

A Clinical Evaluation of the Effects of Administration of Midazolam on Ketamine-Induced Emergence Phenomenon

LOHIT K, SRINIVAS V, CHANDA KULKARNI, SHAHEEN

ABSTRACT

Ketamine administration in anaesthetic practice is known to induce postoperative 'emergence phenomenon'. In the present study we evaluated effect of peri-operative midazolam on postoperative emergence phenomena following ketamine anaesthesia. This was a comparative, prospective, cross-sectional, observational study. Total of 60 cases, posted for surgical procedures with 30 each, who received either ketamine or ketamine with midazolam, for elective and emergency surgical procedures, were evaluated applying inclusion and exclusion criteria. Data was collected for type of surgery, dose of anaesthesia and occurrence of postoperative events for four hours after surgery, including subjective symptoms and adverse effects related to anaesthetic agents. There were more males [78.30%] than females [21.70%], with majority

between 1-20 years (45%) of age. Surgical procedures included 50% from general surgery, 33% urology and 16.70% orthopaedic departments. Overall postoperative recovery was complete in 60%, satisfactory in 28.33% and poor in 11.66%. Occurrence of postoperative emergence phenomenon (EP) was seen in 76.66% cases during 2nd and 3rd hour in ketamine group, while a significant reduction in occurrence of adverse events was observed during 4 hrs postoperative period, along with complete recovery in 100% patients who received combination of ketamine with midazolam. In conclusion, perioperative administration of midazolam with ketamine in the present study was found to be effective in controlling EP, leading to a smooth post surgical recovery. Therefore, combined use of ketamine with midazolam may be recommended in future anaesthetic practice.

Key Words : Ketamine, Midazolam, Emergence phenomenon

INTRODUCTION

Ketamine [K], an anaesthetic agent is routinely used intravenously or intramuscularly for the induction and maintenance of general anaesthesia. It is often a first-line agent for short, painful procedures in the emergency department or outside the operating room.[1] Ketamine is known for its unique properties that make it useful in cases at risk of hypotension like emergency surgery, when the patient's state of fluid volume is unknown and in those with co-existing bronchospasm including certain paediatric procedures.[2] Patients on ketamine are reported to have electrophysiological dissociation termed as "dissociative anaesthesia" characterized by profound analgesia, unresponsiveness to commands, amnesia, while preserving cardiovascular stability, spontaneous respirations and protective airway reflexes even when exerting its full effect.[1,2] This cataleptic state is accompanied by some side effects like nystagmus with pupillary dilation, ataxia, salivation, lacrimation, spontaneous limb movements with increased overall muscle tone.[3] Emergence delirium, a frequent complication of Ketamine is characterized by hallucinations, vivid dreams, and illusions, that can result in serious patient dissatisfaction and can complicate postoperative management and recovery.[4]

Midazolam [M], has a potent anxiolytic, amnesic, sedative, hypnotic, anticonvulsant, and skeletal muscle relaxant properties. Intravenous midazolam is frequently indicated for procedural and pre-operative sedation, induction of general anaesthesia, and to sedate ventilated cases in critical care units.

The sedative regimen of combining intravenous ketamine with midazolam is reported to be safe and effective and to greatly

reduce anxiety when used for diagnostic and therapeutic procedures in children.[5]

However, limited data is available regarding the usefulness of ketamine with midazolam, combination among subjects of wide age range, undergoing invasive procedures.

Therefore, the primary objective of the present study was to evaluate the extent and pattern of emergence phenomena [EP] following ketamine, as well as influence of administration of peri-operative midazolam on postoperative ketamine-induced emergence phenomena.

SUBJECTS AND METHODS

This was a prospective, cross sectional, comparative, observational study, conducted at a tertiary care hospital, by the Department of Pharmacology in collaboration with Department of Anaesthesia. The data from 60 patients posted for surgery from departments of general surgery, urology and orthopaedics receiving ketamine or ketamine with midazolam as anaesthetic agent was collected after obtaining the informed consent. The cases meeting following inclusion and exclusion criteria were considered for further evaluation.

Inclusion Criteria:

1. Patients of either gender, up to 60 years of age.
2. Patients irrespective of type of diagnostic and/or therapeutic surgical procedures who received ketamine or ketamine with midazolam anaesthesia.

