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Comparison between oral midazolam and oral clonidine as a pre-anaesthetic medication in a paediatric age group for general anaesthesia.

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ABSTRACT

Anxiety is an emotional response to an impending surgery, be it in adults or children. In current practice of medicine, patient satisfaction and quality of life are considered important outcomes. This approach has incorporated issues such as preoperative anxiety management in children undergoing surgeries. The objective of this study is to compare and contrast, oral clonidine with oral midazolam as a premedication in paediatric patients aged between 2-12 years with regards to, sedation and anxiolysis to help in separation of children from their parents along with sedation and anxiolysis at the time of separation from parents and during interventions like mask application and venepuncture. Continuous monitoring of vital signs was established in order to record any changes. The results show that oral clonidine produces significantly better sedation than oral midazolam. In contrast midazolam provided significantly superior anxiolysis at times of venepuncture and mask application.

Keywords: Premedication, midazolam, clonidine, venepuncture, mask ventilation

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INTRODUCTION

Anxiety is an emotional response to an impending surgery, be it in adults or children. Fear of the operation theatre, injections and fear of medical practitioners is quite common. This fear is manifested tenfold in children. The children being separated from their parents into an unfamiliar environment can invariably produce a traumatic experience in their tender minds.

The cause of a patient's preoperative anxiety is multi-factorial, being related to intra-operative awareness, not waking up after anaesthesia and postoperative pain and nausea. Children even preschool, are old enough to appreciate the stress of hospital environment and separation from their family. In current practice of medicine, patient satisfaction and quality of life are considered important outcomes. This approach has incorporated issues such as preoperative anxiety management in children undergoing surgeries.

To parents, their child's safety is the only important issue. But these days with the anesthetic mortality rates being low, safety is expected. Typically parents are not aware of the events that take place during the surgery within the operation theatre. Parents evaluate an anesthesiologist in part based on the separation of their child. That is if their child is upset and in tears their experience will be poor. This issue of satisfaction is not just limited to parents. Most surgeons are aware of the quality of this separation. They have to cope with the parents during post operative visits especially if the children cry of nightmares of surgery. Thus there lies a close connection between the anxiety of a child during the peri-operative period and the satisfaction with the services of the anesthesiologist.

A panel of 72 anesthesiologists has ranked various anesthesia outcomes based on importance and frequency of occurrence [1]. The anesthesiologists reached a consensus on low morbidity clinical outcomes which occur frequently and are important to the patient. The five outcomes with the highest scores were incision pain, nausea, vomiting, preoperative anxiety and discomfort from intravenous cannulation.

Research has documented that a child's resultant fear and distress on the day of surgery extends well beyond the immediate operative period. High levels of stress preoperatively are associated with slower recovery and greater anti-emetic and analgesic requirements post operatively [2]. A recent investigation concluded that 'stormy inductions' are associated with significantly increase occurrence of postoperative maladaptive behavioral changes [3].

Preanesthetic therapy comprises of two parts: psychological preparation and treatment with anxiolytic drugs. Various combination of drugs and routes of administration have been employed for premedication in children. The oral route remains the least threatening and the most accepted method of drug administration in children. It is painless, quick and reliable [4].

An ideal sedative must have a low cost and should be reliable. It should be rapidly acting with no delay in induction and emergence. The side effects of the drug must be minimal. In this study an attempt is made to compare midazolam, premedication in paediatric patients, with an alpha 2 agonist clonidine as a premedication in children which has desirable sedative properties.

SUBJECTS AND METHODOLOGY

This randomized controlled trial was conducted in Raja Muthaiya Medical College in the Department of Anaesthesia, The college ethical committee approval was obtained. 60 patients belonging to ASA class I and II between the age group of 2-12 years scheduled for elective surgery in the hospital were included in the study. An informed consent was taken from the parents of the children enrolled in the study. The study was limited to children older than two years as the cardiac output in younger children is dependent on heart rate and clonidine is known to cause bradycardia.

