

COMPARISON OF THE EFFECT OF ORAL MIDAZOLAM AND ORAL CLONIDINE AS PREMEDICATION IN CHILDREN UNDERGOING SURGERIES UNDER GENERAL ANESTHESIA

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Abstract

Background: To minimize distress in children in the operating room (OR) environment and to facilitate a smooth induction of anesthesia oral premedication is given in paediatric patients before going to OR. This reduces child's anxiety for parental separation, intravenous cannulation, and mask application before induction. A sedative drug, Midazolam is currently available the most commonly used premedication in children given before transfer to OR. Clonidine an α 2-agonist, can also be given for premedication as effective as midazolam. The beneficial effects of both are anxiolysis, and sedation preoperatively, hemodynamic stability intraoperatively and reduction of emergence phenomenon and other complications as PONV postoperatively.

Materials and Methods: 60 children who were in age group of 2-12 years were randomly divided into two groups. In Group I Midazolam 0.5 mg/kg was given orally while in Group II Clonidine 4 μ g/kg was given orally one hour before induction of anesthesia. They were evaluated and compared for benefits of preoperative oral midazolam and oral clonidine on sedation scores, parental separation, venipuncture, quality of induction and mask acceptance, perioperative hemodynamic parameters and analgesic requirements. Independent sample t-test was used and p-value < 0.05 was considered significant. **Result:** We found that oral midazolam tested significantly better efficacy in the preoperative period. As sedative and anxiolytic, midazolam had faster response after premedication. With midazolam (29.5 \pm 9.5) than with clonidine (38.2 \pm 12.3), better cooperation during venipuncture, facemask application p value (p<0.001). Whereas there were significant (P < 0.05) attenuation of hemodynamic response to intubation, surgical stress response and extubation with clonidine as compared to midazolam. None of the patients desaturated in either group. Opioid requirement (72%) was more in midazolam group as compared to clonidine (28%) group. Recovery in clonidine group took slightly longer time (60.00 \pm 13.77 min) as compared to midazolam group (44.40 \pm 13.25 min). **Conclusion:** We conclude that oral midazolam is better premedication than clonidine in children in preoperative period while clonidine is a better premedication for all surgeries to provide more sedation, stable hemodynamics intraoperatively, reduction in stress response, less opioid consumption with no significant side effects.

INTRODUCTION

Preoperative anxiolysis in children effects pre, intra and postoperative outcome of a surgery. The benzodiazepine midazolam, an anxiolytic drug, is the most commonly used premedication.^[1,2] Premedication with midazolam had shown to be

effective in reducing anxiety and improving compliance at induction of anesthesia. The beneficial effects of midazolam include sedation, anxiolysis, and reduction of postoperative vomiting,^[3] fast onset and limited duration of action. A recent evidence-based clinical update had shown that oral midazolam 0.5 mg/kg is effective in

reducing anxiety in children, with minimal effect on recovery time.^[4] However, it causes postoperative behavior changes, cognitive impairment,^[5] paradoxical reactions, and respiratory depression.^[6] Clonidine, an α 2-agonist, have been suggested as another option for premedication and previous studies have shown it to be equally as effective as midazolam. Oral clonidine premedication has also been shown to reduce the incidence of sevoflurane induced emergence agitation. A variety of beneficial effects before, during and after anesthesia, such as sedation, analgesia, increased cardiovascular stability and improved outcome, less respiratory depression have been attributed to clonidine. Clonidine reduced the requirement for volatile anesthetics when assessed by hemodynamic responses.^[7,8]

A national survey of premedication practices conducted by Kain et al,^[9] shows that Midazolam is that it is most commonly ordered premedication in pediatric anesthesia. The benefits of effective premedication include a reduction in both patient and parental separation anxiety, partial anterograde amnesia, facilitation of a smooth anesthetic induction, and a reduction in postoperative behavioral change. We therefore evaluated and compared the effect of oral midazolam and oral clonidine premedication in healthy children under going surgeries and hemodynamic response intra operatively and postoperative analgesic requirement.

MATERIALS AND METHODS

This study was conducted in the Department of Anesthesia, Rama Medical college Hospital and Research Center, Pilkhuwa, Hapur, India. Ethical clearance permission for the study was taken from the institutional ethical committee. A written and informed parental/guardian consent was obtained. 60 children ASA physical status I-II of either sex aged 2 to 12 yrs and anticipated to undergo major surgeries scheduled for tonsillectomy, appendectomy, herniotomy or urethroplasty under general anesthesia were randomly allocated group included in this study The anticipated duration of surgery was ≤ 2 hours. Patients were randomly divided into two groups of 30 patients each to receive one of the following premedication- Group I (Midazolam): Patients received Midazolam orally one hour before induction of anesthesia. Group II (Clonidine): Patients received Clonidine orally, one hour before induction of anesthesia.

