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Original Research Article

A study to compare clinical efficacy and safety of two different doses of intranasal midazolam as premedication for paediatric surgery

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ABSTRACT

Introduction: Intranasal midazolam is convenient form of premedication in children with favourable pharmacokinetics and no side-effects. This study was carried out to compare two different doses of intranasal midazolam as premedication in paediatric surgery.

Materials and Methods: After taking institutional ethics committee approval and informed consent, sixty patients aged 2 to 6 years undergoing elective surgeries were randomised into two groups (n=30 each) to receive 0.2mgkg^{-1} (Group A) and 0.3 mgkg^{-1} (Group B) intranasal midazolam in the pre-operative area. Vital parameters were taken at 5 minute intervals till sevoflurane induction. 5-point sedation score was recorded at 5 minutes, 10 minutes, after parental separation at 15 minutes and modified to show compliance with fack mask induction at 20 minutes. Side effects during the study were also compiled.

Results: Demographic data including age, gender and weight distribution were comparable in both groups. All haemodynamic parameters remained similar in both the groups (P>0.05). Significantly higher number of patients (24 versus 12 in group B and A respectively) had onset of sedation (score 3, 4) at 5 minutes while sedation levels were comparable at 10 minutes. Lesser number became agitated on parental separation and face mask induction (P-values 0.044, 0.126 respectively) in group B, former being significant. No side effects were observed during the study.

Conclusion: Intranasal midazolam in both the dosages provides satisfactory conditions for parental separation and face mask induction in children. However, larger dose can be used for earlier onset, with higher probability of adequate sedation levels, no side effects deterring its use.

1. Introduction

The memory of stressful preoperative experiences has long term repercussions on a child's psychological development, thus important to cater to during preoperative visits. Counselling and parental presence, though useful in this regard, might fail sometimes with premedication being an effective alternative.[1,2] Multiple studies using various drugs for premedication express conflicting views on the ideal regime.

Midazolam is one such drug given through multiple routes as sedative, hypnotic and anxiolytic. The intramuscular and rectal route is painful and invasive for child with latter having unpredictable absorption. Oral route, though most popular, has bitter taste and low bioavailability due to first pass metabolism. It can prolong recovery from general anaesthesia in higher dose.[3] Owing to high mucosal vascularity, intranasal route offers fastest and complete absorption within one-two minutes. Recovery from anaesthesia is also not affected.[4]

The current study evaluated clinical efficacy and safety of two doses of intranasal midazolam as premedicant in children in terms of haemodynamic parameters, 5-point sedation scores analysed at 5 min, 10 minutes, 15 minutes or immediately after parental separation and 20 minutes or

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just after placement of face-mask. Also, any adverse effects seen during the study were compiled at the end.

2. Materials and Methods

After obtaining the institutional ethical committee approval and informed parental consent, this prospective randomised study was conducted in an advanced paediatric care centre from September 2008 to May 2010.

Sixty patients in the age group of 2 to 6 years, belonging to ASA physical status I and II, scheduled for elective surgeries, were included in the study. Subjects were excluded if they had any known history of adverse reaction to benzodiazepines, taking drugs like phenobarbitone, phenytoin, rifampicin, corticosteroids which are enzyme inducers of cyt-P450 and giving history of running nose, nasal infection or allergy.

Randomisation and allocation of groups was achieved by means of opaque sealed envelopes using computer generated random numbers opened by an operation theatre technician who was not involved in recording the observations. The drugs were prepared in their correct dilution per kilogram body weight by the same person. Perioperative parameters were charted by postgraduate resident who was unaware of patient's group allotment. The patients were divided into two equal groups of 30 each to receive midazolam 0.2 mg/kg^{-1} intranasally (Group A) and 0.3 mgkg^{-1} intranasally (Group B) 1 minute after instillation of lidocaine 1% spray in the nostrils. Latter was done to prevent any nasal irritation or teary eyes with the use of concentrated form of midazolam. One of the parents was asked to take the child in his/ her lap in recumbent position and administer the drug prepared as two aliquots in both the nostrils by using syringe.

