

Comparison of oral Midazolam with Ketamine versus oral Midazolam as a premedication in children

Sonal S. Khatavkar¹, Trupti P. Deshpande², Sameer Zayed³, Manoj Zingraji Misal^{4,*}, Pranita Kate⁵

¹Associate Professor, ²Assistant Professor, ³Senior Registrar, ^{4,5}Resident, Dept. of Anesthesia, Dr. D.Y. Patil Medical College & Hospital, Pune

***Corresponding Author:**

Email: doc.misalmanoj@gmail.com

Abstract

In paediatric patients midazolam and ketamine are commonly used as premedicants. This prospective randomized study was conducted to compare the efficacy of oral midazolam versus combination of midazolam and ketamine as premedicants in paediatric age group in 60 children. 30 in each group, aged 2-6 years, undergoing major and intermediate surgery were included in the study. Forty five (45) minutes prior to surgery group A received oral midazolam (0.5mg/kg) and group B received oral midazolam 0.25mg/kg and oral ketamine (3mg/kg) in recovery room.

The observations included onset of sedation, reaction to emotions, sedation score, response to intravenous cannulation and face mask acceptance. The data was analysed using chi-square test and unpaired t-test. The results observed in midazolam and ketamine group were statistically significant than in midazolam group alone. Intraoperatively, haemodynamic parameters were comparable in both the groups. There was significant post-operative analgesia in midazolam and ketamine (M+K) group.

Thus we conclude oral premedication allays anxiety significantly and results in a calm and co-operative patient. Midazolam as well as midazolam and ketamine (M+K) offers sedation of superior quality. No significant side effects were observed in both the groups.

Aims: Midazolam and Ketamine are used in children commonly for premedication. Aim of our study was to find premedicant effects of oral midazolam and midazolam with ketamine in children and any advantages of combination of oral midazolam with ketamine.

Methods and Material: Sixty children of age group 2–6 years of A.S.A grade 1 and 2 were selected.

Group A-midazolam [0.5mg/kg]

Group B- midazolam [0.25 mg/kg + ketamine 3mg/kg]

Both groups received drug orally 45min before surgery in recovery room with monitored anesthesia care. Onset of sedation, reaction to emotions, score of sedation, mask acceptance and intravenous cannula acceptance were studied.

Statistical analysis used: Chi square test and Unpaired t-test.

Results: Sedation score, anxiolysis, attitude, reaction to Intravenous cannulation, face mask acceptance, reaction to emotions were studied in both groups. Midazolam and ketamine group results were significant than midazolam group. Intra operatively in both groups pulse rate, oxygen saturation, respiratory rate had no significant difference also post operatively no significant difference was observed in above parameters, post-operative analgesia was significantly better in midazolam with ketamine group.

Conclusions: Oral premedication provides good pre-operative condition in terms of co-operation and anxiety. Midazolam as well as combination of Midazolam with ketamine offers sedation of superior quality. No significant side-effects were observed in both groups.

Key-words: Pediatric anesthesia, Oral midazolam, Ketamine.

Key Messages: Oral premedication is easily acceptable by children and allows predictable sedation in children. Midazolam with ketamine offers superior quality of sedation and separation reaction as compared to midazolam.

Access this article online	
Quick Response Code:	Website: www.innovativepublication.com
	DOI: 10.5958/2394-2797.2016.00010.1

Introduction

Induction of anesthesia in paediatric age group is a challenging job. Fear of alien environment, separation anxiety and fear for injections and needles can result in an agitated and crying patient which can add to the

difficulty in inducing anesthesia. It becomes a skill full speciality as fear of operation theatre and injection can produce traumatic experience in tender minds of young children⁽¹⁾.

70% of children before anesthesia show lot of stress and anxiety⁽²⁾. Preoperative anxiety can have negative physiological and psychological effects on child⁽³⁾. Anxious child is difficult to induce thus various interventions are used to overcome this difficulty and hence premedication has become popular.

Different kind of medical products have been used for premedication like benzodiazepines, ketamine, opioids etc.⁽⁴⁾.

Key features of ideal premedication are ease of administration, quick onset and smooth recovery and minimal side effects⁽⁵⁾.

