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Original Article

Ketamine with Midazolam and Ketamine alone as oral premedication in children: a randomized trial

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Abstract

Background
Fear of operation, injections, physicians and peculiar operation theatre environment where children are separated from their parents prior to anesthesia invariably produce traumatic experiences in tender mind of young children. Midazolam and Ketamine are useful for oral premedication in children to allay anxiety, allow separation from parents and to ensure smooth induction.

Methodology
It was a prospective, randomized, double-blinded and comparative study conducted in 80 children of ASA I and II aged 1-6years undergoing elective ophthalmological procedures under general anesthesia. Children were randomized and divided into two groups, K received 4mg/kg of Ketamine and MK received 0.2mg/kg of Midazolam+2mg/kg of Ketamine peroral. Sedation level, ease of parental separation and ease of mask acceptance were evaluated within 20-30minutes on a 4-point scale. The time to achieve modified Aldrete score of ≥9 was also noted.

Results
Two groups were identical regarding age, sex, weight and ASA status. In sedation score, 31(77.5%) children in groupK and 35(87.5%) children in groupMK were awake, calm and quite (score3)(p=0.50). In parental separation score, 34(85%) children in groupMK and 25(62.5%) children in groupK have good separation, awake and calm (score2)(p=0.04). In mask acceptance score, 34(85%) children in groupMK and 17(42.5%)children in groupK were calm, awake, cooperative, accepting mask(score1)(p=0.001). Time of recovery in groupK was 17.92±6.50min whereas in groupMK was 17.80±4.059min(p=0.91).

Conclusion
Ketamine 4mg/kg and combination of Midazolam 0.2mg/kg with Ketamine 2mg/kg are equally effective but low dose combination is safe and superior.

Key words: ketamine, midazolam, premedication

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Introduction

Surgery and anesthesia procedure produce considerable emotional stress on children and parents.[1] When the children are separated from their parents, fears of injections, operation, peculiar operation theatre environment and physicians invariably produces

traumatic experiences in young children.[2] Premedication is used in children to facilitate anxiety-free and smooth separation from the parents and smooth induction of anesthesia. Children's ideal premedication should be available in a preparation that is easily accepted by children, have expected outcome, and no side effects (respiratory obstruction, hemodynamic instability or delayed recovery).[3] The oral route is generally preferred (esp. in children) because it is less traumatic than others, but it requires 20–45 min to achieve desired effect.[4]
The goal of oral premedication has been changing. In 2000 A.D., Funk et al[5] had considered low success for awake state, but in 2005 Ghai B et al[6] considered excellent for awake state as long as there is good anxiolysis allowing successful separation. They accepted calm, quiet and awake child as a good result because it avoids loss of head control or balance, loss of airway control and hypoxemia, etc. associated with deeply sedated child.

Midazolam is among one of the most popular pediatric premedicant. It's onset is rapid, duration of action is short, side effects are not significant and effects are predictable.[3] A compliant child separating from parents without crying can be obtained by oral dose of 0.25 to 0.33 mg/kg (maximum, 20 mg).[7]

Ketamine has also been investigated as an alternative oral premedicant because after oral administration it has similar pharmacodynamics. It has been used as a sedation medication in doses of 5 to 6 mg/kg for 1 to 6 years children.[8] Maximal sedation occurred within 20 minutes. However, it may cause dysphoria and hallucinations, excessive secretions, nausea and vomiting.[5]

The midazolam and ketamine combination has also been used as an oral sedative. This study was designed to compare efficacy of a combination of oral ketamine 2 mg/kg and midazolam 0.2 mg/kg with ketamine 4 mg/kg alone for achieving calm, quiet and awake child allowing smooth parental separation, accepting mask and having minimal recovery time.

