Comparative study of oral and trans nasal midazolam as a sedative premedication in paediatric patients

Dipak L. Raval, Tahir S. Gunga

Department of Anaesthesiology, M.P. Shah Govt. Medical College, Jamnagar, Gujarat, India

Correspondence address: Dr. Dipak L. Raval, “AUM”, Axar Vatika, Near halar house and forest office, Nagnath gate, Jamnagar – 361001, Gujarat, India. E-mail: dr.dipakraval@gmail.com

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ABSTRACT

Background: Premedication in pediatric patient before induction of anaesthesia is of vital importance. Midazolam is a benzodiazepine which produces anxiolytic, amnestic, hypnotic and skeletal muscle relaxant effects. Objectives: To evaluate the safety, acceptability, level of sedation and ease of administration of midazolam by using oral and trans nasal route as a sedative premedication in paediatric patient. Materials and Methods: Sixty paediatric patients of ASA grade I or II, aged 2-10 years, undergoing elective surgery were randomly divided into two groups. Group I received oral syrup midazolam 0.5mg/kg and Group II received nasal spray midazolam 0.25mg/kg. Demographic profile, response to drug administration, level of sedation, separation from parents, venipuncture, induction and postoperative recovery scores were noted and statistically analyzed. Results: The study shows that children receiving oral midazolam has better acceptability (group I, 76.66%) than when administered through intranasal route (group II, 53.33%). Sedation score were better at 20 min. in intranasal group (3.06 versus 2.96) than oral group. Post anesthesia recovery scores were similar in both groups. Conclusion: On the basis of our study, we concluded that oral syrup midazolam has better acceptability while intranasal spray midazolam has slightly faster onset without prolonging recovery from anesthesia. Key words: Intranasal spray midazolam, oral syrup midazolam, pediatric patients, preanaesthetic sedation

INTRODUCTION

Some form of medication is necessary to make the patient calm and lessen the anxiety related to surgery and anesthesia. Hospital place, fear of operation and painful procedure, anxiety because of unfamiliar human faces covered by mask and cap, operation theatre environment, unwillingness to breath through an anaesthetic face mask etc. will create stormy anesthetic induction in unpremedicated paediatric patient [1,2], which may create post-operative maladaptive behavioural changes. It has been associated with many negative behavioural changes during and after the surgical experience like post-operative pain, sleeping disturbances, parent child conflict and separation anxiety. It also activates the human stress response, leading to increased levels of serum cortisol and epinephrine and natural killer cell activity.[3] In 17% of post-operative follow up cases, there were personality changes, bed wetting and night mares and this has been attributed to the unpleasant induction and crying at the time of induction of anaesthesia (Eckenhoff J.E., 1953).[3]

Generally, anaesthetic management begins with the preoperative psychological preparation of the patient and administration of a drug or combination of selected drugs to produce specific pharmacological responses prior to induction of anaesthesia. Traditionally this initial psychological and pharmacological component of anaesthetic management is referred to as preoperative medication.

Midazolam is a benzodiazepine which produces anxiolytic, amnestic, hypnotic and skeletal muscle relaxant effects. It can be administered via the intranasal, sublingual, rectal or oral route. There
are combinations of drugs used for premedication like narcotics, barbiturates, anticholinergic, phenothaizines, benzodiazepines, phencyclidine (ketamine) etc. each drug and route has its own advantage and disadvantages.

Midazolam has been used for paediatric procedural and operative sedation for many years by conventional methods. However with the recent availability of nasal mucosal atomization device and oral midazolam formulation (syrup), these routes of administration have been revisited. The aim of our study is to compare safety, acceptability, level of sedation, parent-child separation, ease of induction of anaesthesia and duration of post-operative recovery.

**MATERIALS AND METHODS**

In our study, 60 paediatric patients of ASA grade-I or II, aged 2-10 years, scheduled for elective surgical procedure were studied. Approval from institutional ethical committee and informed written consent from parents of children were obtained.

All patients were brought to reception area of OT complex with their parents and were randomly allocated into one of 2 groups, each group containing 30 children. Group I had received midazolam 0.5mg/kg oral formulation and group II received midazolam 0.25mg/kg by nasal atomizer. Those suffering from respiratory system dysfunction (like rhinorrhea, bronchial asthma, nasal polyp), age below 2 years and above 10 years of age, history of allergic reaction to atomizer who refused to take medication, with epilepsy and raised intracranial tension were excluded from study. Demographic profile of two groups is given in Table 1.