Selection of Cases: Patients Children less than 2 years or more than 12 years or with physical status ASA-III or more or undergoing emergency operations or with any chronic medical illness or respiratory or cardiovascular disease, allergic to the drugs (benzodiazapines or clonidine) or NSAIDS alcoholic and psychiatric were excluded from study. Informed and written consent for participation in the study was obtained from each patient parents prior

to inclusion in the study. A thorough preoperative evaluation of each patient children was done. A detailed medical history and a general physical and systemic examination of each patient children was performed. All routine laboratory biochemical test, microbiological viral marker like HCV, HBsAg, HCV and hematological tests was done. ECG and X-Ray was obtained. At the time of this checkup, they were familiarized with sedation score. Patients The children were divided into two equal groups of 30 each viz. Group M and Group C. The child baseline behavior was noted during pre anaesthetic visit as clam, apprehensive, crying and thrashing. Children were fasted for 6-8 hrs prior to surgery. All sedative hypnotic premedication was avoided before the surgery. Baseline vitals heart rate, blood pressure, O₂ saturation, sedation score before giving premedication was recorded. Tab. Oral Midazolam 70.5 mg/kg or Tab.oral Clonidine 1004 μ g/kg orally one hour before induction of anaesthesia. In the operation room patient was monitored for ECG lead II, Heart induction. Heart Rate by Pulse Oximeter, Non-invasive Blood Pressure (Systolic BP, Diastolic BP and Mean BP). O₂ saturation, temperature, end tidal volume and urine output were noted just prior to induction of anesthesia (Pre induction), after intubation (Post intubation), and at the end of surgery (End of surgery). Sedation score before induction and after extubation was observed using CHEOPS sedation score. Before induction, patients were preoxygenated with 100% Oxygen. Anesthesia was induced with inj. Propofol 2mg / kg and Inj. Fentanyl 2.0 μ g / kg. After giving Inj. Vecuronium bromide 0.1 mg / kg body wt. IV. and ventilating the patient with O₂ and N₂O for 3 minutes, trachea was intubated with cuffed oral endotracheal tube of appropriate size and anesthesia was maintained with Isoflurane Nitrous oxide and oxygen with controlled ventilation to keep EtCO₂ within normal range. During maintenance of anesthesia, administration of Inj Fentanyl 0.5 to 1 μ g / kg body wt. was added depending upon clinical condition like (movement, swallowing, lacrimation, sweating,) and alteration of hemodynamic parameters like, a 20 % increase in the systolic blood pressure or heart rate from the base line values. At the end of the surgery neuromuscular blockade was reversed with Inj. Neostigmine (0.04 mg/kg) and Inj. Glycopyrrolate (0.01 mg/kg). In the last all patients children were given inj. Ondansetron 42 mg/kg for prevention of PONV. Post operatively patients were kept in post anaesthesia care unit (PACU). Time to achieve full Aldret score was noted for patient to be ready to be shifted from PACU.

RESULTS

By using 2 independent sample t-test p-value > 0.05 therefore there was no significant difference between Group midazolam and Group clonidine with respect to demography.

and with respect to type of surgical procedures performed.

As regard to the level of apprehension all 30 children in both groups had no anxiety just before separation from parents i.e. both drug resulted in anxiolysis with no significant difference between the two group till the time children were with parents. After separation from parents, As the level of apprehensions in terms of sedation also, both the drug resulted in good level of sedation till the time children were kept with their parents with no significant difference between two group. After separation from parents in group M children were awake/clam and quiet whereas in Group C only 19 children were awake and quiet. Therefore it was observed towards midazolam resulted in a better level of sedation as compared to clonidine after parental separation and induction. Reaction of the children to venipuncture for intravenous access and to the application of face mask was also assessed in both group. In group M none of the children were crying at the time of venipuncture, where as in group C 22 (51%) children were crying. Similarly during facemask application 17 children in group M had excellent response but in group C only 2 children readily accepted facemask. So midazolam certainly resulted in a better facemask acceptans.

