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Emergence agitation in children: A comparison of effect of intravenous midazolam and ketamine

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Abstract---Background- Emergence agitation (EA) is one of the most challenging conditions to manage in pediatric patients undergoing general anesthesia with sevoflurane as it can even lead to physical harm. Various pharmacological interventions are being used in anesthesia to manage this condition. So, the objective of this study is to compare the effects of intravenous midazolam and intravenous ketamine given as premedication, on the incidence and severity of EA and to assess parent separation anxiety and postoperative pain and analgesic requirement in the 2 groups. Methodology- This is a randomized control trial consisting of 70 children aged 3-7years, 35 in each midazolam and ketamine group that received 0.05mg/kg of i.v. inj. midazolam and 1mg/kg of i.v. inj. ketamine respectively, undergoing general anesthesia with sevoflurane. Emotional status of the child assessed and then allocated into either group through a computer-generated programme. A blinded anesthesiologist assessed the incidence and severity of emergence agitation based on WATCHA scale and Children and Infant Postoperative Pain Scale (CHIPPS). Results- The mean WATCHA and CHIPPS scores were lower in ketamine group at all timepoints versus midazolam group ($p < 0.05$ which is statistically significant). Requirement of rescue analgesia and

mean time taken to shift patient out of post-anesthesia care unit (PACU) was significantly higher in midazolam group versus ketamine group. Preoperatively anxious and crying children were associated with higher incidence of EA. Conclusion- Intravenous ketamine is more effective in decreasing the incidence and severity of emergence agitation along with decreasing requirement of rescue analgesia and earlier discharge from PACU.

Keywords---emergence agitation, sevoflurane, ketamine, midazolam

Introduction

Emergence agitation, i.e., dissociated state of consciousness following general anesthesia, generally self-limiting, however can be severe, resulting in physical harm to the child thus posing a challenge for post anesthesia care providers.^[1] Factors affecting EA can be inhalational anesthesia (particularly sevoflurane), pain, surgery, high level of preoperative anxiety. Various pharmacological interventions given as premedication or just prior to extubation have been used to prevent the incidence and severity of EA. In this study we have compared the effects of intravenous ketamine and midazolam in preventing the same in pediatric patients undergoing sevoflurane anesthesia.

Hypothesis- intravenous ketamine is more effective than intravenous midazolam in decreasing the incidence and severity of emergence agitation in pediatric patients undergoing general anesthesia with sevoflurane.

Primary end point- to compare the incidence and severity of emergence agitation in pediatric patients premedicated by intravenous midazolam versus ketamine undergoing elective surgery.

Secondary end point- to assess parent separation anxiety and postoperative pain and analgesic requirement in the 2 groups.

Materials and Methods

This randomized control study was conducted in 70 patients aged 3-7 years belonging to ASA I or II category. Patients who were posted for elective surgeries under general anesthesia were included in the study. Patients of known psychiatric disorder (ADHD), developmental delay, chronic pain, pre-existing mental or physical health disorders were excluded.

After local Ethics Committee approval, a written informed valid consent was taken from patients' parents for this study. Before surgery, demographics and data regarding the child's medical and surgical history was recorded.

Emotional status of each child assessed using three-point scale (1-Calm, 2-Anxious but not crying and 3- anxious and crying)

Intravenous access obtained after applying topical anesthesia.

