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A CROSS-SECTIONAL COMPARATIVE OBSERVATIONAL STUDY ON ORAL PREMEDICATION EFFECT OF ALPRAZOLAM AND DIAZEPAM ON SELECT PSYCHOLOGICAL FUNCTIONS

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ABSTRACT

Background: Anxiety is an emotional state characterized by apprehension and fear resulting from the anticipation of a threatening event.Preoperative anxiety may lead to various problems and a wide range of physiological and psychological responses. Various factors influencing anxiety in a patient planned for surgery include age, gender, the extent and type of surgery, previous hospital experiences, susceptibility to and ability to cope with stressful experiences, and preoperative information. So the benefits of effective premedication include a reduction in patient's anxiety, facilitation of smooth anaesthetic induction, reduction in reported undesirable postoperative behavioural changes, and reduction in recoverytime.

Aim: To evaluate and compare the effects of oral Diazepam and oral Alprazolam on preoperative anxiety, sedation, alertness, psychomotor and cognitive functions on the morning of surgery.

Primary objective:

To compare oral premedicants Alprazolam and Diazepam in terms of sleep quality and alertness on the morning of surgery.

Secondary objectives:

To compare oral Alprazolam and Diazepam in terms of

1. Level of anxiety andsedation
2. Psychomotor and cognitivefunction
3. Vitalparameters
4. Adverse effects, ifany

Methods: After obtaining institutional ethics committee clearance and informed consent from the patients scheduled for surgery, 94 patients were divided into two groups, A (Alprazolam) and D (Diazepam) by the consultant anaesthesiologist.

Patients were given tablet Alprazolam or tablet Diazepam at 9 p.m. in the preoperative night and 7 a.m. in the morning. Each patient's Non-Invasive Blood Pressure (NIBP), Heart Rate (HR), and Respiration Rate (RR) were monitored before premedication at 9 p.m. and after morning premedication at 7

a.m. The APAIS was used to assess the patient's level of anxiety and state of mind just before the evening premedication was administered. The Digit Symbol Substitution Test (DSST) and the Trail Making Test (TMT) were used to provide a comprehensive assessment of the participant's cognitive and motor skills before premedication at night and after morning premedication. After giving morning premedication at 7.00 a.m., the patient‟s sedation level was assessed at 8.00 a.m. using Richmond Agitation and Sedation Score (RAAS), the patient's alertness and the previous night's sleep was studied using Karolinska Sleep Diary (KSD) scoring. The patient‟sorientation was assessed using Galveston Orientation Amnesia Test (GOAT) in the morning. Categorical values were calculated using the Chi-square test and Fisher's exact test. Continuous variables were calculated using Unpaired t-tests, and Mann-Whitney U-test. Any value of P less than 0.05 was regarded to be statistically significant.

Results: Both groups were comparable demographically. Baseline haemodynamic parameters were also similar across the groups. After premedication, the patients in the Diazepam group have taken a longer time to complete Trail Making Test (TMT B) when compared to patients in the Alprazolam group. This indicates executive functioning was preserved in the Alprazolamgroup.

In the (KSD) assessment, patients in the Alprazolam group felt refreshed after waking up and ease of waking up also was more in patients with the Alprazolam group as premedication when compared to the Diazepam group.

Conclusion: We conclude that Alprazolam is a better premedication when compared to Diazepam as morning alertness was better and it retained executive functions. Thus Alprazolam is a better premedication when compared to Diazepam in terms of preserving select psychological functions.

Keywords: Alprazolam, Diazepam, Preoperative anxiety, Modified Richmond Agitation-Sedation Scale, Galveston Orientation And Amnesia Test.

INTRODUCTION

Anxiety is an emotion that comes from feeling uneasy about something bad happening in the future. Concern about hospitalization, anaesthesia, surgery or the unknown may lead to a sense of uneasiness or tension known as preoperative anxiety (1).

