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Original Article

A Comparative Study Between Intranasal Midazolam and Ketamine as Premedication in Pediatric Patients

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Abstract

Introduction: Surgery and anesthesia can be a traumatic experience for a child. Stormy induction of anesthesia in children can lead to an increased incidence of post-operative behavioral problems. Thus, sedative premedication may be used in children to aid smooth induction of anesthesia. Hence, this study was conducted to compare the preanesthetic sedative effects of intranasal midazolam and ketamine.

Materials and Methods: This study was carried out on 60 ASA Grades I and II pediatric patients aged 2–5 years undergoing emergency or elective surgery lasting for 30 min–2 h. The exclusion criteria were established. Patients were included after written informed consent of the parent/guardian. They were randomly divided into two groups: Group M and Group K. Pre-operative, intraoperative, and post-operative parameters were observed.

Results: Statistically significant tachycardia and increased blood pressure (BP) (both clinically insignificant) were observed in both the groups (more persistent in the ketamine group). The sedation by both the drugs was adequate in terms of parental separation score, acceptance of facemask and response to venipuncture with no statistically significant difference. There were also no significant side effects (namely, respiratory depression, increased secretions or emergence reaction).

Conclusion: Both the drugs midazolam and ketamine provide adequate preanesthetic sedation through intranasal route and are safe to use in pediatric patients without any significant side effects.

Key words: Cardiorespiratory depression, Emergence reaction, Intranasal, Ketamine, Midazolam, Parental separation, Pediatric, Preanesthetic, Sedation

INTRODUCTION

Hospitalization introduces a new set of circumstances for which the child is unprepared. Surgery and anesthesia can be a traumatic experience for a child. Stormy induction of anesthesia in children can lead to an increased incidence of post-operative behavioral problems.[1] These problems can be reduced to some extent by psychological preparation of the child and parents. However, pharmacological adjunct may be more reliable and better suited in case of preschool children. Thus, sedative premedication may be used in children to aid the smooth induction of anesthesia.[2] It is desirable that these premedications have ease of application, rapid onset, short duration of action, and free from significant side effects.

Out of the various routes of administration, the intranasal route is one of the recently studied routes of drug administration. It has certain advantages. Due to high mucosal vascularity, intranasal route offers rapid and virtually complete absorption within 1–2 h into systemic circulation.

As midazolam[3] and ketamine[4] have high hepatic clearance, avoidance of hepatic first-pass metabolism offers greater systemic bioavailability. Therefore, intranasal administration has faster onset than oral or rectal route.

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In accordance with this, the current study was undertaken to evaluate the efficacy and safety of intranasal midazolam versus intranasal ketamine for preanesthetic sedation in pediatric patients, including assessment of sedation in the post-operative period and side effects, if any.

MATERIALS AND METHODS

This was a randomized, double-blind, and prospective study undertaken after approval from the Institutional Ethics Committee. The study was carried out in 60 pediatric patients aged 2–5 years, ASA Grade I or II and scheduled for elective or emergency surgery lasting for 30 min–2 h. Patients having any upper respiratory infection, allergies or systemic comorbidities (hepatic or renal derangements or congenital anomalies) were excluded from the study. Written informed consent was taken from the parent/guardian. Thorough pre-operative assessment including detailed history taking, clinical examination, and laboratory investigations, was done.

The patients were randomly assigned to either of the two groups:

- Midazolam group (Group M): Received intranasal midazolam 0.2 mg/kg as premedication (5 mg/ml nasal spray)
- Ketamine group (Group K): Received intranasal ketamine 3 mg/kg as premedication (50 mg/ml vial).

Midazolam was administered by a nasal spray, whereas ketamine was administered by a syringe. This took 1–2 min. Patients' vitals were examined before administering premedication and at 5 min intervals after installation.

