Buccal Midazolam Spray as an Alternative to Intranasal Route for Conscious Sedation in Pediatric Dentistry

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***Objectives**: To evaluate the acceptance of midazolam spray through buccal route as compared to intranasal route and compare the efficacy of the drug through both the routes. **Study Design**: 30 patients aged 2-8 years with Grade I or II Frankl's Behaviour Rating Scale were selected who required similar treatment under local anesthesia on two teeth. Midazolam spray was administered randomly through buccal or intranasal routes for the two appointments. Scoring was done for the acceptance of drug and Houpt's score was recorded for the behaviour of patients during the treatment. **Results**: Acceptance of drug through buccal route was significantly better than the intranasal route ($p<0.05$) but no statistically significant difference was found in the behaviour scores for the two routes of administration ($p>0.05$). **Conclusion**: Midazolam spray can be effectively used through the buccal mucosa in children who give poor compliance with the intranasal administration.*

***Keywords**: Buccal midazolam, Conscious sedation, Pediatric dentistry.*

INTRODUCTION

Fear, anxiety and early developmental stage may make it difficult for a child to cooperate with necessary dental procedures. Dental treatment can be significantly compromised by movement and generally uncooperative behavior during restorative care. Sedation when coupled with other behaviour shaping procedures shows great promise in managing highly anxious pediatric patients. Midazolam is known for its anxiolytic qualities and has been effectively used for providing conscious sedation in pediatric dentistry.[1]

The oral route of administration is the most popular among pediatric dentists; however, confrontation and frustration often arise when children refuse to accept the sedative medication. Despite efforts to disguise the often bitter taste, children occasionally spit or regurgitate the medication when administered orally.[2] Parenteral administration is a major cause of anxiety, discomfort, and trauma in children and the trend in pediatrics is to avoid injections whenever possible.[3]

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Transmucosal (intranasal, sublingual, buccal) delivery of sedative medications offers an alternative that provides some benefits in properly selected minor procedures: they have a faster onset than oral or rectal forms and are less painful than injectable forms. The main advantage is avoidance of hepatic first pass effect[4] and better acceptance by the patients.

Intranasal administration of midazolam has been extensively investigated in pediatric dentistry[5-8] and midazolam nasal spray has already reached commercial status. However it is associated with mucosal irritation which leads to crying and refusal by the patient.[9-12] Also intra- and inter-subject variability in nasal mucosal secretion could affect the absorption of drug from this site.[13] Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable[13] and thus can be used as an alternative to intranasal route as the pharmacokinetics remain similar. Thus this study was conducted using aerosolized midazolam (5mg/ml) through buccal route and its efficacy and acceptance was compared with the intranasal administration.

MATERIALS AND METHOD

For this clinical study, 30 patients in the age range of 2-8 years were recruited based on the Frankl's Behavior Rating Scale (Grade I and II) in whom the routine behavior modification techniques had not worked. All the children belonged to ASA Group I and had no medical conditions which contraindicated the use of midazolam sedation. Only those patients were selected who required similar procedure under local anesthesia (e.g. pulp therapy, extraction or restoration) to be done on two different teeth. An informed written consent was taken from the parents of the children regarding the use of midazolam sedation and its involved risks and benefits were also explained. Preoperative instructions were given to the parents regarding the restriction of solids 4 hours and liquids 2 hours prior to the procedure.

Table I. Scoring criteria for acceptance of drug[14]

1	Refused to take medication
2	Took medication with difficulty
3	Took medication without complaint

Table II. Scoring criteria for movement and crying during the treatment[14]

1	Violent movement with or without hysterical crying that interrupts treatment.
2	Continuous movement with crying that makes treatment difficult.
3	Controllable movement with mild crying that does not interfere with treatment.
4	No movement, no crying.

Table III. Scoring criteria for overall behaviour at the end of the treatment[14]

1	Aborted, no treatment rendered
2	Poor -treatment interrupted, only partial treatment completed
3	Fair-treatment interrupted but eventually completed
4	Good -difficult, but all treatment performed
5	Very good -some limited crying or movement
6	Excellent -no crying or interfering movement

For each patient, a similar procedure was planned on two separate appointments. At the day of the appointment, patients were reassessed for their physiological status for sedation. A commercially available Midazolam spray (INSED, Samarth Pharmaceuticals) was administered (0.25mg/kg) randomly through intranasal or buccal route in the first appointment and the alternate route was used in the second appointment. A single researcher was responsible for administering the drug for all the sessions and he also recorded the score for the acceptance of the drug (Table I). Signs of sedation like slight drowsiness, calming or slurring of speech were observed before starting the dental procedure. The heart rate, oxygen saturation and blood pressure of the patients were monitored throughout the appointment. The dental treatment was accomplished by a pediatric dentist who was blinded to the route of administration of drug. A second researcher, who was also blinded to the route of administration, was responsible for recording Houpt score[14,15] during the treatment for movement and crying (Table II) and the overall behaviour at the end of the treatment (Table IV). The patients were kept under observation for about an hour after the procedure and were discharged after giving post-operative instructions.

