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# A study on role of oral melatonin as premedicant in general anaesthesia at tertiary care hospital

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**Abstract**
**Background:** Reducing anxiety is an important goal in good anaesthesia management. Preoperative anxiety can be reduced with certain pharmacological interventions.
**Aim:** The present study was carried to assess the potential role of oral Melatonin as a premedicant to general anaesthesia and its effect on induction dose of Propofol.
**Methodology:** A prospective randomized double blind placebo controlled study was planned on 80 patients of ASA I & II physical status aged between 18- 55 yrs. scheduled to undergo different elective surgeries and satisfying all the inclusion criteria. They were randomly divided into 2 groups –
1. Group M = Oral melatonin 3 mg
2. Group P = Placebo

Pre-operative Visual Analogue Scale for anxiety (VAS-A) score, sedation and orientation score were noted, along with the dose requirement of Propofol during induction in both the groups. Haemodynamic and adverse effect profile along with time to recovery from anaesthesia were also observed.
**Results:** Patients who received premedication with melatonin were less anxious, better sedated and had had no effect on the orientation compared to placebo. Oral melatonin was associated with significant decrease in induction dose of Propofol and did not delay recovery from anaesthesia. It has a favourable hemodynamic profile with no major adverse effects.
**Conclusion:** Oral melatonin 3mg can be an effective premedication for preoperative anxiolysis and sedation and an adjuvant to induction drug Propofol.

**Keywords:** melatonin, visual analogue scale for anxiety (VAS-A), sedation, anxiolysis, propofol adjuvant

## Introduction
Anxiety is common in surgical patients during the preoperative period [1]. Preoperative anxiety is described as an unpleasant state of uneasiness or tension that is secondary to a patient being concerned about a disease, hospitalization, anaesthesia and surgery, or the unknown [2]. It may cause patients to avoid planned surgery. If anxiety is sufficiently marked it causes all the signs of sympathetic stimulation and stress [3]. High levels of preoperative anxiety have unfavourable effects on induction and maintenance of anaesthesia as well as on the recovery from anaesthesia and surgery. Anxious patients require higher doses of anaesthetic induction agents and postoperative analgesic drug [4]. Hence the most important single reason for premedicating patients before surgery is to reduce anxiety. Reducing anxiety is an important goal in good anaesthesia management. Preoperative anxiety can be reduced with certain pharmacological interventions. Benzodiazepines are the most commonly used drug to reduce preoperative anxiety. However, midazolam has several drawbacks, including the paradoxical reactions, interactions with opioids, variable bioavailability and elimination half-life as well as delayed discharge from post-operative anaesthesia care unit [5].
Melatonin (N-acetyl-5-methoxy tryptamine), is a naturally occurring neurohormone in the human body secreted by the pineal gland [6]. Several studies reported that Melatonin cause pre-operative anxiolysis and increase the level of sedation without impairing orientation [7, 8, 9]. The hypnotic property of melatonin endows this neurohormone with the profile of a novel hypnotic and anaesthetic sparing effect. It has a wide range of safety margin. It has been used at a dose of 0.2 mg/kg safely [10]. Several studies reported that melatonin has analgesic potential in addition to anxiolytic and sedative effects without disturbances of the cognitive

and psychomotor skills and thus improves the quality of recovery [11, 12, 13].

Considering these facts, the present study is planned to assess the effects of melatonin premedication on preoperative anxiolysis and sedation. Its hypnotic and anaesthetic sparing properties is studied by evaluating the induction dose of Propofol.

**Aims and objectives of the study**

1. To study the effect of oral Melatonin on preoperative anxiety.
2. To study the effect of oral Melatonin on preoperative sedation.
3. To study the effect of oral Melatonin on induction dose of Propofol.

**Patients and methods**

Hospital ethics committee clearance was obtained for this study. Informed consent was taken from all the patients. Patients included in study were posted for general anaesthesia from departments of general surgery, orthopaedics and gynaecology.

**Source of data**

Adult patients of physical status ASA I & II scheduled for different elective surgical procedures under general anaesthesia at hospital attached to Shadan Institute of Medical Sciences, Hyderabad.

**Sample size**

Total of 80 patients with 40 patients in each group to make up for possible drop outs and better validation of results.

