Original article

Comparative study of a combination of midazolam and ketamine versus midazolam and ketamine alone as oral premedication in children: A randomized double-blind study

[1]Dr Niraj M. Nalawade , [2]Dr Yogesh V. Gavali , [3]Dr Vidya S. Kelkar , [4]Dr Bapusaheb L. Kakade ,[5] Dr Kalpana V. Kelkar , [6]Dr Ajay S. Chandanwale

[1]Assistant Professor, Department of Anaesthesia, B J Medical College , Pune
[2]Associate Professor, Department of Anaesthesia, B J Medical College , Pune
[3]Professor, Department of Anaesthesia, B J Medical College , Pune
[4]Assistant Professor, Department of Anaesthesia, B J Medical College , Pune
[5]Professor & Head Department of Anaesthesia, B J Medical College , Pune
[6]Professor & Dean, B J Medical College , Pune
Corresponding author: Dr Niraj M. Nalawade

Abstract:

Introduction: Comparative study of a combination of midazolam and ketamine versus midazolam and ketamine alone as oral premedication in children: A randomized double-blind study.

Background and Aims: Surgery and anaesthesia can be a traumatic experience to a child and considerable emotional stress for both parents and children. In children preanaesthetic medication are frequently administered as a pharmacological adjunct to help to alleviate the stress and fear of surgery as well as to ease child-parental separation and provide smooth induction of anaesthesia. The primary aim of this study was to evaluate the efficacy of oral midazolam (0.5mg/kg) and oral ketamine (6mg/kg) separately with the combination of oral midazolam (0.25mg/kg) and oral ketamine (3mg/kg) as a preanaesthetic medication.

Methods: Ninety children of either sex, aged between 2-6years with American Society of Anaesthesiologist physical status I-II, undergoing elective surgery under general anaesthesia were enrolled into this randomized double blind study. The children were assigned to 3 groups namely Group M (received oral midazolam 0.5mg/kg), Group K (received oral ketamine 6mg/kg) and Group MK (received a combination of oral midazolam 0.25mg/kg and oral ketamine 3mg/kg). After administering premedication, the vital parameters were assessed every 15min and the effect of drug was evaluated for Sedation, Anxiolysis, Parental separation and Venepuncture on 4 point scale.

Result: The combination provides better quality of sedation and Anxiolysis and could be easily separated from parents. Also successful Venepuncture without any resistance can be achieved. **Conclusion:** The present study shows that the combination provides better preanaesthetic medication without significant change in vital parameters and with no side effects-than the two drugs used alone.

Keywords: Preanaesthetic medication, Midazolam, Ketamine, Sedation, Anxiolysis.

INTRODUCTION:

Surgery and anaesthesia can be a traumatic experience to a child and considerable emotional stress for both parents and children. Children experience general fears related to hospitalization viz. fear of separation from parents, fear of pain, unknown orun familiar surroundings and uncertainty of limits of behaviour.[1]

Every efforts should be made to make the ordeal of surgery as tolerable and pleasant as possible. Thus

the development of a sedative premedicant[2] in children, which is atraumatic, well accepted, easily administered, acts rapidly, has minimal side effects and does not prolong emergence from anaesthesia is the demand of the hour today.So a need exists for a safe and effective oral preanaesthetic medication for the use in children undergoing elective surgery. In children preanaesthetic medications are frequently administered as a pharmacological adjunct to help to alleviate the stress and fear of surgery as well as to ease child-parental separation and provide smooth induction of anaesthesia. Key features of good premedication are easy application, rapid onset with short duration of action and lack of significant side effects.

Midazolam is a water soluble bezodiazepam with imidazole ring in its structure that accounts for stability in aqueous solution and rapid metabolism.[3]Midazolam is characterized by a pH dependant 'ring opening phenomenon' in which the ring remains open at pH values of <4, thus maintain water solubility of the drug. The ring closes at pH value >4, when the drug is exposed to physiologic pH, thus converting midazolam to a highly lipid soluble drug.[4] Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and anterograde amnesic effect. It can be given by intramuscular, intravenous, oral, nasal, rectal and through epidural and intrathecal routes.