Subjects were randomly allocated in 2 groups using computer generated random number technique- **group midazolam(M)** subjects received 0.05 mg/kg of i.v. inj. midazolam and **group ketamine (K)** received 1mg/kg of i.v. inj. ketamine as premedication, under observation in waiting room, 5 minutes before taking the patient for surgery. During parent separation, emotional status of the patient assessed again using three-point scale mentioned above. The patient was shifted to the operating room with monitoring for oxygen saturation, ECG, non-invasive blood pressure (NIBP) and pulse oximetry. Induction and maintenance of anesthesia was kept uniform in both groups. General anesthesia was induced with inj. glycopyrrolate 0.004 mg/kg, inj. propofol 2mg/kg i.v., and inj. fentanyl 2mcg/kg, inj. scholine (2 mg/kg). Endotracheal intubation was done. Anesthesia was maintained by sevoflurane and 50% nitrous oxide in oxygen and inj. atracurium for muscle relaxation. Analgesia provided by inj. paracetamol 25mg/kg and diclofenac suppository. At the completion of surgery, sevoflurane was discontinued and residual neuromuscular relaxation reversed with i.v. 0.05µg/kg inj. neostigmine and i.v. 8µg/kg inj. glycopyrrolate. After thorough oropharyngeal suction, extubation was done after confirming adequate gag reflex, facial grimace, and purposeful movements.

The patients were then transferred to PACU.

A “blinded” anesthesiologist assessed the incidence and severity of emergence agitation based on Watcha Scale (table 1) in recovery room at 15 minutes intervals for one hour. Also, postoperative pain based on Children and Infant Postoperative Pain Scale ((CHIPPS)table 2) and the need for additional medication for pain relief was assessed. If required, rescue analgesic in the form of Inj. Pentazocine 0.5mg/kg was administered to the patient in recovery room. Any adverse events such as nausea, vomiting or/and shivering and time taken to shift the patient from recovery room was recorded.

Table 1
(Watcha Scale)

Behavior	Score
Asleep	0
Calm	1
Crying, but can be consoled	2
Crying, but cannot be consoled	3
Agitated and thrashing around	4

*Degree of severity of emergence agitation increases directly with the score
 † EA absent, if score ≤ 1, ‡ EA present, if score ≥ 1

Table 2
(Chipps Score)

Item	Score 0	Score 1	Score 2
Crying	None	Groaning	Screaming
Facial expression	At ease or smiling	Pouting	Expression of pain
Trunk posture	Middle	Tossing & turning	Buckling & stiffness
Lower limb posture	Relaxed or straightened	Kicking around	Tightened in both legs
Restlessness	None	Consolable	Irritated & disturbed

*Middle: Neutral, the stillness of the body, in a relaxed posture, no activity

Ethical Considerations

1. Institutional ethics committee's approval was obtained before conducting the study.
2. Possible Benefits of the Study: this study may provide information that in future might help doctors to provide more efficient prevention of emergence agitation in pediatric patients.
3. Right to Withdraw from the Study: Participation in this study was entirely voluntary. Their decision did not affect any further treatment at this institute.
4. Confidentiality: All study records were kept confidential at all times. Participant's identity was not revealed except as required by law. The results of the treatment (details: laboratory test, photographs, x-rays etc.) may be published for scientific reasons. Participant's identity will not be revealed in these publications.

Statistical analysis was done using SPSS software version 27. Chi-square test and Fisher's exact test were used to compare the qualitative data and unpaired student t test used to compare the quantitative data in the two groups. $p < 0.05$ was considered significant.

Results

Demographic and baseline details

The mean age was found to be statistically comparable between the ketamine and midazolam study groups ($p > 0.05$). Majority of children in both the study groups were between 3-6 years, and the age range noted in both groups was 1.5 years to 8 years. All patients belonged to ASA grade 1 in the study. Majority patients in both the study groups had emotional status of grade 1 prior to pre-medication. The patient distribution in both groups bases on age distribution and emotional status prior to pre-medication administration were comparable statistically ($p > 0.05$).

Table 3
Below describes the demographic and baseline details of enrolled patients.

