PRE MEDICATION WITH MIDAZOLAM IN CHILDREN FOR SMOOTH SEPARATION FROM PARENTS: A COMPARISON OF TWO DIFFERENT ROUTES OF ADMINISTRATION

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Summary

Premedication with midazolam is widely used in paediatric anaesthesia to reduce fear, anxiety, emotion, psychological trauma and ensure smooth separation from parents. However, various routes and dosing regimens are recommended for paediatric premedication and variable efficacy is found when use in different routes. The aim of our study to compare the efficacy and acceptable route between intranasal versus sublingual midazolam premedication for smooth separation from parents before entering the operation theater.

It will be a comparative, cross-sectional prospective clinical study. 120 unmedicated children, ASA I or II, Age 1–6 years, who will be scheduled for routine elective surgery and who will be planned to receive midazolam as a premedicant drug, will be randomly assigned to one of the two groups. Group–I receives intranasal midazolam 0.2 mg kg^{-1} and Group–II receives sublingual midazolam 0.2 mg kg^{-1} after having obtained the parent's informed consent. Heart rate, Systolic blood pressure, SpO_2, Sedation and Anxiolysis Scores will be assessed in 4-point scale by the anaesthesiologist every 3 min prior to surgery. Sixty patients will be enrolled in each group, I and II. Data will be compiled and analyzed in computer, using statistical software package SPSS.

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Key words
Premedication; Midazolam; Intranasal; Sublingual; Smooth separation.

Introduction

The anaesthesiologist faces anxious child as one of the most common problems in everyday experience and one they can handle with least success [1]. A child entering the hospital often faces a new environment and surrounding and separation from their parents represent the major hurdles. A child overwhelmed by stimulation at the very moment of separation from his/her mother. The separation of children from their parents before entering the operation theater usually unwanted. This separation is an important cause of neurotic anxiety [2,3]. Continual endeavors and perseverance is going on to find-out some means to overcome these situations successfully.

Sedative premedication 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 disturbances are greater in children just before they are able to talk. Between 3-6 months a baby recognizes its mother and by 7 months of age he/she shows clear signs of distress when separated from his/her and resists approaches from strangers. Separation anxiety can be a problem throughout childhood and it is experienced most intensely by children less than 4 years of age [4,6].

Parental presence during induction of general anaesthesia is controversial. Although early studies suggested reduced patient's anxiety and increased co-operation [7,8]. Most recent reports indicates that parental presence may not always be beneficial [9,10,11]. Bevan et al reported that children of anxious parents were more anxious by having a parent present during induction than if they were separated earlier [9]. The unmotivated mother are so anxious that they are unable to support their children in the operation theatre

rather they continue to inject confusion, fear and general upset, which are detrimental. Anaesthesiologists will need to assess how much stress a mother can tolerate and decide at which point the mother must be separated from her child [10].

For anxiolysis and sedation, premedication regimens are recommended with different agents like benzodiazepines, ketamine and chloral hydrate.[11] Among them midazolam is found safe, efficient, less bioavailability and widely used without delaying recovery even after ambulatory surgery [12,13]. Thum, P et al described that midazolam is well known for its anxiolytic, euphoric, amnestic and sedative qualities [14].

Midazolam can be administered by a variety of routes like oral, intramuscular, intravenous, rectal, sublingual and intranasal. The intravenous midazolam is not used for paediatric premedication. Intramuscular route is associated with fear of needles, pain and anxiety. Rectal administration appears sometimes as a fearful and agonizing procedure to the patients and of course, it introduces an unpleasant experience of exposing private parts, may be they are tiny child. Delayed gastric absorption, first pass metabolism, a bit bitter in taste and an unavailability of palatable oral formulation are the drawbacks of oral route. Moreover, pre-operative anxiety induced gastrointestinal symptoms like dry mouth, difficulty in swallowing; epigastric discomfort and anorexia may make the situation cumbersome to feed the baby orally.

