

Oral Clonidine and Midazolam as Premedication in Pediatric Anesthesia- Efficacy and Outcome in Comparison with Oral Promethazine

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ABSTRACT

Background: In most of the centers of developing country no premedication is used in cases of anesthesia in paediatric population. Many centers use oral promethazine on the night before to ensure good sleep. There is dilemma of using premedication with a fear of losing control over baby. There are controversial results regarding the effectiveness of clonidine compared with midazolam as premedication in children. **Aim:** The aim of this study is to evaluate the efficacy of oral clonidine and midazolam as a premedication and compare to with that of conventional promethazine in pediatric patients. **Methods:** This prospective randomized controlled study was carried out in Combined Military Hospital, Dhaka, among 90 children aged 2 to 7 years of ASA grade I & II scheduled for elective surgery under general anaesthesia during the period of Jan 2012 to Dec 2013. All the children were randomly divided in three groups, 30 children received only syrup promethazine as per body weight (Group-P, n=30) at night. In the study groups, after the syp promethazine at night in addition they were also given oral clonidine 4 µg/kg mixed with honey (Group-C, n=30) and midazolam 0.5 mg/kg mixed with honey (Group-M, n=30) at 60 and 20 min before separation of baby from parents lap respectively. The protocol of general anesthesia like induction, intubation, maintenance, reversal and postoperative analgesia was the same for all three groups. Patient's sedation status, separation anxiety, venipuncture, mask acceptance, anesthetics requirement, salivation, analgesia, post operative nausea vomiting (PONV) and emergence agitation were recorded by an observer blind of the patient's group. **Results:** Children characteristics were similar in all three groups. Children who had received clonidine as well as midazolam had more satisfactory sedation upon parent separation and less separation anxiety than promethazine; compared with midazolam & promethazine, clonidine premedication was associated with better mask acceptance; children who had received clonidine had significantly less incidence of salivation and less rescue antisialagogue; children received clonidine were better managed both intra & post operatively and needed less rescue analgesics; children who had received clonidine had significantly less episodes of PONV and also required less rescue antiemetic; incidence of emergence agitation was less in clonidine group in comparison with other two groups. **Conclusion:** The findings of the study suggest that both midazolam and clonidine are safe and effective as anaesthetic premedication in paediatric population. It can be concluded that oral midazolam premedication is effective as far as sedation is concern but considering multifarious anesthetic function oral clonidine is much superior premedicant. However, the risks of heart rate and blood pressure decreases, and the prolonged onset of sedation associated with clonidine should be considered. We recommend further multi-centre studies with larger samples to validate findings of our study.

Keywords: Clonidine, Midazolam, Premedication, Antisialagogue, PONV

INTRODUCTION

One of the challenge for pediatric anesthesiologists is to minimize psychological upset and scaring for children in the operating room environment and to facilitate a smooth induction of anesthesia.¹ Children are occasionally frightened and become uncooperative during the induction of anesthesia.^{2,3} It has been reported

that more than 40% of children aged 2–10 years display some distress behavior during the induction of anesthesia and more than 30% of children resist anesthesiologists during induction.⁴ The use of positive reinforcement to handle severely anxious and scared children may lead to postoperative behavioral problems.^{5,6} Thus, the use adequate premedication to provide anxiolysis may be beneficial for the facilitation of peaceful separation and the induction of anesthesia in these children.

Pre-operative anxiety is known to prolong the induction of anesthesia and lead to new-onset of maladaptive behavior in the post-operative period.^{7,8} Premedication in children prior to anesthesia induction provides anxiolysis, facilitate the separation from parents, and lessens the adverse psychological effects of hospital

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stays.^{9,10} Non-parenteral routes of administration for premedication is preferred in children because they perceive intravenous (IV) or intramuscular (IM) medication as more invasive than the procedure itself.^{11,12}

In most of the centers of developing country no premedication is used in cases of anesthesia in paediatric population. Many centers use oral promethazine on the night before to ensure good sleep. There is dilemma of using premedication with a fear of losing control over baby. There are controversial results regarding the effectiveness of clonidine compared with midazolam as premedication in children.

METHODS

This prospective randomized controlled study was carried out in Combined Military Hospital, Dhaka, among 90 children between 2 to 7 years of age. Study was conducted among children scheduled for elective surgery under general anaesthesia having American Society of Anesthesiologists (ASA) grade I & II during the period of Jan 2012 to Dec 2013. Exclusion criteria included known allergy or hypersensitive reaction to promethazine, clonidine or midazolam. We also excluded children having organ dysfunction, cardiac arrhythmia, congenital heart disease, mental retardation, airway abnormalities and severe obesity. Pre-anaesthetic checkup was done 24 hrs prior to surgery and the procedure was explained to the parents and written consent was obtained. They were randomly allocated to one of three groups by blind envelope technique.

