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Original Article

USE OF ORAL BROMAZEPAM AS PREMEDICANT AND IT'S EFFECTS IN PERI-OPERATIVE PERIOD –A COMPARATIVE STUDY WITH ORAL DIAZEPAM

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ABSTRACT :

Anaesthetic management begins with the pre operative psychological preparation of the patient and administration of a drug or drugs selected to produce specific pharmacological responses prior to the induction of anaesthesia. Preoperative medication should increase the likelihoods that patient will enter the preoperative period free from apprehension, sedated but easily arousable and fully co-operative[1]. A prospective randomized controlled trial was performed in adult patient of different surgical approach to see the effectiveness of bromazeparn as a premedicant and the haemodynarnic changes in patients at perioperative period. Ninety patients of ASA grade I and II, aged 20 to 50 years of both sexes undergoing different type of surgery under general anaesthesia of 30 to 150 minutes duration and were divided randomly into three groups. Control group (Group-C) has no medication preoperatively. Group-D were given oral diazepam 5 mg at night before the operation and 5 mg at morning on the day of operation and Group-B were given bromazeparn 3 mg at night before and 3 mg at morning on the day of operation. Observations were carried in during preoperative assessment on the day before surgery, in the anaesthetic room at morning, before induction and in postoperative ward (after extubation). Anxiety level was measured by Visual Analogue Scale (VAS), which was reduced significantly at morning on the day of operation, before induction and 24 hrs after operation in Group-B (p< 0.001). Pulse rate, blood pressure (systolic and diastolic) at different time in perioperative period (in Group-D and group Group-B) was stable in comparison to Group-C (p<0.001). Sedation score that was measured at morning on the day of operation before induction in different groups was seen and found that in Group-D, (36.66%) patients were drowsy but responds to verbal commands in comparison to Group-B (6.66%) (p<0.001). Recovery statuses were measured by Aldrete Recovery Score and have seen recovery scores was better in bromazepam taken group (73.33%) in comparison to diazepam taken group (56.66%). Postoperatively nausea was more in diazepam taken group (20.00%) than bromazepam taken group (16.16%). It was concluded that oral bromazepam at divided dose as a premedicant relief anxiety, and patients are haemodynamically stable in perioperative period with a well recovery.

INTRODUCTION:

Surgical patients have high incidence of anxiety and there is an inverse relationship between anxiety and smoothness of anaesthesia [2.] level of anxiety is associated with increased central and autonomic nervous system activity, psychological and physical symptoms[3]. There are many reason for preoperative anxiety; fear of the unknown or of postoperative nausea or pain; fear of the loss of control during anaesthesia; and fear based on previous experience or the experience of others of not being asleep during surgery[4]. There are many possible reasons for administering premedication, but the main one is to relieve fear and anxiety[6].

One major benefit of a preoperative assessment clinic may be to reduce patient anxiety. When we see a patient for the first time in the preoperative holding area, we may sense that the patient is anxious. The patient may have felt anxious from the time he learned that surgery was necessary and this feeling of anxiety may last up to several days after surgery[f']. Relief from anxiety is accomplished most effectively by non-pharmacological mean, which may be termed psychotherapy. In some patients, reassurance and explanation may be insufficient to allay anxiety.

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In these patients, it is appropriate to offer anxiolytic medication[2].

Benzodiazepines are the most popular premedicants for pharmacological sedation and anxiolysis because of their minimal side effects. When medication is the treatment of choice to reduce anxiety, the benzodiazepine namely midazolam, diazepam, lorazepam, triazolam and temazepam are the drugs routinely used. Nevertheless, there is no single drug without any side effects. Most benzodiazepine has a sedating and as well as an anxiolytic action. Amnesia is another action of benzodiazepine thought to be advantageous. But some studies show that only a minority of patients would choose amnesic premedication[7]. Benzodiazepine produces anxiolysis in doses that do not produce excessive sedation, and this is advantageous if respiratory function is compromised[2].

Diazepam, which is available in tablet form and is a popular drug for reduction of pre operative anxiety, specially when patients can be treated earlier than one day before surgery. The distribution half-life of diazepam is 1 hour and excretion half-life is 32.9 ± 8.8 hours[8].

