Original Research Article

Evaluation of the sedative and anxiolytic effects of Midazolam and Clonidine as oral premedicant in paediatric patients undergoing elective surgery under general anaesthesia

Sangeeta Meena[1*], Kanta Bhati[2], Meera[3]

[1]Senior Resident, [2]Professor, [3]Assistant Professor
Department of Anesthesiology, Sardar Patel Medical College, Bikaner, Rajasthan, India
[*]Corresponding author email: **sangeetameena053@gmail com**

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Abstract

Background: The preoperative period is stressful in the paediatric patients; oral premedications make the experience of anaesthesia and surgery more pleasant and less traumatic.

Aim: To evaluate and compare the effects of midazolam and clonidine as oral premedicant for sedation, ease of parental separation, facemask acceptance at the time of induction of anesthesia, hemodynamic stability, postoperative recovery and complications.

Materials and methods: Total fifty children of either gender belonging to ASA grade I and II between 2-8 years age scheduled for elective surgery under general anesthesia were randomly and equally divided in two groups, 25 patients in each. Group M received oral midazolam (0.5 mg/kg) and group C, oral clonidine (4 µg/kg) 90 minutes before induction of anesthesia. Drug acceptability score, sedation score and parental separation score at 60 minutes and 90 minutes after the test drug administration and facemask acceptance at the time of induction were recorded. Hemodynamic stability and postoperative recovery were also observed.

Results: At 60 minutes after the test drug administration, the level of sedation and parental separation score were better in midazolam group while at 90 minutes, better in clonidine. Drug acceptability and

quality of induction score, hemodynamic stability and postoperative recovery was better in clonidine group.

Conclusion: We concluded that if we have proper time before induction, then oral clonidine is better sedative and anxiolytic drug, if not then oral midazolam is better sedative and anxiolytic drug in pediatric patients.

Key words

Children, Midazolam, Clonidine, Premedication.

Introduction

The preoperative period is very stressful in the pediatric patients and related to anxiety and fear of operation, injections, operation theatre environment, and parental separation. Almost 50% of children show signs of significant preoperative fear and anxiety [1].

Premedicating the pediatric patients has always been a challenge to the anesthesiologist because of their lack of co-operation, preferred non-traumatic route of drug administration and susceptibility to respiratory depression. Various pharmacological and behavioral interventions are used to treat preoperative anxiety in children and their parents. No drug or combination of drugs has been found to be ideal for premedication. Among the various routes of administration, oral route is best preferred in children [2].

Benzodiazepines have anxiolytic and hypnotic properties so routinely used as premedicants in children and adults. Midazolam has rapid onset and relatively short duration of action. A dose of 0.25-0.5 mg/kg of midazolam orally has proven to be efficacious in children with fewer side-effects [3]. We used oral syrup of midazolam (2 mg/ml) according to body weight (0.5 mg/kg).

Clonidine, although less popular, has been shown to produce preoperative sedation and anxiolysis, has analgesic properties, provide perioperative hemodynamic stability, and decreases narcotic and volatile anesthetic requirements. However, several studies on clonidine have revealed controversial results about its usefulness with some favouring its use while others discouraging its usefulness.

Thus, we thought it is worthwhile to evaluate sedation score and parental separation score of oral premedicants midazolam and clonidine at 60 and 90 min after the drug administration. Drug acceptability score, facemask acceptability score, hemodynamic stability and postoperative recovery were also evaluated and compared.

Materials and methods

After permission from institutional ethical committee, the study was conducted as hospital based prospective, randomised observational study.

The pediatric patients (n=50) of either gender belonging to ASA grade 1 and II between 2-8 years age, scheduled for elective surgery under general anesthesia were randomly selected and equally divided into two groups by ‘chit in box’ method. Group M received oral midazolam syrup (0.5 mg/kg) and group C received oral clonidine tablet 4 µg/kg (100 µg adult tablets crushed and mixed to fixed volume with honey) 90 minutes before the surgery. The Patients with a known allergy to the drugs used in the study, a history of reactive airway disease, asthma, neuromuscular disorder, an anticipated-to-be difficult airway, cardiovascular disease and shock were excluded.

