

Original Article

Comparison between Bromazepam and Lorazepam as premedicant to reduce anxiety in patients undergoing elective surgery under General Anaesthesia

Colonel Md Enayet Karim^{1*}, Major Arif Imtiaz Chowdhury², Brig Gen (Retd) Reza Ershad³
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Abstract:

Background: The majority of patients admitted to the 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 the preoperative period in patients of elective surgery is essential for surgical preparation. Benzodiazepines are the most commonly used drugs for this purpose.

Materials and Methods: The study was carried out on a series of 60 consecutive patients, aged 18-60 years, admitted for elective surgery under General Anaesthesia, in Combined Military Hospital, Chattogram during the period September 2021 to February 2022. Patients receiving bromazepam or lorazepam as preoperative medication were selected. Anxiety was scored using VAS (Visual Analogue Scale), sedation was scored by using the Ramsay Sedation scale and anterograde amnesia by asking about preoperative events after 24 hours of premedication.

Results: While evaluating mean anxiety reduction only, mean reduction is greater in the lorazepam group compared to that of bromazepam. Sedation level was less achieved with bromazepam. In the lorazepam group, a greater number of patients could not recall preoperative events but incidence of adverse effects was significantly more in this group.

Conclusion: The standard administration of bromazepam before the procedure provides patients with a moderate reduction of periprocedural anxiety. Premedication of lorazepam is associated with a high incidence of adverse effects. Therefore, this study does not support the routine use of lorazepam as premedication to reduce anxiety before surgery.

Keywords: Bromazepam, Lorazepam, Premedication.

Introduction

Many patients develop negative emotions when they are scheduled for a surgical procedure. These may include anxiety, depression, aggression, fatigue and physical complaints. Anxiety is the most well known and prominent preoperative complaint. Preoperative anxiety can have adverse effects on the perioperative course because it correlates with high postoperative anxiety, increased postoperative pain, increased need for analgesics, postoperative nausea and vomiting and prolonged hospital stay. Furthermore, it has been shown that preoperative anxiety has a negative effect on the induction of anaesthesia and recovery^{1,2,3}. Drugs of different classes like sedative-anxiolytic drugs, opioids, anticholinergics, neuroleptics, H₂ blocker and antiemetics have been used for

premedication⁴. The purposes of preoperative medication are to prevent psychic shock, regulate metabolism, elimination 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. Preoperative treatments also aim at reducing the emergence agitation occurring during recovery^{5,6,7}.

The incidence of anxiety has been found variable in different studies. The overall rate of anxiety was observed in 72.7% patients scheduled for elective caesarian section. Around 23.4% of patients were found to be anxious regarding General Anaesthesia (GA). Female showed a higher incidence of anxiety (35.1%) than male (11.1%)⁸. The incidence is high in those having lower educational level. Human emotions like acute emotional arousal increase sympathetic activity⁹.

Anxiolytic premedication by benzodiazepines could be a useful treatment for patients who suffer from preoperative anxiety. 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 depends on the anaesthesiologist's ability to detect anxiety during the preoperative visit¹⁰. We could find only one study comparing bromazepam and lorazepam as premedicant in case of gynaecological surgeries. This evaluation provides the frequency of the use of bromazepam or lorazepam as preoperative medication in elective surgeries under general

1. Classified Specialist in Anaesthesiology, Combined Military Hospital, Chattogram.
2. Graded Specialist in Anaesthesiology, Combined Military Hospital, Chattogram.
3. Professor of Anaesthesiology, Uttara Adhunik Medical College and Hospital, Dhaka.

***Correspondence:**

Colonel Md Enayet Karim
Classified Specialist in Anaesthesiology
Combined Military Hospital, Chattogram
Email: enayet852@yahoo.com

anaesthesia in different types of surgeries. This study has been undertaken with a view to evaluate the comparative efficacy of bromazepam and lorazepam regarding onset, duration and degree of anti anxiety, sedation and amnesia during surgery under general anaesthesia.

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, Chattogram during the period September 2021 to February 2022. Patients receiving bromazepam and lorazepam as preoperative medication were taken. Patient of either sex, different ages with mild to moderate systemic disease (ASA I and ASA II) and scheduled for elective surgery under GA were taken as subjects. Exclusion criteria included pregnant or lactating females, 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.

