Comparison of the Onset of Action and Behavioral Responses to Intranasal and Sublingual Routes of Midazolam Sedation in Children - A Randomized Controlled Trial

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Abstract

Aims: The aims of the study were to assess the the onset of action and the behavioral response to intranasal and sublingual midazolam sedation.

Study Design: Forty children aged 3 to 7 years were randomly assigned to Group A (N=20) intranasal or Group B (N=20) sublingual midazolam (0.2 mg/kg) sedation. The behavioral responses like sleep, cry and movement were assessed at various time periods by two calibrated pediatric dentists from recorded videos using Modified Houpt behavior rating scale. The drug's onset of action was noted by observing the signs of sedations every 2 minutes after drug administration. Wilcoxon signed rank test and Mann Whitney U test were used for statistical analysis using SPSS version 19.0.

Results: There was no significant change in behavior of the children (sleep, cry and movement) at various time periods between the intranasal and sublingual group. The movement of the child increased significantly in both intranasal ($p=0.014$) and sublingual ($p=0.046$) groups during local anesthetic administration. Intranasal route of drug administration showed a faster onset ($p<0.001$) of action than the sublingual group.

Conclusions: Both intranasal and sublingual administrations of midazolam along with basic behavior guidance techniques were equally effective in managing the child's behavior in the dental clinic**.**

Key Words: Midazolam, Administration sublingual, Administration intranasal

Introduction

Young children with serious oral illnesses and non compliance often test the patience and skills of the Pediatric dentists. Children aged 3 to 7 years with severe pain and pathology are more anxious and have difficulty in communicating properly to the dentist [1]. Pain and the treatment procedures as such influence the behavior of the children in the dental office. These children require local anesthetic drug administration to alleviate the pain. The reaction of the child to local anesthetic drug administration can be a sign of emerging perception which further affects the behavior of the children in the dental office. Pharmacologic behavior management might be needed to manage them. Moderate sedation as described by American Academy of Pediatric Dentistry (AAPD) refers to drug induced depression of consciousness during which patients respond purposefully to verbal commands [2]. Transmucosal sedation has gained a lot of importance in pediatric dentistry in the last decade. The term transmucosal means "through, or across a mucous membrane". Transmucosal drug delivery system includes drugs administration through rectal, intranasal and sublingual routes. These routes offer a rapid onset and bypass first pass metabolism. Being non invasive, these routes can be child friendly. Among the medications available, midazolam has gained a lot of attention as a good pediatric sedative agent in the recent years. It is a short acting benzodiazepine with rapid onset, faster recovery, anxiolytic and anterograde amnestic effects. The rapid onset of midazolam makes it an ideal sedative agent to be used in dental office as a sedative agent. Recent studies [3-5] have shown that intranasal and buccal routes have also been used as alternative routes for midazolam administration. There is limited literature in the use of sublingual midazolam sedation in pediatric dentistry. Hence this study was planned to assess the onset of action and behavior of the children after intranasal and sublingual midazolam sedation.

Methodology

Study design and ethical approval

A randomized controlled trial was planned and the study protocol was approved by the Institutional Review Board, KSR Institution of Dental Science and Research, (KSRIDSR) Tiruchengode, Tamil Nadu. Ethical clearance was obtained. The study followed the principles for medical research involving human subjects described by Helsinki declaration. Sample size was calculated based on the work of Shashikran et al. [6] with type I error 5% and power of test 80% and it was calculated to be 36. Hence 48 apprehensive children who reported to the Department of Pedodontics and Preventive dentistry, KSRIDSR during the study period (August 2013 to August 2014) and who needed treatment under sedation were selected for the study. The study protocol was shown in *figure 1*.

Inclusion and exclusion criteria

Children aged 3 to 7 years who had Frankl behavior rating score II or III and ASA category I or II during their first