After complete pre-anesthetic assessment, the procedure was explained to the parents and written informed consent was taken one day before surgery. All children were kept nil per orally 6 hour before surgery.

On the day of surgery, the baseline vitals (Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure, pulse rate and

O_2 saturation) were recorded and then the pre-calculated dose of the test drug was given to the child orally 90 min prior to surgery. Drug acceptance score was recorded.

Then allow the parents to keep the child in a quiet, undisturbed area. Vital monitoring was done continuously in preoperative period. Level of sedation & ease of parental separation were noted at 60 min and 90 min after the test drug administration. The child was shifted in Operation Theatre after 90 min of the drug administration.

In the operating room intravenous access was secured and sedation score was noted. Standard intra-operative monitoring was used. Heart rate (HR), respiratory rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and oxygen saturation were noted before induction of anaesthesia. Inj. glycopyrolate 4-8 µg/kg was given to the child. Quality of anaesthetic induction in terms of acceptance of face mask was graded via four point quality of induction score.

The child was induced by inhalational agents (with 33% oxygen in 66% nitrous oxide and 8% sevoflurane) via face mask ,when adequate depth of general anaesthesia (stage III plane I =fixation of eyeball centrally, attenuation of eyelash reflex and pattern of respiration (deep and slow)) was achieved then appropriate sized classic LMA was pushed along hard palate using index finger in classic sniff position of head and cuff inflated and fixed centrally after checking bilateral air entry equal in both sides of chest.

Anesthesia was maintained with 66% nitrous oxide in 33% oxygen and sevoflurane in concentration 3% to 4% with supplemental doses of vecuronium (0.025 mg/kg.) as and when required for controlled ventilation. Inj. fentanyl (1-2 µg/kg) was given as per need. Intra-operative hemodynamic parameters were recorded. After completion of the surgical procedure the child was reversed with injection neostigmine (40 to 80 µg/kg) and injection glycopyrolate (4 to 8 µg/kg) and removes the LMA after return of adequate muscle power and regular spontaneous respiration.

Post-operative recovery was assessed by using modified Aldrete's recovery score. The Child was observed for 2 hour in PACU (post anaesthesia care unit) for any postoperative complications like nausea, vomiting, hypotension, bradycardia, respiratory depression, agitation, arrhythmias and treated with appropriate measures.

Statistical analysis

The data was complied and subjected to statistical analysis using statistical package for social sciences (SPSS), version 10. The demographic profile and hemodynamic profile were compared by using ANOVA test. The compliance score, quality of induction score and sedation scores were analyzed by using the Chi-square test. $P<0.05$ was considered as statistically significant and $p<0.001$ considered as statistically highly significant.

Results

A total of fifty pediatric patients completed the study. The two groups were comparable with respect to age, sex, weight and ASA grade (**Table – 1** and **Table - 2**).

Table - 1: Patients characteristics.

Characteristics	Group M	Group C
Number	25	25
Gender ratio M/F	17/8	21/4
Age* (Year)	5.38±2.09	4.86±2.21
Weight <20 Kg Weight >20 Kg	13ǂ 12ǂ	21 4

*= mean age, ǂ= number of patients

Drug acceptance was better in clonidine (100%) than midazolam group (92%) where 8% children refused midazolam syrup (**Figure – 1**).

Sedation score at 60 minutes was better in group M where 80% patients scored 2 compared to

group C where all patients were awake and oriented (score 1) (**Figure – 2**). At 90 minutes level of sedation was better in group C where 80% scored 3 and 16% had score 2 while in group M 100% patient had score 2.

At 60 minute, 56% children in group M were calm and sleepy (score 1) easily separated from their parents compared to group C where 84% were apprehensive (score 2) (**Figure – 3**).

At 90 minute, separation score was better in group C compared to group M (96% vs. 84%) in score 1.

On statistical analysis of parental separation score at 60 and 90 minutes were highly significant in group C ($p<0.001$), significant in group M ($p<0.05$).

