

## Pre-eminence of oral clonidine when juxtaposed with oral midazolam as pre-anaesthetic medication in children: a prospective randomised double blind study

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### Abstract

**Background & Objectives:** Drugs administered before anaesthesia to decrease anxiety and to obtain a smoother induction, maintenance and emergence from anaesthesia is a part of preanaesthetic medication. Clonidine, a central  $\alpha_2$  agonist and Midazolam, a benzodiazepine, are among drugs used as preanaesthetic medication which plays a vital role in producing sedation and reducing anxiety especially in children. Hence, the aim of this study was to evaluate the role of oral Clonidine and oral Midazolam as an ideal preanaesthetic medication in children to produce sedation and reduce anxiety.

**Methods :** A prospective randomised double blind study was done involving 70 children (2-10) years scheduled for elective surgery between the period of January 2014 to July 2015 in Department of Anaesthesia, K.S. Hegde Medical College and Hospital, K.S.Hegde Medical (Affiliated to NITTE university), Deralakatte, Mangalore, Karnataka, India. They were randomly divided in to two groups as group A (Oral Midazolam, 0.5mg/kg) and group B (Oral Clonidine, 4mcg/kg). The drugs were administered to the subjects 45 minutes before induction of anaesthesia and evaluated for sedation and anxiety based on scores as per protocol.

**Results:** Anxiety scores showed a decrease in both Midazolam and Clonidine group with a value of 3.35(p<0.001) and 4.12(p<0.00) respectively. Similarly, sedation scores showed an increase in both Midazolam and Clonidine group with a value of 4.25(p<0.001) and 5.51(p<0.000) respectively.

**Interpretation & conclusions:** Oral Clonidine (4mcg/kg) is a potent and efficacious preanaesthetic medication in children when juxtaposed with oral Midazolam (0.5mg/kg) in producing sedation and reducing anxiety along with analgesic sparing effect.

**Keywords:** Anxiety, Clonidine, Midazolam, Pre-anaesthetic, Sedation

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### Introduction

The preoperative period is stressful for many individuals undergoing surgery<sup>1</sup>. This is especially true for children. Anxiety is a normal emotional response to impending surgery. Child's stress during the preoperative period results from multiple sources which includes limited understanding of their illness, pain, hospitalization and need for surgery. Fear of operations, injections, physicians, and an unfamiliar operation theatre environment, where the children are separated from their parents prior to anaesthesia, invariably produces traumatic experiences in the tender minds of young children<sup>2</sup>.

Consequences of preoperative stress and anxiety leads to long term psychological problems and behavioural effects like night time crying, enuresis, separation anxiety, temper tantrums, sleep or eating disturbances<sup>3</sup>.

An ideal premedication should eventually yield a patient free from anxiety, pain and sedation, but easily arousable and cooperative. Midazolam and Clonidine satisfy many of the characteristics of an ideal premedication. Clonidine, and central  $\alpha_2$  agonist has significant sedative and analgesic properties. It was introduced as a paediatric premedication in 1993 and although it is less popular than midazolam, its use has been constantly increasing. It has been shown that oral Clonidine effectively produces pre-operative sedation and anxiolysis in children along with sympatholytic activity and analgesic activity<sup>3,4</sup>. The favourable effect of Midazolam, a short acting benzodiazepine, as preanaesthetic medication includes sedation, anxiolysis, amnesia and reduction of post-operative vomiting<sup>5-12</sup>.

### Material and Methods

Institutional Ethics Committee approval was obtained from K.S.Hegde Medical Academy (Affiliated to NITTE university), Ref. No. INST.EC/E.C/100/2013-2014 dated 30/09/2013 before conduction the study. An informed written consent was taken from the parents of the children enrolled in the study. Pre anaesthetic evaluation was done for all the patients. 70 paediatric patients belonging to American Society of Anaesthesiologists physical status I and II (ASA PS) between the age group of 2-10 years undergoing elective surgeries under general anaesthesia

in K S Hegde Hospital, Deralakatte, Mangalore, were included in the study.