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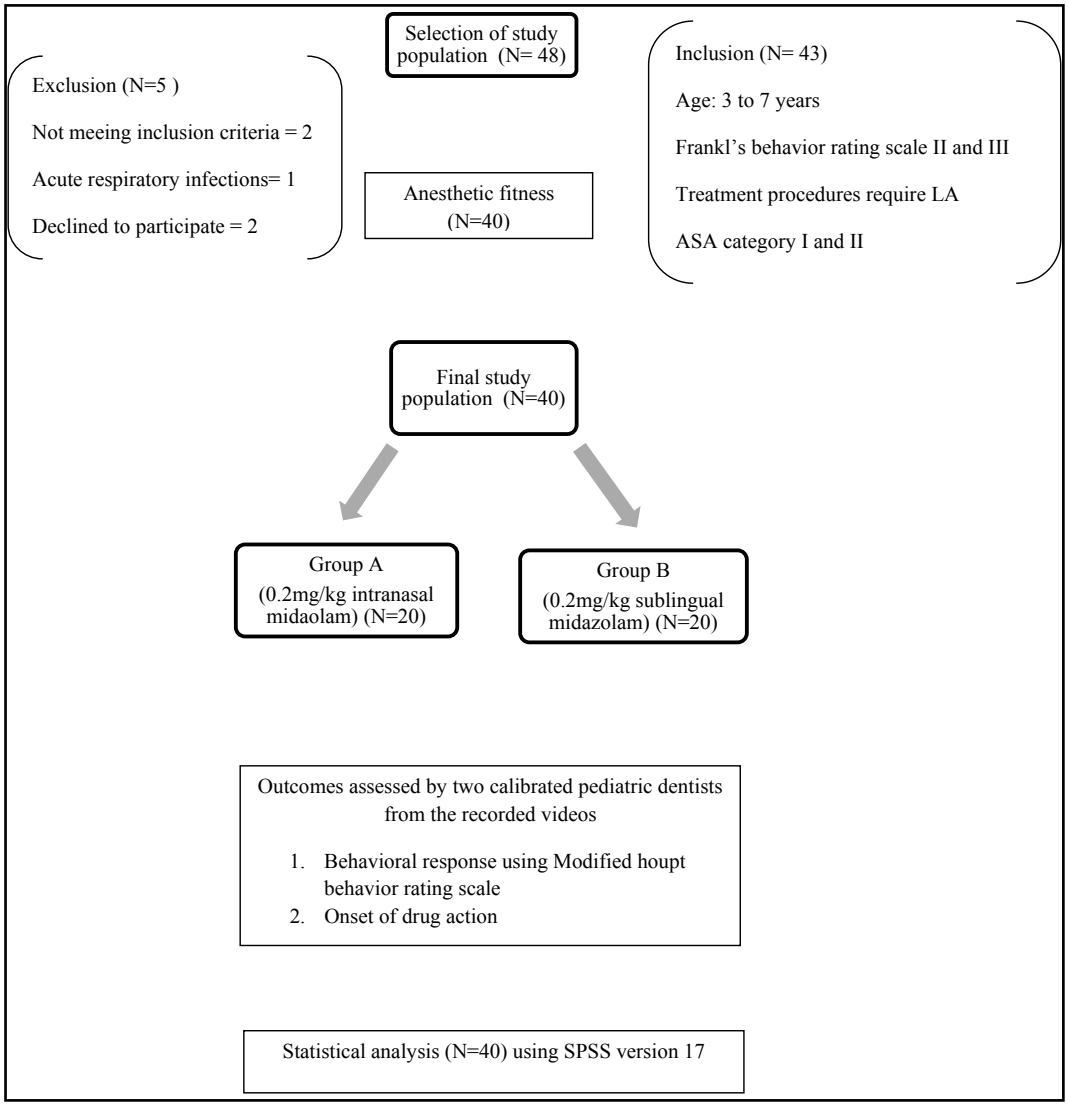

Figure 1. *Consort study protocol. ASA- American Society of Anesthesiologists; LA- Local anesthetic administration.*

dental visit, were advised for management under moderate sedation. Those children who required local anesthetic (LA) administration for their dental procedures were included in this study. The children were given appointment for treatment under moderate sedation after obtaining anesthetic fitness. Written consent was obtained from the parents, after explaining the merits and demerits of moderate sedation. Children with acute respiratory illness, allergic reactions, medically compromised children and children whose parents were not willing for treatment under sedation were excluded from the study. Hence a total of 40 children participated in the study. Care was taken to include a sample size that was sufficient to estimate the difference between the intranasal and sublingual midazolam groups, with a power of 80% at a significance level of 0.05. All the children followed the preoperative fasting criteria according to AAPD guidelines: Light meal, non-human milk and infant formula – 6 hours; clear liquid – 2hours. The baseline values of the vital signs (blood pressure, heart rate, oxygen saturation) were recorded using cardiac monitor unit. These vital signs were monitored throughout the procedure (5 minutes interval) till the recovery and discharge of the patient. To avoid inter-observer variations in the assessments the same anesthetist was involved throughout the course of the study.