Bromazepam is a benzodiazepine used clinically for its anxiolytic effects and comparative studies on psychiatric patients have shown that it is superior in this respect to diazepam and lorazepam[9]. Its pharmacokinetic properties are consistent with rapid complete absorption from the gastrointestinal tract, peak level being attained in between 1- 4 hours. It is metabolically degraded and has a mean half-life of 11.9 hours. The metabolites are secreted as conjugated glucoronides and after 72 hours only 2.3% is detectable unchanged in the urine [10]. There is some evidence from studies that the degree of sedation produced by bromazepam is less than that produced by diazepam while the anxiolytic effect is greater[11]. The drug is completely absorbed after oral administration and is eliminated form the blood with a mean half-life of 12 to 20 hour as opposed to 20 to 100 hours for diazepam[11,12]. Bromazepam is a powerful psychotropic agent; in lower doses it selectively reduces tension and anxiety. In high doses, it has sedative and muscle relaxing properties.

Though bromazepam has been used for a long time as a psychotropic agent, to investigate the further relative potency we carried out a double blind, placebo-controlled study comparing it with diazepam as a premedicant to relieve anxiety in anaesthetic practice.

MATERIALS AND METHODS:

90(ninety) patients of ASA physical status I & II, age between 20 & 50 of both sexes undergoing different type of surgery under general anaesthesia were included in a double blind randomized study at the department of Anaesthesia, Analgesia and Intensive Care Medicine, BSMMU, Dhaka. The approval of hospital ethical committee was duly taken before carrying out the study. The purpose of the study was clearly explained & informed written consent was taken from each patient. The patient's refusal to participate in the study, history of hypersensitivity to any benzodiazepine group of drugs, major psychological disturbances and low intelligence, patient with any renal or and hepatic impairment, debilitated patients, pregnancy, breast-feeding, uncontrolled hypertension, myasthenia gravis and chronic use of hypnotics or sedatives were excluded from the study. The patients were allocated randomly into three groups, thirty in each. Group-C (control group), patients in this group was not given any medication but the placebo, Group-B patients were given oral bromazepam 3mg at 10.00 PM before the day of operation and 3mg at 6.00 AM on the day of operation and Group-D subjects were given oral diazepam 5mg at 10.00 PM before the day of operation and diazepam 5mg at 6.00 AM on the day of operation.

Counseling was done about operation and the general anaesthesia. After demonstrating to all patients, we assessed anxiety level by visual analogue scale (VAS) (A 10 cm scale, left end of which denoted 'no anxiety' designated by '0' and the other end maximum anxiety designated by '10'). Pulse rate and arterial blood pressure was recorded as a base line parameter. Before going to operating theater at morning the patient was assessed for anxiety level and asked whether they had experienced nausea, vomiting or any others symptoms. Before venepuncture, pulse rate and arterial blood pressure (Systolic and Diastolic) were recorded.

The sedation levels were also evaluated by the anaesthetist just before the induction of anaesthesia and in the recovery room 30 and 60 minute after operation. Sedation was evaluated

on a score of 1- 4; 1= alert /active, 2= awake/calm, 3= drowsy but respond readily to verbal commands, 4= asleep. Anaesthesia was induced with fentanyl L 5-µgm/kg body weight and thiopental sodium 5 mg/kg and endotracheal intubations was done with suxamethonium I mg/kg. Anaesthesia was maintained with 70% $_{N20}$ in oxygen, fentanyl 0.05 µgm /kg every 30 minutes interval. All these were supplemental with halothane at the lowest possible concentration. Muscle relaxation was achieved with vecuronium (Norcuron) 0.05 mg/kg initially and 0.01 mg/kg subsequently if needed. Before and 10 minutes after intubations and throughout the operative period at 10 minute interval pulse and blood pressure were recorded. At the end of operation muscle relaxation was reversed with a mixture of neostiglnine 0.05 mg/kg and atropine 0.02 mg/kg and tracheal extubation were done. Total duration of surgery was noted. After extubation and finally in the postoperative ward in addition to the above parameter recovery status were measured by Aldrete recovery score [13]. Approximately 24 hours after the anaesthesia the last assessment was carried out in the ward. The patient was also asked whether he or she could recollect any events immediately to induction and whether had any awareness or dreams (pleasant or unpleasant) during the operation.