Preservative-free midazolam (5mg/ml ampoules) were used to administer drug in the nostrils. This helped in limiting the drug volume, which has got major pharmacokinetic importance in a route. Any incidence of sneezing or coughing was counted as premedication failure and excluded from analysis.

Heart rate (HR), systolic and diastolic blood pressures (SBP, DBP), respiratory rate (RR) and state of sedation were observed before administering the drug and then at five min interval. The fifteen min measurement was made immediately after the child was separated from their parents and so represents the response to separation. The twenty min measurement was done just after face mask placement for inhalational induction of anaesthesia.

Using a five-point sedation scale (adapted from Wilson and colleagues),[5] the degree of sedation was assessed:

5- Point Score	Mental State after premedication and parental separation	Description
5	Agitated	Patient clinging to parents and/or crying.
4	Alert	Patient is aware but not clinging to parent, may whimper but not cry.
3	Calm	Sitting or lying comfortably with spontaneous eye opening.
2	Drowsy	Sitting or lying comfortably with eyes closed, but responding to minor stimulation.
1	Asleep	Eyes closed, arousable but does not respond to minor stimulation.

Patients were induced with oxygen (02), nitrous oxide (N20) and sevoflurane by facemask. Intravenous line was secured after inhalational induction and injection atropine was administered. Effectivity of midazolam for intravenous cannulation was not studied as it has no analgesic properties. It would have been unethical for the child to bear cannulation pain, so secured only after induction.

The response to mask placement was assessed by modifying the above scale:

5-Point Score	Mental State after face mask induction	Description
1	Agitated	Previous criteria and/or refuses mask
2	Alert	Previous criteria and/or initially refuses mask, but accepts after persuasion
3	Calm	Previous criteria and accepts mask
4	Drowsy	Previous criteria and accepts mask
5	Asleep	Previous criteria and accepts mask

Thus, if a patient was drowsy but refused mask induction, then the patient was recorded in score 1 and not 4.

Tracheal intubation was done with appropriate sized endotracheal tube after administration of standard non-depolarizing muscle relaxant. Anaesthesia was maintained by 02, N20, sevoflurane at MAC_5 and analgesia was provided by fentanyl 2 microgram/kg. Ventilation was controlled by Jackson-Rees modification of Ayre's T-piece during induction and was maintained on pressure controlled mode of mechanical ventilation. Residual neuromuscular paralysis was reversed at the end of operation by appropriate dose of neostigmine and atropine. Patients were shifted to post anaesthesia care unit after checking adequate respiratory efforts and motor response.

3. Results

Sample size was adequate keeping power of the study at 80% with alpha-error of 5% and 95% confidence limit based on sedation score at parental separation and face mask placement in both the groups. 102 patients were enrolled in the study out of which 17 patients did not meet the inclusion criteria- 1 had history of adverse reaction to benzodiazepines, 7 were taking drugs like phenobarbitone, phenytoin, rifampicin, corticosteroids and 9 had history of nasal infection, pathology and allergy. 85 patients were randomised into two groups of 40 and 45 respectively to receive 0.2mgkg^{-1} and 0.3 mgkg^{-1} midazolam. Out of these, 25 patients were excluded from analysis as they expelled their drug by sneezing. Hence, data from 60 patients was taken for final analysis. The allotment of study groups were as follows (Diagram 1).

Statistical analysis was performed using SPSS 21.0 version of Microsoft Windows. The obtained data was expressed as mean ± standard deviation and relative frequencies as percentages. Intergroup comparison of quantitative variables was done using Student t-test and for intragroup comparison paired t-test was used. For comparing categorical data, Chi-square test was performed where a probability value (P-value) less than 0.05 was considered statistically significant.

Both the groups were comparable in terms of age, weight, sex distribution and haemodynamics before premedication (Figure 1). Systolic blood pressure, diastolic blood pressure, pulse rate and respiratory rate before premedication were compared with 5,10,15,20 minutes after premedication in both groups using line diagram which came to be favorable in both the groups (Figure 2 showing haemodynamic parameters namely pulse rate, systolic and diastolic blood pressures and respiratory rate before and after premedication).

