

**“ANXIOLYTIC EFFICACY OF ORAL MIDAZOLAM VERSUS ORAL ALPRAZOLAM”**

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**ABSTRACT**

**Background:** Preoperative anxiety is a challenging concept in preoperative care of the patient going surgery experiencing varying levels of anxiety. Anxiety prior to surgery may be due to perceived danger of surgical procedure, pain, anesthesia, outcome of surgery and worries about the family.

**Objective:** To compare the efficacy of oral Midazolam versus oral Alprazolam as a premedicant during regional anesthesia to relieve anxiety.

**Methods:** Two sample populations each of 30 persons were selected. Utmost care was taken to that the samples are from same population. The drugs Midazolam and Alprazolam were administered on two separate sample population. In the sample population, observations in terms of changes in Blood Pressure, heart rate, Oxygen Saturation, sedation and anxiety were measured and compared to the effects of these drugs on two separate sample.

**Results:** There is a significant difference between the midazolam and Alprazolam sample with respect to the anxiety level after the administration of these drugs on the persons in their respective samples. For Midazolam sample the mean anxiety level decreased from 14 to 5.93 and for the Alprazolam sample the mean sedation decreased from 14 to 8.93.

**Conclusion:** The results of our study concluded that Midazolam performs better than Alprazolam as it maintains a significant higher SPO<sub>2</sub> level in comparison to Alprazolam and reduces anxiety significantly in comparison to Alprazolam.

**KEYWORDS:** Midazolam, Alprazolam, SPO<sub>2</sub>, Anxiety, Sedation

**INTRODUCTION**

Preoperative anxiety is a challenging concept in preoperative care of the patient going surgery experiencing varying levels of anxiety.<sup>1</sup> Anxiety prior to surgery may be due to perceived danger of surgical procedure, pain, anesthesia, outcome of surgery and worries about the family.<sup>2</sup> Oral route for conscious sedation is very easy to administer and has good acceptance. Various drugs are used for premedication to produce anxiolysis.<sup>3</sup> Many patients anxious before surgery yet there is sometimes a reluctance to provide sedative medication because it is believed to delay discharge from hospital.<sup>4</sup> Anxiety is an unpleasant emotion and may cause patients to avoid a planned operation.<sup>5</sup> It may also adversely influence anesthetic induction and patient recovery, as well as decrease patient satisfaction with the perioperative experience.<sup>6</sup> Preoperative anxiety can be divided into three distinct dimensions of anxiety. that is fear of the unknown, fear of feeling ill and fear for one's life. The first factor correlates highest with the different measures of anxiety.<sup>7,8,9</sup>

Preoperative anxiety affects most patients and some factors contribute for this: separation from the family, postoperative pain, disability, and loss of independence.<sup>10</sup> Studies have

demonstrated that midazolam has several benefits and among them, we could mention a reduction in preoperative anxiety, better cooperation, and it has a short half-life and good absorption after oral administration.<sup>11,12,13,14</sup> It would be desirable to find a benzodiazepine for oral premedication with a strong anxiety-reducing effect and minimal psychomotor impairment. Midazolam premedication is associated with increased sedation. However, it doesn't affect the recovery profile.<sup>15</sup> Its short duration of action makes it a recommended benzodiazepine for surgical procedures in out-patients. Alprazolam at 0.5 mg has the second highest anxiolytic activity (index of 2.26).<sup>16</sup> It has an onset time of 1.4 h and an elimination half-life of 10.6h in normal weight subjects. Given these pharmacokinetic properties and its major anxiety-reducing effects in patients with primary anxiety and panic attacks, alprazolam could be a possible alternative to midazolam for premedication in surgical outpatients. Although the sedative, anxiolytic and amnesic properties of midazolam may be desirable before the induction of oral anesthesia, residual effects in the immediate post-operative period may contribute to intra-operative sedation as well as delayed recovery and readiness for discharge after brief outpatient surgery.

Ideal drug should have the following properties:

- Easily administered
- High anxiolytic index
- Predictable sedation
- Quick onset of action
- Short half life
- Minimal hemodynamic effects
- Minimal or no cognitive derangement
- No respiratory depression

## **MATERIAL AND METHODS**

After institutional ethical committee review, board approval and written informed consent, 60 patients undergoing various procedures under subarachnoid block were enrolled in this prospective randomized controlled trial.

