COMPARISON OF INTRA NASAL MIDAZOLAM VERSUS KETAMINE AS PREMEDICATION IN 2-5 YEARS OLD PAEDITRIC SURGERY PATIENTS

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ABSTRACT:

Background and Aim: Surgery and anesthesia can cause considerable distress and psychological consequences for children. In children, preanesthetic medications are frequently administered as pharmacologic adjuncts to help alleviate the stress and fear of surgery as well as to ease child-parental separation and promote a smooth induction of anesthesia. Oral, rectal, intravenous and intramuscular preanesthetic medication administration have been used. However, each route has disadvantages. Pre anaesthetic medication administered nasaly, due to its rapid and reliable onset of action, avoidance of painful injections and ease of administration have made it a convenient way to premedicate children.

The aim of the present study is to compare the sedative effect of ketamine and midazolam administered nasaly as premedication.

Patients and Methods: 130 children aged 2-5 years and with ASA class I-II randomly allocated in three groups and 20 minutes before operation time received either 0.2mg/kg midazolam or 5mg/kg ketamine or 2ml normal saline, intranasally. After administration of intranasal premedication the children were under direct observation of anesthesiology resident near their parents. At the time of separation and at the time of IV line insertion, on the basis of Sury and Cole sedation score they received a sedation score.

Results: According to statistical analysis, at the time of separation from parents in midazolam group, 90% of patients were sedated (60% had mild sedation, 30% had good sedation), in ketamine group, 89% were sedated (32.5% had mild sedation, 59.5% had good sedation) while in placebo group, 47.5% showed sedation (40% mild, 7.5% good). At the time of intra venous line insertion, in midazolam group, 86% of patients were sedated (56% had mild sedation, 30% had good sedation), in ketamine group, 80% were sedated (57.5% had mild sedation, 22.5% had good sedation) while in placebo group 22.5% (20% had mild sedation, 2.5% had good sedation) showed sedation.

Conclusion: On the basis of results midazolam and ketamine administered intra nasaly are effective in inducing sedation. Comparing these drugs with placebo, they are effective adjunctive premedicant.

KEY WORDS: Nasal drug delivery, midazolam, ketamine

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INTRODUCTION

Surgery and anaesthesia induce considerable emotional stress upon children.[1] The consequences of this stress may remain in the child's psyche long after the hospital experience has passed, and it was first deseribed by dupuytren in 1834.[2,3] Although it is difficult to determine which component of a child's hospitalization experience result in psychological problems, age, parental anxiety level, previous hospital experiences and type of surgery are factors that

can influence a child's anxiety level and psychological well being.[2] Preoperative anxiety stimulates sympathetic, para sympathetic and endocrine system leading to an increase in heart rate, blood pressure and cardiac excitability. These reactions reflect the child's fear of separation from parents and home environment, fear of physical harm, fear of unfamiliar routines, surgical instruments and hospital procedures.[4] Maladaptive behavioral responses such as general anxiety, night time crying, enuresis separation anxiety, temper tantrums occur up to 44% of children two weeks after surgery, and about 20% of these children will continue to demonstrate negative behaviors 6 months after surgery.[4] The preoperative interventions directed towards reduction of anxiety can be grouped into psychological and pharmacological methods. The introduction of new drugs and new routes of administration in last decade like transmucosal (Intra Nasal) route[5,6] by avoiding painful intra muscular injections, the most horrifying experience for a child, has facilitated a more rational approach to premedication for paediatric patients.

It has been suggested that sedative premedication may be more effective in reducing anxiety during induction of anaesthesia than is the presence of parents.[1,2,7] Keeping in view the necessity of reducing preoperative anxiety and its post operative psychological problems in paediatric patients, we compared the sedative properties of midazolam a water soluble benzodiazepine and ketamine, a pheneyelidine derivative administered intra nasaly to 2-5 years old paediatric surgical patients, regarding ease of separation from parents and at the time of intravenous line insertion for induction of anaesthesia.

PATIENTS AND METHODS

To compare the sedative effects of midazolam and ketamine administered intra nasaly as preanaesthetic medication, 130 children aged 2-5 years with American society of anaesthesiologists (ASA) physical status I and II scheduled for elective surgery were selected for this randomized double blind clinical trial. The study was performed in paediatric surgical department of Nemazee hospital affiliated to University of Medical Sciences, Shiraz, Iran. Full explanation regarding the aim and the route of administration of the study drugs was given to the parents of the children and their written consent was obtained individually. Patients were allocated randomly to one of three groups.

