



ORIGINAL RESEARCH PAPER

Anaesthesiology

A COMPARATIVE STUDY OF ORAL PRE-MEDICATION IN CHILDREN: MIDAZOLAM VERSUS CLONIDINE.

KEY WORDS:

clonidine, midazolam, premedication, children

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ABSTRACT

Introduction: The perioperative period is stressful for many individuals undergoing surgery. Children’s stress during the perioperative period results from multiple sources which include limited understanding of their illness, pain, hospitalisation, need for surgery. The consequence of this perioperative stress and anxiety leads to long term psychological problems and behavioural effects. A need exists for a safe and effective oral preanaesthetic medication for use in children undergoing elective surgical procedures

Aim & objectives: this randomized double blind study was designed to compare oral pre-medication in children: Midazolam versus clonidine.

Method: : 60 patients ASA 1 AND 2 in the age group of 2 to 10 years were randomly divided into two groups including 30 patients in each group . Group m : Oral Midazolam tablet (0.5mg/kg) 30mins before induction

Group c: Oral clonidine (4mcg/kg) 45mins before induction.

All children were monitored with pulseoximeter for SpO₂, HR and RR. Vitals were recorded before pre-medication, 15mins after premedication and at the time when sedation score is 3 or less. Sedation level was evaluated by child’s appearance using the 5 point sedation scale. Each child was observed for level of consciousness and acceptance of drug at the time of administration by 2 point scale. Anxiety level of each child was recorded using 4 point scale at the time of separation from parents and at the time of acceptance of face mask.

Result: The result of our study suggest that oral midazolam (0.5mg/kg) effectively reduced the anxiety associated with parental separation and mask application than oral clonidine(4mcg/kg). The sedation action of both the drugs are comparable. The onset of sedation and peak sedative effect was significantly slower after oral clonidine compared with oral midazolam. The side effects of oral clonidine was lesser than oral midazolam.

Conclusion: In conclusion the results of our study suggest that oral midazolam(0.5mg/kg)effectively reduced the anxiety associated with parental separation and mask application more than oral clonidine(4mcg/kg).

Introduction:

The perioperative period is stressful for many individuals undergoing surgery, and this is especially true for children. Children's stress during the perioperative period results from multiple sources which include limited understanding of their illness, pain, hospitalisation, need for surgery.¹ Fears of injections, operation and the peculiar operation theatre environment where the children are separated from their parents prior to anaesthesia and surgery invariably produces traumatic experiences in the tender minds of young children. The consequence of this perioperative stress and anxiety leads to long term psychological problems and behavioural effects. Maladaptive negative behavioural effects include new onset general anxiety, night time crying, enuresis, separation anxiety, temper tantrums, sleep or eating disturbances.²

Familiarity with a child's clinical and psychological status as well as parental concerns is essential for delivery quality anaesthesia care. Good anaesthesia practice, as well as attention to the pharmacological and physiological issues, should address the psychological aspects of perioperative care of children. Preoperative anxiety and postoperative behaviour of children and parental anxiety are becoming important issues which is evident by recent work using newly validated measures of these outcome. Motivation for interventions directed at relieving children's anxiety, such as parental presence during anaesthetic induction and preparation programs has increased. This is partly due to increased parent participation in children's hospital stay and a more holistic approach to children's care by nursing and medical staff.³

Parents of children undergoing surgery are very anxious and worried. Increased parental preoperative anxiety has been shown to result in increased preoperative anxiety in their children. Parental anxiety is also less when the child receives a premedication. Furthermore, separation from parents and induction of anaesthesia have been found to be the most stressful times during the surgical/anaesthesia experience of a child.² An atraumatic premedication can minimise these problems when a

calm separation from parents and smooth induction of anaesthesia with fewer airway problems is achieved. This intervention of sedative premedication, has changed due to advent of short acting benzodiazepines.

Over the years, various types of premedications, via various routes like intramuscular, intravenous, rectal, sublingual, nasal or oral route have been administered. Although most of these routes are effective, each has drawbacks. The injectables due to fear of needles are especially unacceptable in children. The oral route which does not hurt and if flavoured is the most acceptable method of drug administration. A need exists for a safe and effective oral preanaesthetic medication for use in children undergoing elective surgical procedures.

Previously there was no commercially prepared forms for oral administration so parenteral, preservative free forms of drugs such as Midazolam and clonidine were used as premedication in children. Now a commercially prepared oral tablet form of drug Midazolam is available in India which has been used as premedicant in adults but not in children. The present study aims at comparing the efficacy of clonidine and oral formulation of Midazolam as premedicants in children vis- a vis their advantages and disadvantages.

MATERIAL AND METHODS

TYPE OF STUDY:

The study was a prospective, randomized study consisting of 60 patients as a part of Dissertation.