Methods

This was a double-blinded, prospective, randomized and comparative study done at Tilganga Institute of ophthalmology (TIO), Kathmandu, Nepal. After obtaining approval from the IRB, NAMS and Research Committee of TIO and written informed consent from the guardians, the children were recruited in the study. Eighty children of ASA I and II aged 1 to 6 years undergoing elective ophthalmological procedures under general anesthesia were randomized with lottery method and divided into two groups (K and MK). Exclusion criteria were refusal by guardian, any contraindications to any of the drugs used and ASA III or higher. A box containing 80 chits, 40 of each group, was given to child and asked to take out 1 chit. The group allocated was written in separate paper by an anesthesiologist, decoding was done later after completion of all data collection. Group K were given 4 mg/kg oral ketamine (50 mg/ml parental form) and group MK were given 2 mg/kg oral ketamine with 0.2 mg/kg oral midazolam (1 mg/ml parental form). Both the medications were mixed in 25% Dextrose solution (total approx 10 ml) in a bowl by the anesthesiologist and given to parents to feed their child. The time of drug administration was noted and monitored clinically for sedation. Once the child was sedated, between 20 to 30 minutes, another anesthesiologist evaluated the preoperative sedation score, the child was separated from their parents and parental separation score was evaluated, taken to Operation Table and mask was given, mask acceptance score was evaluated as per on Table 1.
Anesthesia induction done with oxygen and nitrous oxide (50:50) and halothane administered via the anesthetic face mask and pediatric breathing circuit titrating according to response. Intravenous access was achieved. Intravenous fluid (DNS) was given as calculated by 4-2-1 formula. LMA of appropriate size was inserted. For analgesia Inj Paracetamol 15 mg/kg iv slowly was given. Anesthesia was maintained with oxygen, halothane (0.5–1%), titrated to clinical response and spontaneous assisted ventilation. Steroids and ondansetron were given as per anesthetic protocol of individual surgical procedure, TIO.

Monitoring done with pulse oximeter, noninvasive blood pressure measurement, electrocardiogram, eye ball movement and precordial stethoscope. At the end of surgery halothane was discontinued. LMA was removed. Suctioning of oral cavity was done as required and was shifted to postanesthesia recovery unit (PACU).

In the PACU, time taken to achieve Modified Aldrete score (Table 2) of ≥9 and presence of nausea and vomiting or

other complications, if any, was noted. The primary variable of this study was sedation score and secondary variables were parental separation score, mask acceptance score and recovery time.

Table 1: Evaluation scores[6]

A. Sedation scores
   1 – Asleep
   2 –Drowsy, responds to verbal commands/gentle stimulation
   3 – Awake, calm, quiet
   4 – Anxious, depressed/agitated/crying

B. Parental separation score
   1 – Asleep
   2 – Good separation, awake, calm
   3 – Awake, anxious, can be easily reassured
   4 – Crying, cannot be reassured

C. Mask-acceptance score
   1 – Excellent, asleep, calm, awake, cooperative, accepting the mask
   2 – Slight fear but can be reassured easily
   3 – Moderate fear and reassured with difficulty
   4 – Crying, needs restraint

Table 2: Modified Aldrete Recovery Score:[9]

1. Oxygenation
   SpO_2 > 92% on room air 2
   SpO_2 > 90% on oxygen 1
   SpO_2 < 90% on oxygen 0
2. Respiration
   Breathes deeply and coughs freely 2
   Dyspneic, shallow or limited breathing 1
   Apnea 0
3. Circulation
   Blood pressure ± 20 mm Hg of normal 2
   Blood pressure ± 20–50 mm Hg of normal 1
   Blood pressure more than ± 50 mm Hg of normal 0
4. Consciousness
   Fully awake 2
   Arousable on calling 1
   Not responsive 0
5. Activity
   Moves all extremities 2
   Moves two extremities 1
   No movement 0

Sample size calculated on the basis of a previous study[6] and using sample size estimation formula when the primary comparison is a mean i.e. $n > [2(Z\alpha + Z\beta)^2 \times SD^2] / d^2$. here, type I error taken as <5%, so $Z\alpha=1.96$ ($p<0.05$) and type II error taken as <20%(power=80%), so $Z\beta=0.842$, SD=standard deviation and d= difference in the means. For sedation score, calculated sample size is >39.05. So sample size taken as 40 in each group.