Group I (midazolam), group II (ketamine), group III (placebo). The study drugs, midazalom 0.2mg/kg, ketamine 5mg/kg, diluted with physiological saline to reach 2ml. in volume and 2ml. physiological saline as placebo in coded syringes were precalculated and prepared by an anaesthesiologist. The drugs were instilled half amount in each nares by a senior anaesthesia resident 20 minutes before the induction of anaesthesia. The same resident was in constant attendance after pre medication to observe and handle any adverse reaction. The codes were broken at the conclusion of the study.

The reaction of the child at the time of separation from parents and also at the time of intravenous line insertion before induction of anaesthesia was evaluated according to the sedation score of Sury and Cole.[8] In our study we assumed no sedation as Go, mild sedation as G1, good sedation as G2, and over sedation as G3. The results of three groups were evaluated by Kruska-Wallis test and for comparing the results of group 2 with group 3 and group 1 with group 3 Mann-Whitney test was used. Results with P-value <0.05 were regarded meaningful.

RESULTS

In our study 130 patients randomly assigned to 3 groups. Their means of age and 95% confidence interval for means are shown in Table-I.

On the basis of analysis of variance (ANOVA) test; F statistic is equal to 1.24 and p=0.29. It shows that there is not any difference between means of age in 3 groups.

Table-I: Demographic status of subjects
(Mean of age and 95% confidence interval for mean)

Grp	Intranasal agent	No. of pts	Mean of age	95% CI	
				Lower bound	Upper bound
1	Midazolam	50	2.94	2.66	3.21
2	Ketamine	40	3.25	2.96	3.53
3	Serum physiology	40	3.13	2.83	3.44

Each group received a score according to "Sury and Cole sedation score" at the time of separation from parents and insertion of inravenous line. Because no patient was too sedated in any group; after statistical consultation we decided to exclude "score G3" in analysis. The results of sedation score are shown in Figure 1 & 2.

According to nonparametric Kruskal-Wallis test sedation scores in 3 groups, both at the time of separation from parents and intravenous line insertion showed significant statistical difference ($p<0.001$).

For more precise evaluation of their differences we used Mann-Whitney test. Comparing group II whit III and I with III at the time of separation from parents p-value was less than 0.001, while the p-value was=0.02 when comparing groups I with II. That means, there are significant difference between all of the groups.

Comparing Group I with III and II with III at the time of intravenous line insertion p-value was less than 0.001. This shows there are differences between induced sedation by ketamine and midazolam with placebo. However when the sedation score of group I with II were compared, p-value was 0.332. It means, there was no significant difference in induced sedation by midazolam and ketamine at the time of intravenous line insertion.

DISCUSSION

Preoperative anxiety in unpremedicated children is two fold. First they are very afraid of being separated from their parents (sepration anxiety) and secondly they are worried about physical harm like needle puncture or intravenous line insertion. Children aged 2 to 5 years are especially vulnerable to this problem, since their understanding is limited.[9] The fact that preoperative anxiety in children can lead to post operative maladaptive behaviors in the form of eating problems, bad dreams, enueresis, increased fear of doctors and hospital, temper tantrums is well known.[2,10,11] Hence all paediatric patients be premedicated in order to decrease preoperative anxiety, allow

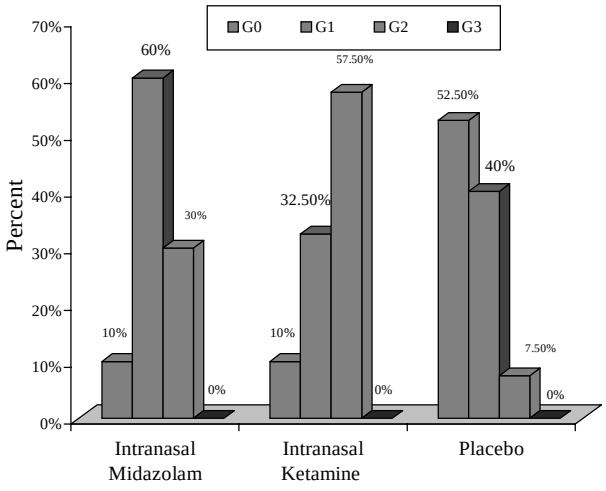

Figure 1: Sedation Score at the Time of Separation from parents.
G0 = Very restless, crys, shows resistance to separation
G1 = Slightly restless, shows mild resistance to separation
G2 = Relax, calm, cooperative, does not resist to separation
G3 = Too sedated and not responsive to commond

