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Original Research Article

Assessment of Midazolam for Attenuating Psychomimetic and Cardio-Vascular Side Effects of Ketamine

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ABSTRACT

Background: In comparison to other drugs, midazolam combined with intravenous ketamine has been proven to be more safe and effective for relief of anxiety and sedation for diagnostic and therapeutic procedures and also emergence reactions are fewer with midazolam. So, we planned the present study for assessment of midazolam for attenuating psychominmetic and cardio-vascular effects of ketamine.

Materials and methods: For the study, 60 patients with American Society of Anesthesiologists (ASA) Grade I and II scheduled for minor short surgical procedures were selected. In all the cases, the duration of surgery was equal to or less than 40 minutes.

Results: Significant effect on the occurrence of emergence phenomenon and unpleasant dreams of ketamine were observed with administration of midazolam premedication. Non-significant effects were observed on the occurrence of excitatory effects of ketamine (P<0.5).

Conclusion: This can be concluded that for reduction of psychic sequelae of ketamine anesthesia midazolam is an effective premedicant and in comparison to other benzodiazepines, midazolam is a better premedicant.

Keywords: Ketamine, Midazolam, Preaneasthetic medication, Dissociative anaesthesia.

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INTRODUCTION

Ketamine is an excellent intravenous anesthetic. It is a dissociative anesthetic agent having rapid action. Ketamine has properties like rapid induction, good analgesia, and amnesia with short recovery period. So it is commonly used for short surgical procedures. But there are drawbacks in its use such as intraoperative cardiovascular stimulation, muscular hypertonia and association of postoperative psychomimetic effects with recovery.[1] These incidences are dose related and ranges from 5% to 30%.[2] Researchers have experimented on various drugs, to overcome these drawbacks. For preventing these emergence reactions associated with administration of ketamine, researchers have used drugs like opiates, neuroleptics, benzodiazepines, physostigmine, and alpha-2 adrenoreceptor agonists with varying success.[3]

Of all the drugs above, the use of benzodiazepines with ketamine has proved satisfactorily in improving the adverse effects during the perioperative period. But, there are some disadvantages with use of each benzodiazepine such as administration of flunitrazepam leads to prolonged mental activity impairment and amnesia, with lorazepam slower onset of action and delayed recovery is experienced and with diazepam incidence of unpleasant dreams is increased.[3] Midazolam used in dosage <0.5 mg/kg has potent anxiolytic effect with amnesia, sedation, skeletal muscle relaxant activity and significant lack of side effects.[4] In comparison to otherdrugs, midazolam combined with intravenous ketamine has been proven to be more safe and effective for relief of anxiety and sedation for diagnostic and therapeutic procedures and also emergence reactions are fewer with midazolam.[5] So, the present study was planned for comparative evaluation of midazolam, droperidol alone and in combination for attenuating psychominmetic and cardio-vascular effects of ketamine.

MATERIALS AND METHODS

The study was conducted on 60 patients with American Society of Anesthesiologists (ASA) Grade I and II scheduled for minor short surgical procedures. In all the cases, the duration of surgery was equal to or less than 40 minutes. Patients having medical history of hypertension, hyperthyroidism or psychiatric disorders were excluded from the study. The approval for the study was taken from the ethical committee of the institution. An informed written consent was obtained from the patients after explaining the procedure for the study to the patients.

Before the induction of anesthesia by ketamine, premedication was administered to the patients in the form of inj.Atropine 0.6 mg i.v. 30 minutes before and inj. Midazolam 0.05 mg/kg i.v. 5 minutes before. Pulse oximeter was connected to all the patients and recording of continuous monitoring of respiration, oxygen saturation, pulse rate, electrocardiogram (ECG) and blood pressure in the form of record form was done. Before the premedication, basal values of pulse and blood pressure were recorded.

Initial induction dose of ketamine 1mg/kg i.v. was given over one minute. Surgical procedure was permitted only after the establishment of surgical anesthesia, i.e, appearance of nystagmus. For analgesia, patients were made to breathe 67% Nitrous oxide+33% Oxygen through Boyle's machine. Whenever the patient showed movements during the surgery, intermittent doses of 0.25mg/kg of ketamine was administered to maintain surgical anesthesia. Throughout the surgery, intra-operatively blood pressure, heart rate, excitatory phenomena (tremors, involuntary movements and hyper tonus) and duration of surgical procedure were recorded.

