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Original Research Article

A comparison of oral clonidine with oral midazolam for premedication in paediatric anaesthesia

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Abstract

Background: Midazolam is currently the most commonly used premedicant, but newer drugs such as the α2-agonists have emerged as alternatives for premedication in children. Hence the present study was undertaken to compare the clinical effects of oral clonidine and oral midazolam for premedication in paediatric anaesthesia.
Method: In a prospective, observational study, 60 children of age range from 2-10 years, ASA grade I and II were randomly assigned in two groups to receive either oral clonidine 4mcg/kg (Group C) or oral midazolam 0.5mg/kg (Group M) prior to induction of anaesthesia. Drug acceptance, preoperative sedation, anxiolysis, parenteral separation, venepuncture, quality of mask acceptance and induction, perioperative haemodynamic stability, postoperative sedation and behavior were noted.
Results: Both the drugs were palatable with honey out of 30 patients in each group, 9(30%) patients in group-C and 8(26.66%) patients in group-M taste as indifferent but palatable. Onset of sedation was significantly faster after premedication with midazolam (31.00 ± 8.03 min) than with clonidine (40 ± 7.88 min). At 30 to 50 minutes, anxiolysis was better in group M than group C while the quality of parental separation was better in group-C than group-M. At the time of venous cannulation children were more sedated in group C than in group M. Oral clonidine was better premedicant than oral midazolam in paediatric patients in terms of mask acceptance, quality of induction, hemodynamic stability and post operative behaviour.
Conclusion: From the above results, current study recommends use of oral clonidine 4mcg/kg as a novel premedicant in paediatric anaesthesia.
Keywords: Midazolam, α2-agonists, Premedication, Clonidine, Anxiolysis, Anaesthesia.

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1. Introduction

Anaesthesia induction appears to be the most stressful procedure that children experience during the peri-operative period. It has been associated with negative behaviors during and after the surgical experience, like post-operative pain, sleeping disturbances, parent child conflict and separation anxiety [1]. For reducing the incidence of pre-operative anxiety in children, a number of pharmacological (e.g., sedatives) and non-pharmacological (e.g. parental presence, behavioural preparation programs, music, acupuncture, etc) approaches have proven to be useful[1]. The oral route of administration of premedication has gained wide acceptability in achieving sedation and anxiolysis not only in the pre-operative room, but for undergoing various procedures outside the theatre.

The ideal premedicant for children scheduled for ambulatory surgery should: (1) be available in a preparation that is readily accepted by the children; (2) have a relatively rapid and reliable onset; (3) provide anxiolysis with mild sedative effects; (4) have anxiolytic and sedative effects of sufficient duration to accommodate delays in operating room scheduling without delaying discharge; (5) be free of side effects that would necessitate high levels of nursing supervision; and (6) provide for a rapid recovery and return to alertness postoperatively, thereby permitting early discharge from the recovery area [2].

Since, century various drugs used to relieve anxiety like cloral hydrate, promethazine, diazepam, midazolam.

Oral midazolam is the pharmacological agent of choice as pediatric premedication. However, an increased incidence of adverse postoperative behavior changes [3], hiccups [4], paradoxical reactions [5], and impaired post-operative cognitive function [6,7] observed with midazolam has resulted into the search for other ideal agents. 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 [8,9]. However, several studies on clonidine have revealed controversial results about its usefulness with some favoring its use[10,11] while others discouraging its usefulness [12,13].

With the background of above studies the present study was conducted to compare multiple characteristics of oral clonidine and oral midazolam as a premedication in children, in terms of pre-anesthetic sedation, anxiolysis, palatability, parental separation, effect on hemodynamics, cooperation during venepuncture and face mask application and quality of induction.

2. Materials and Methods

After obtaining Institutional Ethical Committee approval and parent's written informed consent, this prospective, observational study was conducted in 60 pediatric patients, aged 2–10 years of ASA grade I or II, scheduled for elective surgery under general anaesthesia. Children with age >10 years and <2 years, ASA grade 3 or 4, weight more than 25 kg, surgeries lasting for more than one hour, children with suspected coagulopathy or bleeding disorders, active neurological disease, any active respiratory tract infection, allergy to any of the study drugs being used or history of asthma and mental retardation were excluded from the study. Patients were fasted for at least 6 hr prior to surgery for solid, 5 hr for milk and 3 hr for clear fluids. They were randomly divided into two groups of 30 each. Group C- received 4mcg/kg oral clonidine. Tablet clonidine 100 mcg was crushed n mixed with 5 ml of honey, dose calculated according to body weight and then given to the child. Group M- received 0.5mg/kg oral midazolam. Injection midazolam was dissolved in 5 ml of honey and then given to the child according to body weight orally.

