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Original Article

Anaesthesia Section

Midazolam Pre-medication in Paediatrics: Comparison of the Intranasal and Sublingual Routes by Using an Atomizer Spray

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ABSTRACT

Introduction: Most of the children suffer from severe anxiety and apprehension when they are separated from their parents or family members for the induction of anaesthesia.

Materials and Methods: In a prospective randomized double blind study, the intra-nasal and sub-lingual administration of midazolam in paediatric patients who were undergoing root canal procedures which required general anaesthesia was evaluated in 60 children who were aged between 2-6 years, with ASA physical status I and II by using a new midazolam atomiser spray. The patients were divided into two groups of 30 patients each and they received midazolam 0.3mgkg-1 either intranasally or sub-lingually in a randomized manner. The heart rate, oxygen saturation (spo2), respiratory rate and the degree of sedation before and at 5 min, 10 min and 15 min (separation score) after the drug administration, during the mask application (mask acceptance score), before induction (induction score) and during the recovery at 10 min, 20min and 30mins (recovery score) were recorded and compared.

Results: In our study, 60% of the paediatric patients cried during the administration of midazolam by the intra-nasal route, while only 16% of the paediatric patients cried during its administration by the sub-lingual route. A bitter taste was observed in 45% (14/30) of the patients who received midazolam by the sub-lingual route. Although there was a slight increase in the heart rate in the intra-nasal group, no statistically significant variation in the heart rate, the respiratory rate and the oxygen saturation was found from the baseline in both the groups (P>0.05). A sedation score of >3(approx) was achieved in both the groups within 10 minutes of the drug administration. The response to the child parent separation, the mask application score , the induction score and the recovery score did not differ significantly between the two groups (P >0.05).

Conclusion: Both the intra-nasal and sub-lingual administration of midazolam as a Pre-medication is safe and equally effective in paediatric patients.

Key Words: Pre-medication, Paediatrics, Intra-nasal, Sub-lingual, Midazolam Atomiser spray

INTRODUCTION

Most of the children suffer from severe anxiety and apprehension when they are separated from their parents or family members for the induction of anaesthesia [1]. The unfamiliar faces and the environment inside the operating room compound a sense of insecurity in the children [2]. Thus, pre-operative anxiety can largely affect the smoothness of the induction, the emergence from anaesthesia and also the psychological and emotional state of the children in the remote future [3]. Maladaptive behavioural response such as general anxiety, nighttime crying, enuresis and separation anxiety occur in up to 44% of the children, two weeks after the operation. Twenty percent of these children will continue to demonstrate a negative behaviour even 6 months after the surgery [3].

Although non-pharmacological means in the form of friendly visits by the anaesthesiologist to establish a rapport with the children and briefing about the procedure whenever feasible help to minimize the children's anxiety, pharmacological agents are often helpful to provide sedation and to promote a smooth induction. Even parental presence inside the operation theatre may not be fully effective. Sedative Pre-medication may be more effective in this regards [4].

Sedative Pre-medications can be administered orally, intra-muscularly, intravenously, rectally, sub-lingually or nasally. Although most of these routes are effective and reliable, each has drawbacks. Oral or sub-lingual Pre-medication do not hurt, but they may have a slow onset or may be spit out and drug taste is the main determinant for the success of their administration.

Intra-muscular medications may hurt and may result in a sterile abscess. Intravenous medications may be painful during injection or at the start of the infusion. Rectal medications may sometimes make the children feel uncomfortable and they may cause defecation, and occasionally burns. Nasal medications can be irritating, although their absorption is rapid.

The ideal agent should have a rapid onset, a predictable duration and a rapid recovery. There are many drugs which are used for pre-medicating children. Ketamine, clonidine, fentanyl, buprenprphine and midazolam are the ones which are most commonly used in the clinical practice.

We used a new midazolam atomiser spray. In this spray, the drug is delivered in puffs which contain very minute particles which spread over a large surface area. The present study was designed to compare the safety, the acceptability and the degree of sedation which was produced by intra-nasal and sub-lingual midazolam as a pre-anaesthetic medication in paediatric patients who were undergoing elective dental procedures under general anaesthesia.