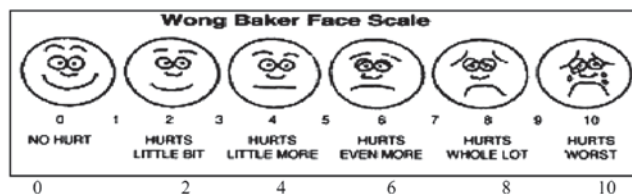
Thirty patients were premedicated with bromazepam 3mg orally two hours before surgery and 30 patients were premedicated with lorazepam 1mg.p.o. A random number table, with numbers from 1-60, which indicated the total number of participants, was used to randomly allocate each of the participants to either of the bromazepam or lorazepam groups. Participants with odd number received bromazepam and even number received lorazepam. 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 of premedication.

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) 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.

The 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).

Result:

In this observational study, 60 (30 in each group) patients were taken. The mean age of the group bromazepam and lorazepam were 41.42 and 42.5 years respectively (Table I). Anxiety reduction from baseline to pre procedure was found to be statistically significant in the lorazepam group. While evaluating mean anxiety reduction only, the mean reduction is greater in the lorazepam group compared to that of bromazepam. (Table II). Anxiety reduction was defined as the absolute difference in VAS score between baseline and pre procedure.

Patients receiving bromazepam were found to be little more anxious, and less tranquil than lorazepam. Sedation level was less achieved with bromazepam (Table III).

In the lorazepam group, a greater number of patients could not recall preoperative events. In the bromazepam group, a greater number of patients could recall the same preoperative events (Table IV).

Adverse drug effects were uncommon in participants premedicated with bromazepam (3.3%, 1/30). In contrast, a substantial number of participants premedicated with lorazepam (23.33%, 7/30) experienced one or more side effects like drowsiness, dizziness, low peripheral oxygen saturation, physical agitation (Figure 1) etc.

Table I : Demographic data of the patients under study

Variables	Bromazepam Group (mean±SD)	Lorazepam Group (mean±SD)
Mean age (in years)	41.42±8.85	42.50±8.32
Mean weight (in Kg)	59.33±6.31	60.62±7.13
Male	12	13
Female	18	17
ASA grade I	17	19
ASA grade II	13	11

Types of surgery

Cholecystectomy	14	16
Appendectomy	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	Bromazepam Group (mean±SD)	Lorazepam Group (mean±SD)	p value
VAS Baseline	4.2±2.4	4.1±2.6	
VAS preprocedure	3.9±2.3	3.0±2.1	<0.05
p value	0.38	0.04	

Table III : Assessment of sedation in patients under study

Sedation level	Bromazepam	Lorazepam
1	11	00
2	14	22
3	05	07
4	00	02
5		
6		
p value	<0.05	

Table IV : Assessment of anterograde amnesia in patients under study

	Bromazepam		Lorazepam		p value
Preoperative events	Yes	No	Yes	No	
Being taken into operation theatre	21	09	08	22	<0.05
Being shifted from stretcher to operation table	23	07	10	20	<0.05
Being shown operation theatre surgical light	21	09	11	19	<0.05

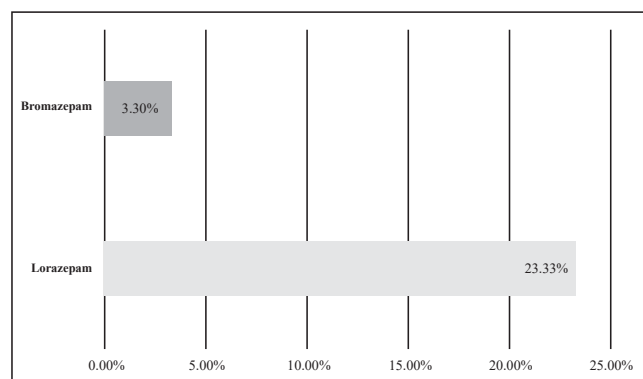


Figure 1 : Incidence of adverse drug effects for different premedications

Discussion

Benzodiazepines compounds fall into three major categories: long acting compounds- diazepam, chlordiazepoxide, chlorazepate, flurazepam, halazepam, and prazepam; intermediate acting compounds- clonazepam, lorazepam, bromazepam, quazepam, and estazolam; and short acting compounds- alprazolam, oxazepam, temazepam, midazolam, and triazolam^{9,10}. Bromazepam was approved for medical use in 1974. Its pharmacokinetic properties are consistent with rapid complete absorption from the

gastrointestinal tract, peak level being attained in between 1-4 hours. The drug is completely absorbed after oral administration and is eliminated from the blood with a mean half-life of 12-20 hours¹¹. Lorazepam is the ortho-chlorophenyl derivative of the main metabolite of diazepam, desmethyl-diazepam. Oral absorption is reliable, with an effective concentration after 60 minutes and a peak plasma concentration 2 hours after administration. Its mean half-life of elimination is about 15 hours. The pharmacokinetics of lorazepam are unaltered with advancing age. It has no active metabolites¹².

