

Original Article

Separation Time of Children From Parents: A Randomized Comparison Between oral versus Atomized Intranasal Administration of Midazolam

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Abstract:

Background: Sedation has become more common for children undergoing procedures in the emergency department, dentistry, and day care surgery. A desirable sedative agent has a rapid onset with short duration of action and is effective and safe. Midazolam as a sedative agent that fulfills these criteria. However controversy surrounds regarding its route of administration, particularly with respect to its ease of administration and patient acceptance. Although the oral route of administration is the most popular among pediatric surgeons and dentists, confrontation and frustration often arise when children refuse to accept the sedative medication.

Objectives: To evaluate the outcome (satisfactory anxiolysis and smooth early parental separation) between oral midazolam (OM) and intranasal midazolam(INM)spray in children for conscious sedation before general anaesthesia.

Methods: Children aged 1 – 6 years scheduled for routine elective surgery were included to receive midazolam as premedication drug. A total of 80 children were recruited consecutively. Of them 40 were randomly assigned to either single dose of 0.5 mg/kg via oral route (OM0) or 0.5 mg/kg of body weight by intranasal spray(INM). The outcome variables were smooth separation of children from their parents at the level of conscious sedation and time to smooth separation.

Results: No change in sedation score was evident in first 3 minutes following midazolam administration. Then the sedation score of INM group increased sharply to assume a mean score of 2 at 9 minutes. No demonstrated change was further noted up to the end of observation. Meanwhile the sedation score of OM group began to increase steadily up to the end of observation when it assumed a mean score of 1.5. The INM group attained a good level of sedation much earlier than its OM counterpart. The mean sedation scores were significantly higher in the former group than those in the latter group. During the first 3 minutes of midazolam administration no change in anxiolysis was noted. Then the score began to increase in both the INM and OM groups, but INM group experienced a much faster increase than the OM group so that the former group reached a mean score of almost 3 and the latter group to a mean score of nearly 2 at 15 minutes interval. The levels of anxiolysis attained by the intranasal group were significantly higher compared to those attained by the oral midazolam group (table II). All but 1 children (97.5%) in the INM group were separated from their parents smoothly as opposed to 90% in the OM group ($p = 0.148$). In the INM group 12.8% of children were separated at 9 minutes, 69.2% from 10 – 12 minutes (over two-thirds) and 18% from 15 – 18 minutes. In the OM group 13.9% were separated at 15 minutes, about 39% at 18 – 21 minutes, 22.3% at 24 minutes and the rest 11.1% at 27 minutes after premedication. Overall more than 80% of the children in the INM group were separated at 9 – 12 minutes following midazolam administration when none of the children in the OM group was separated ($p < 0.001$). Complications like nasal irritation was staggeringly higher in the INM group shown on table IV.

Conclusion: Despite the intranasal route causes a substantial proportion of children to suffer from nasal irritation, it is the preferred route over oral route, because intranasal route induces much faster sedation and anxiolysis and helps easy and smooth separation of children from their parents.

Introduction:

The anaesthesiologist faces anxious child as one of the most common problems in everyday experience and one they can handle with least success¹. A child entering the hospital often faces a new environment and surrounding and is overwhelmed by stimulation at the very moment of separation from his/her parents. This separation may be an important cause of neurotic anxiety and may persist throughout their childhood². Sedative preanaesthetic medication is rarely indicated for infants aged less than 6 months, as they appear relatively undisturbed when separated from their mothers. Psychologists generally agree that fear and emotional disturbance are greater in children just before they are able to talk, when they show clear signs of distress if separated from his/her mother and resists approaches from strangers. For anxiolysis and sedation, premedication regimens are recommended with different agents like benzodiazepines, ketamine and chloral hydrate³. Among them midazolam is found safe, efficient, less bioavailable and widely used without delaying recovery even after ambulatory surgery⁴. Thum et al (1998) describes that midazolam well-known for its anxiolytic, euphoric, amnesic and sedative qualities. Midazolam can be administered by a variety of routes like oral, intramuscular, intravenous, rectal, sublingual and intranasal. Each route has its merits and demerits. Intra-nasal midazolam (INM) as premedication in children is comparatively easier and smooth maneuver. Absorption through this route is prompt and effective bypassing the first-pass metabolism when parenteral formulation is used as injectable solution (15 mg in 3 ml)⁵. Some authors reported that the nasal route required less patient cooperation and was simple, convenient, painless and reliable alternative to oral drug administration⁶, while others reported INM to be noxious, painful and poorly tolerated⁷. Low patient tolerance was the result of the injectable solution, stabilized by storage in 3.3 pH solution, irritating the nasal mucosa with a burning sensation.