Patients were observed for at least 30 minutes postoperatively in the quiet recovery room. Every 10 minutes, pulse, blood pressure and respiration were monitored. Recovery time, the time from the last dose of ketamine to when patient opened eyes was recorded. Other manifestations such as emergence delirium, nausea, vomiting and retching were observed in the patients. Classification of emergence delirium was done as mild and severe. Mild emergence delirium included patients with manifestations such as, purposeless movements and hallucinatory movements. Severe emergence delirium included those patients with screaming and violent involuntary movements which were disturbing to attendants and other patients. Patients were shifted to the postoperative ward from the recovery room after patient regained fully consciousness. The occurrence of emergence delirium was questioned to the patient's attendants at visits made at 6 and 24 hours after the operation and patients were questioned about the occurrence of dreams which were grouped as pleasant or unpleasant according to their content. Subjective symptoms of the patients were also noted during this period.

The data was expressed as mean ± S.D (standard deviation). The statistical significance of the data was checked using SPSS software for windows. Statistical significant value was considered at P<0.05.

RESULTS

The details of the parameters of the patients are given in the Table 1. Total no. of patients that were administered with Ketamine- Midazolam anesthesia was 45. There were 27 males and 18 females in the study. Mean age of the patients was 33.56± 8.87 years. Mean weight of the patients was 54.21 ± 8.23 kg. The mean duration of surgery was 28.84 ± 51minutes. The mean total dose administered was 58.16 ± 12.72 mg.

Table 1: Details of patients receiving Ketamine-Midazolam anesthesia

No of patients (n)	45
Male/Female	27/18
Age (years)	33.56 ± 8.87
Weight (kg)	54.21 ± 8.23
Duration of surgery (min)	28.84 ± 51
Total dose (mg)	58.16 ± 12.72

Table 2: Number of patients with incidence of excitatory phenomenon during anaesthesia, emergence delirium, unpleasant dreams and patient acceptance. (Comparison with Ketamine alone)

Parameters	Ketamine alone (n=30)	Midazolam (n=45)
Excitatory phenomenon	9	6*
Emergence delirium	15	4**
Mild delirium	6	4
Severe delirium	9	NIL
Dreams		14
Pleasant	***	12
Unpleasant	12	2
Nausea and/or vomiting	13	NIL
Patient acceptance	7	29

