

## A Comparative Study between Oral Melatonin and Oral Alprazolam as Premedication on Preoperative Anxiety, Sedation and Cognitive Functions in Patients Undergoing Surgeries Under General Anaesthesia

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Conflict of interest: Nil

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### Abstract

**Background:** In this study we wanted to evaluate the effect of oral melatonin on pre-operative anxiety, sedation, orientation and cognitive functions, the effect of oral alprazolam on pre-operative anxiety, sedation, orientation, and cognitive functions and compare the efficacy of oral melatonin and oral alprazolam on pre-operative anxiety, sedation, orientation, and cognitive functions.

**Methods:** This was a randomised clinical carried out in the Department of Anaesthesiology and Critical care, Kempegowda Institute of Medical Sciences, Bangalore among two groups of 50 subjects each over a period of 18 months. Simple random sampling was done. Hundred patients aged between 18 years and 60 years of physical status ASA grade 1 and ASA grade 2 undergoing elective surgeries under general anaesthesia was included in the study after ethical clearance from the college ethical committee.

**Results:** Oral melatonin 3mg produces greater decrease in anxiety than alprazolam 0.5mg/kg at the end of 60 minutes and was statistically significant. Oral melatonin 3mg produces more sedation after administration compared to alprazolam 0.5mg thus calming and preparing the patient for induction of anaesthesia though it was statistically insignificant with p value < 0.001. Oral melatonin 3mg and oral alprazolam 0.5mg both didn't affect the orientation of the patient after administration and postoperatively.

**Conclusion:** Oral melatonin 3mg affects patients mental balance, attention, concentration, delayed and immediate recall, visual and verbal retention after administration due to its sedative effects but was restored postoperatively which was better compared to the effects of oral alprazolam 0.5mg after administration for smoother induction of anaesthesia. Oral melatonin 3mg and oral alprazolam 0.5mg does not cause cognitive dysfunction of the patient postoperatively. Oral melatonin 3mg and oral alprazolam 0.5mg did not produce any adverse effects.

**Keywords:** Oral Melatonin, Oral Alprazolam, Premedication, Preoperative Anxiety, Sedation, Cognitive Functions, General Anaesthesia

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## Introduction

There is an increasing interest in the peri-operative use of melatonin predominantly as anxiolytic. Melatonin (N-acetyl-5-methoxy tryptamine) is a naturally occurring neurohormone in the human body secreted by the pineal gland from amino acid tryptophan. [1,2] Melatonin has also been reported to cause preoperative anxiolysis and increase in levels of sedation without impairing orientation [3,4]. Its anxiolytic, sedative, hypnotic, analgesic and anti-inflammatory, antioxidative, and chronobiotic properties distinguish it as an attractive alternative premedicant. [5] Melatonin when compared to benzodiazepines exerts a promoting effect on sleep by amplifying day/night differences in alertness and sleep quality and displaying a modest sleep-inducing effect, quite mild as compared to that seen with benzodiazepines [6] The hypnotic property of melatonin endows this neurohormone with the profile of a novel hypnotic and anesthetic sparing effect. It has a wide range of safety margin. [5]

## Objectives of the Study

- To study the effect of oral melatonin on pre-operative anxiety, sedation, orientation and cognitive functions.
- To study the effect of oral alprazolam on pre-operative anxiety, sedation, orientation and cognitive functions.
- To compare the efficacy of oral melatonin and oral alprazolam on pre-operative anxiety, sedation, orientation and cognitive functions.

## Materials and Methods

This was a randomised clinical carried out in the Department of Anaesthesiology and Critical care, Kempegowda Institute of Medical Sciences, Bangalore among two groups of 50 subjects each over a period of

18 months. Simple random sampling was done. Hundred patients aged between 18 years and 60 years of physical status ASA grade 1 and ASA grade 2 undergoing elective surgeries under general anaesthesia was included in the study after ethical clearance from the college ethical committee.

## Inclusion Criteria

- ASA grade I & II status.
- Age between 18-60yrs of either sex.
- Weight between 40 to 80 kgs.
- Patients scheduled to undergo elective surgical procedures under general anaesthesia.

## Exclusion Criteria

- ASA physical status grade III or greater.
- Pregnant and lactating females
- Patients with h/o psychiatric disorders or on any anti psychotic drugs.
- Patients with language or communication difficulties.
- Patients with sleep disorders.
- Patients with severe renal or hepatic derangement.
- Patients having inability to read and write basic alphabets
- Hypersensitivity to melatonin or alprazolam.
- Patient taking opioids, benzodiazepines, other drug/alcohol abuse.
- Anticipated difficult airway and difficult intubation.

