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The effect of nasal midazolam premedication on parents-child separation and recovery time in dental procedures under general anaesthesia

ABSTRACT

Aim *For many children medical and dental procedures, unfamiliar dental staff and treatment places are disturbing and stressful. Stress in children often makes them uncooperative. General anaesthesia is indicated for anxious uncooperative children or those who are disabled, immature or too young to undergo dental treatment by other means. Moreover parents' separation while entering the operative room is a traumatic experience for children. Thus premedication such as midazolam is recommended to decrease child's stress. In these situations the increased recovery time was considered as one of the midazolam side effects. There is no study that evaluated the effect of midazolam both in parents-child separation and recovery time in long dental procedure. The purpose of this study was to evaluate the effect of nasal midazolam premedication with placebo on parents-child separation and recovery times in uncooperative paediatric patients undergoing long-lasting general anaesthesia for dental procedures.*

Materials and methods *Study design: This randomised, double-blind study was done on 60 uncooperative patients (ASA physical status I or II) aged 2-4 years who were scheduled for general anaesthesia for dental treatment. Group A received 0.2 mg/kg intranasal midazolam as premedication, and group B received the same volume of intranasal placebo 20 minutes before entering the operating room for general anaesthesia. General anaesthesia was done with the same method for all patients, then parent-child separation and recovery times were compared between the two groups. Statistical analysis: Statical significance was set at P≤0.05. Statically analysis was performed using SPSS version17.Chi-squared and student t-tests were applied to analyse the data.*

Results *We found significant differences in parents-child separation assessment between two groups. Nasal midazolam premedication had a positive effect on parents-child separation; but there was no significant difference between the two groups in terms of recovery time.*

Conclusion *Premedication of nasal midazolam before induction of general anaesthesia did not prolong recovery time but made the separation of children from their parents easier by showing a better behaviour.*

Keywords *Nasal midazolam; Premedication; Recovery time; Separation.*

Introduction

Dental treatment in uncooperative paediatric patients may be a difficult situation for both the child and dentist [Tavassoli-Hojjati et al., 2014; al-Rakaf et al., 2001]. One of the methods to solve this problem is general anaesthesia. This method is now available to treat children who are very young, disabled, anxious, or too immature to undergo dental treatment by other means [Hosey et al., 2009; Macpherson et al., 2005]. Fears of unfamiliar medical environment, where children are separated from their parents, before general anaesthesia, usually is a traumatic experience for paediatric patients [Baldwa et al., 2012; Beeby and Hughes, 1980]. Planning a procedure to easily overcome this stage would be pleasant for the children [Verma et al., 2012]. Premedication prior to general anaesthesia may reduce the adverse psychological and physiological sequelae of separation from parents and side effects related to the induction of anaesthesia in a distressed child [Baldwa et al., 2012]. Midazolam is often used as a premedication prior to stressful medical procedures requiring general anaesthesia [Richardson et al., 1997].

Midazolam is used in intravenous, intramuscular, oral, rectal and nasal routes. Although the intravenous

route is the most effective one, it is not recommended for young children. Oral and rectal routes are indicated in cooperative patient [Kupietzky and Houpt, 1993].

The intranasal administration of midazolam as noninvasive with good bioavailability [Baldwa et al., 2012], and it has been found safe and feasible in numerous clinical studies [Klein-Kremer and Goldman, 2007; Wolfe and Macfarlane, 2006; Harbord et al., 2004; Ahmad et al., 2006; Scott et al., 1999]. Ayurvedic practitioners believe that "the nose is the door to the brain" [Klein-Kremer and Goldman, 2007]. The hypervascularity and large surface [180 cm^2], of nasal mucosa and neighboring olfactory mucosa, produce a direct pathway for drug absorption into the blood and cerebrospinal fluid. Therefore, the nasal route is a good method for administration of medication [Klein-Kremer and Goldman, 2007]. In this technique, first reported by Wilton et al. [1988]. In theory midazolam premedication can cause postoperative sedation and delays the recovery time after general anaesthesia [Horgesheimer et al., 2001]. To the best of our knowledge, there is no study that evaluated the concomitant effect of midazolam both in parents-child separation and recovery time in long dental procedure.

The purpose of this study was to evaluate the effect of nasal midazolam premedication on parent-child separation and recovery time in long dental procedures under general anaesthesia in uncooperative children.