Oral route for premedication is preferable as it can be easily administered and accepted by children without much hesitation. Easy acceptance, rapid onset, short duration of action and lack of significant side effects are desirable qualities in a good pre-medication⁽⁶⁾. Midazolam and ketamine are commonly used by oral, nasal and rectal routes. Oral and rectal application of midazolam and ketamine are widely used in this age group⁽⁷⁾. Both the drugs result in slow onset time of 15-30 minutes and produce a calm child for anaesthesia⁽⁸⁾.

We conducted a randomized double blind study to evaluate efficacy and safety of 2 regimes by using oral midazolam (0.5mg/kg) versus oral midazolam (0.25mg/kg) + ketamine (3mg/kg) as premedication. Warner, cabaret and velling have reported that a combination of midazolam plus ketamine provides better premedication rather than midazolam alone⁽⁹⁾. This was a randomized double blind study which was done for observation of sedation, response to intravenous cannulation, facemask acceptance,

separation from parents, palatability and any side effects.

Subjects and Methods

After ethical committee clearance sixty children of either sex, age between 2-6 years, undergoing paediatric general surgery, orthopaedic, ophthalmic, plastic surgery lasting for 30-120 minutes with ASA grade I & II were included in the study. ASA III and children with URTI, metabolic disorders and systemic illness were excluded from our study. A randomized controlled study of children were assigned to two groups of 30 each.

Group (A) oral Midazolam [0.5mg/kg]. Group (B) oral Midazolam [0.25mg/kg] with Ketamine [3mg/kg]. All patients were examined and written informed consent was taken. Drugs of premedication was given 45 minutes before surgery.

All children were assessed continuously for PR, RR, B.P. and SP02 at 0, 10, 20, 30, 40 min and scoring was done at the end of 40 min.

Sedation Scale

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

The child was observed preoperatively for 30 minutes, intra-operatively and postoperatively. The anesthesiologist involved in preoperative assessment of patient was unaware of type of pre-medicant. Observer and investigators (staff nurse and resident doctor) were unaware of agent given, they only observed and assessed patients. Baseline pulse rate, oxygen saturation was noted preoperatively and after premedication.

All monitors attached in operation theatre. Inj.glycopyrrolate 0.04mg/kg, inj.ondansetron 0.1mg/kg and inj.fortwin 0.03mg/kg was given.

General anesthesia was induced with sevoflurane 6% and air & oxygen (60:40), trachea was intubated by appropriate size endotracheal tube after intravenous (IV) Atracurium 0.7mg/kg. Intra-operative sedation was not given and analgesic was provided by caudal block with inj. Bupivacaine 0.25% 1ml/kg for intra operative anesthesia. Reversal and extubation was uneventfull in all patients. Sedation score was estimated by single observer according to sedation scale.

Parameters observed were:

- Level of sedation and score of sedation.
- Emotional reaction: crying, apprehension and calm.
- Separation reaction: crying, apprehension and good.
- Acceptance reaction to face mask.
- Reaction to intravenous cannulation.
- Side-effects and recovery time.

Sedation, anxiolysis, co-operation were recorded immediately after giving oral drug at following intervals: 5min, 10min, 20min, 30 min, 40 min.

Heart-rate and oxygen saturation were monitored throughout the procedure.

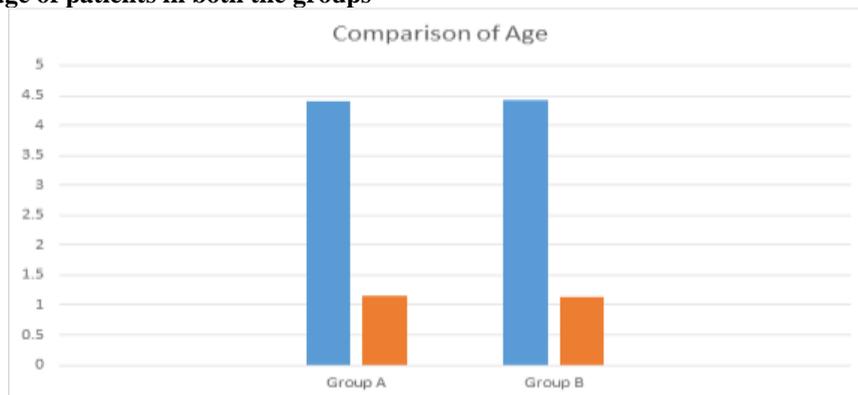
The statistical analysis by unpaired t-test and chi square test.