Patients on sedative medications and those having central nervous system or gastrointestinal disorders, are obese and any who have had previous reactions to clonidine or benzodiazepine were excluded. The children were randomly allocated into one of two groups. Group I (MG1) received oral midazolam 0.5mg/kg (maximum of 15mg) along with atropine 0.04mg/kg 30 minutes before induction. The medication used was injectable preparation of 5mg/ml preservative free ampoules. It was mixed with honey to mask the

bitter taste of administration. Group II (CG2) received oral clonidine 4µg/kg (maximum 200µg) along with atropine 0.04mg/kg 90 minutes before induction. Oral clonidine was prepared by dissolving crushed tablets of clonidine 100µg (arkamine) as per body weight dose in honey. Children, who could not completely ingest or retained the medication was excluded from the study.

The children were evaluated for:

1. Baseline anxiety and sedation (before giving the premedication)
2. Levels of sedation and anxiety at the time of separation from parents
3. Levels of sedation and anxiety at the time of venepuncture.
4. Levels of sedation and anxiety at the time of mask application/induction of anaesthesia.

All measurements of sedation and anxiety in this study were completed by the same investigator to minimize inter-observer variability. The vital signs were carefully monitored (heart rate and systolic blood pressure) in every child.

Sedation score used was numbered 1 to 4 wherein 1. Alert 2. Awake 3. Drowsy and 4. Asleep. A score of 3 or 4 was considered adequate sedation.

Similarly Anxiolytic score was graded from1 to 4 wherein 1. Poor (afraid and agitated, difficult to control, panicky) 2. Fair (fearful, moderate apprehension, moaning) 3. Good (slightly apprehensive, but withdrawn from the surroundings) and 4. Excellent (no fear, calm and sleepy, friendly) A score of 3 or 4 was considered to be adequate anxiolysis [5].

Demographic data including age, weight and sex of the children were recorded. The baseline anxiety and sedation, if any (before pre-medication) of the children were graded as per the scoring system adopted. The acceptability of the premedication by the children was also noted. Thereafter the children were carefully observed for changes in mood, behavior and appearance in the pre operative holding area. The sedation score, anxiety score and heart rate and blood pressure were noted at the time of separation from the parents and venepuncture. The child was brought into the theatre and an intravenous fluid, ringer lactate was started. Monitors were attached and vitals noted. The sedation score, anxiety score and heart rate and blood pressure were noted at the time of mask application. Anaesthsia was induced with titrated doses of thiopentone sodium and after adequate muscle relaxation, endotracheal intubation was done. Anaesthesia was maintained with oxygen, nitrous oxide and halothane, analgesia was provided with intravenous pethidine and surgery was started.

Statistical Analysis: Vital signs were compared using students t test and the sedation and anxiolysis score were compared using the Wilcoxon signed rank test and the chi square analysis. A p value less than 0.05 was considered statistically significant.

RESULTS

Sedation score during separation from parents: 53.3% subjects had a sedation score of 3 in CG2 as compared to 20% of MG1. 30% cases had a sedation score of 30% in the clonidine group. Hence it can be inferred that clonidine offers better sedation than midazolam during separation from parents. (Fig 1)

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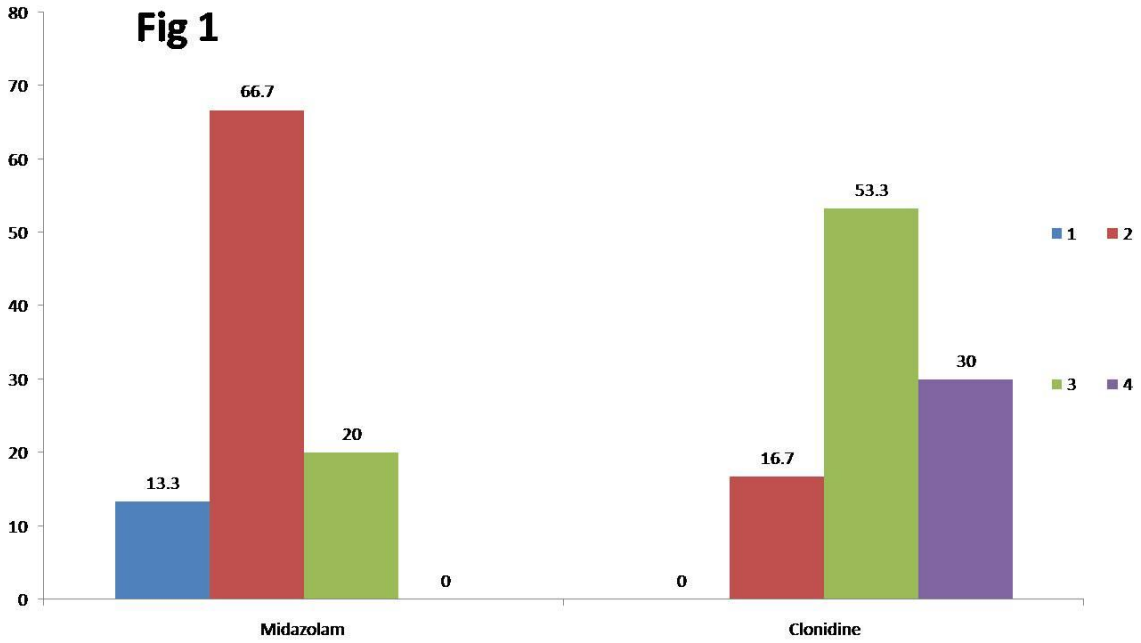

