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Original Research Article

Oral versus intramuscular midazolam for paediatric preanaesthetic medication

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ABSTRACT

Background: The need for effective preanesthetic medication in children is obvious and midazolam has proven to be one reliable choice. The aim of the present study was to compare the efficacy, acceptability and reliability of the oral and intramuscular routes of administration of midazolam towards paediatric preanesthetic medication at various doses.
Methods: Hundred eligible patients in the age group of 1 to 10 years undergoing ambulatory or routine planned, minor or major surgery during study period were allocated to one of the four groups of 25 participants each, formed on the basis of premedication they received. Haemodynamic parameters, level of sedation and anxiety and induction score were noted before premedication and after each 15 minutes interval for next 45 minutes in all the four groups. Postoperative assessment included sleep level, anterograde amnesia, picture recall and occurrence of complications.
Results: The sedative and anxiolytic effects were observed to be maximum at 45 minutes after premedication in all the four groups and better sedation, anxiolysis and quality of induction were achieved with higher doses for both oral as well as intramuscular routes. Postoperatively, the sleep level did not increase with higher dose and 64% patients were awake with 0.75 mg/kg oral midazolam. The sleep level was more with higher dose with the Intramuscular route, with 60% patients feeling drowsy with 0.1mg/kg dose. 0.75 mg/kg dose showed better anterograde amnesia (64%) than 0.5 mg/kg (28%), while it was present in 64% participants premedicated with 0.8 mg/kg intramuscular does and 72% in 0.1 mg/kg intramuscular dose.
Conclusions: Intramuscular midazolam at 0.1 mg/kg dose seems to be the ideal dose and route for paediatric preanesthetic medication, with oral midazolam at 0.75 mg/kg to be considered an effective and acceptable alternative.

Keywords: Intramuscular, Midazolam, Oral, Preanesthetic medication

INTRODUCTION

Preoperative period is a stressful event for majority of the individuals undergoing surgery. This is especially true in paediatric patients and is related to the limited understanding of nature of illness and the need of surgery by young children. As many as 50% of children have been reported to show signs of significant preoperative fear and anxiety.[1] Correlations between heart rate, blood pressure, and behavioural ratings of anxiety have already been well documented, along with the observation that stormy anaesthetic induction in children lead to increased incidence of post-operative behavioural problems.[2,3]

The major objectives of preanesthetic medication are to decrease the stress response with preservation of haemodynamic parameters, facilitate anaesthesia induction and produce amnesia. This can be diminished by psychological preparation, however, a pharmacological adjunct may be more reliable, considering immature age of the patients. Different pre-medications like promethazine, trimeparazine, ketamine, morphine etc. have been used with individual advantages/disadvantages and varying success.[4] Midazolam, with its rapid onset, relatively shorter duration and sedative, anxiolytic, amnesic, hypnotic properties, has been postulated as an ideally suited agent for the purpose.[5] Oral, rectal, and intramuscular routes of midazolam administration have been used.[6] The general perception is, medications administered without a needle are more pleasant for the children. However, the efficacy and reliability can't be compromised for acceptability of mode of administration of a drug in the setting of requirement of surgery, none less.

The aim of the present study was to compare the efficacy, acceptability and reliability of the oral and intramuscular routes of administration of midazolam towards paediatric preanesthetic medication at various doses.

METHODS

The present comparative observational study was carried out in the department of anaesthesia at a tertiary care government hospital in central India over two years. The study population consisted of patients in the age group of 1 to 10 years undergoing ambulatory or routine planned, minor or major surgery during study period.

Selection criteria

- Age between 1-10 years
- American society of anaesthesiologists (ASA) physical status I and II, without central nervous system diseases[7]
- No usage of sedative or hypnotic drugs within the month preceding surgery
- Not allergic to benzodiazepines
- No prior history of sleep apnoea or severe respiratory disorder
- Parent willing to consent for the study

After obtaining Institutional Research Ethics Board approval for the study and written informed consent from all the participants, a total of 100 eligible patients were finally enrolled for the study and were allocated to one of the four groups of 25 participants each on the basis of premedication they received. The four study groups thus formed were as follows:

- Group I: Patients received 0.5 mg/kg of oral Midazolam (5 mg/ml of parenteral preparation) with honey as a vehicle making a volume of 0.1 ml/kg
- Group II: Patients received 0.75 mg/kg of oral Midazolam (5 mg/ml of parenteral preparation) with honey as a vehicle making a volume of 0.1 mg/kg
- Group III: Patients received 0.08 mg/kg Midazolam intramuscularly
- Group IV: Patients received 0.1 mg/kg Midazolam intramuscularly.