Anxiety before surgery may cause a variety of issues and various emotional and physical reactions. Tachycardia, hypertension, a higher-than-usual body temperature, profuse perspiration, feelings of nausea, and an amplified sensitivity to touch, smell, or hearing are all physiological reactions. Behaviours like anxiety, and aggressiveness might be indicators of psychological reactions. It makes inducing anaesthesia more difficult because of peripheral vasoconstriction, autonomic fluctuation, delayed jaw relaxation, coughing, and increased anaesthetic need. The recovery time will prolong and there might be increased chances of infection, and also there will be a higher probability of discomfort, nausea, and vomiting after surgery (2).

As a result, the anaesthesiologist should screen for the presence of anxiety in every patient before surgery as part of the standard preoperative anaesthetic examination, and provide counselling to those with a particularly high degree of anxiety (1).

Age, gender, type of procedure, past hospital experiences, sensitivity to and capacity to deal with stressful situations, and preoperative information all play a role in a patient's anxiety before surgery. The advantages of successful premedication include a shorter recovery period and less reported negative postoperative behavioural changes, as well as a decrease in the anxiety level of the patient.

Nowadays, time limitations make it difficult to assess patients' levels of apprehension before elective surgeries. Premedications, a preoperative visit from the anaesthesiologist, preoperative counselling, and preoperative videos are some of the measures that need to be taken to alleviate the patient's concerns before the surgery (3).
The better location to relay important information and answer patients' queries is the pre-operative consultation clinic (3).
The patient with a high degree of anxiety should be scheduled for an additional counselling session with the anaesthesiologist, in addition to the standard preoperative examination.
Alprazolam and Diazepam are the most commonly used premedicants. However, the common side effects of these drugs include drowsiness, lightheadedness, dizziness, irritability, talkativeness, memory problems, confusion, hallucination, increased salivation, seizures, weakness, problems with coordination,and gastrointestinal discomfort. The onset of action of both Alprazolam and Diazepam is 15 to 60 minutes. The duration of action of Alprazolam is 6-12 hours whereas the duration of action of Diazepam is 15-30 hours.
Currently, there is not enough data available comparing the sedatives, Diazepam and Alprazolam, and their premedication effect. Hence, we decided to compare and bring out the better drug for premedication which is a good sedative, has adequate freshness on the morning of surgery, and doesn't impair cognitive and psychomotor functions.

MATERIALS AND METHODS

- After obtaining Institutional Ethics Committee clearance and informed consent, patients were divided into Group A (oral Alprazolam) or Group D (oral Diazepam) by the consultant anaesthesiologist.
- ***Sample size:*** Based on the work of Kim et al(4), the Standard deviation of group 1 (0.5) and standard deviation of group 2 (0.7), the mean difference is 0.35, the effect size is 0.583, at a 5 percent level of significance, and 80 percentage power, the required sample is 47 per group (Total=94). This was calculated using n-Master Software version 2.0

Inclusion Criteria:

- All consenting adult patients coming for surgery under anaesthesia in the weight group ≥50 -≤80 kilogram
- ASA PS grades 1, 2,3

Exclusion Criteria:

-People on psychotropic medications

-People on regular alcohol consumption and other drugs excluding tobacco

-Allergic to any drug used in the study

-Patient who cannot comprehend the scores of the study

Premedication was prescribed according to the preference of the concerned consultant anaesthesiologist. The drugs used in our study were oral Alprazolam 0.5 mg and oral Diazepam 10 mg. Each patient received either of the drugs based on the treating consultant. The patients were given tablet Alprazolam or tablet Diazepam at 9 p.m. in the preoperative night and 7 a.m. in the morning. Each patient's Non-Invasive Blood Pressure (NIBP), Heart Rate (HR), and Respiration Rate (RR) were monitored before premedication at 9 p.m. and after morning premedication at 7 a.m. The APAIS was used to assess the patient's level of anxiety and state of mind just before the evening premedication was administered. The DSST and the TMT were used to provide a comprehensive assessment of the participant's cognitive and motor skills before premedication at night and after morning premedication. After giving morning premedication at 7.00 a.m., the patient's sedation level was assessed at 8.00 a.m. using RAAS, patient's alertness, and the previous night's sleep was studied using KSD scoring. The patient's orientation was assessed using GOAT in the morning.