Group-P

In promethazine group, patient received only syrup promethazine as per body weight (Group-P, n=30) at night.

Group-C

In clonidine group, after syp promethazine at night in addition patients were also given oral clonidine 4 µg/kg mixed with honey (Group-C, n=30) at 60 min before separation of baby from parents lap.

Group-M

In midazolam group, after syp promethazine at night in addition patients were also given oral midazolam 0.5 mg/kg mixed with honey (Group-M, n=30) at 20 min before separation of baby from parents lap.

Children had premedication in preoperative holding area in the presence of one parent. Baseline HR, oxygen saturation (Sp_o₂), and BP were measured before any drug administration. In pre-op hold area, children belong to group-P received only syrup promethazine at night was

quiet and awake at parents lap. Children belong to group-C received oral clonidine 4 µg/kg mixed with honey 60 min before separation of baby from parents lap. On the other hand, children belong to group-M received oral midazolam 0.5 mg/kg mixed with honey 20 min before separation of baby from parents lap. HR, Sp_o₂, and BP were measured before and every 15 min after drug administration until transfer to the theater. The level of sedation was assessed by using a 3-point scale: 1 = awake, 2 = drowsy and 3 = asleep. A sedation score of ≥2 was considered as satisfactory (Table-1).

When a sedation score of 2 or 3 was reached, the children were transferred to the operating room. Nurses used to accompany the child inside theater if no satisfactory sedation level was achieved these children were excluded from the study. The duration of premedication was approximately 60 min; however, it could be longer or shorter depending on the schedule of the OT list. On arrival at operation theatre again baseline preinduction parameters like heart rate, NIBP, SpO₂ were recorded. The protocol/ technique of general anesthesia like induction, intubation, maintenance, reversal and postoperative analgesia was same for all three groups. Patient's venipuncture, mask acceptance, anesthetics requirement, salivation, analgesia, post operative nausea vomiting (PONV) and emergence agitation were recorded by an observer blind of the patient's group. At the end of surgery children were placed in recovery position and allowed to wake up naturally in the postanesthesia care unit (PACU).

RESULTS

A total 90 patients were included in this study. Demographic characteristics for all three groups are summarized in Table 2. Patients' characteristics were similar in the three groups. There was no statistically significant difference between the groups with respect to sex, age and weight. But in clonidine group, there are significant differences in the mean values of heart rate, systolic and diastolic blood pressures in comparison with other groups (Table 2).

Children of clonidine and midazolam groups had more satisfactory sedation upon parent separation and less separation anxiety than promethazine group (Table 3).

Compared with midazolam & promethazine, clonidine premedication was associated with better mask acceptance (Table 4).

Table 1: Sedation scale

Score	Definition
1	Awake
2	Drowsy
3	Asleep

Table 2: Patients' demographic data

Variables	Promethazine group (n=30)	Clonidine group (n=30)	Midazolam group (n=30)	P value
Mean age (years)*	3.73±1.75	3.38±1.76	3.25±1.44	0.51 ^{ns}
Sex**				
Males	17 (56.7%)	18 (60.0%)	16 (53.3%)	0.87 ^{ns}
Female	13 (43.3%)	12 (40.0%)	14 (46.7%)	
Mean weight* (kg)	10.38±4.40	9.67±4.37	10.17±4.67	0.82 ^{ns}
Mean time of surgery (min)*	33.30±7.84	32.53±7.45	36.80±7.87	0.08 ^{ns}
Preanesthetic mean heart rate*	97.87±8.91	91.80±7.56	95.30±7.96	0.02 ^s
Mean systolic pressure*	82.83±7.95	75.33±4.72	81.83±7.37	<0.001 ^s
Mean diastolic pressure*	40.17±4.64	36.00±2.75	38.83±3.87	<0.001 ^s

*ANOVA test, **Chi-square test, ns=Not significant, s=Significant

Table 3: State of sedation and separation anxiety

Variable	n=30, n (%)			P value
	Promethazine group	Clonidine group	Midazolam group	
Well sedation & no separation anxiety	2 (6.67)	28 (93.33)	30 (100)	P<0.001 ^s
Poor sedation & separation anxiety	28 (93.33)	2 (6.67)	0.0	$\chi^2=73.20$

P value reached from Chi-square test, s=Significant

Table 4: Better mask acceptance

Variable	n=30, n (%)			P value
	Promethazine group	Clonidine group	Midazolam group	
Better mask acceptance	2 (6.66)	28 (93.33)	20 (66.67)	P<0.001 ^s
Poor mask acceptance	28 (93.33)	2 (6.67)	10 (33.33)	$\chi^2=47.88$

P value reached from Chi-square test, s=Significant

Children who had received clonidine had significantly less incidence of salivation and less rescue antisialagogue (Table 5).

