Original Research Article

A comparative study between midazolam, ketamine and combination of both as a premedication in pediatric surgeries

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Abstract

Background: Midazolam andketamine are widely used oral pre anesthetic medication. This study was planned to compare midazolam and ketamine alone with combination of midazolam and ketamine as oral pre-anesthetic medication in children (2-10 Years) with respect to assess the levels of sedation, anxyolysis, behavior at parental separation and side effects. **Methods:** This prospective randomized study was conducted among childrenadmitted in various departments of Meenakshi Medical College Hospital and Research Institute, Kanchipuram during month of June 2014 to April2015. 150 patients between age 2-10 years, who belongs to ASA grade I and IIwere included. Patients with history of prematurity, developmental delay, increased intracranial pressure and increased intra ocular pressure were excluded. Children were randomized and divided into three groups and group A-midazolam (0.5mg/kg), group B -ketamine (6mg/kg) and group C - midazolam (0.5mg/kg) and ketamine (3mg/kg). The results were assessed in terms of levels of sedation, anxyolysis, behavior at parental separation and side effects. **Results:** Acceptable sedation score, anxyolysis score and behavior at parental separation score following midazolam use was 58%, 72% and 72%, respectively.Following ketamine use, 52% of children had acceptable sedation score, anxyolysis score and behavior at parental separation score. Combination of midazolam and ketamine use reported acceptable sedation score, anxyolysis score and parental separation score was reported as 68%, 82% and 82%, respectively. There was no significant difference in sedation in the 3 groups ($p>0.05$). Also, both anxiolysis and behavior at parental separation scores were significantly better in midazolam alone or in the combination group. **Conclusion:** Even though, the combination did not produce statistically better sedation, anxiolysis or behavior at parental separation than midazolam, the combination did produce distinctly better premedication characteristics than either midazolam or ketamine alone when given through oral route.

Key Words: Midazolam, ketamine, pre anesthetic medication, children.

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INTRODUCTION

Anesthesia and surgery are stress inducing factors not only in adults but also in children. Among children, the reasons for stress include separation of child from parents, strange surroundings, painful and frightening procedure[1]. Also, extreme preoperative anxiety may prolong the induction of anesthesia may lead to new onset postoperative negative psychological effects such as nightmares, eating disturbance and enuresis[2,3]. The effective solution for these anesthesia and surgery related stress and anxiety is use of effective pre-anesthetic medication for children undergoing surgery. If the pre medication administered in proper time and dose, it will reduce the apprehension regarding surgery, reduce the

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trauma of separation and facilitate induction of general anesthesia without prolonging the post anesthetic recovery period[4]. A variety of pre-medications administered via various routes have been introduced. The ideal premedication for procedures should be easy to administer, have a rapid and predictable onsetand produce both amnesia and analgesia without significantly affecting cardiovascular and respiratory functions. Route of administration is another important factor for those patients who do not already have established venous access since starting intravenous access to administer sedation may be as traumatic, as the procedure itself. Therefore use of orally active agent is highly encouraged for pre-anesthetic medication[5].Recent reports suggest that both oral midazolam[4] and oral ketamine[6] may fulfill many of these criteria. Midazolam, a benzodiazepine has been found to be better than most of the other commonly used pre mendicants[7,8] It exerts a reliable anxiolytic effect with mild to moderate sedation. It produces minimal cardiovascular and respiration effect and brings about anterograde amnesia which helps to reduce the psychological trauma of anesthesia and surgery. Ketamine has well characterized sedative, anesthetic and analgesic properties. It also has advantages over other sedative anesthetic drugs because it stimulates the cardiovascular system and cause minimum respiratory depression[9]. Studies have shown that a combination of midazolam plus ketamine provides better premedication than midazolam or ketamine alone[10,11]. Thus, this study was planned to compare three groups, midazolam and ketamine alone with combination of midazolam and ketamine as oral pre-anesthetic medication in children (2-10 Years) with respect to assess the levels of sedation, anxyolysis, behavior at parental separation and side effects.