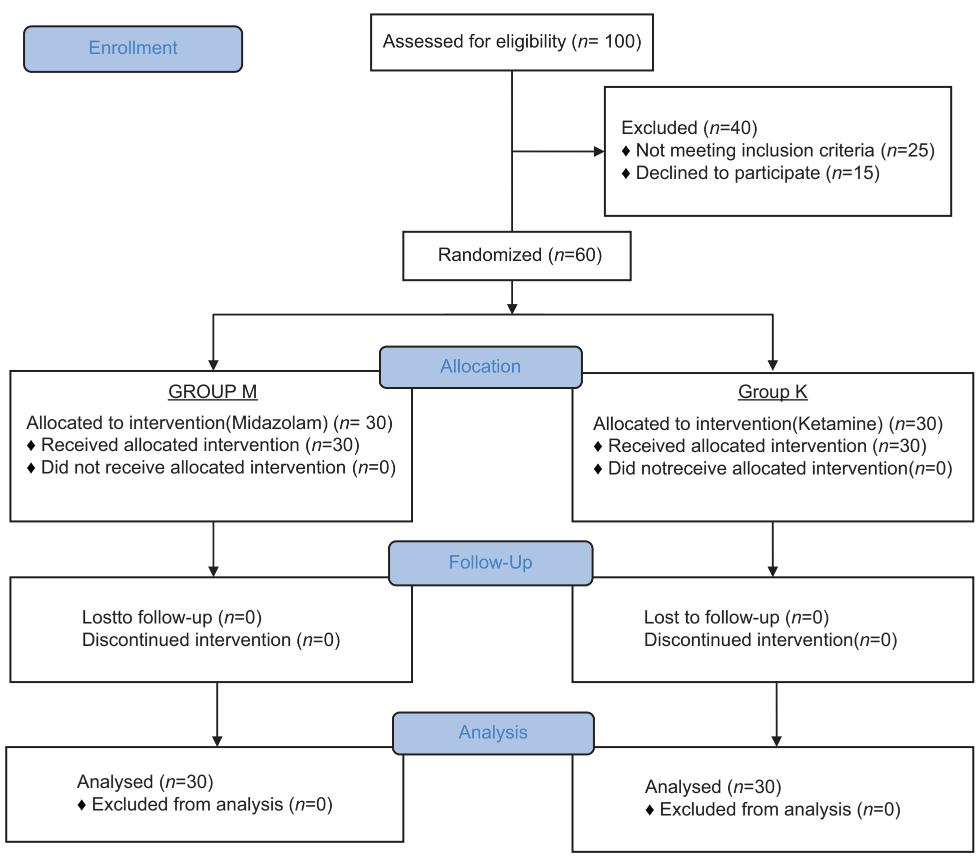
After observation for 20 min, the patient was shifted to the operation theater. Response to separation from parents was observed.

Degree of sedation was assessed using a five-point scale[5]:

1. Agitated: Patient clinging to parents and/or crying
2. Alert: Patient aware but not clinging to parents; may whimper but does not cry
3. Calm: Sitting or lying comfortably with spontaneous eye-opening
4. Drowsy: Sitting or lying comfortably with eyes closed, but responding to minor stimulation
5. Asleep: Eyes closed, arousable but does not respond to minor stimulation.

Preoxygenation was done by facemask, and the response was assessed similar to the above score as follows:

1. Agitated: Previous criteria and/or refuses mask
2. Alert: Previous criteria and/or initially refuses mask, but accepts after persuasion
3. Calm: Previous criteria and accepts mask
4. Drowsy: Previous criteria and accepts mask
5. Asleep: Previous criteria and accepts mask.



I.V. line was secured. Response to it was assessed. Degree of sedation was assessed using a five-point scale similar to the previous one.

1. Agitated: Previous criteria and/or refuses venepuncture
2. Alert: Previous criteria and/or initially refuses venepuncture, but allows after persuasion
3. Calm: Previous criteria and allows venepuncture
4. Drowsy: Previous criteria and allows venepuncture
5. Asleep: Previous criteria and allows venepuncture

Premedications were given. General anesthesia was induced, and intubation was done as per the standard protocols. At the end, after the reversal of neuromuscular blockade and extubation, post-operative sedation was assessed within 10 min of extubation with a three-point scale[6] as follows:
0: spontaneous eye opening,
1: eye opening to speech,
2: eye opening in response to physical stimulation.

Patients were observed in the recovery unit for 6 h, for any side effects.

Statistical Analysis

The data were analyzed by SPSS software using appropriate statistical tests (Paired and Unpaired *t*-test for quantitative data and Chi-square test for qualitative data). $P < 0.05$ was considered significant.

RESULTS

Both the groups were similar in terms of demographic variable (namely, age and gender), physical attributes (weight), and type and duration of surgery.

In each group, the majority (80%) of the patients had a parental separation score of three or more. This shows that most of the children separated well. The difference between scores of both the groups was statistically and clinically not significant ($P = 0.94$).