Children received clonidine were better managed both intra & post operatively and needed less rescue analgesics (Table 6).

Children who had received clonidine had significantly less episodes of PONV and also required less rescue antiemetics (Table 7).

Finally, the incidence of emergence agitations was less in clonidine group in comparison with other two groups (Table 8).

DISCUSSION

To evaluate the efficacy of oral clonidine and midazolam as premedication and to compare with that of conventional promethazine in pediatric patients this study was conducted in Combined Military Hospital, Dhaka.

Reduction of anxiety experienced by children is important for humanitarian reasons and to improve cooperation with medical staffs. Anxiety at induction of anesthesia is associated with distress on awakening in the recovery area and with later postoperative behavior problems.¹³

Perioperative anxiety has been associated with much negative behaviour during and after the surgical experience, like post-operative pain, sleeping disturbances, parent child conflict and separation anxiety.^{14,15}

It also activates the human stress response, leading to increased levels of serum cortisol and epinephrine and natural killer cell activity.¹⁶ Children are particularly vulnerable to the global surgical stress response because of the limited energy of the reserves, large brain masses and the obligatory glucose requirements.¹⁷

Limitation of the study was that potential alteration in the absorption of drugs based on pH changes induced by the diluents - honey in this case was not addressed in the study.¹⁸

This study demonstrated that age old practice of providing promethazine at night neither reduces perioperative anxiety nor humanitarian. In contrast, clonidine and midazolam effectively reduced separation anxiety which is consistent with Rubina et al, R2 Rony et al and Halldin-Lindahl et al study.^{14,19,20} Besides, clonidine was a suitable alternative to midazolam as a premedication in children which is consistent with Rubina et al, R2 Rony et al study. Furthermore, clonidine acts as a sedative and analgesic because of its central alpha-2 adrenergic agonism as well as provides better hemodynamic stability, mask acceptance and reduces salivation, PONV, emergence agitation which corresponds with Rubina et al, R2 Rony et al & Halldin-Lindahl et al study.^{14,18,20}

CONCLUSION

The findings of the study suggest that both midazolam and clonidine are safe and effective as anesthetic premedication

Table 5: Incidence of salivation

Variable	n=30, n (%)			P value
	Promethazine group	Clonidine group	Midazolam group	
Incidence of salivation	30 (100)	1 (3.33)	30 (100)	P<0.001 ^s $\chi^2=85.57$
No incidence of salivation	0.0	29 (96.67)	0.0	

P value reached from Chi-square test, s=Significant

Table 6: Rescue analgesics

Variable	n=30, n (%)			P value
	Promethazine group	Clonidine group	Midazolam group	
Incidence of salivation	30 (100)	1 (3.33)	30 (100)	P<0.001 ^s $\chi^2=85.57$
No incidence of salivation	0.0	29 (96.67)	0.0	

P value reached from Chi-square test, s=Significant

Table 7: No post operative nausea vomiting (PONV)

Variable	n=30, n (%)			P value
	Promethazine group	Clonidine group	Midazolam group	
Incidence of salivation	30 (100)	1 (3.33)	30 (100)	P<0.001 ^s $\chi^2=85.57$
No incidence of salivation	0.0	29 (96.67)	0.0	

P value reached from Chi-square test, ns=Not significant

Table 8: Incidence of emergence agitation

Variable	n=30, n (%)			P value
	Promethazine group	Clonidine group	Midazolam group	
Incidence of emergence agitation	26 (86.66)	8 (26.66)	20 (66.67)	P<0.001 ^s $\chi^2=23.33$
No incidence of emergence agitation	4 (13.33)	22 (73.33)	10 (33.33)	

P value reached from Chi-square test, s=Significant

in pediatric population. It can be concluded that oral midazolam premedication is effective as far as sedation is concern but considering multifarious anesthetic function and demands of providing anesthesia oral clonidine is much superior premedicant. However, the risks of heart rate and blood pressure decreases, and the prolonged onset of sedation associated with clonidine should be considered. We recommend further multi-centre studies with larger samples to validate findings of our study.

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