The recordings of 5-point sedation scale showed that after 5 minutes of premedication, 12 patients (40%) were still partially sedated with sedation score 4 and 18 completely agitated with score 5 (60%) compared to 24 with sedation score 4 (80%) and 6 with score 5(20%) in group B, P-value being statistically significant (P-value 0.002).

After 10 minutes, 22 patients had achieved score of 3(70%) compared to 27(90%) in the other group (P-value 0.095). Hence, onset of sedation after 5 min of receiving premedication was significantly better (80% versus 40%) in group B than group A while at 10 minutes interval, it was not significant.

Sedation score after 15 minutes was adequate (score 3) in 29 patients (96%) in group B compared to 24 (80%) in group A (P-value 0.044) and 1 versus 6 patients had inadequate anxiolysis with score 4. Thus, most of the patients (29) in group B were easily separated from the parents as compared to 24 in group A, result being statistically significant.

All except 1 patient in group B were calm (score 3) and accepted mask easily at 20 minutes, while in group A, 5 patients were inadequately sedated with score 4 while one patient was completely agitated on keeping mask with sedation score of 5 (P-value 0.126).

None of the patients had score of 1, 2 throughout the time period of observation. No side effects like respiratory depression, nasal irritation, itching, shivering, nausea/vomiting, hypotension, bad taste, watering of eyes and increased salivation were observed with both the doses during the study.

4. Discussion

In our study, preservative-free midazolam ampoules in 5mgml^{-1}dilution and 0.2 - 0.3 mgkg^{-1} were given intranasally, as lesser doses have been found ineffective while 0.5mgkg^{-1} dose required higher volumes causing mucosal irritation and spillage of the drug.[6] We did not consider placebo control because the superiority of 0.2mgkg^{-1}-0.5mgkg^{-1} midazolam by intranasal route to placebo has already been well established in previous studies.[6–8]The children were selected in the age group of 2-6 years, because they have limited scope for psychological counselling. We opined that parental administration of drug would lower the incidence of stranger anxiety during administration and non-compliance, hence was adopted in the methodology of our research.

The unique findings in our study were better sedation scores and earlier preparedness for parental separation with higher dose (0.3 mgkg^{-}1). Us, anaesthesiologists, are reluctant in giving higher doses due to fear of side-effects and unacceptability. However, our study proved that midazolam is associated with minimal adverse effects and the difference in acceptability does not appreciably differ (25% versus 33% in Group A and B respectively). Also, recent advent of concentrated nasal sprays for drug administration has solved the problem to a great degree. The comparison of Pk/Pd of intranasal route by droplet and spray formulations is similar,[9] only difference being the larger volumes to be injected in former which is uncomfortable for small child. Hence, our results were identical to other studies done with intranasal midazolam spray.

The haemodynamic parameters showed minimal alteration after premedication in both the groups which is similar to previous studies by Hebaallah M and Nitturi S et al where pulse rate, blood pressure and respiratory rate were insignificantly changed by intranasal midazolam in comparison to dexmedetomidine.[10,11]Thus, midazolam in both the doses offers excellent haemodynamics before and during induction of anaesthesia.

Both the doses of intranasal midazolam produced an effective anxiolytic and sedative response in paediatric patients, which is comparable with the other reported studies.[6,10] A calming effect was seen after five min in

