ORIGINAL ARTICLE

NATIONAL JOURNAL NJMR MEDICAL RESEARCH

Comparative Evaluation of Midazolam and Ketamine with Midazolam Alone as Oral Premedication in Children

Shreya Modi[1*], Subhash Patel[2]

[1]Department of Anesthesia, Surat Municipal Institute of Medical Education & Research, Surat, India
[2]Department of Anesthesia, Surat Municipal Institute of Medical Education & Research, Surat, India

Keywords:
Midazolam,
Ketamine,
Pediatric Premedication

***Corresponding author**:
Dr. Shreya Modi
Department of Anesthesia,
Surat Municipal Institute of Medical Education & Research (SMIMER),
Surat, India - 3945010
E-mail: modishreya9@gmail.com

Date of Acceptance:
Jan 2, 2023

DOI:
10.55489/njmr.13012023938

ABSTRACT

Introduction: The main aims of preanesthetic medication in children are to reduce anxiety associated with the unfamiliar environment, facilitate the separation of the child from their parent and allow smooth induction of anesthesia. Both oral midazolam and oral ketamine fulfil many of these characteristics and are useful.

Method: As 48 patients of ASA grade 1 and 2, aged between 2-10 years undergoing elective surgery were allocated to one of two study groups using random numbers: Group 1 received midazolam 0.5mg/kg and group 2 received midazolam 0.25 mg/kg with ketamine 3 mg/kg. The medications were prepared and mixed with 25% dextrose up to a maximum volume of 0.3 ml/kg.

Result: Uniform and acceptable sedation scores were seen in both the groups, without any serious side effects. However, the combination offered significantly more children in an awake, calm and quiet state, who were easily separated from their parents. The induction scores, Recovery room characteristics and time to achieve satisfactory Aldrete score were also comparable between the two groups.

Conclusion: Oral midazolam alone and a combination of midazolam with ketamine provide equally effective anxiolysis and separation characteristics. However, the combination provided more Benefits.

INTRODUCTION

Preanesthetic medications in children are to reduce anxiety associated with the unfamiliar environment, facilitate the separation of the child from their parent (if required) and allow smooth induction of anesthesia. [1-4] Key features of good premedication are easy application, rapid onset, short duration of action and lack of significant side effects. Both oral midazolam and oral ketamine fulfill many of these characteristics and are useful for preanesthetic medication in children. [3,4]

Midazolam provides anxiolysis, while Ketamine has sedative and analgesic properties. Anxiolysis and sedation with oral midazolam are common practices in pediatric anesthesia. In contrast, oral ketamine was found to have adverse side effects, such as increased salivation, hallucinations, and dysphoria, when administered alone as premedication at a dose of 6 mg/kg. [5] Only 60% to 80% of the time oral midazolam produce good or excellent results. It has been discovered that using midazolam and ketamine together is more successful for sedating patients than using either drug alone, either rectally [6] or orally [7].

We aimed to identify potential synergism more precisely, if the combination of two "half" doses had a greater effect than the separate "full" doses, by selecting dosages for the combination that were half the amount used for the individual drugs. Lower doses of each agent in the

combination might have the advantages of improved reliability with faster recovery and fewer adverse effects compared to the single agents.

In a prospective, randomized, double-blind trial, we examined whether a low dose of oral ketamine combined with midazolam is more effective as a pre-medication than either oral midazolam or ketamine alone, given the limited data base and absence of investigations on potential psychotomimetic side effects. We decided to combine midazolam 0.5 mg/kg with ketamine 3 mg/kg to maintain the anxiolytic benefits of midazolam while also introducing the sedative and analgesic properties of ketamine without psychedelic side effects.

METHODOLOGY

After getting approval from Institutional Ethical Committee, written informed consent was obtained from all the parents.

Children under American Society of Anesthesiologists classification grade I or II and age between 2 years to 10 years posted for elective surgery of more than 30 min expected duration, were included in this study. Children with ASA III or higher category, severe dysfunction of the CNS or increased intracranial pressure, upper respiratory tract infection, malformations of the cardiovascular system, hyperthyroidism and long-term therapy with theophylline or hepatic enzyme-inducing drugs were excluded from this study.