	<i>Ketamine group (n=35)</i>	<i>Midazolam group (n=35)</i>	<i>p value</i>
Mean age (years)	4.83 ± 1.89	4.8 ± 1.9	0.41
Number of patients by age-group (%)			
< 3 years	5 (14.29%)	6 (17.14%)	0.97
3-6 years	20 (57.14%)	21 (60%)	
>6 years	10 (28.57%)	10 (28.57%)	
Number of patients by emotional status grading before premedication (%)			
Grade 1	19 (54.29%)	18 (51.43%)	0.59
Grade 2	12 (34.29%)	10 (28.57%)	
Grade 3	4 (11.43%)	7 (20%)	

*p<0.05 considered significant

† Mean age comparison by unpaired t test, other p values by chi-square test

Watcha score and CHIPPS Score

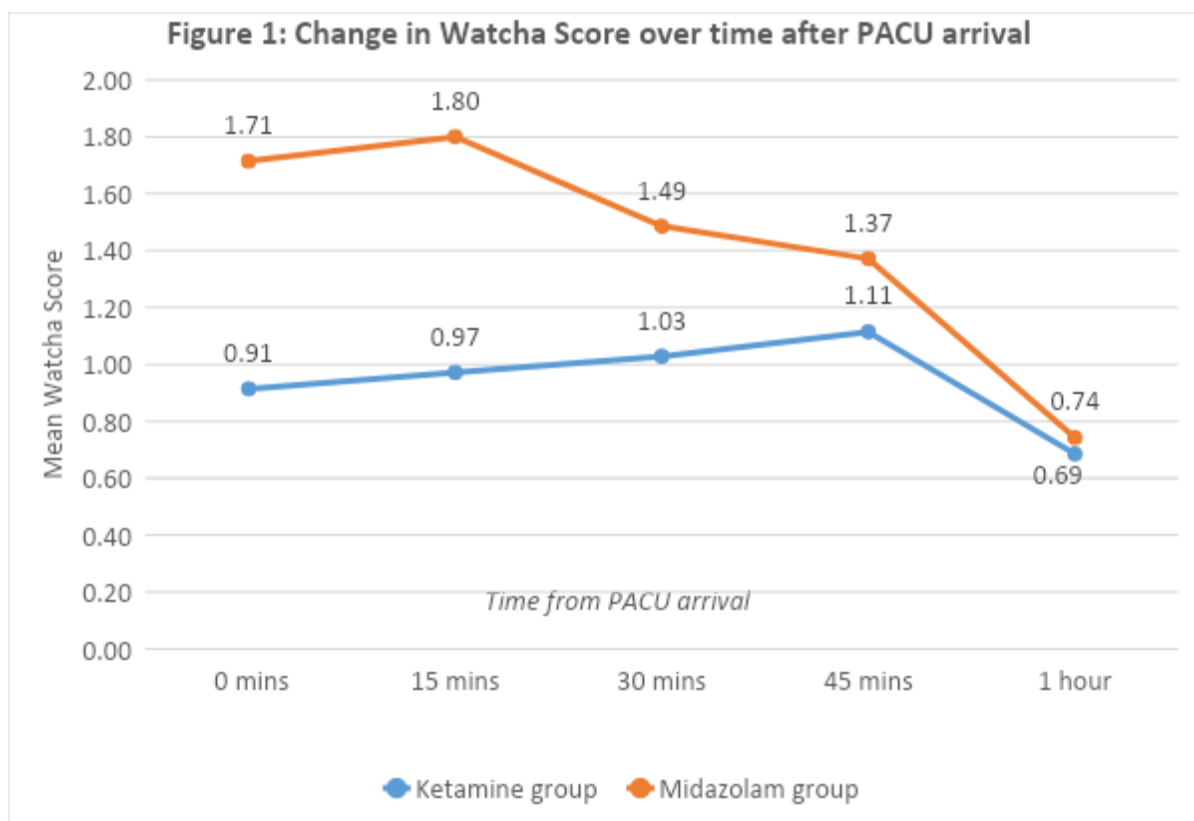
The mean Watcha score and CHIPPS score was found to be significantly lower in the ketamine study group at all time-points of assessment, versus the midazolam group (p<0.05). On intragroup analysis, both the study groups showed a significant decrease in the Watcha score and CHIPPS score over time-period of assessment after PACU arrival (p<0.05). (Table 4, figure 1, figure 2)

