

Comparative Study of Oral Clonidine and Midazolam as Premedication in Pediatric Patients Undergoing Tonsillectomy

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Abstract

Background and Aim: Anxiety and fear of operation, injections, physicians, operation theatre environment and parental separation are all traumatizing experiences in children. The aim of the study was to compare the effects of oral midazolam and oral clonidine as premedication in children undergoing tonsillectomy. The preoperative sedation, anxiolytic, acceptance of mask for induction of anaesthesia, intravenous cannulation and post-operative recovery were assessed in both groups.

Methods: A prospective randomized double blinded study of 100 patients of age group 4-12 yrs undergoing tonsillectomy under general anaesthesia were selected. They were divided into 2 groups of 50 patients each. Group A (oral clonidine) received 4 mcg/kg 90 minutes before induction. Group B (oral midazolam) received 0.5 mg/kg 90 minutes before induction. The sedation and anxiety score was noted at the time of parental separation. The reaction to IV cannulation was assessed by sedation and anxiety scoring at the same time all of them were taken under GA with controlled ventilation. The mask acceptance was graded by 5 point scoring system. Grade 3, 4 and 5 are satisfactory. They were monitored throughout the surgery for any complications. Post operative status was assessed by Modified Objective Pain score.

Results: The sedation score and anxiety score at venipuncture was better with clonidine group with statistical significance ($p < 0.000$ and < 0.003). The mask acceptance was better with clonidine group with statistical significance ($p < 0.000$). Post-operative score was also better with clonidine group with statistical significance of p value < 0.000 .

Conclusion: We concluded that oral clonidine and midazolam can be used as better premedicants to produce optimal sedation and emotional state. Clonidine 4 μ g / kg has been shown to be a more effective premedication for children undergoing elective tonsillectomy than midazolam 0.5mg/kg.

Keywords: Oral Clonidine, Oral Midazolam, Premedication, Pediatric Population, Tonsillectomy

Introduction

A need exists for an efficient premedicant drug especially in paediatric age group undergoing elective surgical procedures. Anxiety and fear of surgery, needles, physicians, operation theater environment, and parental separation are all traumatizing experiences in young children resulting in postoperative maladaptive behavioral changes [1]. Premedicants should yield a child who is calm, free of anxiety and pain, sedated, but easily arousable and fully co-operative. The concept of premedication was introduced

in early 1900s. The drugs administered before the induction and maintenance of anaesthesia is Preanaesthetic medication. The term premedication was first used in the 1920s. One of the commonly used premedicant in paediatric anaesthesia drug worldwide is midazolam. Clonidine, an alpha 2 agonist, central sympatholytic agent used as antihypertensive agent is a trial in this category [2]. In spite of all existing premedicants anaesthetic practitioners are still in search for an ideal premedication agent with better efficacy and minimal side effects. So we decided to compare the efficacy of midazolam and clonidine as oral premedication in children undergoing elective tonsillectomy. The aim of the study was to compare the clinical effects of oral midazolam and oral clonidine as premedication in

children undergoing tonsillectomy. We compared the preoperative sedation, anxiolysis, acceptance of mask for induction of anaesthesia, intravenous cannulation and postoperative recovery in between oral clonidine and oral midazolam.

Materials and Methods

- Setting: The study was conducted in a single centre, in a Tertiary teaching Hospital.
- Study Design: Prospective randomized double blinded study of 100 patients.

A study group of 100 patients of age group 4 -12 yrs undergoing tonsillectomy under general anaesthesia were selected. They were divided into 2 groups of 50 patients each by lots taking method. All even numbers were assigned to Group I and all odd numbers were assigned to Group II. The drug administrator and the investigator didn't know about which drug is in group I or II. Group I (oral clonidine) received 4 mcg/kg 90 minutes before induction.

Group II (oral midazolam) received 0.5 mg/kg 90 minutes before induction. The inclusion criteria was age: 4-12 years of both sexes, ASA 1-2 and Malampatti 1 & 2. Children with ASA 3-4, MALAMPATTI 3 & 4, CNS disorder, Obesity (weight >95 percentile) and allergic to study drug were excluded.

Methodology

An Ethical committee approval from Institution and written consent from the parents were obtained.

In group I (Clonidine): 100 µg/tab of clonidine was crushed into powder, dissolved in sugar syrup and given to the patients in the dose of 4µg/kg, 90 minutes prior to induction. 100µg/ tablet was dissolved in 5ml of sugar solution and the dose calculated as per weight of children was given through mouth after getting consent from the older children and from the mother of smaller children.