**Study design**

A prospective randomized double blind placebo controlled study was conducted on 80 adult patients scheduled to undergo different elective surgical procedures under general anaesthesia and satisfying all the inclusion criteria.

**Inclusion criteria**

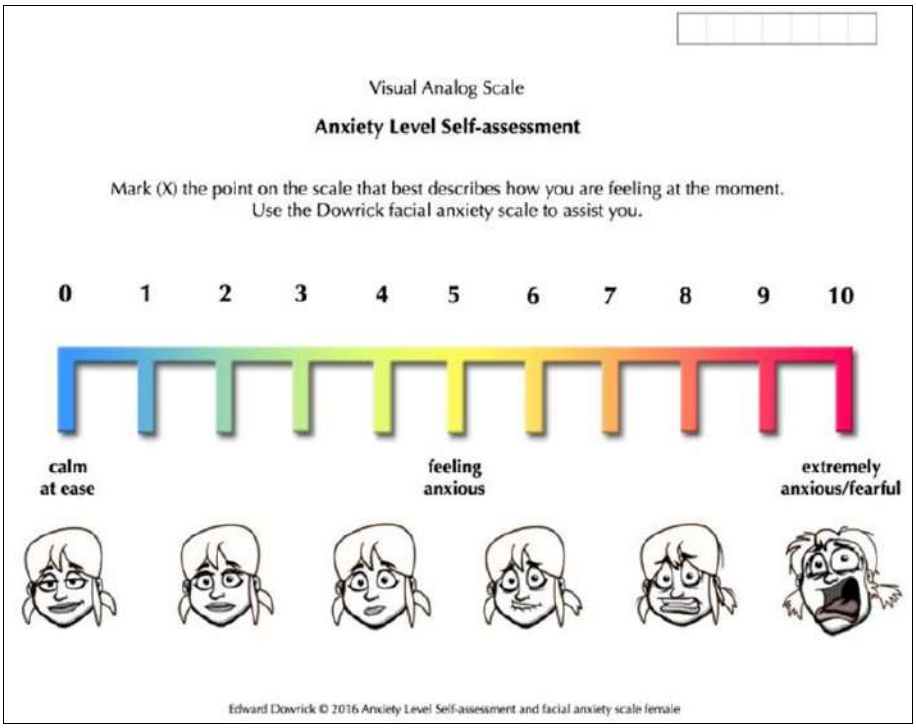
1. Patients with ASA physical status grade I and II.
2. Patients aged between 18-55yrs of either sex.
3. Patients weighing between 40-80 kgs.
4. Patients giving valid informed consent.

**Exclusion criteria**

1. Pregnant and lactating woman.
2. Patients with psychiatric disorders or on antipsychotic drugs.
3. Patients with sleep disorders.
4. Patients with language or communication difficulties.

**Preanaesthetic examination and preparation**

Preanaesthetic assessment was done one day prior to the surgery. A detailed history of present and past medical illness, past h/o of anaesthetic exposure, concomitant history of drug allergy and any medications in preoperative period was recorded. General physical examination and systemic examination of the patients was carried out. Routine investigation and relevant specific investigations were done. ASA Physical status was evaluated. Weight in kgs was recorded. An informed and written consent was taken after explaining the anaesthetic procedure in detail. Patients were advised overnight fasting for 8 hours and premedicated with Tab. Ranitidine 150mg and Tab. Alprazolam 0.25mg on the previous night of surgery. The Visual Analogue Scale for anxiety (VAS-A) was explained and the anxiety score was recorded using the Edward Dowrick Visual Analogue Scale (i.e. 0=calm at ease, 10=extremely anxious/fearful).




On the day of surgery patient was shifted from the ward to preanaesthetic room 2 hours before surgery. The Visual Analogue Scale for anxiety (VAS-A), sedation score and orientation score were recorded along with hemodynamic parameters (heart rate, blood pressures) and oxygen saturation.

| Sedation score | | Orientation score | |
|---|---|---|---|
| 1 | Awake | | |
| 2 | Drowsy | 0 | None |
| 3 | Asleep but, arousable to voice | 1 | Oriented to either place or time |
| 4 | Asleep but, not arousable to voice | 2 | Oriented to both place and time |

Patients were randomly assigned to 2 groups Melatonin (M) and Placebo (P), according to a computer generated random numbers. Group M received Tab Melatonin 3 mg orally and Group P received placebo (sugar free tablet). The drug was given to the patient by a resident not involved in study, 60 minutes before induction time in a thick opaque similar looking envelope. Patient had to take the drug orally with 10 ml of water. An Anaesthesiologist blinded to the randomization sequence and premedication quantified the VAS anxiety score, sedation score and orientation score at 0, 15, 30, 45, 60 minutes after premedication and just before induction. Patients were monitored with non-invasive BP (NIBP) and pulse oximeter and data collected at 0, 15, 30, 45 and 60 minutes after premedication.