Ponnudurai R et al conducted a randomized double blind trial of bromazepam 6 mg versus lorazepam 2 mg as oral premedicant agent in patients scheduled for gynaecological surgeries only.¹² A total of 153 patients were studied; 78 received bromazepam and 75 lorazepam. Objective and Subjective assessments of sedation, amnesia, nausea and vomiting were performed. No significant difference between the two groups was found¹². Our study included patients of both sex who were scheduled for different types of surgeries. In our study lorazepam showed significantly more anti anxiety, sedative and amnesic effect than bromazepam; but bromazepam had much less adverse effects.

Islam MS et al. performed a prospective randomized controlled trial in adult patient of different surgical approach

to see the effectiveness of bromazepam as a premedicant. The participants were divided randomly into three groups: the Control group (Group C) had no medication preoperatively, Group D was given oral diazepam 5mg in the morning on the day of operation and Group B were given bromazepam 5mg p.o. Anxiety level was measured by Visual Analogue Scale (VAS), which was reduced significantly in Group B ($p < 0.001$). Sedation score that was measured in the morning on the day of operation, found that in Group D (36.66%) patients were drowsy but responded to verbal commands in comparison to Group B (6.66%) ($p < 0.001$). Postoperatively nausea was more in the diazepam group (20.00%) in the than bromazepam taken group (16.16%)¹¹. Our study showed moderate anti-anxiety effect of bromazepam and less side effects but did not include diazepam or any control group. Moreover, we studied the amnesic effect of bromazepam which was not done by Islam MS et al.

Eman M et al. performed a prospective double blind randomized trial on 60 healthy infertile female patients who were scheduled for embryo transfer by IVF. They received either Pregabalin (300mg) (group A), Bromazepam (3mg) (group B), or placebo (folic acid 0.5 mg) (group C) 90 min before surgery as oral premedication. A significant increase in sedation scale without respiratory depression was observed in both premedicated groups when compared with baseline sedation level and the control group. Preoperative anxiolysis and sedation were higher in the oral pregabalin group compared with the oral bromazepam group, but the difference was statistically nonsignificant. However, there was a significant increase in sedation score in the pregabalin group at recovery in comparison with the other two groups. The incidence of postoperative dizziness in the pregabalin group was higher (6 patients, 30%), than that in bromazepam group (2 patients, 10%). They also found that a significant decrease in postoperative pain scores in most times of measurement in both the pregabalin and bromazepam groups, as well as a significant decrease in analgesic consumption postoperatively. Many patients required only single dose of meperidine (30 ± 4.5 mg)¹³. Our study did not include pregabalin because it belongs to a different pharmacological class and has more post procedure adverse effects. We found moderate anti anxiety effect of bromazepam but did not study post-operative effects except amnesia which was not included in above study.

Erb T et al performed a randomized placebo controlled double blind study on 60 patients, ASA physical status II & III, older than 60 years, scheduled for ophthalmic surgery under regional anaesthesia. The patients were randomized to receive either bromazepam 3 mg, clorazepate-dipotassium 20 mg or placebo. The study drugs were given at 10 p.m the night before surgery and 90 min before surgery. Using the State-Trait Anxiety Inventory (STAI), the patients' anxiety was assessed at the end of the preoperative visit, on the next morning before the study drug was given and on arrival at the operating theatre. Bromazepam induced a marked anxiolytic effect as documented by a significant reduction in the STAI State values after both applications ($p < 0.01$). Clorazepate did

not differ from placebo at any evaluation time with regard to the STAI and haemodynamic values. Sedative effects and oxygen saturation were comparable in all groups¹⁴. Our study did not include Clorazepate as it is now rarely used and we included patients aged below 60 scheduled for general anaesthesia only. Moreover we found moderate anti anxiety effect of bromazepam as opposed to the above study which may be explained by their geriatric age group.