Patients were allocated randomly to either Group A or Group B

### **Group A:**

These patients received Tablet Midazolam (7.5 mg) orally 1 hour before the scheduled procedure.

### **Group B:**

These patients received Tablet Alprazolam (0.5 mg) orally 1 hour before the scheduled procedure.

### **INCLUSION CRITERIA:**

- Age: 20 —40 years
- ASA Grade I & II
- Elective Lower Abdominal Surgery
- Elective Pelvic Surgery
- Elective Lower Limb Surgery
- Duration within 3 hours

### **EXCLUSION CRITERIA:**

- Consent not available
- ASA Grade III and IV
- less than 20 years

- Previous history of adverse reactions after regional anesthesia
- Patients who had undergone general anesthesia
- Patients allergic to Midazolam or Alprazolam
- Alcoholic
- Patients on anti-psychiatric, antidepressant, antiepileptic and analgesic medication
- Patients with significant cardiovascular, respiratory, hepatic, renal, neurological, psychiatric and metabolic disorders.

**Operative Workup:**

In the proforma we documented the patient's demographics, hospital details, and ASA grade. The spinal anesthetic procedure, the use of premedication, and the current study were all clearly explained to the patients. At the pre-anesthesia checkup, a valid written informed consent was obtained. The study only included patients who met the inclusion criteria. Prior to surgery, the patient will be nil by mouth for 6 hours for solids and 2 hours for clear fluids.

**On the day of surgery**, before giving any pre-medication baseline values of heart rate, blood pressure and oxygen saturation were noted. Tablet Alprazolam / Midazolam were sealed in identical packets and were given to the patients by a nurse who was not involved in the study either intra-operatively or postoperatively. The patients received either drug based on computer generated random numbers. The premedication was given 1 hour prior to surgery with sips of water. The patient was taken to the operation theatre. Pulse oximeter probe was attached, ECG leads were connected, blood pressure cuff was tied on the arm of the patient and readings were noted. Intravenous cannulation was done with appropriate sized IV cannula and intravenous fluid was started.

**SCORE USED FOR EVALUATION OF INTRA-OPERATIVE ANXIETY AND SEDATION**

- Observer assessment of alertness /sedation scale
- Ramsay sedation score

The objectives of the study are to understand and compare the effects of the drugs Midazolam and Alprazolam on two separate samples in terms of the changes in BP, heart rate, SPO<sub>2</sub>, sedation and anxiety.

**Methodology:**

Two sample populations each of 30 persons were selected. Utmost care was taken to ensure that the samples are from same population. The drugs Midazolam and Alprazolam were administered on two separate sample population. In the sample population, observations in terms of changes in BP, heart rate, SPO<sub>2</sub>, sedation and anxiety were measured and compared to the effects of these drugs on two separate sample.

**Statistical Analysis:**

The SPSS21 software was used to present the statistical data in the form of tables.

**OBSERVATION AND RESULTS**

Variables	Mean Midazolam	Mean Alprazolam	P-Value	Significance level
AGE	36.57	35.67	0.569	0.05
Gender			0.29	0.05
Weight	66.33	63.27	0.021	0.05
Height	164.87	163.77	0.433	0.05

ASA Grade			0.567	1.05
Systolic BP before the drug	123.33	124.86	0.567	0.05
Diastolic BP before the drug	74.2	72.83	0.396	0.05
Heart rate before the drug	85.16	86.1	0.667	0.05
SPO2 before the drug	100	100	0.001	0.001
Sedation before the drug	1	1	0.001	0.001
Anxiety before the drug	14	14	0.001	0.001

Table 1: Distribution based on different variables

The above table shows that, except for the weight of the sample populations, in all other parameters the calculated probability is higher than the significance level 0.05. So it's concluded that for the sample parameters age, sex, height and ASA grade, there are no significant difference in the sample population for Midazolam and sample population of Alprazolam. However, there is Significant difference observed in the weight of the persons in above mentioned samples.

The frequency distributions of age, sex, height, ASA grade of the two samples looks to be identical -confirming to the finding of no significant differences between the two samples on the above parameters.

