

COMPARATIVE STUDY OF ORAL MIDAZOLAM, ORAL KETAMINE AND THEIR COMBINATION AS PREMEDICATION IN PEDIATRIC CARDIAC SURGERY

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BACKGROUND: Midazolam and ketamine are useful premedication orally to decrease anxiety in children. We compared the effects of high dose midazolam with ketamine and with low dose combination of midazolam and ketamine both.

METHODS: 75 children between 6 months to 10 years with congenital heart disease were posted for surgeries were randomly selected for 3 groups. Group A received midazolam 0.75mg/kg p.o., Group B received ketamine 8mg/kg p.o., and Group C received midazolam 0.5mg/kg and ketamine 4mg/kg p.o. Heart rate, blood pressure, respiratory rate, oxygen saturation, anxiety score and sedation score were noted at 10, 20, 30 minutes after premedication and at time of parental separation and face mask application. Standard general anaesthesia technique was employed.

RESULTS: There were linear decreasing trends in sedation score and anxiety score were noted compare to pre sedation score. However, group C shows superior effect at the time of parental separation and face mask application. Hemodynamic changes were similar in all groups.

CONCLUSIONS: Combination of oral midazolam and ketamine at low dosage is excellent premedication for sedation and anxiolysis at the time of parental separation and face mask application and are highly acceptable to children and their parents with minimum side effects.

KEY WORDS: Premedication, Pediatric patients, Oral midazolam, Oral ketamine

Introduction:

Ketamine and midazolam are widely used drugs for sedation, reducing pain and as premedication in pediatric age group ^[1, 2]. It plays an important role by decreasing anxiety and vagal stimulation, peaceful separation from their parents and easy induction in the operation room. Mostly, intravenous medications are being used for premedication but they come at the cost of hypotension, apnea and seizures like side effects. These side effects are more pronounced in pediatric population if enough caution is not taken. Purpose of our study was to check efficacy and side effects of combination of oral ketamine and midazolam as pre-medication prior to intubation in pediatric population undergoing cardiac surgery. The other purpose was to compare oral midazolam versus oral ketamine with a combination of both of them.

Material methods:

Institutional Ethics Committee approval and parental consent was obtained for participation in the study. Pediatric patients undergoing cardiac surgeries ranging in the age group of 6 months to 10 years were randomly divided into three groups for premedication. Group A patients received oral midazolam (0.75mg/kg body weight), Group B patients received oral ketamine (8mg/kg body weight) and Group C patients received a combination of oral midazolam (0.5mg/kg body weight) and oral ketamine (4mg/kg body weight).

The following parameters were assessed before premedication and at 10, 20 and 30 minutes after administering premedication and at the time of parental separation and face mask application. Anxiety score: 4- Anxious, Combative, Uncooperative; 3- Anxious but Cooperative; 2- Calm, Cooperative, Minimal Resistance; 1- Respond only to deep pain; 0- Unresponsive. And sedation score: 4- Awake; 3- Drowsy, Responds to verbal command; 2- Sleeping, responds to light tactile stimulation; 1- Responds only to deep pain; 0-Unresponsive, Heart rates, blood pressure (BP), respiratory rate, oxygen saturation by pulse oximetry (SpO₂) were monitored. Patients were closely monitored for all possible side effects like hypotension, seizures, apnea, excessive salivation etc. Statistical analysis was done with IBM SPSS v20. Analysis of variance (ANOVA) was performed for comparison of mean sedation score and anxiety score also repeated measurement Anova was performed to carry out significant decrement in score of Sedation and Anxiety for three given drugs as time increases. Regression analysis was performed to measure the impact on anxiety score and sedation score in different groups.

Results:

Twenty five patients in each of the three groups were enrolled. Baseline demographics and type of surgeries were comparable amongst all three groups (Table-1). There were no significant differences in basal heart rate, blood pressure and respiratory rates after pre-medication also. Mean sedation and anxiety scores are shown in Table-2 and Table-3 respectively. By using one-way repeated measurement ANOVA, the assumption of sphericity is violated and $\epsilon < 0.75$. The significant value (p value) of Greenhouse-Geisser correction is < 0.01 . This significant value indicates that significant decrement in score of Sedation and Anxiety for three given drugs as time increases. Linear regression analysis of sedation score revealed statistically significant differences in the type of premedication during parental separation even after adjusting for age, sex and body weight (p=0.038, 95% CI -0.302 to -0.008). Group-C (combination of oral

ketamine-midazolam) was superior. Similarly, linear regression analysis of anxiety score during parental separation, type of medication/s remained statistically significant in spite of adjusting for age, sex and body weight ($p=0.042$, 95% CI -0.307 to -0.005). This was suggestive that oral midazolam and oral ketamine combination was very much effective for good sedation and reduce anxiety prior to intubation in pediatric population. Also this was suggestive that combination was more effective than either drug alone particularly at lower dosage compared to when used alone. None of the patients experienced hypotension, seizures, oxygen desaturation, apnea or bronchospasm. Two patients in the ketamine group (Group-B) reported excessive salivation but none of the patients experienced vomiting. The results suggested that both medications, either alone or in combination at aforesaid dosages are well tolerated without major side effects.