MATERIALS AND METHODS

This prospective randomized, double blinded study was conducted among children admitted in department of general surgery, ENT and Orthopedics in Meenakshi Medical College Hospital and Research Institute, Kanchipuram duringmonth ofJune 2014 to April 2015, for elective surgical procedures. 150 patients between age 2-10 years, who belongs to American Society of Anesthesiologists (ASA) grade I and II with expected surgical procedure time between 20 minutes to 2 hours and fit for surgical procedure were included in the study. Patients with history of prematurity, developmental delay, increased intracranial pressure and increased intra ocular pressure were excluded from the study. The study was approved by the ethical committee of this institution. Informed consent was obtained from the child's parents, before stating the study. The study patients were randomized and divided into three groups with 50 participants in each group. Patients of group A received midazolam 0.5mg/kg orally, group B received ketamine 6mg/kg orally andgroup C received midazolam 0.5 mg/kg and ketamine 3 mg/kg orally. In the preoperative room, baseline recording of heart rate, respiratory rate, systolic blood pressure and activity of child were noted. The premedication was prepared using orange syrup and administered to the patients at the dose of 0.5 ml/kg upto a maximum of 10ml. This was administered to children 30 minutes before induction. Those children who refused to take the whole dose were excluded from the study. The child's condition which includes quality of sedation, anxiolysis, behavior at parental separation and side effects were evaluated just before induction with a four point scoring scale[12] (Table 1) by the anesthetist, after 30 minutes of administering pre-anesthetic medication. The patient and all observers including anesthesiologists, surgeons and nurses were blinded about the contents of the oral premedication used. The results were analyzed using SPSS16 and chi square test was used to compare the different groups. Also, scores III and IV were considered as acceptable scores and scores I and II were considered as unacceptable scores.

OBSERVATIONS AND RESULTS

Table 1: Scoring scale[12]

Score	Sedation score	Anxiolysis score	Parentaral separation score
I	Alert	Panic	combative, clinging to parents
II	Awake	Moaning	Anxious, consolable
III	Drowsy	Composed	Calm
IV	Asleep	Asleep	Asleep

In group A there were 20 (40%) children in the age group less than 5 years, 17(34%) children in the age group of 5 – 7 years, 13(26%) children in the age group of 8 – 10 years. In group B there were 21(42%) children in the age group less than 5 years, 16(32%) children in the age group of 5 – 7 years, 13(26%) children in the age group of 8 – 10 years. In group C there were 14(28%) children in the age group less than 5 years, 17(34%) children in the age group of 5 – 7 years, 19(38%) children in the age group of 8 – 10 years. The mean age of children in group A, group B and group C were 5.7 ± 2.6 years, 5.4 ± 2.5 and 6.2 ± 2.6, respectively and majority of the participants were male (74%). The mean weight of children in group A, group B and group C were 18.22 + 6.3 kilograms (kgs), 19.25 + 5.69 kgs and 19.22 + 5.75 kgs, respectively. Also majority of the children (131) were belongs to ASA group I and 19 belongs to ASA group II. (Table 2)

Table 2: Characteristics of the participants

Variables	Group A N= 50 (%)	Group B N= 50 (%)	Group C N= 50 (%)
Age groups			
2 – 4 years	20 (40%)	21 (42%)	14 (28%)
5 – 7 years	17 (34%)	16 (32%)	17 (34%)
8 – 10 years	13 (26%)	13 (26%)	19 (38%)
Age: Mean±SD	5.7±2.6 years	5.4±2.5 years	6.2±2.6 years
Gender			
Male	39 (78%)	37 (74%)	35 (70%)
Female	11 (22%)	13 (26%)	15 (30%)
Mean weight			
Mean ± SD	18.22 ± 6.3 Kgs	19.92 ± 5.69 Kgs	19.22 ± 5.75 Kgs
ASA grade			
Grade I	42 (84%)	44 (88%)	45 (90%)
Grade II	8 (16%)	6 (12%)	5 (10%)
Surgical procedures			
Tonsillectomy	9 (18%)	8 (16%)	6 (12%)
Circumcision	8 (16%)	7 (14%)	6 (12%)
Orthopedic cases	6 (12%)	5 (10%)	11 (22%)
Herniotomy	4 (8%)	10 (20%)	4 (8%)
Tongue tie release	4 (8%)	6 (12%)	1 (2%)
Other ENT procedures	10 (20%)	8 (16%)	5 (10%)
Others	9(18%)	6 (12%)	17 (34%)