Table 1. *Demographic profile of the study population.*

Sl.No	Variable	Particulars	Group A	Group B
1	Age (years)	Mean ± S.D N Minimum-Maximum	5.10 ± 1.07 20 3-7	5.20 ± 1.15 20 3-7
2	Sex	Male Female	12 8	12 8
3	Weight (kgs)	Mean ± S.D N Minimum-Maximum	17.50 ± 4.39 20 12-24	17.40 ± 4.33 20 12-26

Randomization and drug administration

Randomization was done using software with an allocation ratio of 1:1. Forty children were allotted randomly to either group A (Intranasal, N=20) or group B (Sublingual, N=20). Care was taken to randomly divide them based on age and sex as shown in table 1. The children in group A and group B received undiluted midazolam (5mg/ml) 0.2mg/kg by intranasal route or sublingual route respectively. In group A the solution was sprayed into both the nostrils using a sterile Mucosal Atomizing Device (MAD) [3] (MAD100, Wolfe Tory Medical Inc., USA) with the children in semi reclined position. In group B, the children were asked to touch the incisor teeth with the tip of the tongue and the solution was sprayed below the tongue using the sterile MAD (MAD100,

Wolfe Tory Medical Inc., USA). The children were instructed not to swallow the drug for 30 seconds after which they were allowed to swallow the drug [7].

Operative procedures

A single operator performed all the dental procedures in both the groups. The operative procedure was started 20 minutes after the drug was administered. Topical gel (Precaine, Pascal International, USA) application was done prior to the local anesthetic (LA) injection procedure. The injection was given using cartridge syringe (Septodont, France) which consisted of 2% lignocaine with 1:80,000 adrenaline. One of the following treatments was rendered: extraction or pulp therapy. All the procedures were planned to be completed within 20 to 30 minutes. Behavior management techniques such as tell-show-do, voice control and restraints were used based on the behavior of the child. The whole procedure was videotaped from the time the drug was administered till the procedure was completed.

Outcome measures and assessment

The time of administering the drug was noted and the onset of sedation was noted by observing the signs of sedations such as slurred speech, slight drowsiness, dropping of eyelids or calming of the child every 2 minutes after drug administration. Behaviors of the children were assessed using Modified Houpt Behavior Rating Scale (Table 2). This scale included the following parameters: sleep (1-3), cry (1-4), movement (1-4) and overall behavior of the child during the procedure (1-5). The overall score was calculated based on the scores obtained in sleep, cry and movement categories. Scores 1 and 2 in the overall behavior was considered as an acceptable behavior while scores 3, 4 and 5 represented unacceptable behavior. It records different types of behaviors with varying degrees of expression more precisely and accurately within a given time period [8]. The disadvantage of this scale was the rater's inability to assign a rank among the subcategories by recalling

Table 2. *Modified Houpt Behavior Rating Scale.*

Sleep (1-3)	3	Fully awake, alert • Continuous crying, hysteria, or continual moderate movement considered level 3
	2	Drowsy, disoriented • Patient may have some slight crying of moaning • Patient may still be able to communicate weakly with operator or surroundings, no real resistance
	1	Asleep • Eyes are closed and patient is clearly asleep
Movement (1-4)	4	Violent movement interrupting treatment • Aggressive, hysterical movements • Patient clearly trying to remove himself/herself from papoose wrap or manages to escape from wrap because of movement • May require another assistant to help restrain
	3	Continuous movement making treatment difficult • May require assistant to hold head firmly • Patient actively resisting procedure and may require some restraint • Treatment can be continued, but with some difficulty
	2	Controllable movement that does not interfere with treatment • May see some movement in papoose wrap • May require slight intervention from operator or assistant (control head during LA) • Movement not aggressive and patient not really resisting
	1	No movement • Slight movement caused by operator pressure
Crying (1-4)	4	Hysterical crying that demands attention • Continuous screaming rather than crying • Operator may need to pause treatment to calm patient
	3	Continuous persistent crying that makes treatment difficult • Crying may be loud and patient may be clearly unhappy • Patient not overly aggressive and treatment can continue, though with some difficulty
	2	Intermittent, mild crying that makes treatment difficult • Occasional cry that is not continuous • Continuous moan without any real crying
	1	No crying • Very slight, occasional low moan is acceptable
Overall behavior (1-5)	5	No treatment provided due to behavior • Operator not able to proceed as planned, movement level 4
	4	Poor: Treatment interrupted or planed treatment altered due to behavior • crying level 4 or movement level 3-4 most of the time
	3	Fair: may be a challenge, but treatment performed without anv interruption • Movement level 3 most of the time, no interruptions • No adjustments needed from operator, but firm head-holding may be needed
	2	Good: Some limited crying or movement • Crying level 2-3 and movement level 1-2 most of time • Patient may be crying, but holding quite still for treatment • Treatment may be performed with relative ease
	1	Excellent: No crying or movement level 1

