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Original Article

Prevention of emergence phenomena after ketamine anaesthesia: A comparative study on diazepam vis-a-vis midazolam in young female subjects

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ABSTRACT

The undesirable psychological reactions that occur during awakening in subjects who were given ketamine anaesthesia are known as emergence reactions. Diazepam and Midazolam are the common benzodiazepines used to combat emergence reactions associated with ketamine anaesthesia. The current study is aimed at comparing the anti-emergence action of the commonly used Midazolam and diazepam. MATERIAL AND METHODS**:** The current prospective study was carried out at Government General Hospital Anantapuramu from January 2014 to July 2014 involving 50 young female subjects with an age group ranging between 16 to 30 years in two divided groups after obtaining the clearance from the institutional ethical committee. Results: All the subjects considered for the study were female. Mean age of the subjects in the Group-A was 24+/- 2.97 years while that in the Group-B was 23.72+/- 2.75.

Key words: Emergence phenomenon, Ketamine anaesthesia, short gynaecological procedures young female subjects

INTRODUCTION

The undesirable psychological reactions that occur during initial sixty minutes of awakening from ketamine anaesthesia are termed as emergence reactions. The common manifestations of these reactions will vary in severity and classification and may range from vivid dreaming, extra corporeal experiences (sense of floating out of body) to illusions (the misinterpretation of real, external sensory experience). Often the incidents of dreaming and illusions are associated with excitement, confusion, euphoria and fear.

A number of drugs have been used to reduce the incidence and severity of post-operative reactions to ketamine. However, benzodiazepines seem to be the most effective group of drugs to attenuate or treat ketamine emergence reactions of which Midazolam and Diazepam are trust worthy drugs as to combat with the emergence reaction. The exact mechanism of action is not known but it is attributed that both relative and amnestic actions of benzodiazepines make them superior to other sedative/hypnotic drugs. Midazolam is a newer water soluble, short acting intravenous benzodiazepine whereas diazepam is a lipid soluble drug with a prolonged action. The current study is a comparison between Diazepam and Midazolam in prevention of emergence reactions in young female subjects' in short gynaecological procedure. To study the effect of Diazepam and Midazolam as premedicant in prevention of emergence phenomena after ketamine anaesthesia in short gynaecological procedures involving young female subjects.

MATERIAL AND METHODS

The current prospective study was carried out at Government General Hospital Anantapuramu from January 2014 to July 2014 involving 50 young female subjects with an age group ranging between 16 to 30 years in two divided groups after obtaining the clearance from the institutional ethical committee. An informed consent is taken prior to the proposed interventions after thoroughly explaining the proposed procedure in detail from all the patients. All relevant and routine investigations were carried out prior to the proposed short gynaecological procedures.

Group-A consisted 25 cases and all of them received intravenous Diazepam in a dose of 0.14

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mg/Kg body weight and Atropine in a dose of 0.6 mg half an hour prior to surgery whereas Group-B which consisted of 25 patients received intravenous Midazolam in a dose of 0.07 mg/Kg bodyweight in place of Diazepam. For all the patients fit to ASA (American Association of Anaesthesiologists) Grade-I and Grade-II criteria and their heights and Weights were recorded preoperatively. After shifting to the operation theatre, all the subjects of both groups received intravenous ketamine anaesthesia according to their body weights. Blood pressure and pulse rate and Respiration watched carefully. All patients breathed room air spontaneously. All the patients were observed 12 hours in the post-operative period.

All the data was tabulated in a pretested Proforma and thus obtained results was analysed using appropriate statistical procedure (Chi square test).

RESULTS AND ANALYSIS

Demographic data(Table No.1): All the subjects considered for the study were female. Mean age of the subjects in the Group-A was 24+/- 2.97 years while that in the Group-B was 23.72+/- 2.75. Average weight of the subjects in the both groups was about 52 +/- 4kgs and average height ranged from 150-156 cms.

S.No.	Diazepam + Ketamine (Mean +/-S.D)	Midazolam + Ketamine (Mean +/- S.D.)
No. of patients	25	25
Sex	Females	Females
Age (Years)	24 $\pm$ 2.97	23.72 $\pm$ 2.75
Weight (Kg)	52.24 $\pm$ 4.36	52 $\pm$ 3
Height (Cms)	152 $\pm$ 4.727	150 $\pm$ 6.63

Table No. 1: **Demographic data**

Incidence of Emergency phenomenon (Table No.2): emergence phenomenon was observed in 68% of the subjects belonging to diazepam groups where as in Group-B the incidence of emergence phenomenon is only 20%. During injection of premedicant drug Diazepam and Midazolam patients are watched for subjective feeling of pains which revealed that 10 subjects of group-A complained of pain at the site of injection. It can be concluded that Midazolam is comparatively safer than Diazepam.