Sample size [8] was calculated using open EPI software (power 95%, confidence interval 99%) and 48 Children were included in this study. Children were allocated to one of the two study groups using computer generated random numbers (MS-EXCEL). Group A(n=24): Patients received a combination of oral midazolam 0.25 mg/kg and oral ketamine 3 mg/kg and Group B(n=24): Patients received oral midazolam 0.5 mg/kg. The medications were prepared and mixed with 25% dextrose up to a maximum volume of 0.3 ml/kg and administered 30 minutes before surgery by an anesthesiologist in the recovery area. No children refused or vomited the solution. The children were observed by another anesthesiologist who was blinded to the medications given to children in the recovery area. Heart rate, blood pressure, respiratory rate, and arterial haemoglobin oxygen saturation (SpO2) were noted every 5 minutes.

Heart rate, blood pressure, respiratory rate, and arterial haemoglobin oxygen saturation (SpO2) were noted every 5 minutes. Sedation state was noted every 10 minutes for 30 minutes using the sedation score devised by Epstein and colleagues [9].

We also noted the ease and optimum time of separation of the child from the parents every 10 minutes. The time needed to achieve best parental separation and the score at that time were noted. The child's response to induction of general anesthesia was also evaluated (Table 1).

Table 1 Evaluation scale [9]

Sedation score
1. Awake active.
2. Awake, calm and active.
3. Drowsy, readily responds to verbal commands and/or gentle Stimuli.
4. Asleep, slowly responds to verbal commands and/or gentle Stimuli.
5. Asleep, not readily arousable.
Parental separation score
1. Excellent, patient unafraid, co-operative or asleep.
2. Good, slight fear and/or crying, but quiet with reassurance.
3. Fair, moderate fear and/or crying, not quiet with reassurance.
4. Poor, crying with need for restraint.
Response to induction score
1. Fear, crying with mask, needs restraint.
2. Moderate fear and crying with mask.
3. Slight fear with application of mask.
4. Unafraid or asleep, readily accepts mask.
Emergence score
1. Crying, thrashing, need for restraint.
2. Constant crying.
3. Occasional crying.
4. Quiet

Scoring of sedation, anxiolysis and behavior was performed immediately after the parents were out of sight, with no further transfer. In all children general anesthesia was induced using a standardized anesthesia technique and was maintained according to anesthetist's usual practice. Postanesthetic recovery was evaluated using a modified Aldrete score every 10 min. Sedation score was also recorded until the patient was discharged from the post-anesthesia care unit.

Any undesirable side-effects, which could be related to the premedicant drugs, such as nausea, vomiting, hallucination, abnormal behavior, excessive secretions, and sedation were also noted.

The rating scales were taken from papers published in journals looking into pediatric premedication. [10-13] For preoperative sedation and response to induction scores of 1 or 2 were considered "bad" and scores of 3 or 4 "good" or "acceptable". A score of 5 was considered a complication and not included as either a good or bad score. For evaluation of parental separation 1 or 2 were considered a "good" score and 3 or 4 "bad". Quantitative data from the two groups were compared using analysis of variance, while frequency data were compared using Chi-square. Statistical significance was considered to be a P value <0.05.

RESULT

A total of 48 analyzable subjects (24 in each group) were comparable in age, sex, weight, intervention, and duration of anesthesia. Demographic data and duration of surgical procedure were similar in the two groups (Table 2). The acceptance of the premedication drug was good in all Groups.

In the preoperative period, the SpO2, blood pressure, respiratory rate, and heart rate were within normal limits in all two groups and there was no significant difference between them. At 10 minutes after premedication, three (12.5%) of the patients in group A had a good sedation score but none in the other group (P=0.05). After 20 min, transfer was initiated. At 20 minutes 13(54.16%) of the children in the combination group had a good sedation score, five (20.83%) children in the M group. (P=0.008). At 30 minutes there were no significant differences in the sedation score or sedation level (Table 3). There were no significant differences in the parental separation scores in the two groups. It was possible to separate the children from their parents, much earlier in combination group A (mean time 19±8 min) compared to group B (28±7min). There were no significant differences in the mean response to induction score, emergence score. (Table 4)

Table 2: Demographic and distribution of surgical procedure data

Characteristics	Group A (n=24)	Group B (n=24)
Age (years)*	4.3±2.3	3.4±1.9
Sex (Male/female)	19/5	17/7
Weight(kg)*	13±3.8	11.7±4.1
Duration of surgery (min)*	40.1±12.9	55.7±52.1