Intra-nasal and sublingual administration of midazolam as premedication in children is comparatively easier and smooth maneuver. Absorption of this route is prompt and effective. It bypasses the first-pass metabolism. Parentaral formulation (15 mg in 3 ml) can be used. Walberg et al demonstrated a very rapid increase in plasma midazolam concentration to a mean peak of 72.2 ng ml^{-1} within 10 minutes of intranasal and sublingual administration of 0.1 mg kg^{-1} midazolam [12]. They explained this rapid increase in plasma concentration by the very effective mucosal absorption of the drug. The proposed therapeutic plasma threshold concentration for 'sedation' with midazolam is 40 ng ml^{-1}.

Sedation and Anxiolysis will be measured before the drug administration and thereafter every 3 minutes. Sedation will be assessed by using a four-point scale: 1 = Alert / Active, 2 = Awake / Calm, 3 = Drowsy but responds readily to verbal commands, light touch, 4 = Asleep.

Anxiolysis will be assessed using four-point scale: 1 = Tearful/Combative, 2 = Anxious but easily reassured, 3 = Calm, 4 = Asleep. A score of 2 or 3 will be considered to indicate adequate 'conscious sedation' and anxiolysis.

Materials and methods

This prospective clinical study was conducted after obtaining approval from institutional ethical committee and was carried out in the Department of Anesthesiology with collaboration of the Department of Pediatric Surgery over a period 2 years from January 2006 to December 2007.Children aged 1 – 6 years scheduled for routine elective surgery and were planned to receive midazolam as premedicant drug were the study population. The eligibility criteria of the patients are ASA physical grade I and II,emergency operation,routine use of sedative or hypnotics in the month before study,enrollment in a drug study in the preceding 6 months,genetic or central nervous system abnormalities, known hypersensitivity to benzodiazepines, upper respiratory tract infection. A total of 120 sample patients were selected as per inclusion criteria because of limitation of data collection period and unavailable of patient, by using Simple Random Sampling by allocating Cards. The required number of patients was consecutively included in the study and were randomly assigned to either 0.2 $mg.kg^{-1}$ intranasal or 0.2 $mg.kg^{-1}$ sublingual groups as follows. For random allocation of patients into groups there were 2 cards. One card was marked with 'A' and another marked with 'B', Patients with above mentioned criteria consented for participating in the study were asked to draw a card blindly. Patients who drew cards marked 'A' were allocated into Intranasal Group who received 0.2 $mg.kg^{-1}$ midazolam and patients with cards marked 'B' were allocated into Sublingual Group who received 0.2 $mg.kg^{-1}$ midazolam. The demographic variables included in the study were age, sex and body weight. The baseline haemodynamic variables were pulse (Autocorr : Model no -3304 pulse oxymeter) systolic blood pressure (ALPK2 Aneroid sphygmomanometer

with pediatric cuff), SpO_2 (Autocorr : Model no-3304 pulse oxymeter). The sedation and anxiolytic scores before midazolam premedication (Baseline) were also recorded. The same variables were measured at every 3 minutes intervals upto 20 minutes from midazolam administration. Keeping compliance with Helsinki Declaration for Medical Research Involving Human Subjects 1964, parents of the study subjects were informed verbally about the study design, the purpose of the study, and right for withdrawing their children from the project at any time, for any reason, what so ever. Parents who gave informed consent to allow their children to participate in the study were included as study sample (Appendix –V). A structured data collection form was developed containing all the variables of interest which was finalized following pretesting (Appendix-IV). Data were collected by interview, observation and clinical examination. On the day of operation patients were first taken to the preoperative room. A pulse oximeter probe (Autocorr : Model no - 3304 pulse oxymeter) was placed on all children and SpO_2 and pulse rate were recorded before premedication with midazolam. Systolic blood pressure (ALPK2 Aneroid sphygmomanometer with pediatric cuff) sedation and anxiolysis scores were also recorded. Pareneteral formulation of midazolam 5 mg/ml (Dormicum Roche pharma) was used in both intranasal and sublingual groups. In patients of intranasal group, 0.2 mg/kg body-wt was instilled through the anterior nares of the patients by dropper while they were in the laps of their parents. In case of sublingual group the same dose was given sublingually mixed with 0.4ml of liquid saccharine while they were in the laps of their parents. Resuscitative equipment was immediately available at the bedside to deal with emergencies.