TABLE 1: TEST PERFORMED- MORNING OF SURGERY & PREVIOUS NIGHT OF SURGERY

TEST PERFORMED	MORNING OF SURGERY	PREVIOUS NIGHT SURGERY
APAIS		✓
GOAT	✓	
DSST	✓	✓
TMT	✓	✓
KSD	✓	

STATISTICAL ANALYSIS

To illustrate qualitative factors, we used frequency and percentages. Mean, Standard Deviation, and Confidence Interval were used to display quantitative variables. Categorical values were calculated using the Chi-square test and Fisher's exact test. Continuous variables were calculated using Unpaired t-tests, and Mann-Whitney U-test. Any value of P less than 0.05 was regarded to be statistically significant.

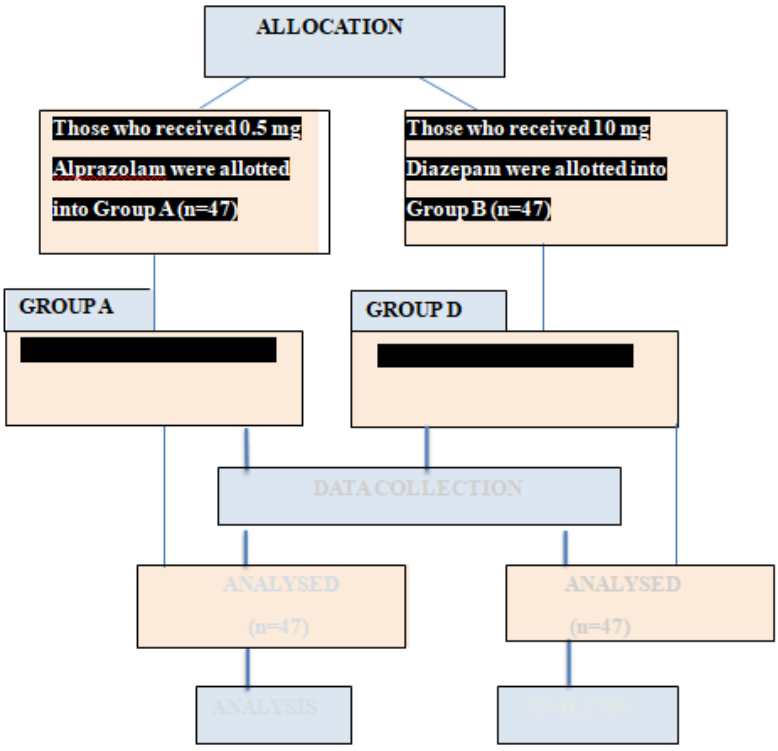


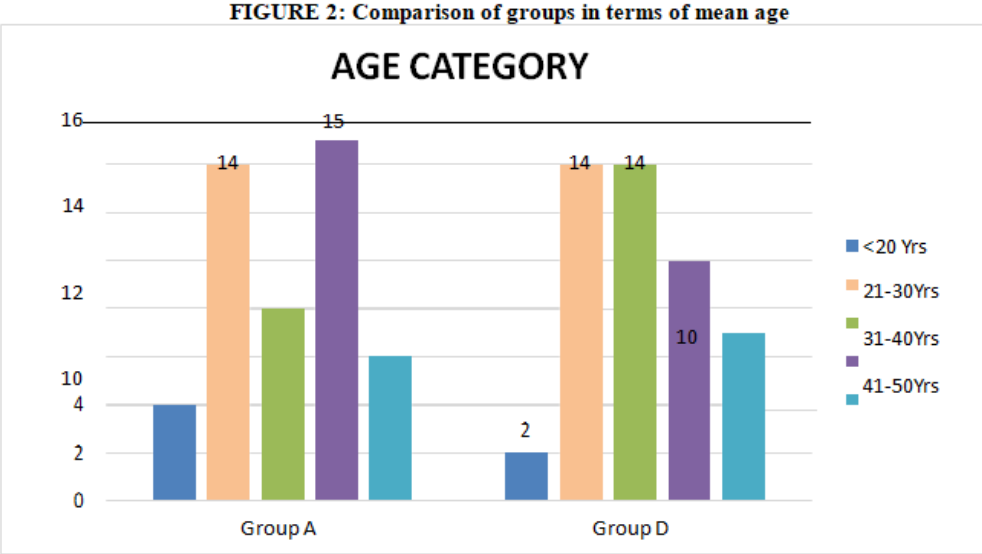
Figure 1: CONSORT DIAGRAM

RESULTS

The two groups were comparable in terms of demographic data, baseline hemodynamic parameters, baseline TMT-A & TMT-B, baseline DSST.