Data entry and statistical analysis were performed using Statistical Package for the Social Sciences (SPSS) version 16.0 for windows. Chi-square tests were used to compare the qualitative data. Unpaired t-tests were used to compare the quantitative data. Overall significance level was maintained at 'p' value < 0.05.

Results

A total of 80 patients who met the inclusion criteria were included in this study. None of the patients were excluded from the study. The details of the patients flow throughout the study has been shown in figure 1.

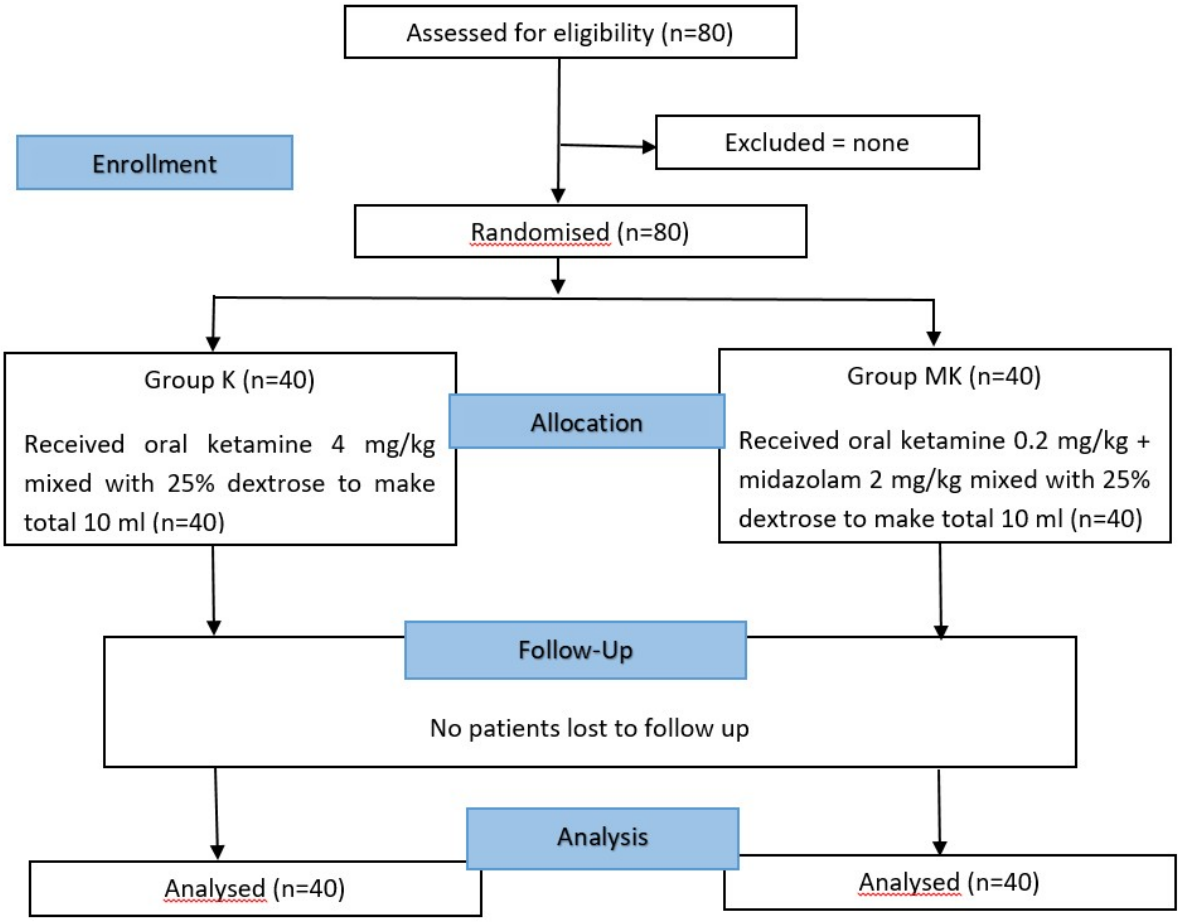

Figure 1: CONSORT 2010 flow-diagram

As the two groups were identical regarding age, sex, weight, and ASA status, both the groups were comparable.