Facemask acceptance was better in group C where 72% children had score 4 (excellent) and 24% scored 3 (good) compared to group M where 44% had score 4 and 52% had score 3, 4% children had score 2 in each group. The result was statistically highly significant ($p<0.001$) when compared two groups (**Figure – 4**).

Table - 2: Comparison of various scores between Midazolam and Clonidine groups.

Scores	Group M	Group C	P value
Drug acceptability score –			
1 = Good - readily takes medicine	23 (92%)	25 (100%)	
2 = Fair - accepts medicine with persuasion	Nil	Nil	0.193
3 = Poor - spits it out	Nil	Nil	
4 =Refuses medicine	2 (8%)	Nil	
Five point the Wilson sedation score (90 min.)			
1 = Child awake and oriented	Nil	1 (4%)	<0.001
2 = Drowsy	25 (100%)	4 (16%)	
3 = Eyes closed but arousable to command	Nil	20 (80%)	
4 = Eyes closed, but arousable to mild physical stimulation	Nil	Nil	
5 = Eyes closed, but unarousable to mild physical stimulation	Nil	Nil	
Four point separation score (90 min.)			
1 = Calm and sleepy	21 (84%)	24 (96%)	<0.001
2 = Apprehensive but withdrawn from surroundings	4 (16%)	1 (4%)	
3 = Crying	Nil	Nil	
4 = Agitated but difficult to control	Nil	Nil	
Acceptance of facemask via four point score			<0.001
1 = Poor - afraid, combative, crying	Nil	Nil	
2 = Fair - moderate fear of mask, not easily calmed	1 (4%)	1 (4%)	
3 = Good - slight fear of mask, easily calmed	13 (52%)	6 (24%)	
4 = Excellent - unafraid, cooperative, accepts mask easily	11 (44%)	18 (72%)	

Hemodynamics

There was a decrease in mean pulse rate, mean blood pressure in both groups at 90 minutes after drug administration and 10 and 20 minutes after induction (mask application and LMA insertion) from their respective baseline values as per **Table - 3,** but the decreased was more significant in group C ($p < 0.05$).

Figure - 1: Drug Acceptability Score /compliance score.

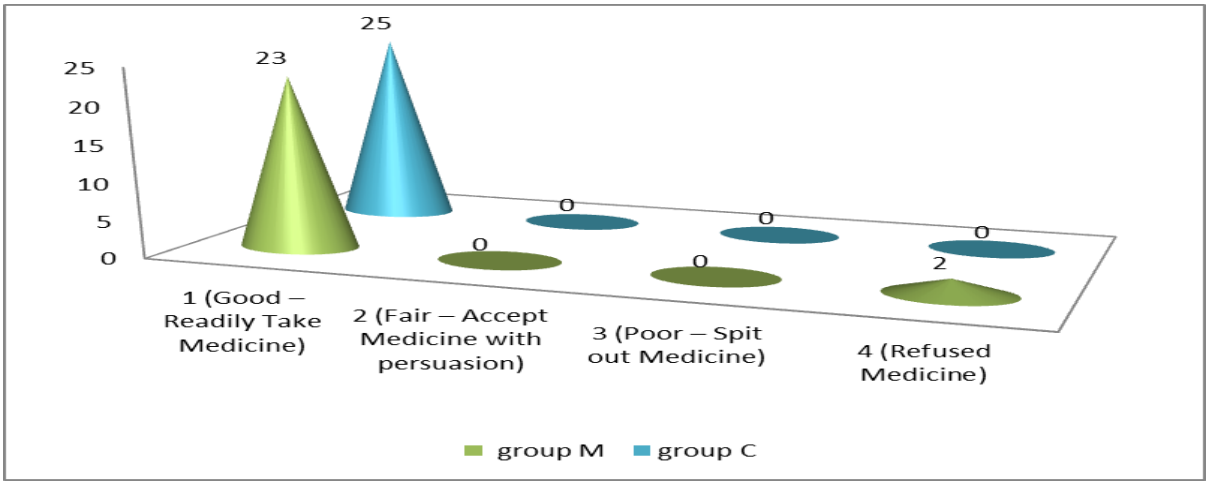

Figure - 2: Sedation score (recorded at 60 and 90 minutes after drug administration).