**Preparation of operating room**

Anaesthesia work station was checked. Appropriate size endotracheal tubes, working laryngoscope with medium and large size blades, stylet and working suction apparatus were kept ready before procedure. After shifting patient to the operating room, IV access was obtained on the forearm with 18G IV cannula and ringer lactate started. The VAS-A score, sedation score, and orientation score were recorded. Patient's baseline vitals heart rate, NIBP, pulse oximetry was recorded. Intraoperative monitoring of ECG, $SpO_2$, NIBP, Capnography continued.

Following 3 minutes preoxygenation, induction of anaesthesia was done by injecting Inj. Propofol, 10mg over 5secs every 15 seconds into a rapidly flowing IV infusion until the response to loss of verbal commands and eye lash reflex. Patient was asked to repeat a number slowly till he gets sleep. Loss of response to verbal commands and loss of eyelash reflex was evaluated simultaneously and the total propofol dosage calculated.

Inj Fentanyl 2mcg/kg was administered intravenously. Tracheal intubation was accomplished using Inj Vecuronium 0.1mg/kg intravenously. Intraoperative maintenance of anaesthesia was with Nitrous oxide in Oxygen (60:40) with titrated dose of Isoflurane. At the end of surgery, the patients were reversed with Inj Neostigmine and Inj Glycopyrrolate and extubated. The time to achieve recovery score of 9 or greater on Modified Aldrete Scoring System after extubation was recorded.

The modified Aldrete scoring system for determining when patients are ready for discharge from the post anesthesia care unit

| Discharge criteria | Score |
|---|---|
| **Activity: Able to move voluntarily or on command** | |
| Four extremities | 2 |
| Two extremities | I |
| Zero extremities | 0 |
| **Respiration** | |
| Able to deep breathe and cough freely | 2 |
| Dyspnea, shallow or limited breathing | I |
| Apneic | 0 |
| **Circulation** | |
| Blood pressure +/ - 20 mm of preanaesthetic level | 2 |
| Blood pressure +/ - 20-50 mm prcanaesthesia level | I |
| Blood pressure +/ - 50 mm of pre-anaesthesia level | 0 |
| **Consciousness** | |
| Fully awake | 2 |
| Arousable on calling | I |
| Not responding | 0 |
| **$O_2$ saturation** | |
| Able to maintain $O_2$ saturation >92% on room air | 2 |
| Needs $O_2$ inhalation to maintain $O_2$ saturation >90% | I |
| $O_2$ saturation <90% even with $O_2$ supplementation | 0 |

A score > 9 was required for discharge.

Front Aldrete JA. The post anaesthesia recovery score revisited [letter]. J Clin Anesth 1995;7:89-91

**Parameters observed were**

- Visual Analogue Scale for anxiety (VAS-A) score, sedation score, orientation score was recorded before premedication and at 0, 15, 30, 45 and 60 minutes after pre-medication and just before induction.
- Pulse oximetry, non-invasive blood pressure and heart rate were recorded, before pre-medication, and at 0, 15, 30, 45 and 60 minutes and just before induction.
- During induction, the dose of IV propofol at which loss of response to verbal command, loss of eye lash reflex was recorded.
- The duration of surgery and anaesthesia was noted.
- The time to achieve recovery score of 9 or greater on Modified Aldrete Scoring System was recorded.
- Occurrence of side effects if any for melatonin like headache, nausea, enuresis and dizziness were observed.

**Statistical analysis**

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate tables.