In each of the groups, the majority (80%) of the patients had a facemask acceptance score of three or more. This shows that most of the children accepted the facemask well. The response in both the groups was similar, and the difference in response to facemask was statistically and clinically nonsignificant ($P = 0.93$).

In Group M, 80% patients and 77% patients in Group K had a response to venepuncture scores of three or more. This shows that most of the children allowed venepuncture to be done peacefully. There was no statistically significant difference between the groups ($P = 0.93$).

Tachycardia (clinically insignificant) was observed in both the groups, which returned to baseline at 10 min in Group M and at 15 min in Group K. Although the tachycardia was statistically significant within the group, the difference in tachycardia between the groups was significant up to 10 min only [Tables 1 and 2].

Similarly, there was a slight increase in blood pressure (BP) (clinically insignificant) both the groups [Table 3]. However, the difference of increase in BP between the groups was statistically significant up to 10 min only [Table 4].

No respiratory depression (Rate and SpO_2) was noted in any group, and the difference was statistically insignificant ($P > 0.05$).

After the surgical procedure was over, the patients were reversed and extubated after fulfilling all the extubation criteria. Regarding the post-operative sedation, 43% of the patients in Group M and 50% in Group K had spontaneous eye opening after surgery, within 10 min of extubation. The levels of sedation were found to be similar in both the groups ($P = 0.87$).

Vomiting was the only side effect noted in both the groups (one case in Group M and two cases in Group K). However, the difference was not statistically significant ($P = 0.17$).

DISCUSSION

The sedative premedications administered to the children before surgery to lessen the trauma. There are various routes of administration, each having its own advantages and disadvantages. Needles inculcate bad memories and negative psychological effects. Rectal administration

Table 1: Comparison of trends of pulse rate in Groups M and K (within group)

Parameter	Group M				Group K			
Time	Mean pulse rate in group A	Paired *t*-value	*P*-value	Statistical significance	Mean pulse rate in group B	Paired *t*-value	*P*-value	Statistical significance
0 min	100.80	-	-	-	99.87	-	-	-
5 min	106.80	8.4	<0.001	Significant	110.67	15	<0.001	Significant
10 min	99.73	2.2	0.03	Significant	103.93	18	<0.001	Significant
15 min	99.53	2.6	0.012	Significant	98.87	2	0.045	Significant
20 min	98.33	5.2	<0.001	Significant	97.67	4.6	<0.001	Significant

leads to psychiatric embarrassment in older children and unreliable absorption, especially if the rectum is full of feces. Oral route has low bioavailability (15–27%)[7] due to high first-pass metabolism, so a higher dose (0.5–1 mg/kg) is required, and the peak effect is also delayed.[8,9] The bitter taste is also a limiting factor and cause for rejection as well as low compliance. Sublingual administration requires the drug to be held under the tongue for at least 30 s[10] which requires cooperation that is difficult to achieve in preschool children.

The nasal route has certain advantages. Due to high nasal vascularity, there is rapid and nearly complete absorption in 1–2 h into the systemic circulation.[11] It has a faster onset than oral or rectal route as well as time to reach maximal sedation.[12]

Therefore, in this study, the effects of intranasal midazolam with intranasal ketamine were compared, as preanesthetic sedation in children.

Both the groups were comparable in terms of demographic variables, physical attributes, type, and duration of surgery.

Pulse Rate

In both the groups, there was an initial increase (clinically insignificant) in pulse rate, which later settled to the baseline. However, the settling back was delayed in Group K (by 20 min) than in Group M (by 10 min). Furthermore, the rise was significantly more in Group K than Group M. This was comparable to the study by Narendra *et al.*,[13] where the tachycardia was more and persistent in the ketamine group. This may be due to absorption of ketamine and its sympathomimetic effects and not merely due to agitation of the patients.

Table 2: Comparison of effects on pulse rate in Groups M and K (between groups)

Time	Group	Mean±Standard deviation	*P*-value	Statistical significance
0 min	M	100.80±4.944	0.43	Not significant
	K	99.87±4.100		
5 min	M	106.80±5.671	0.005	Significant
	K	110.67±4.49		
10 min	M	99.73±3.886	<0.001	Significant
	K	103.93±2.95		
15 min	M	99.53±4.058	0.47	Not significant
	K	98.87±3.048		
20 min	M	98.33±3.968	0.48	Not significant
	K	97.67±3.198		

BP

There was a small decrease in BP in Group M, which was not clinically significant. The BP in Group K showed a statistically significant (clinically insignificant) rise up to 5 min and reached the baseline value by 15 min. At 5 and 10 min, the rise in BP in case of ketamine group is significantly more than that in midazolam group. This was similar to the study by Garcia-Velasco *et al.*,[14] where it was observed that the systolic arterial pressure was higher in the ketamine group as compared to midazolam group 20 min after administration of the drug and up on arrival in the operating theater.

