



PREANESTHETIC MEDICATION IN CHILDREN: A COMPARATIVE STUDY AMONG INTRANASAL DEXMEDETOMIDINE, ORAL MIDAZOLAM AND ORAL CLONIDINE

Anamika Mishra	M.D. Anaesthesia Senior Resident, Dept of Anaesthesia & Critical Care S.N.Medical College, Agra (U.P)
Yatendra Gupta	M.D. Anaesthesia Dept of Anaesthesia & Critical Care S.N.Medical College, Agra (U.P)
Rajeev Puri*	M.D. Anaesthesia Asst. prof., Dept. of Anaesthesia & Critical Care S.N.Medical College, Agra (U.P) *Corresponding Author
Shailendra Chak	M.D. Anaesthesia Dept. of Anaesthesia & Critical Care S.N.Medical College, Agra (U.P.)
Trilok Chand	M.D. Anaesthesia Head & prof., Dept. of Anaesthesia & Critical Care S.N.Medical College, Agra (U.P)

ABSTRACT The aim of this prospective study was to compare intranasal dexmedetomidine, oral clonidine & oral midazolam as premedicating agent on children undergoing surgeries under general anaesthesia. This study was conducted on 96 patients of ASA grade 1 & 2 of either sex between 2-12 years age undergoing routine surgeries. Patients are randomly allocated in 3 groups-M, C and D on basis of premedication given and were assessed on the basis of Preoperative degree of sedation and change in behavior, separation anxiety, effect of emergence agitation after surgery & adverse effects. Sedation status at parental separation of children from group D were significantly different from group C & M. Emergence agitation scores of children from group C & D were significantly different from group M. Children between 2-5yr age showed statistically significant reduction in emergence agitation in group D. No statistically significant difference groupwise regarding ease in separation of child from parents & post operative nausea vomiting (PONV) among 3 groups. So to conclude sedation and attenuation in emergence agitation was best with dexmedetomidine followed by clonidine and least with midazolam.

KEYWORDS : Dexmedetomidine, Clonidine, Midazolam, Sedation, Parental Separation.

INTRODUCTION

In modern anaesthesia practice the goal of premedication is to allay anxiety, thereby making the experience of surgery less traumatic and more pleasant [1]. As a general notion, in pediatric patient apprehension and anxiety should be controlled before they are taken to Operating room. Anxiety is a subjective feeling of apprehension, fear and nervousness [2]. Premedication is frequently administered, prior to anaesthesia induction to provide anxiolysis, proper sedation facilitate separation from the caregiver and lessens adverse psychological effects of hospital experiences. The difficult I/V access is more frequently encountered in pediatric patients nonetheless.

The development of parental anxiety is also an important factor in the development and evolution of child's anxiety. Therefore, routine clinical practice frequently makes use of non-parenteral routes of administration for the initiation of sedation or for premedication prior to anaesthesia induction [3].

The selection of premedicating drug before general anaesthesia affects not only degree of sedation, anxiolysis, and smoothing of induction but also postoperative pain and recovery. Besides, it improves the emergence agitation frequently encountered after general anaesthesia, which can be defined as inconsolable crying, combative behavior or thrashing after surgery. Many drugs have been used traditionally as preoperative medication to eliminate or to suppress the stress reaction to anaesthesia and surgery and to control the fear and anxiety experienced by many patients. They simultaneously potentiate the effects of general anaesthetic agents, reduce their dose requirements and attenuate sympathoadrenal response to noxious stimuli encountered during anaesthesia and surgery, thus providing improved haemodynamic, metabolic and hormonal stability.

These drugs include Benzodiazepines, opiates barbiturates, histamine antagonists as well as anticholinergic agents. It has now become evident that α -adrenoceptor agonists may also be useful class of drugs in conjunction with anaesthesia. Clonidine & Dexmedetomidine belongs to this class and is used as a premedicant.