## Results

**Table 1:** Demographic & other basic data of the patients

| Patient Characteristic | Melatonin Group (n=40) | Placebo Group (n=40) |
|---|---|---|
| No of patients | 40 | 40 |
| Age(yrs) Mean±SD | 35.40±10.98 | 36.98±9.80 |
| Sex(M:F) | 30:10 | 26:14 |
| Weight (kgs) Mean±SD | 58.08±8.64 | 58.73±9.11 |
| ASA grade(1:2) | 32:8 | 34:6 |

**Table 2:** Age distribution of patients studied

| Age in years | Melatonin Group (n=40) | | Placebo Group (n=40) | |
|---|---|---|---|---|
| | No | % | No | % |
| 18-20 | 0 | 0 | 0 | 0 |
| 20-30 | 20 | 50.0 | 11 | 27.5 |
| 31-40 | 6 | 15.0 | 16 | 40.0 |
| 41-50 | 10 | 25.0 | 9 | 22.5 |
| 51-55 | 4 | 10.0 | 4 | 10.0 |
| Total | 40 | 100.0 | 40 | 100.0 |
| Mean±SD | 35.40±10.98 | | 36.98±9.80 | |

The Mean Age among two groups was comparable.

**Table 3:** Gender distribution of patients studied

| Gender | Melatonin Group (n=40) | | Placebo Group (n=40) | |
|---|---|---|---|---|
| | **No** | **%** | **No** | **%** |
| Female | 30 | 75.0 | 26 | 65.0 |
| Male | 10 | 25.0 | 14 | 35.0 |
| Total | 40 | 100.0 | 40 | 100.0 |

The gender distribution among two groups matched (P value = 0.329)

**Table 4:** Weight (kg) distribution of the patients studied

| Weight (kg) | Melatonin Group (n=40) | | Placebo Group (n=40) | |
|---|---|---|---|---|
| | No | % | No | % |
| 40-50 | 9 | 22.5 | 9 | 22.5 |
| 51-60 | 16 | 40.0 | 13 | 32.5 |
| 61-70 | 14 | 35.0 | 15 | 37.5 |
| 71-80 | 1 | 2.5 | 3 | 7.5 |
| Total | 40 | 100.0 | 40 | 100.0 |
| Mean ± SD | 58.08±8.64 | | 58.73±9.11 | |

Mean weight in both groups was comparable (P value = 0.744)

**Table 5:** ASA physical status of the patients studied

| ASA physical status | Melatonin Group (n=40) | | Placebo Group (n=40) | |
|---|---|---|---|---|
| | No | % | No | % |
| ASA I | 32 | 80.0 | 34 | 85.0 |
| ASA II | 8 | 20.0 | 6 | 15.0 |
| Total | 40 | 100.0 | 40 | 100.0 |

Patients belonging to ASA physical status I and II were comparable between the groups. (p=0.566)

**Table 6:** Surgeries in two groups of patients studied

| Type of Surgery | Melatonin Group (n=40) | | Placebo Group (n=40) | |
|---|---|---|---|---|
| | No | % | No | % |
| Abdominal | 12 | 30 | 10 | 25 |
| Laparoscopic | 10 | 25 | 13 | 32.5 |
| Orthopaedic | 12 | 30 | 10 | 25 |
| Head and Neck | 1 | 2.5 | 1 | 2.5 |
| Others | 5 | 12.5 | 6 | 15 |
| Total | 40 | 100 | 40 | 100 |

The types of surgeries between the two groups were comparable

**Table 7:** Comparison of duration of Surgery and Anaesthesia in two groups studied

| In minutes | Melatonin Group (n=40) | Placebo Group (n=40) | P value |
|---|---|---|---|
| Duration of Surgery(min) | 69.99±18.84 | 70.03±11.44 | 0.194 |
| Duration of Anaesthesia(min) | 86.00±19.65 | 80.13±13.16 | 0.103 |

Duration of surgery (P value = 0.194) and anaesthesia (P value = 0.103) were comparable between the groups

