Available online at www.jsan.org.np
Journal of Society of Anesthesiologists of Nepal

Original Article

Effects of ketamine and ketamine with midazolam on emergence agitation in children following sevoflurane anesthesia

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Abstract

Background

Emergence agitation is a distressful phenomenon associated with inhalational agents such as Sevoflurane in short surgical procedures. Various drugs have been used in the past but some come at the cost of increased complications. We aim to study the effects of ketamine alone and ketamine with midazolam on emergence agitation and their effects on recovery and discharge times.

Methods

We conducted a prospective randomized controlled trial among 94 patients aged two to ten years presenting for ophthalmic surgeries in which 45 patients were allocated to each group: group K (Ketamine) and group KM (Ketamine with Midazolam). Group K received Ketamine 0.3 mg/kg IV and Group KM received Ketamine 0.3 mg/kg IV and Midazolam 0.03 mg/kg IV. Intraoperatively heart rate and post-operatively emergence agitation, recovery times, discharge times were studied.

Results

Demographic variables were comparable between the two groups. Median Pediatric Anesthesia Emergence Delirium (PAED) score of 6 with IQR (4-6) in group K was comparable to the median score of 5 with IQR (4-6) in group KM. The mean recovery time of 22±4.82 min in group K was significantly lower compared to the mean time of 25.75±3.32 min in group KM. Mean time to discharge of 67±11 min from the hospital in group K was significantly shorter compared to that in group KM (108±18 mins).

Conclusion

We concluded from our study that ketamine alone is as effective as ketamine with midazolam in reducing the emergence agitation following Sevoflurane anesthesia for ophthalmic surgery.

Key words: ketamine, sevoflurane, emergence agitation

Article History

Received	26th August 2017
Accepted	5th February 2018
Published	6th August 2018

How to cite this article: Sharma A, Rana RB. Effects of ketamine and ketamine with midazolam on emergence agitation in children following sevoflurane anesthesia. Journal of Society of Anesthesiologists of Nepal (JSAN) 2017;4(2):57-65.

Introduction

Emergence agitation is a state of restlessness, distress, and a dissociated state of consciousness where a child is

either moaning, sobbing, or crying inconsolably[6] occurring in the immediate post-operative period, particularly in children. Sevoflurane, young age, no previous surgery, and other intravenous agents[7], are commonly implicated for this condition. However, several studies have stressed upon the fact that rapid emergence from Sevoflurane anesthesia especially in short surgical procedures and inadequate pain control lead to emergence agitation in children who are susceptible.[5,8–11] Although there are no clinical evidences of long term effects of this condition[12], it is unforgiving not only to the anesthetist who aims for 'smoothness' in induction, maintenance, and recovery of anesthesia, but also to the parents who are concerned about the clinical condition of their child.

In one study, the reported incidence of emergence agitation with Sevoflurane often as high as 80%[13] to 100%[14] (when not premedicated) was reduced to 33% with premedication. Several studies using different agents like propofol, ketamine, dexmedetomidine as adjuvants have already been done but none of them have been completely successful in eliminating this quandary.[5,10,11,15,16] Ketamine and Midazolam, in particular, have been the ideal agents as in pediatric anesthesia because of their easy availability and very well-known pharmacology.

Ketamine produces dissociative anesthesia and acts by binding noncompetitively to phencyclidine recognition site on N-methyl-D-aspartate (NMDA) receptors and inhibits the activation of this receptor by glutamate. Several studies have compared and contrasted the beneficial effects of Ketamine in reducing the incidence of emergence agitation in pediatric population when used along with Midazolam.[13,17–19]

Midazolam is a water-soluble benzodiazepine with an imidazole ring in its structure. Midazolam premedication is thought to reduce the frequency of postoperative nausea and probably vomiting and increases patient satisfaction.[20] Although Midazolam has not independently been used to decrease the incidence of emergence agitation, it is presumed to certainly have an effect because of its anxiolytic property and is considered superior to other premedication drugs[16,17] as preoperative anxiety is thought to increase the incidence of emergence agitation.[21]