## Statistical Analysis

Parametric data assessed with independent sample T test or paired T test. Non parametric data assessed with chi-square test or Fischer exact test.

## Results

Age distribution among the study groups was equivalent in all the age groups being 20-29 yrs, 30-39yrs, 40-49 yrs and 50-59 yrs were considered. Percentage distribution of the patient for melatonin and alprazolam in the age group 20-29 yrs was 34% and 32% respectively, for 30-39 yrs it was 36% and 34% respectively, for 40-49 yrs it was 16% and 16%

respectively, for 50-59 yrs it was 14% and 18% respectively. Hence our data was comparable in terms of age distribution for melatonin and alprazolam. We had allotted equal number of males and females for the study group; hence our data was comparable in terms of sex distribution.

#### Observation of Changes in VAS Scores

**Table 1: Comparison of two Groups with visual analogue Scores before, after and one day after drug administration**

	Melatonin (N=50)		Alprazolam (N=50)		P value
	Mean	SD	Mean	SD	
Before	3.38	1.227	3.38	1.398	1.000
After	3.38	1.105	3.52	1.359	0.573
One day after	6.14	1.325	5.94	1.252	0.440

Comparison of VAS score for melatonin before and after administration was same 3.38 but increased by 6.14 one day after the operation which cannot be correlated to the drug effects due to interference with surgical pain. Comparison of VAS score for alprazolam before and after administration was 3.38 and 3.52 respectively. Hence there was a slight increase in the trend rather than usual decrease in VAS score showing that alprazolam was not effective as premedication in reducing anxiety.

Postoperatively score was 5.94 which were comparatively higher which was not correlating to the effects of drug administration because of the interference of the surgical pain. Hence melatonin was better than alprazolam in alleviating preoperative anxiety with significant statistical difference (p value- 1.0, 0.573 and 0.44 respectively for before, after and one day after drug administration.

#### Observation of Changes in Sedation Scores

**Table 2: Comparison of two Groups with Sedation Scores before, after and one day after drug administration**

	Melatonin (N=50)		Alprazolam (N=50)		P value
	Mean	SD	Mean	SD	
Before	0.00	0.000	0.00	0.000	-
After	0.70	0.463	0.12	0.328	<0.001
One day after	0.00	0.000	0.00	0.000	-

Sedation score for melatonin after administration was 0.7% compared to the alprazolam scores 0.12% illustrating that melatonin was more sedative compared to the alprazolam even though statistically not significant (<0.001). Hence

premedication with melatonin was good as premedicant for smoother induction of anaesthesia.

#### Observation of Changes in Orientation Scores

Orientation score for melatonin and alprazolam before, after and one day after the administration remained the same

illustrating that both drugs did not affect the persons orientation irrespective of time interval of administration of the drug.