Comparison of sedation scores between the groups: In group A, child with sedation scores I to IV were 18%, 24%, 46% and 12% respectively. In group B, Child with sedation scores I to IV were 12%, 36%, 36% and 16% respectively. In group C, child with sedation scores I to IV were 6%, 26%, 48% and 20% respectively. Acceptable sedation scores were reported among 58%, 52% and 68% in group A, group B and group C, respectively and unacceptable sedation scores were reported among 42%, 24% and 32% in group A, group B and group C, respectively. However, on comparing the sedation scores, there is no significant difference between the three groups (p>0.05). (Table 3)

Table 3: Comparison of sedation scores between the groups

Sedation score	Group A N= 50 (%)	Group B N= 50 (%)	Group C N= 50 (%)
I (Alert)	9 (18%)	6 (12%)	3 (6%)
II (Awake)	12 (24%)	18 (36%)	13 (26%)
III (Drowsy)	23 (46%)	18 (36%)	24 (48%)
IV (Asleep)	6 (12%)	8 (16%)	10 (20%)
Acceptable	29 (58%)	26 (52%)	34 (68%)
Unacceptable	21 (42%)	24 (48%)	16 (32%)

X^2=2.71, p=0.26 (p>0.05), Not Significant

Comparison of anxyolysis between the groups: In group A, child with anxyolysis scores I to IV were 12%, 16%, 62% and 10% respectively. In group B, Child with anxyolysis scores I to IV were 20%, 28%, 40% and 12% respectively. In group C, child with anxyolysis scores I to IV were 2%, 16%, 60% and 22% respectively. Acceptable anxyolysis scores were reported among 72%, 52% and 82% in group A, group B and group C, respectively and unacceptable anxyolysis scores were reported among 28%, 48% and 18% in group A, group B and group C, respectively. Also, the difference in anxyolysis scores between three groups was found to be statistically significant (p<0.01) and on comparing anxyolysis scores of group B and group C alone, the difference was found to be statistically significant (p<0.01) whereas on comparing anxyolysis scores of group A and group C, the different was found to be statistically not significant (P=0.23) (Table 4).

Table 4: Comparison of anxyolysis between the groups

Anxiolysis Score	Group A N= 50 (%)	Group B N= 50 (%)	Group C N= 50 (%)
I (Panicky)	6 (12%)	10 (20%)	1 (2%)
II (Moaning)	8 (16%)	14 (28%)	8 (16%)
III (Composed)	31 (62%)	20 (40%)	30 (60%)
IV (Asleep)	5 (10%)	6 (12%)	11 (22%)
Acceptable	36 (72%)	26 (52%)	41 (82%)
Unacceptable	14 (28%)	24 (48%)	9 (18%)

X^2=10.8, p<0.01, Significant

Comparison of behavior at parental separation between the groups: In group A, child with parental separation scores I to IV were 8%, 20%, 68% and 4% respectively. In group B, Child with parental separation scores I to IV were 24%, 24%, 40% and 12% respectively. In group C, child with parental separation scores I to IV were 4%, 16%, 62% and 18% respectively. Acceptable parental separation scores were reported among 72%, 52% and 82% in group A, group B and group C, respectively and unacceptable parental separation scores were reported among 28%, 48% and 18% in group A, group B and group C, respectively. Also, the difference in behavior at parental separation score was found to be statistically significant between the three groups (p<0.01) and on comparing behavior at parental separation score of group B and group C alone, the difference was found to be statistically significant (p<0.01) whereas on comparing behavior at parental separation score of group A and group C, the different was found to be statistically not significant (P=0.43). (Table 5)

Table 5: Comparison of behavior at parental separation between the groups

Parental separation Score	Group A N= 50 (%)	Group B N= 50 (%)	Group C N= 50 (%)
I (Combative clinging)	4 (8%)	12 (24%)	2 (4%)
II (Anxious consolable)	10 (20%)	12 (24%)	8 (16%)
III (Calm)	34 (68%)	20 (40%)	31 (62%)
IV (Asleep)	2 (4%)	6 (12%)	9 (18%)
Acceptable	36 (72%)	26 (52%)	41 (82%)
Unacceptable	14 (28%)	24 (48%)	9 (18%)