Sedation and anxiolysis were measured before the drug administration and thereafter every 3 minute intervals upto 20 minutes. Sedation was assessed by using a four-point scale: 1 = Alert/Active, 2 = awake/Calm, 3 = drowsy but responds rapidly to verbal commands, light touch, 4 = asleep. anxiolysis was also assessed using a four-point scale, where 1 = tearful/combative, 2 = anxious but easily reassured, 3 = calm, 4 = asleep. A score of 2 or 3 were considered to indicate adequate 'conscious sedation' and anxiolysis (Levine et al 1993). Data were processed and analysed using SPSS (Statistical Package for Social Sciences). The test statistics used to analyse the data were descriptive statistics, Student's t-Test and repeated measure. 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

A total of 120 children scheduled for routine elective surgery under general anesthesia and were planned to receive midazolam as premedicant drug were allocated randomly into two groups – intranasal group (Receiving midazolam intranasally) and sublingual group (Receiving midazolam sublingually). To observe any changes in haemodynamic state, haemodynamic parameters of the two groups were recorded before premedication with midazolam and at every 3 minutes following administration of the drug until the child achieved a level 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. The findings derived from the data analysis are documented below.

Demographic Characteristics of the Patients

Table I demonstrates that 4 – 6 years age category was somewhat higher in the sublingual group compared to intranasal group with mean age of intranasal and sublingual and groups being 3.7 ± 1.5 years and 4.0 ± 1.8 years respectively (p=0.205). There was no significant difference between the groups in terms of sex (p = 0.490).

Table I : Demographic characteristics between two groups

Demographic characteristics	Group		p-value
	Intranasal (n = 60)	Sublingual (n = 60)	
Age (Years)			
1 – 2	7(11.7)	9(15.0)	
2 – 4	23(38.3)	14(23.3)	0.205
4 – 6	30(50.0)	37(61.7)	
Mean ± SD	3.7 ± 1.5	4.0 ± 1.8	
Sex (Male/Female)	37/23	43/17	0.490

Figures in the parenthesis denote corresponding %, χ^2 Test was employed to analyse the data.

Table II : Pulse rate at different time interval between groups

Pulse/minute	Group		
	Sublingual (n = 60)	Intranasal (n = 60)	p-value#
At baseline	106 ± 11	106 ± 12	0.810
At 3 minutes	104 ± 16	106 ± 12	0.450
At 6 minutes	105 ± 11	106 ± 12	0.788
At 9 minutes	105 ± 11	106 ± 13	0.970
At 12 minutes	104 ± 10	103 ± 12	0.694
At 15 minutes	102 ± 10	101 ± 11	0.857
At 18 minutes	101 ± 10	101 ± 12	0.994

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

The pulse rate of the two groups was maintained within normal range throughout the observation period and there was no significant difference between the groups at any level of evaluation (Table II) ($p > 0.05$).

Table III : SBP at different time interval between groups

Systolic blood pressure (mmHg)	Group		
	Sublingual (n = 60)	Intranasal (n = 60)	p value
At baseline	86.0 ± 8.3	89.4 ± 8.8	0.032
At 3 minutes	86.4 ± 8.4	89.9 ± 10.4	0.034
At 6 minutes	85.5 ± 6.7	88.5 ± 7.9	0.037
At 9 minutes	84.9 ± 6.2	88.1 ± 8.0	0.016
At 12 minutes	83.5 ± 5.9	87.5 ± 9.6	0.008
At 15 minutes	82.3 ± 6.6	85.6 ± 10.7	0.038
At 18 minutes	81.5 ± 6.5	85.5 ± 9.7	0.010

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

The difference in systolic blood pressures between two groups at each level of evaluation throughout the observation period was evident ($p < 0.05$) (Table III).