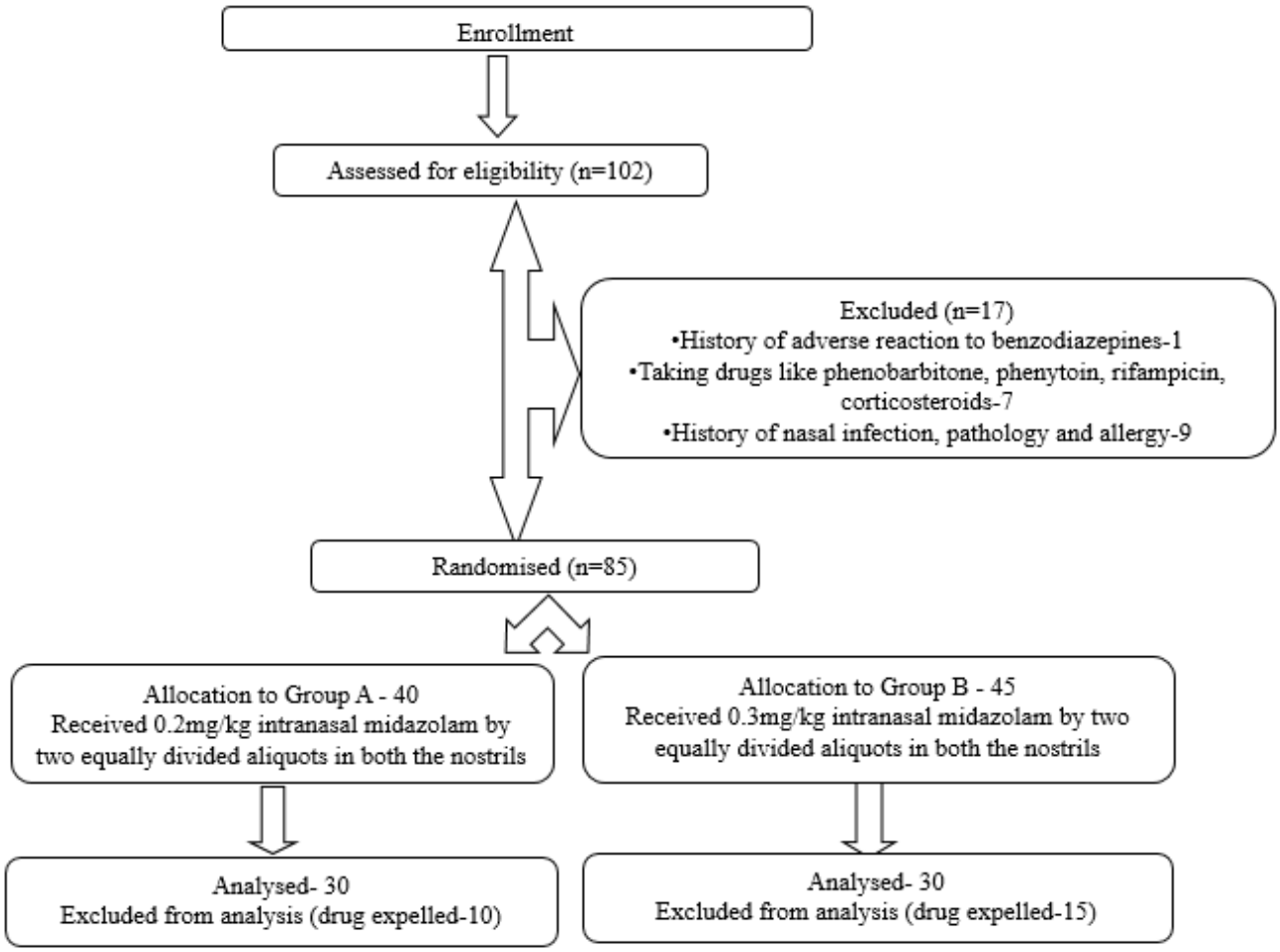
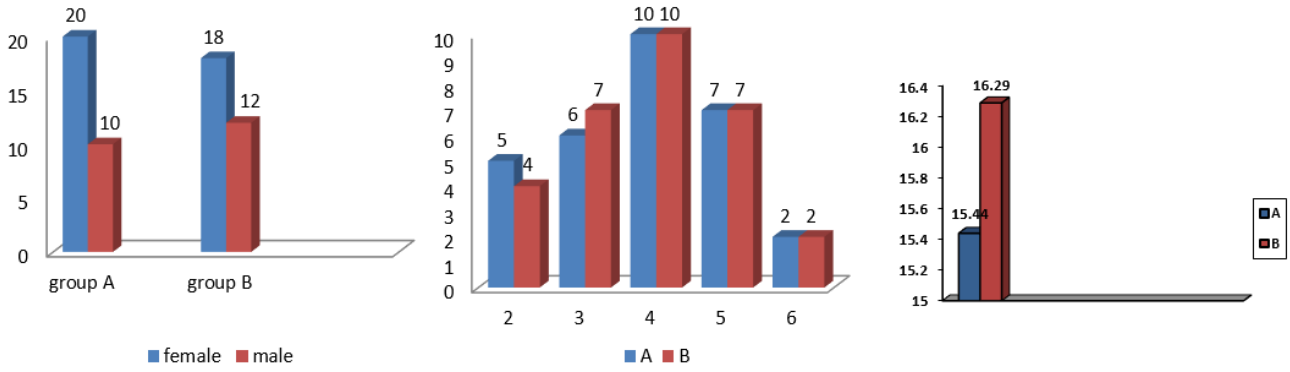


