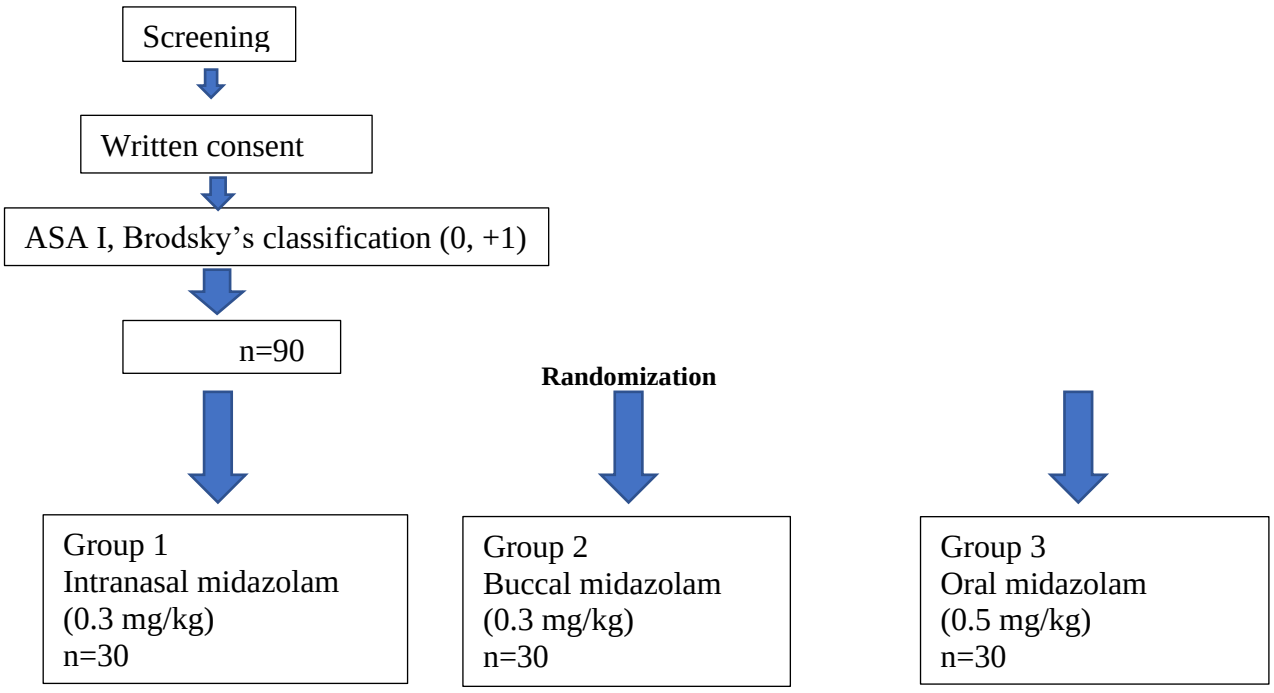

Table 1: Demographic characteristics of all the three groups

Demographic Characteristics	Group 1 (n=30) (%)	Group 2 (n=30) (%)	Group 3 (n=30) (%)	t/χ^2 value	p value
Age (years)					
Mean ± SD	5.57	5.38	5.30	0.67	0.54
Range	3-10	3-9	3-8		
Median	6.5	5.25	4.5		
Gender					
Male	18	20	15	1.43	0.71
Female	12	10	15		

Table 2: Acceptance of drug of all the three groups

Acceptance of drug rating	Group 1 (n=30)		Group 2 (n=30)		Group 3 (n=30)		χ^2 value	P Value
	N	%	N	%	N	%		
Crying & struggling	14	46.67	7	23.33	0	0	51.38	<0.01*
Struggling	9	30	2	6.67	0	0		
Crying	3	10	16	53.33	0	0		
Quiet	4	13.33	5	16.67	30	100		

Table 3: Sedation rating scale of all the three groups

Sedation rating scale	Group 1 (n=30)		Group 2 (n=30)		Group 3 (n=30)		χ^2 value	P Value
	N	%	N	%	N	%		
No sedation	4	13.33	16	53.33	7	23.33	32.78	<0.01*
Minimal sedation	10	33.33	14	46.67	19	63.33		
Moderate sedation	14	46.67	0	0	4	13.33		
Deep Sedation	2	6.67	0	0	0	0		

Table 4: Ease of treatment completion of all the three groups

Ease of treatment completion	Group 1 (n=30)		Group 2 (n=30)		Group 3 (n=30)		χ^2 value	P Value
	N	%	N	%	N	%		
Prohibitive	7	23.3	18	60	11	36.7	9.57	0.033*
Poor	9	30	10	33.3	13	43.3		
Fair	4	13.3	2	6.67	4	13.3		
Good	4	13.3	0	0	2	6.67		
Excellent	6	20	0	0	0	0		

Table 5: Onset, Recovery and Discharge time of all the three groups

Parameter	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	F value	p value
Onset time (minutes)	17.90±2.63[a]	19.90±2.20[a]	28.40±2.62[b]	6.89	0.003*
Peak sedation time (minutes)	23.18±1.83[a]	26.05±1.94[b]	37.38±1.81[c]	7.03	<0.01*
Recovery time (minutes)	60±10.48[a]	60±8.76[a]	90±13.21[b]	10.73	0.007*
Discharge time (minutes)	100.42±11.37[a]	107.5±8.36[a]	124.21±10.64[b]	11.31	0.004*