There was statistically significant difference seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to HR from baseline b- Pre-Induction, c-After Intubation, d-End of Surgery, e- At CHEOPS scale. There was significant attenuation of heart rate in clonidine group as compared to midazolam group. In group M, there was a significant increase in heart rate and blood pressure before induction as compared to the base line values and in group C, there was a significant decrease in both the heart rate and blood pressure. During laryngoscopy and endotracheal intubation and also 5 minute after extubation, there was a significant increase in the heart rate and blood pressure above the base line, however, this increase was much more heigher in group M as compared to group C. Overall in inter group comparison clonidine resulted in a better haemodynamic parameter in perioperative period.

There was statistically significant difference seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to BP from baseline b- Pre-Induction, c-After Intubation, d-End of Surgery, e- CHEOPS score immediate and after early post operative period. There was significant attenuation of blood pressure in clonidine group as compared to midazolam group.

There was statistically insignificant (2 independent sample t-test p-value > 0.05) difference seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to O2 saturation. None of the group desaturated at any point of time.

There was statistically significant difference (p value <0.001) seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to sedation

score from baseline, Pre-Induction and post operatively. Clonidine group patients were more sedated as compared to midazolam group after post operative.

There was statistically significant (p value<0.001) difference seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to opioid /analgesic requirement.

There was statistically significant (p value<0.001) difference seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to CHEOPS score. Full CHEOPS score achieved earlier in midazolam group as compared to clonidine group. The mean CHEOPS score in the immediate (with in 2 hour) and early(2-12 hours) postoperative period in group M were 5.61±1.91 and 6.10±1.61 respectively against 3.30±1.11 and 5.03±1.71 in group C. So clonidine resulted in better pain relieve than midazolam. Need of rescue analgesics in latter group where 9 children required rescue analgesics within 2 hour and 17 children in group required analgesics in subsequent 2-12 hours postoperatively. Whereas only 1 child required in first 2 hour and 1child required in 2-12 hours.

[Table 1] For scoring of palatability, venipuncture, Face mask acceptance, Night sleep pattern and Parental satisfaction score.

Score	Midazolam	Clonidine
Palatability (drug acceptance)		
1	–Readily accepts	
2	Dislike but accepts	
3	Forcefully accepts	
4	Refuse to open mouth	

Venipuncture score

Crying

Vocalizing

Moving to limb

Noreaction

Face mask acceptance score

Excellent

Good (easily clams downwith assurance)

Moderate (does not clam down with assurance)

Poor (reject the mask or struggles)

Night sleep pattern

0=Mostly sleeping

1=Awake several times

2=Mostly awake

Parental satisfaction score

3= Mostly sleeping

2= Awake several times

1= Mostly awake

0= Extremely dissatisfied

Data are reported as number of patients using chi square analysis. P value <0.05, statistically significant.

[Table 2]

CHEOPS scale

Parameter	Finding	Points
Cry	No cry	1
	Moaning	2

Crying 2
 Screaming 3
 Smiling 0
 Compose 1
 Grimac 2
 Child verbal Positive 0
 None 1
 Complain other than pain 1
 Pain complain 2
 Both pain and non complains 2
 Torso Neutral 1
 Shifting 2
 Tense 2
 Shivering 2
 Upright 2

Restrained 2
 Touch Not touching reach 1
 Touch 2
 Grab 2
 Restrained 2
 Legs Neutral 2
 Squirming kicking 1
 Drawn up tensed 2
 Standing 2
 Restrained 2

Interpretation: The total CHEOPS score is obtained by adding all scores given each parameter, minimum score: 4, maximum score: 13, CHEOPS = Children's Hospital of Eastern Ontario Pain Scale.

Table 1: Demographic characteristics of patients

	Group1	Group2	P value
Age	5.40±2.1	5.5±2.1	0.67
Weight	19.1 ±6.0	21.1 ± 7.0	0.39
Sex M/F	25/5	24/6	0.67
Duration of surgery	1.35 ± 0.31	1.46 ± 0.3	0.65
ASA(I/II)	13/12	13/12	0.45

Table 2: Surgical Procedures Performed

Type of Surgery	Group 1		Group 2		P value
	Frequency	%	Frequency	%	
Tonsillectomy	5	8%	4	8%	1.000
Appendectomy	3	8%	2	12%	0.637
Urethroplasty	7	8%	7	24%	0.123
Herniotomy	15	4%	17	0%	0.312

Table 3: Comparison of Heart Rate in Group 1(midazolam) and Group 2 clonidine

HR	Group 1	Group 2	P value
	Mean ± SD	Mean ± SD	
HRa	86.30 ± 1.2	83 ± 2.7	<0.001
HRb	93.6 ± 4.5	75.9 ± 4.6	<0.001
HRc	128.2 ± 6.3	93.6 ± 4.5	<0.001
HRd	120.4 ± 4.6	86.3 ± 1.3	<0.001