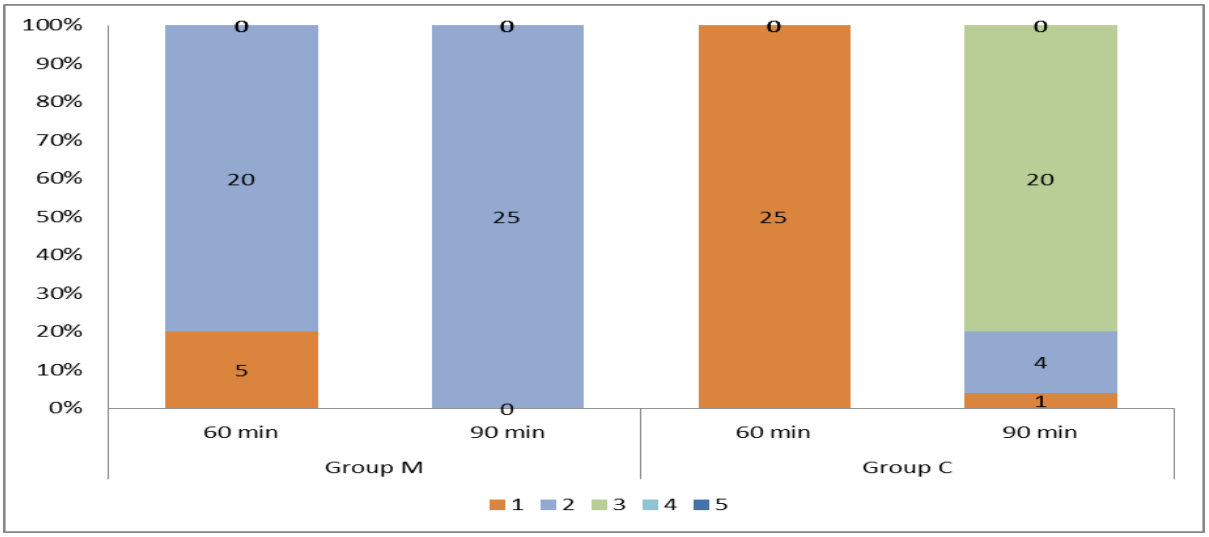

Figure -3: Parental separation score (at 60 and 90 minutes after drug administration).

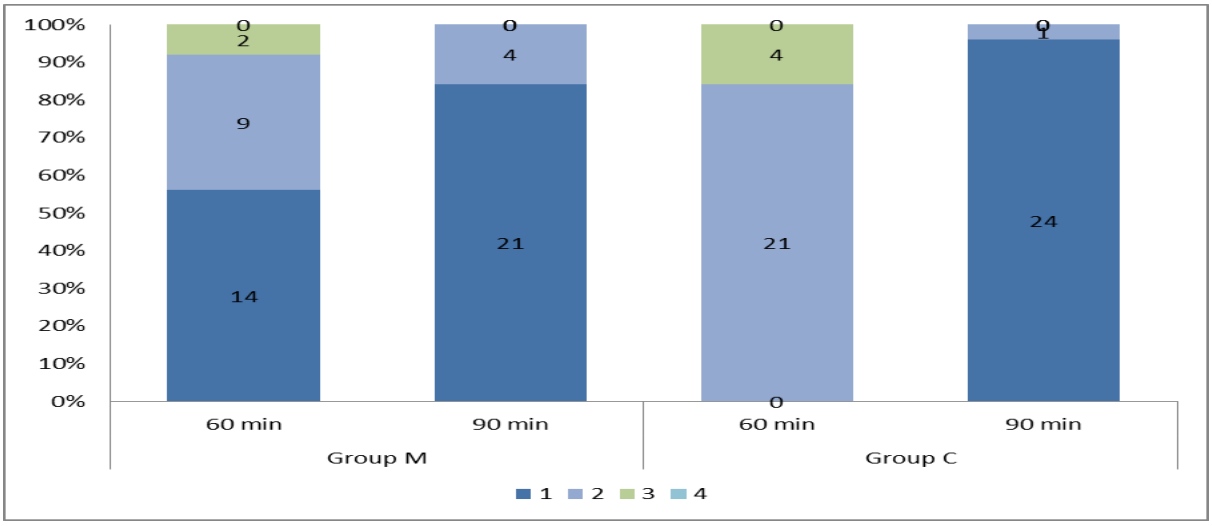

Figure - 4: Facemask acceptability score.