the behavior observed. To overcome this disadvantage in this study two qualified and calibrated Pediatric dentists rated the behavior of the children from recoded videotapes. Two qualified and calibrated pediatric dentists who were blinded to the routes of drug administration assessed the behavior from the recorded videos using Modified Houpt Behavior Rating Scale at the following time intervals – S (20 minutes after drug administration), during LA administration and every 5 minutes till the end of the dental procedure (T_1, T_2, T_3, and T4)

Vital signs monitoring

The physiological parameters were recorded using a cardiac monitoring unit (ASPEN V1, India) at the following time periods: B (Baseline – before sedation), S (20 mins after sedation) and every 5 minutes till the end of the procedure (T_1, T_2, T_3 and $T_{4)}$. The children were assessed post operatively (1 hour after treatment) for discharge using a ten point recovery scale (Aldrette scale) which assessed the patient's airway, color, movement, level of consciousness and blood pressure. Patients with score ≥9 were discharged.

Statistics

The results were tabulated and statistically analyzed using SPSS version 17.0 software (SPSS Inc., Chicago Ill, USA). As Kolmogoro-smirnov test revealed that the values were not normally distributed, Mann Whitney U and Wilcoxon Signed Rank tests were used appropriately for statistical analysis. p value<0.05 considered significant.

Results

Onset of action

The mean onset of action for intranasal and sublingual midazolam was 9.40 ± 1.84 minutes and 13.80 ± 2.04 minutes respectively. There was a significant difference in the onset of action of midazolam (p<0.001) between the two routes as illustrated in *figure 2*.

Modified houpt behavior rating scale

There was no significant difference in the mean scores of sleep, cry and movement between the two groups at various time periods as shown in table 3. In both the groups, there was no significant difference in the mean score of sleep and cry when compared between different time periods as shown in table 4 and 5. In the intranasal group, one child attained score 1 (eyes were closed and completely asleep) 20 minutes after the drug administration. In the sublingual group two children attained score 3 (fully awake and alert): one during local anesthetic administration and the other during extraction procedure. The mean cry score after sedation was 1 ± 0 in both the groups. However, in intranasal group the mean cry score of the children increased during local anesthetic administration. This continued during the initial 10 minutes of the treatment procedure after which the mean cry score decreased. The mean

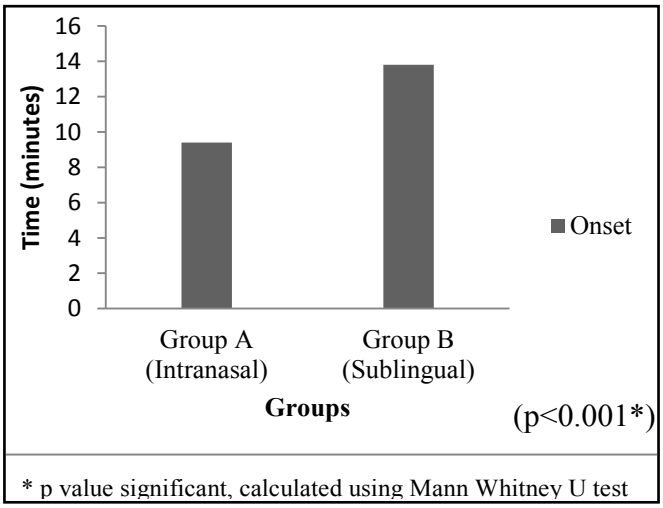

Figure 2. *Bar chart illustrating the onset of action in Group A and B.*

Table 3. *Mean values of sleep, cry and movement assessment in group A and B at various time periods.*

