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Research Article

A double blinded comparative study of oral premedication in children with midazolam alone or in combination with ketamine

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ABSTRACT

Background: Surgery and anaesthesia induction cause considerable emotional stress upon children. In children pre-anaesthetic medications are frequently administered as pharmacological adjunction to alleviate the stress and fear of surgery as well as to ease child-parent separation and promote a smooth induction of anaesthesia.
Methods: Prospective double blinded randomized comparative study of oral premedication in children with midazolam alone or combination of midazolam with low dose ketamine in the age group of 3-10 years undergoing surgical procedures under standardized general anesthesia.
Results: In group M success rate of satisfactory sedation was 68.99% as against 76.59% in group MK, whereas success rate of anxiolysis was 80.00% in group M compared to 93.33% in group MK. 93.32% children were easily separated from parents in M Group compared to 96.66% in MK group. Also 73.32% children co-operated for IV line insertion in M group as against 96.66% in group MK and 83.33% children showed better mask acceptance in M group compared to 93.33% in MK group.
Conclusions: From present study, it was concluded that addition of low dose of ketamine improves quality and success rate of satisfactory sedation, anxiolysis, parental separation, co-operation for IV line and mask acceptance.

Keywords: Sedation, Anxiolysis, Parental separation, Co-operation for IV line and mask acceptance

INTRODUCTION

Surgery and anaesthesia induction cause considerable emotional stress upon children.[1] The consequence of this stress may remain in the child's psyche, long after the hospital experience has been passed away.[2] Planning and carrying out smooth transition from awake state to surgical anaesthesia in a child is always been a challenge for the anesthesiologist.

Fears of operation, injections, physicians and peculiar operation theatre environment where the children are separated from their parents prior to anaesthesia invariably produces traumatic experiences in the tender mind of the young children.[3] It has been associated with many negative effects during and after the surgical experience, like post-operative pain, sleep disturbances, parent child conflict and separation anxiety.[4] But it is difficult to determine which components of a child's hospitalization result in psychological problems.

In children pre-anaesthetic medications are frequently administered as pharmacological adjunction to alleviate the stress and fear of surgery as well as to ease child-parent separation and promote a smooth induction of anesthesia.[5,6]

Out of various routes for premedication oral and trans-mucosal routes has been most popular as these are most accepted by children. The intravenous and intramuscular

routes are traumatic. The rectal route is marked by variable absorption thus difficult in predicting depth of sedation and often not well accepted by children above three years of age. The intranasal route is similarly marked by variable absorption, may be irritating to nasal mucosa and drug administered may traverse directly into the central nervous system through the cribriform plate by travelling along olfactory nerves.[7]

The ideal pre-medication in children should possess following attributes.[8]

- An acceptable preparation (readily accepted by children)
- Rapid and reliable onset and with significant duration of action to accommodate delays in operating room schedule
- Provide anxiolysis and sedative effects
- Free of side effects that would necessitate high level of supervision
- Provide rapid recovery with early discharge.

Oral midazolam especially in the dose of 0.5 mg/kg has become one of the most frequently used pre-anaesthetic medication given to children scheduled for a surgical procedure. However good to excellent results are seen in only 60-80% of cases.[8,9]

Ketamine has similar pharmacodynamics after oral administration and has been investigated as an alternative.[10-13] However, when used as a sole pre-medicate, it has not been found to be very effective but may cause excessive secretions, dysphoria, and hallucinations.[14,15]

The addition of different doses of ketamine to oral midazolam has been tried and found to have varying results on the success rate of premedication with low but variable side effect profile.[16,17]

The main aim was to study the effect of oral midazolam versus midazolam- ketamine combination as premedication in children scheduled for elective surgery under general anaesthesia.

METHODS

Prospective double blinded randomized comparative study of oral premedication in children with midazolam alone or combination of midazolam with low dose ketamine in the age group of 3-10 years undergoing surgical procedures under standardized general anaesthesia.

Table 1: Type of score before and after medication.