Fig 1: Comparison of sedation scores (1, 2, 3 and 4) at separation between midazolam and clonidine, where X axis denotes the two groups and Y axis denotes the percentage.

Sedation score during venepuncture: In CG2 26.7% had a score 3 while 3.3% had a score of 4. In MG1 adequate sedation was achieved in 23.3% with sedation score of 3. The p value was not significant. (Fig 2)

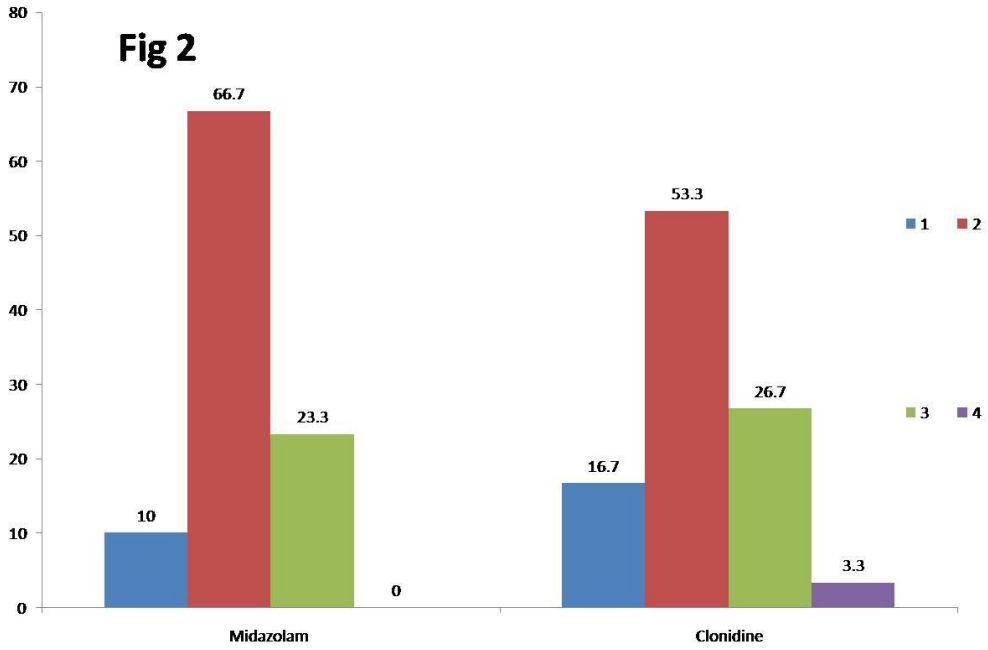

Fig 2: Comparison of the sedation scores (1, 2, 3 and 4) between midazolam and clonidine during venepuncture, where X axis denotes the two groups and Y axis denotes the percentage.

