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

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ABSTRACT

Background: This study was done to compare effects of intranasal midazolam and intranasal midazolam with ketamine for premedication of children aged 1-12 yrs undergoing intermediate and major surgeries.**Aims:** Midazolam and Ketamine have already been used as premedicants in children. Our aim was to find out advantage of combination of midazolam with ketamine over midazolam by nasal route. **Methods:** Sixty children of age group 1-12 yrs of American Society of Anesthesiologists (ASA) grade 1 and 2 were selected. Group A- midazolam (0.2 mg/kg), Group B- midazolam (0.15 mg/kg + ketamine 1 mg/kg). Both groups received drug intranasally 30 min before surgery in recovery room with monitored anesthesia care. Onset of sedation, sedation score, emotional reaction, intravenous cannula acceptance, and mask acceptance were studied. **Statistical Analysis:** Unpaired *t* test and chi square test. **Results:** Sedation score, anxiolysis, attitude, reaction to intravenous cannulation, face mask acceptance, and emotional reaction were significantly better in midazolam with ketamine group. Intra operatively, in both groups, pulse rate, oxygen saturation, and 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:** Intra nasal premedication allows rapid and predictable sedation in children. Midazolam as well as combination of Midazolam with ketamine gives good level of sedation and comfort. But quality of sedation, analgesia, and comfort is significantly better in midazolam with ketamine group. No significant side effects were observed in both groups.

Key words: *Intranasal, Ketamine, midazolam, pediatric anesthesia*

INTRODUCTION

The pre-anesthetic management of infants and children can be a challenge for anesthesiologist. Fear of operation theatre, injections, and separation from parents prior to anesthesia produces traumatic experiences in tender mind of young children.[1]

Premedication by atraumatic method can minimize problems about separation from parents. The effective anxiolysis and conscious sedation to improve condition for parental separation, were the objectives of our study. The ideal premedication for children should have rapid and reliable onset, atraumatic, minimal side effects, and rapid recovery.[2,3]

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Thus, intranasal route was selected as all the criteria for an ideal premedication were satisfied.[4] Midazolam and Ketamine have already been used as premedicants by various routes. Oral and rectal application of midazolam[5] and ketamine are widely used in this age group. With an onset time between 15-30 min,[6] they show slow onset of sedation and first pass hepatic metabolism results in low and unpredictable systemic availability.[7,8] Intranasal midazolam for premedication in preschool children was first described and advocated by Wilton and colleagues.[9] Racemic ketamine as a premedicant has been successfully administered via the nasal route.[10,11] Midazolam plus ketamine have

complementary actions. The aim of our study was to evaluate efficacy and safety of two regimes by using intranasal midazolam 0.2 mg/kg versus intranasal midazolam 0.15 mg/kg with ketamine 1 mg/kg. In addition to this, we had an aim to evaluate effects on sedation level, emotional reaction, separation reaction, face mask acceptance, intravenous (IV) cannulation, and post-op recovery, after administration of these two regimes.

METHODS

After hospital ethics committee approval, 60 children of either sex, age between 1 year and 12 years undergoing pediatric, orthopedic, ophthalmic, and plastic surgery lasting for 30-120 minutes with American Society of Anesthesiologists (ASA) grade 1 and 2 were included in the study. Patients were subjected to thorough preoperative examination. Those with running nose, upper respiratory tract infection and emergency surgeries were excluded. Written informed consent was obtained from parents. The children were randomly allocated into two groups of 30 each.

Group (A) Intranasal Midazolam (0.2 mg/kg), Group (B) Intranasal Midazolam (0.15 mg/kg) with Ketamine [1 mg/kg]. Premedicant was given by 2 ml syringe into both nares over 15-20 seconds, while child was still in mother's lap. The child was observed preoperatively for 5-20 min, intraoperatively, and postoperatively. Observer (anesthesiologist) was not blind to choice of premedication due to the shortage of personnel, but investigators (staff nurse and resident doctor) were blind to agent given, they only observed and assessed patients. Pulse oximeter was used to monitor heart rate and oxygen saturation. General anesthesia was induced with sevoflurane 6% and air and oxygen (60:40), trachea was intubated by appropriate size endotracheal tube after IV Atracurium 0.7 mg/kg. Intraoperative no sedative and analgesic were given. All patients were extubated awake. Postoperative analgesia was provided by rectal paracetamol suppository 20 mg/kg.