**Table 8:** VAS for anxiety (VAS-A) score in two groups studied

| VAS-A Score | Melatonin Group (n=40) | Placebo Group (n=40) | P value |
|---|---|---|---|
| Day before surgery | 4.80±0.85 | 5.75±0.95 | 0.420 |
| Before premedication | 4.88±1.00 | 5.77±0.92 | 0.182 |
| 0 min | 4.98±1.00 | 5.77±0.92 | 0.182 |
| 15 min | 2.63±0.80 | 4.93±0.81 | <0.001* |
| 30min | 1.43±0.83 | 4.90±0.66 | <0.001* |
| 45 min | 1.10± 1.07 | 4.80±0.66 | <0.001* |
| 60 min | 0.48±0.71 | 4.80±0.75 | <0.001* |
| Before induction | 1.53±0.65 | 5.00±0.88 | <0.001* |

- The baseline Mean VAS-A scores on the day before surgery and before premedication in melatonin and placebo group were 4.80±0.85 and 5.75±0.95, (P =0.420) and 4.88±1.00 and 5.77±0.92 (P=0.182) respectively, and was comparable between the group.
- After premedication, at 0 min the VAS-A scores were comparable between the groups. (P=0.182).
- At 15.30,45 and 60 minutes after premedication the VAS-A value decreased in both the groups but, was clinically significant in melatonin group and statistically strongly significant between the two groups (*P*<0.001).
- In Melatonin group, the VAS-A score decreased from 4.88±1.00 before premedication to 0.48±0.71 at 60 minute after premedication. The greatest reduction when compared in between the time interval within the group was at 60 minute after premedication.
- In Placebo group, the VAS-A score decreased from 5.77±0.92 before premedication (on the day of surgery) to 4.80±0.66 at 45 minutes after premedication.
- There was increase in anxiety from 0.48±0.71 and 4.80±0.75 at 60 minute to1.53±0.65 and 5.00±0.88 at induction in melatonin and placebo group respectively, but the increase was below the baseline.

**Table 9(a):** Comparison of Sedation score in two groups studied

| Sedation score | Melatonin Group (n=40) | | Placebo Group (n=40) | | P value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| **Day before surgery, Before premedication and 0 min** | | | | | |
| Awake(1) | 40 | 100.0 | 40 | 100.0 | 1.000 |
| Drowsy(2) | 0 | 0.0 | 0 | 0.0 | |
| Asleep but arousable(3) | 0 | 0.0 | 0 | 0.0 | |
| Asleep but not arousable(4) | 0 | 0.0 | 0 | 0.0 | |
| 15 min | | | | | |
| Awake(1) | 12 | 30.0 | 40 | 100.0 | <0.001* |
| Drowsy(2) | 26 | 65.0 | 0 | 0.0 | |
| Asleep but arousable(3) | 2 | 5.0 | 0 | 0.0 | |
| Asleep but not arousable(4) | 0 | 0.0 | 0 | 0.0 | |
| 30min | | | | | |
| Awake(1) | 2 | 5.0 | 40 | 100.0 | <0.001* |
| Drowsy(2) | 21 | 52.5 | 0 | 0.0 | |
| Asleep but arousable(3) | 17 | 42.5 | 0 | 0.0 | |
| Asleep but not arousable(4) | 0 | 0.0 | 0 | 0.0 | |
| 45 min | | | | | |
| Awake(1) | 1 | 2.5 | 40 | 100.0 | <0.001* |
| Drowsy(2) | 12 | 30 | 0 | 0.0 | |
| Asleep but arousable(3) | 27 | 67.5 | 0 | 0.0 | |
| Asleep but not arousable(4) | 0 | 0.0 | 0 | 0.0 | |
| 60 min | | | | | |
| Awake(1) | 0 | 0.0 | 40 | 100.0 | <0.001* |
| Drowsy(2) | 2 | 5.00 | 0 | 0.0 | |
| Asleep but arousable(3) | 38 | 95.0 | 0 | 0.0 | |
| Asleep but not arousable(4) | 0 | 0.0 | 0 | 0.0 | |

- There was no significant difference between the two groups Day before surgery, before premedication and at 0 min.
- The sedation score between the group was statistically significant *P*<0.001 at 15, 30, 45 and 60 minutes after premedication.
- At 15 min after premedication 30% were awake, 65%were drowsy, 5% were asleep but arousable to voice in melatonin group. All patients were awake in placebo group.
- At 30 minutes after premedication 5%, 52.5%, 42.5% of the patients were awake, drowsy, asleep but arousable to voice respectively in melatonin group. All the patients were awake in the placebo group.
- At 45 minutes after premedication 2.5%, 30%, 67.5% of the patients were awake, drowsy, asleep but arousable to voice respectively in melatonin group. All the patients were awake in the placebo group.
- At 60 minutes after premedication none were awake, 5% drowsy, 95% asleep but arousable to voice in melatonin group. In placebo group all were awake
- None of the patients in both the groups were ever in an unarousable state i.e. Asleep but not arousable (4).

