

# Comparison of Sublingual Melatonin, Alprazolam and Melatonin - Alprazolam Combination on Anxiolysis and Sedation in Cataract Surgery: A Double Blinded Randomised Controlled Trial

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## Abstract

**Background:** Preoperative anxiety is described as a state of uneasiness that most patients awaiting elective surgery experience and is a challenging concept in the preoperative care of the patients. Benzodiazepines are the most commonly used to reduce this anxiety. **Materials and methods:** This prospective double blind study was designed to compare the effects of sublingual melatonin, alprazolam and melatonin alprazolam combination for premedication of adult patients during cataract surgery under topical anesthesia. 120 patients aged 40-80 years scheduled for cataract surgery procedure were classified into three groups. Group 1 patients received melatonin 10mg, group 2 received alprazolam 0.5mg, group 3 received melatonin 3mg and alprazolam 0.25mg combination, and all drugs were given sublingual 60min before the procedure. Sedation, anxiety and orientation score were quantified before premedication (T1) and 30min (T2), 60min (T3) and 90mins (T4). **Results:** Mean age of the study subjects was 61.3±7.92, 63.2±7.19 and 63.55±7.15 respectively. On applying t test, there was statistically significant difference between group 2 and group 3 at T3 and T4, also between group 1 and group 3 at T3. **Conclusion:** Melatonin and melatonin alprazolam combination reduced anxiety scores, better sedation and provided excellent operating condition without hang over effect.

**Keywords:** Benzodiazepines; Melatonin; Melatonin; Cataract; Sublingual.

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## Introduction

Most cataract surgeries in recent years are performed under topical anaesthesia, with topical anaesthesia patients has to cooperate for an akinetic eye. The anxiety on the part of patient scheduled for the cataract surgery is more acute. Both insufficient and deep sedation may lead to sudden movement by patients which may potentially result in harmful complications during open eye surgery [1]. Several drugs such as Propofol, opioids, dexmedetomidine, clonidine

and benzodiazepines have been used for sedation [2,3]. Benzodiazepines are amongst the most popular preoperative medication to produce anxiolysis and sedation.

Alprazolam is a triazolone analogue of benzodiazepine, it has got more anxiolytic than the other benzodiazepine premedicants like midazolam, lorazepam or diazepam [2,4,5]. Benzodiazepines are associated with increased episodes of arousable during sleep, restlessness and hangover effects. With the availability of relatively new drug melatonin with no adverse effect, its

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potential clinical advantage as a premedication in cataract surgery needs to be evaluated.

Melatonin is a hormone of darkness, N- acetyl -5-methoxytryptamine, an endogenous pineal hormone when given orally as a premedicant results in anxiolysis and sedation in the preoperative period. It neither impairs cognitive and psychomotor skills nor the quality of recovery. Its anxiolytic, sedative, hypnotic, analgesia, anti-inflammatory, anti-oxidative, chronobiotic properties, wide safety profile in terms of dose and virtual lack of toxicity distinguish it as an alternative premedicant [2,6,7].

Several studies have used oral melatonin dose ranging from 3mg to 0.4mg /kg body weight without any major side effects.

Benzodiazepines are associated with the suppression of endogenous melatonin level. Arousal episodes produced by alprazolam, a benzodiazepine can be reduced by melatonin alprazolam combination which might promote sound sleep and reduce anxiety [2].

The aim of the proposed study is to compare the effect of sublingual melatonin, alprazolam and melatonin alprazolam combination on anxiolysis, sedation and orientation in cataract surgery. Secondary objective is to evaluate the effects of melatonin, alprazolam and melatonin alprazolam combination on haemodynamic parameters.

## Materials and Methods

The present study is a double blinded randomised controlled trial in which the patients, investigators, anaesthesiologist and the surgeon were blinded to the given drug. After getting approval from the institutional ethics committee, patients posted for cataract surgery were included. Written informed consent was obtained before the study began. Around 120 patients aged 40-80 years posted for cataract surgery were randomly allocated to one of the three groups with 40 patients in each group. Exclusion criteria were patients with sleep disorders, autoimmune disease, diabetes, depressive disorder, epilepsy, deafness, allergy to the study drug, ongoing treatment with hypnotics or psychotropic drugs, beta blockers, patients with severe renal or hepatic derangement.

Group one patients received tablet containing the melatonin 10mg, group two patients received alprazolam 0.5mg and group three patients received melatonin 3mg and anxit 0.25mg combination

sublingual 60mins before arrival in the operating room. Randomisation was based on computer generated codes. The sample size was determined based on previous studies [1,8].

The assumption that the placebo would have an effect in reducing the anxiety in 20% of patients, whereas melatonin and alprazolam reported to produce a reducing effect in at least 40% of patients and to provide an 80% power with an error equal to 0.05, a sample size of 34 patients/group was determined to be sufficient. To compensate for dropouts cases and shifting from normality in data distribution 40 cases were studied in each group.