It is a known fact from several studies done previously that anxiety, post-operative pain, and rapid emergence from Sevoflurane anesthesia are the most common causes of emergence agitation.[22] Thus, this study not only compares and contrasts the individual efficacy of Ketamine with Ketamine and Midazolam but also help understand to what extent the above-mentioned risk factors play roles in emergence agitation. The use of Midazolam has been shown to delay recovery after ambulatory surgery when used in children undergoing Sevoflurane anesthesia.[23]

We, therefore, have to aim to decrease the incidence, severity and complications of emergence agitation with the use of agents like Midazolam and Ketamine and probably other agents, which are being studied separately. Various studies have shown that ethnicity has influence on drug response and action due to difference in genetic makeup which determines the drug metabolizing enzymes, receptors, and transporters.[24] Many of these studies comparing Ketamine and Ketamine with Midazolam have been done in the western population, and those results are extrapolated to this part of the world. This makes those results unreliable because the race, ethnicity, and genetic makeup of population in this part of world are different. We, thus, found a need to conduct a study comparing the beneficial effects of Ketamine and Midazolam on emergence agitation in our context. This study is one of such attempts.

Methods

Following approval from Institutional Review Board (IRB) of NAMS, and research committee of Tilganga Institute of Ophthalmology (TIO), this prospective, randomized, parallel trial was conducted at TIO from April 2016 to June 2016. Sample size calculation was done based on previous study by Cravero et al[13] taking 95% confidence interval and 80% power. A total of 94 American Society of Anesthesiology Physical Status (ASA PS) I and II patients from 2 to 10 years of age and undergoing elective surgeries ranging from 15 to 60 minutes were included in the study. Parental refusal, presence of upper respiratory infection, documented allergies to interventional drugs, neurodevelopmental disorders, and history of malignant hyperthermia were among the exclusion criteria. The primary outcome measure of the study was to compare the incidence of emergence agitation between the two groups and secondary objectives were to compare recovery times, discharge times, and side effects profile between the two groups.

After obtaining a written informed consent, full pre-anesthetic check was done that included a detailed history, physical examination and relevant laboratory investigations. Guardians were instructed to keep the children fasted as per standard ASA fasting guidelines. No oral premedication was given.

Patients enrolled were randomized into either group by lottery method in which a trained staff, not involved in any other part of the study, withdrew chit from a sequentially numbered container. A computer generated random allocation sequence was used to allocate the patient to either group. Only the sequence as a code was used in the intra-operative record for which was later decoded using the master record form. No other details of the patient were mentioned in any of the record forms. Other trained staff prepared the drugs into identical 5-ml syringes, which were sequentially numbered. Thus, neither the investigator nor the subjects knew to which group they were allocated.

Standard monitors like electrocardiogram (ECG), and pulse oximeter were attached as soon as possible.

Patients who were not co-operative enough to let the opening of IV cannula prior to induction had their IV lines opened after induction. For others, IV cannula was opened prior to administration of inhalational agents. Following application of a facemask, an experienced anesthesiologist induced all children of both the groups and time was recorded. Sevoflurane with oxygen and nitrous oxide (50/50) at 4 L/min was introduced in increments of 1% Sevoflurane every three breaths to a maximum of 8% Sevoflurane. Then, one of the following study regimes was given:

1. **Group K**: Ketamine 0.3 mg/kg[25] + Paracetamol 15 mg/kg IV
2. **Group KM**: Ketamine 0.3 mg/kg + Midazolam 0.03 mg/kg + Paracetamol 15 mg/kg IV

After achievement of adequate depth of anesthesia, appropriate size flexible laryngeal mask airway (flexible LMA^{TM}) was inserted and the time recorded. Patient was maintained on spontaneous with assisted ventilation when required. Intra-operatively, heart rate (HR), and respiratory rate (RR) were recorded every 5min. inj. ketamine 0.1 mg/kg IV (one time dose) was repeated if surgery lasted >30 minutes.