*Values in mean±SD

Table 3: Percentage of "Good" sedation score at different time intervals

Time Interval (Minutes)	Group A (n=24) (%)	Group B (n=24) (%)	P value
10	3 (12.5)	0	0.05
20	13 (54.1)	5 (20.8)	0.003
30	17 (70.8)	16 (66.6)	NS

Table 4: Distribution of preoperative sedation (at 30 minutes), parental separation, induction score, emergence scores, time to reach Aldrete 10 & best parental separation time

Variables	Group A (n=24) (%)	Group B (n=24) (%)	P value
Preoperative sedation			
Good	19(79.1)	17(70.83)	(NS)
Bad	5(20.8)	7(29.16)	(NS)
Complication	0	0	
Parental separation			
Good	21(87.5)	20(83.33)	(NS)
Bad	3(12.5)	4(16.66)	(NS)
Response to induction			
Good	18(75)	16(66.66)	(NS)
Bad	6(25)	8(33.33)	(NS)
Emergence			
Good	20(83.33)	19(79.1)	(NS)
Bad	4(16.66)	5(20.8)	(NS)
Best parental separation time in minutes	19±8	28.4±7.4	<0.001 (significant)
Time to reach Aldrete in 10 min	22.7±5.6	36.3±11.7	<0.001 (significant)

Table 5: Comparison of side effects between groups

Side effect	Group A	Group B	P Value
PONV	6 (25%)	5 (20.8%)	<0.05
Excessive Salivation	0	0	NS
Irrelevant Talk	0	0	NS
Breath holding	0	0	NS

Recovery, as measured by the time to reach a modified Aldrete score of 10, was significantly faster in the combination group (22±5 min) compared to the midazolam (36±11 min). Success rates for anxiolysis and separation were greater than 90% with the combination, approximately 70% with midazolam alone. The success rate of sedation was low in all groups.

The incidence of PONV was similar in all the two groups (Table 5). Salivation was similar with all premedicant and was not of concern during induction of anesthesia. Oxygen saturation before induction was >= 97% in all children. Excessive sedation did not occur.

DISCUSSION

Induction of general anesthesia in children requires developmentally appropriate methods to minimize distress at induction and at the time of parental separation. Both psychological and pharmacological approaches may be helpful, but neither guarantees success. To minimize adverse psychological sequelae and allow a smoother induction of general anesthesia, a number of drugs have been tried as preanesthetic medication by various routes of administration with a variable success rate. [14]

Our study provides evidence that a combination of midazolam and ketamine results in better premedication than the individual drugs given alone, which suggests that these drugs may have synergistic effects.

Oral midazolam is the most widely used premedicant drug in children. It has many of the properties of an ideal premedicant, including a short elimination half-life. However it is not reliable, with reported success rates varying from 60 to 80%. [6]

With midazolam 0.5 mg /kg , investigators from the Hospital for Sick Children in Toronto found a comparably low success rate for sedation using the same score. However, anxiolysis (score comparable with our 'separation') in their study was very successful. In our study, in the patients who received oral midazolam, good preoperative sedation was seen in 68 % and unstressed separation of the children was possible in 80%. [15]

Oral ketamine has been used with good results and no significant change in hemodynamics, respiratory rate or side-effects. Oral ketamine was used in the 1970s by dentists to facilitate the treatment of mentally handicapped children. In 1982, Cetina[16] found that rectal or oral preanesthetic medication with ketamine 15 mg/kg combined with droperidol was superior to i.m. or i.v. premedication. At first glance,15 mg/kg seems to be a very high dose, but only 16% of oral ketamine is bioavailable because of high hepatic first pass metabolism. [17] Part of the clinical effects of oral ketamine are attributed to its metabolite norketamine which has approximately one-third the potency but reaches higher blood concentrations. Ketamine 6 mg/kg did not improve success but increased side effects such as nystagmus and vomiting.