One day prior to the surgery, on the preanaesthetic visit, all the patients were explained about the nature of the study and various scales used. A 10cm linear Visual Analogue Scale (VAS) was used to assess their anxiety levels. The extremes of the VAS anxiety scales were marked as no anxiety at the 0 end and anxiety as bad as ever can be at the 10cm end. Sedation was assessed using Ramsay Sedation Score (RSS) in which score 1 indicates anxious, 2 indicates calm, awake 3- sleepy, but open eyes to vigorous verbal commands 4- sleeping, only answers to vigorous verbal commands 5- sleeping, responding to painful stimulus of glabellar compression 6- absence of answer to painful stimuli. Orientation with a three point scale 0- none, 1- orientation either to place or time, 2- orientation to both time and place.

On the day of surgery the patient was shifted from the ward to a preoperative room, a 20 gauge cannula was secured for the patient and the drug was given to the patient sublingual by the nurse 60mins before surgery. Before giving the tablets, patients anxiety score, Ramsay sedation score and orientation score i.e., T1 was assessed by the investigator. The identity of the tablet was not revealed to the patient or to the investigator on both occasions. Patients were monitored with electrocardiogram, blood pressure, heart rate and SpO<sub>2</sub>. At T2- 30min, on arrival to the OT ie T3-60min, T4-90 min after the premedication patient was assessed again with the same parameters and the test was repeated again.

VAS anxiety scores, sedation score, orientation score, haemodynamics, heart rate, blood pressure, any side effects of melatonin and alprazolam was noted. After completion of surgery, in the recovery room patients received standard postoperative care oxygen administration via face mask, and monitoring of heart rate, respiratory rate, non-invasive blood pressure and SpO<sub>2</sub>. We observed for any episodes of nausea, vomiting, dizziness, headache, they were also asked whether they would like to receive same premedication in the future if required.

**Results**

Patients in the three groups were comparable in age. There was no significant difference in VAS for anxiety measurement between the groups after giving premedication at 30, 60 and 90 min. There was significant difference in orientation score between the groups. Furthermore patients in the alprazolam group showed significant sedation compared with melatonin, melatonin and alprazolam combination at 30 and 60 min. Orientation score was similar except in alprazolam group 2 patients and 5 patients at 60, 90min were either oriented to time place (Tables 1 & 2).

On applying t test, there was statistically significant difference between group 2 and group

3 at T3 and T4, also between group 1 and group 3 at T3.

Sedation score also had significant statistical difference between group 1 and group 3 at T3 T4, also between group 2 and group 3 at T1 and T3.

Orientation score had significant statistical difference between group 1 and group 3 only at T4, also between group 2 and group 3 at T3 and T4 (Table 3).

**Discussion**

Benzodiazepines are the most common premedicant before surgery to alleviate preoperative anxiety. Benzodiazepines enhance the neuro-

**Table 1:** Profile of the study subjects

	Group 1	Group 2	Group 3
No of patients	40	40	40
Gender			
Males	18	16	17
Females	22	24	23
Age	61.3± 7.92	63.2±7.195	63.55±7.15

**Table 2:** Distribution of the study based on their vitals

	Group 1 (Mean± SD)	Group 2 (Mean± SD)	Group 3 (Mean± SD)
Systolic Blood Pressure			
1	146.1±7.14	147.45±8.42	146.35±9.02
2	144.6±8.33	142.37±9.42	140.07±8.23
3	142.0±8.49	136.73±9.48	133.23±8.29
4	141.3±7.57	132.1±8.84	127.77±8.0
Diastolic Blood Pressure	Group 1	Group 2	Group 3
1	82.6±6.24	82.35±6.72	81.85±6.22
2	79.8±6.42	77.75±6.88	77.3± 5.01
3	77.6±6.25	75.1±6.31	72.75±4.22
4	75.9±5.71	72.5±4.29	70.75±2.38
Pulse			
1	92.6±11.35	86.2±11.41	86.2±11.41
2	85.7±10.34	82.2±21.31	79.7±10.50
3	80.7±9.82	74.3±9.35	74.3±9.35
4	74.6±9.54	69.3±9.08	69.3±9.08

**Table 3:** Anxiety, sedation and orientation scoring of the study subjects

Anxiety Score	Group 1 (Mean± SD)	Group 2 (Mean± SD)	Group 3 (Mean± SD)
T1	3.9± 0.9	3.9± 0.5	3.9± 0.7
T2	1.6± 0.5	1.7± 0.6	1.5± 0.5
T3	1.1± 0.3	1.3± 0.5	1.0± 0.0
T4	1.0± 0.0	1.1± 0.3	1.0± 0.0

transmitter gamma amino butyric acid which has sedation, anxiolysis, amnesia, muscle relaxation and anticonvulsant effects [2].

For long time benzodiazepines mainly, alprazolam is being used as premedicant for cataract surgery to reduce anxiety. The ophthalmologist are of concern as they need full cooperation of the patient while performing surgery. Anseau et al calculated an anxiolytic index for benzodiazepines and found alprazolam at 0.5mg has the second highest anxiolytic activity without causing amnesia [2,4,5].