Ketamine is a water soluble molecule that structurally resembles phencyclidine. It produces "dissociative anaesthesia", which is characterized by evidence on EEG of the dissociation between the thalamocortical and limbic system.[5]The patients become non-communicative although wakeful. Ketamine is a cataleptic analgesic[6, 7, 8] and anaesthetic with hypnotic properties. It can be given intramuscular, intravenous, oral, nasal, rectal and through epidural routes. Here in this study, oral midazolam and oral ketamine alone and combination of the two drugs are used for preanaesthetic medication in children.

Methods:

After obtaining institutional ethical committee approval and taking written consent from patients, ninety children of either sex between 2 to 6 years of age having American Society of Anaesthesiologist grade I or II physical status were posted for elective surgical procedure lasting for 30minutes to 2hours. Children having American Society of Anaesthesiologist grade III onwards, CNS or psychiatric dysfunction, hyperthyroidism and congenital heart diseases were excluded.

Using a randomized double blind method the children were assigned to one of the three groups comprising 30 each. Group M received oral midazolam 0.5mg/kg in honey (0.1ml/kg). Group K received oral ketamine 6mg/kg in honey (0.1ml/kg). Group MK received a combination of oral midazolam 0.25mg/kg and oral ketamine 3mg/kg in honey (0.1ml/kg).

All patients were thoroughly examined on the day before surgery. Patients and parents were informed about the study and informed written consent was taken from the parent both for the conduct of the study as well as for the administration of general anaesthesia. Just before the premedication, the vital parameters i.e. pulse rate, respiratory rate, blood pressure and SpO_2 were taken as baseline. The premedication in appropriate dosage was mixed with honey and was given by a dropper 45minutes before the surgery.

All the vital parameters were continuously assessed at 0, 15, 30 and 45minutes after premedication. The scoring was done on a four point scale[9] (table1) consists of sedation, anxiolysis, parental separation and venepuncture, at the end of 45minutes and again at the time of venepuncture.

As soon as a stable level of sedation was achieved the child was separated from the parents. At this

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time the state of anxiolysis or emotional state of the child to separation from the parents was noted and graded according to a 4 point scale. The patient was transferred to the operating room. In operation theatre an intravenous line with appropriate gauge intravenous cannula was established using all aseptic precautions. At this time the level of sedation, emotional state was noted and graded according to four point scale.[9] Side effects of this premedication if any were noted preoperatively. Continuous SpO_2 monitoring was done with pulse oximeter. General anaesthesia was given to all the patients. Post operatively patients were monitored in the recovery room for vital parameters and side effects if any.

The level of sedation was graded by four point scale (1-alert, 2-awake, 3-drowsy, and 4-asleep). The behaviour at the time of parental separation was assessed when the child was separated from the parents to shift to operating room using the separation score (1-needs to restrain, 2-separated with cry, 3-separated without cry and 4-happily separated).

The demographic parameters such as age and weight were expressed with standard deviation. Four variables i.e. sedation, anxiolysis, parental separation and venepuncture were compared in all the three groups (M, K, MK). For this statistical comparison one way ANOVA test was applied and for multiple comparison Dunnett t test was used. Statistical significance was considered to be a P value <0.05. Results were reported as standard deviation.

Results:

The age and weight were comparable in all the three groups. Comparing the pulse rate and blood pressure change (table 2 & 3) among these three groups, the baseline pulse rate and blood pressure change in all the three groups were statistically not significant. But comparison at 15minutes pulse rate in midazolam and the combination group does not change while there was rise in pulse rate and blood pressure at 15 min in ketamine group, which was statistically significant(p=0.01).

On premedication while assessing sedation, the combination has better level of sedation than midazolam and ketamine used alone and which is highly significant(p=0.001). On assessing anxiolysis or emotional state (table 6), the combination has better level of anxiolysis than midazolam and ketamine used alone and which is highly significant(p=0.017).

On comparison of separation score, midazolam and ketamine groups having no significant change, while in the combination group it is highly significant(p=0.002) denoting better parental separation in combination group than above two drugs used alone.At the time of venepuncture, the combination group was having significantly better outcome than the two drugs used alone.