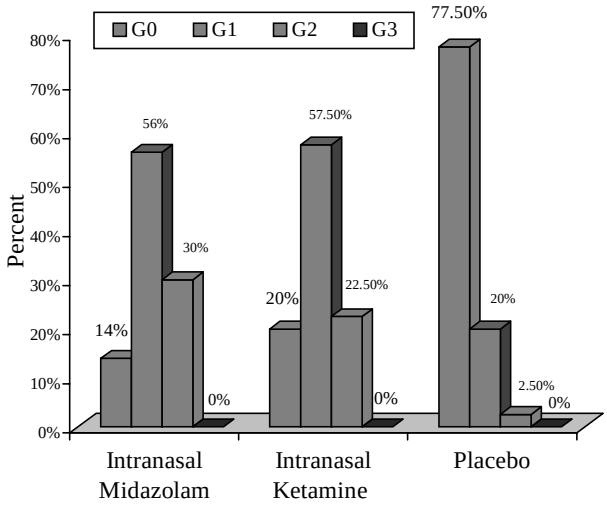

Figure 2: Sedation Score at the Time of IV Line Insertion.
G0 = Very restless, crys, shows resistance to separation
G1 = Slightly restless, shows mild resistance to separation
G2 = Relax, calm, cooperative, does not resist to separation
G3 = Too sedated and not responsive to commond

smooth induction, and prevent post operative psychological insult and behavioral changes.[12,13]

The route of administration for premedication in paediatric age group should also be considered carefully. Intra muscular injections are painful, oral premedication in gastro intestinal disturbance is not effective and often rejected by small children.[1,9]

Children and their parents are very reluctant to allow rectal administration of drugs. The intra nasal route administration of pre medications has been used successfully and safely by different researchers.[5,6,9,14-21] Since the use of nose drops is widely known in general public, this route could be well accepted by children and their parents for premedication administration.

Midazolam is a water soluble benzodiazepine. It produces sedation, anxiolysis and some antegrade amnesia, it can be administered intranasaly. The recommended dose is 0.2 to 0.25 mg/kg onset of sedation usually occours within 10-20 minutes.[15,16]

Ketamine is a unique medication that is particularly useful in paediatric sedation. It is a derivative of phencyclidine that creats trance like dissociative state characterized by sedation, amnesia, analgesia, and catalepsy. There are several reports about intra nasal administration of ketamine (5-6mg/kg) with good efficacy and no adverse effects for pre medication and sedation in children.[17-19,21]

In a study performed by Garcia-Velascop et al.[15] intra nasal midazolam (0.25mg/kg) and ketamine (5mg/kg) in paediatric patients found that the nasal route of administration of the drugs is well accepted in both groups and midazolam and ketamine are equally effective as sedative premedication.

Another study performed by Kahreci Kt, et al.[16] Studied the effect of intranasal midazolam, ketamine, alfentanil and fentanil premedication in 2-7 years old children regarding reaction to separation from parents and response to intravenous cannulation. They concluded that all drugs, compared to placebo were effective: midazolam and alfentanil produced early sedation compared to ketamine but alfentanil due to its early recovery was superior to other drugs. Abrams F, et al[19] studied the safety and sedative effects of intranasal midazolam (0.4mg/kg) and ketamine (3mg/kg).

Both drugs showed good sedative effect; they reported two cases of obtundation in ketamine group, but such complication was not seen in midazolam group.

In our study we found that intranasal midazolam (0.2 mg/kg) and ketamine (5mg/kg) produce a good level of sedation regarding child's separation from parents and response to intravenous line insertion in comparison to placebo (Figure 1,2).

In addition the comparison of midazolam and ketamine groups, we found that intranasal ketamine is more effective than intranasal midazolam regarding separation of child from parents (G2=57.5% and 30% respectively, p-value=0.02). As regards to response of child to intravenous line insertion, the sedative effects of intranasal midazolam and ketamine was equal (G2=30% and 22.5 respectively, p-value=0.33)

CONCLUSION

Midazolam 0.2mg/kg and ketamine 5mg/kg adminsterd intranasaly in 2-5 years old children is equally effective for easier separation of children from their parents and obtunding their response to intravenous line insertion.

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