Melatonin is a naturally occurring pineal hormone in the human body which regulates the circadian rhythm. Although exact mechanism of the action of melatonin is still not known, there is accumulating evidence that a synergy exists between the melatonergic and GABAergic systems [6,9]. Available data suggest that exogenous administration of melatonin has been found to facilitate sleep onset and improves quality of sleep [7]. The sleep inducing property of melatonin reduced the standardized mean difference (95% confidence interval) preoperative anxiety score by 0.88 [10].

The anxiolytic effect of melatonin premedication is supported with previous clinical trial [11]. In older patients who were premedicated with oral melatonin 10mg, preoperative anxiety decreased by 33% compared with a 21% reduction in the placebo group [9]. The selected dose of sublingual melatonin 10mg was based on a previous study in elderly patients [12].

Capuzzo et al reported that melatonin premedication did not reduce anxiety more than placebo in elderly patients undergoing surgery. However in their study the level of anxiety scores decreased by 33% after melatonin premedication [12,13].

Pokharel et al have found that patients who received sublingual melatonin and alprazolam combination drug produced the maximum reduction in anxiety VAS (3(1-4.3)) from baseline at 60min ( $p < 0.05$ ) and addition of melatonin to alprazolam had superior anxiolysis compared with either drug alone or placebo [2].

Melatonin half-life, apparent total clearance and apparent volume of distribution are similar for both low and high dose surge sustained melatonin formulations in older adults consistent with linear pharmacokinetic behaviour [14].

Samarkhand et al. and Naquib demonstrated that premedication with sublingual/oral melatonin unlike midazolam was associated with preoperative

anxiolysis and sedation which did not impair psychomotor skills or impact the quality of recovery [9]. However, as a premedication before anaesthesia and surgery the sublingual route is preferred [15].

In this study we have found that the melatonin, melatonin alprazolam combination did not worsen sedation than the alprazolam group. Almost all the patients receiving melatonin alprazolam combination preferred to have the same premedicant in the future. All the premedicant drugs were safe in terms of the side effects.

Melatonin for patients undergoing cataract surgery under topical anaesthesia provided anxiolytic effects, enhanced analgesia, decreased intraocular pressure resulting in better operating condition [11].

Rajaratnam et al. demonstrated using higher dose of melatonin causes a significant reduction in sleep latency in melatonin group and numerous randomized control trials support melatonin effectiveness for improving various aspects of normal sleep [16].

Benzodiazepines mainly alprazolam commonly used as premedicant to decrease anxiety. Alprazolam at 0.5mg presents the second highest anxiolytic activity [4,5].

Choi et al observed that the ACTH and cortisol levels in the operating room were significantly lower after alprazolam premedication [5]. Alprazolam has been effective alternative to midazolam for anxiety reduction without causing amnesia, however, it is known to cause greater impairment of psychomotor function in the early postoperative period [4], hence an alternative premedicant or in combination will definitely have a widespread appeal. One study - Ionesu 2008 measured postoperative anxiety using STAI-S six hours postoperatively and showed no significant difference between the two groups. Clinical studies have shown that alprazolam has a side-effect profile similar to that of other benzodiazepines [17].

Especially alprazolam interaction with the serotonergic and noradrenergic pathways to the limbic system and brainstem structure (locus coeruleus) contributes to its clinical effectiveness in the treatment of anxiety [18].

Assessment of anxiety in the present study is the use of VAS rather than state-trait anxiety inventory score STAI- the gold standard for anxiety evaluation. STAI -its architecture of 20 multiple choice questions for anxiety alone limits its use. Additionally studies showed that VAS correlated

well with STAI and is a valid measure of preoperative anxiety [19,20].

In the present study there was no significant differences between groups w.r.t haemodynamic variability unlike previous studies which showed melatonin could decrease mean arterial pressure in healthy women and men [21,22]. The mechanism of action on circulation is complex that melatonin may bind to receptors in the blood vessels interfering with the vascular response to catecholamines [23]. There is only limited evidence for studying the sleep regulatory effect of melatonin and diagnosis of circadian rhythm disorders in elderly surgical patient that might be documented by the use of perioperative actigraphy [24].

Most common side effects of melatonin are headache, dizziness, nausea and drowsiness which was not seen in the present study.

The limitation of our study include a small sample size, limited tests of the orientation score and lack of facility to measure plasma levels. Further studies are required to measure plasma levels of melatonin. Future studies could also investigate the effect of larger doses of melatonin given approximately one week preoperatively and continuing until one week postoperatively to explore the possibility of even larger effects on postoperative anxiety in the delayed postoperative period.

Additionally the optimum dose and route of administration of melatonin alprazolam as premedication during cataract surgery needs to be determined.

## Conclusion

Premedication with combination of sublingual melatonin alprazolam better than either drug alone for premedication of adult patients undergoing cataract surgery.

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