Sedation score was estimated by single observer according to sedation scale adapted from Wilton and Colleagues who performed composite evaluation based on sedation, anxiolysis, and co-operation leading to determination of sedation level scored 1-5 [Table 1].

Parameters observed

1. Level of sedation.
2. Emotional reaction:
   i. Crying
   ii. Apprehension
   iii. Calm
3. Separation reaction:
   i. Crying
   ii. Apprehension
   iii. Good
4. Face mask Acceptance
5. Intravenous cannulation
6. Post operative recovery time and side effects

Sedation, anxiolysis, co-operation were recorded immediately after giving intranasal drug at following intervals: 2.5 min, 5 min, 10 min, and 20 min.

Heart-rate and oxygen saturation were monitored throughout the procedure. Immediate reactions to premedication were recorded. Adverse effects, if any, especially odd behavior or unexplained distress and excessive salivation were recorded.

The statistical tests applied were unpaired *t* test and chi square test.

RESULTS

All children accepted the intranasal drug instillation well without any vomiting. The drug was not palatable as reported by older children (more than 3 yrs).

Sixty children were studied in two groups, Group-A (Midazolam) and Group-B (Midazolam + Ketamine). The groups were comparable with respect to age, weight, gender, and distribution of operative procedure. Statistically, no significant difference was observed with respect to age, sex, and weight [Figure 1].

Table 1: Sedation level scored (Wilton and colleagues)

Sedation level	Child untouched	Additional assessment of co-operation
Agitated	Clinging to parents/ crying	Vigorous refusal
Alert	Awake may whimper, not crying	Accepts with persuasion
Calm	Sitting/lying comfortably with eyes open	Helps to perform manipulation
Drowsy	Lying comfortably with eyes closed, responds to minor stimulus	Accepts manipulation
Asleep	Eyes closed, no response to minor stimulus	Accepts manipulation

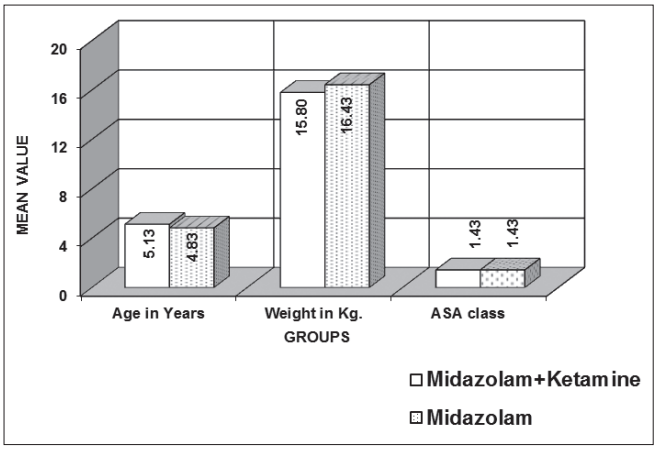

Figure 1: Group wise distribution of age weight and ASA class

Table 2 shows sedation score 3 and 4 at 20 minutes in 80% of children in Group A, while in Group B, sedation score 3 and 4 at 20 minutes was observed in 94% of children; rest of them were awake. None of the children had sedation score of 5.

Table 3 shows that 30% children in Group A were calm after 15-20 minutes of drug instillation, while it was 63.3% in Group B. Apprehension was seen in 63.3% in Group A, while only 36.7% in Group B.

Table 4 shows 57% of patients in Group B were easily separable from parents, while in group A, only 26.70% of patients were easily separable.

Acceptance to IV cannulation was without cry in 13.3% in Group A, while it was 43.3% in Group B.

Face mask acceptance was without cry in 50% in Group A. In Group B, face mask acceptance was good in 52.70%.

Intraoperative pulse rate and oxygen saturation had no significant difference in Group A and B [Figure 2].

Preoperative acceptance was good, no spilling was observed.

Post operative results summarized in Table 5 were analyzed by student's unpaired *t*-test (onset of sedation and post operative recovery time).