X^2=10.2, p<0.01, Significant

Comparison of adverse events in the groups: Vomiting was reported among 6% children in Group B while it did not occur in either of other groups. Nystagmus was seen in 14% children in group B while 4% children each in the group A and group C. Group B reported more cases with of salivation (10%) followed by group C (6%) and group A (4%). Tachycardia occurred in 8% children in group C while group A reported 4% and group B reported 2%. Group A reported 2% children with bradycardia. Excitement was seen in 8% children in group B. Involuntary movements was observed in 4% children in group A and 2%children in group B and respiratory depression was noted in 2% of children in group A.(Figure 1)

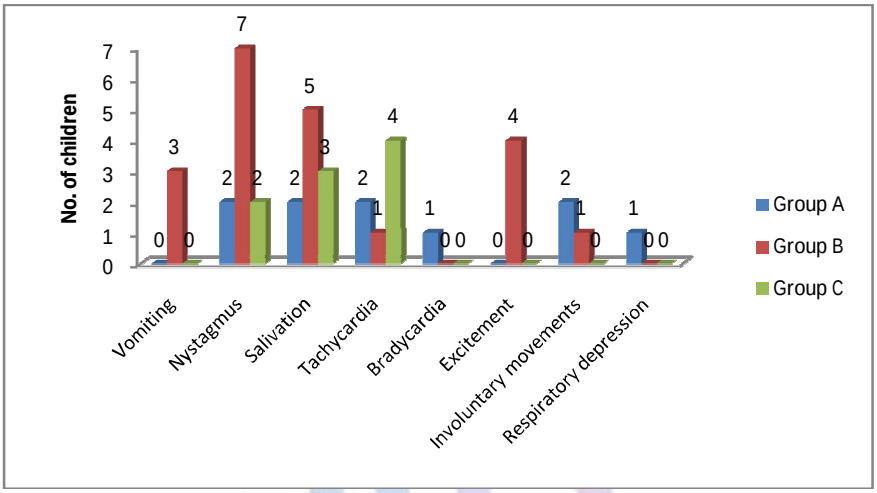

Figure 1: Comparison of adverse events in three groups

DISCUSSION

Still, there is no complete satisfactory way to pre-medicate children and ensure smooth induction of anesthesia. Among pre anesthetic medications oral midazolam and oral ketamine fulfill many of the characteristics of ideal premedications and thus these drugs were widely used. In this study, effect of midazolam, ketamine and combination of both were assessed, as taking it as group A, group B and group C, respectively. No placebo arm was included in this study since both midazolam and ketamine has been found to be superior to placebo for pre anesthetic sedation and anxiolysis and this was a comparative study to compare three different pre medications.

Midazolam alone: Midazolam exerts a reliable dose dependent anxiolytic effect without over sedation and produces minimal cardiovascular and respiratory side effects. Also, the anterograde amnesia produced by midazolam should help to reduce the psychological effects of anesthesia and surgery. Also, gastric absorption of midazolam is variable and results in large difference in the time it takes for different patients to become adequately sedated. The sedative effect of midazolam was found to be maximal at 30 minutes after oral administration in a study by Weldon BC *et al*[13]. McCluskey A *et al*[14], observed that oral midazolam 0.5mg/kg promotes smooth and satisfactory induction of anesthesia and reduces the psychological effects of hospitalization in children. McMillan Co *et al*[15], compared three different doses of oral midazolam (0.5, 0.75 and 1mg/kg) and found all three to be equally effective in providing sedation and anxiolysis in children at the time of separation from parents 30 minutes after premedication and also they reported doses greater than 0.5mg/kg were found to be associated with more side effects. Acceptable sedation score, anxyolysis score and behavior at parental separation score following midazolam use in this study was 58%, 72% and 72%, respectively. These reports were consistent with the study done by Funk W *et al*[10], which reported the acceptable sedation score, anxyolysis score and behavior at parental separation score as 58%, 75% and 68% respectively. Suranjit Debnath *et al*[16] reported sedation and anxyolysis score following midazolam use as 36% and 70%, respectively. P.J. Alderson *et al*[17] reported anxyolysis and parental separation score following midazolam use as 80% and 70% respectively.