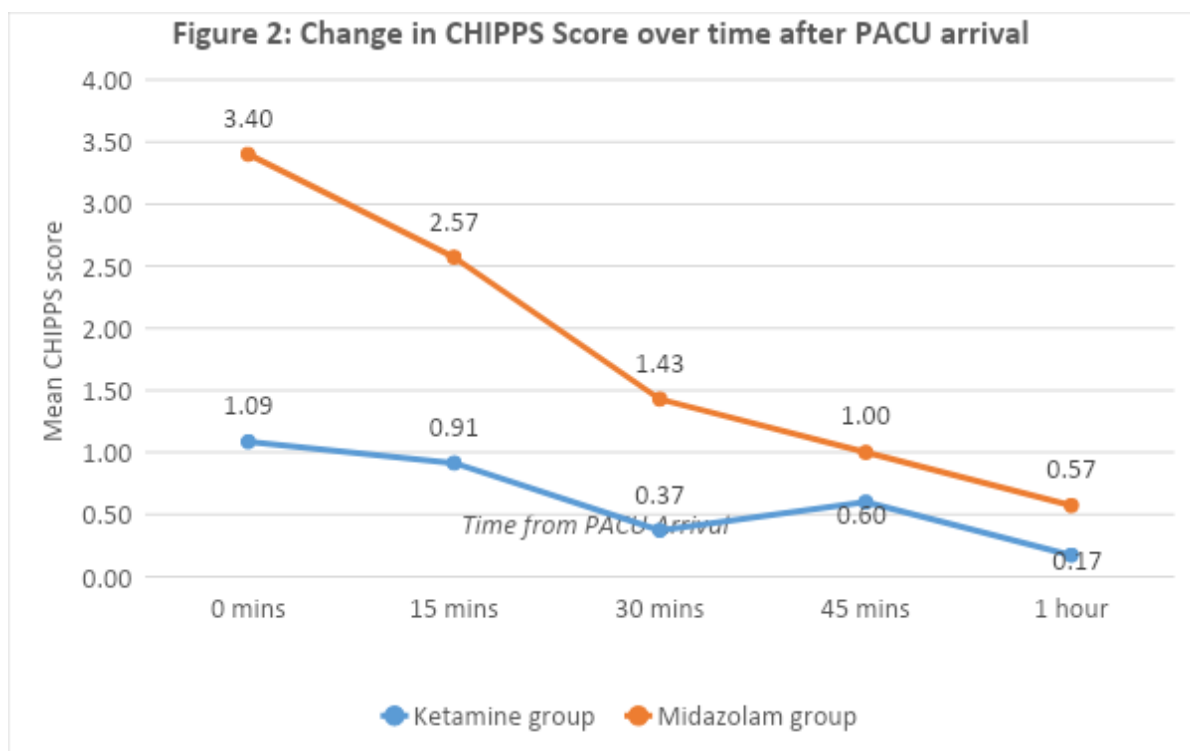
Table 4
Comparison of Watcha Score and CHIPPS score between study groups

	<i>Time from PACU arrival</i>	<i>Ketamine group (n=35)</i>	<i>Midazolam group (n=35)</i>	<i>p value</i>
Watcha Score	0 minute	0.91 ± 0.85	1.71 ± 1.05	<0.01*
	15 minutes	0.97 ± 1.80	1.8 ± 1.16	<0.01*
	30 minutes	1.03 ± 0.75	1.49 ± 0.95	<0.01*
	45 minutes	1.11 ± 0.47	1.37 ± 0.84	<0.01*

	1 hour	0.69 ± 0.58	0.74 ± 0.7	0.03*
CHIPPS Score	0 minute	1.09 ± 1.2	3.4 ± 2.09	<0.01*
	15 minutes	0.91 ± 1.17	2.57 ± 1.69	<0.01*
	30 minutes	0.37 ± 0.65	1.43 ± 1.38	<0.01*
	45 minutes	0.6 ± 1.01	1 ± 0.8	<0.01*
	1 hour	0.17 ± 0.57	0.57 ± 0.61	<0.01*

*Mean scores compared between groups using Mann-Whitney test, $p < 0.05$ considered significant.





