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Research Article

Oral premedication for pediatric anaesthesia: a comparison between midazolam and clonidine

Anupam Das[1]*, Kishore Das[2], Minoti Baruah[1], Manigreeva Krishnatreya[3], Amal Chandra Kataki[4]

[1]Department of Anaesthesia, Dr. B Borooah Cancer Institute, Guwahati, India
[2]Department of Head and Neck Oncology, Dr. B Borooah Cancer Institute, Guwahati, India
[3]Department of Epidemiology and Biostatistics, Dr. B Borooah Cancer Institute, Guwahati, India
[4]Department of Gynecologic Oncology, Dr. B Borooah Cancer Institute, Guwahati, India

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***Correspondence:**
Dr. Anupam Das,
E-mail: dr.dotdas@gmail.com

ABSTRACT

Background: In children any anticipated surgery is associated with profound psychological stress to the patients. To allay this stress and anxiety, wide variety of pharmacological interventions are used.
Methods: A prospective observational study was carried out between July'2005 and June'2006 in a tertiary care hospital in Assam. The study included children undergoing surgery under general anaesthesia in age group 2-10 years. Sixty children were divided into two groups, in one group patients received oral midazolam and other group received oral clonidine as pre-medicant.
Results: In the midazolam group 23 (76.67%) children had no apprehension after parental separation and at induction ($P<0.001$), sedation score at induction was significant higher in midazolam group versus clonidine group (93.33% versus 66.6%, $P<0.01$), clonidine resulted in a more stable pulse and blood pressure peri-operatively ($P<0.05$).
Conclusion: Oral midazolam has better efficacy in terms of preoperative sedation and oral clonidine had stable hemodynamic profile and better analgesia in the clonidine group.

Keywords: Clonidine, Midazolam, Pediatric, Pre-medications

INTRODUCTION

Any operation, be it a major or a minor, causes profound emotional stress to the patient. The fear and anxiety associated with an anticipated operation can result in a variety of unwanted physiological changes and alteration in the hemodynamic profile of the patient, which can sometimes lead to disastrous intraopearative and postoperative consequences. Moreover the drugs used to induce anesthesia are themselves associated with a large number of side effects. This is more so in case of children, who are likely to undergo profound psychological trauma because of parental separation, unaccustomed environment of the operation theatre, insertion of intravenous cannula prior to surgery.[1] Now it is established that the risk of developing behavioral or personality disorder is higher in children following a traumatic induction of anesthesia.[1]

Preoperative medication has long been an active area of interest in paediatric anesthesia. Though many drugs are studied and tried in this field, but none has been found to be truly satisfactory. An ideal pre-anaesthetic medication should ease separation from parents, facilitate patient's acceptance of intravenous cannula and face mask during induction of anaesthesia without prolonging recovery. It

should promote good cardio respiratory stability along with minimization of postoperative complications.

A wide variety of drugs and routes of administration has been described for paediatric patients, with each drug and each route having its own drawbacks. Oral route is the choice of most anaesthetists with a definite advantage of being less traumatic and easily acceptable.

Midazolam has been the gold standard paediatric premedicant for past so many years. But there are unwanted side effects attributable to midazolam like postoperative cognitive impairment behavioral changes, hiccups, and paradoxical reactions.[2-6] These unwanted side effects of midazolam have resulted in the search for an ideal premedicant for pediatric patients.

The α-2 agonist, clonidine, an imidazoline derivative appears to fulfill many of the criteria required for an ideal premedicant.[7,8] Its beneficial effects in adult are well documented and this has encouraged the study of this drug in paediatric anaesthesia setting as well.

The present study is designed to compare oral clonidine and oral midazolam in terms of preanaesthetic sedation, anxiolysis, and facilitation of separation of children from their parents, cooperation during venepuncture and application of face mask, effect on postoperative analgesia, haemodynamics and any noticeable postoperative complication in children undergoing some selected surgical procedures.

METHODS

This study was a thesis conducted in the department of Anaesthesiology, Assam Medical College and Hospital in the period between July 2005 and June 2006. This was a prospective observational study. Patients in the age group of 2-10 years, ASA-I undergoing elective appendicectomy, herniotomy and urethroplasty were selected. The patients were divided in to two equal groups of 30 each, viz. Group M and Group C to receive oral midazolam (0.5 mg/kg) and oral clonidine (5 µg/kg) respectively. The child's baseline behavior was noted during pre-anaesthetic visit as calm, apprehensive, crying or thrashing. Then according to the group assigned the child was given either oral midazolam or oral clonidine on the morning of operation. At the time of drug administration, the reaction of the child was noted. Pulse and blood pressure (BP) were recorded every 10 minutes from prior to drug administration till 60 minutes after extubation. Child's level of anxiety and sedation were evaluated, before premedication, before and after separation from parents, at the time of induction, in the immediate postoperative period (at 2 hours) and in the early postoperative period (at 4 hours). After 60 minutes of drug administration, the children were separated from their parents and at that time their behavior was noted. Pain assessment was done using the CHEOPS scale (Children's Hospital of Eastern Ontario Pain Scale) every 30 minutes during the first two postoperative hours and then every 2 hours up to next 12 hours. In the present study, children with CHEOPS score more than 7 received recue paracetamol syrup. During the recovery period, the occurrence of any untoward effect likes vomiting, and shivering was looked at.