Diagram 1: Consort diagram



Gender Distribution Age distribution in years Mean weight in kg

Fig. 1: Demographic profile

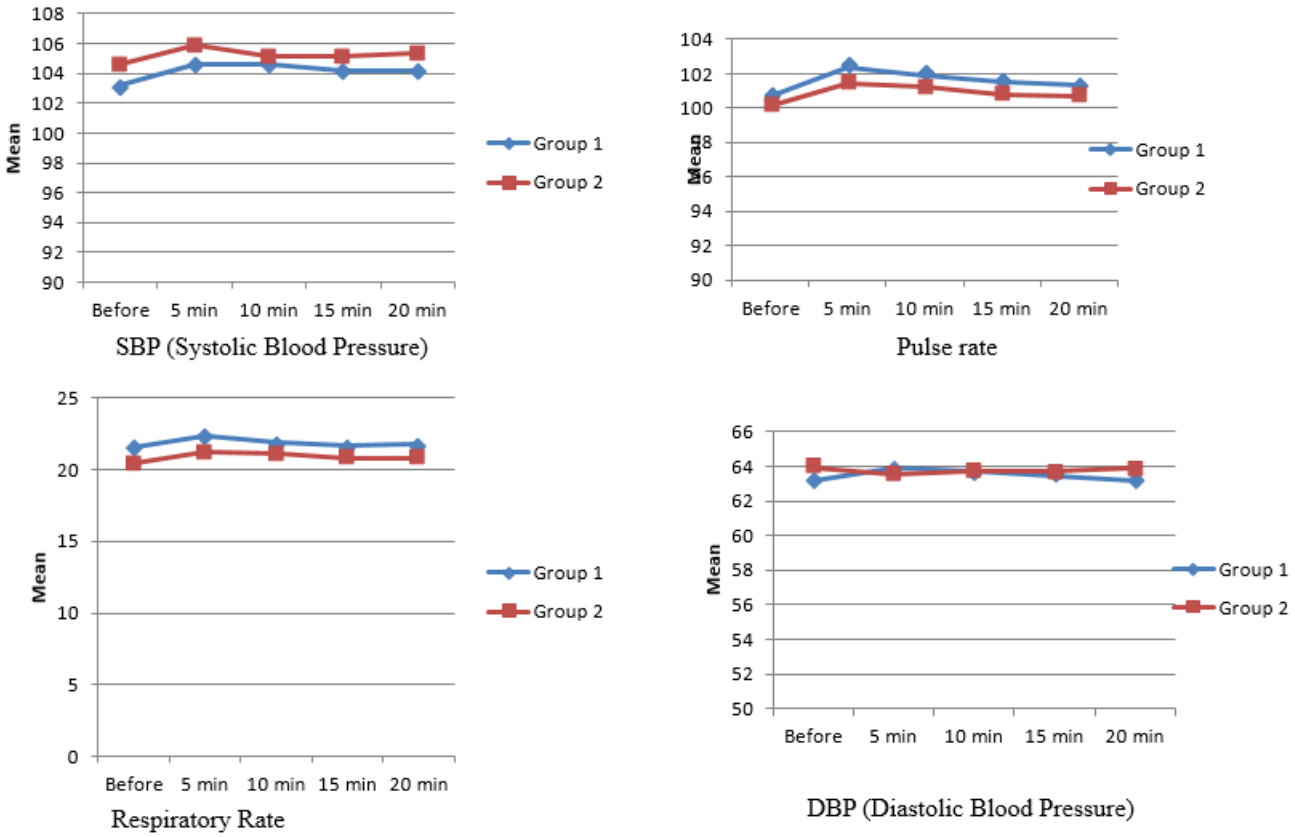


Fig. 2: Line diagram depicting haemodynamic parameters after premedication

Table 1: Five-point sedation score after 5 min of premedication in both the groups

SS-5		Group A	Group B	Total
4.00	Count %	12 (40.0%)	24 (80.0%)	36 (60.0%)
5.00	Count %	18 (60.0%)	6 (20.0%)	24 (40.0%)
Total	Count %	30 (100.0%)	30 (100.0%)	60 (100.0%)

Data are expressed as≠n(percentage) ; SS5- Sedation score at 5 minutes
p=0.002 (Highly Significant)

Table 2: Five-point sedation score after 10 min of premedication in both the groups

SS-10		Group A	Group B	Total
3.00	Count %	22 (73.3%)	27 (90.0%)	49 (81.7%)
4.00	Count %	8 (26.7%)	3 (10.0%)	11 (18.3%)
Total	Count %	30 (100.0%)	30 (100.0%)	60 (100.0%)

Data are expressed asnumber or percentage; Chi-square test applied
NS*-Non-Significant(P-value>0.05)

Table 3: Five-point sedation score after 15 min of premedication in both the groups

S S separation		Group A		Total
3.00	Count %	24 (80.0%)	29 (96.7%)	53 (88.3%)
4.00	Count %	6 (20.0%)	1 (3.3%)	7 (11.7%)
Total	Count %	30 (100.0%)	30 (100.0%)	60 (100.0%)

Data are expressed as≠n(percentage) ; SS sep- Sedation score at parental separation
p=0.044 (Significant)

Table 4: Five-point sedation score after 20 min of premedication in both the groups

SS Mask		Group A	B	Total
3.00	Count %	24 (80.0%)	29 (96.7%)	53 (88.3%)
4.00	Count %	5 (16.7%)	6 (3.3%)	24 (10.0%)
5.00	Count %	1 (3.3%)	0 (.0%)	1 (1.7%)
Total	Count %	30 (100.0%)	30 (100.0%)	60 (100.0%)

Data are expressed as≠n(percentage) ; SS Mask- Sedation score at face mask induction
p=0.126 (Non-significant)