With the approval of Ethics Committee, a well-informed written consent after satisfying all queries was obtained from the child's guardian.

All children fulfilling inclusion criteria undergoing elective surgery under general anaesthesia were included in the study. All included children had to undergo a short general examination and routine investigations like Hb, CBC. Randomization was done using a

random no table. Included children were then randomly assigned into one of the two groups (30 children in each group):

Group m : Oral Midazolam tablet (0.5mg/kg) 30mins before induction

Group c : Oral clonidine (4mcg/kg) 45mins before induction
In group m oral Midazolam tablet in a dose of 0.5mg/kg was crushed, mixed with 10ml of 5%dextrose and given. Midazolam tablet was easily broken into two halves & given according to weight of the child. Each midazolam tablet is of 7.5mg

In group c oral clonidine tablet will be crushed and mixed with 10ml of 5%dextrose and given in a dose of 4mcg/kg. Clonidine tablet is not film coated, it can be easily broken into two halves. Each tablet is of 100mcg.

Midazolam were given 30mins and clonidine 45mins prior to induction. Thereafter the child was constantly observed to see changes in mood, behaviour & appearance. All children were monitored with pulseoximeter for SpO₂, HR and RR. Vitals were recorded before pre-medication, 15mins after premedication and at the time when sedation score is 3 or less. The time of onset of sedation score 3 or less were noted. Onset of sleepiness, closure of eyes & any side-effects like nausea, vomiting, increased salivation, hallucination, bradycardia, dryness of mouth, nystagmus, hiccough, itching, etc were noted. Sedation level was evaluated by child's appearance using the 5 point sedation scale. Each child was observed for level of consciousness and acceptance of drug at the time of administration by 2 point scale. Anxiety level of each child was recorded using 4 point scale at the time of separation from parents and at the time of acceptance of face mask. Finally presence of any side-effects after pre-medication were recorded. When a sedation score of 3 or less was reached, the child was transferred to the operating room and induced with suitable anaesthesia depending on the surgery. The child was observed for a day after surgery for any side-effects. Various observations were made in a blinded-manner by one person to avoid inter-observer variation.

STATISTICAL ANALYSIS

The t test was used for between-group comparisons of HR, SBP, DBP, and SpO₂.

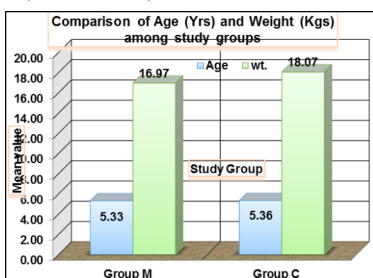
Repeated-measures ANOVA was used for within-group comparisons.

the Fisher exact test was used to analyze extubation and sedation scores, sex, and adverse events. P < 0.05 was considered statistically significant.

The primary outcome measure of this study was the effect of dexmedetomidine and fentanyl on extubation quality in surgery for supratentorial SOL. The secondary outcome measures were hemodynamic responses to extubation, postoperative sedation scores, extubation time, awakening time, orientation time, and prevalence of adverse events.

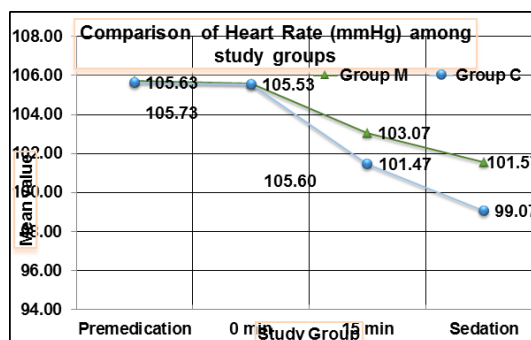
RESULTS

The two groups were similar with respect to age, weight, gender and physical status. 6.25 % of patients (2 out of 32) in the midazolam group (group m) rejected the medication entirely and were excluded from the study protocol, while no child in the clonidine group refused the premedication.



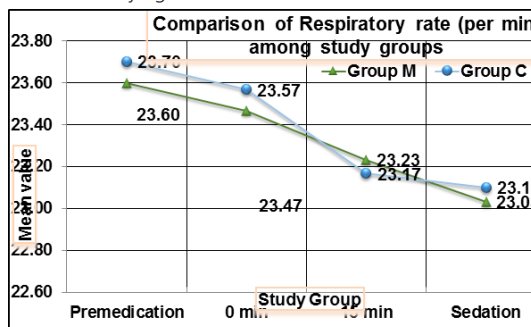
Comparison of change in Heart Rate(HR) before and after premedication in group m and group c patients :

The following table shows the change in heart rate of children before and after sedation with tablet Midazolam 0.5mg/kg in Group m and clonidine 4mcg/kg in group c by the paired t test (p <0.0001). The change in heart rate was found to be not statistically significant.