Results

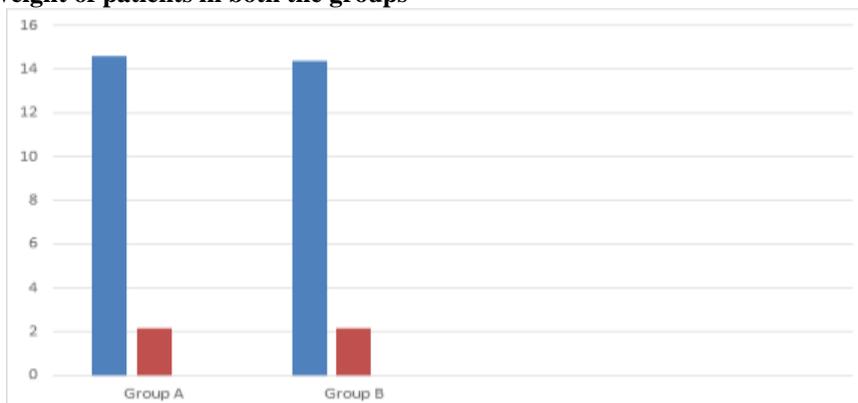
All children accepted the oral drug well without any vomiting. The drug was palatable as reported by older children (more than 3 years) as drug was mixed with rose syrup.

Sixty children were studied in two groups, Group-A (Midazolam) & Group-B (Midazolam + Ketamine). Study showed comparable results when age, gender weight and operative procedure time was taken in consideration. Statistically no significant difference was observed with respect to age, sex, weight.

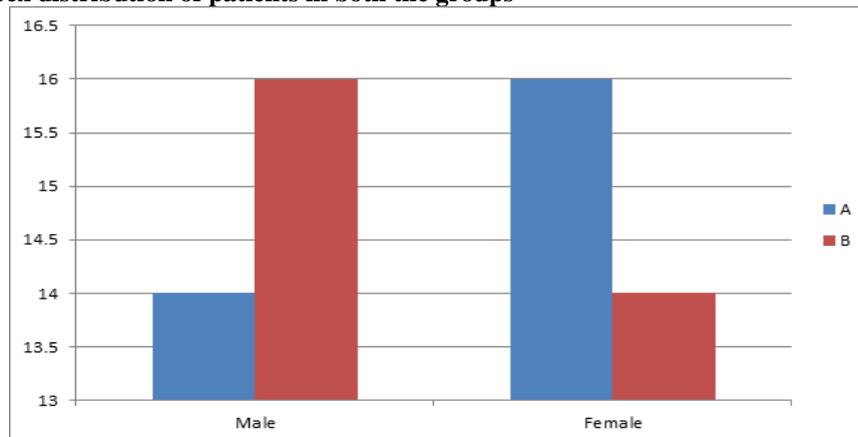
Comparison of age of patients in both the groups



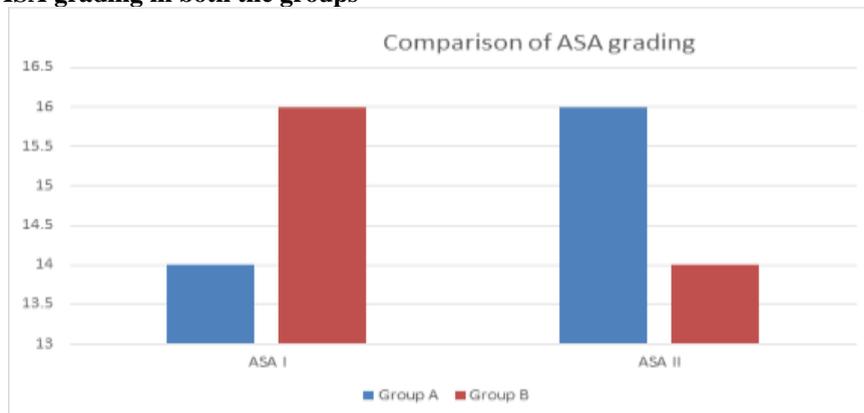
Comparison of weight of patients in both the groups