Methods:

The present study was a prospective randomized clinical trial. Patients included children ranging from 1 – 6 years of either sex with ASA grade-I or well-controlled systemic diseases such as asthma or uncomplicated diabetes (ASA grade-II) and

excluded from the study were emergency operation, routine use of sedative or hypnotics in the month before study, enrollment in a drug study in the preceding 6 months, known hypersensitivity to benzodiazepines and upper respiratory tract infection. A total of 80 patients were recruited. Of them 40 were assigned to INM spray group and 40 to OM group.

For random allocation of patients into groups, there were two cards. Parents (either father or mother) of children scheduled for receiving sedation premedication were asked to draw a card blindly. If the card drawn was marked with 'INM' his or her children received intranasal midazolam spray (0.5 mg/kg) and the next patient went to OM group to receive oral midazolam (0.5 mg/kg). The sedation and anxiolytic scores before midazolam premedication were recorded. The main outcome variables were sedation and anxiolysis which were measured at every 3 minutes intervals up to 20 minutes from midazolam administration. The time to smooth separation from their parents were recorded. The side-effects produced by the two regimens were also recorded.

Haemodynamic parameters of the two groups were recorded before premedication and at every 3 minutes following midazolam administration of the drug until the child achieved a level of conscious sedation adequately enough to be smoothly separated from their parents. Sedation and anxiolytic scores were also recorded before and at every 3 minutes after midazolam administration to compare which route allows earlier and smoother separation of child from his/her parents. Data were processed and analysed using SPSS. The test statistics used to analyse the data were descriptive statistics, Chi-square (χ^2) Probability Test Student's t-Test. For all analytical tests, the level of significance was set at 0.05 and $p < 0.05$ was considered significant. The summarized data were presented in the form tables and charts.

Results:

Comparison of sedation score between groups

Fig.1 demonstrates the changes in sedation score following midazolam administration between groups. The mean sedation score at baseline was 1 in both the groups. No change in sedation score

was evident in first 3 minutes of observation. Then the sedation score of INM group increased sharply to assume a mean score of 2 at 9 minutes. No demonstrated change was further noted up to the end of observation. Meanwhile the sedation score of OM group began to increase steadily up to the end of observation when it assumed a mean score of 1.5.

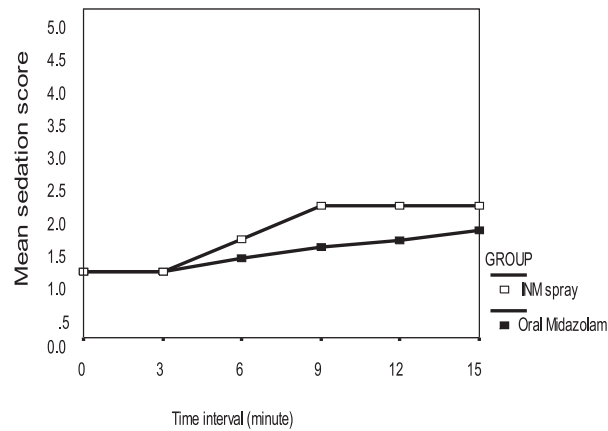


Fig 1 Monitoring of sedation score at different time interval

Table I Sedation score at different time interval between groups

Sedation score	Group		p-value
	INM (n = 40)	ON (n = 40)	
At baseline	1 ± 0	1 ± 0	Not computable
At 3 minute	1 ± 0	1 ± 0	Not computable
At 6 minute	1.5 ± 0.5	1.2 ± 0.4	0.010
At 9 minutes	2.15 ± 0.49	1.37 ± 0.49	< 0.001
At 12 minutes	1.98 ± 0.22	1.68 ± 0.47	< 0.001
At 15 minutes	1.99 ± 0.40	1.90 ± 0.40	< 0.001