MATERIALS AND METHODS

After obtaining written and informed consent from the parents, sixty ASA I and II children who were aged between 4-10 years and were scheduled for elective surgical procedures under general anaesthesia were enrolled in the study. Children with respiratory and cardiac diseases or those who had upper respiratory tract infections were excluded from the study. All the patients were brought to the reception area of the operation theatre complex along with their parents and were randomly allocated to one of the two groups of 30 patients each. Group I (the sub-lingual group) received midazolam 0.3mgkg-1. The children were asked to touch their upper teeth with the tip of their tongues and then, the midazolam atomizer was sprayed beneath the tongue, while not permitting the children to swallow the drug for 20 seconds. In group II (the intra-nasal group), the midazolam 0.3mgkg-1 atomizer was sprayed in both the nostrils with the children in a semi-recumbent position or in a parent's lap. To avoid interobserver variations, the same anaesthesiologist was involved in all the assessments, who was also kept blind to the route of administration which was used by the attending nurse. The patient's responses to the drug administration were noted. The heart rate, respiratory rate and oxygen saturation rate were recorded before and at 5 and 10 minutes after the administration of the drug. The degree of sedation also was assessed at 0.5 and 10 minutes after the drug administration, by using a 5 point sedation scale, as shown in [Table/Fig-1a]. At 15 minutes, the children were separated from their parents and were taken to the operating room. The responses to the child parent separation were assessed by using a separation score and they were graded according to a 4 point separation score as was used by Davis et al [Table/Fig-1b] [5].

By using a five-point sedation scale, the degree of sedation was assessed.	
1.	Agitated: Patient was clinging to the parents and/or crying.
2.	Alert: Patient was aware but was not clinging to the parents; might have whimpered but had not cried.
3.	Calm: Sitting or lying comfortably, with spontaneous eye opening.
4.	Drowsy: Sitting or lying comfortably with eyes closed, but responding to minor stimulation.
5.	Asleep: Eyes closed, arousable, but did not respond to minor stimulations.

[Table/Fig-1a]: Sedation Scale

A sedation score of 3 and above was considered as satisfactory, and a score of 1 and 2 as unsatisfactory.

1.	Excellent: Patient unafraid, co-operative, asleep
2.	Good: Slight fear, crying, quiet with reassurance
3.	Fair: Moderate fear, crying, not quiet with reassurance
4.	Poor: Crying, need for restraint

[Table/Fig-1b]: Seperation and Induction Scale

Scores 1 and 2 were considered as satisfactory and scores 3 and 4 as unsatisfactory.

The intravenous line was accessed. The patients were pre-medicated with glycopyrrolae 0.008mg/kg and tramadol 1mg/kg intravenously. Just before induction, the sedation was assessed by using an induction score. The patient was induced with oxygen (O2), nitrous oxide (N2O) and halothane by using a facemask. The response to the mask was assessed by using a mask acceptance scale [Table/Fig-2].

1.	Agitated: Previous criteria and/or refuses mask.
2.	Alert: Previous criteria and/or initially refuses mask
3.	Calm: Previous criteria and accepts mask.
4.	Drowsy : Previous criteria and accepts mask.
5.	Asleep : Previous criteria and accepts mask

[Table/Fig-2]: Mask Acceptance Score (Based on the sedation scale)

Thus, if a patient was drowsy but refused mask induction, then the patient was recorded to have score 1 and not 4. Scores 1 and 2 were considered as unatisfactory and score 3 and above as satisfactory.

The induction score was assessed in the children just before the induction of anaesthesia. Nasotracheal intubation was facilitated by using suxamethonium 2mg/kg i.v. Anaesthesia was maintained by using oxygen, nitrous oxide, halothane 0.5 to 1% and atracurium. The ventilation was controlled by using Jackson Ree's modification of Ayre's T-piece. The patients were reversed by using neostigmine 0.08mg/kg and glycopyrrolate 0.016mg /kg. Extubation was done after the children were fully awake.

The post-operative sedation was assessed in the post anaesthesia recovery unit (PACU) at ten min intervals for thirty min by using a ten point recovery scale which assessed the patient's colour, airway, respiration, the level of consciousness and movement (each on a scale of 0-2) to give a maximum cumulative total of 10.

Side effects were noted in both the groups, if any. The data was compiled and analyzed statistically by using the Student's 't' test and a 'p'-value of <0.05 was considered as significant. All the scores in our study were analyzed by using the Student's t test and the sex ratio was analyzed by using the Chi-Square test. The software which was used for the statistical analysis was "Trimer of Boistatistics".

RESULTS

The groups were comparable with respect to age, gender and weight [Table/Fig-3] There was no statistically significant difference in the heart rate, the respiratory rate and the oxygen saturation between the two groups before the administration of the drug (p>0.05). 18(60%) children in the intra-nasal group cried in response to the drug administration, as compared to only 5(16.6%) children in the sub-lingual group. This difference between the two groups was statistically highly significant [p<0.001].