Heart rate, respiratory rate, O₂ saturation and level of sedation were observed before administration of drug. After giving the drug, response to drug administration was observed and categorized as satisfactory or unsatisfactory on the basis of acceptance of the patient [Table 2].

<table>
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<tr>
<th>Table 1: Demographic data of two groups</th>
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<tr>
<td>Demographic data</td>
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<tr>
<td>Total no. of patients</td>
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<tr>
<td>Mean age (years) ± S.D.</td>
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<tr>
<td>Mean weight (Kg) ± S.D.</td>
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<tr>
<td>Male : Female ratio</td>
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<td>Duration of anaesthesia (min)</td>
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</table>

After administration of the drug, level of sedation was assessed at 2 minute and then every 5 min interval by using 5 point sedation score used by Nial C Wilton [4] suggested by Beeby.[2] Sedation score of 3 and above was considered as satisfactory and 1 or 2 were considered as unsatisfactory. Satisfactory means drug accepted willingly, not spitted and swallowed easily without sneezing, nasal irritation and crying. Unsatisfactory means do not like taste of drug seen by facial expression, nasal irritation, sneezing and crying.

At 20 minutes, child was separated from parents and was taken to operating room. The response to child-parents separation was assessed and graded according to separation and induction score suggested by Davis et al[5] [Table 3].

<table>
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<tr>
<th>Table 2: Showing response to drug administration</th>
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<tr>
<td>Response to drug administration</td>
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<tr>
<td>Satisfactory</td>
</tr>
<tr>
<td>Unsatisfactory</td>
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</table>

In operation theatre, IV line secured, face mask was applied and patient was induced with incremental dose of sodium thiopentone followed by inj. Succinylcholine, tracheal intubation was done with appropriate sized oral portex cuffed/uncuffed (according to age) endotracheal tube. After endotracheal intubation, paracetamol suppository was kept for analgesia and anaesthesia was maintained with O₂, nitrous oxide, injection vecuronium and inhalation agent (halothane). Ventilation was controlled with Jackson Reese’s modification of Ayre’s T-piece. Residual neuromuscular paralysis reversed at end of operation by appropriate dose of inj. neostigmine and glycopyrrolate. Post-operative sedation was assessed in post anesthesia recovery room at 10 minute interval up to 60 minutes [Figure 1] by using same scoring system suggested by Nial C. Wilton.[4] In the recovery room, all the patients were also monitor according to Aldrete scoring system[6] and when patient had achieved a score of 9 or more, they were shifted to surgical ward. Patients were also observed for

<table>
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<th>Table 3: Mean emotional score during separation</th>
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<td>Emotional score</td>
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<tr>
<td>At separation from parents</td>
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<tr>
<td>At venipuncture</td>
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<td>At induction</td>
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</table>
any side effect like O₂ desaturation, laryngospasm, bradycardia, nausea, vomiting and transient nasal irritation etc.

The study data were analysed with the help of different statistical methods for different data analysis. Comparisons of variables between two groups were done by using unpaired Student’s t-test. Incidence of particular behaviour states like acceptance of drug was compared between two groups using the chi-square analysis.

RESULTS

Demographic profiles were comparable in two groups [Table 1].

Response to drug administration:

In our study shows that children receiving oral midazolam had better acceptability (group I, 76.66%) than when administered through intranasal route (group II, 53.33%) [Table 2].

Separation and induction score:

When separation score was evaluated at 20 min in both groups, it was noticed that trans nasal group achieved better separation score as compared to oral syrup group. But statistically not significant. [Table 3].

Post-operative course:

In the post-operative period, patients were assessed for time of spontaneous eye opening, length of stay in post anaesthesia recovery room [Table 4] by using scoring system suggested by Aldrete[6] and presence of any complications.

In both groups midazolam does not create any post-operative complication like nausea, vomiting, excessive sedation, laryngospasm, respiratory depression, tongue fall or need of airway support. But we had observed intranasal spray of midazolam causes nasal irritation and sneezing in 6 patients. So we recommend to use 4% lidocaine spray prior to midazolam spray for reducing nasal irritation.