RESULTS

30 patients aged 2-8 years (mean age= 3.8±1.4) participated in this study out of which 23 were males and 7 were females. The weight of the patients ranged from 8-21 Kgs (mean weight=13.4±2.8). The acceptance of the drug was considered 'good' for a score of '3' and 'poor' for a score of '1' or '2'. 83.3% of patients accepted the drug without any complaints when midazolam spray was administered through the buccal mucosa while only 16.7% showed 'good' acceptance with the intranasal route. Chi-square test was applied

Table IV. Comparison of Scores for Buccal and Intranasal routes of Administration

	Intranasal Route	Buccal Route	p-value (x^2)
Good Acceptance of drug (Score 3)	5/30 (16.6%)	25/30 (60%)	P=0.017 (S)
Acceptable behaviour during treatment (movement & crying Score 3-4)	18/30 (60%)	20/30 (66.7%)	P=0.086 (NS)
Treatment completed successfully (overall behaviour score 4-6)	17/30 (56.7%)	20/30 (66.7%)	P=0.056 (NS)

(S= statistically significant, NS=statistically not significant)

and statistically significant difference in the acceptance of drug was found for buccal route as compared to the intranasal route ($p<0.05$).

Behaviour during the treatment was considered acceptable for a movement and crying score of '3-4'. Acceptable behaviour was seen in 66.7% of patients with buccal route and 60% with the intranasal route of administration and the difference between the two was not found to be statistically significant ($p>0.05$). Similarly, the treatment was considered to be 'successfully completed' if the overall behavior scores were '4-6' and 'unsuccessful' for the scores of '1-3'. The treatment was completed successfully in 66.7% patients for buccal route and in 56.7% for intranasal administration. No statistically significant difference in the success of the treatment was observed ($p=0.056$) for both the routes.

DISCUSSION

A sedative must have an acceptable, atraumatic route of administration in addition to other characteristics needed for such a drug.[9] Midazolam is a benzodiazepine that is widely used as a sedative in conscious sedation or monitored anesthetic care because of its good anxiolytic properties.[16] The advantages and limitations of using different administration routes for midazolam, especially with respect to the ease of administration and patient acceptance is controversial.[2] Intranasal midazolam has been extensively researched in pediatric dentistry[5-7] and it has been found to be effective in reducing the anxiety of patients with mild to moderate apprehension. Because of rapid uptake and high bioavailability, intranasal midazolam has the advantages of high potency, rapid onset, stable sedative effects and short duration of action.

The disadvantages reported with nasal administration in previous studies were burning sensation in the nose,[7] nasal stinging[9] and sneezing during administration and inapplicability in patients with nasal discharge.[6] Refusal to accept the drug has been the major reason for drop outs in a study conducted by Kjungman *et al* on intranasal midazolam.[11] In the present study also, there was poor compliance of the patients during intranasal administration with 60% of children refusing to take the medication because of burning sensation in the nose. 14/30 children cried with the intranasal administration. One patient was excluded from the study because he did not allow the drug to be administered through intranasal route and rest of the sprays had to be given through the buccal mucosa.

The mucosa in the oral cavity is relatively permeable with a rich blood supply, it is robust and shows short recovery times after

stress or damage, and the virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens.[13] Furthermore, oral transmucosal drug delivery bypasses first pass effect and avoids pre-systemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.[13] In a study conducted by Schwagmeier *et al,*[16] the bioavailability of buccal midazolam was found to be 74.5% which was comparable to that following intranasal route (78%). Midazolam solution has been used previously via sublingual route to achieve sedation but the preparation was very bitter and had to be mixed with flavoring agents to be retained under the tongue.[12] This resulted in either swallowing of the liquid drug or expelling it, leading to suboptimal availability.[4] Schwagmeier *et al* suggested that a rapid and reliable buccal absorption could be achieved if a more concentrated midazolam solution could be administered to the buccal mucosa in a more dispersed manner.[16] In our study, we have used aerosolized form of midazolam which is administered with the help of an atomizer which causes the medication to be propelled over a larger surface area in the form of a spray. This allows a greater percentage of the medication to be absorbed via the mucosal surface with a direct route to the blood stream leading to faster and more reliable onset of action.

In our study, the acceptance of the drug given with buccal route was significantly ($p<0.05$) better than the intranasal administration. 25/30 patients readily accepted the buccal administration without any complaints of bitter taste or discomfort to the mucosa. Only one patient refused to accept the drug and 4/30 complained of an unpleasant taste in the mouth. This is also evident in a study by Klein *et al* [17] where nasal and buccal aerosolized midazolam were compared with oral midazolam for laceration repair. Less distress was observed in the buccal group while nasal group was the most poorly tolerated. However they found that intranasal route demonstrated a greater proportion of patients with optimal activity scores, greater proportions of parents wanting similar sedation in the future, and faster onset.[17] In the present study, Houpt Rating Scale was used to assess efficacy because of its demonstrated reliability and frequent use in other studies.[8] Our study showed no significant difference ($p>0.05$) in the Houpt scores of the patients with both the routes of administration. The similar crying, movement, and overall behavior scores indicate that buccal midazolam was as effective as intranasal route for conscious sedation.

In this study, 0.25mg/kg of dose was used to achieve moderate sedation using midazolam spray through buccal mucosa. No side effects were observed in any patient and there was no incidence of any respiratory depression or oversedation.

CONCLUSION

Buccal midazolam was definitely better tolerated by the patients as compared to the intranasal route; however the effectiveness of conscious sedation was not influenced by the route of administration. Thus buccal midazolam was found to be as effective and safe as intranasal route for achieving sedation for minor dental procedures in children with an added benefit of excellent acceptance by the patients.

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