DISCUSSION:

There is no premedication regime for pediatric population that altogether makes patients, parents and physicians happy. Ideal drug for premedication in pediatric patients should be easily administrable, well accepted, with rapid onset of action and with minimum side effects^[3]; particularly in patients undergoing cardiac surgery with either cyanotic or acyanotic heart diseases.

All injectable drugs have a price to pay in the form of hypotension, respiratory depression and other side effects, while drugs with other routes of administration like nasal, rectal, intramuscular have unpredictable effects^[4]. Inhaled route requires specialized delivery instrument and acceptable only to older children^[5]. Oral route is highly acceptable to children as well as to the parents. Oral chloral hydrate was used since long but onset of sedation is somewhat delayed. Feld and co-workers^[1] observed that even with a high dose of oral midazolam (0.75 mg.kg^{-1}), some children (28%) remained anxious or combative when separating from parents; postoperative amnesia was not evaluated in this study. Cetina found that rectal or oral preanaesthetic medication with ketamine 15 mg.kg^{-1} combined with droperidol was superior to intramuscular or intravenous premedication. Gutstein and co-workers^[2] observed that sedation occurred in 15-20 minutes after administration of oral ketamine which is comparable to other oral premedication regimens. The bioavailability of oral ketamine and oral midazolam are 10 - 16% and 40 - 50% respectively due to extensive first pass hepatic excretion. Stewart and co-workers^[6] compared the efficacy of oral ketamine 10 mg.kg^{-1} to intramuscular morphine 0.1 mg.kg^{-1} , both in combination with trimeperazine 3 mg.kg^{-1} , as anaestheticpremedicant in 40 children presenting for cardiac surgery. No significant differences in patient arousal or cooperation with induction of Anaesthesia were found. Our study evaluated the efficacy of oral ketamine and oral midazolam at high dosage and combination of both at low dosage as premedication in pediatric patients. Earlier studies revealed superiority of oral ketamine and midazolam to placebo^[2, 7-13] and therefore we did not include the placebo group.

Baseline sedation and anxiolysis were comparable in all the three groups. Sedation and anxiety score decreased in all groups as time increased; it was statistically significant at parental separation and face mask application. Anxiety score and sedation score were significantly less with midazolam group and the combination group as compared to ketamine group alone at 30 min and at the time of parental separation and face mask application. Sedation score were comparable in midazolam group alone and in combination group; but anxiety score was significantly low in combination group at face mask application and parental separation as compared to midazolam group alone (p value 0.0045 and 0.0069 respectively). In our study, we found no cardiorespiratory compromise after premedication in all the three groups. Heart rate,

blood pressure and oxygen saturation were comparable to the baseline. There were no side effects like nausea, vomiting, desaturation, hypotension, bronchospasm in all the three groups. Only two patients in ketamine group had excessive secretion that did not require any intervention. In a study by Mishra LD,^[14] oral premedication with midazolam (0.75 mg/kg) demonstrated better efficacy than 0.5 mg/kg or 1 mg/kg dosage in terms of acceptable sedation profile and safe recovery characteristics in pediatric patients. However, we have found that combination of midazolam and ketamine at low dosage is more effective at 30 minutes and at time of parental separation and face mask application than to high dose of midazolam alone with lesser side effects. Gutstein et al^[2] and McMillan^[13] also observed the benign effects of oral ketamine and oral midazolam on cardio respiratory system respectively. Lerman and co-workers^[15] compared the clinical characteristics of oral ketamine and oral midazolam and found that no important side effects were attributable to either premedication. Gringrich^[16] aborted his study after undesirable side effects, including increased secretions, laryngospasm, hallucination and dysphoria from oral ketamine at 6 mg/kg. We did not find any side effects with either ketamine or with combination, except hypersecretion in ketamine group.

Conclusion:

Combination of oral midazolam and ketamine at low dosage is excellent premedication for sedation and anxiolysis at the time of parental separation and face mask application and are highly acceptable to children and their parents with minimum side effects.

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Table 1: Demographic data

	Oral Midazolam (Mean±SD)	Oral Ketamine (Mean±SD)	Oral Midazolam + Oral Kaetamine (Mean±SD)
No of patients	25	25	25
Age (Months)	43.7±31.8	42.7±36.6	63.0±45.9
Weight (Kg)	10.16±4.17	10.24±4.99	13.56±6.36
Sex (M/F) Ratio	13/12	12/13	17/8

**Table 2:
Mean
Sedation
Scores in the**

Pre-treatment Arms

Mean sedation score	Oral Midazolam	Oral Ketamine	Oral Midazolam + Ketamine	p value
Pre-sedation	4	4	4	NA
10 min after medication	3	3.08	2.8	0.003
20 min after medication	2.64	2.96	2.16	0.000
30 min after medication	2.2	2.72	2.04	0.000
Time of parental separation	2.56	2.76	2.28	0.002

Table 3: Mean Anxiety Scores in the Pre-treatment Arms

Mean Anxiety score	Oral Midazolam	Oral Ketamine	Oral Midazolam + Ketamine	p value
Pre-sedation	3.96	4	4	0.373
10 min after medication	2.96	3	2.68	0.001
20 min after medication	2.2	2.6	2	0.000
30 min after medication	2.08	2.44	2	0.000
Time of parental separation	2.32	2.8	2	0.000