**Inclusion criteria:**

- ASA physical status I and II
- Age group 2-10 years
- Elective surgeries

**Exclusion criteria:**

- Central nervous system dysfunction like cerebral palsy, mental retardation
- On recent or chronic medication with sedatives, anticonvulsants
- If child vomits after drug intake

Children were randomly allocated into two groups as Group A and Group B. Group A received oral Midazolam 0.5mg/kg and Group B received oral Clonidine 4mcg/kg, 30 minutes before induction. Oral Midazolam was available in syrup form which was given 0.5mg/kg. Oral Clonidine was prepared by dissolving crushed tablets of Clonidine 100mcg with 10ml of 5% dextrose and given in a dose of 4mcg/kg. Study subjects were constantly observed for evaluating changes in mood, behaviour and appearance. All the study subjects were constantly monitored with pulse oximeter. Vitals were recorded before, 15 minutes after premedication and also at the time of recording anxiety and sedation scores. Onset of sleep, closure of eyes and any visible side effects were also noted.

**Statistical Analysis**

Mannwhitney U Test was used to analyse the data and observations are mean±SD. p<0.05 was considered as statistically significant.

**Results**

In our study, we found that about 28(80%) and 7(20%) belonged to ASA I and II classification respectively in Midazolam group, whereas in Clonidine group, 26(74.3%) and 9 (25.7%) belonged to ASA I and II classification respectively (Table 1).

Anxiety scores (AS) before premedication in children were found to be high with a value of 0.172(p>0.05). Anxiety scores showed decrease in both Midazolam and Clonidine group with a value of 3.35(p<0.001) and 4.12(p<0.00) respectively, but significant decrease in anxiety was found in Midazolam when juxtaposed with Clonidine after separation from parents and after induction of anaesthesia (Table 2 & Fig. 1).

Similarly, sedation scores (SS) before premedication in children were found to be less with a value of 1.47 (p>0.05). Sedation scores showed an increase in both Midazolam and Clonidine group with a value of 4.25(p<0.001) and 5.51(p<0.000) respectively, but significant increase in sedation was found in Clonidine when juxtaposed with Midazolam after separation from parents and after induction of anaesthesia (Table 3 & Fig. 1).

**Table 1: Showing ASA classification of oral Midazolam and Clonidine group**

ASA classification	Group		Total
	Midazolam	Clonidine	
I	28 (80%)	26 (74.3%)	54 (77.1%)
II	7 (20%)	9 (35.7)	16 (22.9%)
Total	35 (100%)	35 (100%)	70 (100%)

ASA-American Society of Anaesthesiologists

**Table 2: Comparison of anxiety scores before premedication, after separation from parent and induction of anaesthesia within group**

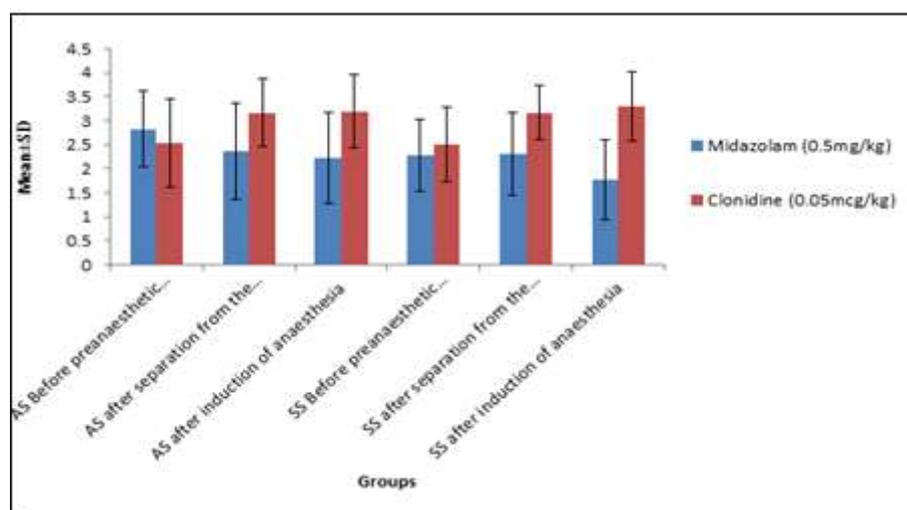
	Group	Number	Mean±SD	Mannwhitney U test	
				Z value	P value
AS before pre-anaesthetic medication	Midazolam	35	2.83±0.79	1.37	0.172*
	Clonidine	35	2.54±0.92		
AS after separation from parents	Midazolam	35	2.37±1.00	3.35	0.001**
	Clonidine	35	3.17±0.71		
AS after induction of anaesthesia	Midazolam	35	2.23±0.94	4.12	0.000**
	Clonidine	35	3.20±0.76		