**Table 9(b):** Mean Sedation scores in the two groups studied

| Sedation score | Melatonin Group (n=40) | Placebo Group (n=40) | P value |
|---|---|---|---|
| Day before surgery | 1.00±0.00 | 1.00±0.00 | 1.000 |
| Before premedication | 1.00±0.00 | 1.00±0.00 | 1.000 |
| 0 min | 1.00±0.00 | 1.00±0.00 | 1.000 |
| 15 min | 1.75±0.54 | 1.00±0.00 | <0.001* |
| 30min | 2.38±0.59 | 1.00±0.00 | <0.001* |
| 45 min | 2.83±0.38 | 1.03±0.16 | <0.001* |
| 60 min | 2.98±0.16 | 1.00±0.00 | <0.001* |
| Before induction | 2.25±0.44 | 1.00±0.00 | <0.001* |

- The data shows that the baseline Mean sedation scores day before surgery, before premedication and at 0min after premedication were comparable between the two group (P=1.000).
- The sedation scores were statistically significant between the two groups after premedication ($P$<0.001) at 15,30, 45,60 minutes after premedication and at induction.
- In the melatonin group sedation score progressively increased after 15min (1.75±0.54) and was highest at 60 min (2.98±0.16) and decreased before induction (2.25±0.44).
- There was no significant change in sedation score in the placebo group.

**Table 10:** Orientation scores in the groups studied

| Orientation score | Melatonin Group (n=40) | Placebo Group (n=40) | P value |
|---|---|---|---|
| Day before surgery | 2.00±0.00 | 2.00±0.00 | - |
| Before premedication | 2.00±0.00 | 2.00±0.00 | - |
| 0 min | 2.00±0.00 | 2.00±0.00 | - |
| 15 min | 2.00±0.00 | 2.00±0.00 | - |
| 30min | 2.00±0.00 | 2.00±0.00 | - |
| 45 min | 2.00±0.00 | 2.00±0.00 | - |
| 60 min | 2.00±0.00 | 2.00±0.00 | - |
| Before induction | 2.00±0.00 | 2.00±0.00 | - |

Data shows no change in orientation score between the two groups.

**Table 11:** Comparison of $SpO_2$ in the groups studied

| $SpO_2$% | Melatonin Group (n=40) | Placebo Group (n=40) | P value |
|---|---|---|---|
| Day before surgery | 98.05±0.39 | 97.95±0.32 | 0.211 |
| Before premedication | 97.83±0.96 | 97.73±0.64 | 0.585 |
| 0 min | 97.85±0.83 | 97.62±0.77 | 0.215 |
| 15 min | 96.43±1.32 | 97.18± 1.01 | 0.101 |
| 30 min | 96.80±1.22 | 97.48±0.88 | 0.746 |
| 45 min | 96.60±1.39 | 97.53±0.85 | 0.464 |
| 60 min | 96.43±1.41 | 98.00±0.82 | 0.608 |
| Before induction | 98.10±0.87 | 98.53±0.85 | 0.117 |

There was no significant difference in measured $SpO_2$between the two groups.

**Table 12:** Comparison of Heart rate (bpm) between the groups studied

| Heart rate (bpm) | Melatonin Group (n=40) | Placebo Group (n=40) | P value |
|---|---|---|---|
| Day before surgery | 91.30±9.38 | 90.60±9.41 | 0.203 |
| Before premedication | 92.05±13.39 | 89.70±8.92 | 0.359 |
| 0 min | 94.23±14.06 | 89.23±9.38 | 0.065 |
| 15 min | 81.25±12.84 | 86.63±10.18 | 0.041* |
| 30min | 77.10±12.26 | 86.33±9.35 | <0.001* |
| 45 min | 74.28±12.18 | 86.20±8.38 | <0.001* |
| 60 min | 71.95±11.04 | 86.90±8.45 | <0.001* |
| Before induction | 78.80±12.46 | 97.83±8.79 | <0.001* |

- The Mean baseline heart rates were comparable between the groups.
- The decrease in heart rate from baseline was significant in melatonin group at 15 min (P =0.041).
- At 30, 45 and 60 minutes after premedication the decrease in heart rate was strongly significant ($P$<0.001) when compared to the placebo group.
- Before induction the decrease in heart rate was strongly significant ($P$<0.001) when compared to the placebo group.
- There was increase in heart rate just before induction in both the group but, less than baseline in melatonin group and more than baseline in placebo group.
- In the placebo group the decrease in heart rate was not significant within the group.