Table 3: Demographic Distribution:

Group	Group K	Group MK	P value
Age in years (mean ± SD)	3.20 ± 1.95	3.88 ± 1.99	0.13
Sex (M/F)	21/19	20/20	0.82
ASA I	40	40	1.0
Weight in kg	12.85 ± 3.29	13.95 ± 4.06	0.18
Interval between premedication to induction (min)	26.20 ± 2.66	26.58 ±2.74	0.53
Duration of surgery (min)	27.72 ± 20.97	33.30 ± 24.24	0.27

In sedation score, 31 (77.5%) children in group K and 35 (87.5%) children in group MK were awake, calm and quite (score 3) (p=0.50). In parental separation score, 34 (85%) children in group MK and 25 (62.5%) children in group K have good separation, awake and calm (score 2) (p=0.04). In mask acceptance score, 34 (85%) children in MK group and 17 (42.5%) children in group K were calm, awake,

cooperative, accepting mask (score 1) (p=0.001). The time of recovery in group K was 17.92 ± 6.50 min whereas in group MK was 17.80 ± 4.059 min (p=0.91). Neither of the children in our study spat the drug out nor they had nausea, vomiting or any other complication

Table 4: Data showing sedation, parental separation, mask acceptance scores and average recovery time.

	Groups		P-value
	K	MK	
Sedation scores			
1	5 (12.5%)	4(10%)	0.502
2	1 (2.5%)	0	
3	31 (77.5%)	35 (87.5%)	
4	3 (7.5%)	1 (2.5%)	
Parental separation scores			
1	3 (7.5%)	3 (7.5%)	0.047
2	25 (62.5%)	34 (85%)	
3	9 (22.5%)	1 (2.4%)	
4	3 (7.5%)	2 (5%)	
Mask-acceptance Scores			
1	17 (42.5%)	34 (85%)	0.001
2	5 (12.5%)	3 (7.5%)	
3	5 (12.5%)	0	
4	13 (32.5%)	3 (7.5%)	
Average recovery time (min)	17.92 ± 6.506	17.80 ± 4.059	0.918

Discussion

Anesthetic management for patients begins with preoperative assessment and, if necessary, preoperative medication. Adequate preoperative planning and medication facilitate smooth perioperative course.[10] Out of the various goals of premedication, relief of anxiety and

production of sedation are most important. Premedication is widely used in pediatric anesthesia in order to provide anxiolysis, sedation, reduction in emotional stress and to facilitate smooth induction. Different routes of drug administration are available, but for children oral is considered good as it is not painful but associated with slow onset or be spit out; drug taste and child cooperation are the main determinants of success.
In this study 80 children undergoing routine ophthalmic procedures under general anesthesia were selected and randomly divided into two groups as group K- ketamine and MK-midazolam+ketamine group of 40 each. The demographic data such as age, sex, weight and ASA were comparable. There was no statistical difference in time interval between premedication and induction and also between duration of surgery.