In Group II (Midazolam): Preservative free parenteral form of midazolam in the strength of 5 mg/ml was given orally in the dose of 0.5 mg/kg 90 minutes prior to induction. In our study none of the children vomited or spit out the drug during administration. The reaction to drug administration was evaluated using scores (1. Crying, 2. Not crying.) After 90 minutes in Group I and Group II, sedation level was graded by evaluating the child's appearance with the help of four point sedation score described as below. (1- Alert, 2- Awake, 3 - Drowsy, 4- Asleep) The anxiety or emotional state of children while separating from mother, was assessed by using four point anxiety score (1- Crying, 2.-Anxious, 3- Calm, but not cooperative, 4-Calm, cooperative or asleep) Then we also observed the level of anxiety on application of mask (acceptance of mask), graded by using the following scores (11) (1- Combative crying, 2-. Moderate fear of mask, 3- Cooperative with assurance, 4-Calm and cooperative, 5-Asleep). The reaction at the time of intravenous cannulation was graded by using sedation and anxiety score at that point of time. Post operative status was assessed by using Modified objective pain scores

Modified objective pain score

Tears

Absent	0
Present, but child can be consoled	1
Present and child cannot be consoled	2

Movements

Absent	0
Moderate agitation (does not sit still)	1
Intense agitation (risk of trauma)	2

Behavior

Sleeping or calm	0
Grimacing, trembling voice, can be calmed down	1
Frightened, sticks to parents, cannot be calmed down	2

All the patients were monitored with pulse oximetry, NIBP and ECG. IV line was secured with appropriate size IV cannula. The reaction to IV cannulation was assessed by sedation and anxiety scoring at the same time. They were preoxygenated with 100% O₂ for 3 minutes before induction. Mask acceptance was graded by above scoring system. Grade 3, 4 and 5 are satisfactory. Injection glycopyrrolate 10 mcg/kg was given IV for all patients. They were induced with Injection propofol 2mg/kg, fentanyl 1 2mcg/kg, atracurium 0.5mg/kg. They were intubated with appropriate sized cuffed endotracheal tube. All of them were intra operatively maintained with O₂, N₂O, Atracurium 0.1 mg/kg and sevoflurane 1%. At the end of the surgery all the patients were reversed with Inj Neostigmine 40 mcg/kg and glycopyrrolate 10mcg/kg. All of them were extubated after adequate reversal of neuro muscular blockade. They were monitored throughout the surgery for any complications and were recorded if any.

Statistical Analysis: The collected data were analysed with IBM. SPSS statistics software 23.0 Version to describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups the unpaired sample t-test was used. To find the significance in categorical data Chi-Square test and Fisher's Exact was used. In all the above statistical tools the probability value 0 .05 is considered as significant level.

Results

Table 1: Demographic profiles of the patients

Criteria	Clonidine (Group I)	Midazolam (Group II)	Test of significance (P Value)
Age	6.92	7	0.853
Sex(Male/Female)	39/11	38/12	0.812
Weight(Kg)	23.44	23.7	0.837

Significance of T Test for age is 0.853, insignificant. Significance of Chi square Test for Sex is 0.812, insignificant. Significance of T Test for Weight is 0.837, insignificant

Both our study groups were comparable with respect to age, sex and weight. All the patients were hemodynamically stable throughout the procedure and HR, BP and Spo₂ were comparable between both the groups.

Table 2: Reaction to Drug Administration

Count		Group		Total
		clonidine	Midazolam	
Reaction to drug	Crying	3	2	4
	Not crying	47	48	95
Total		50	50	100

The number of children crying at the time of administration of drugs was comparable in both the study groups and was statistically insignificant.

Table 3: Intensity of sedation on separation from mother

Score	Grade	Clonidine (Group I)	Midazolam (Group II)	Total
1	Alert	2	2	4
2	Awake	10	31	41
3	Drowsy	27	16	43
4	Sleep	11	1	12

11 children in clonidine group were asleep, 27 were drowsy, 10 were awake and 2 were alert at time of separation from parents. In midazolam group 1 was asleep, 16 were drowsy, 31 were awake and 2 were alert. The sedation score was found to be better in clonidine group with statistical significance of 0.0

Table 4: Level of anxiety on separation from mother

Score	Grade	Clonidine (Group I)	Midazolam (Group II)	Total
1	Crying	0	4	4
2	Anxious	9	30	39
3	Calm/ uncooperative	20	15	35
4	Calm/cooperative/ Asleep	21	1	22

In clonidine group no children were crying, 21 were calm and cooperative, 19 were calm and uncooperative and 9 were anxious at the time of separation. In midazolam group 4 children were crying, 30 were anxious, 16 were calm and cooperative and 1 was calm and cooperative at the time of separation from the parents. The sedation score was better in clonidine group with a significance of 0.000.