Traditionally, Midazolam is the most commonly used drug best given by oral route in children as a premedication to relieve undue anxiety

and agitation. Although rapid onset, short duration & amnesia is a good advantage of Midazolam, but restlessness and negative postoperative behavioral changes are drawbacks in calling it as ideal premedication. Clonidine, an α_2 -adrenergic agonist can produce sedation and analgesia without compromising respiratory function. It has been found to be as efficient as Midazolam as far as premedication is concerned [4]. Clonidine also reduce emergence agitation after sevoflurane anaesthesia.

Dexmedetomidine, a drug of non-barbiturate class is a potent and highly selective α_2 -adrenergic agonist with sedative, analgesic and anxiolytic effects as well as prevent emergence agitation following general anaesthesia.

Keeping these factors in mind, we evaluated the effect of Midazolam, Clonidine and Dexmedetomidine as premedication in children undergoing various surgical procedures under general anaesthesia in the department of Anesthesiology and critical care, S.N. Medical College, Agra.

MATERIAL & METHODS

After ethical clearance, the study was conducted on 96 patients in the department of Anaesthesiology and critical care, SNMC, Agra between January '11 to September '12.

This study included children aged 2-12 years, undergoing elective surgery under general anaesthesia.

Patient selection-96 patients of ASA grade I & II of either sex aged between 2-12 years of age, who underwent elective surgery under general anaesthesia were randomly selected for the study after having obtained written and informed consent. Demographic characteristics were comparable in all the patients. All patients were subjected to a thorough pre-anesthetic checkup as per the institutes protocol and were randomly divided into 3 groups of 32 each on the basis of drug given for premedication and a double blinded randomized controlled trial was conducted.

Exclusion criteria were Mental retardation, Psychological/Emotional/Cognitive abnormality, Cardiac arrhythmia / Significant cardiac

abnormalities, Recent respiratory infection, Any neurological condition that limits patients ability to communicate or understand, Allergic to study drugs.

Timings of premedication was decided on the basis of previous studies. Children received the drugs in presence of the parents in the preoperative holding area. The mean onset time of action for Intranasal 1µg/kg Dexmedetomidine was 45-60 mins, for oral clonidine 60-90 minutes & that for oral Midazolam it was 30 mins.

Group D – Children received 1µgm/kg intranasal Dexmedetomidine 45 mins before surgery and oral placebo at 30 mins before surgery in form of saline.

Group M- children received oral Midazolam 0.5 mg/kg 30 mins before surgery and received intranasal placebo 45 mins before surgery.

Group C- received oral Clonidine 4mcg/kg 60 mins before surgery and received intranasal placebo 45 mins prior and oral placebo 30 mins prior to surgery

Preparation of premedication drugs-
 Intranasal Dexmedetomidine was prepared from 100µg/ml parenteral preparation in 1ml Syringe; 0.9% of saline is added to make a final volume of 0.5ml and given in both the nostril in recumbent position.
 Oral Midazolam was taken from ampoule of 1mg/ml parenteral preparation orange juice was added to make it palatable. Saline was added in both oral and nasal placebo.

To facilitate blinding the volume of intranasal and oral medication were kept same in all the groups, intranasal 0.5 ml and oral 5 ml.

Anaesthesia protocols: Intravenous cannulation was the first step in all the patients. Induction was either by inhalational or intravenous route and was decided by the attending Anaesthetist as per requirement.

Parameters recorded were

- 1) Demographic data(Name of the patient, Age and sex, Weight)
- 2) Type of surgery, duration of surgery were also noted.
- 3) Heart rate, Blood pressure & SpO2 were recorded before giving any premedication, every 15 mins during premedication and induction period, then after every 30 mins intraoperatively and then just after shifting the child in postoperative unit.
- 4) Acceptability of route of drug: Oral / Nasal : Yes/No
- 5) Sedation and behavior status: At parental separation, at induction, proportion of children who had change of sedation and behavior from satisfactory to unsatisfactory at induction.
- 6) Separation from parents: Easy/ Difficult-A parent was allowed to accompany the child to operating room if the child refused to be separated from parents.
- 7) Intraoperative: Reaction to I/V cannulation: Crying / Not crying
- 8) Post Operative: When surgery was finished, the child was placed in the recovery position and allowed to wake up in the anaesthesia post operative care unit. The quality of recovery from anaesthesia was assessed by recording -Emergence agitation score & The incidence of post operative nausea and vomiting.