Discussion

Pediatric dentists are in search of an effective, safe, and non-invasive route for sedative and anxiolytic drug administration for common dental procedures in young children. Oral route for sedation is the oldest, most commonly used, and easily accepted route among children but it is unreliable because of first-pass metabolism, delayed onset, longer recovery time and a reported efficacy of 60% to 76% [6,7] Transmucosal drug administration is an attractive alternative to oral and parenteral routes of administration, due to its non-invasive nature. It can reduce or completely bypass first-pass metabolism, avoid gastrointestinal degradation and provide rapid onset of action. The intranasal route for procedural Sedation has gained momentum in the past few years as reported by Lowhagen et al [8] Wood M [9] who inferred that the intranasal route has faster onset which maybe because of the rapid reaching of adequate cerebrospinal fluids level of the drugs and due to the communication to the subarachnoid space through the olfactory nerve and its sheath. Buccal route of sedation was brought into light by Primosch RE [10]. He found that buccal route was effective because of the rich mucosal blood supply.

Benzodiazepines like midazolam, lorazepam, and diazepam are preferred agents for procedural sedation. Midazolam is a potent benzodiazepine [11]. Its short duration of action, cardiorespiratory stability, anxiolytic and amnestic properties make it a preferred sedative for short procedures. The present study was thus planned to access the effectiveness and safety of midazolam through non-invasive routes as we did not come across any study done on pediatric dental patients comparing these three non-invasive routes (Intra-Nasal, Buccal, Oral) of Midazolam administration together. Though in one study by Elieen J. et al., [12] done for laceration repair, these routes were compared in Children aged 0.5 to 7 years. It was found that aerosolized buccal or intranasal midazolam is an effective and useful alternative to oral midazolam for laceration repair.

For all three groups, the subjects were age and sex-matched. The compliance for drug administration with oral and buccal route was found to be better. For oral route, flavoring vehicle was used to mask the bitter taste of the drug [13,14]. The child enjoyed the sweetened juice containing Midazolam without complaining of bitter taste of solution which was a concern in previous studies [15]. The children in the intranasal group complained about the nasal irritation. A similar finding was reported by Johnson E et al., [16] who observed that oral sedations were more successful than intranasal sedation in terms of patient compliance during drug administration. (Table 2). This finding is contrary to the study by Primosch RE, Bender F [10] as they found no significant difference between child's compliance to accept the medication with the intranasal and oral routes.

Intra-nasal and oral group provided minimal to moderate sedation. Whereas buccal route provided only minimal sedation in 46.67% patients and no sedation in 53.33% patients. (Table 3). The results in the present study showed that the Oral group had delayed onset time and peak sedation time as compared to intranasal group. This is because when the drug is administered orally, it passes through the intestinal wall and travels to the liver before being transported via the bloodstream to its target site. The intestinal wall and liver metabolize the drugs, decreasing the amount of drug reaching the bloodstream. When the drug is administered buccally or intranasally it can dissolve through mucosa and gets absorbed directly into the small blood vessels. Substances absorbed through the mucosa bypass gastrointestinal enzymatic degradation and the hepatic first-pass effect. In addition, the mucosa is resistant to damage or irritation because of the rapid cell turnover and frequent exposure to food. The drugs administered using nasal route have higher bioavailability.

Ease of treatment was found to be better in intranasal and oral groups on comparison with buccal group (Table 4). This was because the effect of sedation was better in intranasal and oral groups. Children were alert and awake in the Buccal group. In the studies by Chopra et al [17], Sunbul et al [18], and Yousr et al [19] no statistically significant differences were found between intranasal and buccal groups with a dosage 0.3 mg/kg for both groups based on overall behaviour rating, efficacy, and drug acceptance. But, in the present study intranasal group provided better sedation and anxiolysis and better ease of treatment completion when compared to the buccal group. This may be due to more amount of absorption of drug through nasal mucosa whereas through buccal route some amount of drug was ingested in the body with saliva as it was difficult to isolate. Buccal midazolam can be given in the range 0.3-0.5 mg/kg [20], but in most of the previous studies [17-19] 0.3 mg/kg dose was used for buccal route and was effective for sedation. In the present study also 0.3 mg/kg dose for buccal route was taken. Further studies can be done with 0.5 mg/kg dose expecting better results than 0.3 mg/kg for buccal route.

In all the experimental groups, the pulse rate, blood pressure, and oxygen saturation remained within acceptable physiological limits. In the present study, none of the three routes showed any side effects / postoperative complications. Intra-nasal and buccal groups showed early recovery time when compared to the oral group (Table 5).

Conclusions

Based on the observations done during course of study, following conclusions were made:

- Intranasal and oral routes were equally effective in providing minimal to moderate sedation while buccal route was least effective among all and could not provide satisfactory sedation in majority of patients.
- Acceptance of drug was better with oral and buccal routes when compared to intranasal route.
- Time of onset and peak sedation effect was fastest with intranasal route, followed by buccal route while oral route showed delayed onset and peak sedation effect.
- No intra-operative and post-operative complications were reported with any of these routes.

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