Pre operative assessment, necessary routine investigations like Hb%, CBC, urine routine microscopy as mentioned were done and patient vitals were noted. The oral midazolam and oral clonidine were administered 30 and 60 minutes prior to induction of anaesthesia respectively. Patient's response to premedication was observed in both the groups with regards to preoperative sedation, drug acceptance, anxiolysis, parenteral separation, venepuncture, quality of mask acceptance and induction, perioperative haemodynamic stability, postoperative sedation and behavior and noted using standard scoring systems. When a sedation score of 3 or 4 reached, the children were transferred to the induction room. If no satisfactory sedation level was achieved, the children were excluded from the study.

In the induction room, an intravenous line was secured and intravenous infusion was started with Isolyte-P. Injection Atropine 0.012mg/kg i.v. was given prophylactically in both the group. Anaesthesia was induced with sevoflurane 3 – 5% in oxygen through mask and maintained according to the usual practice. All the patients received rectal acetaminophen or diclofenac according to discretion of anaesthesiologist, for post-operative analgesia. Vital parameters were monitored continuously and noted every 10 minutes. At the end of surgery and discontinuation of anaesthesia, behaviour at awakening was noted. The child were shifted to the recovery room and observed for vital parameters and post operative sedation score, any adverse effect like hypotension, bradycardia, respiratory depression, nausea/vomiting, shivering and were treated accordingly.

2.1 Statistical Analysis

The data was collected and compiled using Epi info 7.2. The qualitative variables were expressed in terms of proportions and the difference between the two proportions was tested by Chi square or Fisher exact test. The quantative variables were either categorized and expressed in percentages or expressed in terms of mean and standard deviation. The difference between two means was tested by t test. All analysis was two tailed and the significance level was set at 0.05.

3. Observations and Results

There was no statistically significant difference observed between two groups with respect to demographic data, type and duration of surgery, (Table 1). As well the preoperative values of hemodynamic parameter (heart rate, SBP, DBP, RR, and SpO_2) were comparable between two groups and found no significant difference. The drug acceptance by the children was noted with respect to their tastes. We observed that both the drugs palatable with honey out of 30 patients in each group, 9(30%) patients in Group-C and 8(26.66%) patients in group-M taste as indifferent but palatable.

Table 1: Demographic Data, Type and Duration of Surgery

Variable		Group C	Group M	P Value
Age (yrs)		5.60±1.52	5.37±1.85	0.7983
Sex	Male	20 (66.67%)	22 (73.33%)	0.5713
	Female	10 (33.33%)	8 (26.67%)	
Weight (kg)		13.33 ± 2.51	13.13 ± 2.48	0.7967
Type of Surgery	Herniotomy	20 (70%)	18 (60%)	0.542
	Circumcision	10 (30%)	12 (40%)	
Duration of surgery (min)		35.0±5.088	38 ± 7.50	0.785

At 30-40 min, sedation score of 3 and 4 was achieved in midazolam group and score 1 and 2 was achieved in clonidine group. This difference was statistically significant as the action of clonidine was yet to start, so oral midazolam was better at 30-40 min. At 50 minute score 4 achieved in 83.33% of patients in both the groups so both the groups were comparable at 50 minutes. At 60minutes in group C 93.33% of patients achieved score 4 while in group M 83.33% patients achieved score 4 (Table 2), but level of sedation was significantly better in group-C than group-M. The time to onset of the satisfactory sedation score of ≥3 was 40 ± 7.88 minutes in group-C and it was 31.00 ± 8.03 minutes in group-M. This difference was statistically significant (P<0.0001).

Table 2: Distribution of subjects based on sedation scores during sedation in both groups

Time Intervals During Sedation	Group C				Group M				P value
	1 (%)	2	3	4	1	2	3	4	
10 min	30 (100)	0 (0)	0 (0)	0 (0)	30 (100	0 (0)	0 (0)	0	1.000
20 min	30 (100)	0 (0)	0 (0)	0 (0)	30 (100)	0 (0)	0 (0)	0	1.000
30 min	27 (90)	3 (10)	0 (0)	0 (0)	1 (3.33)	9 (30)	20(66.67)	0	<0.001
40 min	21 (70)	9 (30)	0 (0)	0 (0)	1 (3.33)	7 (23.33)	19 (80)	3 (10)	<0.001
50 min	0 (0)	2 (6.67)	3 (10)	25 (83.33)	0 (0)	2 (6.67)	3 (10)	25 (83.33)	>0.05
60 min	0 (0)	0	2 (6.67)	28 (93.33)	0 (0)	2 (6.67)	3 (10)	25 (83.33)	<0.006