EVALUATION SCORES

1. SEDATION STATUS-

Sedation status was categorized as being satisfactory: if condition of child relates to 1 of the following 4 points:

- Does not correspond to mild prodding or shaking
- Responds only to mild prodding or shaking
- Responds after name is called loudly or repeatedly.
- Lethargic response to name spoken in normal tone.

Sedation status was categorized as being Unsatisfactory : if condition of child related to 1 of the following 2 points:

- Appear asleep but respond readily to name spoken in normal tone.
- Appear alert awake, response readily to name spoken in normal tone.

BEHAVIOUR STATUS-

Behavior status was categorized as being satisfactory: If condition of child relates to 1 of the following 2 points:

- Calm and cooperative
- Anxious but reassurable
- Behavior status was categorized as being unsatisfactory: If

condition of child relates to 1 of the following 2 points:

- Anxious but not reassurable.
- Crying or resisting.

EMERGENCE AGITATION SCALE

1. Obtunded with no response to stimulation
2. Asleep but responsive to movement or stimulation
3. Awake and calm , non irritating to touch
4. Awake and irritated to touch
5. Crying.
6. Thrashing behaviour that require restraint.

RESULTS:

STATISTICAL ANALYSIS -

Sample size calculation from power analysis revealed that 32 patients per group would be required to provide 80% power at 0.05 level of significance to detect a 35% difference in the proportion of children, who attained satisfactory sedation with oral midazolam, oral clonidine and intranasal Dexmedetomidine.

Differences in the age, weight, duration of surgery and duration of surgery & hemodynamic variables among the three groups were compared by one-way analysis of variance (ANOVA). When a significant result was obtained, the Turkey test was applied for post hoc pairwise comparisons. Variation in heart rate & blood pressure, Sedation , behavior and wakeup-behavior scores were analyzed by Kruskal -Wallis test. When a significant result was obtained, the Mann-Whitney U-test was applied for post hoc pairwise comparison. Categorical data were analyzed by chi- square test. The adjusted P value was applied to the post hoc pairwise comparison for nonparametric and categorical data. The adjusted P value for the 0.05 level of significance was 0.017.

There was no significant difference groupwise regarding age, sex & weight distribution among 3 groups. Most of the patients were male.

No statistically significant difference groupwise regarding duration & type of surgery. Most of the surgeries were limited to less than 1 hr and maximum were penile surgeries. All children accepted oral/nasal drugs given.

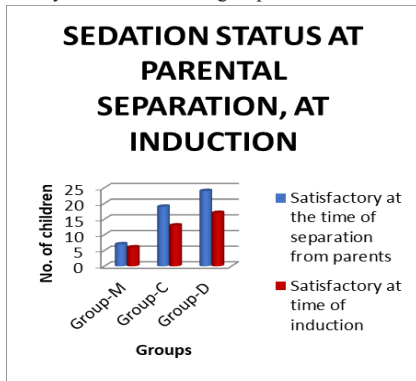
- There was a statistically significant reduction in heart rate & systolic blood pressure(SBP) after 45 & 60 minutes of premedication in group D (p value<0.001) while no statistically significant reduction in groups M & C. In all groups, a slight reduction in diastolic blood pressure(DBP) was seen in period from premedication to induction but it was statistically insignificant.
- There was no statistically significant difference in heart rate, SBP, DBP during intraoperative and postoperative period in all groups (p value>0.05).
- No child had a reduction of SPO2 to below 95% throughout the perioperative period in all the groups.
- There was no statistically significant difference groupwise regarding reaction to I/V cannulation among 3 groups.
- Sedation status at Parental Separation , At induction, Proportion of children who had change sedation from satisfactory to unsatisfactory at induction