Comparison of Sex distribution of patients in both the groups



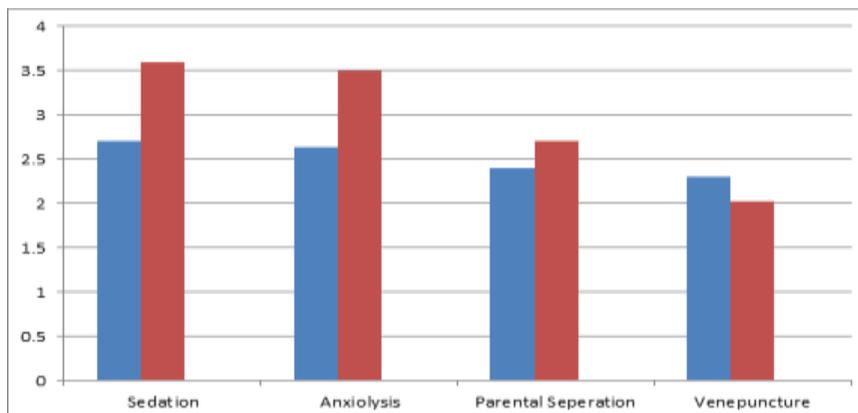
Comparison of ASA grading in both the groups



Sedation Score

Score	Group A		Group B		P Value
	Mean	SD	Mean	SD	
Sedation	2.7	0.47	3.6	0.56	<0.0001
Anxiolysis	2.63	0.49	3.1	0.4	<0.001
Parental Separation	2.43	0.5	2.77	0.43	<0.05
Vene Puncture	2.33	0.48	2.57	0.5	>0.05
Total	10.1	1.18	12.03	1.35	<0.0001

Comparison of sedation, anxiolysis, parental separation and vene puncture scores in patients of both the groups



Graph 2: Group wise distribution of Oxygen saturation & Pulse rate at various intervals

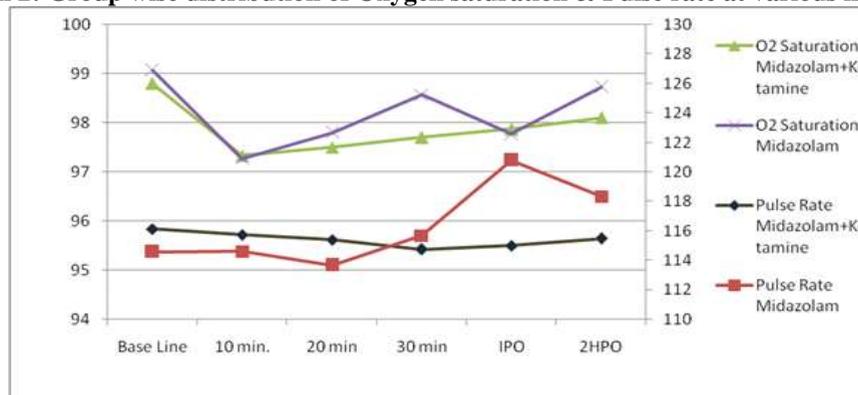


Table 5: Summary of results

Observation	Group (A) Midazolam	Group (B) Midazolam + Ketamine	p values	Statistical data
Onset time of sedation	22.35(+/- 3.35min)	22.05(+/-3.15 min)		difference is NOT significant
Post-operative recovery time	20(+/-8.17min)	25.3(+/- 6.15min)		difference is significant
Side effects secretions	3.70%	5%	0.381	difference is NOT significant
Nausea/vomiting	0%	6.70%	0.150	difference is NOT significant
Post op analgesic requirement	60%	33.30%	0.038	difference is significant

Preoperative acceptance was good, no spilling was observed.

Post-operative results summarized in table 5 were analyzed by student's unpaired t-test.

Sedation score, anxiolysis score, pre-operative and postoperative side effects were analyzed with chi square test.

Mean sedation score was 2.7 +/- 0.47 in M group while it was 3.6 +/- 0.56 in B group, which was significant statistically.

Anxiolysis score as shown in table and graph was 2.63 +/- 0.49 in A group which it was 3.1 +/- 0.4 in B group. Hence it was observed that combination of two drugs produce significant anxiolysis than alone.

Parental separation score was 2.77 +/- 0.43 in A group and 2.77 +/- in B group which was statistically significant.

Score of response to venepuncture was 2.33 +/- 0.48 in A group while it was 2.57 +/- 0.5 in B group which shows better result but not significant statistically.

Total score of all 4 score in M- 10.1 +/- 1.18 which is comparable to combination of M+K is 12.03 +/- 1.35 which is highly significant.

Intraoperative vitals i.e. PR and SPO2 were compared and no significant difference was noted.

Side effects like secretion, nausea and vomiting were minimal. Nystagmus was observed in 3.41 patient. Post-operative analgesia requirement was 60% in group A, while it was 33.30 in M+K which was (p - 0.038) and statistically significant.