Type of score	Satisfactory score	Unsatisfactory score
Sedation score 1. Agitated 2. Awake 3. Sleepy, eyes open, less active 4. Asleep but arousable with soft voice 5. Barely arousable, asleep needs shaking to arouse	3, 4	1, 2, 5
Anxiolysis score 1. Crying, panicking, clinging to parents 2. Moaning 3. Apprehensive, tentative behavior 4. Friendly or calm	3, 4	1, 2
Behaviour score of child at separation from parents 1. Combative, clinging 2. Anxious, consolable 3. Calm 4. Sleeping	3, 4	1,2
Behaviour of child at time of puncture for IV line 1. Fight without success 2. Fight with success 3. Minor resistance 4. No reaction	3, 4	1,2
Behaviour at the time of application of mask 1. Restless, struggling, restraint necessary 2. Calm. no restraint necessary	2	1

A total of 60 children scheduled for surgeries under general anaesthesia were enrolled in this study. Patents are dived into 2 groups 30 in each. Group M - children received syrup midazolam 0.5 mg/kg orally 30 min before surgery and group MK children received syrup midazolam 0.5 mg/kg and oral ketamine 3 mg/kg. Randomization was done by using computer generated random numbers. Drug was administered as per weight of child. Code numbers were put on the patient's record sheet. Decoding was done at the end of the study for statistical analysis.

Inclusion criteria

- Age group 3-10 years
- ASA grade I and II
- Either sex

Exclusion criteria

- History of recent respiratory tract infection
- Patient with airway problems
- ASA Grade III and above
- Patients with any CNS disorder or convulsion
- Hypersensitivity to midazolam or ketamine
- Expected duration of surgeries less than 30 minutes
- Patient with gastrointestinal disorder that can affect drug absorption
- Patient with long term therapy on hepatic enzyme inducing drug.

Base line parameters like heart rate, blood pressure, respiratory rate, oxygen saturation and basal sedation and anxiety score were recorded prior to premedication.

The score of 9 points was considered sufficient for discharge to the ward and time taken for discharge from PACU was recorded. During study following adverse effects were effects were looked for and noted down.

Statistical analysis

Parametric data were reported as arithmetic mean±standard deviation and analysed using Student's unpaired t-test. Ordinal data (scores) were analysed using Mann-Whitney U-test and chi square test. $P<0.05$ was considered as significant.

RESULTS

A total of 60 cases were enrolled in the study where 30 patients received oral midazolam syrup and 30 patients received combination of oral midazolam syrup and oral ketamine.

The patients were randomly divided into two groups.

Group M children received syrup midazolam 0.5 mg/kg orally (syrup Mezolam 2 mg/ml) 30 minutes before expected time of surgery.

Group MK children who received syrup midazolam 0.5 mg/kg (syrup Mezolam 2 mg/ml) and parenteral prep of ketamine orally 3 mg/kg (parenteral preparation of ketamine dissolved in 5% dextrose) 30 minutes before expected time of surgery. The demographic data was noted according age, weight, sex, ASA and duration of surgery (Table 2).

Table 2: Demographic data.

Parameters	Group-M (n = 30)	Group-MK (n = 30)	P value
Age (year) (mean±SD)	6.40±2.08	6.07±2.00	0.529
Weight (kg) (mean±SD)	13.93±3.42	14.47 ± 3.93	0.577
Sex (M/F)	15/15	19/11	0.297
ASA(I/II)	30/0	30/0	-
Duration of surgery (minutes)	90.87±20.23	91.17±20.83	0.955

* p value of<0.05 is considered significant.

Sedation

The mean sedation score after 10, 20 and 30 minutes of premedication in group MK was 1.97±0.41, 2.93±0.74, 3.33±0.76 as compared to group M was 1.57±0.50, 2.57±0.57 and 3.03±0.81. This difference was statistically not significant (p>0.05).

Majority of children in M-group had sedation score of 3 (sleepy, eyes open, less active), whereas MK-group children had sedation score of 4 (a sleep but arousable with soft voice), with only 2 children in MK-group had excess sedation with sedation score of 5 while none in M-group had excess sedation and satisfactory sedation was achieved at 30 minutes both groups (Table 3).

This suggests that addition of low dose ketamine improved the sedation score but did not cause excess sedation as adverse effect in significant no. of patients.

Table 3: Proportion of children with respect to sedation score at 30 minutes between two groups.

Sedation score	M-group	MK-group
1	0 (0%)	0 (0%)
2	9 (30%)	5 (16.66%)
3	11 (36.66%)	10 (33.33%)
4	10 (33.3%)	13 (43.33%)
5	0 (0%)	2 (6.66%)
Total	**30**	**30**

Anxiolysis

The baseline anxiolysis score in each MK-group and M-group is 1.30±0.47. No significant difference is noted between two groups (p>0.05). The mean anxiolysis score after 10 minutes of premedication in MK-group was 1.87±0.35 as compared to 1.57±0.50 in M-group. After applying Mann-Whitney test significant difference is noted (p=0.046). After 20 minutes of premedication mean anxiolysis score in MK-group was 2.73±0.45 as compared to 2.80±0.41 in M-group. This difference was statistically not significant (p>0.05). Whereas the mean anxiolysis score after 30 minutes of premedication in MK-group was 3.67±0.61 as compared to 3.40±0.81 in M-group. Here at the end of 30 minutes anxiolysis score of both groups not comparable (p>0.05).