**Table 13:** Comparison of Systolic BP (mm Hg) between groups studied

| Systolic BP (mm Hg) | Melatonin Group (n=40) | Placebo Group (n=40) | P value |
|---|---|---|---|
| Day before surgery | 126.63±10.69 | 126.88± 11.46 | 0.920 |
| Before premedication | 133.28± 14.86 | 132.55± 10.70 | 0.803 |
| 0 min | 132.93±14.81 | 131.20± 10.67 | 0.552 |
| 15 min | 114.80± 10.79 | 129.20±10.23 | <0.001* |
| 30min | 113.18±10.45 | 126.13±8.42 | <0.001* |
| 45 min | 111.00± 10.17 | 126.20±7.58 | <0.001* |
| 60 min | 109.68±9.18 | 127.05±7.92 | <0.001* |
| Before induction | 118.43± 11.44 | 140.10±9.99 | <0.001* |

- The mean baseline Systolic BP is comparable.
- Systolic BP at 15, 30, 45 and 60 minutes decreased in melatonin group and statistically strongly significant ($P$<0.001) compared to placebo group.
- Before induction the decrease in Systolic BP was strongly significant when compared to the placebo group.
- Before induction the Systolic BP was high in both the group but, less than the baseline in melatonin group and more than baseline in placebo group.
- In the placebo group the decrease in Systolic BP in was not significant within the group.

**Table 14:** Comparison of Diastolic BP (mmHg) in the groups of patient studied

| Diastolic BP (mm Hg) | Melatonin Group (n=40) | Placebo Group (n=40) | P value |
|---|---|---|---|
| Day before surgery | 80.90±8.54 | 79.20±9.29 | 0.397 |
| Before premedication | 83.70±9.22 | 83.50±7.18 | 0.914 |
| 0 min | 82.75±9.31 | 83.03±7.60 | 0.885 |
| 15 min | 73.53±8.26 | 80.05±6.71 | <0.001* |
| 30min | 70.88±8.66 | 78.90±5.93 | <0.001* |
| 45 min | 70.23±8.35 | 77.93±7.16 | <0.001* |
| 60 min | 70.13±10.15 | 79.25±7.07 | <0.001* |
| Before induction | 73.73±8.68 | 87.65±5.94 | <0.001* |

- The mean baseline Diastolic Blood Pressure (DBP) is comparable.
- DBP at 15, 30, 45 and 60 minutes decreased in melatonin group and statistically strongly significant ($P$<0.001) compared to placebo group.
- Before induction decrease in DBP was strongly significant when compared to the placebo group.
- Before induction the DBP was high in both the group but, less than the baseline in melatonin group and more than baseline in placebo group.
- In the placebo group the decrease in DBP in was not significant within the group.

**Table 15:** Comparison of Mean Arterial Pressure (mm Hg) between the groups

| Mean Arterial Pressure (mm Hg) | Melatonin Group (n=40) | Placebo Group (n=40) | P value |
|---|---|---|---|
| Day before surgery | 95.70±9.38 | 94.45±9.35 | 0.552 |
| Before premedication | 100.00±9.55 | 99.60±7.99 | 0.839 |
| 0 min | 98.93±9.36 | 98.68±7.74 | 0.897 |
| 15 min | 87.10±8.14 | 95.95±6.37 | <0.001* |
| 30min | 84.85±8.32 | 94.45±6.47 | <0.001* |
| 45 min | 83.55±8.24 | 94.20±5.86 | <0.001* |
| 60 min | 83.28±9.34 | 94.68±6.63 | <0.001* |
| Before induction | 88.20±10.09 | 104.35±7.28 | <0.001* |

- The baseline Mean Arterial Pressures (MAP) were comparable.
- MAP at 15, 30, 45 and 60 minutes decreased in melatonin group and statistically strongly significant ($P$<0.001) compared to placebo group.
- Before induction the decrease in MAP was strongly significant when compared to the placebo group.
- Before induction the MAP was high in both the group but, less than the baseline in melatonin group and more than baseline in placebo group.
- In the placebo group the decrease in MAP was not significant within the group.