Discussion

Preoperative period is a stressful event for the majority of individuals under-going surgery. Thus anxiolysis is primary aim in paediatric surgical procedures.

It has been reported co-relation between pulse rate, blood pressure and behavioral rating of anxiety⁽³⁾. Thus to allay anxiety various premedication are given in preoperative period.

Oral premedication are easy to administer and easily acceptable by children. Oral premedication doesn't increase risk of aspiration pneumonia⁽¹⁰⁾.

Oral premedication with many drugs have been tried but midazolam orally is most popular.

Oral ketamine added to Midazolam helps to attenuate action.

Premedication was given 45 minutes before surgery and all vitals like PR, BP, SPO2, RR were observed.

Onset of time of sedation was 22 +/- 3.35 min in A group while it was 21 +/- 2.50 min in B group. Peak action came after 40 min thus all scores were noted after 40 min.

Four variables sedation, anxiolysis, parental separation and venepuncture were compared in two groups.

Before premedication all patient's score was ¼. After 40 min in A group mean sedation score was 2.7 +/- 0.47 and 3.6 +/- 0.56 in B group, difference was statistically significant.

Darlong et al in 2004 compared combination of oral midazolam and oral ketamine and oral ketamine and found early onset of sedation after 20 min which supports with our result⁽¹¹⁾.

Anxiolysis score was comparable.

Separation score matches with Ghai et al 2005 - M+K where patients were more awake, calm, quiet and easily separable⁽¹²⁾.

Venepuncture score Funk and Jacob et al 2000 reported combination of M+K provide significantly better effect to venepuncture⁽¹³⁾.

All vitals were comparable in both groups. Minimal secretions, nausea and vomiting like symptoms were seen. Nystagmus were seen in 3-4% of patients.

Separation of children from parents peacefully is main concerns, thus various premedication are in research. Quality of ideal premedication is easy administration, rapid onset and smooth recovery.

Premedication should be performed in all pediatric patients, in order to decrease preoperative anxiety allow

smooth induction and prevent postoperative psychological and behavioral changes.^(11,12)

Midazolam and Ketamine also possess ideal criteria for premedication such as rapid onset, good anxiolysis, sedation, rapid recovery.

Oral route is easiest mode for premedication, onset is slow and requires 30-40 minutes for sedation and according to Mc millan dose is 0.5mg-0.75mg for oral route⁽¹⁴⁾.

Combination of midazolam and ketamine given orally or rectally offer results better than either drug used alone⁽⁹⁾.

In our study onset of sedation started in A group by 22.35(+/-3.35mins), while it started in 22.05(+/-3.15mins) in B group. Difference between both groups was not significant. Peak action came after 30 minutes, so all observations at 40 minutes are tabulated.

Sedation score 3 & 4 in Group (A) was up to 80%, while in Group B it was 94% thus showing significant statistical difference(p<0.05). These results were similar to those noted by Diaz et al⁽¹⁵⁾.

Attitude, facemask acceptance and Intravenous cannulation were excellent in Group (B) as compared to Group (A). These observations were also noted by Diaz et al⁽¹⁵⁾.

Separation reaction was good in 26.67% in group (A), while it was 56.70% in group (B). These observations were similar to results observed by Ljungman et al⁽¹⁶⁾.

Intra operative oxygen saturation, pulse rate and respiratory rate had no significant difference in Group (A) and Group (B) as per study by Gulstien et al⁽¹⁷⁾ and Wilton et al.

In one study in 2005 effectiveness of oral midazolam (0.5 mg/kg) and oral ketamine (5mg/kg) on sedation, reaction to separation of children from parents and acceptance for mask ventilation by children was better in midazolam with ketamine group as compared to midazolam group. In Darlong et al. study efficacy of oral midazolam (0.25 mg/kg), oral ketamine (3 mg/kg), and combination of them were studied on sedation degree, children behavior type, and separation of children from parents peacefully. In combination group, desirable sedation scores after 10 and 20 min were significantly specific than other group. Children separation and behavior type score was not significant among groups. This finding of Darlong et al. study did not co-relate with our study. Oral midazolam, ketamine, and midazolam with ketamine offered sedation and effect compared at 20, 30 minutes which showed that combination of midazolam with ketamine provided superior quality than individual midazolam and ketamine, which was also observed in study by Banerjee et al⁽¹⁸⁾. In this study, Group M received 0.5 mg/kg oral midazolam and Group M+K received 0.25 mg/kg oral midazolam with 3 mg/kg oral ketamine. Both groups provided equally effective anxiolytics and separation characteristics. However, the combination

group provided more children in an quiet, calm, and awake state who could be separated easily from parents.⁽⁷⁾ before premedication. Nystagmus and other side effects like vomiting, increased salivation were not seen in both groups. Post operatively side-effects were minimal as observed in study done by none of the patients had any emergence reaction in our study done by Agrawal Nidhi et al⁽¹⁹⁾.