*P<0.5=Not significant; **P<0001=Significant

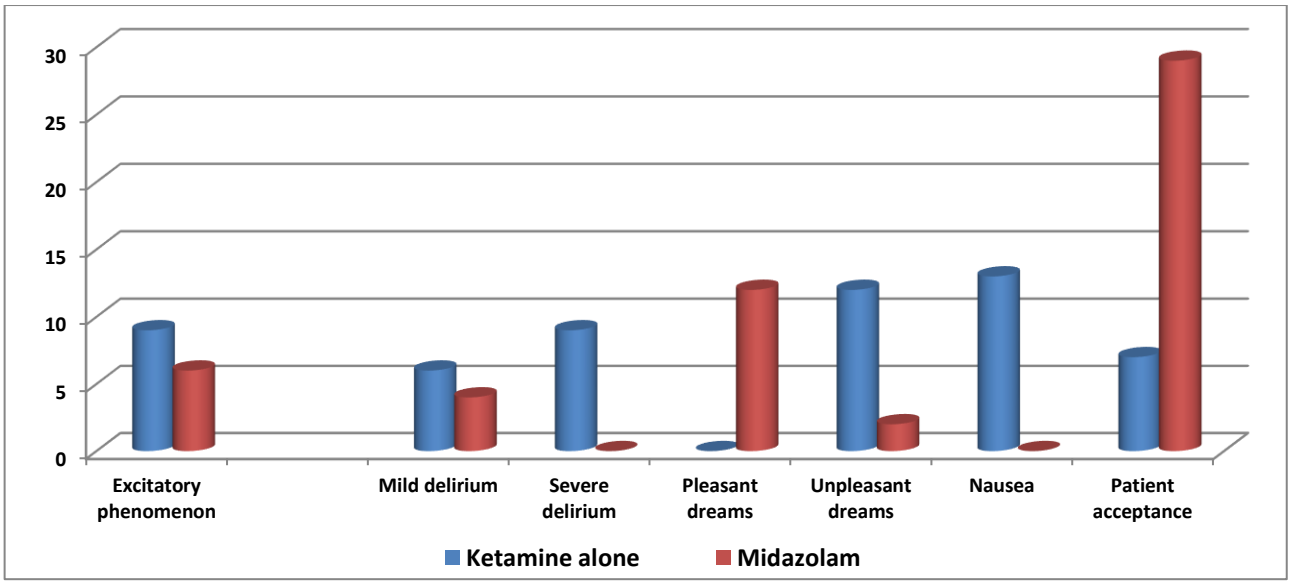

Fig 1: Number of patients with incidence of excitatory phenomenon during anaesthesia, emergence delirium, unpleasant dreams and patient acceptance. (Comparison with Ketamine alone)

The relevant findings of the present study are summarized in Table 2 and these findings are compared with ketamine alone (figure 1). Significant effect on the occurrence of emergence phenomenon and unpleasant dreams of ketamine were observed with administration of midazolam premedication. Non-significant effects were observed on the occurrence of excitatory effects of ketamine (P<0.5). No excitatory phenomenon was observed during induction and smooth induction was observed. Supplement dose of ketamine was administered in most of the cases.Mild delirium was experienced by 6 patients in case of ketamine alone and 4 patients in case of midazolam-ketamine anesthesia (P<0.05). The occurrence of severe emergence delirium was virtually abolished in the preoperative administration of midazolam but mild delirium was experienced by patients occasionally (n=4) (P<0.001). Similarly, significant reduction was observed in the occurrence of unpleasant dreams in the postoperative period with preoperative midazolam administration. Only 2 out of 45 patients experienced unpleasant dreams. The universal acceptance of ketamine anesthesia with midazolam premedication was the most important finding.

DISSCUSSION

Undesirable psychic sequelae are observed in ketamine induction. Nothing significant has been reported about the neurochemical basis for emergence, but for its occurrence various neurochemicals and receptors have been connected like N-methyl-D-aspartate (NMDA), opiates, dopamine, acetylcholine, etc. Studies have reported 15 to 55% of the incidence of excitatory phenomenon and emergence delirium without depressant premedication.[6] For the prevention and reduction of incidence of these undesirable sequelae, a number of drugs have been tried viz. diazepam, lorazepam, droperdol, etc. with different success rates.[7] among all of these benzodiazepines have been shown to be advantageous because of compensatory pharmacodynamics effects of benzodiazepines in producing muscle relaxation, anxiolysis, central sedation and in attenuating the emergence sequelae and cardiostimulation of ketamine.[8]

In the present study, reduction in the incidence of excitatory effects of ketamine by midazolam premedication was observed. As compared to other studies conducted by Lilburn et al[9] on other benzodiazepines viz. diazepam, lorazepam, flunitrazepam and J.W Dundee and J.K Lilburn[10] on various routes of lorazepam, the incidence was significantly reduced. The significant reduction in the incidence of emergence delirium was observed with midazolam premedication (4 out of 45 patients) and the incidence of occurrence of severe emergence delirium (0 patients) in the post-operative period was virtually abolished.

Perumal DK et al.[11] evaluated the effect of midazolam on hemodynamic stability and postoperative emergence phenomenon following ketamine anesthesia. In this study, 30 adult patients with American Society of Anesthesiologist physical grades I and II scheduled for elective short surgeries under ketamine anesthesia were selected. Before the administration of ketamine (1mg/kg, intravenously), patients were given midazolam (0.02mg/kg, intravenously) as premedication. Postoperatively, recording of pain score by visual analogue scale score and psychomimetic effects was done. It was observed that postoperatively mean ± standard deviation of heart rate, systolic blood pressure, diastolic blood pressure, and respiratory rate are decreased (85.3 ± 11.4, 120.7 ± 8.2, 79.2 ± 5.5, 13.5 ± 1.8, respectively) in comparison to intraoperative period (88.53 ± 14.1, 123.83 ± 13.8, 83 ± 9.1, 14.13 ± 2.0, respectively). The decrease in systolic and diastolic blood pressure was statistically significant (P =0.03) and (P = 0.002) respectively but the decrease in heart rate and respiratory rate was non-significant. They concluded that midazolam premedication in ketamine anesthesia effectively attenuated the hemodynamic pressor response and postoperative emergence phenomenon. Hence, the combination of midazolam with ketamine can be safely used for short surgical painful procedures in adults.