Data were analysed using Student's t-Test and were presented as mean ± SD.

The INM group exhibited a good level of sedation score much earlier than its OM counterpart. The mean sedation scores at 6, 9, 12 and 15 minutes of observation were significantly higher in the former group than those in the latter group (p = 0.010, p < 0.001, p < 0.001 and p < 0.001 respectively) (Table I).

Comparison of anxiolysis score at different time interval:

Fig.2 shows the comparison of changes in anxiolysis scores between groups at different time intervals. During the first 3 minutes of midazolam administration no change in anxiolysis was noted. Then the score began to increase in both the INM and OM groups, but INM group experienced a much faster increase than the OM group so that the former group reached a mean score of almost 3 and the latter group to a mean score nearly 2 at 15 minutes interval.

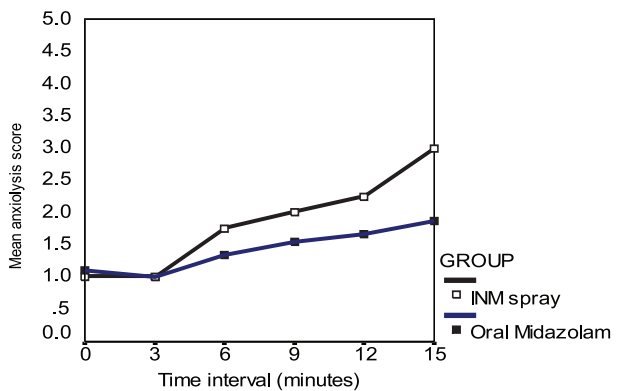


Fig 2 Monitoring of anxiolysis score at different time interval

Table II Anxiolysis score at different time interval between groups

Anxiolysis score	Group		p-value
	INM (n = 40)	OM (n = 40)	
At baseline	1.0 ± 0.0	1.1 ± 0.3	0.963
At 3 minutes	1.0 ± 0.0	1.0 ± 0.0	Not computable
At 6 minutes	1.7 ± 0.5	1.3 ± 0.5	< 0.001
At 9 minutes	2.0 ± 0.3	1.5 ± 0.7	< 0.001
At 12 minutes	2.2 ± 0.5	1.7 ± 0.7	< 0.001
At 15 minutes	3.0 ± 0.1	1.9 ± 0.7	< 0.001

Data was analysed using Student's t-Test and was presented as mean ± SD.

The levels of anxiolysis attained by the intranasal group at 6, 9, 12 and 15 minutes intervals were significantly higher compared to those attained by the oral midazolom group (p < 0.001 in each case) (Table II).

Smooth separation of children from their parents:

All but 1 children (97.5%) in the INM group were separated from their parents smoothly as opposed to 90% in the OM group ($p = 0.148$) (Fig. 3).

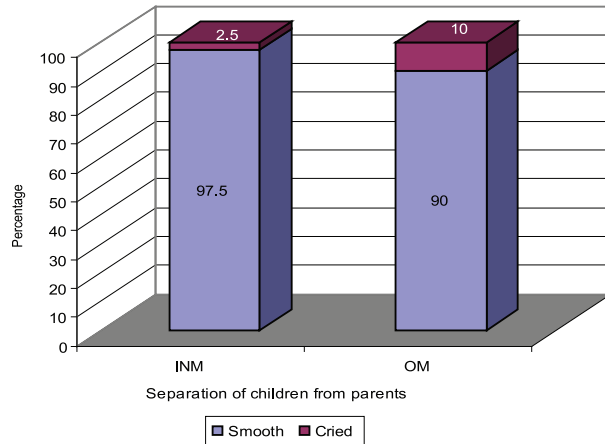


Fig 3 Comparison of smooth separation of children between two routes

Time to smooth separation of children from their parents:

