Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL12, ISSUE 01, 2021

Original research article

A comparison of effect of intravenous midazolam and ketamine on Emergence agitation in paediatric age group

[1]Dr. Dhawale Rajeshri Nivrutirao, [2]Dr. Vrushali Sadashiv Rajgire, [3]Dr. Ganesh Laxman Khandarkar, [4]Dr. Prasad Sule

[1,2,3,4] Assistant professor, Department of Anesthesiology, SRTR GMC Ambajogai, Maharashtra, India

Corresponding Author:
Dr. Hanumantharaya GH

Abstract

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.

Keywords: Emergence agitation, sevoflurane, ketamine, midazolam

Introduction

Emergence agitation is a postanesthetic phenomenon that develops in the early phase of general anesthesia recovery, and is characterized by agitation, confusion, disorientation, and possible violent behavior. Though agitation is observed more frequently in pediatric patients, the incidence in adults has been reported at 4.7% or 21.3%. Emergence agitation can lead to serious consequences such as self-extubation, removal of catheters, hemorrhage, and even severe injuries from falling out of the bed. Furthermore, it may increase the demand on human resources and cause medical staff injuries[1].

While its pathogenesis remains unclear, previous studies reported that ENT (ear, nose, and throat) surgical procedures have a higher incidence of emergence agitation in children. Especially, it was our clinical impression that nasal surgical patients admitted to the postanesthesia care unit (PACU) have suffered emergence agitation more frequently than other surgical patients, possibly due to a sense of suffocation during emergence from anesthesia. This phenomenon has been frequently studied in pediatric patients. 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.

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.

ISSN:0975 -3583,0976-2833 VOL12, ISSUE 01, 2021

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

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.

	Ketamine group (n=35)	Midazolam group (n=35)	p value
Mean age (years)	4.81 ± 1.86	4.7 ± 1.2	0.41
Number of patients by age-group (%)			
< 3 years	5	6	0.97
3-6 years	20	21	
>6 years	10	10	
Number of patients by emotional status grading before premedication (%)			
Grade 1	19	18	0.59
Grade 2	12	10	
Grade 3	4	7	

*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

	Time from PACU arrival	Ketamine group (n=35)	Midazolam group (n=35)	p value
Watcha Score	0 minute	0.92 ± 0.84	1.7 ± 1.04	<0.01*
	15 minutes	0.96 ± 1.81	1.8 ± 1.16	<0.01*

ISSN:0975 -3583,0976-2833 VOL12, ISSUE 01, 2021

	30 minutes	1.03 ± 0.75	1.49 ± 0.95	<0.01*
	45 minutes	1.12 ± 0.47	1.36 ± 0.84	<0.01*
	1 hour	0.68 ± 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	0.36 ± 0.65	1.41 ± 1.38	<0.01*
	45 minutes	0.61 ± 1.01	1.01 ± 0.8	<0.01*
	1 hour	0.16 ± 0.57	0.5 ± 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

	Ketamine group (n=35)	Midazolam group (n=35)	p value
Rescue analgesia status in study groups (%)			
Required	1	21	<0.01*
Not required	34	14	
Emergence agitation status in study groups (%)			
Present	5	21	<0.01*
Absent	30	14	
Adverse effects in study groups (%)			
Present	4	9	0.22
Absent	31	26	

*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

ISSN:0975 -3583,0976-2833 VOL12, ISSUE 01, 2021

fentanyl, alfentanyl 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 (±25.59mins) 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

ISSN:0975 -3583,0976-2833 VOL12, ISSUE 01, 2021

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.

References

1. Voepel-Lewis, Terri & Malviya, Shobha & Tait, Alan. A Prospective Cohort Study of Emergence Agitation in the Pediatric Postanesthesia Care Unit. Anesthesia and analgesia. 2003;96:1625-30.
2. Xu H, Mei XP, Xu LX. Cause analysis, prevention, and treatment of postoperative restlessness after general anesthesia in children with cleft palate. J Dent Anesth Pain Med. 2017;17(1):13-20. doi:10.17245/jdapm.2017.17.1.13
3. Kyung Mi Kim, Ki hwa lee and Yong Han Kim, Comparison of effects of intravenous midazolam and ketamine on emergence agitation in children: randomized controlled trial. Journal of International medical research. 2016;44(2):258-266,
4. Veyckemans F. Excitation Phenomena during Sevoflurane Anaesthesia in Children. Current Opinion in Anesthesiology, 2001;14:339-343.
5. DDL Wong, CR Bailey, Emergence delirium in children. Journal of Association of Anaesthetists. 2015;70(4):383-387,
6. Guthrie AM, Baum RA, Carter C, Dugan A, Jones L, Tackett T, Bailey AM. Use of Intranasal Ketamine in Pediatric Patients in the Emergency Department. Pediatr Emerg Care. 2021 Dec 1;37(12): e1001-e1007. doi: 10.1097/PEC.0000000000001863. PMID: 31290798.
7. Dahmani, S, Delivet, H, Hilly, J. Emergence delirium in children: an update. Curr Opin Anaesthesiol. 2014;27:309-315.
8. Breschan, C, Platzer, M, Jost, R. Midazolam does not reduce emergence delirium after sevoflurane anesthesia in children. Paediatr Anaesth. 2007;17:347-352.
9. Eghbal, MH, Taregh, S, Amin, A. Ketamine improves postoperative pain and emergence agitation following adenotonsillectomy in children. A randomized clinical trial. Middle East J Anesthesiol. 2013;22:155-160.
10. Elshammaa, N, Chidambaran, V, Housny, W. Ketamine as an adjunct to fentanyl improves postoperative analgesia and hastens discharge in children following tonsillectomy - a prospective, double-blinded, randomized study. Paediatr Anaesth. 2011; 21:1009–1014.
11. Jeong, WJ, Kim, WY, Moon, MG. The effect of ketamine on the separation anxiety and emergence agitation in children undergoing brief ophthalmic surgery under desflurane general anesthesia. Korean J Anesthesiol 2012;63:203–208.
12. Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, Feng R, Zhang H. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg. 2004 Dec;99(6):1648-1654. doi: 10.1213/01.ANE.0000136471.36680.97. PMID: 15562048.