There was no significant difference for the sample variables like BP, Heart rate, SPO2, Sedation and Anxiety in two samples before the administration of the drugs.

Parameters	Before MDZ (1)	After 1 hr of MDZ (2)	Before surgery (3)	Mean of 1	Mean of 2	Mean of 3	P-Value
SBP	Before MDZ	After 1 hr of MDZ	-	123.33	120.67	-	0.28
	-	After 1 hr of MDZ	Before surgery		120.67	119.37	0.61
	Before MDZ	-	Before surgery	123.33	-	119.37	0.12
	Before MDZ	After 1 hr of MDZ	Before surgery	123.33	120.67	119.37	0.27
DBP	Before MDZ	After 1 hr of MDZ	-	74.20	71.37		0.09
	Before MDZ	-	Before surgery	74.20		70.53	0.02
	Before MDZ	After 1 hr of MDZ	Before surgery	74.20	71.37	70.53	0.05
HR	Before MDZ	After 1 hr of MDZ	-	85.17	82.20	-	0.21
	-	After 1 hr of MDZ	Before surgery	-	82.20	81.50	0.75
	Before	-	Before	85.17	-	81.50	0.12

	MDZ		surgery				
	Before MDZ	After 1 hr of MDZ	Before surgery	85.17	82.20	81.50	0.24
SPO2	Before MDZ	After 1 hr of MDZ	-	100.0	99.73	-	0.0019
		After 1 hr of MDZ	Before surgery	-	99.73	99.70	0.78
	Before MDZ	-	Before surgery	100.0	-	99.70	0.0008
	Before MDZ	After 1 hr of MDZ	Before surgery	100.0	99.73	99.70	0.004
Sedation	Before MDZ	After MDZ		1.0	3.1		2.48E-17
	Before MDZ	After MDZ		14.0	5.9		3.33E-45 xz

**Table 2: Metrodonazole**

Parameters	Before MDZ	After 1 hr of MDZ	Before surgery	Before ALP	After 1 hr of ALP	Before surgery	Mean MDZ	Mean ALP	P-Value
SBP	Before MDZ		-	Before ALP	-	-	123.33	124.86	0.568
	-	After 1 hr of MDZ	-	-	After 1 hr of ALP	-	120.67	121.8	0.668
	-	-	Before surgery	-	-	Before surgery	119.36	121.5	0.41
	Before MDZ	After 1 hr of MDZ	Before surgery	Before ALP	After 1 hr of ALP	Before surgery	-	-	0.96
DBP	Before MDZ		-	Before ALP	-	-	74.2	72.83	0.38
	-	After 1 hr of MDZ	-	-	After 1 hr of ALP	-	71.37	70.23	0.46
	-	-	Before surgery	-	-	Before surgery	70.53	68.8	0.24
	Before MDZ	After 1 hr of MDZ	Before surgery	Before ALP	After 1 hr of ALP	Before surgery			0.963
HR	Before MDZ		-	Before ALP	-	-	85.16	86.1	0.67
	-	After	-	-	After	-	82.2	82.7	0.806

		1 hr of MDZ			1 hr of ALP				
	-	-	Before surgery	-	-	Before surgery	81.50	81.86	0.85
	Before MDZ	After 1 hr of MDZ	Before surgery	Before ALP	After 1 hr of ALP	Before surgery			0.979
SPO2	-	After 1 hr of MDZ	-	-	After 1 hr of ALP	-	99.73	99.43	0.02
	-	-	Before surgery	-	-	Before surgery	99.36	99.43	0.023
	Before MDZ	After 1 hr of MDZ	Before surgery	Before ALP	After 1 hr of ALP	Before surgery	99.73	99.43	0.02
Sedation	After MDZ			After ALP			3.06	2.33	0.00035
Anxiety	After MDZ			After ALP			5.93	8.93	3.6E-18