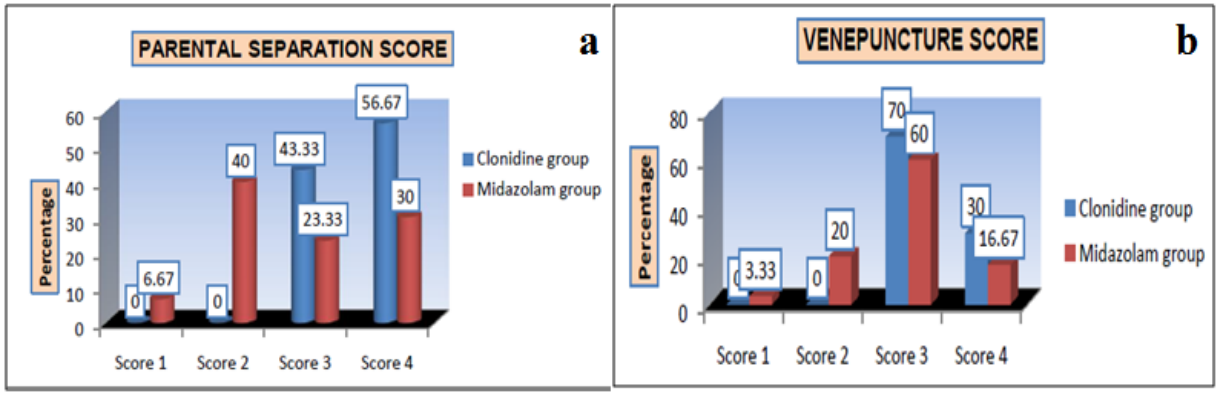
At 30 minutes, none of the patients in group C achieved satisfactory anxiety score ≥ 3 while 46.67% of patients of group M achieved satisfactory anxiety score which was statistically significant (p<0.001) but at this time clonidine action yet to start. At 40 minutes only 16.67% patients in group C achieved satisfactory anxiety score (score 3) while 46.67% of patients in group M achieved score 4 which was statistically significant. (p<0.001) At 50 minutes, anxiolysis was better in group M where already the action of clonidine has started. At 60 minutes, score 4 was achieved in 60% of patients of group C while in group M 66.67% of patients achieved score 4, which was statistically insignificant.(p=0.592). So, at 30 to 50 minutes midazolam was better than clonidine as anxiolysis of the patient was concerned (Table 3).

Table 3: Distribution of subjects based on anxiety scores during sedation in both groups

Time Intervals During Sedation	Group C				Group M				P value
	1	2	3	4	1	2	3	4	
10 min	30 (100)	0 (0)	0 (0)	0 (0)	30 (100	0 (0)	0 (0)	0	1.000
20 min	30 (100)	0 (0)	0 (0)	0 (0)	30 (100)	0 (0)	0 (0)	0	1.000
30 min	19 (63.3)	11 (36.67)	0 (0)	0 (0)	2 (6.67)	11 (36.67)	14 (46.67)	3 (10)	<0.001
40 min	9 (30)	16 (53.33)	5 (16.67)	0 (0)	1 (3.33)	1 (3.33)	14 (46.67)	14 (46.67)	<0.001
50 min	0 (0)	6 (20)	20 (66.67)	4 (13.33)	0 (0)	0	8 (26.67)	22 (73.33)	<0.001
60 min	0 (0)	0	12 (40)	18 (60)	0 (0)	0	10 (33.33)	20 (66.67)	0.5920

The quality of parental separation was better in group-C than group-M and which was statistically significant (p=0.0003), (Figure 1a). At the time of venous cannulation, children were more sedated in group C than group M (Figure 1b).

Figure 1: Distribution of the study subjects based on the parental separation score (a) and Venepuncture score (b)



The mask acceptance and quality of induction score 4 was achieved in 53.33% of patients in group-C and in 46.67% of patients in group-M, while score 5 was achieved in 43.345 of patients in group-C and 6.67% of patients in group-M. The mask acceptance and the quality of the induction were significantly better in the clonidine group as compared to those in the midazolam group (p=0.0002), (Table 4).