	GROUP – M		GROUP – C		GROUP – D		P- VALUE
	NO.	%	NO.	%	NO.	%	
AT SEPARA-TION FROM PARENTS							
SATISFACTORY	7	21.9	19	59.4	24	75	<0.001
UNSATISFACTORY	25	78.1	13	40.6	8	25	
AT INDUCTION							
SATISFACTORY	6	18.8	13	40.6	17	53.1	0.016***
UNSATISFACTORY	26	81.3	19	59.4	15	49.9	
CHANGE **							0.828
NUMBER OF CHANGED / TOTAL	1/7	14.3	6/19	31.6	7/24	29.2	

*Significantly different between group M & C and also between M & D at 0.05 level

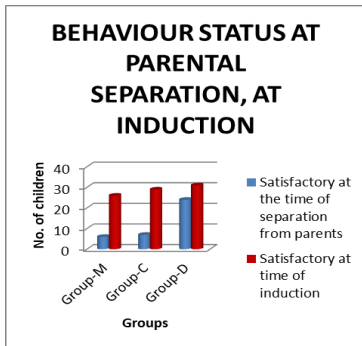
**Proportion of children whose sedation status changed from satisfactory to unsatisfactory at induction

***Significantly different between group M & D at 0.05 level



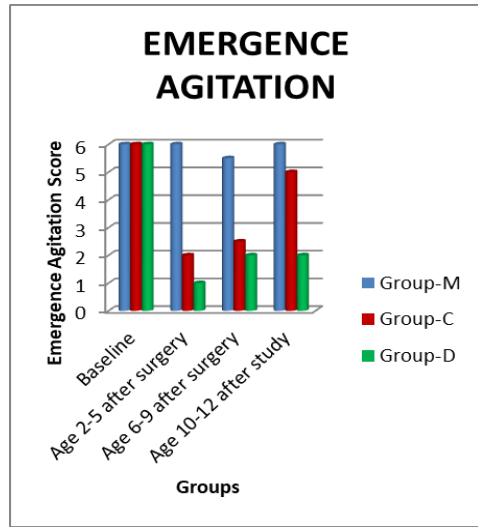
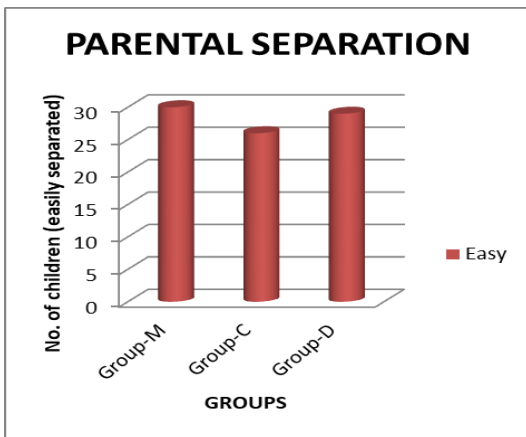
- Behaviour status at Parental Separation, at Induction, proportion of children who had change sedation from satisfactory to unsatisfactory at induction

	GROUP - M		GROUP - C		GROUP - D		P- VALUE
	NO.	%	NO.	%	NO.	%	
AT SEPARATION FROM PARENTS							
SATISFACTORY	6	18.8	7	21.9	24	75	<0.001*
UNSATISFACTORY	26	81.3	25	78.1	8	25	
AT INDUCTION							
SATISFACTORY	26	81.3	29	90.6	31	96.9	0.148
UNSATISFACTORY	6	18.8	3	9.4	1	3.1	
CHANGE **							0.012
NUMBER OF CHANGED / TOTAL	6/32	18.8	1/30	3.3	0/31	0	



- *Significantly different between group M & D at 0.05 level
- **Proportion of children whose behaviour status changed from satisfactory to unsatisfactory at induction
- Parental Separation : Easy/Difficult

	GROUP - M		GROUP - C		GROUP - D		P- VALUE
	NO.	%	NO.	%	NO.	%	
EASY	3	96.9	26	81.3	29	90.6	<0.148
DIFFI-CULT	1	3.1	6	18.8	3	9.4	



Groupwise Emergence agitation scores of children from group C & D were significantly different from group M. Age-wise children between 2-5yrs showed statistically significant reduction in emergence agitation (p<0.001) in group D.