Sedation score during mask ventilation: In CG2 20% had a score 3 while 3.3% had a score of 4. In MG1adequate sedation was achieved in 20% with a score of 3. The p value was not significant. (Fig 3)

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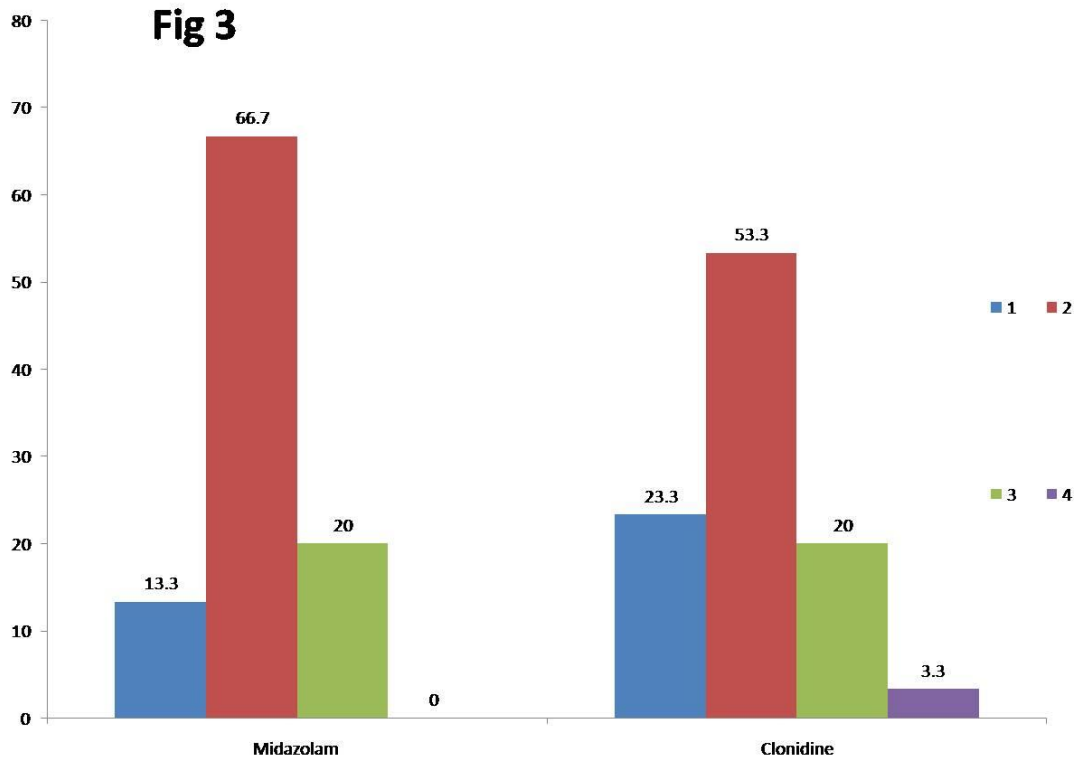

Fig 3: Comparison of the sedation scores(1, 2, 3 and 4) between midazolam and clonidine at mask ventilation, where X axis denotes the two groups and Y axis denotes the percentage.

Anxiety score during separation from parents 40% subjects in CG2 had a score 3 and 20% had a score 4 had an adequate anxiety level. In MG1adequate levels were achieved in 43.3% with sedation score of 3 and 36.7% cases had a score of 4. The p value 0.14. (Fig 4)