Table 4: Distribution of the study subjects based on the acceptance of mask and quality of induction score

Score	Group-C		Group-M		P value
	No	%	No	%	
Score 1	0	0	0	0	
Score 2	0	0	1	1.33	
Score 3	1	3.33	13	43.34	0.0002
Score 4	16	53.33	14	46.67	
Score 5	13	43.34	2	6.67	

Haemodynamic parameters (HR, SBP, DBP), respiratory rate and oxygen saturation after sedation was noted in both the groups at the interval of 10 minutes up to 60 minutes. Also all these parameters were noted during venepuncture, during induction and intraoperatively every 10 minutes till the procedure completes and postoperatively at 10 min, 30 min, 60 min, 90 min, and 120 minutes. Both the groups were comparable with respect to HR, SBP, DBP, respiratory rate and oxygen saturation and change in all these parameters from baseline after sedation was clinically insignificant (p>0.05). Similarly, all the parameters were within the normal limits and comparable between the groups during sedation, during intraoperative period and postoperative period.

In addition, post operative sedation score was comparable in both the groups at 0-60 minutes and found no significant difference. At 90 and 120 minutes more number of patients was calm and quiet in group C as compared to group M while patients were alert and awake in group M, (Table 5).

Table 5: Post operative sedation score in both the groups

Time Intervals	Group C				Group M				P value
	1	2	3	4	1	2	3	4	
0 min	0 (0)	17 (56.67)	13 (43.33)	0 (0)	0 (0)	17 (56.67)	13 (43.33)	0 (0)	1.000
10 min	0 (0)	17 (56.67)	13 (43.33)	0 (0)	0 (0)	17 (56.67)	13 (43.33)	0 (0)	1.000
30 min	0 (0)	21 (70.00)	9 (30.00)	0 (0)	0 (0)	22 (73.33)	8 (26.67)	0 (0)	1.000
60 min	0 (0)	25 (83.33)	5 (16.67)	0 (0)	0 (0)	25 (83.33)	5 (16.67)	0 (0)	1.000
90 min	5 (16.67)	25 (83.33)	0 (0)	0 (0)	6 (20.00)	24 (80.00)	0 (0)	0 (0)	1.000
120 min	5 (16.67)	25 (83.33)	0 (0)	0 (0)	7 (23.33)	23 (76.67)	0 (0)	0 (0)	1.000

Table 6 shows the postoperative behavioural score in both the groups. At 30 minutes, 30% of children in group C had behavioural score of 4 (i.e. calm and cooperative) as compared to 26.67% of children in group M. At 120 minutes, 56.67% of children in group C had behavioural score of 3 as compared to 53.33% of children in group M. Hence, in the post operative period more number of patients was calm and cooperative in group C than group M, this difference in number was statistically not significant (p>0.05).

Table 6: Post operative behavioural score in both the groups

Time Intervals	Group C				Group M				P value
	1	2	3	4	1	2	3	4	
0 min	0 (0)	0 (0)	12 (40.00)	18 (60.00)	0 (0)	0 (0)	11 (36.67)	19 (63.33)	0.7906
10 min	0 (0)	0 (0)	17 (56.67)	13 (43.33)	0 (0)	0 (0)	17 (56.67)	13 (43.33)	1.000
30 min	0 (0)	13 (43.33)	8 (26.67)	9 (30)	0 (0)	13 (43.33)	9 (30.00)	8 (26.67)	0.9429
60 min	0 (0)	13 (43.33)	8 (26.67)	9 (30)	0 (0)	13 (43.33)	9 (30.00)	8 (26.67)	0.9429
90 min	0 (0)	13 (43.33)	17 (56.67)	0 (0)	0 (0)	13 (43.33)	17 (56.67)	0 (0)	1.000
120 min	0 (0)	13 (43.33)	17 (56.67)	0 (0)	0 (0)	14 (46.67)	16 (53.33)	0 (0)	1.000

4. Discussion

In the present study route of drug administration was oral route as it easily acceptable by children. Studies mentioned that rapid onset of oral midazolam in children due to very efficient trans-mucosal absorption and lesser extent gastrointestinal absorption [14]. Clonidine is rapidly absorbed after oral administration. Since oral preparations of midazolam are not widely available, we used the injection midazolam mixed with honey to make it palatable. Injection midazolam has been mixed with plane syrup, flavored syrup, apple juice etc. Various authors [1,15,16] used honey to make injection midazolam more palatable while Desai *et al* [14] used cherry syrup to make it more palatable. We used dose of midazolam 0.5 mg per kg of weight, this was similar to dose given in various studies [2,17,18] and dose of clonidine used was 4 mcg per kg of weight, also this was similar to dose given in previous studies [14,19]. Different studies [20-23] shows that the time to onset of action of injection midazolam with oral route in dose of 0.5 - 0.75 mg/kg within 20-30 minutes and oral clonidine in dose range of 3-5 mcg/kg within 60 – 90 minutes. In current study we administered oral clonidine 4 mcg/kg and oral midazolam0.5 mg/kg 60 minutes prior to induction of anaesthesia.