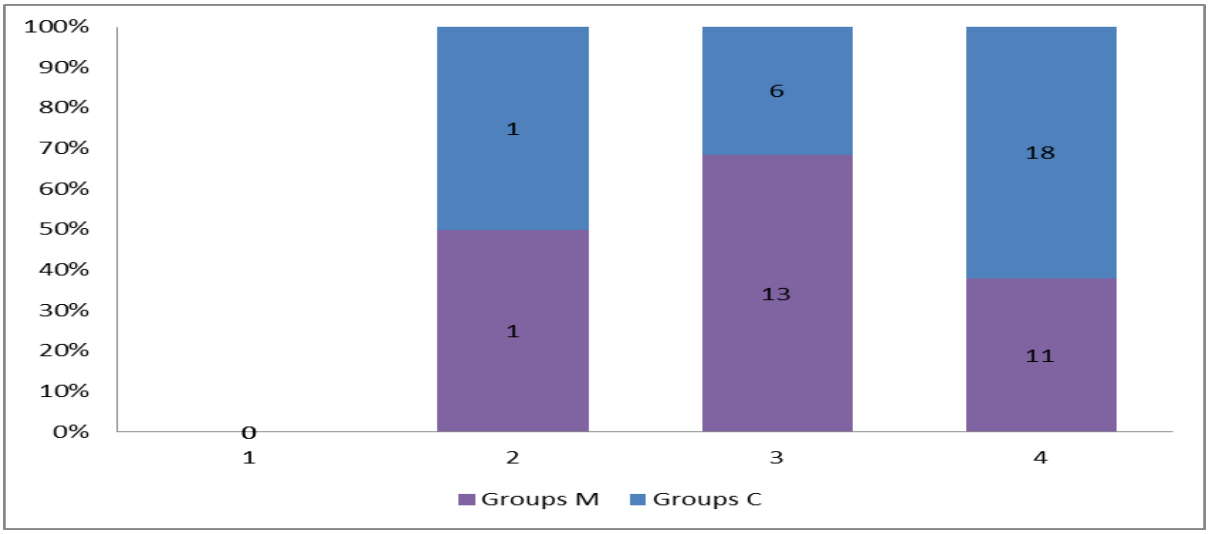

Table- 3: Hemodynamic parameters.

Time	Group M	Group C
Mean pulse rate		
Baseline	***121.76±20.86***	112.52±15.17
90 minutes after drug administration	117.28±14.86	109.52±18.40
10 minutes after induction	112.59±14.69	106.52±18.53
20 minutes after induction	115.61±12.72	103.13±14.67
Mean blood pressure		
Baseline	88.72±15.10	82.19±6.87
90 minutes after drug administration	87.40±13.67	78.76±7.49
10 minutes after induction	86.45±17.72	80.12±9.88
20 minutes after induction	88.33±13.17	80.79±8.92

Recovery profile

Modified Aldrete's recovery score was used to evaluate the initial recovery in the child with the discontinuation of anesthesia. The children in group C were fully conscious and cooperative, had score 9.76±0.89, while in Group M some children were drowsy and rest were fully conscious and cooperative. The recovery score were 9.40±0.81 in group M. Statistical comparison was insignificant (p >0.05).

Complications

Only one patient in group C developed bradycardia after giving clonidine which was treated with appropriate dose of atropine. Emergence agitation was seen in two patients of group M. Side effects like nausea, vomiting, respiratory depression, resedation were not observed.