Statistical analysis

Chi square analysis was used. Statistically, $p<0.05$ was accepted as significant. For the analysis of differences between baseline, intubation and after extubation haemodynamics, student's paired 't' test was used.

RESULTS

As regard to drug acceptability, only 7 (23.33%) children in group M readily accepted the drug in comparison to all 30 (100%) children in group C. This was statistically significant ($P < 0.001$). Clonidine had better acceptability than midazolam.

As regard to the level of apprehension, all 30 (100%) children in both the groups had no anxiety just before separation from parents i.e. both the drugs resulted in anxiolysis with no significant difference between the two groups till the time the children were with their parents.

We observed that the number of children with no apprehension after separation from parents and at induction were statistically highly significant ($P < 0.001$) in Group M as compared to their respective numbers before premedication, Whereas, in Group C, we did not observe any significant difference in the level of apprehension after separation from parents and at induction as compared to their respective level before premedication. Amongst the two groups, midazolam had a better suppression of apprehension after separation from parents and at induction (Table 1).

As with the level of apprehension, in terms of sedation also, both the drugs resulted in good level of sedation till the time the children were kept with their parents with no significant difference between the two groups. After separation from parents, in Group M, 8 (26.67%) children were drowsy/readily responding to gentle stimulation and 22 (73.33%) children were awake / calm and quiet. Whereas, in Group C, only 20 (66.67%) children were awake / calm and quiet and 10 (33.33%) children were awake and active, i.e. midazolam resulted in significant number of children who were awake / calm and quiet after separation from parents, but this was not so with clonidine. Similarly at induction, in Group M, 28 (93.33%) children were awake / calm and quiet, whereas, in Group C, only 20 (66.67%) children were awake / calm and quiet and 10 (33.33%) children were awake and active. Therefore, it was observed that midazolam resulted in a better level of sedation as compared to

clonidine after parental separation and at induction (Table 2). Sedation levels were also assessed in both the groups in the immediate postoperative period (2 hours) and in the early postoperative period (4 hours). In Group M, all 30 (100%) children were awake and active in both immediate and early postoperative period, i.e. midazolam didn't result in any sedation in the postoperative period. In contrast, in Group C, all 30 (100%) children were drowsy / readily responding to gentle stimulation in the immediate postoperative period and were awake / calm and quiet in the early postoperative period. So clonidine provided good level of sedation in both immediate (2 hours) and early (4 hours) postoperative period compared to midazolam (Table 3).

Table 1: Apprehension score at separation and at induction.

	Apprehension score after separation from parents			Apprehension score at induction		
	Midazolam	Clonidine	P value	Midazolam	Clonidine	P value
1 = none	23 (76.67%)	6 (20%)	<0.001	23 (76.67%)	6 (20%)	<0.001
2 = little / minimal expression of fear	7 (23.33%)	12 (40%)	>0.05	7 (23.33%)	12 (40%)	>0.05
3 = moderate / expresses fear / apprehension	Nil	10 (33.33%)	<0.001	Nil	10 (33.33%)	<0.001
4 = excessive / vocal display of fear / apprehension	Nil	2 (6.67%)	>0.05	Nil	2 (6.67%)	>0.05

Table 2: Sedation score after separation and at induction.

	Sedation score after separation from parents			Sedation score at induction		
	Midazolam	Clonidine	P value	Midazolam	Clonidine	P value
1 = asleep / not readily arousable	Nil	Nil		Nil	Nil	
2 = asleep / responds slowly to gentle stimulation	Nil	Nil		Nil	Nil	
3 = drowsy / readily responds	8 (26.67%)	Nil	<0.01	2 (6.67%)	Nil	>0.05
4 = awake / calm and quiet	22 (73.33%)	20 (66.67%)	>0.05	28(93.33%)	20 (66.67%)	<0.01
5= Awake / active	Nil	10 (33.33%)	<0.001	Nil	10 (33.33%)	<0.001

Table 3: Sedation score in the immediate (2 hours) and early (4 hours) postoperative period.