Table III described the time to smooth separation of children from parents. In the INM group 12.8% of children were separated at 9 minutes, 69.2% from 10 – 12 minutes (over two-thirds) and 18% from 15 – 18 minutes. In the OM group 13.9% were separated at 15 minutes, about 39% at 18 – 21 minutes, 22.3% at 24 minutes and the rest 11.1% at 27 minutes after premedication. Overall more than 80% of the children in the INM group were separated at 9 – 12 minutes following midazolam administration when none of the children in the OM group was separated ($p < 0.001$).

Table III Comparison of time to smooth separation of children between groups

Time to smooth separation	Group	
	INM (n = 39)	OM (n = 36)
9 minutes	5(12.8)	0(0.0)
10 minutes	14(35.9)	0(0.0)
12 minutes	13(33.3)	0(0.0)
15 minutes	4(10.3)	5(13.9)
18 minutes	3(7.7)	7(19.4)
21 minutes	0(0.0)	7(19.4)
22 minutes	0(0.0)	5(13.9)
24 minutes	0(0.0)	8(22.3)
27 minutes	0(0.0)	4(11.1)

Complications encountered:

Complications encountered by the patients between groups showed that nasal irritation was staggeringly higher in the INM group than that in the OM group (77.5% vs. 7.5%, $p < 0.001$), whereas dry mouth was solely observed in OM group (35%) ($p < 0.001$). Additional medications needed in 3(7.5%) cases of the INM group ($p = 0.120$).

Table IV Comparison of complications between groups

Complications	Group		p-value [#]
	INM (n = 40)	OM (n = 40)	
Nausea/vomiting*	24(60.0)	31(77.5)	0.091
Nasal irritation*	31(77.5)	3(7.5)	< 0.001
Dry mouth*	0(0.0)	14(35.0)	< 0.001
Additional medication needed [#]	3(7.5)	0(0.0)	0.120

* Data were analysed using Chi-square (χ^2) Test;

Data were analysed using Fisher's Exact Test.

Discussion

The results of the present study demonstrated no change in sedation score in either intranasal or oral group in first 3 minutes following midazolam premedication. From 3 minutes onwards it began to increase in both intranasal and oral groups but the increase was much faster in the former than the latter group. At 9 minutes of observation INM group assumed a mean sedation score of 2.01 ± 0.51 and OM group a mean score of 1.5 ± 0.40 . Kogan et al. (1996) demonstrated that all the four non-invasive routes of midazolam administration (0.3 mg/kg in intranasal and sublingual routes and 0.5 mg in oral and rectal routes) had comparable efficacy with regard to anxiolysis (83 – 93%)⁸. The intranasal route provided a faster effect compared to the oral sublingual and rectal routes. Average sedation and anxiolysis increased with time achieving a maximum at 20 minutes in the intranasal group and at 30 minutes in the oral, sublingual and rectal group.

In the present study INM group exhibited a good level of sedation and anxiolysis scores much earlier than its OM counterpart. The levels of anxiolysis attained by the former group at 6, 9, 12, 15, and 18 minutes intervals were significantly higher

compared to those attained by the latter group. Although all children in the INM group and 36 children in the OM group were feasible to be separated smoothly from their parents after midazolam administration, the INM group augmented a significantly faster separation (over 80% within 12 minutes) as opposed to none in the OM group during the same period. In the OM group separation started at 15 minutes and continued up to 27 minutes. Fuks et al (1994) with random assignment to 0.2 mg/kg or 0.3 mg/kg of intranasal midazolam in 30 children documented that intranasal midazolam had a rapid onset and short duration⁹.