All statistical analysis was carried out using SPSS statistical analysis software. All results are expressed as mean ± SD or in frequencies as applicable. The results were compiled and analyzed statistically using two way and One-Way ANOVA and Chi-square test as appropriate. Results are considered significant if $p<0.05$. (Confidence interval; Cl- 95%)

RESULTS:

The groups were similar in age, weight, ASA grading & duration of surgery (Table -I). There were no significant differences between groups in anxiety level by VAS during preoperative assessment. VAS was significantly different in Group-C (p=0.002) and Group-B (p=0.000) with Group-D (p=0.29) at morning on the day of operation, before induction of anaesthesia and 24 hours after operation (Table-II).

Pulse rate during pre operative assessment at different groups were similar (Fig-1). Pulse rate rises before induction in Group-C & in Group-D but it reduces in Group-13 (Fig-1). There is significant change in pulse rate in between groups & within groups at different times after induction & after recovery.

During pre operative assessment the mean systolic & diastolic blood pressures at different groups were similar (Fig-2 & Fig-3)_ Systolic & diastolic blood pressures vary at different time. Before induction significant changes were observed in between the groups (Group-C, Group-D & Group-B). However within the groups at different after induction there was no [significant] changes in Group-B.

Sedation score that were measured on arrival in Operation Theater at morning (just before the induction of anaesthasia) in three different groups (Table-III). There was a significant change in sedation score in between the groups. Recovery score that were measured after extubation by Aldrete recovery score (minimwn score '0'& maximum score '10') (Appendix -1& Table-IV). It was seen that patient in Group-C & Group-B recovered well in comparison of group-D. Post operatively nausea, vomiting & increased secretion was observed (Table-V). Nausea was more in group-C (26.66%). Less vomiting was seen in group-B & group-D (6.66%).

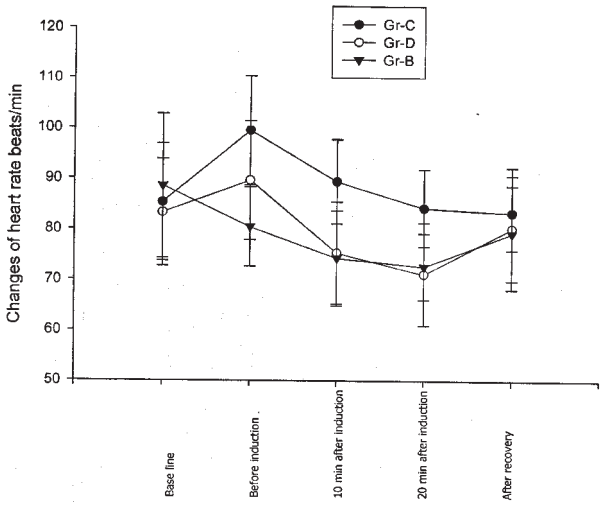

Fig.-1 : *Changes of heart rate (beat / min) in three studied groups*

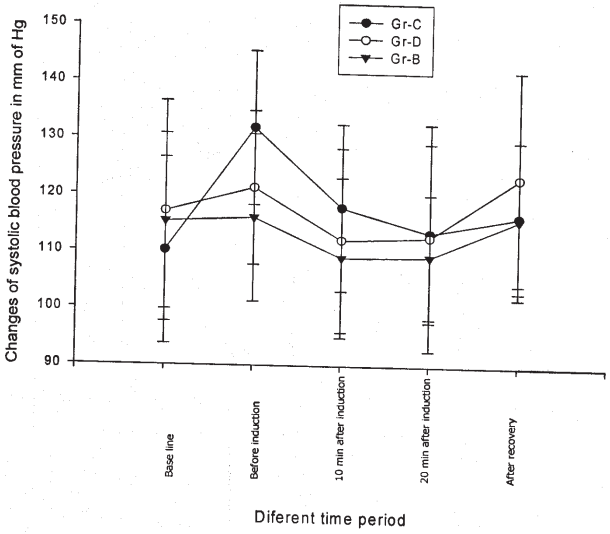

Fig.-2 : *Changes of systolic blood pressure in different time of three studied groups.*