Levänen J et al.[12] conducted a double-blind, randomized and comparative parallel-group study with 40 volunteers having ASA physical status 1 scheduled for elective superficial surgery under ketamine anesthesia. Before administering intravenously ketamine (2mg/kg) to the patients for induction of anesthesia, premedication with dexmedetomidine (2.5 micrograms/kg, n = 20) or midazolam (0.07 mg/kg, n = 20) was administered intramuscularly. It was observed that after administering dexmedetomidine and midazolam intramuscularly equal sedative and anxiolytic effects are experienced but preoperative psychomotor impairment and anterograde amnesia are significantly less as compared to midazolam. But, the need for intraoperative ketamine was reduced with dexmedetomidine and also, adverse central nervous system effects were more significantly reduced with dexmedetomidine as compared to midazolam. It was concluded by the authors that premedication with 2.5 micrograms/kg dexmedetomidine is effective in attenuating the cardiostimulatory and post anesthetic delirium effects of ketamine.

CONCLUSION

This can be concluded that for reduction of psychic sequelae of ketamine anesthesia midazolam is an effective premedicant and in comparison to other benzodiazepines, midazolam is a better premedicant.

REFERENCES

1. Sawhney S, Agarwal RP. Combination of low dose ketamine and pentazocine - A clinical experience. Indian J Anaesth 2003;47:439-42.

2. White PF, Ham J, Way WL, Trevor AJ. Pharmacology of ketamine isomers in surgical patients. Anesthesiology 1980;52:231-9.

3. Somashekara SC, Govindadas D, Devashankaraiah G, Mahato R, Deepalaxmi S, Srinivas V, et al. Midazolam premedication in attenuating ketamine psychic sequelae. J Basic Clin Pharm 2010;1:209-13.

4. Kain ZN, Mayes LC, Bell C, Weisman S, Hofstadter MB, Rimar S. Premedication in the United States: A status report. Anesth Analg 1997;84:427-32.

5. Deng XM, Xiao WJ, Luo MP, Tang GZ, Xu KL. The use of midazolam and small-dose ketamine for sedation and analgesia during local anesthesia. Anesth Analg 2001;93:1174-7.

6. Magbagboela JAO. Ketamine-relaxant-air anaesthesia for abdominalsurgery in the developing countries. Br. J. Anaesth. 1987; 45:1217.

7. Reids D L and Silvay G. Ketamine: an update on the first twenty-fiveyears of clinical experience. Can J Anaesth. 1989; 36 (2): 186-97.

8. Langrehr D, Agoston S, Erdmann W and Newton D. Pharmacodynamicsand reversal of benzodiazepine-ketamine ataranalgesia. SouthAfrican Medical Journal. 1981; 59: 425-28.
9. Lilburn JK, Dundee JW, Nair SG, et al. Ketamine sequelae; Evaluationof the ability of various premedicants to attenuate its psychicactions. Anaesthesia. 1978; 33: 307-11.
10. Dundee JW and Lilburn JK; Ketamine-lorazepam; Attenuation of psychicsequelae of ketamine by lorazepam. Anaesthesia. 1978; 33: 312-14.
11. Perumal DK, Adhimoolam M, Selvaraj N, Lazarus SP, Mohammed MA. Midazolam premedication for Ketamine-induced emergence phenomenon: A prospective observational study. J Res Pharm Pract 2015;4:89-93
12. Levänen J, Mäkelä M L, Scheinin H. Dexmedetomidine premedication attenuates ketamine-induced cardio stimulatory effects and post anesthetic delirium. Anesthesiology. 1995 May; 82 (5):1117- 25.

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