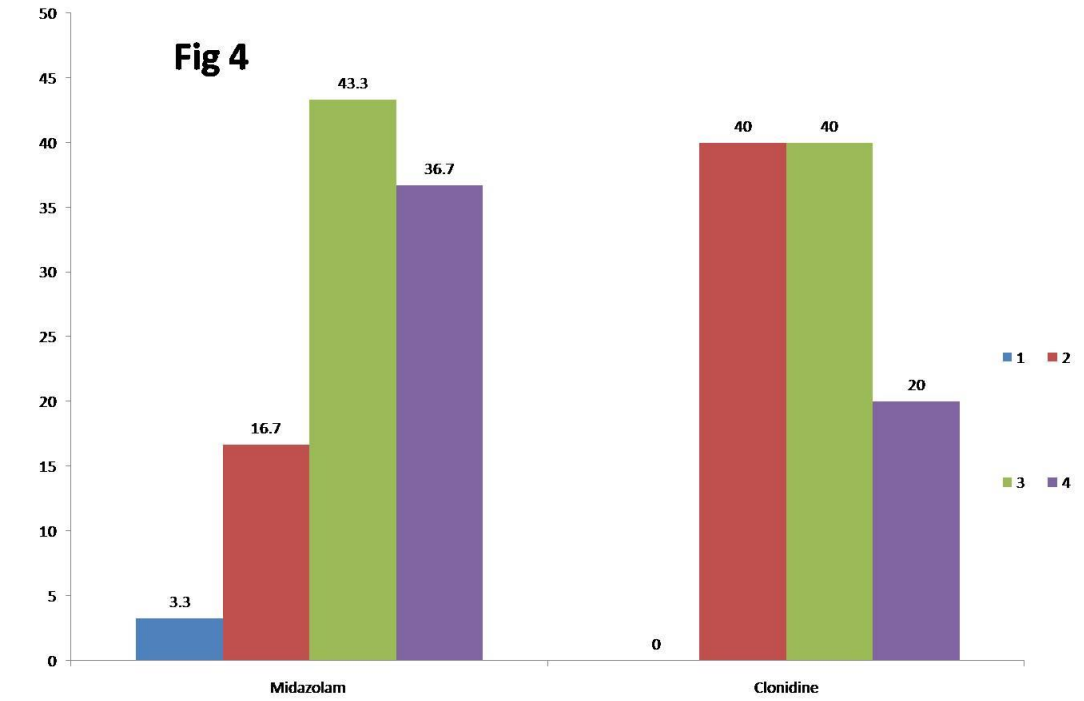

Fig 4: Comparison of anxiety scores (1, 2, 3 and 4) at separation from parents, between midazolam and clonidine at mask ventilation, where X axis denotes the two groups and Y axis denotes the percentage.

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Anxiety score during venepuncture: 30% of CG2 had a score 3 and 6.7 % had a score 4, showing an adequate anxiety level. In MG1adequate levels were achieved in 36.7% with a sedation score of 3 and 33.3% a score of 4. The p value was 0.02 and is significant with midazolam achieving a better anxiety level. (Fig 5)

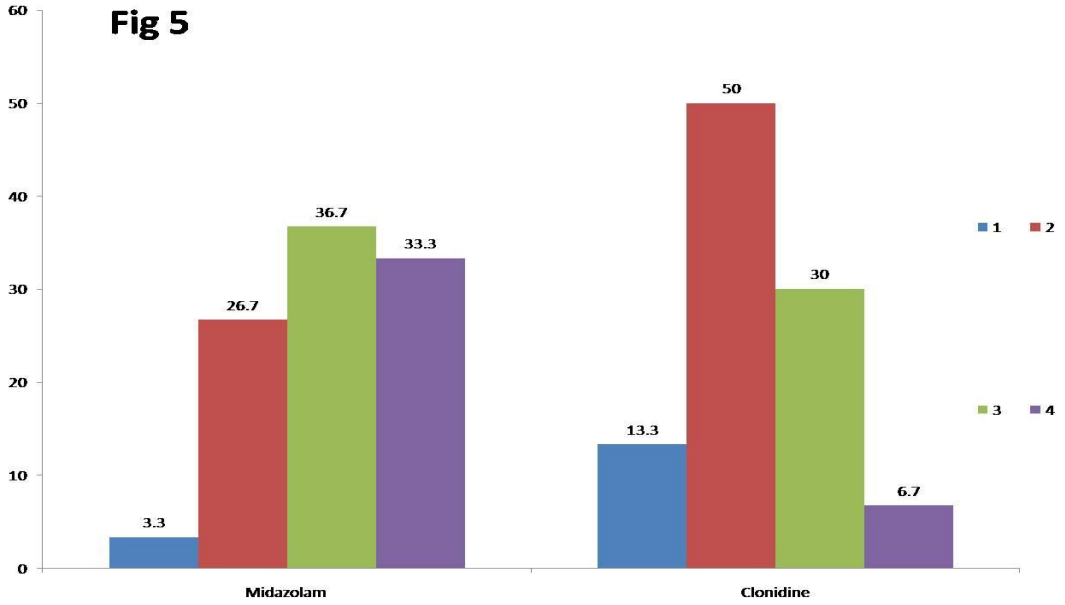

Fig 5: Comparison of anxiety scores (1, 2, 3 and 4) at venepuncture, between midazolam and clonidine at mask ventilation, where X axis denotes the two groups and Y axis denotes the percentage.