Exclusion Criteria:

1. Patients with hypertension, severe angina, myocardial infarction or other cardiovascular disorders.
2. Patients with increased intracranial tension.

1. Light sleep / sedation	5. Nystagmus
2. Increased muscle tone	6. Hallucination
3. Vomiting	7. Diplopia
4. Delirium	8. Salivation
9. Night mares	

[Table/Fig-1].: Postoperative adverse events as a part of emergence phenomena after ketamine and ketamine with midazolam administration

- Elderly patients with glaucoma.
 - Patients with a history of psychiatric illness.
- Study procedure, follow up and assessment:

The present study was an observational study. A total of 60 patients who received ketamine alone 1 to 3 mg/kg, i.v. [Group K, n = 30] or a combination of ketamine and midazolam, 1 to 2.5 mg, i.v. [Group K + M, n = 30] as decided by anaesthesiologist were considered for assessment of postoperative emergence phenomena. The investigators of the study involved in assessment of patients during post-surgical period were blinded to the treatment allocation.

The data regarding patient demographic characteristics such as age and gender, including type of surgical procedure, dose and type of anaesthesia, was collected and recorded from their respective surgical notes. All the patients who met inclusion / exclusion criteria and those who received ketamine or ketamine with midazolam were considered for evaluation. All the study patients were observed closely and assessed for presence or absence of various parameters as a part of emergence phenomena during four hours postoperative period and these were recorded. The various postoperative events assessed are shown in [Table/Fig-1]. A specially designed Case Record Form [CRF] was used to collect the data.

The subjective symptoms as reported by patients during assessment period were recorded as either present or absent. The postoperative recovery was graded as – complete, satisfactory and poor based on assessment of severity of symptoms.

The statistical analysis of the mean values for each parameter in 30 patients was calculated separately and compared using paired 't' test. Between the group comparisons for various emergence phenomena parameters in patients receiving ketamine and ketamine with midazolam groups, was carried out using ANOVA.

RESULTS

The evaluation of gender wise distribution, among total of 60 cases showed male preponderance [78.3 %] over females [21.7%]. Majority of the cases were in the age group of < 20 years [45 %] followed by other age groups with 28.3% and 26.7% each in the age range of 21-40 years and 41-60 years respectively.

Type Of Surgery	Surgery		Urology		Orthopedics		Total
	K Group	K + M Group	K Group	K + M Group	K Group	K + M Group	
Emergency	16	5	2	0	1	5	29
Elective	2	7	7	11	2	2	31
Total %	18 30%	12 20%	9 15%	11 18.33%	3 5%	7 11.66%	60 100%

[Table/Fig 2] : Department wise distribution and the type of surgical procedures in patients who received ketamine (K) or ketamine with midazolam (K+M)

The type of surgical procedures showed, 50% from general surgery with 35% emergency and 15% elective procedures. Out of 33.33% cases from urology, there were 3.33% from emergency and 30% elective. The department of orthopaedics had 16.66% cases, with 10% emergency and 6.66 % elective procedures [Table/Fig-2].

A further, analysis of emergency procedures from department of general surgery included maximum number of laparotomies and debridement [13.30% each], followed by appendicectomies 5%. The department of urology, had maximum number [15%], of cystoscopies followed by circumcision [6.6%], and while the department of orthopaedics had more number of incision and drainage 6.6% followed by debridement 5%.

The extent of occurrence of post-operative emergence phenomena was seen maximally among cases receiving ketamine alone 76.66%, while none in those who received ketamine with midazolam. Also, age wise distribution of emergence phenomena was 100% among patients > 20 and 63.15% in patients < 20 years of age who received ketamine alone [Table/Fig 3].

Varying degree of severity of adverse effects were seen in the Group which received ketamine alone, during 4 hrs postoperative observation period. Complete recovery in 23.33% cases in this group was seen. The rescue medications were used by the anaesthetists if need was felt. The group which received ketamine with midazolam, the adverse effects were less frequent and showed statistically significant improvement along with 100% recovery within 3 hrs postoperative period [Table/Fig 4].