Discussion:

Hospitalization introduces a new set of circumstances for which child is unprepared. Stormy anaesthesia induction in children can lead to an increased incidence of postoperative behavioural[10, 11, 12]problems. These problems can be diminished to some extent by psychological preparation of the child and parents, however our pharmacological adjunct may be more reliable and better suited. Thus, a good premedicant is required to minimize the psychological stress and to control a distressed child. It should make the child calm and quiet during induction of anaesthesia and should have no adverse effects. It should be reliable in the onset of action and should provide rapid recovery and return to alertness postoperatively permitting easy discharge from recovery room.

The world of preanaesthetic medication is crowded with many drugs viz. anticholinergic, anxiolytics, sedatives, hypnotics etc. Of these, sedatives occupy

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an important position. Oral premedications are widely used as it is readily acceptable and least threatening to children. So, several sedative premedicants are being used orally in children today. These premedicants have few undesirable attributes. Thinking of these undesirable effects, makes one wonder whether the quest for an ideal sedative premedicant in children has really reached its goal? Nevertheless an ideal drug has not yet been found and the need to evaluate newer drugs for oral preanaesthetic medication in children persists.

Keeping this in mind, the present study was undertaken to evaluate the safety and efficacy of oral midazolam and oral ketamine as preanaesthetic sedative medication in paediatric patient and to compare the efficacy of the combination of these two drugs. Oral midazolam having variable success rate and larger dose of ketamine giving higher success rate but with more side effects, so we decided to study whether combination of these two drugs in lesser doses improve the efficacy without increasing side effects.The dose range selected for the study is obtained after the review of literature of oral midazolam and oral ketamine in paediatric patients[13, 14, 15].

By this study the efficacy of oral midazolam and oral ketamine as well as the combination of above two drugs have been studied in terms of sedation, anxiolysis, parental separation and venepuncture. Also change in vital parameters were noted in all three groups throughout the study. The age and weight distribution of the patients in all the three groups were comparable.

Comparing the pulse rate and blood pressure change(table2 & 3) among these three groups, we found no pulse rate change in midazolam(M)group but small change in blood pressure, which is not significant, while in combination(MK) group, there was no significant rise in pulse rate as well as blood pressure.In the previous studies[9, 16], they have found the same results. In contrast to above two groups,ketamine(K) group at 15min showed significant rise in pulse rate as well as blood pressure.

The study conducted by Suresh c et al[17], where he noted that there was no significant change in the respiratory status in both midazolam and ketamine group. In our study, we have not found any significant change in respiratory status in terms of respiratory rate and SpO_2(table 4 & 5). So,the results of our study is in line with it.

Four variables i.e. sedation, anxiolysis, parental separation and venepuncture were compared in all three groups (M, K & MK). Each variable was assessed on four point scale. On comparing sedation, we found that the combination had early onset and better sedation(3.5±0.57) than with the midazolam(2.76±0.43) and ketamine(2.9±0.54) group. These findings go with the results of study done by Darlong and Shende et al[13]. In this clinical study, excellent anxiolysis was obtained in 80-90% of the children. The midazolam and ketamine group have good anxiolysis score, which were comparable, but the combination provide better anxiolysis than these two groups.

On comparing separation score (table 6), there were equal number of children with successful separation in midazolam and ketamine group. There is far better separation score of combination group, where more children were in much calm and quiet state who could easily separate from parents. In a similar study[5], they have concluded the same findings.

Though midazolam and ketamine are known to cause respiratory depression, there was no episode of apnoea, airway obstruction or fall in SpO_2 in all the three groups. The most probable reason is that the route by which the drugs have been

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administered and the doses in which they have been given.

The oral preparation provides one of the better way for the route of administration of premedication in children, which fulfils the most of the criteria of ideal preanaesthetic medications. Midazolam and ketamine are well accepted by this route without showing significant side effects.

Midazolam known to cause fall in blood pressure but in the dose of 0.5mg/kg by oral route, it did not cause significant hypotension. Also no bradycardia was seen. Ketamine is known to cause tachycardia and hypertension, which have been seen to some extent when it was used in the dose of 6mg/kg orally.