Majority of children in M-group and MK-group children had anxiolysis score of 4 (friendly or calm) (Table 4). Thus addition of ketamine improved the anxiolysis score though it was not statistically significant.

Table 4: Proportion of children with respect to anxiolysis score at 30 minutes among the two groups.

Anxiolysis score	M-group	MK-group
1	0 (0%)	0 (0%)
2	6 (20%)	2 (6.66%)
3	6 (20%)	6 (20%)
4	18 (60%)	22 (73.33%)
Total	**30**	**30**

Onset of action

The onset of sedation (i.e. time required to increase sedation score by 1 plus) is 17.33±6.91 minutes in M-group and 14.33±6.79 minutes in MK-group. This was not statistically significant after applying unpaired t test (p=0.064) whereas as in anxiolysis, onset of action in M-group is 16.67±5.47 minutes and 14.00±5.63 minutes in MK-group. This was not statistically significant after applying unpaired t test (p=0.576).

Behaviour score of child at separation from parents

In M-group and MK-group behaviour score of child at separation from parents had score of 3 (calm) (Table 5). The mean behaviour scores of the child at separation from parent are better in MK-group than M-group.

Table 5: Proportion of children with respect to behaviour score at separation from parents.

Behaviour score	M-group	MK-group
1	0 (0%)	0 (0%)
2	2 (6.66%)	1 (3.33%)
3	26 (86.6%)	19 (63.33%)
4	2 (6.66%)	10 (33.33)
Total	**30**	**30**

Behaviour score of child at time of puncture for IV line

Table 6 shows satisfactory behaviour (behaviour score of 3 and 4) in M-group as 73.32% and 96.66% in combination group with respect to behaviour at IV insertion. Significant difference was noted between the two groups with p value of 0.030. This suggests that addition of low dose ketamine to midazolam results in better co-operation of child for IV insertion than midazolam alone. Thus addition of low dose ketamine to midazolam results in better co-operation of child for IV insertion than midazolam alone.

Table 6: Proportion of children with respect to behaviour score at puncture for IV line.

Behaviour score	M-group	MK-group
1	0 (0%)	0 (0%)
2	8 (26.6%)	1 (3.33%)
3	20 (66.6%)	15 (50%)
4	2 (6.66%)	14 (46.66%)
Total	**30**	**30**

Behaviour score of child at application of mask

The success rate (i.e. behaviour score of 2) was 93.33% MK-group whereas in M-group it was 83.33%, which suggests better mask acceptance in MK-group compared to M-group (Table 7).

Table 7: Proportion of children with respect to behaviour score at time of application of mask.

Behaviour score	M-group	MK-group	P value
1	5 (16.66%)	2 (6.66%)	
2	25 (83.33%)	28 (93.33%)	0.421
Total	**30**	**30**	

The satisfactory level of sedation in M-group was 69.9% compared to 76.59% in MK-group. Whereas satisfactory score in anxiolysis was found in group M was 80.00% and in group MK it was 93.33%. Similarly satisfactory

separation score was 93.32% in M-group compared to 96.66% in MK-group and shows no statistically significant difference between both of them (p>0.05). Satisfactory behaviour in M-group as 73.32% and 96.66% in combination group with respect to behaviour at IV insertion. Significant difference was noted between the two groups with p value of 0.030. The success rate was 93.33% MK-group whereas in M-group it was 83.33%, which suggests better mask acceptance in MK-group compared to M-group (Table 8).

Table 8: Satisfactory and unsatisfactory scores.

Type of score	M-group	MK-group	P-value	Chi- square test
Sedation				
Satisfactory	21 (69.99%)	23 (76.59%)	0.770	0.085
Not satisfactory	9 (30%)	7 (23.32%)		
Anxiolysis				
Satisfactory	24 (80%)	28 (93.33%)	0.255	1.289
Not satisfactory	6 (20%)	2 (6.66%)		
Behaviour score of child at separation from parents				
Satisfactory	28 (93.32%)	29 (96.66%)	1.000	0.00
Not satisfactory	2 (6.66%)	1 (3.33%)		
Behaviour score puncture for IV line				
Acceptable	22 (73.32%)	29 (96.66%)	0.030	4.706
Unacceptable	8 (26.66%)	1 (3.33%)		
Behaviour score of child at application of mask				
1	5 (16.66%)	2 (6.66%)	0.421	0.647
2	25 (83.33%)	28 (93.33%)		

Table 9 shows mean behaviour score of the child at separation from parent in MK-group to be 3.33±0.55 compared to 3.00±0.37 in the M-group. After applying Mann-Whitney test significant difference is noted (p=0.038), whereas the mean behaviour score of the child time of puncture for IV line to be 2.80±0.55 in M-group compared to 3.40±0.56 in MK-group. After applying Mann-Whitney test highly significant difference is noted (p=0.001), and mean behaviour score of the child time of application of mask was 1.87±0.43 in M-group compared to 1.93±0.25 in MK-group. After applying Mann-Whitney test no significant difference was noted (p=0.647).