DISCUSSION

Ketamine is widely used for procedural sedation as well as for its analgesic and amnestic properties in routine clinical practice. It is reported not to cause sedation along a continuum, and is not known to affect degree of sedation with titrating doses. The dissociation with ketamine is reported to be either present or absent with a very narrow transition zone and in fact, titration of dosing once dissociation is achieved is said to be only used in prolonging the dissociative effect.[3-5] However, its benefits as a dissociative anaesthetic agent are still being explored.[6]

Several receptors as well as neurochemical mechanisms have been hypothesized to be implicated in the occurrence of EP, viz – NMDA, opiates, dopamine, acetylcholine etc. Hence, a wide variety of drugs belonging to different class are being tried to prevent or treat symptoms of emergence phenomena with some success, however none appear to be completely effective. Hence, the search for supplementary or combination drugs like promethazine,[7] haloperidol,[8] propofol,[8] midazolam,[2,9,10] etc continues, to explore most appropriate option in anaesthetic practice and their use till date remains empirical.[1,4]

Department	Emergence phenomenon K Group (n = 30)				Emergence phenomenon K + M Group (n=30)			
	Age range(yr)				Age range(yr)			
	0-20	21-40	41-60	Total	0-20	21-40	41-60	Total
Surgery	7/11	4 / 4	3 / 3	14 /18	2	0 / 6	0 / 4	0/12
Urology	4 / 7	2 / 2	0 / 0	6 / 9	0 / 1	0 / 1	0 / 9	0/11
Orthopaedics	1 / 1	2 / 2	0 / 0	3 / 3	0 / 5	0 / 2	0 / 0	0/7
TOTAL (%)	12/19 (63.15%)	8/8 (100%)	3/3 (100%)	23 / 30 (76.66%)	0 / 8 (0%)	0 / 9 (0%)	0 / 13 (0%)	0/30 (0%)

[Table/Fig 3]: Extent of postoperative emergence phenomenon in patients who received ketamine(K) and ketamine with midazolam(K + M)

In the present study a significant proportion of patients receiving ketamine exhibited emergence phenomena and was observed in a wide age range of patients. Further, occurrence of emergence phenomena was irrespective of the type of procedure [elective/emergency] as well as type of surgical specialty. In patients who received combination of ketamine with midazolam did not exhibit occurrence of emergence phenomena, thus demonstrating beneficial effects of this combination.

Many of the effects and some adverse events of ketamine such as cardiovascular stimulation with tachycardia, hypertension, hyper tonicity, including hallucinations, nightmares and other transient psychotic effects are linked with its sympathomimetic actions.[11] The incidence of these phenomena increases with age and with psychiatric co morbidities. In addition, ketamine has been known to exacerbate established psychosis and is thus, contraindicated in this condition.[12] In the present study such patients were not included.

Delirium is reported to occur less frequently in children. It is said that benzodiazepines reduce the incidence of emergence delirium. But the combined use of ketamine with benzodiazepines in children is still controversial.[4,5] Also, the association between dose of ketamine and severity of emergence phenomena, it's optimal dose required to avoid occurrence of emergence phenomena have not been defined.[3,13] Results of the present study appear encouraging as there was lack of age dependent variation in occurrence of severity of emergence phenomena in the group receiving ketamine and complete absence of emergence phenomena following ketamine with midazolam administration, in all the patients irrespective of the age.

Fixed doses of intravenous ketamine and midazolam were used in our study as recommended by the anaesthetist based on

body-weight and hence it is difficult to relate if the emergence phenomena observed was a dose dependent effect and to comment on the comparative effects of I.V. route of administration with various other routes of ketamine and midazolam administration like oral or rectal. [13-17] It is also, difficult to comment if the dose of midazolam used could be considered as an ideal dose that can be combined with ketamine in future practice.

A clinical trial has demonstrated beneficial effects of using ketamine and midazolam combination in regional neuraxial anaesthesia to prevent shivering and showed that ketamine and midazolam doses were higher when used separately and could be reduced when used in combination.[9] Another study has demonstrated safety and efficacy of ketamine with midazolam combination for procedural sedation and analgesia in children posted for oncology procedures.[10] Doses of ketamine and midazolam, used in their study were 0.5-1 mg/kg and 0.05-2 mg/kg respectively, by intravenous route. In the present study, relatively higher doses of K and M were used, with no serious adverse effects. Lack of untoward effects despite large doses in Indian population reflects on better tolerability, however the same is difficult to justify and hence this aspect may need further evaluation.