Rescue analgesia, emergence agitation and adverse event status

In the ketamine group, 97.14% of the enrolled cases did not require rescue analgesia, while 60% in the midazolam group required rescue analgesia. This difference was found to be statistically significant. Emergence agitation was noted in 14.29% cases in the ketamine, while 60% of cases in midazolam group experienced it, which was a significant difference ($p < 0.05$). Adverse effects were numerically higher in the midazolam group (9 vs 4), but this was not a statistically significant finding ($p > 0.05$). (Table 5)

Table 5
Rescue analgesia, emergence agitation and adverse event status of enrolled patients

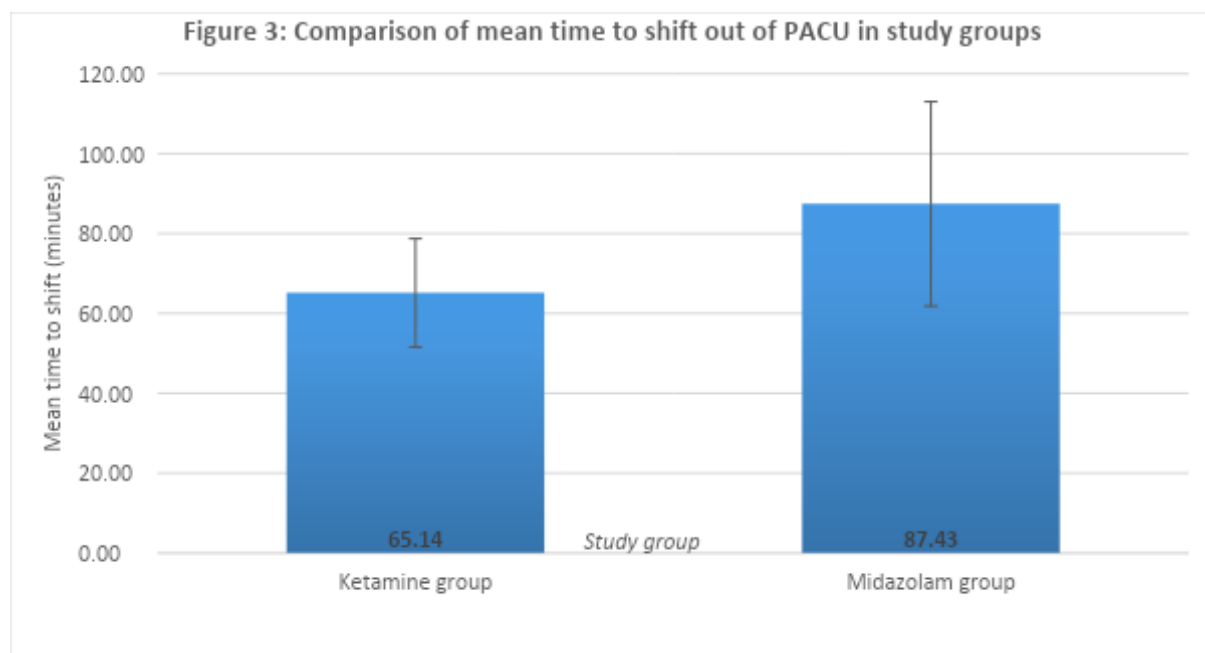
	<i>Ketamine group (n=35)</i>	<i>Midazolam group (n=35)</i>	<i>p value</i>
Rescue analgesia status in study groups (%)			
Required	1 (2.86%)	21 (60%)	<0.01*
Not required	34 (97.14%)	14 (40%)	