	Sedation score in the immediate postoperative period (2 hours)			Sedation score in the early postoperative period (4 hours)		
	Midazolam	Clonidine	P value	Midazolam	Clonidine	P value
1 = asleep / not readily arousable	Nil	Nil		Nil	Nil	
2 = asleep / responds slowly to gentle stimulation	Nil	Nil		Nil	Nil	
3 = drowsy / readily responds	Nil	30 (100%)	<0.001	Nil	Nil	
4 = awake / calm and quiet	Nil	Nil		Nil	30 (100%)	<0.001
5= Awake / active	30 (100%)	Nil	<0.001	Nil	Nil	<0.001

Reaction of the children to venepuncture for intravenous access and to the application of face mask was also assessed in both the groups. In Group M, none of the children were crying at the time of venepuncture, whereas, in Group C, 23 (76.67%) children were crying. Similarly during face mask application, 16 (53.33%) children in Group M had excellent response (no protest) and the rest 14 (46.67%) children showed good response (easily calms down with assurance) but in Group C, no children readily accepted the face mask. Midazolam certainly resulted in a better face mask acceptance.

Postoperative pain was assessed using CHEOPS score. The mean CHEOPS score in the immediate (within 2 hours) and early (2-12 hours) postoperative period in Group M were 6.13±1.69 and 7.6±1.22 respectively against 3.2±0.96 and 4.3±1.20 in Group C. So, clonidine resulted in better pain relieve than midazolam as reflected by the need of rescue analgesics in the latter group where

10 (33.33%) children required rescue analgesics within 2 hours and all the remaining children in the group required analgesics in the subsequent 2-12 hours postoperatively. Whereas, no children in the clonidine group required analgesics in the first 2 hours and only 2 (6.67%) children required analgesics in the subsequent 2-12 hours.

Table 4: The haemodynamic changes before induction, during laryngoscopy and intubation and at 5 minutes after extubation.

Midazolam Group							
	Baseline	Before induction	P value	During laryngoscopy and intubation	P value	5 min after extubation	P value
Pulse rate (per min)	86.93±9.49	96.8±9.31	<0.001	130.66±11.35	<0.001	123.66±10.57	<0.001
BP(mmHg)	98.66±6.91/ 65.86±4.32	91.8±6.08/ 59.33± 3.94	<0.001	132.06±4.37 / 82.40±2.48	<0.001	125.13±4.56 / 77.33±3.29	<0.001
Clonidine Group							
	Baseline	Before induction	P value	During laryngoscopy and intubation	P value	5 min after extubation	P value
Pulse rate (per min)	85.93±7.69	76.0±7.93	<0.001	97.86±7.71	<0.001	87.33±7.13	<0.05
BP(mmHg)	100.46±7.34/ 65.13±4.71	89.66±6.54 / 56.26±3.95	<0.001	114.93±7.69/ 76.06±4.74	<0.001	104.66±6.58 / 68.46±4.65	<0.001

We also observed the effects of both the drugs on the haemodynamics before induction, during laryngoscopy and intubation and at 5 minutes after extubation. In Group M, there was a significant increase in the pulse rate and a decrease in the blood pressure before induction as compared to the baseline values and in Group C, there was a significant decrease in both the pulse rate and the blood pressure (Table 4). During laryngoscopy and endotracheal intubation and also at 5 minutes after extubation, there was a significant increase in the pulse rate and blood pressure above the baseline level, however, this increase was much higher in Group M as compared to Group C (Table 4). Overall, in intergroup comparison clonidine resulted in a better haemodynamic profile in the perioperative period. As far as untoward effects are concerned, only 3 (10%) children in Group M had postoperative nausea and vomiting and 1 (3.33%) children had postoperative shivering. But this was statistically not significant.

DISCUSSION

Several studies have demonstrated the beneficial effects of good pre-anesthetic medication in children.[9-12] Previous studies have shown that both midazolam and clonidine are effective oral pre-medicants in children.[9,11,13-18]

Though several routes of administration of the pre-medicant has been studied, the oral route is the least traumatic for children.[16,19,20-27] Nicholson et al in their study, suggested that oral preanaesthetic medication may be as efficacious as intramuscular preanaesthetic medication in paediatric patients.[23]

We selected only elective surgeries because of two reasons. Firstly, in emergency cases we would not have got enough opportunity to administer the drugs orally in the stipulated time interval, and secondly, emergency cases would have presented with full stomach and thus could have resulted in increased incidences of perioperative vomiting. To maintain uniformity in the duration and type of surgical procedure, we selected only cases undergoing herniotomy, appendicectomy or urethroplasty.