Table 5: Intensity of sedation on Venipuncture

Score	Grade	Clonidine (Group I)	Midazolam (Group II)	Total
1	Alert	10	23	33
2	Awake	19	25	44
3	Drowsy	20	2	22
4	Asleep	1	0	1

In the clonidine group 10 children were alert, 19 were awake at the time of venopuncture. In the midazolam group 23 children were alert, 25 were awake at time of venopuncture. The sedation was found to be better in clonidine group than in midazolam with statistical significance of 0.000.

Table 6: Level of Anxiety on Venipuncture

Score	Grade	Clonidine (Group I)	Midazolam (Group II)	Total
1	Crying	7	14	21
2	Anxious	14	21	35
3	Calm/ Uncooperative	19	15	34

4	Calm/ cooperative / asleep	10	0	10
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In the clonidine group 7 children were crying, 14 were anxious at the time of venopuncture in the midazolam group 14 were crying, 21 were anxious at the time of venopuncture. The anxiety score was better in clonidine group with statistical significance of 0.003.

Table 7: Anxiety on Mask Acceptance

Score	Grade	Clonidine (Group I)	Midazolam (Group II)	Total
1	Combative/crying	7	13	20
2	Moderate fear for mask	4	22	26
3	Cooperative on assurance	22	14	36
4	Calm/cooperative	12	1	13
5	Asleep	5	0	5

In the clonidine group 12 children were calm and cooperative, 5 were asleep, 22 were cooperative on assurance on face mask application. In the midazolam group 13 children were crying, 14 were cooperative on assurance and one was calm and cooperative on mask application. Hence Mask.

Table 8: Post-Operative Status

Groups	Score1	Score 2	Score3
Clonidine (Group I)	11	32	7
Midazolam (Group II)	0	31	19
Total	11	63	26

The post operative status was assessed 30 minutes after extubation in post operative care room. In the clonidine group 11 children had tears and could be consoled with score of 1, 32 children had tears and facial grimace with a score of 2 and 7 children had tears, moderate agitation and facial grimace with a score of 3. In midazolam group 31 children had tears and facial grimace with score of 2 and 19 children had tears, moderate agitation and facial grimace with a score of 3. The clonidine group had better post operative status than the midazolam group with a statistical significance of 0.000.

Discussion

The practice of anesthetic premedication was introduced soon after ether and chloroform were introduced as general anesthetics in the middle of the 19th century. By applying opioids, benzodiazepines and anticholinergics before surgery, the patients undergoing surgery can achieve a less anxious state, and they would also acquire a smoother course during the tedious and dangerous induction stage.

The current practice of anesthetic premedication incorporates several aspects of patient care such as decreasing anxiety, dampening intraoperative noxious stimulus and its associated neuro endocrinological changes, and reducing postoperative adverse effects of anesthesia and surgery. The concept of anesthetic premedication was developed in 1850s in order to counteract the side effects of general anesthesia when ether and chloroform were widely used as inhalational anesthetics. In 1864 Nussbaum in Germany and Bernard

in France, found out simultaneously that subcutaneous morphine can relax patients and intensify chloroform anesthesia.

Clonidine an alpha 2 agonist used as antihypertensive agent has been proved to have sedative and analgesic effect, prevents post operative nausea and vomiting. It has been under clinical trial as an efficient premedicant utilizing these properties of the drug. Midazolam has been proved to be effective in reducing the preoperative anxiety level in many studies [3,4,5]. It was found that discharge from the recovery room in outpatient surgery was also not delayed in midazolam used patients. Except for midazolam, α_2 -agonists, antidepressants, and anticonvulsants are all effective in reducing the preoperative anxiety level in our study we compared oral midazolam and oral clonidine as premedication in children undergoing tonsillectomy. Anaesthesia and surgery creates a great psychological stress in most of the patients. The overall frequency of anxiety before anaesthesia was found to be 40 –60% in older children in a study conducted by Norris and Davis 1960) as many as around 80% of patients were found to be anxious in an extensive study conducted by Corman et al in 1958 by using a psychological questionnaire. A greater frequency was found in females than in males.

Premedication was considered essential in children. The pilot study showed that premedicated children had better value of arterial oxygen saturation than unpremedicated anxious and apprehensive children. A positive correlation was reported between anxiolysis and ease of induction of anaesthesia (Lindgren, SaarniVaara, Himberg 1980). This supports the importance of the anxiolytic components of premedication. The relief of apprehension may reduce excessive hormonal and circulatory responses to anaesthesia and may reduce the minimum effective dose of anaesthetic agents [6,7]. Sedation was considered an useful property of premedicant drug [7,8,9]. In our study we used tablet form of clonidine dissolved in sugar syrup and given to the patient. According to Teebeut et al. studied that gastric contents with PH less than 2.5 is notorious to cause aspiration pneumonia [10]. The pH of the prepared clonidine solution is 6.5 and that of midazolam was 3.5 which is more than conservative pH limit of 2.5 thought to promote lung damage after aspiration of gastric contents. We noted a better profile with clonidine when compared to midazolam with respect to PH.