The combination of ketamine and midazolam was described initially in 1992 by Beebe [6] and co-workers for rectal, and in 1993 by Lin, Moynihan and Hackel [14] for oral administration. The combination of midazolam and ketamine, used with the aim of increasing reliability and minimizing adverse effects, has been previously described. Lin and colleagues compared the effect of the combination of oral midazolam 0.5 mg/kg and oral ketamine 3 mg/kg with oral midazolam 0.5 mg/kg and oral ketamine 6 mg/kg alone in 45 patients. They observed that the combination produced sedation faster with less oral secretions, nystagmus and with a short recovery time. No postoperative complications, such as dreaming or nightmares, were observed. [14]

Warner's group also found that the combination of oral midazolam 0.4 mg/kg and oral ketamine 4 mg/kg was more effective than midazolam 0.5 mg/kg or ketamine 6 mg/kg alone. They noted no psychological disturbances in the immediate postoperative period but gave no details about the evaluation of this crucial issue. [7]

In our trial, the combination of oral midazolam and ketamine each given at half the dose of the individual agent groups, had a faster onset of action, faster time to reach a maximum level of sedation, earlier parental separation time and a faster time to recovery with minimal side-effects than either drug alone. This provides some evidence of synergy between the two agents. There was no difference in the level of preoperative sedation score, parental separation score and emergence score between the two groups. Side effects were low and like midazolam alone.

CONCLUSION

In conclusion, this study showed that the combination of oral ketamine 3 mg/kg and oral midazolam 0.25 mg/kg had minimal side-effects and was more effective, faster in onset, and had a more rapid recovery than oral midazolam 0.5 mg/kg alone.

REFERENCES

1. Saarnivaara, Lindgren L, Klemola Um. Comparison of chloral hydrate and midazolam by mouth as premedicants in children undergoing otolaryngological surgery. Br J Anaesth 1988; 61:390-396.
2. Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. Anesthesiology 1990; 73:831-834.
3. Rowbottam SJ, Stewart KG, Sudhaman DA, Aitken AW. Oral ketamine. Anaesthesia 1991; 46:1084-1085.
4. Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanesthetic study in children. Anesthesiology 1992; 76:28-33.
5. Gingrich BK. Difficulties encountered in a comparative study of orally administered midazolam and ketamine. Anesthesiology 1994; 80:1414-1415.
6. Beebe DS, Belani KG, Chang PN et al. Effectiveness of preoperative sedation with rectal midazolam, ketamine, or their combination in young children. Anesth Analg 1992; 75:880-884.
7. Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric premedicant. Paediatr Anesth 1995; 5:293-295.
8. V. Darlong, D. Shende, M. S. Subramanyam, R. Sunder, A. Naik Oral Ketamine or Midazolam or Low Dose Combination for Premedication in Children Department of Anaesthesia and Intensive Care, All India Institute of Medical Sciences, New Delhi, India Anaesth Intensive Care 2004; 32: 246-249
9. Epstein RH, Mendel HG, Witkowski TA et al. The safety and efficacy of oral transmucosal fentanyl citrate for preoperative sedation in young children. Anesth Analg 1996; 83:1200-1205.
10. Cioaca R, Canavea I. Oral ketamine preanaesthetic premedication in children. Paediatr Anaesth 1996; 6:361-365. 11. Mitchell V, Grange C, Black A, Train J.
11. A comparison of midazolam with trimeprazine as an oral premedicant for children. Anaesthesia 1997; 52:416-421. 12. Bevan JC, Veall GR, Macnab AJ, Ries CR, Marsland C.
12. Midazolam premedication delays recovery after propofol without modifying involuntary movements. Anesth Analg 1997; 85:50-54.
13. Alderson PJ, Lerman J. Oral premedication for paediatric ambulatory anaesthesia: a comparision of midazolam and ketamine. Can J Anaesth 1994; 41:221-226.
14. Lin YC, Moynihan RJ, Hackel A. A comparison of oral midazolam, oral ketamine and oral midazolam combined with ketamine as preanaesthetic medication for paediatric outpatients. Anesthesiology 1993; 79:A1177
15. McMillan CO, Spahr-Schopfer IA, Sikich N et al. Premedication of children with oral midazolam. Can J Anaesth 1992; 39:545-550.
16. Cetina J. Schonende Narkoseeinleitung bei Kindern durch orale oder rektale Ketamin-Dehydrobenzperidol-Applikation Anaesthesist 1982; 31: 277–9
17. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effect of IM and oral ketamine. Br J Anaesth 1981; 53: 805–9