Emergence agitation status in study groups (%)			
Present	5 (14.29%)	21 (60%)	<0.01*
Absent	30 (85.71%)	14 (40%)	
Adverse effects in study groups (%)			
Present	4 (11.43%)	9 (25.71%)	0.22
Absent	31 (88.57%)	26 (74.29%)	

*p value calculated by chi-square test, $p < 0.05$ considered significant

Time to shift out of PACU

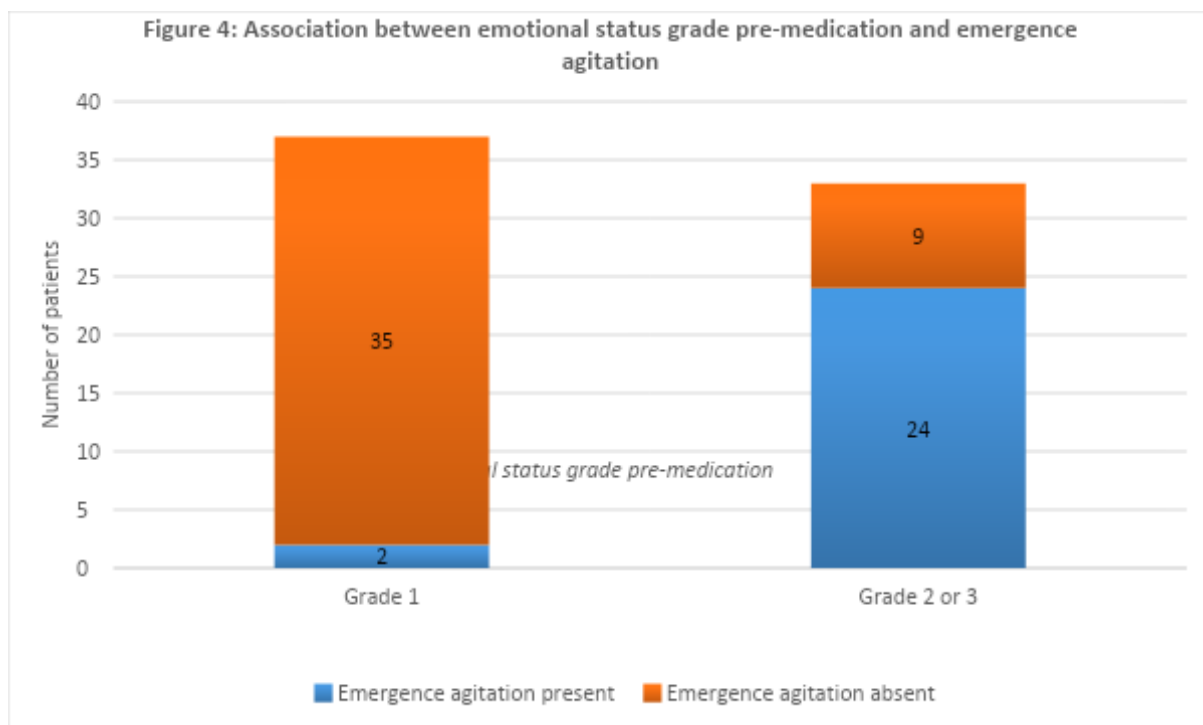
The mean time needed to shift out of PACU was noted to be significantly higher in the midazolam group versus the ketamine study group (87.43 ± 25.59 vs 65.14 ± 13.58 minutes, $p < 0.05$). (Figure 3)



Association between emotional status grade pre-medication and emergence agitation

Overall, 26 patients in study had emergence agitation after medication. Out of these, 24 cases belonged to higher emotional status grade pre-medication (2 or 3

grading) while only 2 cases were of low emotional status grade pre-medication (grade 1). This association between high emotional status grade pre-medication and emergence agitation was noted to be statistically significant ($p < 0.05$). (Figure 4)