Respiration

Midazolam in a bolus dose of 0.15 mg/kg can cause transient apnea. Ketamine relatively preserves the ventilatory drive.

In this study, no significant respiratory depression was noted (respiratory rate and SpO_2).

This was similar to the study by Niall *et al.*,[5] by Narendra *et al.*,[13] by Abhishek *et al.*,[15] and by Khatavkar and Bakhshi *et al.*[16]

Parental Separation Scores

In each group, the majority (80%) of the patients had a score of three or more. This shows that most of the children separated well. However, the difference between scores of both the groups was statistically and clinically not significant.

The results are in accordance with Bhakta *et al.*,[17] where they found that 80% patients receiving intranasal midazolam had scores of three or more and that they separated easily from their parents. This was also similar to the study by Abhishek *et al.*[15] and Khatavkar and Bakhshi *et al.*[16]

Table 3: Comparison of trends of BP in Groups M and K (Within group)

Parameter	Group M				Group K			
Time	Mean BP in group A	Paired *t*-value	*P*-value	Statistical significance	Mean BP in group B	Paired *t*-value	*P*-value	Statistical significance
0 min	77.67	-	-	-	78.00	-	-	-
5 min	78.27	1.96	0.059	Not Significant	84.47	21.67	<0.001	Significant
10 min	78.27	1.96	0.059	Not Significant	80.47	8.27	<0.001	Significant
15 min	76.60	2.72	0.011	Significant	76.73	3.90	0.001	Significant
20 min	76.60	2.72	0.011	Significant	77.00	2.47	0.019	Significant

BP: Blood pressure

Table 4: Comparison of effects on blood pressure in Groups M and K (between groups)

Time	Group	Mean±Standard deviation	*P* value	Statistical significance
0 min	M	77.67±2.928	0.65	Not significant
	K	78.00±2.678		
5 min	M	78.27±2.559	<0.001	Significant
	K	84.47±2.446		
10 min	M	78.27±2.559	0.001	Significant
	K	80.47±2.446		
15 min	M	76.13±3.636	0.50	Not significant
	K	76.73±3.258		
20 min	M	76.13±3.636	0.34	Not significant
	K	77.00±3.353		

Response to Facemask

In each of the groups, the majority (80%) of the patients had a score of three or more. This shows that most of the children accepted the facemask well. The response in both the groups was similar, and the difference in response to facemask was statistically and clinically non-significant.

This is comparable to the study by Weksler *et al.*,[18] where the mask acceptance rate was 78% (67 out of 86) and rated as either excellent or adequate. The results were also comparable to the study by Narendra *et al.*[13] and Khatavkar and Bakhshi *et al.*[16]

Post-operative Sedation Score

After the surgical procedure was over, the patients were reversed and extubated after fulfilling all the extubation criteria. They were monitored for post-operative sedation in the recovery room for a period of 6 h. The level of sedation was rated on a three-point scale.[6] About 43% of the patients in midazolam group and 50% in ketamine group had spontaneous eye opening after surgery, within 10 min of extubation. This was similar to the study by Narendra *et al.*[13]

Side Effects

Despite the inherent side effects of both the drugs, the only side effect observed in both the groups was vomiting. Emergence reactions, though common with ketamine, were not observed in this study. This is in accordance with the study by Weksler *et al.*[18] and Khatavkar and Bakhshi *et al.*[16]

Limitations

The study is limited by the OPD attendance of the patients undergoing surgeries. Therefore, the results may not be generalized. The non-pharmacological interventions might have been confounding factor, which were eliminated by randomization.

CONCLUSION

It can be effectively concluded from the study that both midazolam and ketamine provide adequate preanesthetic sedation (parental separation, facemask acceptance, and response to venepuncture) through the intranasal route. Apart from clinically insignificant tachycardia (more persistent in the ketamine group), no side effects including respiratory depression and post-operative sedation were observed. Therefore, both the drugs are safe for preanesthetic sedation in pediatric population.

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