All the participants were assessed thoroughly before surgery. Demographic data including age, gender, and weight were recorded. Pulse, blood pressure, respiratory rate, along with level of sedation and anxiety were noted at baseline (before premedication) and after each 15 minutes interval for next 45 minutes.

The reaction of the child to the taste of premedication was noted (If the mixture was vomited out, the child was excluded from the study). The level of sedation was assessed on a five point scale where: 0- hyperactive, awake, alert, 1- awake but drowsy, 2- asleep but easily arousable, 3- asleep and difficult to arouse, 4- asleep and not responding to oral commands. Just before entry into operation theatre (OT), the child was shown a picture of cat or fish or a coloured pen. Inside the OT, response of the child to venepuncture or application of face mask was noted. Final assessment of sedation and anxiolysis was done on induction.

The induction score was assessed on a 4 point scale:

- Excellent (Cooperative, unafraid)
- Good (Mildly anxious, easily assured)
- Fair (Apprehensive, not reassured)
- Poor (Resistant, marked crying).

Anaesthesia was induced by inhalational or intravenous (IV) route and Thiopentone 3-4 mg/kg was used. For minor procedures, anaesthesia was maintained on oxygen, N_2O and halothane. For major surgery, the trachea was intubated following a dose of IV Suxamethonium 1-1.5 mg/kg. Children were either allowed to breathe spontaneously or controlled with IV Vecuronium 0.05 mg/kg as a muscle relaxant. Vital parameters were monitored intraoperatively. IM Paracetamol 1-10mg/kg was administered before termination of the surgery for analgesia.

Halothane and N_2O were discontinued at the end of surgery and 100% oxygen was administered for 5 breath after which reversal was achieved with IV Neostigmine 0.05 mg/kg and IV Atropine 0.02 mg/kg. Sleep level was noted along with any side effects like nausea, vomiting, dyspnoea etc. Vital parameters, secretions, consciousness, activity and type of respiration were monitored for an hour. Five-six hours later, the child was asked to recall the picture which was shown to him prior to entry into OT.

The statistical analysis was performed using SPSS (version 17) and paired t-test was applied for comparison

within the group and unpaired t-test for comparison between groups.

RESULTS

The four groups of 25 participants each formed on the basis of premedication received (oral or intramuscular midazolam, in mentioned doses) were similar with respect to age, gender and weight distribution.

Participants in the age group of 6-10 years (n=66) outnumbered those in the age group of 1-5 years (n=34) and there were significantly more males (n=63) than females (n=37) (M:F ratio- 1.7).

Among conditions for which major surgeries were performed, congenital hernia (n=16), squint (n=15) and congenital cataract (n=13) were the commonest ones, followed by appendicectomy (n=10) and mastoid exploration (n=9) completing the numbers. Circumcision was by far the commonest minor surgical procedure performed in the study (n=34), with abscess drainage being performed in 3 patients.

The mean pulse rate didn't vary significantly among the 4 groups at any point in time, but the rise in mean pulse rate was observed to be statistically significant 30 and 45 minutes after premedication in all the groups. The systolic blood pressure (SBP) remained almost unchanged till 30 minutes, but there was significant fall in SBP after 30 and 45 minutes in all 4 groups, as compared to baseline. There was no significant difference between oral and intramuscular groups with respect to reduction in blood pressure though. The rise in respiratory rate was observed to be more with increase in dose in both oral and intramuscular groups (Table 1). The sedative effect was observed to be maximum at 45 minutes after premedication in all the four groups. The onset of sedative effect was earlier and better in the higher dose group between the oral midazolam groups, with mean sedative score at 45 minutes of 1.0±0 in group I and 2.16±0.61 in group II. As for IM midazolam groups, 0.1 mg/kg dose showed better sedation as compared to 0.08 mg/kg.

The mean sedative score at 45 minutes was 1.72±0.66 in group III and 2.12±0.65 in group IV. Maximum anxiolytic effect of midazolam was also observed at 45 minutes in all four groups and better anxiolysis was achieved with higher doses for both oral as well as intramuscular routes (Table 2).

The quality of induction was found to be better in groups with higher dose in both oral as well as intramuscular routes; with 40% in group I, 64% in group II and 76% in group IV having excellent scores. Thus, midazolam IM 0.1 mg/kg was observed to be the ideal route and dose for excellent induction (Table 3).

Postoperatively, the sleep level did not increase with higher dose of oral midazolam and 64% patients were awake in group II. The sleep level was more with higher dose with the IM route, with 60% patients in group IV feeling drowsy.

Table 1: Haemodynamic parameters in the four groups during procedure.