The association between emotional status grade pre-medication and emergence agitation in the two study groups was noted to be significant ($p < 0.05$). In both the study groups, a higher grade of emotional status grade pre-medication was significantly associated with emergence agitation. (Table 6)

Table 6
Association between emotional status grade pre-medication and emergence agitation in study groups

Study group	Emotional status grade pre-medication	Emergence agitation present	Emergence agitation absent	p value
Ketamine	Grade 1	0	19	0.01*
	Grade 2 or 3	5	11	
Midazolam	Grade 1	5	13	<0.01*
	Grade 2 or 3	16	1	

Discussion

Emergence agitation (EA) has been described as a dissociated state of consciousness manifested by restlessness, disorientation, incoherent and inconsolable crying, kicking and thrashing in bed following general anesthesia and is frequently observed in preschool aged children. This presents a challenging situation for post anesthesia care providers. Emergence agitation is generally a self-limiting condition. However, it can be severe and may result in physical harm to the child and in particular to the site of surgery. Prevalence of emergence agitation in children ranges from 25% to 80%.

This randomized controlled study compared the effects of intravenous midazolam and ketamine as pre medication on incidence and severity of emergence agitation in pediatric patients undergoing elective surgeries under general anesthesia with sevoflurane. The underlying mechanism of sevoflurane induced emergence agitation remains unclear. However, rapid recovery of consciousness(emergence) from sevoflurane anesthesia has been proposed as one possible mechanism.^[4]

Various pharmacological interventions like propofol, midazolam, alpha-2 receptor agonists, opioids like fentanyl, alfentanil and ketamine, given as a premedication in oral or intravenous form or intravenously just prior to intubation have been used to prevent its occurrence and reduce the severity of EA. Ketamine and midazolam are one of the most commonly used agents perioperatively in oral as well as intravenous form in pediatric patients to reduce or counter EA mainly caused by sevoflurane. Ketamine, a phencyclidine derivative, is one of the most common induction or premedication agents used in pediatric patients due to its minimal effect on respiration and hemodynamics rendering it safe. Oral as well as intra nasal ketamine has been effective in reducing emergence agitation in children after sevoflurane anesthesia. Continuous ketamine infusion used intra operatively has also shown to have a beneficial effect on emergence agitation without causing delayed recovery. Ketamine has a longer elimination half-life(2.5-2.8hours) than midazolam(1.7-2.6 hours). Ketamine also has an additional analgesic effect mediated predominantly by a combination of antinociception and opioid system sensitization i.e., when ketamine is co-administered with an opioid, the distribution (especially to brain) and clearance of ketamine is enhanced. Hence, a combination of premedication agents is probably more efficacious. ^{[5][6]}

On the other hand, midazolam, a benzodiazepine, is also widely used as a premedication to decrease anxiety in children preoperatively. Premedication with oral midazolam has been used to reduce the incidence of emergence agitation after short surgical and outpatient procedures. However, its efficacy for this purpose has not been established.^[5]

A total of 70 patients were enrolled in the study, 35 patients in midazolam group and 35 patients in ketamine group.

Table 3 showed that mean age was found to be statistically comparable. The age noted in both the groups was 1.5 to 8 years out of which majority of children in both the study groups were between 3-6 years of age (21 and 20 in group midazolam and group ketamine respectively).