### Observation of Changes in Cognitive Function

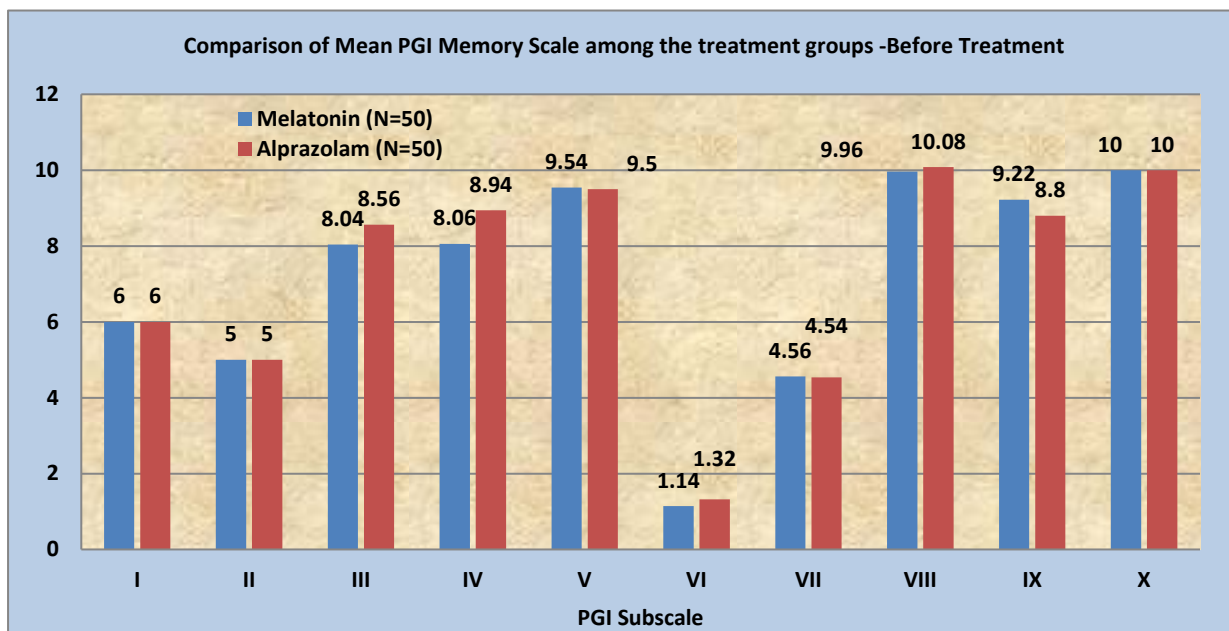


Figure 1

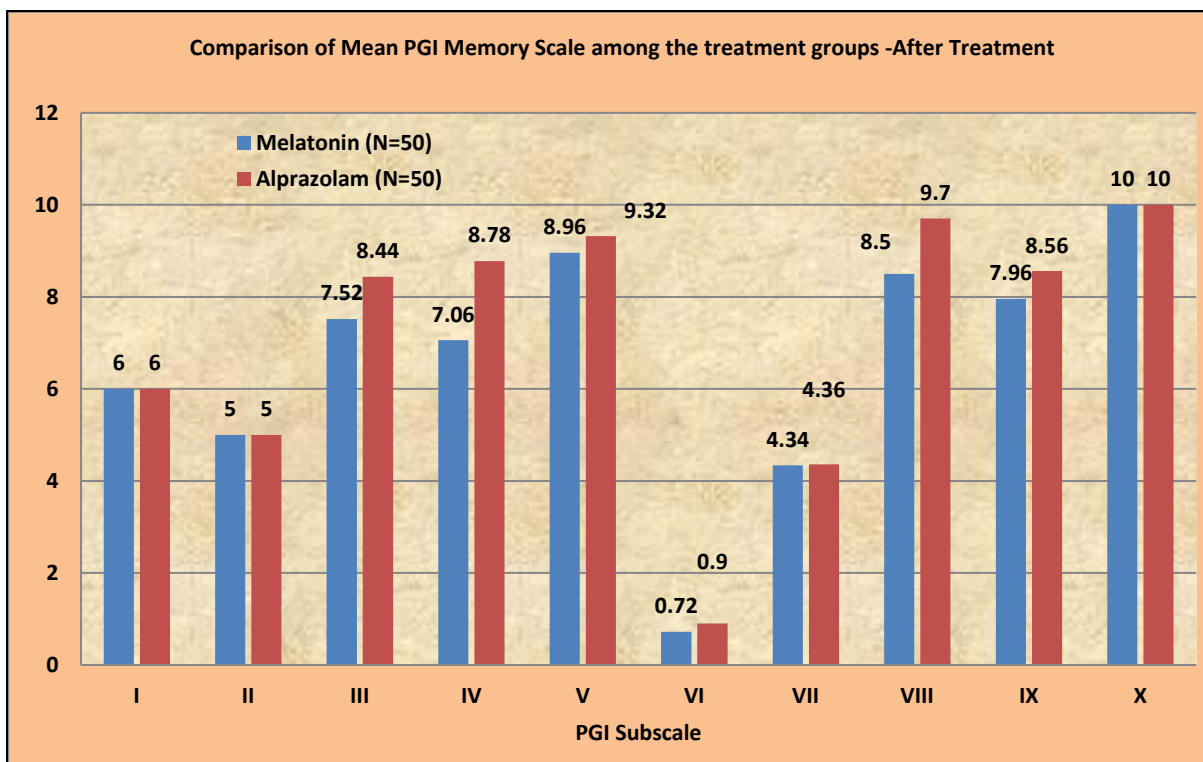
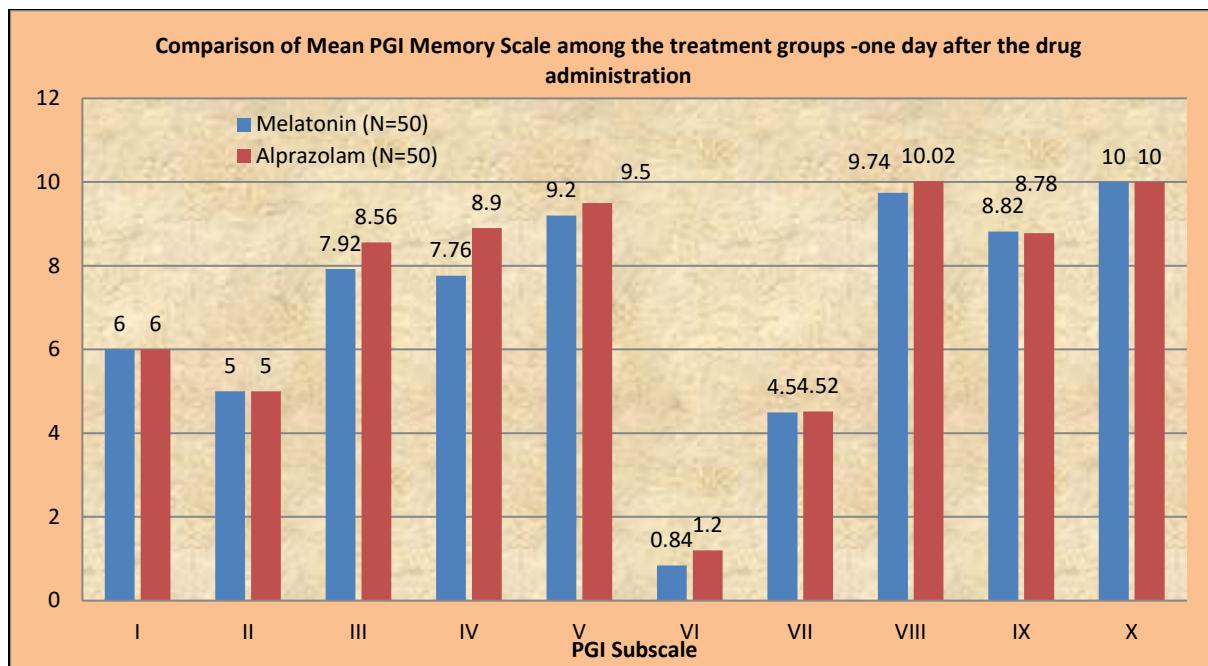