After completion of surgery, LMA was removed without decreasing the sevoflurane concentration in deep plane of anesthesia after proper pharyngeal suction and time was recorded. The patient was kept on operation table until the vitals are settled with unassisted patent airway then shifted to recovery and time recorded.

On arrival at the recovery room vital parameters were recorded every 5 minutes for the first 15 minutes, then at 15-minute intervals subsequently. The recovery scores were recorded using modified Aldrete recovery score[26] continually until it reached to $\geq$ 9 by the recovery staff and the time was recorded. The side effects like vomiting, desaturation, and hallucination in the recovery room were also recorded.

Emergence agitation score was evaluated every 5 minutes for the first 15 minutes and then at 15-minute intervals using the Pediatric Anesthesia Emergence Delirium (PAED)[27] scale by trained recovery staff that was not involved in the study. The PAED scale assesses 5 items (1, makes eye contact with the caregiver; 2, actions are purposeful; 3, aware of surroundings; 4, restless; 5, inconsolable) on a 5-point scale that ranges from 0 to 4. The score for each item was added to obtain the total PAED scale score, with a higher total score indicating more severe EA (0 = no emergence agitation; 20 = extreme emergence agitation). PAED Scores >12 was defined as having emergence agitation[28]. PAED score >15 was defined as severe agitation.[18]

In case of agitation in the recovery, the first measure was to facilitate parental contact. The emergence agitation of >5 minutes (*if any)* would have been treated with fentanyl 1 mcg/kg. If the emergence delirium was not controlled till 10 minutes, same dose would have been repeated and total fentanyl consumption would have been recorded.

Modified Post Anesthesia Discharge Scoring System (mPADSS)[29] score $\geq$9 was noted and recorded. Recovery time was calculated as time from removal of LMA to Aldrete score $\geq$9 and discharge time was calculated as time from LMA removal to discharge from hospital.

Postoperative vomiting was defined as the forceful oral expulsion of liquid or solid gastric contents. Vomiting was treated with injection Ondansetron 0.1 mg/kg. Desaturation was defined as oxygen saturation <92% and oxygen supplementation was provided via face mask.

The collected data was analyzed using various statistical tests by means of statistical software-IBM SPSS Statistics version 21 for Mac. All data were tested for normal distribution using Kolmogorv-Smirnov test. The gender and ASA distributions of the patient were compared using Chi square test. The age of the patient, recovery time, mean heart rate at different time intervals, and discharge times were compared using Student's t test and results are displayed in mean$\pm$ SD. Weight of patients, duration of anesthesia, average PAED score were compared using Mann Whitney U test and results are displayed as median and interquartile range (IQR). The incidence of PAED score >12 and 12-15 were compared using Fisher's exact test. Data were considered to be statistically significant if p value was <0.05.

Results

A total of 94 patients who met the inclusion criteria were included in the study. One patient was excluded because the anesthesia duration was less than 15 mins and 3 were excluded because the surgical duration was more than 60 mins. Details is shown in figure 1 below.