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

DISCUSSION

There is a continuous search for premedicant for children, which would make separation of children from parents

Table 2: Level of sedation at 20 minutes

Score	Group (A) Midazolam (%)	Group (B) Midazolam + Ketamine (%)
Agitated	6	0
Alert	12	6
Calm	25	30
Drowsy	57	64
Asleep	0	0

Table 3: Emotional reaction at 20 minutes

Score	Group (A) Midazolam (%)	Group (B) Midazolam + Ketamine (%)
Crying	6.67	0.00
Apprehension	63.33	36.70
Calm	30.00	63.30

Table 4: Separation reaction at 20 minutes

Score	Group (A) Midazolam (%)	Group (B) Midazolam + Ketamine (%)
Crying	33.30	13.00
Apprehension	40.00	30.00
Good	26.70	57.00

Table 5: Summary of results

Observation	Group (A) Midazolam (%)	Group (B) Midazolam + Ketamine (%)	*P* values	Statistical data
Onset time of sedation	10.27 (±3.25min)	10.16 (±3.50 min)		Difference is not significant
Sedation score[3,4]	80	94	0.033	Difference is significant
Anxiolysis (calm at separation)	30	63.3	0.0377	Difference is significant
Attitude (co-operative)	23.30	53.30	0.045	Difference is significant
Calm at I.V. Cannulation	13.30	43.30	0.031	Difference is significant
Face mask acceptance	50	52.70	0.356	Difference is not significant
Post-operative recovery time	23 (±8.17min)	27.3 (±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

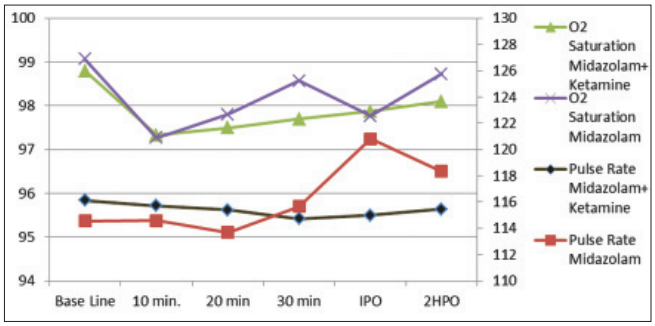

Figure 2: Group wise distribution of oxygen saturation and pulse rate at various intervals

peaceful. According to Weksler *et al.*,[10] ideal premedicant for children should be easy to administer, induce sleep rapidly, and have a quick recovery.

Midazolam and ketamine also possess ideal criteria for premedication such as rapid onset, good anxiolysis, sedation, and rapid recovery.[11]

Oral route is also convenient, but according to McMillan, oral midazolam in dose of 0.5-0.75 mg/kg provides sedation after 30-45 minutes, as onset is slow.[12] So we chose nasal route of administration.

Thus, intra nasal route is best route of administration in children. According to Peter J Devis, rapid and reliable onset of action is observed after nasal route administration. Predictable effects have made this route a convenient way to premedicate.[13]

Combination of midazolam and ketamine given orally or rectally have shown results better than either drug used alone.[14]

The onset time of sedation with midazolam was 10.27 ± 3.35 min, while with midazolam and ketamine combination onset time was 10.16 ± 3.50 min. Our results were similar as Wilton and Pandit *et al.*,[9] found that intranasal midazolam 0.2 mg/kg and 0.3 mg/kg causes sedation in 5-10 minutes and peak action comes by 15-20 minutes. Thus, in our study, all scores mentioned were at the end of 20 minutes.

Alderson *et al.*, had studied comparative effects of oral ketamine 5 mg/kg and oral midazolam 0.5 mg/kg administered 20-30 minutes before separation from parents showed 75% patients were sleepy.[15]

Sedation score 3 and 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 JH.[16] Rest of the patients were awake.

On assessment of emotional reaction, in Group A, 30% patients were calm, while in Group B, 63.3% were calm. This difference was statistically significant ($P < 0.05$). 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.*,[17] who used co-operation index to assess separation reaction.