Table 4: Comparison of Systolic Blood Pressure and Diastolic Blood Pressure in Group 1(midazolam) and Group 2 clonidine

MBP	Group 1	Group 2	P value
	Mean ± SD	Mean ± SD	
SBP/DBP (baseline)	96.60 ±3.01/ 65.2±2.51	101.01 ± 4.20/ 66.23±3.60	0.174
SBPb/DBP (before inductio)	90.8 ± 5.91/ 59.97±5.60	89.80±4.00/ 57.80±2.97	<0.001
SBP/DBPduring (laryngoscopy and intubation)	131.53 ± 2.94/ 81.10±1.64	113.53 ± 5.71/ 73.93±3.75	<0.001
SBP/DBP(5min after extubation)	126.17± 3.13/ 77.81±1.97	104.23. ±3.95/66.9±2.27	<0.001

Table 5: Comparison of O2 saturation in Group 1(midazolam) and Group 2 clonidine

SPO2	Group 1	Group 2	P value
	Mean ± SD	Mean ± SD	
SPO2a	100.00 ± 0.00	100.00 ± 0.00	-
SPO2b	99.88 ± 0.44	99.64 ± 0.76	0.178
SPO2c	100.00 ± 0.00	100.00 ± 0.00	-
SPO2d	100.00 ± 0.00	100.00 ± 0.00	-
SPO2e	100.00 ± 0.00	100.00 ± 0.00	-
SPO2f	100.00 ± 0.00	100.00 ± 0.00	-
SPO2g	100.00 ± 0.00	100.00 ± 0.00	-

Table 6: Comparison of Apprehension score at separation from parents in Group 1(Midazolam) and Group 2 (clonidine)

Apprehension Score	Group 1	Group 2	P value
1 none	20	7	0.001
2 Little fear	10	9	0.001
3 Moderate fear	Nil	11	0.001
4 vocal display of fear	Nil	3	0.001

Table 7: Comparison of sedation score at venepuncture Group 1(Midazolam) and Group 2 (clonidine)

Venepuncture score	Group 1	Group 2	P value
Crying	0	22	0.001
vocalizing	9	7	0.001
Moving the limb	11	1	0.001
No reaction	10	Nil	

Table 8: Comparison of sedation score at face mask acceptance score in Group 1(midazolam) and Group 2(clonidine)

	Group 1	Group 2	P value
Excellent (no protest)	17	2	>0.05
Good(easily calm)	12	11	0.001
Moderate(doesn't calm down with assurance)	1	8	0.001
Poor(rejects mask or struggle)	0	9	0.001

Table 9: Mean CHEOPS score in first 2 hours and early post op period (2-12 hours)

	Midazolam	Clonidine	P value
Mean CHEOPS score in immediate post op period	5.6±1.9	3.3±1.1	0.001
Mean score CHEOPS early post op period(2-12 hours)	6.1±1.6	5.03±1.7	0.005

Table 10: Post op Analgesic requirement

	Midazolam	Clonidine
Analgesic requirement in 2 hours	9	1
Analgesic requirement in 2-12 hours	17	1

DISCUSSION

Sedation and anxiolysis are the essential components of anaesthesia for paediatrics patients before undergoing surgery. Currently, the most commonly used sedative premedicants in the preoperative holding area is midazolam (85%), followed by ketamine (4%), fentanyl (3%), and meperidine (2%). Clonidine, α_2 -adrenergic agonist is a preanaesthetic agent in paediatrics patients and hence has been compared with midazolam, the most common premedication used in children. In our study we found that clonidine group patients were more sedated, calm and less anxious than midazolam group. The result of our study suggest that oral midazolam effectively reduce the anxiety associated with parental separation, venipuncture, and mask application, while with oral clonidine is a better sedative in the postoperative period. We found that after parental separation 51% patients in group C were awake compared to group M where none of children were awakewith significant difference of p value ($p < 0.001$). Our finding slightly different matches with the study of Sequeira Trevor et al,^[10] in 2012 who compared oral clonidine and oral midazolam in pediatric patients and found that at the time of venepuncture, 33.3% of children belonging to the clonidine group were adequately sedated compared to 23.3% in the midazolam group with a P value of < 0.05 . At the time of mask application, 6% of children belonging to the clonidine group were adequately sedated compared to 57.0% in the midazolam group with P value of < 0.001 . Jianping Cao, Xueyin Shi et al,^[11] in 2009 compared oral midazolam 0.5 mg/kg, clonidine(C2) 2 μ g/kg & clonidine (C4)4 μ g/kg and found sedation