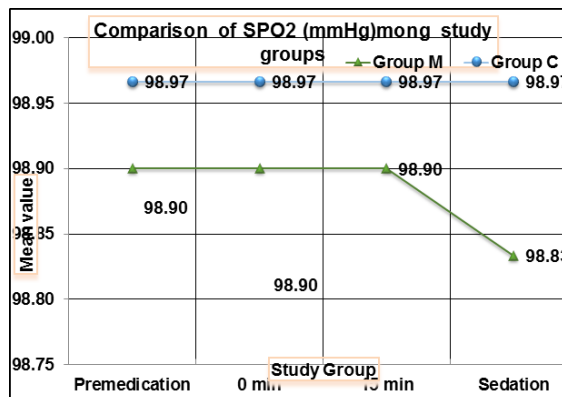
Comparison of change in Respiratory rate (RR) before and after premedication in group m and group c patient :

The following table shows the change in respiratory rate of children before and after sedation with tablet Midazolam 0.5mg/kg in Group m and clonidine 4mcg/kg in group c by the unpaired t test (p <0.0001). The change in heart rate was found to be not statistically significant.



Comparison of change in Oxygen saturation (Spo2) before and after premedication in group m and group c patient :

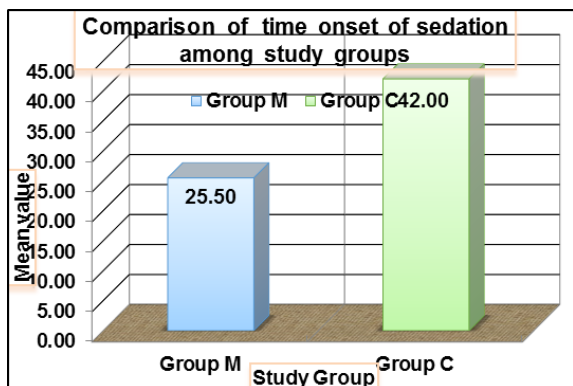
The following table shows the change in oxygen saturation of children before and after sedation with tablet Midazolam 0.5mg/kg in Group m and clonidine 4mcg/kg in group c by the unpaired t test (p <0.0001). The change in oxygen saturation was found to be not statistically significant.



Comparison of onset of sedation between the two groups :

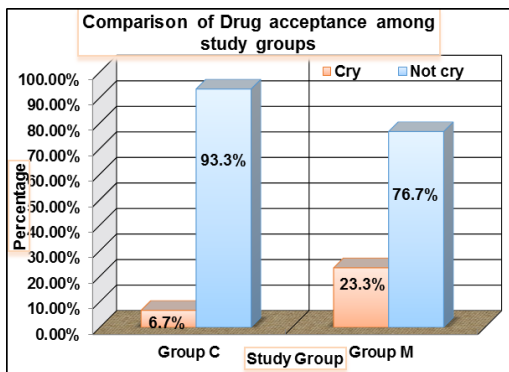
The following table shows mean time required for the onset of sedation, when the sedation score in 3 or less in children receiving Midazolam (Group m) in comparison with children receiving clonidine (Group c). It requires about 25.50 min for onset of

sedation in children receiving Midazolam whereas about 42 min are required for onset of sedation in children with clonidine. This difference was found to be statistically significant by unpaired t test ($p < 0.001$). This shows that children in midazolam Group get sedated earlier than children with clonidine Group.

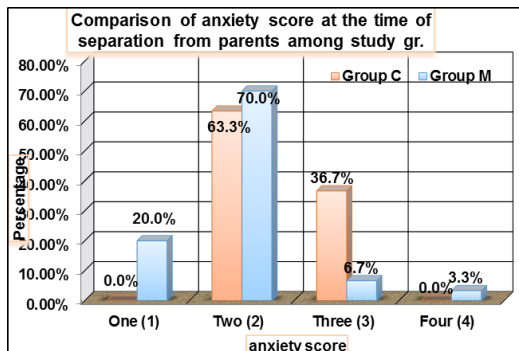


Comparison of the drug acceptance between the two groups:

The following two groups shows similar drug acceptance as their association is statistically not significant

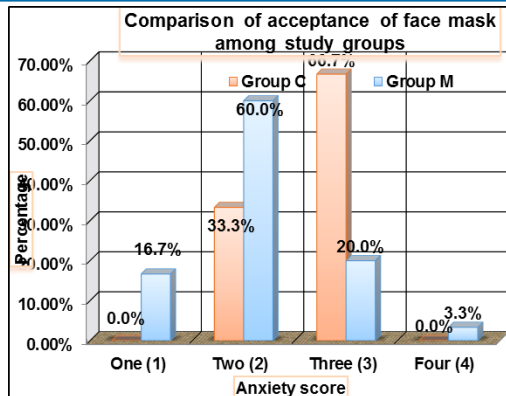


Comparison of the Anxiety Score at the time of Separation from Parents between the two groups:



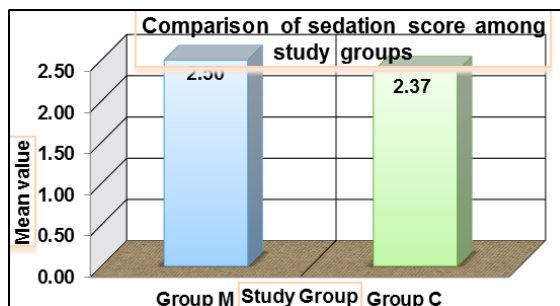
The following table shows anxiety score in Midazolam Group in comparison to clonidine by chi-square test. The following table shows that 20% children in Midazolam Group and 0 children in clonidine group were calm and sleepy at the time of separation from parents. And 90% children in Midazolam Group and 63.3% in clonidine Group were apprehensive but withdrawn from surrounding at the time of separation from parents. 6.7% in Midazolam Group and 36.7% in clonidine Group were crying. 3.3% child in midazolam group and 0% in clonidine group were agitated and difficult to control. The difference was statistically significant. Thus anxiolysis properties of midazolam is better than clonidine.

Comparison of the Anxiety Score at the time of Acceptance of Face-mask between the two groups:



Comparison of sedation score between the two groups:

The sedation score was comparatively similar and statistically insignificant in both the groups



Comparison of different side effects of two groups

In group c 90% of children had no side effects, 6.7% had intraoperative hypotension which get corrected with fluid boluses, and 3.3% had postoperative nausea vomiting. In group m 70.0% of children was without side-effects, but 6.7% had emergence phenomenon post extubation. The 6.7% of children in midazolam group had unusual side-effects of excessive crying, 4% had postoperative nausea and postoperative nausea vomiting, and 3.3% had transient apnea on postextubation which get corrected on itself. The side effects of both groups are statistically and clinically nonsignificant.

DISCUSSION

The results of our study suggest that oral midazolam (0.5mg/kg) effectively reduced the anxiety associated with parental separation and mask application more than oral clonidine (4mcg/kg). The sedative action of both drugs are comparable and statistically insignificant. The doses of midazolam and clonidine used in this study have been established as optimum for preanesthetic sedation (3,5). Children judged the taste of oral clonidine as significantly better than oral midazolam, although both drugs were given with the same 5% dextrose. Midazolam has a bitter taste that is difficult to disguise even when given in a mixture with grape juice (18). Recently, new commercially prepared oral midazolam formulations are reported to be more palatable (19). We observed a 6.25% incidence of failure rate for midazolam, partly because of refusal by the patient to swallow the drug.

Our data confirm that onset of sedation and peak sedative effect was significantly slower after oral clonidine compared with oral midazolam. The mean onset of action for midazolam was 25.50±4.42 and for clonidine was 42.0±5.50. Thus Oral clonidine needs to be administered at least 45 min prior to induction to achieve optimum sedation whereas satisfactory sedation can already be achieved 30 min after ingestion of oral midazolam.

Results of the study by Sequeira Trevor et al in 2012 has partially similar findings as ours. The overall level of sedation was better in the children in clonidine group, but children in the midazolam

group had a greater degree of anxiolysis at the time separation from parents and face mask acceptance. The results of excellent anxiolysis after an oral dose of 0.5mg/kg midazolam at the time of separation from parents are comparable to the results of Mcmillan et al(9) and Debnath et al(10) who also used a 0.5mg/kg dose. The drug acceptance by the child in both groups in our study are comparable and statistically insignificant as suggested by the observation of the study by Almenrader et al.

The superior picture of excellent anxiolysis confirms the superiority of midazolam as a premedication in children. However, this was somewhat scarred by strange behavior of two of the children premedicated with midazolam. The child, who was calm, friendly and playful, became aggressive and excessive crying after premedication with midazolam. Such paradoxical reaction has been documented to midazolam premedication before and the reason for which is not well understood **1d**.

The side effects of clonidine is less than midazolam.

CONCLUSION :-

In conclusion the results of our study suggest that oral midazolam(0.5mg/kg)effectively reduced the anxiety associated with parental separation and mask application more than oral clonidine(4mcg/kg).The sedative action of both drugs are comparable and statistically insignificant.Children judged the taste of oral clonidine as significantly better than oral midazolam.The onset of sedation and peak sedative effect is significantly slower after oral clonidine compared with oral midazolam. There was no significant side effects with both the groups.

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