Table IV : SpO_2 at different time intervals between groups

SpO_2 (minute)	Group		
	Sublingual (n = 60)	Intranasal (n = 60)	o value
At baseline	97.35 ± 1.05	97.33 ± 0.95	0.928
At 3 minute	97.38 ± 0.92	97.37 ± 0.88	0.920
At 6 minute	97.97 ± 2.89	97.17 ± 0.76	0.606
At 9 minutes	96.43 ± 8.93	97.20 ± 1.57	0.514
At 12 minutes	97.40 ± 1.14	97.18 ± 1.13	0.297
At 15 minutes	97.23 ± 1.48	97.02 ± 0.98	0.346
At 18 minutes	96.84 ± 1.20	96.94 ± 0.76	0.587

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

The difference between the two groups, in terms of SpO_2 at every level of evaluation was negligible ($p = .0.928$, $p = 0.920$, $p = 0.606$, $p = 0.514$, $p = 0.297$,
$p = 0.346$ and $p = 0.587$ respectively) (Table IV).

Table V : Sedation score at different time interval between groups

Sedation score	Group		
	Sublingual (n = 60)	Intranasal (n = 60)	p value
At baseline	1 ± 0	1 ± 0	Not computable
At 3 minute	1 ± 0	1 ± 0	Not computable
At 6 minute	1.13 ± 0.34	1.13 ± 0.34	Not computable
At 9 minutes	1.60 ± 0.49	1.37 ± 0.49	0.010
At12 minutes	1.98 ± 0.22	1.68 ± 0.47	< 0.001
At 15 minutes	2.15 ± 0.40	1.90 ± 0.40	0.001
At 18 minutes	2.34 ± 0.51	1.98 ± 0.40	< 0.001

Data were analysed using Student's t-Test and were presented as mean ± SD.
The sublingual group exhibited a good level of sedation score much earlier than its intranasal counterpart. The mean sedation scores at 9, 12 15 and 18 minutes of observation were also significantly higher in the former group than those in the latter group (1.60 ± 0.49 vs. 1.37 ± 0.49, $p = 0.010$, 1.98 ± 0.22 vs. 1.68 ± 0.47, $p < 0.001$, 2.15 ± 0.40 vs. 1.90 ± 0.40, $p = 0.001$ and 2.34 ± 0.51 vs. 1.98 ± 0.40, $p < 0.001$ respectively) (Table V).

Table VI : Anxiolysis score at different time interval between groups

Anxiolysis score	Group		
	Sublingual (n = 60)	Intranasal (n = 60)	p-value
At baseline	1.07 ± 0.36	1.03 ± 0.26	0.563
At 3 minutes	1 ± 0	1 ± 0	------
At 6 minutes	1.53 ± 0.50	1.30 ± 0.46	0.009
At 9 minutes	2.07 ± 0.36	1.37 ± 0.58	< 0.001
At 12 minutes	2.48 ± 0.50	2.15 ± 0.55	0.001
At 15 minutes	3.00 ± 0.41	2.75 ± 0.44	0.002
At 18 minutes	3.23 ± 0.43	3.07 ± 0.25	0.010

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

The levels of anxiolysis attained by the sublingual group at 6, 9, 12, 15, and 18 minutes intervals were significantly higher compared to those attained by the intranasal group (1.53 ± 0.50 vs. 1.30 ± 0.46, p = 0.009; 2.07 ± 0.36 vs. 1.37 ± 0.58, p < 0.001; 2.48 ± 0.50 vs. 2.15 ± 0.55, p = 0.001, 3.00 ± 0.41 vs. 2.75 ± 0.44, p = 0.002 and 3.23 ± 0.43 vs. 3.07 ± 0.25, p = 0.010 respectively) (Table VI).