Table 9: Comparison of behaviour score of children.

Behaviour score	Midazolam+Ketamine (MK-group)	Midazolam (M-group)	Mann-Whitney U test	P value
	Mean±SD	Mean±SD		
At time of separation of parents	3.33±0.55	3.00±0.37	2.070	0.038
At time of puncture for IV line	2.8±0.55	3.4±0.56	3.238	0.001
At time of application of mask	1.87±0.43	1.93±0.25	0.458	0.647

Table 10: Comparison of adverse effects between two groups.

Adverse effect	Group-M	Group-MK	P value
Vomiting	0	1 (3.33%)	0.313
Hallucination	0	3 (10%)	0.076
Salivation	0	1 (3.3%)	0.313
Excessive sedation	0	2 (6.66%)	0.150
Others (desaturation)	0	2 (6.66%)	0.150

Adverse effects

Table 10 shows that 1 patient had vomiting, 3 had hallucination, 1 had salivation, two patients were excessively sedated and two patient were de-saturated in MK-group, whereas in M-group no adverse effects were seen, however these adverse effects were not statistically significant between the two groups.

Discharge from PACU

The mean discharge time from PACU is 56.50±6.58 in M-group compared to 73.17±9.51 in MK-group. After applying unpaired t-test highly significant difference (p=0.000) is found between the two groups. This suggests that discharge time is prolonged in MK-group (Table 11).

Table 11: Comparison of time for discharge from PACU between the two groups.

Variable	Midazolam (Group M)	Midazolam+Ketamine (Group MK)	Unpaired T test	P value
	Mean±SD	Mean±SD		
Discharge from PACU (minutes)	56.5±6.58	73.17±9.51	7.89	0.00

This suggests that addition of low dose ketamine to midazolam results in better co-operation of child for IV insertion than midazolam alone.

Patients/parents satisfaction

The above data shows that there is statistically significant difference between two groups (p=0.008). Thus the patient/parental satisfaction was better with MK-group (Table 12).

Table 12: Comparison of patients/parents satisfaction between two groups.

Study group		Parents/patients satisfaction			Total	p value
		1	2	3		
Midazolam+Ketamine (group MK)	Count	19	10	1	30	0.008
	Percent	63.3%	33.3%	3.3%	100.0%	
Midazolam (group M)	Count	7	21	2	30	
	Percent	23.3%	70.0%	6.7%	100.0%	
Total	**Count**	**26**	**31**	**3**	**60**	
	Percent	**43.3%**	**51.7%**	**5.0%**	**100.0%**	

Chi-square test 9.775

DISCUSSION

Anxiolysis and sedation using preoperative medication is a common practice in pediatric anaesthesia, but there is still no completely satisfactory way to pre-medicate children and ensure smooth induction of anaesthesia.[18] Pre anaesthetic medication should relieve anxiety, reduce the trauma associated with separation from their parents and facilitate induction of anaesthesia without prolonging the recovery period.

Beebe and colleagues, were the first to compare a combination of rectal midazolam 0.5 mg/kg) 1 and rectal ketamine 3 mg/kg) 1 with both drugs alone.[16] They found that midazolam and ketamine alone and combination were equally useful techniques when IV induction of anaesthesia was desired.

Sedation

Present study results were comparable to those with the study conducted by Funk W et al, where they found no statistically significant difference with respect to sedation.[19]

In a similar study performed by Ghai B et al showed that uniform and acceptable sedation scores were seen in both the groups (group-M 95.9%; group-MK 97.96%).[20]

Present study results were also comparable with Foroutan A et al where in their comparative study exhibited satisfactory sedation compared with midazolam (86%) and ketamine (83%) groups.[21] In their study they considered awake but calm as successful sedation and awake anxious as not successful sedation.

Anxiolysis

In our study the onset of action was faster in MK-group compared to M-group, however there was no statistically significant difference between two of them.

