

Comparison between Diazepam and Midazolam as Premedicant to Reduce Anxiety in Patients underwent Elective Surgery Under General Anaesthesia

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ABSTRACT

Background: The majority of patients admitted to hospital for elective surgery experience anxiety preoperatively which can adversely influence the surgical procedure as well as the patient's recovery. Reduction of anxiety and fear at preoperative period in patients of elective surgery is essential for surgical preparation. Benzodiazepines are the most commonly used drugs for this purpose. The purpose of the study to evaluate the comparative efficacy of Diazepam and Midazolam regarding onset, duration and degree of antianxiety, sedation and amnesia during surgery under general anaesthesia.

Materials and methods: The study was carried out in series of 60 consecutive, unselected patients, aged 18-60 years, admitted for the elective surgery under General Anaesthesia, in Combined Military Hospital (CMH) Chattogram during the period September 2019 to February 2020. Patients receiving diazepam or midazolam as preoperative medication were taken. Anxiety was scored using VAS, sedation was scored by using Ramsay Sedation scale and anterograde amnesia by asking preoperative events after 24 hours.

Results: While evaluating mean anxiety reduction only, mean reduction is greater in the diazepam group compared to that of midazolam. Desired sedation level was less achieved with midazolam. In the diazepam group, greater number of patients could not recall preoperative events.

Conclusion: The standard administration of diazepam before procedure provides patients with a moderate reduction of perioperative anxiety. Routinely, administration of midazolam has a limited effects on the reduction of anxiety. Additionally, premedication of midazolam is associated with a high incidence of adverse effects. Therefore, this study does not support the routine use of midazolam as premedication to reduce anxiety.

Key words: Diazepam; Midazolam; Premedication.

Introduction

The majority of patients admitted to hospital for elective surgery experience anxiety preoperatively which can adversely influence the surgical procedure as well as the patient's recovery. Reduction of anxiety and fear at preoperative period in patients of elective surgery is essential for surgical preparation. Drugs of different classes like sedative-anxiolytic drugs, opioids, anticholinergics, neuroleptics, H₂ blocker and antiemetics have been used for premedication. Preoperative treatments also aim at reducing the

emergence agitation occurring during recovery.^{1,2,3} The purposes of preoperative medication are to prevent psychic shock, to regulate metabolism, elimination of any stage of excitement, and the possibility of maintaining a lighter degree of anaesthesia or of using a less toxic anaesthetic that would otherwise be required.⁴

Anxiety is common amongst patients awaiting general anaesthesia. Incidence of anxiety has been found variable in different studies. Overall rate of anxiety was observed in 72.7% patients scheduled for elective caesarian section. Around 23.4% patients were found to be anxious regarding General Anaesthesia (GA) and female showed a higher incidence of anxiety (35.1%) than male (11.1%), The incidence is high in those having lower educational level. Human emotions like acute emotional arousal increases sympathetic activity.^{5,6}

Benzodiazepines increase the effect of the natural neurotransmitter gamma-aminobutyric acid at the receptor site in the brain, which initiates a reduction of neuron excitability with consequently anxiolytic, sedative and amnesic effect. The effectiveness of anxiolytic premedication critically depend on the anaesthesiologist's ability to detect anxiety during the

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preoperative visit. This evaluation provides the frequency of the use of diazepam or midazolam as preoperative medication in the elective surgeries.⁷ This study has been undertaken with a view to evaluate the comparative efficacy of Diazepam and Midazolam regarding onset, duration and degree of anti anxiety, sedation and amnesia during surgery under general anaesthesia.

Materials and methods

The study was carried out in series of 60 consecutive, unselected patients, aged 18-60 years, admitted for the elective surgery under General Anaesthesia after obtaining written consent, in Combined Military Hospital (CMH) Chattogram during the period September 2019 to February 2020. Patients receiving diazepam or midazolam as preoperative medication were taken. Patient of either sex, different ages with mild to moderate systemic disease (ASA I and ASA II), all the patients for elective surgery under GA were taken as subjects. Exclusion criteria were pregnant or lactating female, patients with decompensated hepatic or renal disease, those unable or willing to give informed consent, hypersensitive to or had contraindications to the use of benzodiazepines or any CNS depressant for any reason, history of alcohol, benzodiazepines or other drug abuse.