group B and by ten min in both groups of midazolam. That means, intranasal midazolam 0.03 mgkg-1 had quicker onset than 0.02 mgkg-1. This again corroborated with the earlier study by Baldwa N.M. et al in which atomised nasal spray in a dose of 0.3 $mgkg^{-1}$ achieved faster sedation and better separation scores as compared to 0.2 $mgkg^{-1}$.[12] Conversely, Bhakta P et al in their study found earlier onset of 0.2 $mgkg^{-1}$ dose of midazolam than 0.3$mgkg^{-1}$ and owed it to the lesser acceptance of higher dose and consequent higher volume of drug leading to its wastage by sneezing.[6] We excluded all cases with expulsion of drug, hence the results were reflected more precisely. A newer concentrated form of midazolam has also lead to better volume to weight balance leading to higher acceptance of the drug.[13]

The sedation levels were significantly more satisfactory during separation from parents at fifteen minutes in group B but insignificant during mask placement and induction of anaesthesia. This reveals that higher dose of intranasal midazolam offers greater probability of children to be calm (sedation scale score 3) during separation from their parents and face mask induction compared to lower dose with no adverse effects. This is similar to studies by Baldwa[12] and Peerbay et al[14] where higher doses were found more effective and in contrast to others showing equivalent sedation levels during parental separation, induction and intravenous cannulation with both the doses, probably due to lesser accurate drug delivery of higher dose.[6,15,16]

A study by Al-Rakaf H et al[10] found all three doses (0.3 $mgkg^{-1}$, 0.4 $mgkg^{-1}$ and 0.5$mgkg^{-1}$) of intranasal midazolam effective in modifying the behavior of the uncooperative child to accept dental treatment. However, the probabilities of achieving adequate conscious sedation levels in the three groups were 79%, 96% and 100% with increasing doses resulting in assured results as was in our study.