Demographic data:

FIGURE 2: Comparison of groups in terms of mean age



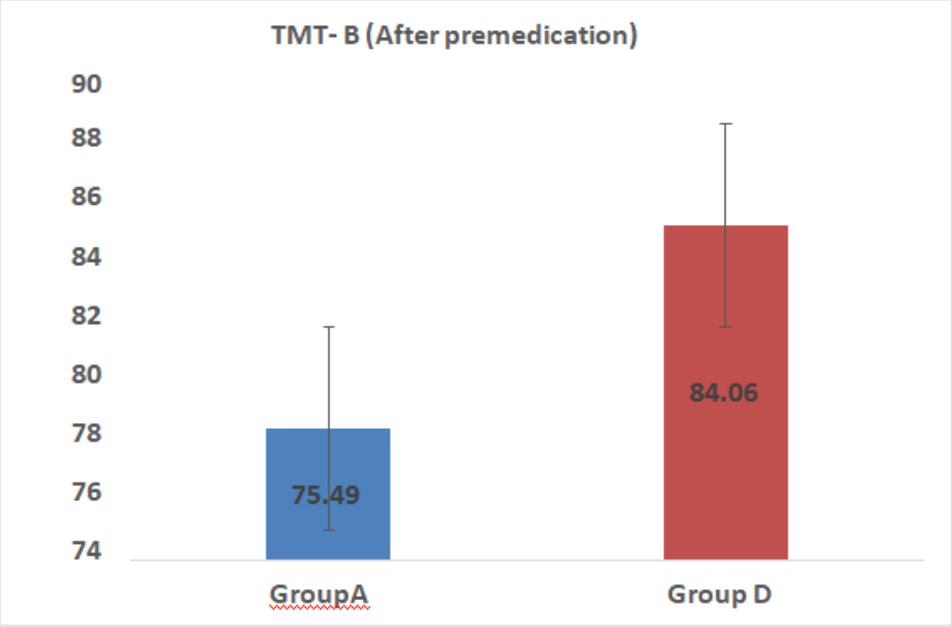
(p-value = 0.893)

TABLE 2: Comparison of groups in terms of gender

GENDER					
			Group A	Group D	Total
Sex	F	Total	20	21	41
		% within Group	42.5%	44.7%	42.2%
	M	Total	27	26	53
		% within Group	57.5 %	55.3%	57.8%
Total		Count	47	47	94
		% within Group	100%	100%	100%

(p-value = 0.835)

After premedication no changes were noted in hemodynamic parameters in both the groups. Comparison of the TMT A between the two groups after premedication proved that cognitive processing speed was similar in both groups(p=0.864). Comparison of the TMT- B between the two groups after premedication showed that participants in the Diazepam group took a longer time (mean value=84.06 sec) to complete TMT-B when compared to participants in the Alprazolam group. Therefore executive functioning was preserved in the Alprazolam group after premedication.(p=0.04)



(p-value = 0.04)

Figure 3: Comparison of TMT- B after premedication

Comparison of DSST after premedication proved that there was no difference between the groups (p=0.408).

Comparison of the two groups in terms of APAIS proved that patient's level of anxiety and need for information was similar in both groups.

Comparison of the two groups in terms of GOAT proved that the orientation and amnesia level of the patient after premedication was similar in both groups

Comparison of the two groups in terms of RASS proved that sedation level after premedication was similar in both groups.

Comparison of the KSD 7 between the two groups proved that feeling refreshed after awakening was more in the Alprazolam group.