Kambara M et al. performed a prospective double blind randomized trial on 77 children for minor surgery, less than 90 minutes in duration, divided into two groups: one group received midazolam syrup and the other received bromazepam suppository. The sedative effect before or after the induction of the anaesthetic, the effect on the circulatory system and the prolongation of the sedative effect after surgery were studied. Regarding the sedative effect before or during the induction of anaesthesia, both medications were effective with no significant difference between the two groups. However, the bromazepam suppository had a significantly better sedative effect 1 or 2 hours after the surgery¹⁵. Our study included only adult patients where bromazepam was used as oral premedicant and did not include midazolam. But bromazepam also showed moderate anti anxiety effect in our study.

Vlastra W et al. found that use of lorazepam generated highest anxiety reduction (Δ VAS= -2.0 ± 2.9 , $p = 0.007$). The use of midazolam (Δ VAS= -1.9 ± 3.3 , $p = 0.13$) did not lead to significant anxiety reduction compared with no premedication¹⁶. In the study by Woodhead et al. anxiety was stated to be equal in all groups. Nevertheless this was measured with a single question that did not quantify anxiety level¹⁷. 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 but did not compare these results to a control group¹⁸. Above studies included only patients scheduled for percutaneous angiogram under sedation only and bromazepam was not included. But we also found significant anti anxiety effect of lorazepam in our study.

Axel M S et al. performed the PremedX study to better understand the relationship between administration of preoperative anxiolytic medication and the overall patient experience. They found that preoperative sedation with lorazepam did not improve the perioperative experience or overall patient satisfaction. Compared with placebo, lorazepam did reduce patient anxiety upon arrival to the operating room. Because there was no overall benefit from preoperative anxiety treatment, it is possible that anxiety arising upon arrival to the operating room does not influence overall patient satisfaction. They also found that preoperative sedation with lorazepam was associated with greater satisfaction with perioperative pain for all patients and less satisfaction with the attention received from caregivers among patients with high levels of preoperative anxiety. A study comparing intramuscular midazolam with placebo as preoperative sedation reported improved postoperative psychological and pain recovery. The mechanisms on which

these effects rely were unclear. Additionally, they found that compared with placebo and no premedication lorazepam was associated with more amnesia. Lorazepam administration was associated with a prolonged time to extubation and decreased rate of cognitive recovery in the PACU (Post Anaesthesia Care Unit). Prolonged recovery could limit the use of sedative premedication in patients receiving day stay surgery¹⁹. We also found significant anti-anxiety and amnesic effect of lorazepam but did not compare it with placebo or no premedication. Our study did not include effect of lorazepam on perioperative pain.

Maurice-Szamburski et al. found no improvement in self reported experience after premedication with oral lorazepam before elective surgery¹. Also, Mijderwijk et al. showed that premedication with lorazepam in day surgery settings had no beneficial effect on quality of recovery²⁰. Patients treated with lorazepam showed even more postoperative anxiety and aggression. Next to a rebound effect, their results could be explained by the fact that day surgery induces less anxiety than major procedures²¹. In our study, we found beneficial effect of lorazepam premedication (anti-anxiety, sedation, amnesia) and no post-operative aggression. The reason may be as the cases were not day case surgeries.

Reves et al. describe the relative potency of midazolam as being approximately twice that of diazepam, depending on the effect measured. Greenblatt et al. describe lorazepam as being approximately four times as potent as diazepam. By inference, lorazepam would be twice as potent as midazolam for the effect of sedation, hypnosis, or anxiolysis. Estimates of potency for sedation and hypnosis may be derived from pharmacokinetic-pharmacodynamic study models that relate electroencephalogram (EEG) changes to the plasma level of the drug. In conscious volunteers, the mean drug concentration of midazolam that produced a half maximum effect (EC_{50}) is approximately 35ng/ml. An estimate of the EC_{50} value for lorazepam using a similar EEG effect as the end point was about 16ng/ml. This would also suggest that lorazepam was twice as potent as midazolam for the effect of increasing brain wave activity in the 13-to-30 Hz range. These indirect comparisons of sedative, hypnotic potencies between midazolam and lorazepam may be misleading, however, due to interstudy variations in dosing and end point effect criteria²². Our study did not include electroencephalographic changes to the plasma level of lorazepam and its comparison with midazolam.

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^{23,24,25,26}.

Study 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 bromazepam before procedure provides patients with a moderate reduction of periprocedural anxiety. However, costs are low and side effects are negligible. Therefore in our opinion standard prophylactic use seems fair. Lorazepam is more effective in reducing preoperative anxiety. But premedication of lorazepam is associated with a high incidence of adverse effects and costs higher. Therefore, this study does not support the routine use of lorazepam as premedication to reduce anxiety before surgery.

Disclosure

There is no conflict of interest.

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