In this study, sedation score in both groups were good and comparable. Thirty-one children (77.5%) in group K and 35 children (87.5%) in group MK were calm, quite and awake (score 3). No significant difference in sedation between the two groups were noted with p value of 0.502. Darlong V et al[11] in 2011 at AIIMS, in their study, they concluded that the combination of low-dose ketamine (3 mg/kg) and midazolam (0.25 mg/kg) (MKL group) is as effective as high-dose ketamine (6 mg/kg) and midazolam (0.5 mg/kg) (MKH group) for achieving optimum anxiolysis than midazolam alone (0.5 mg/kg) (M group). The number of children having 'good' sedation scores increased with time and followed a linear trend i.e. in MKL group 20 (69%), in MKH group 23 (79.3%) & in M group 12 (41.4%) children have good sedation score at 30 min than at 20 min [15 (51.7%) in MKL group, 18 (62%) in MKH group & 6 (20.7%) in M group]. They studied their score at 30 minutes after premedication, which is practically not feasible. In pretesting of 8 children, we found the children get sedated at around 20 minutes of premedication, so we have studied the sedation score at 20-30 minutes. The children were of 1-10 years in their study, but most children above 6 years can be convinced for mask induction, so do not require premedication. In this study age group is 1-6 years. A study done by Ghai B et al[6] in 2005 at PGIMER, Chandigarh, India, they found, in group MK (18.36%, n = 9) lesser children were asleep (score 1) than in group M (39%, n = 19) and greater children 46.93% (n = 23) in MK group were calm, quiet and awake (score 3) than in group M. The difference was statistically significant. The reason may be due to higher doses of drugs in combination group than that of this study. In Horiuchi T et al[12] study, group K (26%) had significantly lower incidence of 'effective' sedation (scores 2 or 3) than group M (39%) (P = 0.036). In addition, group K (37%) had higher incidence of score 5 (agitated) than group M (7%) (P = 0.007). They have used 50 mg ketamine lollipop to all children between 2 to 6 years of age, it may be attractive and acceptable for children and easy to prepare but the dose might be inappropriate. Dose must be calculated in respect to weight. This might be the reason for more agitated children in Group K (37%) than in Group M(7%), where dose was given in accordance to weight (0.5 mg/kg of syrup Midazolam). Funk et al[5] in 2000 at university of Rogensberg, Germany, compared oral ketamine 6 mg/kg with oral midazolam 0.5 mg/kg alone or a combination of oral midazolam 0.5 mg/kg and ketamine 3 mg/kg. Success rate observed was low in all groups. The reason for low success rate may be due to definition of success as asleep (score 4) and awake as no success. In our study we defined success as awake, calm and quite child.

In this study, the parental separation score was relatively better in MK group. Thirty-four children (85%) in group MK and 25 children (62.5%) in group K have good separation, awake and calm. The difference was statistically significant (p=0.047). In Ghai B et al[6] study, they found that for separation score, 23 children (47%) in M group than 10 children (20.4%) in MK group were asleep (score 1). For score 2 (awake, calm children with good separation), percentage was lesser in group M (41%,n=20) than in group MK (73.46%,n=36). Compared to this study, in MK group, greater percent of children were asleep (Parental separation score 1) i.e. 20.4% vs 7% and lesser percent of children were awake, calm with good separation (Parental separation score 2) i.e. 73.46% vs 85%. The reason may be due to higher doses of drugs in combination group than that of this study. Horiuchi T et al[11] found group K had significantly higher incidence of 'poor' (score 3) separation than group M (18.5% vs 0%, P= 0.017). The reason might be inappropriate dose, 50 mg ketamine lollipop to all children between 2-6 years irrespective of weight. Funk et al[5] found success rate for behavior at separation were only 51% in ketamine group, approximately 70% in midazolam group and >90% in

combination group. In our study also success was more with combination group.

In this study, the mask acceptance was also relatively better in MK group. Thirty-four children (85%) in MK group and 17 children (42.5%) in group K were calm, awake, cooperative, accepting mask. And also 13 children (32.5%) in K group were crying, needs restrain while induction in compare to only 3 children (7.5%) in group MK. This difference was also statistically significance (p=0.001). Darlong V et al[11], they found no statistically significant difference in the responses to induction and mask acceptance, > 90% of children in all three groups had good scores. i.e. for Mask acceptance in Group M 26 (89.6%), in Group MKL 27 (93.1%), in Group MKH 27 (93.1%) and for response to induction in Group M 21 (72.4%), in Group MKL 21 (72.4%), in Group MKH 24 (82.8%). The differences were not statistically significance. In Ghai B et al[6] group M has 52.08% (n=25) of score 1 (Excellent, asleep, calm, awake, cooperative, accepting the mask) than in group MK 57.14% (28), comparable induction score. Horiuchi T et al[12] found in mask cooperation scores no statistical differences between the two groups. However, the incidence of 'poor'(score 3) for mask cooperation was significantly higher in group K than group M (26% vs 7%, P = 0.019). The reason might be inappropriate dose, 50 mg ketamine lollipop to all children between 2-6 years irrespective of weight.