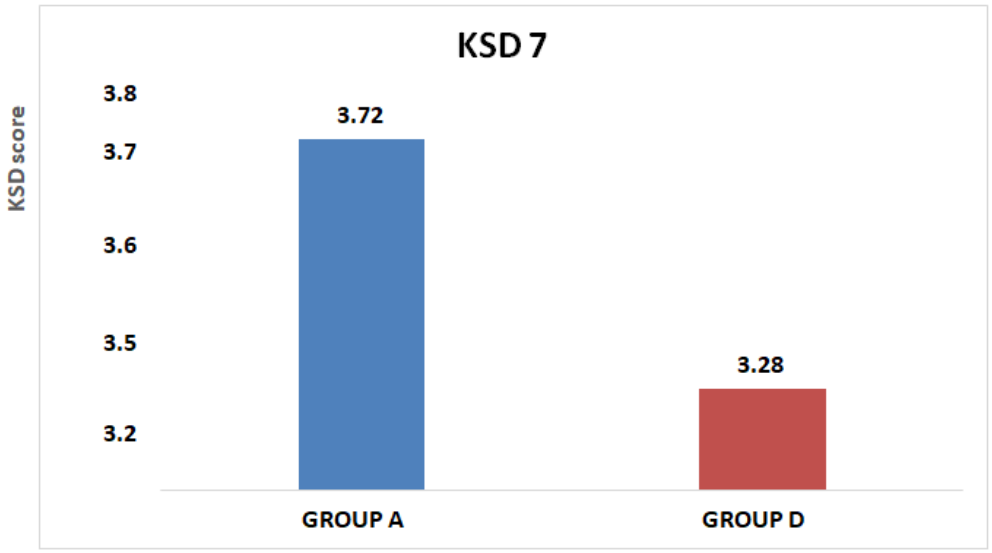
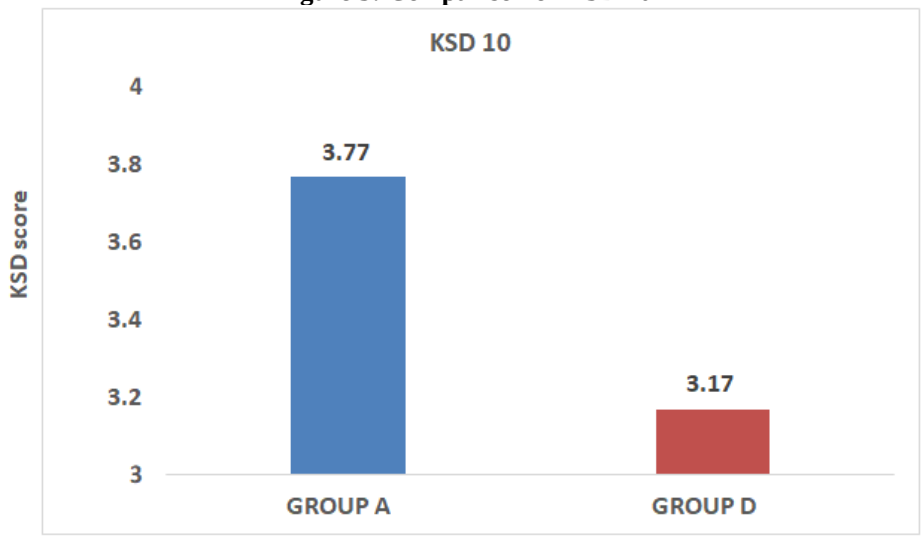


Figure 4: Comparison of KSD 7

Comparison of the KSD 10 between the two groups showed that ease of waking up was more in Alprazolam group when compared to Diazepam group. This was also proved statistically with a p-value of <0.001

Figure 5: Comparison of KSD 10



DISCUSSION

Patients go through a lot of stress and strain before an operation(5) .Premedication aims to alleviate these anxieties through their sedative and anxiolyticeffects (6).

Thus, premedication must be administered at the appropriate time so that the patient is free from preoperative stress (7).

Premedication should be chosen after taking into account the patient's current health condition, age, anxiety level, pain tolerance, anticipated surgical procedure, and any previous reactions to drugs (8).

Though there are studies comparing Alprazolam and Diazepam in anxious outpatient clinics, there are not enough studies comparing the two drugs as premedication in elective surgeries. Hence we decided to compare the two drugs Alprazolam and Diazepam with respect to anxiety, sedation, psychomotor and cognitive functions and analyze the outcome.