score, parental separation and mask acceptance were significantly higher in clonidine 2 μ g/kg and clonidine 4 μ g/kg as compared to midazolam group($p < 0.05$) but sedation was significantly better in group C4 than in group C2 ($p < 0.05$) Leandro Gobbo Braz, M.D et al,^[12] in 2002 compared sedation levels of oral preanesthetic clonidine, midazolam and placebo in clinical and electroencephalographic bispectral analysis. There was significant difference among groups in sedation scale. Clonidine and midazolam group were found to have more sedation scale than placebo. However, there were no significant differences in respiratory, hemodynamic and temperature parameters. In our study there was no significant difference seen between midazolam group and clonidine group with respect to haemodynamics (heart rate & mean blood pressure) from baseline before induction. There was significant ($P < 0.001$) attenuation of hemodynamic response to intubation, surgical stress response and extubation with clonidine as compared to midazolam. There was no episode of bradycardia or hypotension at any point of time in any of the group. This was similar to the findings of V. J. Ramesh, et al,^[13] in 1997 who found that Clonidine 3 mcg/kg produced significant ($P < 0.01$) attenuation of hemodynamic response to intubation as compared to diazepam0.2mg/kg. Clinically significant hypotension and bradycardia were not observed in any of group.^[14] Katsuya Mikawa, MD, et al,^[15] studied the effect of oral clonidine given preoperatively on postoperative pain in children undergoing minor surgeries. Clonidine 4 μ g/kg provided lower CHEOPS scores during 12 hrs post operatively and reduced requirement for supplementary analgesic. In our study, there is

statistically significant difference seen between midazolam and clonidine with respect to time to achieve adequate CHEOPS score in postop for PACU discharge. Recovery in clonidine group took slightly longer time 60.00 ± 13.77 min as compared to midazolam group 44.40 ± 13.25 min. Waldemar Machała et al,^[16] in 2010 compared anaesthetic requirements in patients receiving 150 µg of clonidine, 7.5 – 15 mg of midazolam or placebo as premedication.^[17] Recovery time was shortest in the placebo group ($p < 0.05$), slightly longer in the clonidine group ($p > 0.05$), and longest in the midazolam group ($p < 0.05$).^[18] There was less postoperative adverse effect in clonidine group as compared to midazolam group. Kumkum Gupta et al,^[19] compared between oral pregabalin, clonidine and placebo and found that there were no differences between the groups with respect to awakening and recovery times. They were well oriented and were able to obey commands in the postoperative care unit. Postoperative analgesic need was much less with pregabalin, and clonidine group as compared with control. No significant complication has occurred was seen after use of oral premedication with pregabalin and clonidine. Postoperative nausea and vomiting & shivering were not found in any group. Bergendahl HT, et al,^[17] compared clonidine with midazolam as premedication in children undergoing adeno-tonsillectomy and found no episode of shivering was observed in the clonidine group but was present in five of the patients in the midazolam group ($P = 0.057$). In younger children (< 5 years) the incidence of postoperative confusion was lower in the clonidine group ($P = 0.001$). No difference in the frequencies of PONV incidences. Dahmani S, Brasher C et al,^[18] in 2010 found that premedication with clonidine was superior to benzodiazepines. Clonidine decreased the incidence of emergence agitation ($OR = 0.25 [0.11, 0.58]$) and produced a more effective early post-operative analgesia ($OR = 0.33 [0.21, 0.58]$). Thus, clonidine is finding its way in anaesthesia practice and its safety and efficacy as a preanaesthetic agent has been reasonably well established.

CONCLUSION

Premedication with oral midazolam has better efficacy in the preoperative period, found to be relatively safe and effective method to provide stable hemodynamics intra-operatively in response to stress of anesthesia and surgery. Sedation was more in clonidine group as compared to midazolam post operatively. Opioid consumption was also less with clonidine as compared midazolam. Oral clonidine premedication also offers additional advantage of reduction of postoperative complications such as pain, nausea-vomiting, and shivering. Although time to achieve adequate CHEOPS score was slightly more in clonidine group. Oral clonidine can reasonably be

recommended as premedication for all surgeries in children due to provided good palatability, parental satisfaction, stable perioperative hemodynamics, better postoperative analgesia, night sleep without any noticeable side effect.. However further studies are necessary to find out its efficacy in children and ASA III and IV paediatrics patients and can be a promising paediatrics premedication.

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