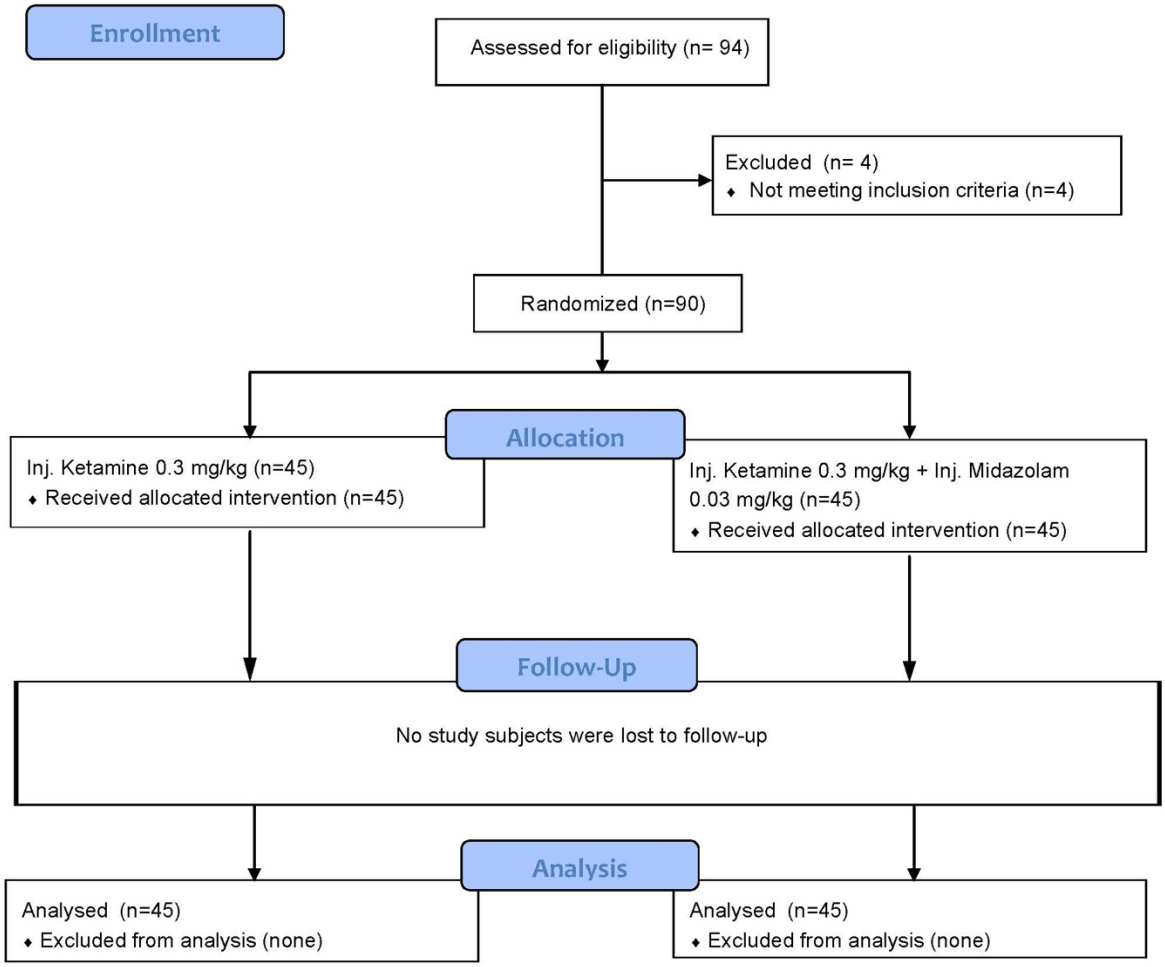

Figure 1 CONSORT Flow Diagram

The patients in both the groups were comparable for age, sex, weight, ASA-PS, and anesthesia duration as shown in table 1.

Table 1 Demographic Data

Variables	Ketamine Group (mean ± SD)	Ketamine with Midazolam Group (mean ± SD)	Test of significance '*p*' value
Age (years)	5.65±2.58	5.62±2.81	0.954
Gender (Male), N (%)	31 (68.88)	29 (64.44)	0.823
Gender (Female), N (%)	14 (31.12)	16 (35.56)	
Weight (kg), median (IQR)	16 (13-19)	16 (12-20)	0.868
ASA I, N (%)	45 (50)	45 (50)	1.0
Anesthesia period (mins), median (IQR)	27 (18-35)	30 (21-50)	0.101

The median PAED score of 6 with IQR (4-6) in Ketamine group was not statistically different from median PAED score of 5 with IQR (4-6) in Ketamine with Midazolam group as summarized in table 3.

Table 2 PAED Score

PAED score	Ketamine Group (N=45)	Ketamine with Midazolam Group (N=45)	Test of significance '*p*' value
Score, Median (IQR)	6 (4-6)	5 (4-6)	0.053
<12, N (%)	42 (93.33)	43 (6.67)	1.00
12-15, N (%)	3 (6)	2 (4.4)	
>15, N (%)	0 (0)	0 (0)	

Other parameters:

Recovery time was significantly lower (p<0.001) in ketamine group than in group with ketamine and midazolam.