When the combination of oral midazolam and oral ketamine in the dose of 0.25mg/kg and 3mg/kg respectively used as a preanaesthetic medication, the hypertensive effect of ketamine was not seen. The most probable reason may be the reduction in the dose of ketamine and adding low dose of midazolam in the combination group. Thus it shows that the combination provides stable vital parameters throughout the study.

Oral midazolam and oral ketamine in the dose 0.5mg/kg and 6mg/kg respectively provide sedation and anxiolysis but the combination group provides far better sedation and anxiolysis and children were easily separated from parents with successful venepuncture without any resistance.

No complications were noted in any of the patients throughout the study as well as in postoperative period.

Conclusion:

Children were premedicated with oral midazolam and oral ketamine alone and in combination. These two drugs were readily accepted, when it is used orally. Though oral preparation of midazolam and ketamine provide good premedication in children, the combination of the above two provides superior conditions besides less side effects and decreased dosages of the drugs. The combination also provides stable vital parameters throughout the study.

Table 1: Scoring system

Score	Sedation	Anxiolysis	Parental separation	Venepuncture
1	Alert	Thrashing	Needs to restrain	Fight without success
2	Awake	Crying	Separated with cry	Fight with success
3	Drowsy	Apprehensive	Separated without cry	Minor reaction
4	Asleep	Friendly	Happily separated	No reaction

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Table 2: Effect of different treatments on pulse rate

Time points	Groups			
	Midazolam	Ketamine	Midazolam+ Ketamine	P Value
Baseline	98.00±5.30	98.00±5.30	98.00±5.30	1.00
15min	98.27±4.89	107.07±4.57	98.27±4.89	0.01
30min	99.60±4.05	99.53±5.22	99.60±4.05	0.94
45min	98.53±4.55	106.67±4.74	98.53±4.55	0.01

P value is significant if P<0.05 and highly significant if P<0.01

Table 3: Effect of different treatments on systolic blood pressure

Time points	Groups			
	Midazolam	Ketamine	Midazolam+ Ketamine	P Value
Baseline	96.73±6.78	96.73±6.78	96.73±6.78	1.00
15min	98.13±6.26	106.53±5.25	97.27±6.14	0.01
30min	98.00±5.53	98.20±5.37	97.53±5.40	0.88
45min	98.40±6.09	106.67±5.29	97.27±5.42	0.01

P value is significant if P<0.05 and highly significant if P<0.01

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Table 4: Effect of different treatments on respiratory rate/min

Time points	Groups			
	Midazolam	Ketamine	Midazolam+ Ketamine	P Value
Baseline	19.40±2.30	19.40±2.30	19.40±2.30	1.00
15min	19.67±2.11	19.53±2.27	19.53±1.87	0.96
30min	19.53±2.15	19.60±1.92	19.60±1.77	0.98
45min	19.57±2.13	19.00 ±2.27	20.00±1.74	0.17

P value is significant if P<0.05 and highly significant if P<0.01

Table 5: Effect of different treatments on SpO_2 (%)

Time points	Groups			
	Midazolam	Ketamine	Midazolam+ ketamine	P Value
Baseline	97.93±0.64	97.93±0.64	97.93±0.64	1.00
15min	98.07±0.58	97.80±0.76	97.73±0.58	0.11
30min	97.97±0.67	97.73±0.64	97.70±0.60	0.21
45min	97.77±0.73	97.83±0.70	97.70±0.60	0.74

P value is significant if P<0.05 and highly significant if P<0.01

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Table 6: comparison of four variables between different groups.

Variables	Groups			P Value
	Midazolam	Ketamine	Combination	
Sedation	2.76±0.43	2.90±0.54	3.50±0.57	0.001
Anxiolysis	2.66±0.47	2.66±0.47	2.96±0.41	0.017
Parental separation	2.40±0.49	2.50±0.50	2.90±0.66	0.002
Venepuncture	2.23±0.43	2.23 ±0.43	2.63±0.49	0.001
Total score	10.06±1.48	10.30±1.62	11.93±1.74	0.001

P value is significant if P<0.05 and highly significant if P<0.01

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