A study done to examine effects of promethazine on ketamine induced emergence phenomena concluded that promethazine effectively controlled the symptoms of emergence phenomena because of its sedative, anxiolytic and anti-emetic activities.[7] However, this study failed to record and report the adverse effect profile of promethazine although it is well known for its untoward effects. In the present study all the patients were closely monitored for four hours during post-operative period and no untoward effects were seen in those patients who received ketamine with midazolam.

Parameter	1st hour			2nd hour			3rd hour			4th hour		
	K	K+M	P value	K	K+M	P value	K	K+M	P value	K	K+M	P value
Light sleep	21	30	0.0001	5	3	0.353	1	0	0.5	1	0	0.5
↑ muscle tone	25	7	0.0001	21	0	0.0001	11	0	0.0001	4	0	0.056
Vomiting	7	0	0.005	10	0	0.0001	4	0	0.056	2	0	0.246
Delirium	3	0	0.119	6	0	0.012	2	0	0.249	1	0	0.5
Nystagmus	3	0	0.119	8	0	0.002	8	0	0.002	2	0	0.246
Hallucination	0	0	-	8	0	0.002	4	0	0.056	1	0	0.5
Diplopia	0	0	-	1	0	0.5	4	0	0.056	4	0	0.056
Salivation	1	0	0.5	4	0	0.056	2	0	0.246	2	0	0.246
Night mares	0	0	-	0	0	-	0	0	-	1	0	0.5

[Table/Fig 4]: Number of patients with adverse events as a part of emergence phenomenon during 4 hrs postoperative period, who received ketamine(K) or ketamine with midazolam(K + M)

It is to be noted that in the present study a variety of invasive procedures were carried out in patients representing different surgical specialties and of wide age range. Interestingly, the results show 100% relief from signs/symptoms of emergence phenomena in patients receiving combination of ketamine and midazolam. Also, the reported outcome in the present study is un-biased as the observations for emergence phenomena was carried out by an intern who was un-aware of the pattern of administration of anesthetic agents and was blinded until 4 hrs of postoperative period. Further, the patients received either ketamine or ketamine with midazolam, randomly as decided by the anesthetist. In this respect the present data is more reliable.

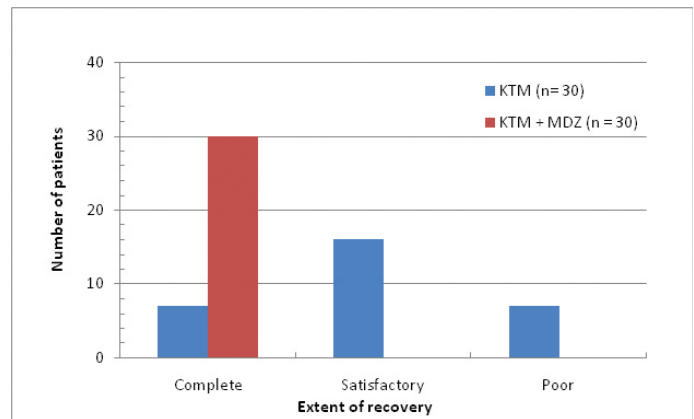
Yet another observation was that the combination of ketamine with midazolam, was administered in maximum number of patients undergoing major surgical procedures as against study by Kothari D, where ketamine was maximally used in short surgical or diagnostic procedures with promethazine.[7] Therefore, present observations add further evidence to the results showing effectiveness of combination in more critically ill patients and to procedures involving major and deeper structures, including orthopaedic surgeries. Hence, the combination of ketamine with midazolam may be considered as a more effective regimen in anaesthetic practice to offer substantial benefit in controlling occurrence of emergence phenomena in a wide variety of surgical procedures.

CONCLUSION

In the present study patients who received ketamine exhibited significant increase in severity and frequency of occurrence of post operative adverse events as a part of emergence phenomena, compared to those who received ketamine with midazolam, who had smooth and complete post surgical recovery. The study shows beneficial effects of midazolam when combined with ketamine. However, more studies in larger number of patients will help in confirming such benefits and guide future practices in controlling symptoms associated with emergence phenomena.