Ketamine alone: Ketamine also has well characterized sedative, anesthetic and analgesic properties. It also has advantages over other sedative – anesthetic drugs, because it stimulates the cardiovascular system, is usually associated with an unobstructed airway and upper airway reflexes and cause minimum respiratory depression. Gustein B *et al*[6] sought to define a dose of oral ketamine

that would facilitate induction of anaesthesia without causing significant side effect. They compared oral ketamine in doses of 3 mg/kg and 6mg/kg with control. They found that 6mg/kg dose was well accepted, provided uniform, predictable sedation, allowed calm separation from parents and provided good induction conditions. The 3mg/kg dose did not always cause sedation and calm separation from parents. Neither does produced significant side effects. Following ketamine use, 52% of children had acceptable sedation score, anxyolysis score and behavior at parental separation score, in this study. Whereas, in the study done by Funk W *et al*[10] reported the acceptable sedation score, anxyolysis score and behavior at parental separation score as 67%, 54% and 50% respectively. Suranjit Debnath *et al*[16] reported sedation in 75% of children and Navdeep *et al*[18] reported acceptable sedation and parental separation score among children as 75% and 70% respectively. P.J.Alderson *et al*[17] reported acceptable anxyolysis and parental separation score as 65% in both categories.

Combination of midazolam and ketamine: The combination of ketamine and midazolam was described initially in 1992 by Beebe *et al*[19] for rectal premedication and in 1993 by Lin YC *et al*[11] for oral administration. In this study, combination of midazolam and ketamine use reported acceptable sedation score, anxyolysis score and parental separation score was reported as 68%, 82% and 82%, respectively. Beebe *et al*[19] reported parental separation was satisfactory with midazolam, ketamine and combination of both as 92%, 60% and 100% respectively but adverse effects were similar between groups. Lin YC *et al*[11] reported success rate of 80% at parental separation, when using combination of both ketamine and midazolam and also they reported that incidence of oral secretions and nystagmus was lesser as compared to using ketamine and midazolam, alone. Warner DL *et al*[20] found the combination of lesser dose of midazolam (0.4mg/kg) and ketamine (4 mg/kg) to be significantly more effective than little higher dose of midazolam (0.5mg/kg) or ketamine (6mg/kg). Funk W *et al*[10] reported success rate for anxiolysis and parental separation was found to be 90% and 92%, respectively and acceptable sedation score was reported among 70% of children only with for combination of midazolam (0.5mg/kg) and ketamine (3mg/kg). In this study, there was no significant difference in sedation in the 3 groups, 30 minutes after receiving the study agents ($p>0.05$). This corresponds to the results obtained by Pan AK *et al*[21] and Funk W *et al*[10] in their studies.Also, both anxiolysis and behavior at parental separation scores were significantly better in midazolam alone or in the combination group. These results were consistent with the results of Funk W *et al*[10] and Warner DL *et al*[20].

Adverse effects: In our study, nystagmus was reported among 14% children in ketamine group and 4% children in each with midazolam alone and combination group. However, none of the children seemed distressed by the nystagmus, which is comparable with the study done by Lin *et al*[11], reported an incidence of 13% for nystagmus with orally administered midazolam. Salivation was noted in 10% and 6% of children in ketamine group and combination group, respectively. In ketamine group, 2% of children had developed involuntary movements. These side effects were similar to the results obtained by Pan AK *et al*[21] and were not clinically significant.

CONCLUSION

The present study reported that oral premedication with midazolam 0.5mg/kg alone produces as good results as the combination of midazolam 0.5mg/kg and ketamine 3mg/kg in children. Although, midazolam 0.5mg/kg produced lesser sedation than the combination, it was no disadvantage as separation from parents was successful and coincided with good anxiolysis. The incidence of side effects was high with ketamine 6mg/kg, especially nystagmus. The combination increases the cost factor and also makes preparation of premedication more complex process. Even though, the combination did not produce statistically better sedation, anxiolysis or behavior at parental separation than midazolam, the combination did produce distinctly better premedication characteristics than either midazolam or ketamine alone when given through oral route.