Discussion

The preoperative period is stressful in the paediatric patients because of fear of body discomfort, separation from parents & an unknown operation theatre environment. Perioperative anxiety is seen in 40%-60% of infants, highest incidence is seen in 1 to 5 years of age. The oral premedications for relieve anxiety in paediatric patients have been used in several previous studies. Many authors have studied recently on oral midazolam or oral clonidine as premedication and found good results. There were no such study occurred in our hospital groups.

So, we decided to carried out this study to evaluate the sedative and anxiolytic effects of midazolam and clonidine in paediatric patients undergoing elective short surgeries like herniotomy, hydrocele etc. We found that the compliance of clonidine (100%) was better than midazolam (92%). Almenrader, et al. [4] and Sahoo, et al. [5] found that clonidine is better acceptable than midazolam.

The level of sedation was higher in group C (score 3 in 80% children) but overall acceptable sedation was in group M (score 2 in 100% children). On statistical analysis the sedation score at 60 and 90 minutes was found highly significant (p value <0.001) in clonidine group (C) and significant (p value <0.05) in midazolam group (M). Almenrader, et al. [4] and Cao, et al. [6] found the level of sedation (score ≥2) significantly better in clonidine when compared to midazolam. Sahoo, et al. [5] found midazolam better sedative and anxiolytic at the time of parental separation and mask induction than oral clonidine which was diverge from our finding.

Parental separation score was better in midazolam compared to clonidine group, at 60 minutes but at 90 minutes better in group C. Trevor, et al. [7] who found that at the time of parental separation 80% of children in clonidine group were adequately sedated (sedation score 3 and 4) compared to 30% in the midazolam group (p value of <0.001). According to Cao, et al. [6] clonidine 4 µg/kg produced better quality of separation from parents than diazepam. Our results differ from Fazi, et al. [8] found that Modified Yale Preoperative Anxiety (mYAS) score at the time of parental separation and at mask induction were higher in the clonidine group (4 µg/kg) than midazolam group. Frank, et al. [9] and Schmidt, et al. [10] observed similar degree of sedation and anxiolysis in oral clonidine (4-5 µg/kg) and oral midazolam (0.1-0.5 mg/kg) in Paediatric surgical patients.

Quality of mask acceptance was excellent in group C in 72% (score 4) than group M (44%). Mikawa, et al. [11] found better quality of mask acceptance in clonidine group (4 µg/kg) than diazepam group (0.4 mg/kg). Cao, et al. [6] observed that the facemask acceptance was significantly higher in clonidine group than midazolam group (score was 2.9±1.0 vs 1.4±0.6 respectively). Fazi, et al. [8] , Almenrader, et al. [4], Sahoo, et al. [5] and Tazeroulti, et al. [12] found that, the mask acceptance was better in midazolam than clonidine group which was differ from our results.

There was a uniform trend of decrease in mean pulse rate and mean blood pressure in both groups as compared to their baseline values. On intergroup comparison revealed that the decrease in vitals were significantly more in clonidine group comparison to midazolam at 90 minutes after the test drug administration, 10 and 20 minutes after induction (p value was <0.05).

Sahoo, et al. [5] found higher incidence of nausea & vomiting and postoperative shivering in midazolam group than clonidine group. However, Fazi, et al. [8] and Cao, et al. [6] found no clinically significant episodes of bradycardia or hypotension in both the clonidine and midazolam groups. We found bradycardia only in one patient in clonidine group and emergence agitation in two patients in midazolam group. No other side effects like nausea, vomiting, hypotension, respiratory depression etc. were observed.

Limitations

- There was no blindness in our study for evaluation of preoperative sedation and parental separation score. It was a open prospective study.
- The clonidine tablet was given with honey while midazolam in a syrup form, the absorption of drugs may be affected by PH of diluents which was not addressed in the study.
- The onset of action of clonidine is (90-110 min.). It is not possible to premedicate the child 90min. before surgery in our hospital setting.

- Proper preoperative vital monitoring was not possible in hectic schedule of pediatric short surgeries in our hospital setting.

Conclusion

We concluded that clonidine is better sedative and anxiolytic drug if sufficient time available before induction, if not then oral midazolam is better drug in paediatric patients. The search for ideal premedication for children is still continuing and need for further studies.

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