Adequate oxygen saturation (>95%) was maintained in all the children in both the groups throughout the study. Changes in the heart rate, respiratory rate and the sedation score after the administration of the drug in the two groups are shown in [Table/Fig-4]. A slight increase in the heart rate was observed in the intra-nasal group after the drug administration as compared to that in the sub-lingual group, but there was no statistically significant variation in the heart rate and the respiratory rate in both the groups when they were compared to the baseline values [p>0.05]. After 10 minutes of drug administration, a sedation score of more than 3 was achieved in 80% of the children in the sub-lingual group, as compared to 82% children in the intra-nasal group, which was statistically significant (p<0.05). Similarly, a satisfactory child parent separation score was observed in 85% and 89% children in the intra-nasal and the sub-lingual groups respectively, whereas the response before induction (the induction score) was also satisfactory in more than 90% of the children in both the groups. The response to the mask application, as was assessed by using

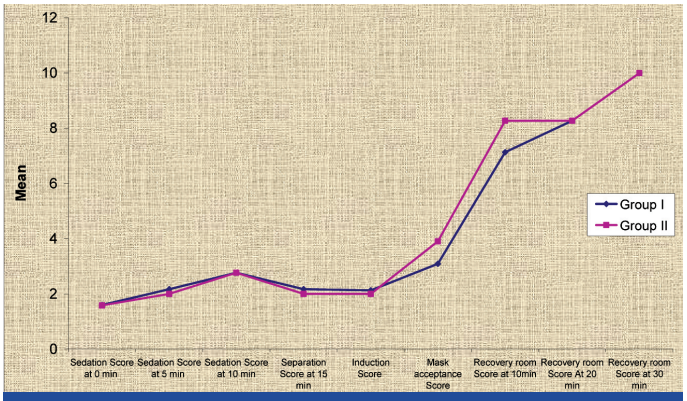
the mask acceptance score, was satisfactory in both the groups. The recovery room score was also comparable in both the groups. No statistically significant difference was noted in both the groups. [Table/Fig-4].

	Group I	GroupII	P value	Significance
Age (in years)	3.57± 0.691	3.72 ±0.759	0.45	N.S
Weight (in kg)	11.83 ±2.267	11.85± 2.508	0.92	N.S
Sex ratio	45:55	45:55	*	*

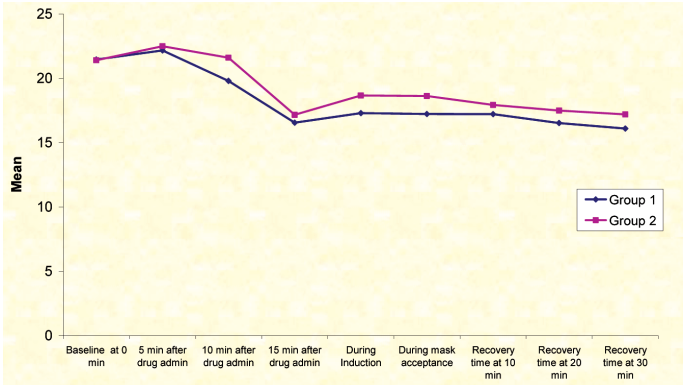
[Table/Fig-3]: Demographic variables in the two groups

	Group I	Group II	P value	Significance
Sedation score at 0 min	1.60 ± 0.498	1.58 ± 0.497	0.79	N.S
Sedation score at 5 min	2.17 ± 0.747	2.10 ± 0.695	0.37	N.S
Sedation score at 10 min	2.766 ± 0.568	2.765 ± 0.819	0.27	N.S
Seperation score	2.17 ± 0.747	2.00 ± 0.693	0.38	N.S
Induction Score	2.13 ± 0.895	2.00 ± 0.691	0.49	N.S
Mask accep score	3.09 ± 0.849	3.90 ± 0.810	1.0	N.S
Recovery score at 10min	7.13 ± 0.430	8.27 ± 0.346	0.32	N.S
Recovery score at 20 min	8.27± 0.450	8.27 ± 0.521	1.0	N.S
Recovery score at 30min	10.00 ± 0.0	10.00 ± 0.0	1.0	N.S
Cry after drug admin	0.2± 0.406	0.6 ± 0.498	0.01	S.S
Bitter Taste	0.5 ± 0.508	0.0 ± 0.000	0.001	S.S

[Table/Fig-4]: Comparison of various scored in Group I and Group II Values are expressed as mean ± SD.