In this study, the time of recovery in both groups were comparable. In group K was 17.92 ± 6.506 min whereas in group MK was 17.80 ± 4.059 min. Darlong V et al[11] found that Recovery was faster in Group MKL (22.2 ± 5.7 min) as compared to Groups M (36.4 ± 12.1 min) and MKH (52.2 ± 21.9 min). Ghai B et al[6] found comparable score of mean postanesthesia recovery time between the two groups (120 ± 24 min in group MK and 128 ± 35 min in group M).

Conclusion

A low dose combination of ketamine 2 mg/kg with midazolam 0.2 mg/kg and ketamine 4 mg/kg are safe and equally effective for sedation, separation from parents, mask acceptance and recovery status. However, for parental separation and mask acceptance status, low dose combination was found to be better which was statistically significant.

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Conflict of Interest: All authors have filled the ICMJE conflict of interest form and declare that they have nothing to disclose.

References

1. Baruch K and Green SM. Sedation and analgesia for procedures in children. NEJM march2000;342(13) 938-44. https://doi.org/10.1056/NEJM200003303421306 PMid:10738053

2. Debnath S, Pande Y. A comparative study of oral premedication in children with ketamine and midazolam. Indian J Anaesth2003;47(1):45-7.

3. McMillan CO, Saphr-Schopfer IA, Sikich N et al. Premedication of children with oral midazolam. Can J Anaesth 1992; 39: 545–550. https://doi.org/10.1007/BF03008315 PMid:1643676

4. Morgan GE, Mikhail MS, Murray MJ. Clinical Anesthesiology. 4th ed. New York: McGraw-Hill; 2006. p.933.

5. Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic medication for children: double-blinded randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. British J Anaesthesia. 2000;83(3):335-40. https://doi.org/10.1093/oxfordjournals.bja.a013435

6. Ghai B, Grandhe RP, Kumar A, Chari P. Com parative evaluation of midazolam and ketamine with midazolam alone as oral premedication. Pediatric Anesthesia 2005;15: 554–559. https://doi.org/10.1111/j.1460-9592.2004.01523.x PMid:15960638

7. Cote CJ. Pediatric Anesthesia. In Miller RD: Miller's Anesthesia, seventh edition;2010(82). https://doi.org/10.1016/B978-0-443-06959-8.00082-0

8. McCann ME, Kain ZN: The management of preoperative anxiety in children: an update. Anesth Analg 2001; 93: 98. https://doi.org/10.1097/00000539-200107000-00022 PMid:11429348

9. Morgan GE, Mikhail MS, Murray MJ. Clinical Anesthesiology. 4th ed. New York: McGraw-Hill; 2006. p.1009.

10. Hata TM, Moyers JR. Preoperative Patient Assessment and Management. In Barash PG,Cullen

BF, Stoelting RK, Cahalan MK, Stock MC.Clinical Anesthesia,6th Edition,2009(23) .

11. Darlong V, Shende D, Singh M, Garg R, Pandey R, Punj J. Low- versus high-dose combination of midazolam-ketamine for oral premedication in children for ophthalmologic surgeries. Singapore medical journal. 2011;52(7):512-6. PMid:21808963

12. Horiuchi T, Kawaguchi M, Kurehara K, Kawaraguchi Y, Sasaoka N, Furuya H. Evaluation of relatively low dose of oral transmucosal ketamine premedication in children: a comparison with oral midazolam. Paediatric anaesthesia. 2005;15(8):643-7. https://doi.org/10.1111/j.1460-9592.2004.01513.x PMid:16029398