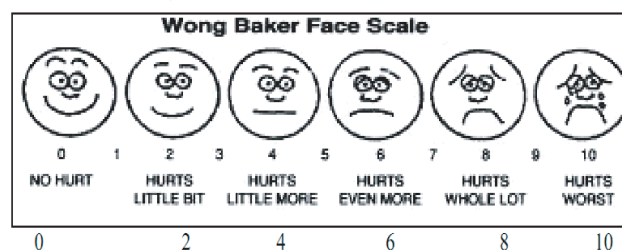
Thirty patients were premedicated with diazepam (10mg) orally two hours before surgery and 30 patients were premedicated with midazolam (7.5mg) p.o. The assessment of anxiety and vital signs were done immediately before drug administration. The efficacy assessment like anxiety and sedation were done after drug administration before taking the patient in Operating Room (OR). However, the anterograde amnesia was assessed after 24 hours of premedication.

Anxiety was scored using VAS (Visual Analogue Scale), sedation was scored by using Ramsay Sedation scale and anterograde amnesia by asking preoperative events after 24 hours.

Ramsay Sedation Scale:

Sedation level	Description
1	Anxious and agitated
2	Cooperative, tranquil, oriented
3	Responds only to verbal commands
4	Asleep with brisk response to light stimulation
5	Asleep without response to light stimulation
6	Non responsive

Visual Analogue Scale :



Anterograde Amnesia:

Being taken into the operation : A

Being shown the surgical light : B

Being shifted from stretcher to the operating table: C

Data was recorded on predesigned proforma and statistical analysis (Student's 't' test and chi square test) was done to carry out the output. Data were expressed in mean, SD and percentage. The value $p < 0.05$ was considered statistically significant. Statistical analysis was done using SPSS software version 17.0.

Patient completed the VAS in the presence of doctors who were available to assist if necessary. The patient self reported level of education was recorded and categorized into low (Less than 10 years of education) intermediate (Between 10 and 12 years of education) and high (More than 12 years of education).

Results

In this observational study, 60 (30 in each group) patients were taken. The mean age of the group diazepam and midazolam are 37.42 and 38.5 years respectively (Table I). Anxiety reduction from baseline to preprocedure was found to be statistically significant in each group. While evaluating mean anxiety reduction only, mean reduction is greater in the diazepam group compared to that of midazolam (Table II). Anxiety reduction was defined as the absolute difference in VAS score between baseline and preprocedure.

Patients receiving midazolam were found to be more anxious, less tranquil than diazepam. Desired sedation level was less achieved with midazolam (Table III).

In the diazepam group, greater number of patients could not recall preoperative events. In midazolam group, unlike greater number of patients could recall the same preoperative events (Table IV).

Adverse drug effects were uncommon in participants premedicated with diazepam (1.5%). In contrast a substantial amount of participants premedicated with midazolam (19.8%) experienced one or more side effects like drowsiness, low peripheral oxygen saturation, physical agitation.

Table I Demographic data of the patients under study

Variables	Diazepam Group (Mean±SD)	Midazolam Group (Mean±SD)
Mean age (In years)	37.42±9.85	38.50±8.32
Mean weight (iIn Kg)	48.33±9.31	47.62±10.13
Male	12	13
Female	18	17
ASA grade I	17	19
ASA grade II	13	11
Types of surgery		
Cholecystectomy	14	16
Appendicectomy	06	04
Septoplasty	03	04
Mastectomy	01	00
Gastrojejunostomy	01	00
Subtotal thyroidectomy	02	04
Tonsillectomy	03	02

Table II Prevalence of anxiety in patients under study

Time	Diazepam Group (Mean±SD)	Midazolam Group (Mean±SD)	p value
Baseline	4.1±2.6	4.2±2.4	
VAS preprocedure	3.0±2.3	3.9±2.1	<0.05
p value	0.03	0.48	

Table III Assessment of sedation in patients under study

Sedation level	Diazepam	Midazolam
1	00	05
2	04	19
3	22	05
4	04	01
5		
6		
p value	<0.05	