Smooth Separation of Children from Their Parents

Fig 1 demonstrates the time at which the children were smoothly separated from their parents following midazolam administration. In sublingual group 10% of the children were separated at 9 minutes, 35% at 12 minutes, 45% at 15 minutes and 10% at 18 minutes. In the intranasal group 6.7% were separated at 9 minutes, 16.7% at 12 minutes, 51.6% at 15 minutes and 25% at 18 minutes. Thus a total of 90% children in the sublingual group and 75% in the intranasal group were separated within 15 minutes. The most noted finding was that all the children in both the groups were feasible to be separated within 18 minutes after midazolam administration. However, the sublingual group ensured a significantly faster separation (45% were separated within 12 minutes) compared to the intranasal group (23.4% were separated within 12 minutes) (p = 0.038).

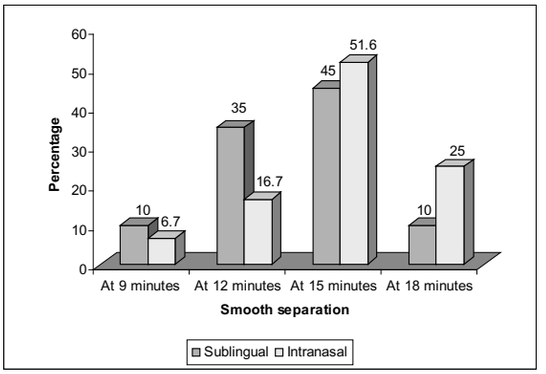

Figure 1 : Smooth separation of children from their parents

Comparison of Better Option Between Two Routes

Fig 2 shows that nearly half (46.7%) of the intranasal group cried following midazolam administration compared to only 23.3% of the sublingual group suggesting that the intranasal midazolam causes significant irritation.