Figure 2



**Figure 3**

### PGI Memory Scale

1. Remote memory was not affected before, after and one day after the drug administration for both melatonin and alprazolam.
2. Recent memory was not affected before, after and one day after the drug administration for both melatonin and alprazolam.
3. Mental balance before the surgery for melatonin and alprazolam was 8.04 and 8.56 respectively which was statistically insignificant p value ( $<0.001$ ). After the drug administration 7.52 and 8.44 were the scores for melatonin and alprazolam which was statistically insignificant p value ( $<0.001$ ). This shows that mental balance was affected after the administration of melatonin. One day after the surgery 7.92 and 8.56 were the scores for melatonin and alprazolam which was statistically insignificant p value ( $<0.001$ ). Scores before drug administration and after the drug administration were comparable for both melatonin and alprazolam but not after administration

of the drug hence proving that melatonin was affecting persons mental balance which was recovered postoperatively.

4. Attention and concentration before the surgery for melatonin and alprazolam was 8.06 and 8.94 respectively which was statistically insignificant p value ( $<0.001$ ). After the drug administration 7.06 and 8.78 were the scores for melatonin and alprazolam which was statistically insignificant p value ( $<0.001$ ). This shows that attention and concentration was affected after the administration of melatonin. One day after the surgery 7.76 and 8.9 were the scores for melatonin and alprazolam which was statistically insignificant p value ( $<0.001$ ). Scores before drug administration and after the drug administration were comparable for both melatonin and alprazolam but not after administration of the drug hence proving that melatonin was affecting persons attention and concentration which was recovered postoperatively.
5. Delayed recall before the surgery for melatonin and alprazolam was 9.54 and 9.5 respectively which was

