Original Article

Comparison Between Clonazepam and Bromazepam as Premedication Drugs to Reduce Anxiety in Patients Undergoing Elective Surgery Under General Anaesthesia

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Abstract

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

Materials and Methods: *The study was carried out in a series of 60 consecutive, randomly selected 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 who received Clonazepam or Bromazepam as preoperative medication were included in the study. 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.*

Results: *While evaluating mean anxiety reduction, mean reduction is not significantly different between the two groups (P value 0.856). Sedation level was more achieved with Clonazepam but that was not statistically significant (mean 2.13 vs mean 2.0, P value 0.557). In the Clonazepam group, greater percentage of patients could not recall preoperative events but that was not statistically significant (average 51.10% vs 39.99%, P value>0.05). Incidence of adverse effects was more in Bromazepam group (16.66% vs 6.66%).*

Conclusion: *The standard administration of Clonazepam and Bromazepam before operation provides patients with a moderate reduction of periprocedural anxiety. Clonazepam produces more amnesia, sedation and less adverse effects.. Therefore, this study favors routine use of Clonazepam as premedication to reduce anxiety before surgery.*

Key words: *Clonazepam, Bromazepam, Premedication, Anxiety.*

Date received: *22.07.2022*

Date accepted: *03.09.2022*

DOI: https://doi.org/10.3329/kyamcj.v13i3.63153 ***KYAMC Journal. 2022; 13(03): 139-144.***

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.[1-3] Drugs of different classes like sedative-anxiolytic drugs, opioids, anticholinergics, neuroleptics, H2 blocker and antiemetics have been used for premedication. 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] Preoperative treatments also aim at reducing the emergence agitation occurring during recovery.[4-6]

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). 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.[7-9]

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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 visit.[10] This evaluation provides the frequency of the use of Clonazepam or Bromazepam as preoperative medication in the elective surgeries. This study has been undertaken with a view to evaluate the comparative efficacy of Clonazepam and Bromazepam regarding onset, duration and degree of anti anxiety, sedation, amnesia and adverse effects during surgery under general anaesthesia.

Materials and Methods

This randomized clinical trial was carried out in series of 60 consecutive, randomly selected 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. Ethical approval was obtained from appropriate authority. Patients consented to receive Clonazepam and Bromazepam as preoperative medication were included in the study. Patient of either sex, different ages of ASA I and ASA II; all the patients for elective surgery under GA were included in the study. Exclusion criteria were pregnant or lactating mother, 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 intake, benzodiazepines or other drug abuse. 30 patients were premedicated with Clonazepam 1mg orally two hours before surgery and 30 patients were premedicated with Bromazepam 3mg orally. 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)8. Patient completed the VAS in the presence of doctors who were available to assist if necessary. (Figure-1) 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

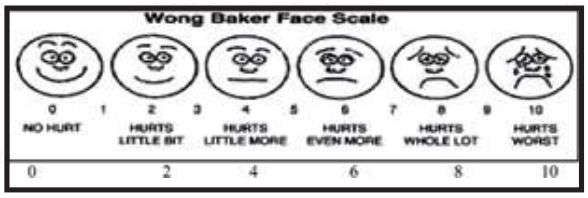

Figure 1: Visual Analogue Scale

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. 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). 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 Clonazepam or Bromazepam groups. Participants with odd number received Clonazepam and even number received Bromazepam.

Results

In this randomized clinical trial, 60 patients (30 in each group) were taken. The mean age of the group Clonazepam and Bromazepam are 41.42 and 42.5 years respectively (Table I). Anxiety reduction from baseline to preprocedure was more in Clonazepam group but that was not statistically significant. While evaluating mean anxiety reduction only, mean reduction is greater in the Clonazepam group compared to that of Bromazepam. (Table II). Anxiety reduction was defined as the absolute difference in VAS score between baseline and preprocedure.
Patients receiving Bromazepam were found to be less tranquil than Clonazepam. Sedation level was less achieved with Bromazepam than Clonazepam, but that was not statistically significant (Table III).

In the Clonazepam group, greater number of patients could not recall preoperative events. In Bromazepam group, greater number of patients could recall preoperative events but the difference was not statistically significant (Table IV).