In this study, patients in the Diazepam group have taken a long time to complete TMT- B (p-value=0.04) when compared to patients in the Alprazolam group. This indicates that executive functioning was lost in the Diazepam group. TMT-A assesses cognitive processing speed. TMT- B assesses executive functioning. Executive functions include self-control, self-monitor, emotional control, flexibility, task initiation, organization, and planning which help in controlling anxiety and stress.

This is consistent with the study conducted by **Sarkar et al** who studied that even a single dose of Diazepam can impair inhibitory control (9).

Specialist pharmacy service NHS foundation (2020) studied choosing an equivalent dose of benzodiazepine and concluded that Alprazolam 250 mcg is approximately equivalent to Diazepam 5mg. **Kim et al** and **Witte et al**(4,10)**.** have told in their studies that oral Diazepam has an anxiolytic index score of 10 mg which is half that of Alprazolam 0.5 mg. Similarly in the present study, we have used 10 mg of oral Diazepam which is equivalent to 0.5 mg of oral Alprazolam.
In the present study, we have observed that patients in the Diazepam group were not fresh after waking up when compared to patients in the Alprazolam group which impaired their daytime functions. This is consistent with the study by **Hillestad et al** who said that the main metabolite of Diazepam, n-desmethyl diazepam, has an appreciable hypnotic action that can affect the patient's daytime functions (11).

Alprazolam is metabolized in the liver by cytochrome P450 3A4 (CYP3A4) to 4-hydroxy alprazolam and alpha-hydroxy alprazolam metabolites. The mean plasma half-life of Alprazolam is about 11.2 hours in healthy adults (12).

In the case of Diazepam, the initial distribution followed by a prolonged terminal elimination half-life in Diazepam is approximately 48 hours. Additionally, the terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Thus it impairs daytime functions and cognitive ability (13).
Patients who received Alprazolam had a better KSD score when compared to patients who received Diazepam as premedication. They felt waking up was easy and felt refreshed as well. Similar to the present study **Wang et al** evaluated the sleep quality of Alprazolam by the Pittsburgh Sleep Quality Index and got positive results (14).

In the present study, we have noticed that decision-making skills which is a component of executive functions were lost in the Diazepam group.Deakin et al have said that Diazepam can influence frontal lobe functions associated with decision-making either by direct effects on GABAA receptors within the frontal cortex or by modulating activity in the ascending reticular system (15).

Therefore, as a premedicant Alprazolam was better in ensuring ease of waking up and morning freshness when compared to Diazepam. Executive functioning which is essential in controlling emotions was also preserved in patients with Alprazolam as premedication.

STRENGTHS OF THE STUDY: The drugs used in this study, Alprazolam and Diazepam are used in routine day-to-daypractice.Participants belonging to ASA PS III were also included in the study as many of the elderly population belong to thisclass. This study wascost-effective.

LIMITATIONS OF THE STUDY: The scales used in the study weresubjective. Intraoperative and postoperative follow-up of the hemodynamic parameters, drug requirements, postoperative pain score, and sedation level was not carried out in the study.

CONCLUSION

We conclude that Alprazolam is a better premedication when compared to Diazepam as morning alertness was better and it retained executive functions. Thus Alprazolam is a better premedication when compared to Diazepam in terms of preserving select psychological functions.

Ethics approval and consent to participate:

All patients were enrolled only after obtaining informed consent. There were no discomfort to the patient. All techniques used in the study were well-established in clinical practice. There were no added risk to the patient. The procedure was beneficial to the participant as it is known to produce a good premedication effect. The autonomy of the patient was maintained. The privacy of the patient was

protected. No extra cost was levied on the patient. Thus, there were no apparent ethical issues. Institutional Ethical Committee clearance was obtained with Institutional Ethical Committee approval number INST.EC/EC/032/2021-22; REG.NO.EC/NEW/INST/2020/834

List of abbreviations

1	APAIS	Amsterdam Preoperative Anxiety and Information Scale
2	DSST	Digit Symbol Substitution Test
3	GOAT	Galveston Orientation and Amnesia Test
4	KSD	Karolinska Sleep Diary
5	RASS	Richmond Agitation-Sedation Scale

Conflicts of Interest

There is no conflict of interest

Funding statement- Nil

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