Result of the present study shows that midazolam produced satisfactory anxiolysis; however its combination with ketamine showed improved anxiolysis score and success rate. Kumar A et al it was concluded that anxiolysis in group MK (80%) was more likely than group M (75%).[22] Their success rate in combination was 80% may be because they used low dose of midazolam in combination group.

The present results were also comparable with Funk W et al and conclude that success rate for anxiolysis >90% in combination group than 70% in midazolam group.[19]

Behaviour of child at time of separation from parents

Our study results are comparable with the study conducted by Ghai B et al that satisfactory separation from parents in combination was 93% compared to 88% in midazolam group.[20]

Beebe et al compared a combination of rectal midazolam and rectal ketamine with both drugs alone.[16] They reported satisfactory parental separation in 92% cases with midazolam and in 100% with combination but in only 60% with the ketamine-alone group.

Lin et al reported no difference in behavior at separation or induction after administration of midazolam (0.75 mg/kg 1 or ketamine 6 mg/kg 1) or a combination of ketamine 3 mg/kg) 1 with midazolam 0.5 mg/kg),which may be because they have used high dose of midazolam.[17]

Behaviour of child at the time of puncture for IV line

Addition of low dose ketamine highly improved behaviour of child at time of puncture for IV line which may be due to analgesic effect of ketamine.

In another study Funk W et al reported that easy venipuncture was seen in 90% of patient in midazolam group and >95% in midazolam plus ketamine group. But there was no significant difference between the two groups.[19] The higher percentage of success in both group was probably due to use of EMLA cream in their study.

Contrary to our study Kumar A et al in similar study found no significant difference in behaviour of child at the time of puncture for IV line in midazolam and midazolam+ketamine group respectively with satisfactory score of 70% in midazolam group 75% in combination group which may be due to low dose of midazolam (0.3 mg/kg) in combination group.[22]

Behaviour at the time of application of mask

Our results were comparable to the study by Foroutan A et al, in similar study had demonstrated that mask acceptance in midazolam plus ketamine group was 82% and 81% in midazolam plus ketamine group with no significant difference between the two groups.[21]

Kumar A et al also in their study comparing midazolam and midazolam plus ketamine found no significant difference between the two groups with respect to mask acceptance; with a success rate of 75% in midazolam group and 80% in combination group.[22] Lower score in combination group may be due to low dose of midazolam they used.

Adverse effects

All adverse effect like vomiting, hallucination etc. was self-limited and did not required pharmacological intervention. However these adverse effects were not statistically significant between the two groups and we found no adverse effect with midazolam alone.

Our results were comparable with Ghai B et al who reported no serious adverse effects in either group except for nausea and vomiting in three patients in group M and two patients in MK group which were self-limiting and did not require pharmacologic intervention.[20]

Discharge from PACU

In our study the patients were discharged to the ward after evaluating their recovery using modified Aldrete score. The score of 9 points was considered sufficient for discharge to the ward. The mean discharge time from PACU was 56.50 minutes i.m M-group compared to 73.17 minutes in MK-group. The difference between the two groups was statistically significant.

Varying results were found In other studies W Funk et al in their study found the discharge time in midazolam group to be 70 minutes, whereas in its combination group with ketamine it was 72 minutes with no statistically significant difference between the two groups.[19]

Whereas in a similar study by Ghai B et al the mean post-anesthesia recovery time, i.e. time to achieve Aldrete score of 10 was comparable between the two groups (128±35 minutes in group M and 120±24 minutes in group MK).[20]

Patient/parents satisfaction

Low dose ketamine significantly improved patient/parents satisfaction. Thus oral midazolam alone caused satisfactory sedation, anxiolysis, separation from parents, mask acceptance and IV line success without any adverse effect but has a failure rate and addition of low dose ketamine improved the quality and overall success

rate of sedation, anxiolysis, parental separation, mask acceptance, IV line access and had a better parental satisfaction without increasing adverse effect significantly but adverse effect did occurred in very few patients with combination. Therefore requires more monitoring compared to midazolam alone.

CONCLUSION

Thus in present study we concluded that addition of low dose of ketamine 3 mg/kg improves quality and success rate of satisfactory sedation, anxiolysis, parental separation, co-operation for IV line and mask acceptance. Therefore combination of midazolam and ketamine is a better premedication especially for securing IV line and mask acceptance. There is possibility of side effects and delay in discharge time thus requires more monitoring as compared to patient of oral midazolam alone. So oral midazolam alone is acceptable and safer in busy operation theatre in which vigilant monitoring may not be possible, but combination midazolam and low dose ketamine is a better choice especially in un-cooperative patient especially with difficult IV provided when monitoring will not be compromised.

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