The demographic data, type and duration of surgery was statistically comparable in both the group. The

baseline parameters like heart rate, SBP, DBP, RR, SpO_2 were recorded after sedation with oral clonidine 4mcg/kg or oral midazolam 0.5 mg/kg and were comparable in both groups. The drug acceptance by the children was noted with respect to their tastes, both the drugs palatable with honey out of 30 patients in each group, 9(30%) patients in group-C and 8(26.66%) patients in group-M taste as indifferent but palatable. The level of sedation was significantly better in midazolam group at 30-40 min. Both the groups were comparable at 50 minutes while at 60minutes, the level of sedation was significantly better in group-C than group-M. These results were compared with previous studies [1,15,19]. The onset of sedation was significantly faster after premedication with midazolam than with clonidine. There was statistically significant difference observed in anxiety score at 30 and 40 minutes but at this time action of clonidine was yet to start. At 50 minutes, anxiolysis was better in group M where already the action of clonidine starts. At 60 minutes, there was no statistically significant difference observed in anxiety score. So, at 30 to 50 minutes midazolam was better than clonidine as anxiolysis of the patient was concerned. These results were correlated with different studies [1,24-26]. The quality of parental separation was better in group-C than group-M and which was statistically significant; this was consistent with findings stated by Mahajan *et al* [1].

Reaction to venous cannulation was in group-C 21(70%) and 9 (30%) number of patients had minor resistance (score 3) and no reaction (score 4) to venous cannulation, respectively. In group-M, 18 (60 %) and 5 (16.67%) number of patients had minor resistance (score 3) and no reaction (score 4) to venous cannulation, respectively. Thus at the time of venous cannulation children were more sedated in clonidine group than in midazolam group (p=0.0388) whereas the mask acceptance and quality of induction were significantly better in clonidine group as compared to those in midazolam group (p=0.0002**).** The findings in our study were consistent with findings stated by other author [1,15,16,27].

The study found oral clonidine 4mcg/kg and oral midazolam 0.5mg/kg both have stable effects on hemodynamics throughout periopertaive period with respect to HR, SBP, DBP, RR, SpO_2. This observation was supported by various earlier studies [1,15]. In group-C, we recorded minimum heart rate of 70beats/minute in 3 patients which was clinically not significant bradycardia to be treated with injection Atropine. None of the patients in both the groups had hypotension (decrease in systolic blood pressure more than 30% from baseline).

At 0-60 minutes, the post operative sedation score was comparable in both the groups with no clinical and statistical difference. At 90 and 120 minutes more number of patients was calm and quiet in group C as compared to group M while patients were alert and awake in group M and this observation was supported by various studies [1,9]. After the end of surgery and discontinuation of anaesthesia, behaviour at awakening and up to 120 minutes postoperatively were noted to found more number of patients were calm and cooperative in group C than group M, (p>0.05). None of the patients in any of the groups showed clinically significant bradycardia as all of the patients in group C and even in group M were given I.V. Atropine 0.012mg/kg prophylactically. Nausea and vomiting was noted in 2 patients (6%) in group C and 4 patients (8%) in group M while shivering was observed in 1 patient (3%) in group C and 3 patients (10%) in group M. This observation was consistent with other studies [1,16, 28].

Limitation of present study was that potential alteration in absorption of the drug based on pH changes induced by diluents- honey. In this case was not addressed in this study.

5. Conclusion

From the observations in the present study, it can be concluded that oral midazolam 0.5mg/kg is better anxiolytic than oral clonidine 4mcg/kg as premedicant in paediatric patients while oral clonidine 4mcg/kg is better premedicant than oral Midazolam 0.5mg/kg in paediatric patients in terms of peri-operative sedation, parental separation, venepuncture, mask acceptance, quality of induction, hemodynamic stability and post operative behaviour. The study recommends use of oral clonidine 4mcg/kg as a novel premedicant in paediatric anaesthesia.

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