Sedation score:

After the administration of midazolam through oral and nasal routes, sedation score were evaluated at 2 minute and then at 5 minute interval. We observed that trans nasal midazolam group achieved a faster sedation score of 3 or more at 20 minutes.

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<th>Table 4: Post-operative course</th>
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<td>Mean recovery score</td>
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<td>At 15 minutes</td>
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<td>At 1 hour</td>
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In post-operative period we had observed the patients in post anaesthesia recovery room and after 60 min, the sedation score comes near pre drug level [Figure 1].

Mean Pulse rate:

As shown in Figure 2, at 2 min after premedication, pulse rate increases in group II, while it decreases in group I. At time of laryngoscopy and intubation, pulse rate increases in both the groups which comes to almost baseline value after 5 minute.

Mean respiratory rate and oxygen saturation:

Respiratory rate and oxygen saturation shows statistically insignificant changes in perioperative period respectively.

DISCUSSION

Premedication is even more important in case of children. First of all they are not capable of understanding what is going to happen to them. They are aware of separation from their parents and of the strange hospital environment. Also they are not able to fully understand the necessity for their surgery, nor are they amenable to reasoned explanation.[1,2,3]

Ideal premedication should be easy to administer and fast and prompt in action with minimal side effect. Almost all the drugs currently available for pre-anaesthetic medication of children, either required injection, administering as a tablet, nasal or rectal administration. Any of these methods could be difficult or traumatic for children. In addition, many of the currently used drugs like narcotics cause respiratory depression and does not provide uniform sedation, amnesia or safety. Oral premedication for children creates a better psychological balance but also had disadvantages like longer duration of onset of action, significant first pass metabolism leading to larger dose.
requirement, unpredictable absorption and bioavailability, unpredictable effects and inter individual variability.[7,8,9,10,11] In response to drug administration we found that oral route had better acceptability as compared to nasal route which was similar to that which was noticed by Tolksdorf W and Fick C.[12]

At 20 min, mean sedation score was higher in the trans nasal group, which was also observed in other study performed by Malinovsky JM[13] who found that nasal group had higher peak plasma concentration earlier than oral route. A faster onset of sedation in the nasal group was due to rapid and nearly complete absorption of the drug, owing to the rich blood supply of the nasal mucosa and the nose brain pathway through olfactory mucosa into the CSF. The effective delivering of the drug through the atomizer in form of droplets which measure 30-100 micron in size[14] in larger dispersion of drug over mucosa and hence result in better absorption. As midazolam has a high hepatic metabolism, a greater systemic bioavailability can be achieved, unlike oral route.

At 20 minutes, the separation score was similar in both groups which was similar in study which was conducted by sunny Alex et al.[15]

Respiratory parameters like respiratory rate and oxygen saturation did not change at any time of
perioperative period in either group. Shafer A and white PF et al [16] found that midazolam did not have any significant effect on Respiratory rate, O₂ saturation and incidence of laryngospasm.

Cardiovascular parameters such as heart rate and mean arterial pressure did not change in either group. But trans nasal group show increase in heart rate as compare to oral group, which correlates with the findings of Naqash and Waqar-ul, et al. [17]

Post-operative recovery time was similar in both groups, which concordance with those in study which was conducted by Davis et al [9] al, they had noticed that recovery from anaesthesia was not prolonged by midazolam. Nasal irritation and sneezing was found in 6 patients in trans nasal group, which can be most likely being attributed to the acidic preparation of midazolam (pH 3.34). Dallman J.A et al [18] suggested use of midazolam solution in cyclodextrin, which result in change in concentration of drug. Lugo R.A. et al [19] recommended spraying of 4% lidocaine spray prior to midazolam spray for reducing nasal irritation without affecting efficacy of midazolam.

CONCLUSION

On the basis of our study, we concluded that oral syrup midazolam 0.5mg/kg, given in paediatric patient as sedative premedication is equally effective premedicant as compared to intranasal midazolam spray 0.25mg/kg. Intranasal spray midazolam has slightly earlier in onset while oral syrup midazolam has better acceptability in paediatric patients.

REFERENCES


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