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REFERENCES

1. Cravero Joseph P. and Jo Rice Linda. Paediatric anaesthesia. Chapter 44m In: Clinical anaesthesia, 4th edn., edt. Paul G. Barash, Bruce F. Cullen, Robert K. Stoelting, 2001. P 1195.
2. Patel D, Meakin G. Oral midazolam compared with diazepam, droperidol and trimeprazine as premedicants in children. Paediatr Anaesth, 1997; 7(45):278-93.
3. Kain Zeev N, Hofstadeter Maura B, Mayes Linda C, Krivutza Dawn M, Alexander Gerianne, Wang Shu-Ming. Midazolam, effects on amnesia and anxiety in children. Anaesthesiology, 2000; 93:676-84.
4. Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in paediatric out patients. Anaesthesiology, 1990; 73:831-4.

5. Tohias Joseph D, Seanphipps, Bruce Smith, Raymond K. Mulhern. Oral ketamine premedication to alleviate the distress of invasive procedures in paediatric oncology patients. Paediatrics, 1992 Oct; 90(4):537-41.
6. Gutstein Howard B, Johnson Kristen L, Heard Maurine B, Gregory George A.Oral ketamine pre-anesthetic medication in children. Anawsthesiology, 1992; 76:28-33.
7. Payne KA, Coetzee AR, Matheyse FJ. Midazolam and amnesia in paediatric premedication. Acta Anaesthesiol Belg. 1991; 42(2): 101-105.
8. Singh N, Pandey RK, Saksena AK, Jaiswal JN. A comparative evaluation of oral midazolam with other sedatives or premedication in paediatric dentistry. J Clinic Paediatr Dent, 2002 winter; 26(2): 161-4.
9. Tanaka M, Masayoshi S, Atsushi S, Toshiaki N. Re-evaluation of rectal ketamine pre-medication in children. Anaesthesiology, 2000; 93:1217-1224.
10. Funk W, Jacob 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 aAnaesth, 2000; 84(3): 335-40.
11. Lin YC, Moynihan RJ, Hackel A. A comparison of oral midazolam, oral ketamine andoral midazolam combined with ketamine as pre anaesthetic medication for paediatric outpatients. Anaesthesiology, 1993; 70:A1177
12. Gharde, P., S. Chauhan "Evaluation of efficacy of intranasal midazolam, ketamine and their mixture as premedication and its relation with bispectral index in children with tetralogy of fallot undergoing intra cardiac repair." Ann Card Anaesth 2006; 9(1): 25-30.
13. Weldon BC, Watcha MR, white PF. Oral midazolam children. Effect of time and adjunctive therapy. Anaesth Analg. 1992 jul: 75:1151-5
14. Mc Cluskey A, Meaken GH. Oral administration of midazolam as a premedicant for paediatric day-care anaesthesia. Anaesthesia, 1994; 49:782-5.
15. Mc Millan Co; Spahr – Schopfer IA, Sikieh N, Hartley E, Lerman J. pre-medication of children with oral midazolam. Can J Anaesth, 1992; 39(6):535-50.
16. Debnath S, Pande Y. A comparative study of oral premedication in children with ketamine and midazolam. Ind J Anaesth, 2003; 47(1): 45-47.
17. Alderson pJ, Lerman J A comparison of ketamine and midazolam as oral poremedicants for ambulatory anaesthesia in children. Anaesthesiology, 1992; 77:A42.
18. Sethi N, Dash, LK Madhusudanan TP, oral premedication for paediatric anaesthesia: a comparison of midazolam and ketamine. Ind J Anaesth, 2001; 45(3):215.
19. Beebe DS, Belani KG, Chang PN, Hesse PS, Suhuh JS, Lia JC. effectiveness of preoperative sedation with rectal midazolam, ketamine or their combination in young children. Anaesth Analg, 1992 Dec; 75(6): 880-4.
20. Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric oral premedicant. Paediatr Anesth, 1995; 295.
21. Pan AK, Rudra A, Ghoseh M, Biswas BN, Sen A, Kar A.Oral pre anaesthetic medication for children: A comparison of midazolam, ketamine and midazolam plus ketamine. J. Indian Assoc Pediatr Surg, 2001; 6:135-142.

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