- statistically significant with value 0.693. After the drug administration 8.96 and 9.32 were the scores for melatonin and alprazolam which was statistically significant with value 0.016. This shows that delayed recall was affected after the administration of melatonin. One day after the surgery 9.2 and 9.5 were the scores for melatonin and alprazolam which was statistically significant with the value 0.028. Scores before drug administration and after the drug administration were comparable for both melatonin and alprazolam but not after administration of the drug hence proving that melatonin was affecting persons delayed recall which was recovered postoperatively.
6. Immediate recall before the surgery for melatonin and alprazolam was 1.14 and 1.32 respectively which was statistically significant with the value 0.547. After the drug administration 0.72 and 0.9 were the scores for melatonin and alprazolam which was statistically significant with the value 0.504. This shows that immediate recall was affected after the administration of melatonin. One day after the surgery 0.84 and 1.2 were the scores for melatonin and alprazolam which was statistically significant with the value 0.209. Scores before drug administration and after the drug administration were comparable for both melatonin and alprazolam but not after administration of the drug hence proving that melatonin was affecting persons immediate recall which was recovered postoperatively.
  7. Verbal retention for similar pair before the surgery for melatonin and alprazolam was 4.59 and 4.54 respectively which was statistically significant with the value 0.843. After the drug administration 4.34 and 4.36 were the scores for melatonin and alprazolam which was statistically significant with the value 0.88. This shows that verbal retention for similar pair was affected after the administration of melatonin. One day after the surgery 4.54 and 4.52 were the scores for melatonin and alprazolam which was statistically significant with the value 0.859. Scores before drug administration and after the drug administration were comparable for both melatonin and alprazolam but not after administration of the drug hence proving that melatonin was affecting persons verbal retention for similar pair which was recovered postoperatively.
  8. Verbal retention for dissimilar pairs before the surgery for melatonin and alprazolam was 9.96 and 10.08 respectively which was statistically significant with the value 0.678. After the drug administration 8.5 and 9.7 were the scores for melatonin and alprazolam which was statistically insignificant p value ( $<0.001$ ). This shows that verbal retention for dissimilar pairs was affected after the administration of melatonin. One day after the surgery 9.74 and 10.02 were the scores for melatonin and alprazolam which was statistically significant with the value 0.328. Scores before drug administration and after the drug administration were comparable for both melatonin and alprazolam but not after administration of the drug hence proving that melatonin was affecting persons verbal retention for dissimilar pairs which was recovered postoperatively.
  9. Visual retention before the surgery for melatonin and alprazolam was 9.22 and 8.8 respectively which was statistically significant with the value 0.268. After the drug administration 7.96 and 8.56 were the scores for melatonin and alprazolam which was statistically significant with the value 0.058. This shows that visual retention was

affected after the administration of melatonin. One day after the surgery 8.82 and 8.78 were the scores for melatonin and alprazolam which was statistically significant with the value 0.92. Scores before drug administration and after the drug administration were comparable for both melatonin and alprazolam but not after administration of the drug hence proving that melatonin was affecting persons visual retention which was recovered postoperatively.

10. Recognition was not affected before, after and one day after the drug administration for both melatonin and alprazolam.
11. Total scores for melatonin and alprazolam before the drug administration were 71.5 and 72.7 respectively which was statistically significant with the value 0.095. After administration of the drug 66.1 and 71.1 were the scores for melatonin and alprazolam which was statistically insignificant p value (<0.001). One day after the surgery for melatonin and alprazolam scores were 69.8 and 72.5 respectively which was statistically insignificant p value (<0.001).
12. Hence we could conclude that mental balance, attention and concentration were affected after melatonin drug administration compared to the alprazolam even though it was statistically insignificant with p value (<0.001). Delayed recall, immediate recall, verbal retention for similar and dissimilar pairs and visual retention were affected after melatonin administration compared to the alprazolam with statistically significant p values. Hence melatonin affecting the above variables it helps in smoother induction of anaesthesia. Finally we can conclude that melatonin can be used as premedicant before surgery which affects persons mental balance, attention, concentration,

delayed and immediate recall, verbal retention for similar and dissimilar pairs and visual retention but was been restored postoperatively.

## Discussion

### Analysis of Data Related to Anxiety

Samarkandi et al compared the effects of melatonin and midazolam with that of a placebo and found that anxiolysis in the melatonin group was comparable to that produced by midazolam group. These studies also showed good anxiolytic effect of melatonin pre-operatively when compared to placebo. The timing of anxiety assessment varied among the trials, but a significant statistical difference in anxiety scores was evident at different points of time in the melatonin group. A study was done by Caumo et al [7] (2007) concluded that preoperative melatonin produced clinically relevant anxiolytic and analgesic effects, especially in the first 24 postoperative hours. In a study by Capuzzo et al [8] (2006) found that there was no significant difference in anxiolysis between melatonin and placebo in their study. This study suggested that perhaps melatonin's sedative/anxiolytic properties diminish over age, and in the elderly its effects may be negligible. In our study, we used Visual Analogue Scale (VAS) [9] for measuring anxiety. The change in vas score before, 60 min after and 24hrs after pre medication was statistically significant in two groups as the p-value was 1.0, 0.573 and 0.44 respectively. The present study revealed that oral melatonin 3mg was effective as premedicant for producing anxiolysis than oral alprazolam 0.5mg.