Materials and methods

This randomised, double-blind study was done on 60 uncooperative patients (ASA physical status I or II) aged 2-4 years who were scheduled for general anaesthesia for their elective dental treatment. The children were allocated randomly into two groups: Group A received 0.2 mg/kg intranasal midazolam as preanaesthetic medication, and group B received the same volume of intranasal normal saline solution before general anaesthesia about 20 minutes before entering the operating room. To prepare midazolam as intranasal preanaesthetic medication a 10-ml syringe was used, where 1ml of 5mg/ml of midazolam ampoule was diluted with 4 cc of normal saline solution. This diluted form of midazolam (containing 1 mg of midazolam in each ml) was used for the study. After obtaining the approval from the Institutional Ethics Committee and informed written consent from the parents, the measured amount of midazolam or normal saline (based on the allocated group) was dropped equally into the child's nose, meanwhile the mother held the child in her lap, trying to keep her/him quiet and still.

All investigators, medical staff, assistants and parents were blinded to the drug administered. All children were separated from their parents into the operating room by the same assistant. Each child's behaviour at the time of separation was documented and scored based on a four-point separation score (Table 1).

General anaesthesia was induced and maintained with the same method for both groups after placement of appropriate monitoring devices as follows: 2mg/kg of fentanil was first injected into IV line as premedication. General anaesthesia was then induced using IV thiopental (6 mg/kg). In order to facilitate endotracheal intubation, 0.5 mg/kg of atracurium was injected into the IV line. The general anaesthesia was maintained with propofol. The net duration of general anaesthesia was about 2-4 hours. All dental treatments were performed by the same dentist. At the end of the dental treatment the anaesthetic medications were discontinued immediately and the patients were taken in the recovery room. The criteria for discharge from recovery room are summarised in table 2. Patients with score higher than 9 had permission for disc harge from the recovery room.

Statistical analysis: Statical significance was set at

Criteria	Grade	Score
Patient unafraid, cooperative, asleep	Excellent	1
Slight fear or crying, quiet with reassurance	Good	2
Moderate crying, not quiet with reassurance	Fair	3
Crying, need for restraint	Poor	4

TABLE 1 Separation score.

Postanaesthesia Recovery Score (Modified Aldrete Score)	
Activity	2=Moves all extremities voluntarily/on command
	1=Moves two extremities
	0=Unable to move extremities
Respiration	2=Breathes deeply and coughs freely
	1=Dyspneic, shallow or limited breathing
	0=Apneic
Circulation	2=BP+ 20mm of preanesthetic level
	1=BP= 20-50 mm of preanesthetic level
	0=BP+ 50 mm of preanesthetic level
Consciousness	2=Fully awake
	1=Arousable on calling
	0=Not responding
Oxygen Saturation	2=Spo2 > 92% on room air
	1= Supplemental O2 required to maintain Spo2> 90%
	0=Spo2 <92% with O2 supplementation
	10=Total score
	Score > 9 required for discharge

TABLE 2 Post-anaesthesia recovery score.

P≤0.05. Statical analysis was performed using SPSS version 17 (SPSS Inc., Chicago, IL, USA). Chi-squared and Student t-tests were applied to analyse the data.

Results

A total of 60 patients were divided in two groups: 31 control patients and 29 in the midazolam study group (Table 3). The mean age of the 60 subjects was 37.88 months. The mean operative time for the control group was 178.25 minutes, and for midazolam group was 155.27 minutes (Table 3), while the mean recovery time for the control group was 27.25 minutes and for midazolam group was 28.25 minutes. We found significant differences in child-parents separation assessment between the two groups (P<0.001). As illustrated in Table 4, in the control group (B) 16.1% of patients had Excellent, 25.8% of patients had Good, 25.8, had Fair, and 32.3% of patients had Poor separation score. In the midazolam group (A) 55.2% had Excellent, 31% had Good, 10.3% had Fair and 3.4% had poor separation scare. The results showed that there were no significant differences in recovery time between the patients who received nasal midazolam and those in the control group (P>0.05).

The mean operative time for control group was longer than that of the midazolam group but there were no significant differences between the two groups in terms of recovery time.

Discussion

To the best of our knowledge, there are no previous studies conducted to assess the effects of nasal midazolam on recovery time in long dental procedures under general anaesthesia. Many researchers have been trying to find the best preanaesthetic medication [Verma et al., 2012; Davis et al., 1995; Bakhta et al., 2007; McMillan et al., 1992]. The premedication should be convenient to administer and well accepted by patients. Midazolam is a water-soluble benzodiazepine that is used in intravenous, intra muscle, oral , rectal and nasal routes [Kupietzky and Houpt, 1993]. Other authors [Davis et al., 1995; Verma et al., 2012] showed that the use of intranasal midazolam in doses of 0.2–0.3 mg/kg caused satisfactory parent-child separation and satisfactory ease of induction in 70% of patients and did not prolong recovery time. The result of our study was consistent with this research.