Adverse drug effects were less in participants premedicated with Clonazepam (6.66%, 2/30). Greater number of participants premedicated with Bromazepam (16.66%, 5/30) experienced one or more adverse effects like drowsiness, dizziness, low peripheral oxygen saturation, physical agitation but the overall difference was not statistically significant ($P>0.05$) (Figure 2).

Table I: Demographic data of the patients under study (N=60)

Variables	Clonazepam Group (n=30) (mean±SD)	Bromazepam Group (n=30) (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 (40%)	13 (43.33%)
Female	18 (60%)	17 (56.66%)
ASA grade I	17 (56.66%)	19 (63.33%)
ASA grade II	13 (43.33%)	11 (36.66)
Types of surgery		
Cholecystectomy	14 (46.66%)	16 (53.33%)
Appendicectomy	06 (20%)	04 (13.33%)
Septoplasty	03 (10%)	04 (13.33%)
Mastectomy	01 (3.33%)	00
Gastrojejunostomy	01 (3.33%)	00
Subtotal thyroidectomy	02 (6.66%)	04 (13.33%)
Tonsillectomy	03 (10%)	02 (6.66%)

Table II : Prevalence of anxiety in patients under study (N=60)

Variable	Clonazepam (n=30) (mean±SD)	Bromazepam (n=30) (mean±SD)	P value
VAS Baseline	4.2±2.2	4.4±2.4	0.856
VAS preprocedure	3.5±2.1	3.9±2.3	
P value	0.32	0.38	

Table III: Assessment of sedation in patients under study (N=60)

Sedation level	Clonazepam (n=30)	Bromazepam (n=30)
1	00	04 (13.33%)
2	26 (86.66%)	22 (73.33%)
3	04 (13.33%)	04 (13.33%)
4	00	00
5		
6		
P value		0.557

Table IV : Assessment of anterograde amnesia in patients under study (N=60)

	Clonazepam	(n=30)	Bromazepam	(n=30)	P value
Preoperative events	Yes	No	Yes	No	
Being taken into operation theatre	16 (53.33%)	14 (46.66%)	20 (66.66%)	10 (33.33%)	0.880
Being shifted from stretcher to operation table	14 (46.66%)	16 (53.33%)	18 (60%)	12 (40%)	0.546
Being shown operation theatre surgical light	14 (46.66%)	16 (53.33%)	16 (53.33%)	14 (46.66%)	0.783

