Original Article

Indian Journal of Anesthesia and Analgesia
Volume 8 Number 2 March-April 2021
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.8221.32

Comparison of oral Midazolam versus Combination of Low Dose Oral Midzolam–Ketamine for Premedication in Paediatric Surgical Patients

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Abstract

Background and need for study: One of the challenge faced by paediatric anaesthesiologist is the allaying of fear of a child in the preoperative period. Among the commonly used premedicant in children, midazolam is the front runner. A combination low dose of ketamine and midazolam have been tried to overcome the deficiencies of ketamine and midazolam alone.

Aims: This research was planned to compare the effectiveness of combination of low dose midzolam–ketamine with oral midazolam alone as a premedicant in paediatric patients in terms of degree of sedation, separation from parents, mask acceptance, and postoperative recovery

Design: Prospective, randomised, double blind controlled study.

Methods: Sixty children of ASA physical status I or II, aged between 1 and 12 years, who were scheduled to undergo elective minor surgery were randomised into two groups M and MK of thirty children each. Children in group M were administered with oral midazolam 0.5 mg.kg-1 mixed with 2 ml of honey and group MK were administered with combination of low dose oral midzolam (0.25 mg.kg-1) & oral ketamine (3 mg.kg-1) for premedication mixed with 2 ml of honey. Patient was assessed for parental separation anxiety, mask acceptance, level of sedation and emergence delirium.

Statistical Analysis: Difference with respect to anxiety at separation from parents and tolerance to mask between the two groups was analysed using chi-square test . Difference with respect to incidence and severity of emergence delirium between the two groups was analysed using an independent sample t test . The $P < 0.05$ was considered significant.

Results: Parental separation was acceptable in 23 patients (76.7%) in group M and 28 patients in (93.3%) in group MK (Table 2, 3). Mask acceptance was satisfactory in 13 (43.3%) in group M and 19(63.3%) in group MK.

Post-operative delirium was noted in one patient in each group.

Conclusion: The low dose mixture of ketamine and midazolam provides better parental separation and mask acceptance with better cooperation during induction of anaesthesia.

Key words: Midazolam; Ketamine; Premedication; Anxiety; Delirium.

How to cite this article:

Santhosh MCB, Umesh NP, Shivakumar G/Comparison of oral Midazolam versus Combination of Low Dose Oral Midzolam–Ketamine for Premedication in Paediatric Surgical Patients/Indian J Anesth Analg. 2021;8(2):227-231.

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Introduction and need for the study

One of the challenge faced by paediatric anaesthesiologist is the allaying of fear of a child in the preoperative period.[1] Anxiety would lead to violent behaviour and also increased postoperative pain, postoperative agitation.[2,3] The primary goal of preanaesthetic medication in children are to decrease fear associated with parent separation and unknown surroundings, and permit trouble free initiation of anaesthesia.

Among the commonly used premedicant in children, midazolam is the front runner.[4] It has a many of advantages: hypnosis, early onset, and relatively short duration of action.[4] Even with these advantages midazolam is at a distance from an ideal premedicant effects because of associated unwanted effects such as paradoxical reaction, respiratory depression, cognitive impairment, amnesia and restlessness.[5,6] Oral midazolam premedication produces good or excellent results in only 60% to 80% of cases.

Ketamine, a non-barbiturate cyclohexamine derivative, is fat soluble and quickly absorbed after intravenous, intramuscular, oral and intranasal administration. Ketamine when used alone as premedication in a dose of 6 mg.kg-1 was found to have undesirable effects, such as excessive salivation, hallucinations and dysphoria.[6]

So combination low dose of ketamine and midazolam have been tried to overcome the deficiencies of ketamine and midazolam alone.

In view of the above, our research was planned to compare the effectiveness of combination of low dose midzolam–ketamine with oral midazolam alone as a premedicant in paediatric patients in terms of degree of sedation, separation from parents, mask acceptance, and postoperative recovery.

Methodology

This study was an prospective, randomised, double blind controlled study. After obtaining institutional ethical committee clearance, written informed consent from the patient's parents or legal guardian, 60 children of ASA physical status I or II, aged between 1 and 12 years, who were scheduled to undergo elective minor surgery. Children with known allergy or hypersensitive reaction to midazolam or ketamine, cardiac arrhythmia or congenital heart disease, increased intracranial tension, intraocular pressure, chronic illness and mental retardation were not included in the study. Randomisation was done using computer generated table into two groups M and MK of thirty children each. Children in group M were administered with oral midazolam 0.5 $mg.kg^{-1}$ mixed with 2 ml of honey and group MK administered with combination of low dose oral midzolam (0.25 $mg.kg^{-1}$) & oral ketamine (3 $mg.kg^{-1}$) for premedication mixed with 2 ml of honey. Investigator 1 who was not involved in the collection of data prepared the study drug and administered the drugs orally 30 min prior to the surgery. The below parameters were recorded by investigator 2 who was blinded about the drugs given to the patient, Heart rate,respiratory rate and oxygen saturation (SPO_2) were monitored continuously and recorded at 5 min interval in the preoperative period. Anxiety of the patient was assessed by using the Parental Separation Anxiety Score (PSAS).