- Episode of postoperative nausea vomiting (PONV)

	GROUP - M		GROUP - C		GROUP - D		P- VALUE
	NO.	%	NO.	%	NO.	%	
NON CRYING	30	93.7	30	96.9	32	100	0.771
CRYING	2	6.3	1	3.1	0	0	

DISCUSSION:

In our study, oral and nasal routes were used for giving premedication drugs because these routes are non-invasive as compared to intravenous and intramuscular routes, which is very important in paediatric cases. Previous studies have shown that the intranasal route is an effective way to administer premedication & sedation to children [5].

In our study, some degree of sedation was provided by all 3 drugs midazolam, clonidine & dexmedetomidine. However dexmedetomidine provided sedation in 75% & 53.1% children at the time of separation from parents & at induction respectively. While midazolam in 21.9% & 18.8% & clonidine in 59.4% & 40.6% children respectively. On statistical comparison, dexmedetomidine proved to be the best among 3 drugs followed by clonidine & midazolam. In contrast to our findings, many studies have shown good sedation in patients receiving midazolam [6,7,8]. This difference in result might be due to better absorption by nasal route in present study. High vascularity of subepithelial surface of nasal cavity & bypassing of first pass metabolism by nasal route provide the better bioavailability. The other problems with oral route are bitter taste & delay in onset.

As far as behavioural changes are concerned, a good proportion of children showed satisfactory behavior at induction with all 3 premedicants in study (81.3%, 90.6%, 96.9% in group M,C,D respectively).

In our study, attenuation in emergence agitation was seen best with dexmedetomidine followed by clonidine but midazolam proved to be ineffective in this regard. Interestingly, age group effect was seen as well here, children of a particular age group only(2-5yrs) showed statistically significant attenuation in emergence agitation(p<0.001). Our results match with most of the previous studies [8,9,10].

The secondary aim of study was to assess adverse effect of study drugs i.e hemodynamic & respiratory effects.

There was no significant change in heart rate in preoperative period in M & C group but in D group there was significant reduction but that too after 45 & 60minutes. Of giving premedication. Although a decline was observed in SBP in period from premedication to induction in all groups but again it was only group D, where the drop was statistically significant that too only after 45 & 60 minutes. But these drops in heart rate, SBP with dexmedetomidine were not clinically significant.

There was no significant change in DBP in any group & also in all hemodynamic parameters in intra & postoperative periods. Some studies shows similar results [11]. While some shows contrasting results [12,13].

As far as parental separation is concerned, there was no significant difference groupwise in M,C,D groups but agewise difference was noticed as all children who showed separation anxiety were of 2-5yrs. One study found that separation anxiety usually begins after 9months of age with children of 1-5yrs having the highest risk for developing extreme anxiety. This result was statistically significant in contrast to our study which may be due to absence of children of 1-2 yrs in our study who should be most prone to develop separation anxiety [14].

CONCLUSION:

1. The three groups were comparable regarding demographic data, duration and type of surgery.
2. Sedation at the time of separation from parents and induction was most satisfactory in children receiving Dexmedetomidine followed by Clonidine. We did not find Midazolam to be effective in this regard.
3. There was no significant change in arterial oxygen saturation Peri-operatively in all groups. However, some patient showed hypotension & decreased heart rate after 45-60 mins of premedication with intranasal Dexmedetomidine but these hemodynamic changes were clinically insignificant
4. Both oral and nasal routes were acceptable by majority of children in all age group
5. Majority of the patients could be separated from their parents easily (96.9%, 81.3%, 90.6% in M, C, D groups respectively)
6. Intravenous cannulation was possible in most children without problem
7. No other significant adverse effects like nausea, vomiting were seen in all groups (except 2 children of group M, and 1 child of grp. C vomited in post operative room.

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