Observations are mean±SD. Mannwhitney U Test. \*p>0.05-Not significant, \*\*p<0.05-Significant, p<0.001-Highly significant, p<0.000-Highly significant. AS-Anxiety Scores

**Table 3: Comparison of sedation scores before premedication, after separation from parent and induction of anaesthesia within group**

	Group	Number	Mean ±SD	Mannwhitney U test	
				Z value	P value
SS before pre-anaesthetic medication	Midazolam	35	2.29±0.75	1.47	0.135
	Clonidine	35	2.51±0.78		
SS after separation from parents	Midazolam	35	2.31±0.87	4.29	0.001**
	Clonidine	35	3.17±0.57		
SS after induction of anaesthesia	Midazolam	35	1.77±0.84	5.91	0.000***
	Clonidine	35	3.31±0.72		

Observations are mean±SD. Mannwhitney U Test. \*p>0.05-Not significant, \*\*p<0.05-Significant, p<0.001-Highly significant, p<0.000-Highly significant. SS-Sedation Scores



**Fig. 1: Anxiety and Sedation scores of Oral Midazolam and Oral Clonidine as Preanaesthesia Medication**  
AS-Anxiety scores, SS-Sedation scores

**Discussion**

The essential components of anaesthesia in paediatric patients before surgery are sedation and anxiolysis. Clonidine, an  $\alpha_2$  adrenergic agonist shares most of the beneficial effects of midazolam. It is an upcoming preanaesthetic agent which is used in paediatric patients. Midazolam a gold standard premedication, has long been considered in the paediatric population. Investigators previously had reported a high incidence of agitation following exposure to short acting anaesthetics during brief, minimally invasive or non invasive procedures. Currently most commonly used premedicant is midazolam followed by ketamine, fentanyl and meperidine. Midazolam is considered to be an ideal premedication in children with regards to certain beneficial effects like amnesia, long term behavioural disturbances and confusion. The need for anxiolysis and adequate sedation is widely accepted. Clonidine on the other hand has some additional effects which includes reduction of anaesthetic requirements, reduction of post operative nausea and vomiting, attenuation of

hemodynamic responses to tracheal intubation and surgical stimuli. Decreased incidence of shivering<sup>14</sup>, effective postoperative analgesia, reduction in postoperative disorientation are some of the other beneficial effects of Clonidine<sup>13-17</sup>.

Our study demonstrated the clinical advantages of oral Clonidine (4mcg/kg) during recovery and perioperative period and compared it with oral Midazolam as a preanaesthetic medication in children. It was found that premedication with oral Clonidine (4mcg/kg), decreased the dose of intravenous anaesthetic agents for the induction of anaesthesia and also reduced maintenance of anaesthesia. However, oral Midazolam (0.05mg/kg) can be considered as better medication for preanaesthetic purpose as an anxiolytic in children as it has insignificant changes in hemodynamics, but on the contrary, the child, who was calm, friendly and playful became violent and aggressive during recovery which was a matter of concern as evident from our study. Qualities of mask acceptance and induction of anaesthesia were significantly better with oral Clonidine (4mcg/kg) and

steal induction with the child asleep could be performed in patients in the Clonidine group which was not much evident in Midazolam group.

The central  $\alpha_2$  adrenergic agonism of Clonidine apart from its analgesic action is also a good sedative where the study subjects can be easily aroused to perform the cognitive tests. Clonidine has an overall better sedative action than Midazolam. In contrast, this study showed that children premedicated with Midazolam, despite having lower sedation scores provided excellent anxiolysis. Midazolam has a shorter half life compared with Clonidine and with less postoperative sedation. Analgesic sparing effect in children undergoing surgery was found in oral Clonidine and was associated with only mild to moderate pain when juxtaposed with oral Midazolam which lacked analgesic action. In the Clonidine group, it was seen that, parental satisfaction was higher than Midazolam group.

### Conclusion

Our study showed that oral Clonidine (4mcg/kg) was preeminent when juxtaposed with oral Midazolam (0.05mg/kg) as accepted by the child during mask induction and produced more effective pre and post operative sedation and also displayed a trend towards better recovery and a higher parental satisfaction.

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