The Parental Separation Anxiety Scale (PSAS) is a 4-point scale as follows:

- 1 = easy separation
- 2 = whimpers, but is easily reassured, not clinging
- 3 = cries and cannot be easily reassured, but not clinging to parents
- 4 = crying and clinging to parents

A PSAS score of 1 or 2 were considered as an acceptable separation, whereas scores of 3 or 4 were considered difficult separations from the parents.

Level of sedation was assessed using five point scale as follows (sedation score)

1 = Agitated

2 = Alert

3 = Calm

4 = Drowsy

5 = Asleep

In the operation theatre, general anaesthesia was induced with oxygen, sevoflurane 3-5% using Jackson Ree's circuit with face mask.

The patient's ability to accept the anaesthesia mask was measured using the Mask Acceptance Scale (MAS).

The MAS scale (4-point Likert scale)

- 1 = excellent (unafraid, cooperative, accepts mask readily)
- 2 = good (slight fear of mask, easily reassured)
- 3 = fair (moderate fear of mask, not calmed with reassurance)
- 4 = poor (terrified, crying, or combative).

Patients who received a score of 1 or 2 were

considered "satisfactory" acceptance of the anaesthesia mask; scores of 3 or 4 were considered "unsatisfactory."

Once the patient was induced, intravenous (i.v) access was secured. Intravenous Fentanyl 2 $\mu g.kg^{-1}$ was given. Airway was managed with suitable size laryngeal mask airway. Anaesthesia was maintained with sevoflurane. Electrocardiogram, SpO_2 heart rate, end tidal carbon dioxide was monitored continuously and documented at 5 min intervals. Non-invasive blood pressure was recorded at 5 min intervals. Any cardiorespiratory or other adverse effects were noted.

For postoperative analgesia, paracetamol rectal suppositories were inserted near the end of the procedure. In PACU, patients vitals were monitored continuously.

In the PACU, emergence delirium was aanalysed using the Watcha scale

Behaviour	Score
Asleep	0
Calm	1
Crying, but can be consoled	2
Crying, but cannot be consoled	3
Agitated and thrashing around	4

Score higher than 2 indicates presence of emergence delirium.

Patients with delirium score higher than 2 were administered with iv midazolam (0.01- 0.02 $mg.kg^{-1}$).

Statistical Analysis

Difference with respect to anxiety at separation from parents and tolerance to mask between the two groups was analysed using chi-square test . Difference with respect to incidence and severity of emergence delirium between the two groups was analysed using an independent sample t test . The $P < 0.05$ was considered significant.

Results

Both the groups were comparable with respect to demographic data (Table 1). Mean age was 3.41 ± 2.03 years, and mean weight was 13.17± 3.72 kg. There was no significant difference in the surgical and anaesthesia duration. Parameters like heart rate, respiratory rate and oxygen saturation were in the normal range in both the groups. Other parameters like Parental separation was acceptable in 23 patients (76.7%) in group M and 28 patients in (93.3%) in group MK (Table 2, 3). Mask acceptance was satisfactory in 13 (43.3%) in group M and 19(63.3%) in group MK.

Post-operative delirium is noted in one patient in both the groups.

Table 1: Demographic data.

	Group M (30)	Group MK (30)	p value
Age 1- 3years	16	12	0.23
Age 3-5 years	09	11	0.12
Age 5-8 years	05	07	0.24
Sex (Male:Female)	22/8	20/10	0.78
ASA status I/II	29/1	28/2	0.82
Anaesthesia time (min)	52 ± 8.31	50 ± 5.97	0.13
Surgical time	42 ± 10.27	38 ± 11.21	0.37

Table 2: Comparison of parenteral separation, sedation score, mask acceptance and postoperative agitation (mean±SD).

	Group M (n=30)	Group MK (n=30)	p value
Parenteral separation score	3.47±0.43	1.47±0.57	0.028
Sedation Score	4.12±0.21	4.05±0.23	0.65
Mask acceptance score	3.10±0.03	1.8±0.05	0.034
Postoperative agitation	1.23±0.34	1.25±0.6	0.42

Table 3: Number of patients with acceptable sedation and parenteral separation.