S.No.	Group-A	Group-B	'P' Value
Emergence reactions	17	5	< 0.001 significant
Dreams(good/bad)	4	0	> 0.05 Not significant
Visual Disturbances	4	2	> 0.05 Not significant

Table No.2: **Patients with emergency reactions, visual disturbances and memory of dreaming**

Duration of Anaesthesia (Table No.3): when duration of anaesthesia is concerned, Midazolam along with ketamine yielded better results than Group-A.

Dose of Ketamine (mg)	Diazepam with Ketamine Mean +/- S.D.	Midazolam with Ketamine Mean +/- S.D.	'P' values
Ketamine in (mgs)	136 $\pm$ 13.23	148 $\pm$ 25.28	< 0.05 significant
Duration of Anaesthesia (Minutes)	32 $\pm$ 5.7	36 $\pm$ 6	< 0.05 significant

Table No.3: Dose and duration of action

Types of gynaecological procedures (Table No.4): Table shows distribution of different gynaecological procedures performed over the subjects of both groups. Most of cases chosen for the study are tubectomies followed by medical termination of pregnancy followed by other cases. These are the cases which are routinely seen during the regular practice where ketamine anaesthesia is required.

Type of Operation	Number of cases Group-A	Number of Cases Group-B
D & C	1	0
MTP & Tubectomy	8	1
Misplaced IUD Removal	1	0
Secondary suturing	2	0
Tubectomy	13	23
Hysteroscopy	0	1
Total	**25**	**25**

Table No.4: Types of operations performed under ketamine anaesthesia

Incidence of Emergence phenomenon (Table No.5): when incidence of the emergence phenomenon is compared between two groups, it is observed that emergence phenomenon is quite common in diazepam group in relation to the Midazolam group.

Emergence Phenomena	Group-A	Group-B
Unpleasant dreams	8%	3 – 12%
Pleasant dreams	16%	--
Visual Hallucinations	16%	--
Auditory Hallucinations	12%	--
Restlessness including	4%	--
Movement	4%	--
Crying	4%	--
Nausea & Vomiting	4%	2 – 8%
Total cases:	**68%**	**20%**

Table no.5: incidence of emergence reactions

DISCUSSION

A number of drugs have been used to reduce the incidence and severity of post-operative reactions to ketamine. The benzodiazepines seem to be the most effective group of drugs to attenuate or treat ketamine emergence reactions of which Midazolam and Diazepam are established to be more useful. The exact mechanism is still in question but this specific action may be attributed to both relative and amnestic actions of benzodiazepines. Randall et al [1], in their studies shows that diazepam acts through the spinal reflex pathways. Midazolam is a newer water soluble benzodiazepine shot acting intravenous anaesthetic agent whereas diazepam is also a benzodiazepine but is lipid soluble and it has prolonged action. However, a study conducted by Cart Wright and Pringel Galle [2] states that single dose of Midazolam was more effective in reducing bad dreams but did not offer any advantage in reducing emergence reactions.

In this study Midazolam, the water soluble Benzodiazepine was studied and compared with Diazepam the merits and demerits in relation to occurrence of emergence phenomenon were evaluated in young female subjects who underwent short gynaecological procedures under ketamine anaesthesia.

Diazepam available in oily preparation which is painful during administration while Midazolam is available as solution and it is stable for longer time. In the current study pain at the site of injection occurred in 10 cases with Diazepam 40% injection while none of the patients experiences pain with Midazolam injection. As in Group-A patients the recovery is prolonged as Diazepam elimination half-life (20-99 hr) is high and so patients are

drowsy and the patients experienced a 48 hrs period of amnesia post operatively who received diazepam. Post-operative emergence reactions more with Diazepam when compared to Midazolam. In contrary, in Group 'B' patients the post-operative recovery was fair and prompt, as Midazolam elimination half-life is (1.5 – 3.5 hrs) short. Hence it can be stated that Midazolam-Ketamine infusion is preferable, especially for operations after which the patients are leaving the hospital on the day or the day after surgery. Same findings were noted by Cart Wright and Galle.