Table 3 Recovery time

Recovery time*	Ketamine group (mins) [mean±SD]	Ketamine with Midazolam Group (mins) [mean±SD]	Test of significance '*p*' value
Time to Aldrete score ≥9	22.00±4.82	25.75±3.32	**<0.001**

* defined as the time from stopping of anesthetic agent to attainment of Aldrete score of ≥ 9

The discharge time was significantly lower (p<0.001) in ketamine group than in ketamine and midazolam group as summarized in table 5 below.

Table 4 Time to discharge from hospital

Time to discharge from hospital*	Ketamine group (mins) [mean±SD]	Ketamine with Midazolam Group (mins) [mean±SD]	Test of significance '*p*' value
Time to discharge from hospital	67±11	108±18	<0.001

*assessed as mPADSS ≥ 9 before discharge from hospital.

One patient in ketamine group and 3 patients in ketamine and midazolam group desaturated in the PACU requiring oxygen supplementation but this was not statistically significant.

Discussion

Emergence Agitation

Emergence agitation is associated with outcomes that is not favorable to either the patients, or the parents as it would be very distressing for any parents to see their beloved child agitated and incoherent in the post-operative period. Sevoflurane use especially in the pediatric outpatient surgeries is going to increase in the days to come such that we will be seeing more of these reactions in the post-operative period unless dramatic measures are taken.

Ketamine and midazolam are both drugs that have a long history of perioperative use in various outsets. These agents have also been used on several occasions for addressing the problem of EA. Ketamine has been used as sole agent for addressing the problem of EA though with differential results. Midazolam by itself hasn't been shown to address the problem EA although its use along with ketamine has long been lauded until the investigators were aware of its relatively negative influence on speeding the recovery and discharge after ambulatory surgeries.

In this study, we assessed the EA by using the most popular PAED scale. Age, preoperative anxiety, surgery type, and postoperative pain are confounding factors for emergence agitation. To minimize anxiety, children were separated from the parents just at the door of pre-anesthetic room. Postoperative analgesia was given according to hospital protocol.

In this study, total 3 patients in ketamine group and 2 patients in ketamine with midazolam group had PAED scores more than 12 whereas none of the patients were severely agitated. No other intervention beside the parental contact was necessary as the agitation didn't last longer than 5 minutes. Kyung Mi Kim, Ki Hwa Lee, et al also compared intravenous Midazolam and Ketamine on emergence agitation in children[30] and they reported emergence agitation (based on Aono's Four Point Scale >3) incidence in the Ketamine group to be 24.2% whereas in the Midazolam group 44.2%. This difference may be attributed first of all to the different scoring system used for emergence agitation and to the ketamine dose of 1 mg/kg which is much higher than the dose used in this study. However, the investigators had used a single 1 mg/kg dose of Ketamine even if the surgery lasted up to 2 hours. Thus, the same dose of Ketamine may have been the reason for emergence agitation in short procedures and the same dose may not have been adequate enough to control post-operative agitation for longer procedures.

Gulcan Erk, Dilsen Ornek, et al[31] also reported a higher incidence of mild agitation in Ketamine-Midazolam group (up to 85.7%) than group Ketamine (up to 67.9%). However, the incidence of moderate agitation was lower in group KM (3.6%) compared to group K (25%) which is also consistent with the results of this study. They also reported incidence of severe agitation of 7.1% in group K (on postoperative day 1) whereas no incidence of severe agitation was noted in group KM similar to our study. Similarly, Ahmed M. Khattab, Zeinab A., El-Seify, et al[32] reported an agitation incidence of 37% in group M and 10.9% in group KM. Their use of Ketamine and Midazolam as oral premedication may suggest altered and possibly inconsistent pharmacokinetics and dynamics compared to IV use of the same drugs. In other study, Shahwan et al[33] have reported an median PAED score as 7 with IQR (0-19) in Ketamine group which is similar to the incidence in this study. In study by Ozcan et al[34] the median PAED score in group Ketamine was 5 which is consistent with this study. The reported incidence of emergence agitation of around 19% in group Ketamine is higher than the incidence in this study. This difference can be attributed to the lower threshold of PAED score (as 10) that the authors have taken in their study compared to our threshold of 12 to define emergence agitation.