Sample size was limited thus complication observed were less. Forceful separation from parents prior to anesthesia with stormy induction with painful injection can be overcome by orally acceptable premedication in addition to psychological preparation of children.

Conclusions

Oral premedication allows rapid and predictable sedation in children. Midazolam as well as combination of Midazolam with ketamine give good level of sedation and comfort. But quality of sedation, analgesia and comfort are significantly better in midazolam with ketamine group. No significant side effects were observed in both groups.

References

1. Kain ZN, Mayes LC, Caramico LA, Hofstadter. Distress during induction of Anaesthesia and postoperative behavioral outcome. *Anaesth. Analg* 1999;88(5):1042-47.
2. Beeby DG, Hughes JO. Behaviour of un-sedated children in the anesthetic room. *Br J Anaesth.* 1980 Mar;52(3):279-81.
3. Williams JGL, Jones JR. Psycho-physiological responses to anesthesia and operation. *JAMA* 1968;203:127-129.
4. Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: a comparison of four routes of administration. *Paediatr Anaesth.* 2002 Oct;12(8):685-9.
5. Lökken P, Bakstad OJ, Fønnelep E, Skogedal N, Hellsten K, Bjerkelund CE, Storhaug K, Oye I. Conscious sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. *Scand J Dent Res.* 1994 Oct;102(5):274-80.
6. Sekerci C, Dönmez A, Ateş Y, Okten F. Oral ketamine premedication in children (placebo controlled double-blind study). *Eur J Anaesthesiol.* 1996 Nov;13(6):606-11.
7. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. ketamine and norketamine plasma concentrations after i.v. nasal and rectal and rectal administration in children. *Br J Anaesth.* 1996 Aug;77(2):203-7.
8. Malinovsky JM, Lejus C, Servin F, Lepage JY, Le Normand Y, Testa S, Cozain A, Pinaud M. Plasma concentrations of midazolam after i.v., nasal or rectal administration in children. *Br J Anaesth.* 1993 Jun;70(6):617-20.
9. Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric oral premedicant. *Paediatr Anaesth* 1995;5:293-295.
10. Riva J, Lejbusiewicz G, Papa M, et al. Oral premedication with midazolam in paediatric anaesthesia. Effects on sedation and gastric contents. *Paediatr Anaesth* 1997;7:191-196.
11. Darlong V, Shende D, Subramanyam MS, Sunder R, Naik A. Oral Ketamine or midazolam or low dose

- combination for premedication in children. *Anaesth Intensive Care* 2004;32:246-9 .
12. Ghai B, Grandhe RP, Kumar A, Chari P. Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication . *Paediatr Anaesth* 2005;15:554-9.
 13. Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic medication for children: Double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. *Br J Anaesth* 2000;84:335-40.
 14. McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. *Can J Anaesth.* 1992 Jul;39(6):545-50.
 15. Diaz JH. Intranasal Ketamine preinduction of paediatric outpatients. *Paediatr Anaesth.* 1997;7(4):273-8.
 16. Ljungman G, Kreuger A, Andréasson S, Gordh T, Sörensen S. Midazolam nasal spray reduces procedural anxiety in children. *Pediatrics.* 2000 Jan;105(1 Pt 1):73-8.
 17. Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanesthetic medication in children. *Anesthesiology.* 1992 Jan;76(1):28-33.
 18. Banerjee B, Bose A, Pahari S, Dan AK. A comparative study of paediatric oral premedication: midazolam, ketamine and low dose combination of midazolam and ketamine. *J Indian Med Assoc.*2011;109:386-8.
 19. Nidhi Agrawal, Dua C.K. and Arya C.P. Clinical evaluation of oral Ketamine and oral Midazolam for premedication in paediatric surgical outpatients. *Journal of Anesthesia and Clinical Pharmacology* 2000;16(1)23-28.