In this current clinical study it is clearly established that Midazolam is more effective than diazepam in reducing dreaming associated with Ketamine. Emergence reactions are not necessarily associated with a memory of dreaming, but they are very distressing to relatives and the nursing staff [4]. Further in a study conducted by Dundee et al [3] and Jensens et al [4] it is established that the incidence of thrombophlebitis is as less as 3-4% at 10-14 days of intravenous injection of 2.5 mg/ml of Midazolam. 50 ASA I and II young females between ages 18 to 30 yr divided into two groups scheduled for minor gynaecological procedure were studied. Group A patients were Premedicated with Diazepam 0.14 mg/kg body weight and atropine 0.6 mg given intravenously 30 mts prior to surgery. Diazepam on dilution with distilled water produces milky white precipitate during surgery. Patients are induced with 2mg/kg body weight ketamine given. Patients were observed for presence or absence of Apnoea, Blood pressure, Pulse rate recorded intra-operatively. About 10 patients complained of pain at the injection site while giving diazepam patients were calm and comfortable during surgery. Post operatively emergence phenomena are recorded up to 12 hrs.

In Group-A, patients complained of auditory, visual hallucinations, dreaming, prolonged recovery from anaesthesia. In group B patients were premedicated with Midazolam. 0.07 mg/kg body weight and atropine 0.6 mg given after securing safe intravenous line 30 mtrs prior to surgery. Midazolam is clear water soluble, short acting benzodiazepine. It does not form any precipitate with water and normal saline. The patients were induced with ketamine 2 mg/kg body weight. Intraoperatively Blood pressure, Pulse rate presence or absence, of apnoea all is observed. Post-operatively the patients were observed for emergence delirium. In Midazolam Premedicated patients, emergence reactions are 20%, post operate recovery is also prompt and good. Midazolam also given to Day care surgery.

Pain at the injection sites with Midazolam is very rare. There was not even a single case of Apnoea, Hypersensitivity reactions is seen in Group B patients. Diazepam produces prolonged post-operative recovery whereas with Midazolam the post-operative recovery is good. Midazolam had high patient acceptance compared to diazepam. Midazolam is more effective than diazepam as premedicant in ketamine anaesthesia in reducing the emergence reactions.

Previously studies conducted by Erbguth et al [5] revealed the influence of chlorpromazine, diazepam and droperidol, emergence from Ketamine anaesthesia in that Droperidol found to increase the occurrence of vivid dreams although it was originally reported to reduce the incidence of adverse emergence reactions patients with droperidol are less alert, less responsive and more disoriented during recovery. Although diazepam is highly effective in preventing vivid emergence reactions and delirium following ketamine a high incidence of floating sensations, dizziness and dreaming and prolonged recovery reported in the presence of Diazepam and Ketamine[6].

Midazolam offers several advantages over diazepam as it prevents dreaming emergence sequelae when used as adjunct to ketamine anaesthesia.

CONCLUSIONS

In the present study, effects of diazepam and midazolam in prevention of emergence phenomena after ketamine anaesthesia were compared. 50 ASA I and II young females between ages 18 to 30 yr divided into two groups scheduled for minor gynaecological procedure were studied. Post-operatively the patients were observed for emergence delirium. In Midazolam Premedicated patients, emergence reactions are 20%, post operate recovery is also prompt and good. Midazolam also given to Day care surgery. Pain at the injection sites with Midazolam is very rare. There was not even a single case of Apnoea, Hypersensitivity reactions is seen in Group B patients. Diazepam produces prolonged post-operative recovery whereas with Midazolam the post-operative recovery is good. Midazolam had high patient acceptance compared to diazepam. Midazolam is more effective than diazepam as premedicant in ketamine anaesthesia in reducing the emergence reactions.

REFERENCES

1. Randall LO, Heise GA, Schallek W, Bagdon RE, Banziger R, Boris A, et al. Pharmacological and clinical studies on valium, a new psychotherapeutic agent of the benzodiazepine class. Curr Ther Res Clin Exp. 1961 Sep;3:405-25.
2. Cartwright PD, Pingel SM. Midazolam and diazepam in ketamine anaesthesia. Anaesthesia. 1984,39:439-42.
3. Dundee JW, Haliday NJ, Harper KW, Brogden RN. Midazolam A review of its pharmacological properties and therapeutic. Drugs. 1984;28;519-43.
4. Jensen S, Schou-Olesen A, Hüttel MS. Use of Midazolam as an induction agent: Comparison with thiopentone. Br J Anaesth. 1982 Jun;54(6):605-7.
5. Erbguth PH, Riemann B, Klein RL. The influence of chlorpromazine; diazepam and droperidol an emergence from ketamine anaesthesia. Anesth Analg. 1972 Sep-Oct;51(5):693-700.
6. Banerjee SC and Gupta SK. Clinical experience with Ketamine along and Ketamine-Diazepam combination for short surgical procedure. Ind. J. Anaeth. 1977;25:93.