### Analysis of Data Related to Sedation

Increased levels of sedation in the melatonin and midazolam group vs placebo were evident at 60 and 90 min after premedication in two studies done by Naguib et al. The midazolam group showed significantly higher levels of sedation than the melatonin group at 30

and 60 min after premedication. In a study done by Acil et al, [10] melatonin group exhibited increased levels of sedation only at 90 min after premedication versus placebo ( $P < 0.05$ ). However, significantly decreased sedation levels were evident in the melatonin versus midazolam group at 10, 30, and 60 min after premedication ( $P < 0.001$ ). There was no statistical difference in the sedation levels among the groups after surgery). [11] This study shows that melatonin produced the minimal sedation after drug administration when compared to alprazolam which was necessary for smoother induction of anaesthesia.

### Analysis of Data Related to Cognition and Psychomotor Functions

- There are no studies on melatonin which have assessed for cognitive function by using tests specific for them. They were simply noted down as the observations in their study. The pgi memory scale has been used to assess the cognition in many psychiatric studies not related to melatonin.
- Hence, it was not possible to compare the present study results regarding this aspect with other studies.
- However there are few studies which have compared the effects of melatonin on cognitive and psychomotor functions by means of other tests. Results of the studies has been discussed below-

In two studies by Naguib and Samarkandi [12,13] (1999 and 2000), Psychomotor performance was evaluated using the digit-symbol substitution test (DSST) and the Trieger dot test (TDT). Midazolam produced significant psychomotor impairment in the preoperative period compared with melatonin or placebo. [14] After operation, patients who received midazolam or melatonin premedication had impairment in performance on the DSST at 15, 30 and

90 min compared with controls. There were no significant differences between the three groups for TDT performance after operation. Acil et al<sup>[10]</sup> Neurocognitive performance was evaluated using the Trail Making A and B and Word Fluency tests. Melatonin premedication was associated with preoperative anxiolysis and sedation without postoperative impairment of psychomotor performance. Our study revealed that mental balance, attention and concentration were affected after melatonin drug administration compared to the alprazolam even though it was statistically insignificant with p value ( $< 0.001$ ). Delayed recall, immediate recall, verbal retention for similar and dissimilar pairs and visual retention were affected after melatonin administration compared to the alprazolam with statistically significant p values. Hence melatonin affecting the above variables it helps in smoother induction of anaesthesia. Hence we can conclude that melatonin can be used as premedicant before surgery which affects persons mental balance, attention, concentration, delayed and immediate recall, verbal retention for similar and dissimilar pairs and visual retention but was been restored postoperatively.

### Limitations of the Study

1. No objective assessment of pre-operative anxiety was done. We used only subjective measurement of anxiety i.e VAS.
2. We did not assess the cognitive functions post-operatively at different intervals, which would had provided some light on usefulness of melatonin for ambulatory or day care surgeries.
3. We could not differentiate changes in postoperative findings due to melatonin or the other drugs used in general anaesthesia.
4. Our study group included only adults between 18-60years. Hence we could



not assess the effects of oral melatonin in children and elderly.

5. We could not get the theoretical results of drugs after testing due to environmental restrictions, patient factors and mental makeup of the patient in operation theatre. Proper patient counselling and separate rooms for the assessment could have made the assessment ideal.

### Conclusion

1. Oral melatonin 3mg produces greater decrease in anxiety than alprazolam 0.5mg/kg at the end of 60 minutes and was statistically significant.
2. Oral melatonin 3mg produces more sedation after administration compared to alprazolam 0.5mg thus calming and preparing the patient for induction of anaesthesia though it was statistically insignificant with p value < 0.001.
3. Oral melatonin 3mg and oral alprazolam 0.5mg both didn't affect the orientation of the patient after administration and postoperatively.
4. Oral melatonin 3mg affects patients mental balance, attention, concentration, delayed and immediate recall, visual and verbal retention after administration due to its sedative effects but was restored postoperatively which was better compared to the effects of oral alprazolam 0.5mg after administration for smoother induction of anaesthesia.
5. Oral melatonin 3mg and oral alprazolam 0.5mg does not cause cognitive dysfunction of the patient postoperatively.
6. Oral melatonin 3mg and oral alprazolam 0.5mg did not produce any adverse effects.

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