Time Periods	Group	Sleep Mean ± S.D	Cry Mean ± S.D	Movement Mean ± S.D
S	A	1.95 ± 0.224	1 ± 0	1 ± 0
	B	2 ± 0	1 ± 0	1 ± 0
LA	A	2 ± 0	1.10 ± 0.308	1.30 ± 0.470
	B	2.05 ± 0.224	1 ± 0	1.20 ± 0.410
T_1	A	2 ± 0	1.20 ± 0.523	1.35 ± 0.671
	B	2 ± 0	1.15 ± 0.489	1.15 ± 0.489
T_2	A	2 ± 0	1.15 ± 0.489	1.10 ± 0.308
	B	2 ± 0	1.20 ± 0.523	1.15 ± 0.489
T_3	A	2 ± 0	1.05 ± 0.224	1.10 ± 0.308
	B	2.05 ± 0.224	1.20 ± 0.523	1.20 ± 0.523
T_4	A	2 ± 0	1.05 ± 0.224	1.10 ± 0.308
	B	2.05 ± 0.224	1.05 ± 0.224	1.20 ± 0.523

Group A – Intranasal; Group B – Sublingual; S- 20 minutes after drug administration; LA – Local anesthetic administration; T_1, T_2, T_3, T_4 – at 5 minutes interval during the operative procedure.

Table 4. *Comparison of sleep, cry and movement assessment in group A between various time periods.*

Time Periods	Sleep		Cry		Movement	
	Z	p value*	Z	p value*	Z	p value*
LA – S	-1	0.317	-1.414	0.157	-2.449	**0.014***
S- T_1	-1	0.317	-1.633	0.102	-2.070	**0.038***
S – T_2	-1	0.317	-1.342	0.18	-1.633	0.102
S – T_3	-1	0.317	-1	0.317	-1.414	0.157
S – T_4	-1	0.317	-1	0.317	-1.414	0.157
LA -T_1	0	1	-1	0.317	-0.333	0.739
T_1 – T_2	0	1	-1	0.317	-1.342	0.18
T_2 – T_3	0	1	-0.816	0.414	-0.816	0.414
T_3 - T4	0	1	0	1	0	1

*p <0.05 significant, p value calculated using Wilcoxon Sign Rank test; Group A -Intranasal; Group B – Sublingual; S- 20 minutes after drug administration; LA – Local anesthetic administration; T_1, T_2, T_3, T_4 – at 5 minutes interval during the operative procedure.

Table 5. *Comparison of sleep, cry and movement assessment in group B between various time periods.*

Time Periods	Sleep		Cry		Movement	
	Z	p value*	Z	p value*	Z	p value*
LA – S	-1	0.317	0	1	-2	**0.046***
S- T_1	0	1	-1.342	0.18	-1.342	0.18
S – T_2	0	1	-1.633	0.102	-1.342	0.18
S – T_3	-1	0.317	-1.633	0.102	-1.633	0.102
S – T_4	-1	0.317	-1	0.317	-1.633	0.102
LA -T_1	-1	0.317	-1.342	0.18	-0.378	0.705
T_1 – T_2	0	1	-1	0.317	0	1
T_2 – T_3	0	1	0	1	-0.577	0.564
T_3 - T4	0	1	-1.342	0.18	0	1

*p <0.05 significant, p value calculated using Wilcoxon Sign Rank test; Group A – Intranasal; Group B – Sublingual; S- 20 minutes after drug administration; LA – Local anesthetic administration; T_1, T_2, T_3, T_4 – at 5 minutes interval during the operative procedure.

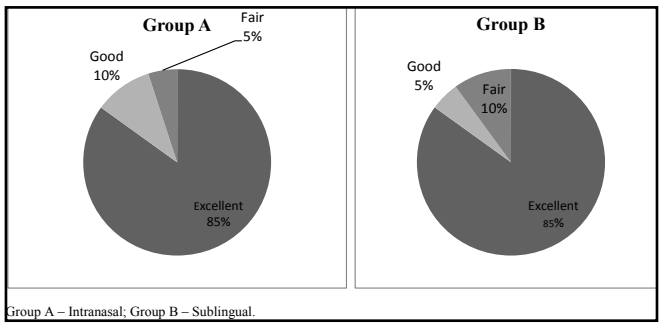

Figure 3. *Pie chart illustrating the overall behavior of the children in Group A and B.*

movement score after the drug administration was 1 ± 0 in both the groups. The movement of the child increased significantly in both intranasal (p=0.014) and sublingual (p=0.046) groups during local anesthetic administration. Around 60% and 70% of the children in the intranasal and sublingual group respectively showed no movement throughout the procedure. There was no significant difference in the overall behavior of the children between both the groups as shown in the figure 3. In both the groups 85% of the children showed excellent behavior throughout the treatment procedure.