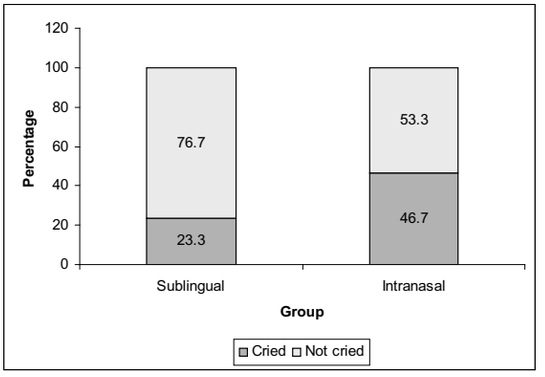

Figure 2 : Comparison of better option between two routes

Discussion

The results of the current study demonstrated no change in sedation score in either intranasal or sublingual group in first 6 minutes following midazolam premedication. From 6 minutes onwards it began increasing steadily up to the end of observation when sublingual group assumed a mean sedation score of 2.34 ± 0.51 and intranasal group a mean score of 1.98 ± 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%) The intranasal route provided a faster effect compared to sublingual, oral 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 sublingual, oral and rectal group. However, Karl et al (1993) reported that intranasal or sublingual midazolam provides maximal sedation and anxiolysis within 10 min after administration. In the present study sublingual group exhibited a good level of sedation and anxiolysis scores much earlier than its intranasal 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 the children in both the groups were feasible to be separated within 18 minutes after midazolam administration, the sublingual group augmented a significantly faster separation (45% within 12 minutes) as opposed to the intranasal group (23.4% within 12 minutes) ($p = 0.038$). Helen et al (1993) compared nasal and sublingual routes of midazolam in paediatric patients and found sublingual route more acceptable to children. Naqash et al (2004) in a similar study reported that sedation score of > 3 was achieved in both the groups within 10 minutes of drug administration, but the frequency was quite high in sublingual group (80%) as compared to intranasal group (60%). (Geldner et al; 1997) and his associates compared the levels of sedation and anxiolysis following midazolam administration through intranasal, sublingual and rectal routes. Plasma levels of midazolam were investigated at 10, 30 and 60 minutes after premedication. In all three groups the plasma levels of midazolam 10 minutes after premedication were higher than 70 ng/ml, considered as a reliable level for good sedation. However, 30 minutes after premedication, the midazolam level in the sublingual group was significantly higher than those in other two groups. Although the total buccal and submucosal area is small and has a pH of 6.2 – 7.4, the potential exists for rapid absorption of drugs since these areas are rich in blood and lymphatic vessels. The drug directly passes into the systemic circulation avoiding the first pass metabolism of the drug (Lim et al 1997). The lower incidence of adequate sedation with intranasal route as observed in our study also could be attributed to the shorter stay time of the drug in the nasal mucosal surface as suggested by Walberg et al (1991) however, 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 drug. 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 as well. In a study evaluating the intranasal and the sublingual routes of midazolam administration in children, Karl et al (1992) noted that the intranasal and sublingual routes were associated with crying in 71% and 18% of the children respectively. Naqash et al (2004) conducted a study similar to the present study and reported that 63% of the children in intranasal group and 16% in the sublingual group cried following midazolam administration. In the present study also the incidence of crying was double in the intranasal group (46.7%) than that observed in the sublingual group (23.3%). The incidence of crying in response to drug administration is though considered as an indication of acceptance of the route of administration in children, Gharde's (2005) study did not support the hypothesis because in his study the parents administered the drugs and very few children were observed to cry following administration of the drug.

Intranasal drugs have been employed primarily in paediatric patients as a means of circumventing the need for injections or bitter tasting oral drugs in children especially in unwilling patients (Kain et al, 1996, Wilton et al 1988 and Saint-Maurice et al 1990)

As a noninvasive technique, both sublingual and intranasal administration have none of the potential side effects and complications like nerve injury, inadvertent intravenous or arterial injection and infection that are associated with intramuscular drug administration (Hanson et al 1963). Absorption of drugs through these routes occurs directly into the central circulation, bypassing the enterohepatic circulation. (Sarkar et al 1992)

Intranasal administration of midazolam has been shown to have a higher bioavailability and shorter onset of actions. (Rey et al 1991, Walbergh et al 1991, Delaenay et al 1991) than has oral or rectal route.

Many published reports on premedication have produced approximately the same results; almost all sedatives are effective (McGarry 1970). The important issue is effectiveness for individual anaesthesiologists at their own institutions. The need for premedication must be individualized according to the underlying medical conditions, the length of surgery, the desired induction of anaethesia and the psychological makeup of the child and family. A premedication normally is not necessary for the usual 6-month-old child but is warranted for the 10 to 12 month-old who is afraid to be separated from the parents.

Premedications may be administered orally, intramuscularly, intravenously, recently, sublingually or nasally. Although most of these routes are effective and reliable, each has drawbacks as well. Intranasal route, though is fairly comparable to sublingual route in terms of efficacy of midazolam, it is mostly irritating which we have already seen in the present study. If we need faster and smooth separation of children from their parents' sublingual route could be used.

Conclusion

The major objectives of a preanaesthetic medication of midazolam given to children are to alleviate anxiety and facilitate smooth separation from their parents at the level of conscious sedation. Both sublingual and intranasal routes of administration of midazolam fulfills these criteria. Sublingual route provided satisfactory, rapidly acting and keep their conscious sedation level earlier and make them calm and quite. Intranasal route causes nasal irritation, patients crying and lower incidence of sedation and anxiolysis.

So, we conclude that sublingual midazolam preanaesthetic medication is earlier, easily manageable and better option for smooth separation from their parents before entering the operation room.

Disclosure

All the authors declared no competing interest.

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