Treatment Group (each group: n=25)	Heart Rate (Per min) (Mean±SD)	Systolic BP (mmHg) (Mean±SD)	Respiratory Rate (Per min) (Mean±SD)
Group I			
Baseline	85.44±6.98	101.6±6.16	20.8±3.85
15 minutes	86.32±5.94	101.6±6.16	24.16±3.19
30 minutes	91.04±3.58	93.88±6.15	29.28±2.79
45 minutes	95.00±4.63	93.12±6.14	29.68±4.71
Group II			
Baseline	86.8±3.81	100.48±8.06	20.88±2.71
15 minutes	90.8±4.47	99.28±8.13	26.56±4.06
30 minutes	96.24±5.06	91.32±8.14	31.76±4.09
45 minutes	101.28±5.95	91.52±8.43	36.00±4.19
Group III			
Baseline	92.72±12.00	104.6±9.54	21.04±2.77
15 minutes	97.92±12.00	104.4±7.0	24.56±2.38
30 minutes	100.96±11.91	95.04±6.32	25.4±2.59
45 minutes	103.44±14.01	94.4±6.40	30.32±2.69
Group IV			
Baseline	86.56±11.31	106.0±8.94	22.16±3.62
15 minutes	91.20±10.63	106.0±8.94	26.48±3.31
30 minutes	95.3±11.04	96.8±12.72	30.24±4.39
45 minutes	100.64±6.41	95.6±9.0	35.36±3.54

Table 2: Comparison of sedation scores and anxiolysis scores in the four groups.

Scores	Group I	Group II	Group III	Group IV
Sedation Score (Mean±SD)				
Baseline	0	0	0	0
15 minutes	0.4±0.19	0.96±0.19	0.96±0.46	1.00±0.0
30 minutes	0.88±0.32	1.72±0.41	1.08±0.39	1.44±0.49
45 minutes	1.0±0.0	2.16±0.61	1.72±0.66	2.12±0.65
Anxiolysis score (Mean±SD)				
Baseline	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0
15 minutes	1.0±0.0	1.27±0.16	1.0 ± 0.41	1.0 ± 0.0
30 minutes	1.06±0.25	2.74±0.56	1.24 ± 0.51	1.64 ± 0.55
45 minutes	1.44±0.49	2.08±0.665	1.96 ± 0.52	2.24 ± 0.58

Table 3: Distribution of induction scores in the four groups.

Treatment Group (each group: n=25)	Induction Score			
	1	2	3	4
Group I	-	-	14	11
Group II	10	11	2	2
Group III	16	7	2	-
Group IV	19	4	2	-

As for anterograde amnesia, group II showed better results (64%) than group I (28%), while amnesia was present in 64% participants in group III and 72% in group IV (Table 4). Nausea, vomiting, secretions, respiratory depression and episodes of unconsciousness were duly noted in the postoperative period and the incidence of all the complications was observed to be significantly less across the four groups, illustrating the efficacy of midazolam (Table 5).

Table 4: Postoperative sleep level, anterograde amnesia and picture recall.

Treatment Group (each group: n=25)	Postoperative sleep level			Anterograde amnesia		Picture recall	
	1	2	3	Present	Absent	Present	Absent
Group I	-	5	20	7	18	18	7
Group II	4	5	16	16	9	9	16
Group III	1	7	17	16	9	9	16
Group IV	3	15	7	18	7	7	18

Table 5: Postoperative complications in the four study groups.

Treatment Group (each group: n=25)	Nausea/vomiting		Secretions		Respiratory depression			Unconsciousness	
	Seen	Not Seen	Present	Absent	Apnoea	Dyspnoea	Absent	Seen	Not Seen
Group I	1	24	3	22	-	-	25	-	25
Group II	1	24	1	24	-	-	25	1	24
Group III	1	24	-	25	-	-	25	-	25
Group IV	1	24	-	25	-	-	25	-	25

DISCUSSION

In the present study, a hundred eligible patients were allocated to one of the four study groups of 25 participants each on the basis of route and dose of premedication with Midazolam that they received; to compare the efficacy, acceptability and reliability towards paediatric preanesthetic medication. Parenteral preparation of midazolam was used for oral administration as well, as the availability of oral form remains an issue. This manner of midazolam administration has been employed and studied successfully before as well.[4] Emergency cases were not considered for the present study for two reasons. Firstly,

in emergency cases, administration of the drugs orally in the stipulated time interval may not have been possible; and secondly, emergency cases would have presented with full stomach and thus could have resulted in increased incidences of perioperative vomiting.