Observer reliability

The intra-observer reliability kappa was 0.926 and 0.865 for observer 1 and 2 respectively. The percentage of agreement between the two observers was 85.3% and the inter-observer reliability kappa was 0.755.

Physiological parameters

There were no significant differences in the physiological parameters such as heart rate, blood pressure and oxygen saturation at various time periods between the intranasal and sublingual group.

Discussion

This study assessed the behavior of the children and onset of action of midazolam after intranasal and sublingual administration. In this study midazolam (0.2 mg/kg) was administered using a MAD either through intranasal or sublingual route. Primosch RE et al. [9] have shown that midazolam administered through MAD improved the behavior of the child than administered as drops. De boer AG et al. [10] and Bjorkman S et al. [11] reported that the high vascularity of the nasal and sublingual mucosa allowed rapid absorption of the drug. The absorption of the drug through sublingual route also depended on various other factors such as local pH, salivary flow and the time the drug is adjacent to the mucosa. Fuks AB et al. [12] suggested that midazolam administered at 0.3mg/kg can lead to respiratory depression. Literature search showed that midazolam administered by transmucosal means at 0.2mg/kg did not have any advantage than 0.3mg/kg. Hence in the present study 0.2mg/kg of midazolam was used.

Onset of action

Onset of action refers to time duration taken for a drug's effect to become prominent after administration. An ideal sedative agent should have a rapid onset of action. Intranasal route had a rapid onset of action than the sublingual route as shown in figure 2. The results were similar to that reported by Rey E et al., AlRakaf H et al., Al-Zahrani AM et al. and Shashikiran ND et al [13-15, 6]. Lejus C et al. [16] reported that intranasal route had rapid onset but poor acceptance. In contrast, a higher sedative plasma midazolam level was obtained at 10 minutes after sublingual administration when compared to intranasal drug administration by Geldner G et al. [17].

Modified houpt behavior rating scale

Shashikiran ND et al. [6] and Lam C et al. [18] showed that 100% and 82% of the children attained drowsy state after intranasal midazolam sedation respectively. Their results were in accordance with the results of the present study. But in sublingual group the results were in contrast to the results shown by Khalil S et al. [19]. He reported that drowsiness was achieved only after 0.75mg/kg of sublingual midazolam administration. Saarnivaara L et al. [20], Feld LH et al. [21] and Parnis SJ et al. [22] reported that an oral dose of 0.5mg/kg was required for adequate sedation.

Cry is a kind of emotion exhibited by children during undesirable situations. Some children exhibit a whining kind of cry, allowing the dentist to continue with the procedure. Hence the cry score can vary at different time periods and this was seen in this study. Lam C et al. [18] reported continuous hysterical crying during local anesthetic administration in 36.5% of the children after intranasal midazolam administration. In intranasal group Johnson E et al. [23] reported a significant increase in the cry score until 30 minutes after the local anesthetic administration. In the sublingual group a increase in the mean cry score was observed during the operative procedures. Chopra R et al. [5] have reported that 17% of the children showed limited cry and movement during the treatment procedure after buccal midazolam administration.

Lam C et al. [18] reported controllable movement in all the children after intranasal midazolam administration. Johnson E et al. [23] reported that children under intranasal group showed increased movement during the start of the treatment, compared to controllable movement seen throughout the procedure in oral group. In this study the movements observed in both the groups were controllable and did not interrupt the dental procedure. Violent movements were not observed in both the groups. In intranasal group, the initial increase in movement and cry may be due to the unpleasant experience felt during drug administration. In sublingual group the increase in movement throughout the procedure may be due to the less efficacy of the drug.

Shashikiran ND et al. [6] and Johnson E et al. [23] reported no significant difference in the overall behavior of the children when treated under intranasal, oral or intramuscular midazolam sedation. Similar results were obtained in the present study.

Conclusion

1. Midazolam by intranasal route had a significantly faster onset of action than the sublingual route.
2. There was no significant difference in the sleep, cry and the overall behavior of the children between group A and B at various time periods.
3. There was a significant increase in the movement of the children in both groups during local anesthetic administration.

Intranasal and sublingual midazolam sedation along with simple behavior management techniques can be used safely by pediatric dentists to effectively manage and instill a positive behavior in young and anxious children.

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