Recovery Time

When compared to other study by Jia-Yao Chen et al[18] with recovery time of 33.5±4.4 min, the recovery time in this study is comparatively shorter. The difference in terms of shorter recovery time may be due to the relatively low dose of Ketamine used and not using a continuous infusion of Ketamine in this study. In a study by Ahmed M. Khattab, et al[15], have reported the mean time to eye opening in the group KM as 9.6±1.3 min whereas in group M as 9±1.4 min which is lower than that in this study. The difference is most likely is due to their reliance only on eye opening as a sign of recovery. Ketamine is thought to cause effect where patient may be opening his/her eyes but not responding to verbal stimuli thus limiting the usefulness of eye opening only as the sole criteria for recovery. In study by Yoon Sook Lee, et al[25], the median time to Aldrete score was calculated as 40 min with IQR of 40 to 50 minutes. The longer recovery times in their study even with similar doses of Ketamine (0.25 mg/kg versus 0.3 mg/kg in our study), can be attributed to their average longer duration of surgery and longer exposure to Sevoflurane.

Discharge Time

In study by Hanna Viitanen, et al[23] who compared Midazolam with placebo in patients undergoing Sevoflurane anesthesia, the mean time to discharge from hospital was 80±23 minutes in Midazolam group compared to 70±23 minutes in placebo group. This result is consistent with the finding of this study. The average longer time to discharge in this study may be due to our use of modified PADSS score of > 9 as a sole criterion for discharge from hospital whereas authors Hanna, et al relied upon subjective assessment of discharge from hospital. In other study by Ahmed M. Khattab, et al[15], the

hospital discharge times in their study in Midazolam group was 211±21 minutes compared to 191±76 minutes in the Ketamine with Midazolam group. This is in contrast to the finding of this study because average duration of anesthesia exposure in their study was 90 minutes and the patients were electively intubated for the surgery. In addition, patients in the Midazolam group had higher incidence of recovery agitation which caused a higher consumption of postoperative fentanyl which might have added to the effect of prolonging discharge time.

Side Effects Profile

In this study, no patients had episodes of nausea or vomiting and hallucinations. One patient in Ketamine group and three patients in Ketamine with Midazolam group had episodes of desaturation where SpO2 was <92% and required supplementation with 100% oxygen in the PACU. The finding of this study is in consistent with other studies involving Midazolam as premedication.

Not using an objective pain scoring method was the limitation of this study as pain is often implicated for emergence agitation. However, subjective assessment for pain was done continuously and no patients were in pain post-operatively.

We conclude from this study that there is no significant difference between Ketamine and Ketamine with Midazolam in terms of emergence agitation and occurrence of side effects.

Generalizability:

The results of our study can be extended to other patient groups as well, for example in any patient group which are to be done on day care basis and where there is requirement of general anesthesia. Orthopedic surgeries like close reduction which are done on outpatient basis can also be done using ketamine for analgesia in the recommended dose and we won't be expecting an increased in emergence agitation.

Conflict of interests

All authors have filled the ICMJE conflict of interest form and declare that they have nothing to disclose.

Acknowledgment

We would like to acknowledge the incessant help and advices of the following persons during the conduction of this study: Prof. Dr. Amir Babu Shrestha, Prof. Dr. Ravi Ram Shrestha, Dr. Abhishesh Shrestha, Asst. Prof. Dr. Pawan Kumar Hamal, Dr. Purna Radha Shrestha, and Asst. Prof. Dr. Abhay Pokharel.

Sources of funding

The authors received no funding from any sources for the study.

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