The groups were similar with respect to age, gender and weight distribution; adding validity to the observations. Haemodynamic parameters along with level of sedation and anxiety were noted before premedication and after each 15 minutes interval for next 45 minutes. The mean pulse rate was observed not to vary significantly across groups, but there was significant rise in mean pulse rate 30 minutes and 45 minutes after premedication in all the groups. Similar rise in heart rate with Midazolam irrespective of route or dose of administration was observed by Rita et al and Taylor et al, among others.[8-10] The systolic blood pressure was also similar in the 4 groups and remained almost unchanged till 30 minutes, when it started falling.

The finding is similar to that of Rita et al, while Taylor et al reported insignificant intraoperative rise in SBP.[8,9] The reason for rise in pulse rate due to Midazolam could be compensation for falling blood pressure (owing to decrease in systemic vascular resistance and vasodilation), to achieve adequate cardiac output. The rise in respiratory rate was observed to be more with increase in dose in both oral and intramuscular groups. The purported explanation is, that Midazolam produces respiratory depression resulting in decrease in tidal volume, which is compensated by increase in the minute volume. The inspiration time remains constant and the respiratory rate increases due to shortening of expiratory time. The scale of changes in haemodynamic parameters so observed, although statistically significant, is clinically irrelevant.

Comparison of sedative effects of the two doses of oral Midazolam revealed that the action of 0.5 mg/kg began only after 30 minutes, while that of 0.75 mg/kg began after 15 minutes and reached significant levels after 30 minutes, with the sedative score being significantly more in the higher dose group at 45 minutes. Feld et al had also reported the onset of sedative effect to be earlier and better in the higher dose group between the oral midazolam groups.[11] Macmillan et al and Riva et al reported both 0.5 mg/kg and 0.75 mg/kg to be adequate oral doses for preanesthetic sedation and the dosage was advocated to be decided on a case to case basis.[12,13] As for IM midazolam groups, 0.1 mg/kg dose showed better sedation as compared to 0.08 mg/kg, results similar to the oral groups, but the difference between the two groups never touched the level of significance, probably due to relatively smaller sample. Feld et al observed significantly better sedation with 0.1 mg/kg dose of IM midazolam in a similar but larger study.[11] The sedation effect of 0.75 mg/kg of oral dose was found similar to 0.1 mg/kg of IM dose. Feld et al, in their earlier study, had reported 0.5 mg/kg of oral Midazolam to be as effective as 0.2 mg/kg IM dose.[11] However, in their later study, regarding the optimal dose of oral Midazolam, confirmed that 0.75 mg/kg oral dose produced effective sedation levels and could be an effective alternative to IM route at that dose.[14] The sedation score was observed to be maximum at 45 minutes after premedication in all the four groups, in agreement with available literature.[11-14]

Maximum anxiolytic effect of midazolam was also observed at 45 minutes in all four groups and better and faster anxiolysis was achieved with higher doses for both oral as well as intramuscular routes. This is similar to observations of previous similar studies, which observed midazolam to be producing consistently good anxiolysis at higher doses with both oral as well as IM route.[8,11,15] The mean anxiolysis scores at 45 minutes was highest in group IV (IM, 0.1 mg/kg), suggesting superiority both in terms of route as well as dose.

The induction score was found to be better in groups with higher dose in both oral as well as intramuscular routes. Further, group II of oral route had excellent induction in 40% of cases in comparison with group IV of IM route, which had 76% excellent induction. Thus, midazolam IM 0.1 mg/kg seems the ideal way of induction in children. This is corroborative of the findings of previous researchers.[8,11]

Postoperatively, the sleep level did not increase with oral dose of midazolam but was more with higher dose with the IM route. As for anterograde amnesia, group II showed significantly better results (64%) than group I (28%), while amnesia was clinically comparable in group III and group IV.

Restricting the occurrence of postoperative anaesthetic complications is an important consideration from preanesthetic medication perspective. Midazolam scores high here. It has been reported to have useful antiemetic properties.[16] With lowered incidence of nausea and vomiting postoperatively, the present study corroborates this finding. No case of unconsciousness was reported in the study, except one case of deep sedation on arrival in recovery room; which may be attributed to longer than normal exposure to inhalational agents during unduly prolonged surgery. No cases of respiratory depression and sporadic occurrence of oral secretions further underlines the efficacy of midazolam in this regard.

In conclusion, it can be said that IM midazolam at 0.1 mg/kg dose is the ideal dose and route for paediatric preanesthetic medication, but with inherent operational advantages in younger population and fairly acceptable outcomes, oral midazolam at 0.75 mg/kg may be considered an effective alternative.

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