McMillan et al. [1992] studied the use of midazolam premedication in paediatric patients undergoing same day surgery in a randomised, placebo-controlled study. Sedation and anxiolysis scores were higher in midazolam treated groups, and anxiolysis at the time of separation from parents was reported excellent in 80%-90% of the children [Horgesheimer et al., 2001]. Child-parent separation score in the midazolam group was consistent with the result of the McMillan study. Baldwa et al. [2012] found that atomised intranasal midazolam premedication in children improved patient's behaviour when separated from their parents. The results of their study were in line with ours except for the route of medication administration.

The analysis of our study showed that the majority of children in group A could be easily separated from their parents, and although the mean operative time in the midazolam group was shorter than the control there were no significant difference in recovery time between the two groups.

Other investigators have reported little difference in recovery time between groups who received midazolam premedication versus placebo [Richardson et al., 1997; Elwood et al., 1995; Vetter, 1993; McMillan et al., 1992]. Hosey et al. [2009] reported that 0.2 mg/kg of transmucosal midazolam did not improve children's behaviour at anaesthetic induction. They mentioned that the reason for this might be due to the use of low dose [0.2 mg/kg] midazolam. However, we used 0.2 mg/kg of midazolam intranasal which improved children behaviour at the time of child-parent separation and anaesthesia

Groups	Midazolam group (n=29)	Control group (n=31)	P value
Age (month)	38.03±7.5	37.74±8.7	0.89
Operative time (min)	155.27±31.7	178.25±35.3	0.01
Recovery time (min)	28.58±4.5	27.25±7.6	0.42

TABLE 3 Demographic characteristics (Mean±SD).

Separation score		1.00	2.00	3.00	4.00	Total
Group B	Count	5	8	8	10	31
	% within group	16.1%	25.8%	25.8%	32.3%	100.0%
Group A	Count	16	9	3	1	29
	% within group	55.2%	31.0%	10.3%	3.4%	100.0%
Total	Count	21	17	11	11	60
	% within group	35.0%	28.3%	18.3%	18.3%	100.0%

TABLE 4 Group separation cross tabulation.

induction. Since the dose of midazolam in the study of Hosey et al. and ours are the same, the different results might be due to the different route of administration for midazolam. In the randomised controlled trial conducted by Lahat et al. [2000], most of the 21 recruited children had an upper respiratory tract infection, but only 3 of them showed ineffective absorption of midazolam and consequent poor febrile seizure control. Nasal secretions can theoretically dilute the midazolam solution and interfere with its contact with the absorbing surface [Klein-Kremer and Goldman, 2007; Lahat et al., 2000]. One of the inclusion criteria for general anaesthesia in our study was absence of upper respiratory secretions. This can explain why our study showed a different result using intranasal midazolam. According to Elwood et al. [1995], midazolam premedication [0.03mg/kg or 0.06mg/kg] had no effect on recovery time after short lasting general anaesthesia in a similar surgical population [Elwood et al. 1995]. In this study we found the same results, though long-lasting general anaesthesia was the topic of study in the current research. These contradictions between published studies may be partially explained by differences in general anaesthesia methods, duration of surgery time, administration methods of midazolam, and in the post-anaesthesia care units [Horgesheimer et al., 2001]. About the limitations of the present study, there were no nasal midazolam product in our market at the time of the study, therefore we used a vial form and diluted it to drop in to the nasal cavity. We deemed it was better to conduct our study in the hospital with the same dentist, anaesthesiologist and personnel; however, arrangement of all these specialists in the hospital at a same time was a difficult process.

This study was primarily intended to investigate the efficacy, safety and acceptability of nasal midazolam to reduce the anxiety of patients before entering the operating room. As indicated by the results of this study, this estimated concentration of midazolam apparently did not prolong the recovery time which was reported as the shortcoming of this medication. Nasal midazolam is reported to have only one side effect which is nasal mucosa burning [Moss et al., 1993]. This side effect, however, can be resolved by the use of midazolam as a nasal spray or as a solution in cyclodextrin [Baldwa et al., 2012]. One of the difficult process in children in general anaesthesia is establishing the intravenous line. In this study, we observed that the patients with nasal midazolam premedication were quiet during this stage. Midazolam nasal spray has become recently available [Verma et al., 2012]. Further studies are recommended to evaluate the efficacy of midazolam nasal spray in children undergoing general anaesthesia.

Conclusion

The result of this study indicated that premedication with nasal midazolam on patients prior to general anaesthesia for lengthy dental treatment procedures (2-4 h), did not prolong the recovery time. This might be due to the half-life of midazolam, being usually between 1.5 and 3.5 hours, both for the nasal route at a dose of 0.2 mg/kg, and the intravenous route. An added benefit is that the children could be separated from their parents more easily.

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