Anxiety score during mask ventilation: In CG2 23.3% had a score 3 and 6.7 % had a score 4, while in MG1adequate levels was achieved in 46.7% with a score of 3 and 30% had a score of 4. The p value was found to be 0.003 and is very significant with midazolam achieving a better anxiety level. (Fig 6)

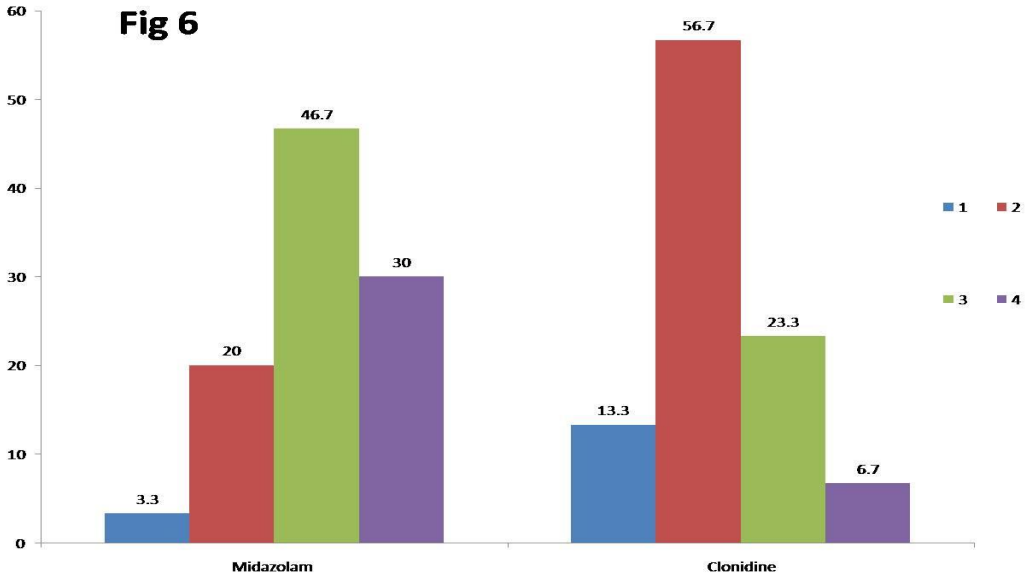

Fig 6: Comparison of anxiety scores (1, 2, 3 and 4) at mask ventilation, between midazolam and clonidine at mask ventilation, where X axis denotes the two groups and Y axis denotes the percentage.

Heart rate: On comparison of heart rate before premedication, after separation from parents, after venepucture and after mask ventilation; it was found to be very significant with p value 0.004, 0.009, 0.001 and 0.001 respectively. Clonidine achieved a better control of the heart rate as compared to midazolam at all junctures. (Fig 7)