	Group M (n=30) (%)	Group MK (n=30) (%)	p value
Parenteral separation score 1 or 2 at 30 min	23 (76.7%)	28 (93.3%)	0.039
Mask acceptance score (1 or 2)	13 (43.3%)	19 (63.3%)	0.042
Postoperative agitation (no)	1 (33.3%)	1 (33.3%)	0.32
Sedation score 3-5 at 30 minutes	24 (80%)	25 (83.3%)	0.46
No. of children asleep at induction	10 (33.3%)	11 (36.7%)	0.53
No of children disturbed at induction	15 (50%)	8 (26.7%)	0.048

Discussion

An anxious fearful fighting child is always stressful for the anaesthesiologists, care givers and parents and may lead to behavioural and psychological disturbances in the child which may affect daily functioning of the child. Children between 1 and 5 years of age appear to be at highest risk for developinganxiety because children under the age of 1 year rarelyexperience separation anxiety.[7]

Perioperative anxiety inchildren can be reduced by pharmacological or behavioural interventions.[8]

All routes of premedication and many premedication drugs have been tried but no single technique or agent has provided complete satisfactory results.

In our study, we have compared effectiveness of oral midazolam (0.5 $mg.kg^{-1}$) and combination of oral midazolam (0.25 $mg.kg^{-1}$) & oral ketamine (3 $mg.kg^{-1}$) in lower dose as premedicants in children undergoing elective surgical procedure. We found that the parenteral separation score (1 or 2) at 30 min, Mask acceptance score (1 or 2), number of children uncooperative at induction was lessin group MK significantly when compared group M. There was no significant difference between the two groups with regard to sedation score 3-5 at 30 minutes, number of children asleep at induction, incidence of postoperative agitation.

Darlong V et al, conducted a study on seventy eight children posted for elective eye surgery. They were divided them into three groups who received oral midazolam 0.5mg/kg or oral ketamine 6mg/kg or combination of lower dose of both midazolam 0.25mg/kg and ketmine 3mg/kg in combination as a premedication. They concluded that combination of oral ketamine and midazolam in low dose had very less side effects and was more effective, faster in onset and had a more rapid recovery when compared to other two groups.[9]

Majidinejad S, Taherian K et al., randomized, double-blinded, clinical trial to compare the combination of oral midazolam and ketamine with oral midazolam alone as sedatives during the procedure among children subjected to computed tomography imaging. The study populationconsisted of patients with age group of 6 months to 6 years with minor head traumamedium-risk, who were advised to undergo brain CT imaging. Patients were randomly divided in to two groups: one group received 0.5 mg/kg midazolam (group OM, n = 33) orally and anothergroup received combination of 0.2 mg/kg midazolam and 5 mg/kg ketamine orally (group OMK, n=33). This study showed that in comparison with Oral midazolam, combination of oral midazolam with ketamine was more effective in providing a satisfactory sedation levelin children undergoing CT examination without any additional side effects; however, both the regimens did not fulfil the clinical needs for sedation during the procedure.[10]

Damle SG, Gandhi M, Laheri V conducted a randomized double-blind study to evaluate the sedative effects of oral ketamine and oral midazolam administered before general anesthesia. Twenty unco-operative children between the age-group of 2 to 6 years were selected after thorough clinical examination and tests. Children were administered eitherwith 0.5 mg/kg oral midazolam or 5 mg/kg ketamine, results showedthat adequate sedation is obtained at the end of 30 min with both the drugs, alsosignificantly better anxiolysisobtained with oral midazolam. Oral ketamine produced slightlyhigher heart rate and respiratory rate. It was noted from the questionnaire that oral midazolam has better response and side effects were more common with oral ketamine.[11]

Darlong V et al conducted a prospective randomised, controlled study in eighty seven children posted forelective ophthalmologic surgeries. One group (M) received oral midazolam 0.5 mg/kg, another group (MKL) received oral midazolam 0.25 mg/kg and ketamine 3 mg/kg, and Group (MKH) received midazolam 0.5 mg/kg and ketamine 6 mg/kg.

Level of sedation and ease of parental separation were noted during general anaesthesia procedure. They concluded that a combination of midazolam and ketamine in lower dose is as equally effective as high-dose midazolam and ketamine for achieving adequateanxiolysis and a rapid recovery, along with lesser incidence of excessive salivation in children undergoing ophthalmic surgery.[12]

With the review of above scientific studies and results of our study is in concordance with the findings of above studies.

Darlong et al had found lesser incidence of salivation and lesser haemodynamic changes in low dose combination group than higher dose combination group. In our study, inspite of administration of ketaminethere was no incidence of excessive salivation or changes in haemodynamic parameters in group MK when compared to group M. Limitation of the study is the number patients studied.

Conclusion

The low dose combination of ketamine and midazolam provides better parental separation and mask acceptance with better cooperation during anaesthesia induction. As there was no difference in the incidence of side effects between the two groups, it can be concluded that low dose combination of ketamine and midazolam can replace midazolam alone as premedicant in children.

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