Oral route for midazolam has been compared by Verma R K,[17] Yildirim[18] and Mehdi[8] et al with intranasal route where only drawback in the latter was its lower acceptance with children. In our study, nearly 100% acceptance was taken as end-point to be included in analysis, thus the results were quite different. The exclusion based on uncertain delivery of the dose was marginally higher in Group B which relates to previous studies suggesting higher rate of non-acceptance with higher dose.[6] But the earlier onset and better results with the latter call for using concentrated solutions of midazolam and nasal sprays for achieving optimal results. Intermittent administration of volumes >0.5 ml at 2-3 minute intervals can also be a potential solution to this problem.

Dexmedetomidine is another premedication acting as selective alpha-2 receptor agonist and evaluated for effectiveness by intranasal route. The results are more promising than with midazolam but for significantly delayed onset, haemodynamic variations and more incidence of emergence delirium.[19–22] Similarly, comparative studies with intranasal ketamine[22,23] favour midazolam for its safety profile and efficacy. Recent researches have experimented on the novel intranasal combination of midazolam and fentanyl[24,25] for the dual action of anxiolysis along with peri-operative reduction in anaesthetic drugs and analgesic requirement.

A comparison of all three namely ketamine, demedetomidine and midazolam for children undergoing bone marrow biopsy was undertaken by Mostafa MG et al. where dexmedetomidine was found to have fastest onset. The three groups had comparable sedation scores till 25 minutes, but dexmedetomidine and midazolam yielded better results for longer duration. The author's results reiterated the overall supremacy of intranasal midazolam

owing to its efficacy, safety, availability and nominal price.[22]

There were no adverse events like hypotension, respiratory depression, nausea and vomiting and delayed recovery from giving midazolam in our study and numerous other studies which makes it the safest drug there is for anxiolysis preoperatively.[6–13]

Malinovisky has suggested neurotoxicity in rabbit with intranasal midazolam and ketamine premedication,[26] however recent researches refute the same by affirming that the low pH of the solution is responsible for neurotoxicity only when given epidurally or intrathecally.[27] Morever, many previous studies have used intranasal midazolam without any evidence of nasal mucosa damage or neurotoxicity.[6–11,13,22]

There are several benefits and limitations to go with our research. All precautions were taken for improving drug acceptance which made premedication results better than all previous studies. We were able to demonstrate faster onset and more satisfactory sedation in larger number of patients with higher dose. Parental administration of drug prevented any stress during the drug delivery. However, even larger dose of 0.5 $mgkg^{-1}$could have been used for better analysis of optimal dose. We could not include more subjects due to limited turnover of paediatric patients in this age-group. The recording of onset of sedation could have been more accurate if observation intervals were shorter during the first fifteen minutes. The use of nasal spray for midazolam administration could have reduced the number of exclusions from the final analysis.

5. Conclusion

Intranasal midazolam in doses of 0.2 and 0.3 $mgkg^{-1}$ provides good effectivity as sedative and anxiolytic during parental separation and mask induction in paediatric patients without any undesirable side effects. Higher dose is associated with faster onset and more reliable results, though volume intolerance is a major drawback. Use of atomizer nasal sprays for future researches is warranted where higher doses can be given unhindered by lower drug acceptance.

6. Source of Funding

Nil.

7. Conflicts of Interest

There are no conflicts of interest.

8. Acknowledgement

The manuscript has been read and approved by all the authors, the requirements for authorship have been met and each author believes that the manuscript represents honest work.

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