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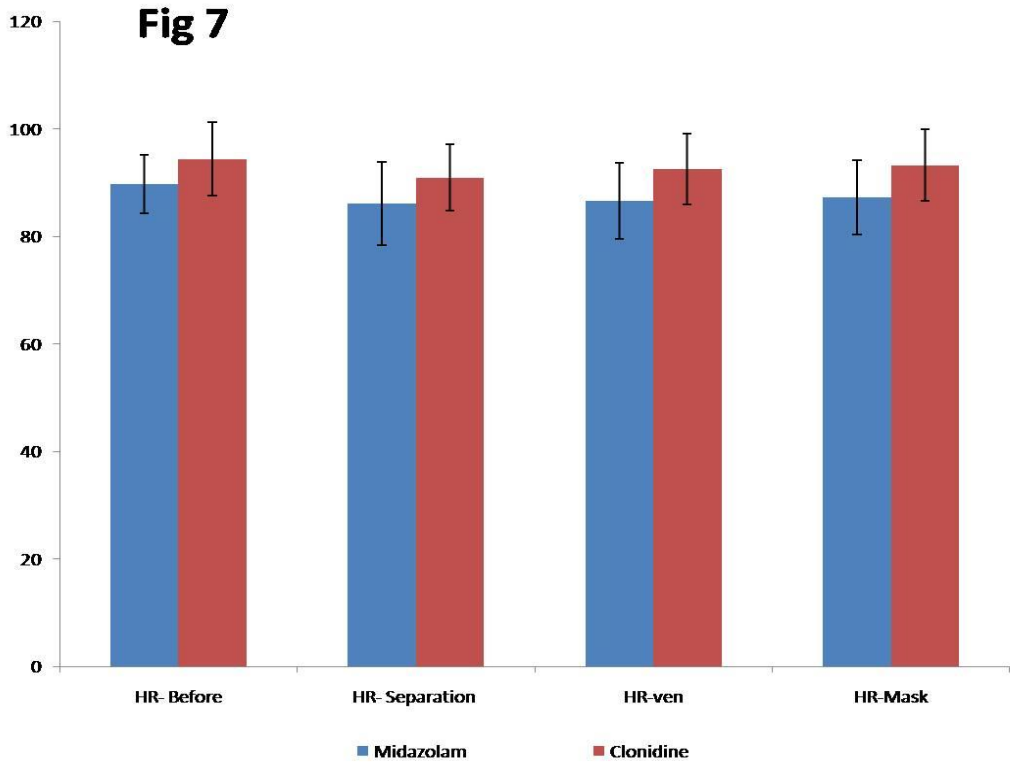

Fig 7: Comparison of heart rates between midazolam and clonidine at mask ventilation, where X axis denotes the two groups and Y axis denotes the mean heart rate.

Systolic blood pressure: On comparison of systolic blood pressure before premedication, after separation from parents, after venepucture and after mask ventilation; it was found to be very significant with p value <0.001. Clonidine achieved a better control of the systolic blood pressure as compared to midazolam. (Fig 8)

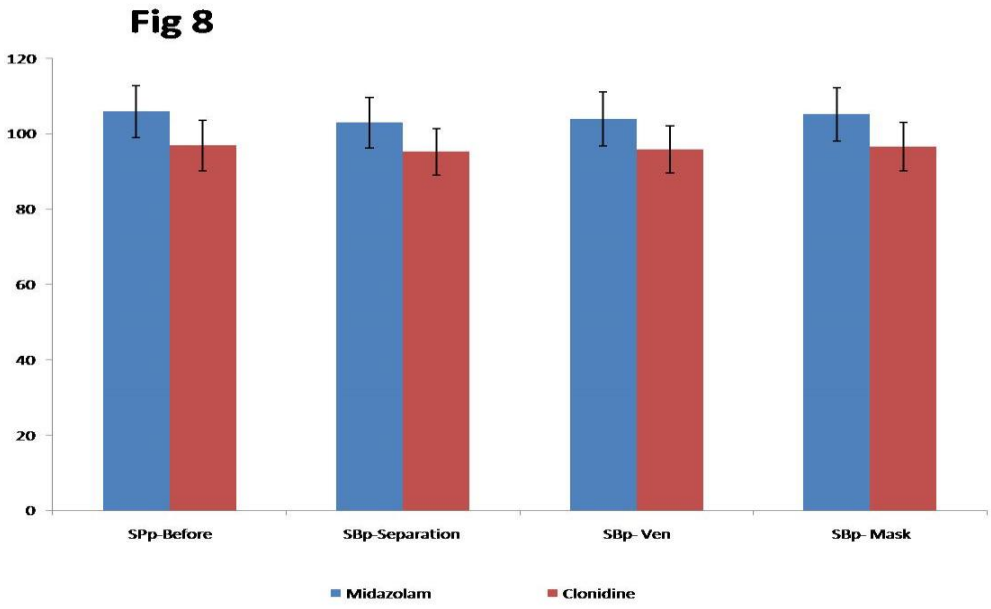

Fig 8: Comparison of Systolic blood pressure between midazolam and clonidine at mask ventilation, where X axis denotes the two groups and Y axis denotes the mean Systolic blood pressure.