Table IV Assessment of anterograde amnesia in patients under study

Diazepam	Midazolam		p value		
	Yes	No	Yes	No	
Preoperative events					
Being taken into operation theatre	09	21	22	08	<0.05
Being shifted from stretcher to operation table	10	20	23	07	<0.05
Being shown operation theatre surgical light	07	23	21	09	<0.05

Discussion

A study by Bergeron et al. (n=62) used the VAS score at two points in time to assess anxiety in patients premedicated with diazepam and lorazepam. Kazemisaeid et al. (n=151) conducted a placebo controlled double blind randomized controlled trial, which showed a significant increase in anxiety reduction (Measured in VAS score) in patients premedicated with intravenous midazolam compared with both diazepam with intramuscular promethazine and a placebo. However, this could possibly be attributed to the fact that patients with higher preprocedural anxiety were premedicated with midazolam, rather than the anxiolytic effect of midazolam itself. Additionally they did not report an increase of side effects in patients premedicated with midazolam.^{8,9}

Kandel S et al. while examining mean anxiety reduction between two groups (Diazepam and midazolam) showed that midazolam has higher mean reduction value from baseline at various time periods. Midazolam showed better antianxiety effect and sedative effect compared to diazepam. The study also showed that intramuscular midazolam rapidly produces an appropriate degree of sedation and better quality of sedation than diazepam in patients awaiting surgery. They also showed that midazolam produces better anterograde amnesia than diazepam. But in that study, diazepam was given orally and midazolam was given intramuscularly.^{10,11}

Diatta B et al. report that midazolam as compared with diazepam can be regarded as a superior intramuscular premedicant. There was significant differences with respect to anxiety after 30 minutes, 100% patients after midazolam and 67% after diazepam. 63% after midazolam and 13% after diazepam were good sedated. Amnesia related preoperative period was more frequent in the midazolam group than in diazepam group: 67% versus 13% (p<0.001). But in their study routes of administration were different for the two drugs¹².

Vetter TR conducted a study in which midazolam (0.5 mg/kg IV) was found to produce a spectrum of central nervous system activity like sedation and amnesia that was similar to diazepam (0.1-0.3 mg/kg IV). However the slope of midazolam dose response curve for sedation appears to be steeper. While comparing their relative sedative-amnesic property and recovery characteristics, the median effective doses of two BZDs, midazolam (0.1 mg/kg IV) found to produce profound sedation and amnesia than diazepam (0.2 mg/kg IV). Patient's acceptance was higher with midazolam compared to diazepam.¹³

Vlastra W et al found that diazepam was associated with a significant but modest anxiety reduction in patients underwent CAG or PCI. The use of Midazolam did not lead to a significant reduction of anxiety compared with patients who did not receive premedication. Additionally a high number of patients treated with midazolam (n=39, 19.8%) developed side effects. In their study, both the drugs were used orally. This was more or less similar findings in this study.¹⁴ Earlier studies reported beneficial effects of non pharmacological interventions to reduce periprocedural anxiety. In three small randomized controlled trials, beneficial effects were seen on periprocedural self reported anxiety in patients who received massage and/or guided imagery prior to the procedure. Similarly a compilation of relaxing music provided by an audio pillow was associated with lower anxiety levels in the time period around the procedure. Finally two small studies showed possible positive effects aromatherapy as well as mindfulness based interventions of anxiety. We did not study these effects, and it is difficult to compare these effects with premedication strategies.¹⁵⁻¹⁸

Limitations

The intervention was not placebo controlled and blinded to neither clinicians nor patients. Additionally, group sizes were small. Consequently the clinical relevance remains undetermined and further studies are necessary to confirm potential benefits between the two commonly used benzodiazepines.

Conclusion

The standard administration of diazepam before procedure provides patients with a moderate reduction of periprocedural anxiety. However, costs are low and side effects are negligible. Therefore for opinion standard prophylactic use seems fair. Routinely, administration of midazolam has a limited effects on the reduction of anxiety. Additionally, premedication of midazolam is associated with a high incidence of adverse effects. Therefore, this study does not support the routine use of midazolam as premedication to reduce anxiety.

Disclosure

All the authors declared no competing interest.

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