REFERENCES

- [1] Mistry RB, Nahata MC. Ketamine for conscious sedation in pediatric emergency care. *Pharmacotherapy* 2005; 25:1104-11.
- [2] Green SM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation in children. *Ann Emerg Med* 2004;460-71.
- [3] Howes MC. Ketamine for paediatric sedation / analgesia in the emergency department. *Emerg Med J* 2004; 21: 275-80.
- [4] Dolansky G, Shah A, Mosdossy G, Rieder M. What is the evidence for the safety and efficacy of using ketamine in children? *Paediatr Child Health* 2008; 13: 307-8.
- [5] Erk G, Ornek D, Dönmez NF, Taspınar V. The use of ketamine or ketamine



[Table/Fig 5]. : Extent of recovery in patients who received ketamine or ketamine with midazolam

- midazolam for adenotonsillectomy. *Int J Pediatr Otorhinolaryngol* 2007; 71: 937-41.
- [6] Nemergut EC. Ketamine: still learning its secrets after 45 years. *J Neurosurg: Pediatrics* 2009; 4: 37-39.
 - [7] Kothari D, Mehrotra A, Jain A.K., Dixit S. Role of promethazine in post ketamine emergence phenomenon - a clinical evaluation *Indian J Anaesth* 2003; 47: 456-57.
 - [8] Glen AM., Maano M. Haloperidol for the Treatment of Ketamine-Induced Emergence Delirium. *J Anesth Clin Pharmacology* 2007; 23: 65-67.
 - [9] Honarmand A, Safavi M. Comparison of prophylactic use of midazolam, ketamine and ketamine plus midazolam for prevention of shivering during regional anesthesia: a randomised double-blind placebo controlled trial. *Br J Anaesth* 2008; 101: 557-62.
 - [10] Borker A, Ambulkar I, Gopal R, Advani SH. Safe and efficacious use of procedural sedation and analgesia by non-anesthesiologists in a pediatric hematology-oncology unit. *Indian Pediatrics* 2006; 43: 309-13.
 - [11] Vardy JM, Dignon N, Mukherjee N, Sami D M, Balachandra G, Taylor S. Audit of safety and effectiveness of ketamine for procedural sedation in emergency department. *Emerg Med J* 2008; 25: 579-82.
 - [12] Honey GD, Phillip R, Corlett, Anthony R. Absalom, Lee M et al. Individual differences in psychotic effects of ketamine are predicted by brain function measured under placebo. *The Journal of Neuroscience* 2008; 28(25):6295-03.
 - [13] Ozdemir D, Kayserili E, Arslanoglu S, Gulez P, Vergin C. Ketamine and midazolam for invasive procedures in children with malignancy: a comparison of routes of intravenous, oral, and rectal administration. *J Trop Pediatr* 2004; 50: 224-28.
 - [14] Wathen JE, Roback MG, Mackenzie T, Bothner JP. Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized, controlled, emergency department trial. *Ann Emerg Med* 2000; 36: 579-88.
 - [15] Kulkarni JA. Oral ketamine for premedication in children. *Bombay Hospital Journal*. 2003; 45(3):6.
 - [16] Damle SG, Gandhi M, Laheri V. Comparison of oral ketamine and midazolam as sedative agents in pediatric dentistry. *J Indian Soc Pedod Prevent Dent* 2008; 26(3): 97-101.
 - [17] RaghuRaman TS, Deshmukh J. Painless invasive procedures. *Indian Pediatric*. 1999; 36: 1023-28

AUTHOR:

1. DR. LOHIT K
2. DR. SRINIVAS V
3. DR. CHANDA KULKARNI
4. DR. SHAHEEN

NAME OF DEPARTMENT(S)/INSTITUTION(S) TO WHICH THE WORK IS ATTRIBUTED:

1. Division of Clinical Pharmacology, St. John's Medical College, Bangalore
2. Department of Pharmacology, Vijayanagara Institute of Medical Sciences, Bellary

NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr.Mrs.Chanda Kulkarni.MBBS;
MD; Ph.D;FSASMS;Cert.Clin.Epilepsy
Professor & Head, Clinical Pharmacology
St.John's Medical College, Bangalore : 560034 India
T 091-80-22065045 [work]
T 091-80-25534994 [home]
E drchandakulkarni@gmail.com

DECLARATION ON COMPETING INTERESTS: No competing Interests.

Date of Submission: **Dec 23, 2010**
Date of Peer Review: **Jan 08, 2011**
Date of Acceptance: **Jan 15, 2011**
Date of Publication: **Apr 04, 2011**
Date of Erratum: **Jun 21, 2011**