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DISCUSSION

This study was done with the intention of comparing the sedative and anxiolytic effects of midazolam and clonidine in paediatric patients, in view of the growing wealth of publications suggesting clonidine as a promising alternative to midazolam.The population sample studied was homogenous as the preanesthetic characteristics (gender, age, weight, preoperative anxiety and sedation) of the patients were quite similar. A placebo group was not used because this is a comparative study between oral clonidine and oral midazolam and the efficacy of both oral clonidine and oral midazolam and the lack of placebo effect in this age group has been demonstrated previously [6].

McMillan [6] studied the sedation and anxiolysis after a 0.5 mg/kg dose of oral midazolam. They observed that at the time of separation from parents, 40 % had good sedation and 80 % had good anxiolysis. Debnath [7] performed a study involving 0.5 mg/kg dose of oral midazolam. They found that 70% children were calm at the time of separating them from their parents and 30% children cried. In our study, at the time of separation from parents 20 % in the midazolam group were adequately sedated and 80% of the children had adequate anxiolysis. Our results of excellent anxiolysis after an oral dose of 0.5 mg/kg midazolam at the time of separation from parents are comparable to the results of McMillan and Debnath. The degree of sedation and anxiolysis in our study using 0.5 mg/kg midazolam are far greater than the results obtained by Field [8]. This 10 fold greater success in effective separation from parents in our study may be attributed to the fixed time interval of separation of children from their parents after premedication which was limited to 20-30 minutes. In the study by Field, however, the evaluation of sedation at the time of separation occurred any time between 30 and 80 min after administration of oral midazolam. Such a wide time interval limits interpretation of the pharmacodynamic effects of oral midazolam. A study done by Levine[5] et al on the time interval between premedication with oral midazolam 0.5 mg/kg and separation from parents recommends that children can be effectively separated as early as 10 min after premedication.

Tazeroulti et al in their study comparing oral clonidine and oral midazolam found the quality of induction was less satisfactory after clonidine than after midazolam premedication [9]. The results of our study are comparable to the above. The inadequate anxiolysis after clonidine in the study done by Tazeroulti may have been because of the short 30 min delay between premedication and induction. This however cannot explain the poor anxiolysis after clonidine in our study induction of anaesthesia was done 90 minutes after premedication. Mikawa [10] recommended that clonidine 4 mcg/kg be administered 105 min before anaesthetic induction, as they found that it induced satisfactory sedation and anxiolysis after this period.

The results of our study shows that clonidine has an overall more sedative action than midazolam, with the degree of sedation decreasing on interventions such as venepuncture or mask application. This goes along the lines of the unique feature of arousabilty on stimulation that is seen with clonidine. However in contrast, this study showed that children premedicated with midazolam, despite having lower sedation scores provided excellent anxiolysis especially during venepuncture and mask application.

On analyzing, the vital signs in our study group, it was observed that no child in the study developed significant bradycardia. However, children in the clonidine group have a significant fall in blood pressure following premedication. These results are comparable to the results of Reimer et al and Malde et al [11], [12]. Although this finding was found to be statistically significant it can be debated whether the numerically small difference between the groups can be regarded as clinically relevant.

This superior picture of excellent anxiolysis with little change in hemodynamics, conforms with the superiority of midazolam as a premedication in children. However this was somewhat scarred by the strange behavior of one of the children premedicated with midazolam. This child, who was calm, friendly and playful, became violent and aggressive after premedication with midazolam. Such paradoxical reaction has been documented [13], [14] before with regards to midazolam premedication, the reason for which is not well understood, although it has been linked to genetic characteristics and personality problems. Paradoxical reactions to benzodiazepines include restlessness, violent behavior, physical assault, act of self-injury and need for restraints. These may occur at variable times after administration of midazolam.

In conclusion, the results show that oral clonidine produces significantly better sedation than oral midazolam. The degree of sedation with clonidine reduces on interventions, such as vene-puncture and mask

application, which is comparable to the sedation in the midazolam group. In contrast midazolam provided significantly superior anxiolysis at times of venepuncture and mask application. In addition midazolam did not cause significant changes in hemodynamics unlike clonidine. However clonidine with excellent sedative properties and other peri-operative benefits like decrease in anaesthetic requirements, reduced need for supplementary analgesics postoperatively, reduced incidence of shivering and postoperative vomiting and decreased incidence of sevoflurane emergence agitation, cannot be discounted as a viable alternative to midazolam in paediatric patients.

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