Table 4 depicts the comparison of Watcha score and CHIPPS score between the study groups. Watcha score depicting the incidence of emergence agitation and CHIPPS score depicting severity of emergence agitation was found to be significantly lower in the ketamine group at all time points of assessment in comparison to the midazolam group. A similar study was conducted by Kyung Mi Kim et al in which the effects of intravenous midazolam and ketamine were compared on emergence agitation in children and no statistically significant between-group differences in CHIPPS were found at any time point.^[3]

Table 5 shows the requirement of rescue analgesia which was found to be statistically (significantly) higher in midazolam group denoting an associated analgesic effect of Ketamine. A similar effect of premedication with ketamine was found in the study done by Kyung Mi Kim et al where a reduced requirement for rescue analgesia was seen in children after sevoflurane anesthesia.^[3]

Table 5 also shows that there is a significantly higher presence of emergence agitation in the midazolam group (60%) in comparison to the ketamine group (14.29%). The result is found to be similar to the study conducted by Kyung Mi Kim et al concluding a more effective prevention of early post operative emergence anesthesia with premedication with ketamine in comparison to midazolam. In a meta-analysis conducted by Dahmani S et al on pharmacological prevention of emergence agitation in children, it was concluded that Midazolam was ineffective in the prevention of emergence agitation.^[7] A similar result was found in a study by Breschan C et al.^[8] On the other hand, studies by Eghbal MH et al and Elshammaa N et al shows the effect of Ketamine in reducing the incidence of emergence agitation in children.^{[9][10]} A study by Jeong WJ et al has shown that administration of ketamine before entering the operating room has an effect on decreasing separation anxiety, degree of post operative pain and incidence of emergence agitation following Pediatric Ophthalmic surgeries under Desflurane anesthesia.^[11]

Adverse effects such as nausea, vomiting and/or shivering were found to be slightly more in midazolam group but it was not found to be statistically significant.

The mean time needed to shift the patient out of PACU was found to be 87.43mins (± 25.59 mins) for Midazolam group whereas it was 65.14mins (± 13.58 mins) for ketamine which was significantly lower in comparison rendering it better in terms of Enhanced Recovery After Surgery (ERAS) and day care surgeries whereas there was found to be only a slight difference in the duration of PACU stay in both the groups (39.26 ± 10.45 vs 38.94 ± 13.68 mins in midazolam vs ketamine groups respectively) in the study done by Kyung Mi Kim et al.^[3] A randomized study by Elshammaa et al in children following tonsillectomy has indicated the role of ketamine in hastening discharge of the patients is consistent with our study.^[10]

Although the pathogenesis of emergence agitation remains unclear, factors including inhalational anesthesia (sevoflurane anesthesia in particular), pain, surgery and a high level of pre operative anxiety are known to affect emergence

agitation. The difficult separation of children from parents before the start of the surgery has been proposed to be a factor contributing to emergence agitation. ^[11] There was found to be an independent association between the emotional status of the child before premedication and emergence agitation in this study. It was evaluated using a three-point scale (1=calm, 2= anxious but not crying and 3= anxious and crying). Children with grade 1 had significantly less incidence of emergence agitation in comparison to children with grade 2 or 3 preoperatively. Five out of 35 patients in midazolam group and 0 out of 35 patients in ketamine group with grade 1 had emergence agitation. Five out of 35 in ketamine group and 16 out of 35 in midazolam group with grade 2 or 3 had emergence agitation (Table 6). In a study conducted by Kain et al on preoperative anxiety and emergence delirium and postoperative maladaptive behaviors, it was found that the odds having marked symptoms of emergence delirium increased by 10% for each increment of 10 points in the child's state anxiety score. ^[12] It was a limiting factor in our study as it directly affected the study parameter.

Some other limiting factors in the study include the stark inability to distinguish between emergence agitation and postoperative pain because of their similar presentation in pediatric patients and the absence of a standardized method of analyzing the incidence and severity of emergence agitation which may lead to discrepancies in the results of various conducted studies.

In conclusion, intravenous ketamine is more effective than intravenous midazolam in decreasing the incidence and severity of emergence agitation in pediatric patients undergoing general anesthesia with sevoflurane. Premedication with ketamine was also associated with decreased requirement of rescue analgesia and an earlier discharge from PACU thus rendering it a better choice for pediatric patients undergoing surgeries under general anesthesia.

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