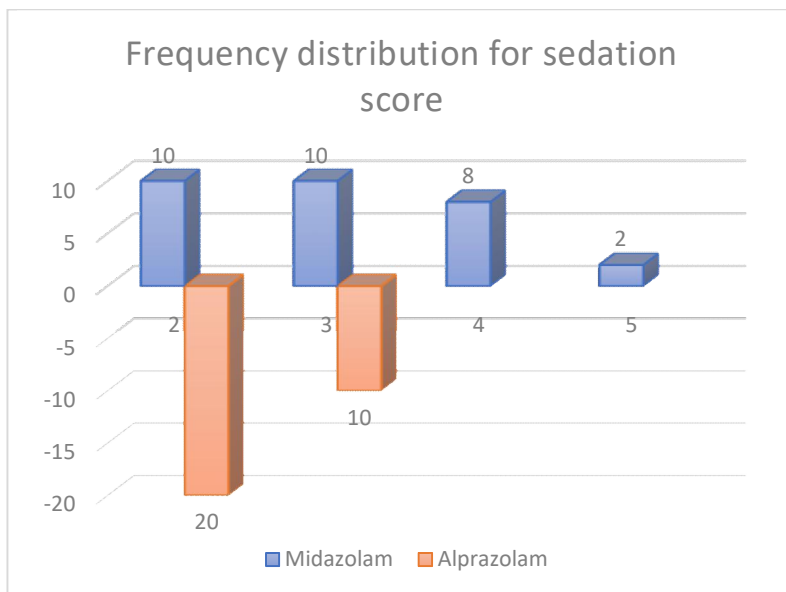
**Table 3: Distribution based on both MDZ and ALP**

**Sedation**

There is a significant difference between the Midazolam and Alprazolam sample with respect to the sedation level after the administration of these drugs on the persons in their respective samples. For Midazolam sample the mean sedation increased from 1 to 3.06 and for the Alprazolam sample the mean sedation increased from 1 to 2.33

Sedation Score	Midazolam	Alprazolam
2	10	20
3	10	10
4	8	
5	2	

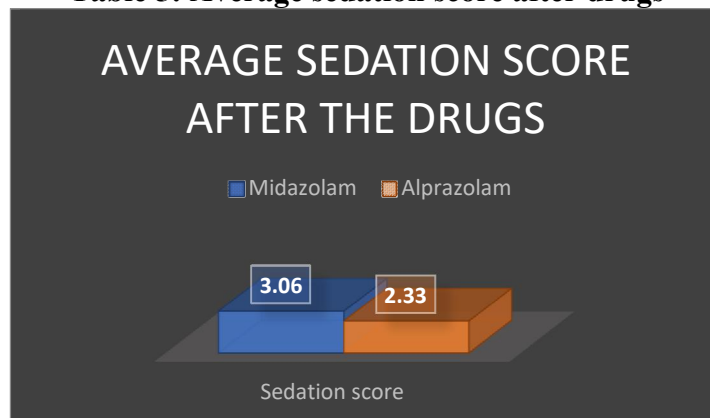
**Table 4: Frequency distribution for sedation score**



**Frequency distribution for sedation score**

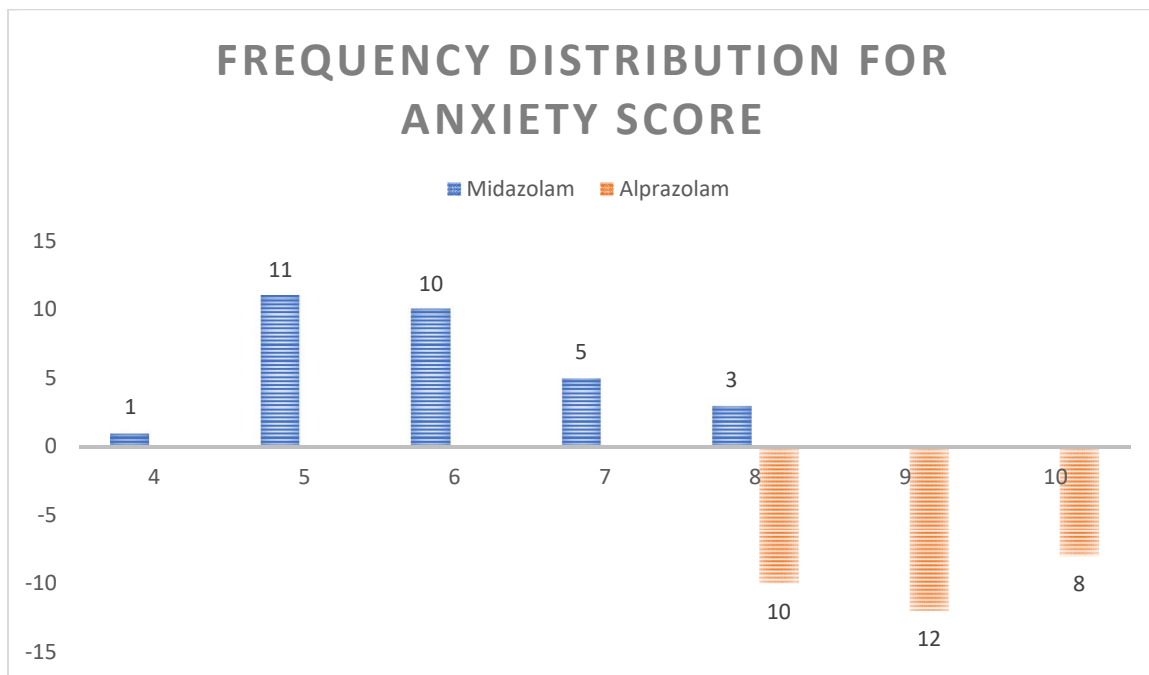
	Midazolam	Alprazolam
Sedation score	3.06	2.33