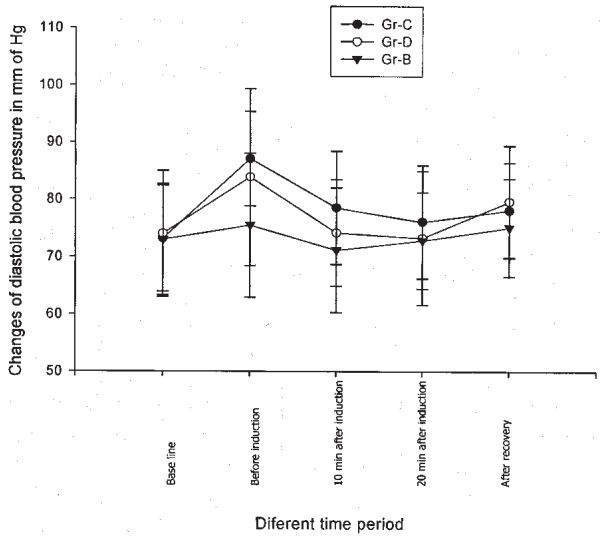

Fig.-3 : *Changes of diastolic blood pressure in different time of three studied groups.*

Table I

Characteristics of Subject

Group/variable	Group-C	Group-D	Group-B	pValue
	n	30	30	30
Age in years	42.43 + 9.14	41.93 ± 9.99	40.33 ± 13.22	0.740
Weight in kg	55.30 + 11.74	55.53 t 9.84	53.70 ± 10.47	0.770
Sex: Male	06(20%)	04(13.33%)	05 (16.70%)	0.560
Female	24(80%)	26(86.66%)	25 (83.30%)	
ASA: I	19(63.3%)	21(70%)	22(73.3%)	
ASA: II	11 (36.7%)	09(30%)	08(26.7%)	0.703
Operation Timein min	65.17 ± 11.17	66.50±15.48	67.00 f 14.47	0.869

Values are expressed as mean ± SD or as frequency. Within parenthesis are percentages over column total. Between groups analysis were done by ANOVA. Values are expressed as significant if $p<0.05$ (CL-95%).

Table-II

Anxiety Level by VAS in three different groups

Time	Group-C	Group-D	Group-B	p value
	n	30	30	30
During Pre-operativeassessment	7.93±1.34	7.83±1.72	8.00± 1.31	0.907
Morning on day of operation	8.67±1.52	6.77±2.11	5.43± 1.54	0.001
Before Induction	8.47±1.43	6.73±1.95	5.17± 1.05	0.001
24 hours afteroperation	7.30±1.49	6.43 ± 1.79	5.10 ± 1.15	0.001
P value	0.002	0.29	0.001	

Table III

Sedation Score in three different groups

Score	Group-C	Group-D	Group-B	x^2	pValue
	n	30	30	30	
1-2	30(100.00%)	19(63.33%)	28 (93.33%)		
3	0 (00.00%)	11(36.66%)	2 (6.66%)	25.06	0.001
4	0 (00.00%)	0(00.00%)	0 (00.00%)		

Values are expressed as frequency. Within parenthesis are percentages over column total. Between groups analysis were done by Chi-square test. Values are expressed as significant if $p<0.05$ (CL-95%).

Table IV

Recovery Score in three different groups

Score	Group-C	Group-D	Group-B	x^2	p
9-10	27(90.00%)	17(56.66%)	22(73.33%)	12.18	0.16
7-8	3 (9.99%)	12(40,00%)	8(26.66%)		
5-6	0(00.00%)	1(3,33%)	0(00.00%)		

Values are expressed as frequency. Within parenthesis are percentages over column total. Between groups analysis were done by Chi-square test. Values are expressed as significant if $p<0.05$ (CL-95%).