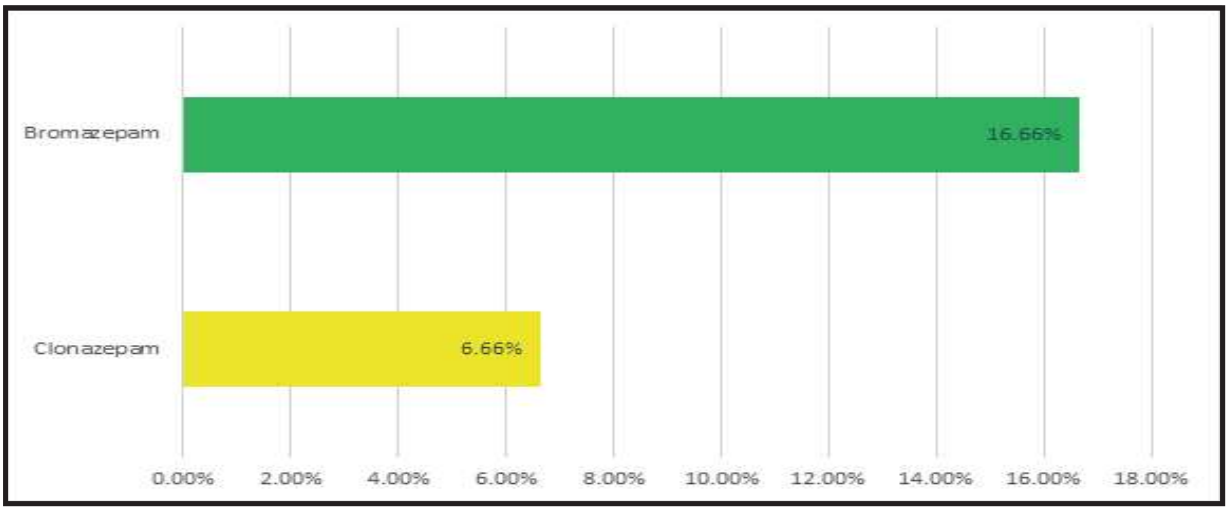

Figure 2 : Incidence of adverse drug effects for different premedications

Discussion

Benzodiazepines compounds fall into three major categories: long acting compounds- diazepam, chlordiazepoxide, chlorazepate, flurazepam, halazepam, and prazepam; intermediate acting compounds- clonazepam, bromazepam, lorazepam, quazepam, and estazolam; and short acting compounds- alprazolam, oxazepam, temazepam, midazolam, and triazolam.9,10 Clonazepam is a benzodiazepine anticonvulsant that has been available for clinical use since 1973. Clonazepam is rapidly absorbed (peak within 30-40 minutes). Among adults, clonazepam is metabolized primarily by hydroxylation, although this metabolic pathway generally is impaired in the newborn. The half life in adult is 20-60 hours10. 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 hours.[11]

Bala et al. observed that preoperative single dose of clonazepam 2 mg is a better premedication than 10 mg of midazolam in relieving anxiety and better sedation score with longer duration of action which is beneficial especially in patients staying in hospital post-operatively 1-2 days. They also found that patients undergoing elective abdominal hysterectomies under spinal anaesthesia, have significantly lower HAM (Hamilton anxiety scale) scores and longer duration of action in clonazepam group compared to midazolam group. It was concluded from their study that midazolam and clonazepam significantly reduce the patient's anxiety without altering the intraoperative haemodynamics. But clonazepam found to be better anxiolytic than midazolam.[12]

Kumar et al. found that buccal clonazepam demonstrated equivalence to I/V midazolam in controlling acute breakthrough seizure. When extrapolated to domiciliary setting it is likely to be safe option with capability of decreasing status episodes, hospitalization and thus reducing economic burden and psychological stress to the family.[13]

Zamiri et al. conducted a randomized double blind controlled trial on clonazepam for the management of anxiety associated with oral surgery. 60 patients were randomly allocated to either a single 2 mg dose of clonazepam or a placebo one hour prior to the surgery. The participants and the outcome assessors were blind to the intervention. Levels of anxiety were recorded using Visual Analogue Scale (VAS) and measuring blood pressure, pulse rate and arterial oxygen saturation percentage. All anxiety determinants (VAS, BP, pulse rate and oxygen saturation) changed significantly one hour after the administration of clonazepam ($p<0.05$). They concluded that clonazepam is an effective anxiolytic drug with minimal side effects which can be used to reduce anxiety in dental patients.[14]

Islam 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: Control group (Group C) had no medication preoperatively, Group D were given oral diazepam 5mg at 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 ($p<0.001$). Pulse rate, blood pressure at different time in perioperative period in Group D and Group B, were stable in comparison to Group C ($p<0.001$). Sedation score that was measured at morning on the day of operation, found that in Group D (36.66%) patients were drowsy but responded to verbal command in comparison to Group B (6.66%) ($p<0.001$). Postoperatively nausea was more in diazepam taken group (20.00%) than bromazepam taken group (16.16%).[11]

Eman 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 pregabalin group at recovery in comparison with the other two groups. The incidence of postoperative dizziness in 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 (30 ± 4.5 mg).[15]

Erb 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 (P0.01). 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 groups.[16]

Kambara 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

surgery.[17] 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 stratigies.[18-21]

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

Administration of Clonazepam and Bromazepam before surgery provides patients with a moderate reduction of periprocedural anxiety. Adverse effects are negligible. Clonazepam has more amnesic, sedative effect and less adverse effects than Bromazepam. This study favors routine use of Clonazepam as premedication to reduce anxiety before surgery under general anaesthesia.

Acknowledgement

We express our heartfelt gratitude to Commandant, Combined Military Hospital, Chattogram, for his support during the study. We are also grateful to the anonymous participants and anaesthesia staff for their co-operation during the study.

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