We assessed the baseline behavior of the children in the ward the evening before surgery so as to avoid the effect of operation theater environment. The doses we used and the timing of drug administration were based on previous studies. Reves et al reported that owing to the rapid hepatic clearance of midazolam, the absolute systemic availability after oral administration is only 40-50%.[28] Thus the oral dose of midazolam must be twice as high as the intravenous dose. They also reported that after oral ingestion, the peak plasma concentration is reached within 1 hour. Feld et al reported that oral midazolam 0.5 mg/kg was as effective as intramuscular midazolam 0.2 mg/kg for preanaesthetic medication in children.[20] The same authors later in 1990 evaluated the effectiveness of three different doses of oral midazolam and concluded that oral midazolam 0.5-0.75 mg/kg is an effective preanaesthetic medication for paediatric outpatients. They have reported that ideal time for oral midazolam is 30 minutes prior to induction.[14] Similarly, McMillan et al in their study concluded that midazolam 0.5 mg/kg is a safe, and effective pre-medicant in children and increasing the dose only increases the possibility of side effects with no additional benefit.[29] Weldon et al studied the influence of

timing of oral midazolam on the perioperative effects in children and concluded that oral midazolam (0.5 mg/kg) 30-45 minutes before induction is effective.[32] Mikawa et al, in their study concluded that oral clonidine 4µg/kg administered 105 minutes before induction is an effective preanaesthetic medication in paediatric patients.[30] Fazi et al and Malde et al administered oral clonidine 60-90 minutes before induction and got beneficial results.33,34 Bergendahl et al used rectal clonidine 5 µg/kg without any noticeable side effects.[31] From the above studies it was concluded that peak action of oral midazolam is after 30-45 minutes and of oral clonidine is after 90 minutes of ingestion. We decided to administer both the drugs 60 minutes before parental separation because it was not possible to administer clonidine earlier because of busy operation theater schedule with long OT list, and we didn't want to increase recovery time from anaesthesia by administering midazolam close to induction as the surgeries we selected were of shorter duration.

Our observation of clonidine to have a better drug acceptability than midazolam is supported by other studies as well. Feld et al reported that midazolam has a bitter taste that is not easily disguised in apple juice and their patients too didn't like the taste.[14] Similar observation was reported by P.J Alderson and J. Lerman.[9] However, we didn't find any data on clonidine acceptability. As regarding the effect on sedation and anxiolysis, both the drugs had a good sedative and anxiolytic effect till the patients were with their parents, however once children were separated from their parents after 60 minutes of premedication and also at induction, though the children in Group M remained calm and sedated but the children in Group C were very anxious and agitated. However, in the immediate postoperative period (2 hours) midazolam didn't result in any degree of sedation whereas, all 30 (100%) children in the clonidine group were drowsy but readily responding to gentle stimulation. Even in the early postoperative period, all 30 (100%) children in Group C were awaked calm and quiet. Thus, in our study, we found that midazolam is a better sedative and anxiolytic preoperatively, whereas, clonidine is better postoperatively in this aspect. Our findings may have been influenced by the timing of drug administration. We might have got better result with clonidine preoperatively if we could have waited a bit longer before separating the children from their parents and in case of midazolam, we might have got better result postoperatively if we had administered the drug 30-45 minutes before induction. Our findings are against the findings of Nishina et al in their study, they reported that preoperative sedation and anxiolysis provided by oral clonidine (4 µg/kg) were equal to oral midazolam (0.5 mg/kg).[35] Our finding is supported by the findings of Fazi et al where they concluded that clonidine premedicated children exhibited intense anxiety on separation from parents and at induction.[33] Our findings on clonidine as regard to postoperative sedation also correlated with the study of Bergendahl et al who reported higher level of sedation with clonidine in the postoperative period as compared to midazolam.[31]

Midazolam premedicated children had a better acceptance of face mask and IV cannula than the children receiving clonidine. Favourable results with midazolam were also found in other studies.[9,14,29,32,36] In our study, we observed that clonidine offered much better analgesia and subsequently lesser need for rescue analgesics compared to midazolam in the immediate and early postoperative period. This observation is supported by the study of Bergendahl et al.[31] Contradictory results were published by Fazi et al where increased postoperative demand for rescue analgesics were reported for clonidine premeditated children in comparison to children receiving midazolam.[31] On haemodynamics, clonidine had a more stable effect on haemodynamics throughout the perioperative period. This observation is supported by various earlier studies.[30,33,34,37]

CONCLUSION

Under the conditions of this study, oral midazolam has better efficacy in terms of preoperative sedation, anxiolysis, IV cannulation and face mask acceptance whereas, oral clonidine provided good perioperative haemodynamic stability, better postoperative sedation and postoperative analgesia. Hence, it has the potential to become a promising preanaesthetic drug in the paediatric age group in the near future.

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