Attitude, facemask acceptance, and IV cannulation were excellent in Group B as compared to Group A. These observations were also noted by Diaz JH.[16]

Intra operative pulse rate, oxygen saturation, respiratory rate had no significant difference in Group A and Group B as per study by Gulstien *et al.*,[18] and Wilton *et al.*[9] Our study supports the data presented by Audenaert and colleagues, who found that combination of intranasally administered racemic ketamine 5 mg/kg and midazolam 0.2 mg/kg did not produce significant cardiovascular and respiratory side effects.[19]

Postoperative oral secretions were minimal in both groups. Nystagmus and other side effects, like vomiting and increased salivation, were not see in both groups. Postoperatively, none of the patients had any emergence reaction in our study consistent with the study done by Agrawal Nidhi *et al.*[20]

Sample size for this study was calculated to examine efficacy, not safety. Thus, we can only state that, based on this limited study, no serious complications were encountered. One theoretical serious complication would be penetration of s-ketamine and midazolam through the cribriform plate, giving rise to high central nervous system levels. However, serious complications are very rare and very large study size would be required to demonstrate safety conclusively.[4]

Because of very rapid onset of sedation, we recommend the use of pulse-oximeter.

The drug given intranasally is absorbed through nasal mucosa as well as significant amount is absorbed through pharynx and remaining will be swallowed.

In conclusion, intranasal premedication allows rapid and predictable sedation in children. Midazolam as well as combination of midazolam plus ketamine gives good level of sedation and comfort. But quality of sedation, analgesia, and comfort is significantly better in midazolam plus ketamine group.

REFERENCES

1. Beeby DG, Hughes JO. Behaviour of unsedated children in the anesthetic room. Br J Anaesth 1980;52:279-81.

2. Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: A comparison of four routes of administration. Paediatr Anaesth 2002;12:685-9.
3. Louon A, Reddy VG. Nasal midazolam and ketamine for paediatric sedation during computerised tomography. Acta Anaesthesiol Scand 1994;38:259-61.
4. Weber F, Wulf H, el Saeidi G. Premedication with nasal s-ketamine and midazolam provides good conditions for induction of anesthesia in preschool children. Can J Anaesth 2003;50:470-5.
5. Lökken P, Bakstad OJ, Fonnelöp E, Skogedal N, Hellsten K, Bjerkelund CE, *et al*. 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;102:274-80.
6. Sekerci C, Dönmez A, Ateş Y, Okten F. Oral ketamine premedication in children (placebo controlled double-blind study). Eur J Anaesthesiol 1996;13:606-11.
7. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth 1996;77:203-7.
8. Malinovsky JM, Lejus C, Servin F, Lepage JY, Le Normand Y, Testa S, *et al*. Plasma concentrations of midazolam after i.v., nasal or rectal administration in children. Br J Anaesth 1993;70:617-20.
9. Wilton NC, Leigh J, Rosen DR, Pandit UA. Preanesthetic sedation of preschool children using intranasal midazolam. Anesthesiology 1988;69:972-5.
10. Weksler N, Ovadia L, Muati G, Stav A. Nasal ketamine for paediatric premedication. Can J Anaesth 1993;40:119-21.
11. García-Velasco P, Román J, Beltrán de Heredia B, Metje T, Villalonga A, Vilaplana J. Nasal ketamine compared with nasal midazolam in premedication in pediatrics. Rev Esp Anestesiol Reanim 1998;45:122-5.
12. McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. Can J Anaesth 1992;39:545-50.
13. Davis PJ, Tome JA, McGowan FX Jr, Cohen IT, Latta K, Felder H. Preanesthetic medication with intranasal midazolam for brief pediatric surgical procedures. Effect on recovery and hospital discharge times. Anesthesiology 1995;82:2-5.
14. Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric oral premedicant. Paediatr Anaesth 1995;5:293-5.
15. Alderson PJ, Lerman J. Oral premedication for paediatric ambulatory anesthesia: A comparison of midazolam and ketamine. Can J Anaesth 1994;41:221-6.
16. Diaz JH. Intranasal ketamine preinduction of paediatric outpatients. Paediatr Anaesth 1997;7:273-8.
17. Ljungman G, Kreuger A, Andréasson S, Gordh T, Sörensen S. Midazolam nasal spray reduces procedural anxiety in children. Pediatrics 2000;105(1 Pt 1):73-8.
18. Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanesthetic medication in children. Anesthesiology 1992;76:28-33.
19. Audenaert SM, Wagner Y, Montgomery CL, Lock RL, Colclough G, Kuhn RJ, *et al*. Cardiorespiratory effects of premedication for children. Anesth Analg 1995;80:506-10.
20. Agrawal N, Dua CK, Arya CP. Clinical evaluation of oral Ketamine and oral Midazolam for premedication in paediatric surgical outpatients. J Anaesthesiol Clin Pharmacol 2000; 16:23-28.

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