Walberg et al. (1991) demonstrated a very rapid increase in the plasma midazolam concentration to a peak of 72.2 ng/ml within 10 minutes of intranasal administration of 0.1 mg/kg of midazolam. They explained this rapid increase by the very effective mucosal absorption of the drug¹⁰. This explanation is strengthened by Kupietzky & Houqt (1993) who discussed the possibility that intranasal route led to the drug being absorbed in the brain and cerebrospinal fluid through cribriform plate, although the exact mechanism of intranasal absorption of medication is not fully understood¹¹. The faster onset of action (sedation and anxiolysis) in the intranasal routes in these studies as well as those obtained in the present study suggest that absorption of the drug through this route is faster.

The present study demonstrated that there were no significant alterations in haemodynamic variables (pulse, blood pressures, SpO₂) following midazolam administration. Although the INM group showed fluctuations in these variables up to first 18 minutes, the variation was within normal physiological range. Consistent with these findings, Connors et al (1994) found that there were no significant differences in behaviours and alteration of vital signs of patients undergoing laceration repair under nasal and oral midazolam administration¹². Lee-Kim (2004) also did not find statistically significant differences in overall behaviour and alterations of vital signs between oral and intranasal midazolam regimens in pediatric dental patients undergoing dental procedures¹³.

Though in many studies intranasal routes have been shown to be faster in providing adequate level

of sedation and anxiolysis, they were mostly associated with side effects like nasal irritation and burning sensation which was observed in the present study in 77.5% of the cases. In a study, Karl et al (1992) noted that the intranasal route was associated with crying in 71% of the children due to burning sensation¹⁴. Naqash et al (2004) conducted a study similar to the present study and reported that 63% of the children in intranasal group cried following midazolam administration¹⁵. The OM route was not free of side-effects. However, the children in the OM route experienced dry-mouth (35%) cases. The nausea and vomiting was observed in both the routes; however it was more so in the OM routes. The advantage of these routes is absorption of drugs through these routes occurs directly into the central circulation, bypassing the enterohepatic circulation¹⁶. Intranasal drugs have been employed primarily in paediatric patients as a means of circumventing the need for injections or bitter tasting of oral drugs in children especially in unwilling patients¹⁷. Intranasal administration of midazolam has been shown to have a higher bioavailability and shorter onset of actions than has oral route¹⁸. The advantages and limitations of using different administration routes for midazolam, especially with respect to the ease administration and patient acceptance, is controversial¹⁹. Although the oral route of administration is the most popular among pediatric dentists²⁰, confrontation and frustration often arise when children refuse to accept the sedative medicine. Despite efforts to disguise the often bitter taste, children occasionally spit or regurgitate the medication when administered orally^{9,21}. Similar controversy existed in the literature regarding patients acceptance of intranasal midazolam (INM). Some authors have reported that the nasal route required less patient cooperation and was a simple, convenient, non-invasive, painless and reliable alternative to oral drug administration²². In contrast other authors reported INM to be noxious, painful and poorly tolerated. Low patient tolerance was the result of injectable solution, stabilized storage in 3.3 pH solution, irritating the nasal mucosa with a burning sensation. Early approaches to the INM sedation used drops²³ but more recently use of an atomizer for intranasal administration has become more popular²⁴. Griffith et al (1998) reported

improved patient tolerance to spray administration using an atomizer over using drops, but the effectiveness of sedation between these two methods of administration was reported as equal²⁵. The intranasal route provided the advantage of rapid absorption into the systemic circulation without first-pass metabolism affecting the agent's bioavailability. Finally, if we need faster and smooth separation of children from their parents' Intranasal route could be used.

Conclusion

The intranasal route achieved satisfactory level of sedation and anxiolysis much earlier than the oral midazolam group. However, the former route is blamed to cause nasal irritation and burning sensation. Despite the intranasal route causes a substantial proportion of children to suffer from nasal irritation, it is the preferred route over oral route, because intranasal route induces much faster sedation and anxiolysis and helps easy and smooth separation of children from their parents.

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