Table V

Side effects observed in three different groups

SideEffects	Group- C	Group- D	Group- B	x^2	Pvalue
	n	30	30	30	
Nausea	08(26.66%)	06(20.00%)	05(16.66%)	0.934	0.627
Vomiting	04(13.33%)	02(06.66%)	02(06.66%)	0.098	0.578
Increasedsecretion	20(66.66%)	16(53.33%)	13(43.33%)	3.315	0.191
Others	0(00.00%)	0(00.00%)	01(03.33%)	2.022	0.364

Values are expressed as frequency. Within parenthesis are percentages over column total.

APPENDIX I

Post anaesthetic Aldrete recover score

Original Criteria	Modified criteria	Point value
Color:	Oxygenation:	
Pink	$SP0_2$ > 92% on room air	2
Pale or dusky	$SP0_2$ > 90% on oxygen	1
Cyanotic	$SP0_2$ < 90% on oxygen	0
Respiration:		2
Can breath deeply & cough	Breath deeply & coughs freely	1
Shallow but adequate exchange	Dyspneic, shallow or limited breathing	0
Apnea or Obstruction	Apnea	
Circulation:		
Blood pressure within 20% of normal	BP±20 mm Hg of normal	2
Blood pressure within 20-50% of normal	BP± 20 -50 mm Hg of normal	1
Blood pressure deviating > 50% from normal.	BP more than ± 50mg Hg of normal	0
Consciousness:		
Awake, alert & oriented	Fully awake	2
Arousable but readily drift back to sleep	Arousable on calling	1
No response	Not responsive.	0
Activity:		
Moves all extremities	Same	2
Moves two extremities	Same	1
No movement	Same	0

DISCUSSION:

Anaesthetists have the opportunity to influence the course of their patient's anaesthetic with a preoperative visit and preoperative medications. Most common reason for administering premedication is to make the experience of anaesthesia and surgery more pleasant and less traumatic. Based on ones own clinical experience and favorite routine, an anaesthetist may order a sedative-hypnotic, narcotic analgesic, major tranquilizer or anticholinergic drug. Frequently a combination two or more compounds from different drug groups is prescribed. It is generally accepted that patient apprehension (or anxiety) is a major factor that should be controlled in the preoperative period.

There is limited study on Bromazepam as a premedicant in comparison with diazepam. Chalmers et al. 1984 studied on gynaecological operation giving diazepam 10 mg in one group and Bromazepam 9 mg in other group between 1.5 and 3 hours preoperatively[11]. No difference was demonstrated between the effectiveness of the two drugs. Our study differs from that regarding the doses and the timing of giving the drugs. We have used bromazepam 3 mg at night before and 3mg at morning on the day of operation and diazepam 5mg at night and 5 mg at morning on the day of operation.

Our study is based on the patient under going different type of surgery and to see the effectiveness of bromazepam as an anxiolytic when

used as premedicant. We used VAS to measure the anxiety status at different period. VAS was significantly changed in different group [in Group-D ($p=0.29$) and in Group-B ($p<0.001$) with Group-C(0.002)] at morning on the day of operation, before induction of anaesthesia and after 24 hours of operation.

These changes are similar to the study of Fontain et al 1983 though the measuring method was different[14] . Fontain et al studied on anxious patient with a primary diagnosis of generalized anxiety disorder with Bromazepam (18 mg/day), diazepam (15mg/day) or placebo. Bromazepam and diazepam was found to be significantly ($p<0.05$) superior to placebo with respect to somatic anxiety factor and total score of Hamilton Anxiety Rating Scale and the fear/ anxiety factor of patients' self-rating symptom scale[14].

In Hallett & Dean 1984 study on general practice to asses the benefit-risk ratio of the bromazepam, in a dose range of 3mg to 9mg daily in divided dose, was effective as and anxiolytic in 79% of the patients and that the acute benefit risk ratio is acceptable with respect to the class of drug and indication for which bromazepam is prescribed[15]. In study of Kerry et al. 1972, a comparison of bromazepam, diazepam and chlor diazepoxide, was found bromazepam was better than diazepam but difference failed to reach statistical significance[16]. Our study also shows a significant difference of effect as anxiolytic between the Bromazepam and diazepam.