[Table/Fig-5]: Comparison of various scores in the Group 1 and Group II



[Table/Fig-6]: Comparison of respiratory rate at various intervals (Mean) in Group 1 and Group II

DISCUSSION

Pre-anaesthetic medication in children is an important adjunct to help in alleviating the stress and the fear of surgery, as well as to case the child parent separation and to promote a smooth induction of anaesthesia.

Midazolam, as a potent imidazo-benzodiazepine, has got all the required properties, namely sedative, hypnotic and anxiolytic activities. Midazolam is used for pre-operative sedation by the intra-muscular (IM) [6,7,8], rectal [9,10], oral [11] and the sub-lingual routes [12,13], but each route has its own advantages and disadvantages.

The use of intra-nasal or sub-lingual midazolam as a Pre-medication has come into practice right from the early nineties[14,15] Intra-nasal midazolam, in this regards, has got some advantage. Owing to its high mucosal vascularity, the intra-nasal route offers a rapid and virtually complete absorption within one-two hours into the systemic circulation [16]. As midazolam has high hepatic clearance, the avoidance of the hepatic first pass metabolism offers greater systemic bioavailability [14,15,16]. It has a faster onset than the oral or the rectal route. The recovery from anaesthesia is also not affected even after minor surgeries.

Although sedation was achieved with 0.2mg/kg midazolam intra-nasally, the sedation by the sub-lingual route of the same dose was inadequate (there were chances of partly swallowing it). Thus, a dose of 0.3 mg/kg was selected for both the routes to make it comparable.

The heart rate and the respiratory rate in both the groups remained stable and they did not show any significant variation from the baseline values in our study. These findings indicated the safety of midazolam which was given by either route and in the doses which were studied. Minor respiratory depression was observed by Fukuta et al [17] with 0.2mgkg-1 of intra-nasal midazolam. Similarly, Malinovsky et al [18] reported a case of respiratory depression in a 30 month old child which was given intra-nasal midazolam, attributing that to the ethmoidal passage of the drug which resulted in high CSF levels. In many studies, it was noted that the oxygen saturation remained above 95% in a majority of the cases which were pre-medicated with transmucosal midazolam. This was confirmed in our study also, where the oxygen saturation was maintained above 95% in all the children, irrespective of whether they were pre-medicated by the nasal or the sub-lingual route. However, the desaturation to less than 93% with 0.2mgkg-1 of intra-nasal midazolam, which was noted by Karl et al [19] in a small percentage of children, suggested close respiratory monitoring and the availability of resuscitation equipment when the intra-nasal route was used.

Adequate sedation (score>3) after 10 minutes of drug administration, which was noted in a majority of the children in the sub-lingual group as compared to the intra-nasal group in our study, was in concordance with the findings of many studies, including the study of Karl et al [19]. Karl et al noted that at the point of maximum anxiolysis, that is, at 10 minutes after the administration, midazolam, by the sub-lingual route, had produced a significant decrease in the apparent anxiety in a majority of the patients. Although the total buccal and sub-lingual area is small and it has a pH of 6.2-7.4, it has a potential for the rapid absorption of drugs, since these areas are rich in blood and lymphatic vessels. The drug directly passes into the systemic circulation and thus the first pass metabolism of the drug can be avoided. The lower incidence of

adequate sedation through the intra-nasal route, as was observed in our study, also could be attributed to the shorter stay time of the drug in the nasal mucosal surface as was suggested by DeBoer et al [20] Since a majority of the children in our study were calm and relaxed (score>3), the child parent separation and the induction scores were satisfactory in both the groups.

In our study, the separation score between the two groups was not statistically significant and there was no major side effect in any group. Nasal irritation and crying was found in 56% of the patients in group I immediately after the drug administration. A bitter taste was reported in 50% of the patients in group II. The increased incidence of crying with respect to the nasal route has been attributed by these authors [12] to the low pH of midazolam (pH 3.3), which causes burning or irritation of the nasal mucosa on administration.

CONCLUSION

Thus, we conclude that both the intra-nasal and the sub-lingual routes of administration of midazolam are equally effective and that they provide adequate sedation for the easy separation of children from their parents and the co-operation from children during the induction of anaesthesia. So, we recommend the routine use of both the intra-nasal and sub-lingual midazolam atomizers as a pre-anaesthetic medication in paediatric patients who undergo dental procedures under general anaesthesia. However, its use in all the paediatric surgeries needs further evaluation.

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