**Table 5: Average sedation score after drugs**



Anxiety Score	Midazolam	Alprazolam
4	1	
5	11	
6	10	
7	5	
8	3	10
9		12
10		8

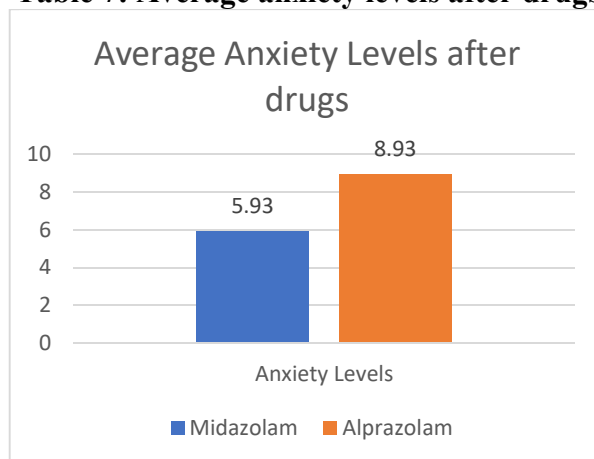
**Table 6: Frequency distribution for anxiety score**



There is a significant difference between the midazolam and Alprazolam sample with respect to the anxiety level after the administration of these drugs on the persons in their respective samples. For Midazolam sample the mean anxiety level decreased from 14 to 5.93 and for the Alprazolam sample the mean sedation decreased from 14 to 8.93.

Variable	Midazolam	Alprazolam
Anxiety Levels	5.93	8.93

**Table 7: Average anxiety levels after drugs**



**Fig: Average Anxiety Levels after drugs**

**DISCUSSION**

**Systolic BP:**

The drug, Midazolam and Alprazolam decreased systolic BP after one hour of administration of the drugs and it further decreased prior to the surgery. The average systolic Bp for Midazolam sample changed from 123.33 prior to drug to 120.67 after one hour of the drug to 119.36 prior to surgery. The average systolic BP for Alprazolam sample changed from 124.86 prior to the drug to 121.8 after 1 Hr. of the drug to 121.5 prior to surgery. However, this decrease in systolic BP with time for both the drugs was not found to be significant.



Also, there was no significant difference between the Midazolam sample and Alprazolam sample with respect to decreasing the systolic BP after 1 hour of administration of drug and systolic BP prior to surgery.<sup>17</sup>

**Diastolic BP:**

The drugs Midazolam and Alprazolam decreased Diastolic BP after one hour of administration of the drugs and it further decreased prior to the surgery, The average diastolic BP for Midazolam sample changed from 74.2 prior to drug to 70.53 prior to surgery. The average diastolic BP for Alprazolam sample changed from 72.83 prior to the drug to 70.23 after 1 Hr of the drug to 68.8 prior to surgery. The decrease in Diastolic BP with time for both the drugs was not found to be significant after 1hr of administration of drug. However, the decrease in diastolic Bp was significant when compared to the diastolic BP prior to the drug and diastolic Bp measured before surgery for both the drugs. Also, there was no significant difference between the Midazolam sample and Alprazolam sample with respect to decreasing the Diastolic BP after 1 hour of administration of drug and Diastolic Bp prior to surgery.<sup>18</sup>