The drug was very well accepted without spitting or vomiting by none patients in our study group. Mikawa et al compared two doses of oral clonidine (2 μ g and 4 μ g) along with oral atropine 0.03mg/kg and concluded that 4 μ g/kg is an effective dose for premedication. Therefore we used 4 μ g/kg of clonidine in the study. According to British Pharmacopoeia, midazolam is practically insoluble in water, freely soluble in acetone, ethanol and methanol. Mcmillan et al compared different doses of midazolam (0.5mg, 0.75mg and 1 mg/kg) and used the parenteral form of midazolam and concluded that 0.5mg/kg is safe and effective premedication [10,11]. In our study we used parenteral form of preservative free midazolam available in the strength of 5 mg/ml in the dose of 0.5 mg/kg.

Nicole Almenrader et al. conducted a prospective open study in 64 children [12]. They were randomly allotted to receive either oral midazolam 0.5 mg / kg or oral clonidine 4 μ g/kg as premedication. This study helps to demonstrate clinical advantages of oral clonidine, in the preoperative period as well as recovery period compared to oral midazolam. Clonidine produced good sedation in 100% of patients of their study population. In clonidine premedication

group 90% of children were asleep before mask induction were as in midazolam group only 10% were asleep. Clonidine causes sedation similar to natural sleep. In the clonidine group patient can be easily aroused to perform cognitive tests. This effect is thought to result from inhibition of spontaneous and evoked activity of central mono aminergic systems involved in modulation of sleep and cortical arousal. In our study, 76% of the patients in clonidine group has sedation scores of 3 and 4 while 34% of patients in midazolam group of the same scores while separation from the parents. Kain et al. selected a group of children and were randomly assigned to one of three groups: (1) 0.5 mg/kg oral midazolam; (2) parental presence during induction of anesthesia; or (3) control (no parental presence or premedication). They used multiple behavioral measures of anxiety, to assess the effect of the intervention on the children and their parents [13]. Finally they concluded that group which received midazolam has better anxiolysis than the one with parents at the time of induction. In our study, regarding anxiety level on separation from parents, 80% of patients in the clonidine group are calm/cooperative but only 34% of patients in the midazolam group are calm / cooperative. Trevour et al investigated that 33.3% of children belonging to clonidine group were adequately sedated when compared to 23.3% of children in midazolam group at the time of veno puncture with statistical significance [14,15]. They found that anxiolysis was better with midazolam group. In our study, 42% of patients in clonidine group had sedation scores of 3 and 4 and only 4% of patients in midazolam group had sedation score of 3 during venopuncture. Regarding the anxiety level at the time of venopuncture, 58% of patients in the clonidine group were calm/cooperative but only 30% of patients in midazolam group were calm and cooperative. They found that children belonging to clonidine group showed better outcome in sedation level and anxiolysis when compared to midazolam group, which was statistically highly significant.

Almenrader et al studied that mask acceptance was comparable between oral clonidine and oral midazolam. Mikawa et al, resulted that mask acceptance was better in patients premedicated with 4mcg/kg clonidine in comparison with clonidine 2mcg/kg and diazepam. In our study, level of mask acceptance when compared 34% of patients in clonidine had score of 4 and 5 and only 2% of patients in the midazolam group had a score of 4. So we noted that mask acceptance was better in clonidine group than midazolam group.

They found that, more emergence agitation was associated with midazolam premedication. The clonidine group had better post operative recovery and significant parental satisfaction. In our study the post operative score graded as 3 according to Modified objective pain score was 14% in the clonidine group and was 38% in the midazolam group. Hence post operative score was also better in the clonidine group. Post operative agitation was seen more in the midazolam group.

During the conduct of the study we didn't encounter any bradycardia, hypotension and respiratory depression. All patients were premedicated with 10 mcg/kg glycopyrrolate. We found that both the drugs produced significant sedation, clonidine produced better sedation than midazolam. Both the drugs provided statistically significant reduction of anxiety level on intravenous cannulation. Children accepted the technique well and parents were satisfied with the outcome. We were able to use this technique effectively in a busy government hospital with the good preoperative monitoring.

Conclusion

We concluded from our study that oral clonidine and midazolam can be used as better premedicants to produce optimal sedation and emotional state. Clonidine 4 µg / kg has been shown to be a more effective premedication for children undergoing elective tonsillectomy than midazolam 0.5mg/kg.

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Conflicts of interest: There are no conflicts of interest

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