Both systolic & diastolic blood pressures were not significantly changed in group-B. In Chalmers et al. 1984 study patients of the diazepam group and Bromazepam group, no significant cardiovascular effects have seen except in one patient who had Bromazepam, suffered from severe hypertension[11]. Our study results are similar to Chalmers et al. regarding no haemodynamic alteration.

In Chalmers et al. 1984 study patient were markedly sedated in diazepam group, whereas no patient of the bromazepam group was markedly sedated. They also showed that 55% of the diazepam group was slightly to moderately sedated and 80% of patient in bromazepam group were so. They concluded that there was no significant change in between the group regarding the sedative effect. In our study, we found 36.66% of patient in diazepam group were drowsy in comparison to bromazepam, which was 6.66%, and no patient in either group were markedly sedated[11]. This differs from Chalmers et al. Study because the dose administered in their study was 10 mg diazepam and 9 mg bromazepam between 1.5- 3 hour preoperatively. Where as in our study bromazepam 3mg and diazepam 5 mg given in divided dose one in night before surgery and another at morning preoperatively.

In the study of Fontain et al. 1983 at generalized anxiety disorder with bromazepam 18 mg/day and diazepam, 15mg/day was seen that 62.5% of the patient drowsy in comparison of the diazepam taken group (50%)[14] which differs from our study as we used bromazepam 3mg and diazepam 5 mg given in divided dose one in night before surgery and another at morning preoperatively. Comparative study done by Ponnudurai & Hardly 1986 between bromazepam and lorazepam as a premedicant, no significant difference in sedation score was found ($p>0.1$)[17]. However, in our Study bromazepam in comparison to diazepam was seen a highly significant change ($p<0.001$).

Recovery from general anaesthesia is a time of great physiological stress. It seeins reasonable to expect that the physical and mental state of the patient will be compromised maximally at which they have just regained consciousness after general anaesthetic. Measures that have been used to assess the patients' state during this immediate recovery period have tented to focus predominantly on physiological or vestibular motor functioning[18].

In general term many of the ways of assessing immediate recovery from anaesthesia appear to show that patient generally make a speedy return to normal functioning depends upon the type of anaesthetic agent used, the duration of surgery, the other intraoperative procedure and variation in premedication[18].

In our study recovery status of patients were measured by Aldrete & Kroulik recovery score". We found in Group- C, twenty-seven (90.00%) patient has a recovery score from 9-10 in comparison to Group-D where it was seventeen (56.66%). In Group-B recovery score of 9-10 was twenty two (73.33%). From this study, it was seen that patient in Group-C and Group-B recovered well in comparison of Group-D. It means that diazepam affect the recovery probably due to it is prolonging half-life.

Postoperatively nausea, vomiting, and increased secretion are observed in some of the patients. Nausea was more in the Group-C, which were eight (26.66%) in comparison to Group-D which was six (20.00%) and Group-B that was five (16.16%). Four patients in the Group-C were vomited after recovery in postoperative room. Less vomiting was seen in Group-B and Group-D, which were two (6.66%). In a comparative study of bromazepam and lorazepam done by Ponnudurai and Hardly it was seen that there were no difference in incidence of nausea, and amnesia although there was less vomiting in the bromazepam group[17]. In Chalmers et al. study one patient (5%) complained of nausea in each group. They studied on forty patient, twenty of each group by giving diazepam 10 mg and bromazepam 9 mg preoperatively at morning on the day of operation[11]. But in our study we found 16.16% of bromazepam group complained about nausea and two (0.66%) patient vomited in post operative room in comparison to control group which was four (13.33%).

These types of side effect are commonly seen in patients undergoing surgery under general anaesthesia. These may be due to the drugs used preoperatively or due to the patient's factor. There were no adverse cardio respiratory reaction nor did we observe any untoward behavioral effects.

CONCLUSION:

From the present study, it is concluded that oral bromazepam at divided doses as a premedicant relief anxiety, and patients are haemodynamically stable in perioperative period than the oral diazepam. Patients those have taken bromazepam recovered well and were less drowsy.

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