**Heart Rate:**

The drugs Midazolam and Alprazolam decreased the Heart Rate after one hour of administration of the drugs and it further decreased prior to the surgery. The average heartrate for Midazolam sample changed from 85.17 prior to drug to 82.20 after one hour of the drug to 81.50 prior to surgery. And the average Heart Rate for Alprazolam sample changed from 86.1 prior to the drug to 82.7 after 1 hour of the drug to 81.86 prior to surgery. The decrease in Heart Rate with time was not found significant in case of Midazolam. However, in case of Alprazolam there was a significant difference in the Heart Rate when the Heart Rate before the drug was compared with the Heart Rate measured before Surgery. Also, there was no significant difference between the Midazolam sample and Alprazolam sample with respect to decreasing the Heart Rate after 1 hour of administration of drug and Heart Rate prior to surgery. So, the significant decrease in Heart rate with Alprazolam is not significant when compared with the decrease caused by Midazolam.<sup>19</sup>

**SPO<sub>2</sub>:**

The drugs Midazolam and Alprazolam decreased the SPO<sub>2</sub> level after one hour of administration of the drugs and it further changed prior to the surgery. The average SPO<sub>2</sub> for Midazolam sample changed from 100 prior to drug to 99.73 after one hour of the drug to 99.70 prior to surgery. And the average SPO<sub>2</sub> for Alprazolam sample changed from 100 prior to the drug to 99.43 after 1 Hr of the drug to 99.36 prior to surgery. The decrease in SPO<sub>2</sub> after one hour of the drug was significant in both the drugs. But there was no significant decrease in SPO<sub>2</sub> after one hour of the drug to SPO<sub>2</sub> measured before surgery for both the drugs. Also it is observed that there is a significant difference in the SPO<sub>2</sub> level after 1 Hr of administration of drugs and SPO<sub>2</sub> levels before surgery between the samples for Midazolam and Alprazolam.

**Sedation:**

The drugs Midazolam and Alprazolam increased sedation after administration of the drugs. The average sedation for Midazolam sample changed from 1 prior to the drug intake, to 3.06 after the drug intake and the average sedation score for Alprazolam sample changed from 1 prior to the drug to 2.33 after the drug. The increase in sedation after the drugs was significant in both Also it is observed that there is a significant difference in the sedation level after the administration of drugs between the samples for Midazolam and Alprazolam. Midazolam induced more sedation than Alprazolam.<sup>20</sup>

**Anxiety:**

The drugs Midazolam and Alprazolam decreased anxiety after administration of the drugs. The average anxiety level for Midazolam sample changed from 14 prior to drug to 5.93 after the drug. And the average anxiety score for Alprazolam sample changed from 14 prior to the drug to 8.93 after the drug. The decrease in sedation after the drugs was significant in both the drugs.

Also, it is observed that there is a significant difference in the anxiety level after the administration of drugs between the samples for Midazolam and Alprazolam. Midazolam induced more decrease of anxiety compared to Alprazolam.<sup>21</sup>

**Limitations:**

As every other study has its own share of limitations, the limitations of this study was

- Small sample size
- The study did not record the duration of hospital stay and did not compare it across groups, which is a variable to examine in terms of health economics.

**CONCLUSION**

In comparing the effect of Midazolam Alprazolam with respect to altering BP, Heart Rate, SPO<sub>2</sub>. Sedation and Anxiety level after 1 hr of drug and prior to surgery it is observed that there is a significant difference between Midazolam sample and Alprazolam sample with respect to SPO<sub>2</sub>, Sedation and Anxiety level.

However, there was no significant difference observed between Midazolam sample and Alprazolam sample with respect to systolic and diastolic BP and Heart Rate after the administration of these drugs in the persons of their respective samples.

So it may be concluded that Midazolam performs better than Alprazolam as it maintains a significant higher SPO<sub>2</sub> level in comparison to Alprazolam and reduces anxiety significantly in comparison to Alprazolam.

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