**Table 16:** Comparison of Propofol dose required between the groups

| Propofol dose requirement | Melatonin Group (n=40) | Placebo Group (n=40) | P value |
|---|---|---|---|
| **Standard dose** | | | |
| Standard dose (mg/kg) | 2.00±0.0 | 2.00±0.00 | - |
| Standard total dose (mg) | 116.15±17.28 | 117.45±18.21 | 0.744 |
| **Total dose required (MG)** | | | |
| Loss of response to Verbal commands | 54.25±13.18 | 79.00±11.50 | <0.001* |
| Loss of Eye lash reflex | 57.75±14.59 | 88.50±13.31 | <0.001* |
| **Dose required (MG/KG)** | | | |
| Loss of response to Verbal commands | 0.93±0.21 | 1.35±0.21 | <0.001* |
| Loss of Eye lash reflex | 1.00±0.24 | 1.51±0.24 | <0.001* |

- The mean standard total Propofol dose (mg) required was comparable between groups.
- The total dose required at different points of induction was decreased and statistically significant (P value <0.001).
- Similarly, the dose required in mg/kg body weight was decreased and statistically significant (P value <0.001).

**Table 17:** Time to recovery score 9 or greater on Modified Aldrete Scoring System

| Time in minutes | Melatonin Group (n=40) | | Placebo Group (n=40) | |
|---|---|---|---|---|
| | No | % | No | % |
| 1-5 | 21 | 52.5 | 14 | 35.0 |
| 6-10 | 19 | 47.5 | 26 | 65.0 |
| Total | 40 | 100.0 | 40 | 100.0 |
| Mean ± SD | 5.88±1.18 | | 6.25±1.37 | |

The time to recovery score of 9 or greater on modified recovery scale of Aldrete is comparable (P=0.194)

## Discussion

Preoperative anxiety has unfavourable effects on induction and maintenance of anaesthesia as well as on the recovery from anaesthesia and surgery. Hence use of premedication for pre-operative anxiolysis is an important goal in good anaesthetic management. Currently, the premeditations used to reduce anxiety has been effective, but not without certain undesirable side effects and complications. An alternative medication which increases the safety of its use and yet maintains a similar degree of anxiolytic effectiveness would be very desirable.

Hypnotic and sedative properties of Melatonin when taken exogenously led to the postulation that melatonin administered orally could potentially and safely be used for anxiolysis and sedation in treating anxious patients [6]. The studies which had examined this potential had showed mixed results, with some reporting that melatonin had good anxiolytic [7, 8, 9] properties, others have not found that melatonin is superior to conventionally used anxiolytics.[14,15] Melatonin also has been evaluated for its capabilities of having synergistic action on anaesthetic agents [12, 16, 17].

Hence the purpose of this study was to examine the effectiveness of oral melatonin as a premedication for anxiolysis and sedation, in adult patients undergoing different elective surgeries under general anaesthesia. The study compared the anxiolytic and sedative property of melatonin versus placebo. This study attempted to further examine melatonin potential for hypnotic and anaesthetic sparing properties and hence cost effectiveness in anaesthesia practice by evaluating dose requirement of propofol for induction of general anaesthesia.

### Dosage of the drugs selected

Several studies have used oral melatonin dose ranging from 3 mg to 10 mg single dose per orally [8, 13]. Naguib M *et al.* [12] used 0.2 mg/kg of oral melatonin in their study. Kain ZN *et al.* [18] safely used oral melatonin in children with the maximum dose of 0.4mg/kg without any major side effects. A low dose of oral melatonin as 3mgwas used in this study to see the effectiveness as previously used by various authors [15, 19].

### Timing of ingestion of drugs

The peak effect of melatonin ranges from 60-150 minutes [8]. Hence, in this study premedication was given 60 minutes before induction.

### Analysis of patient characteristics between the groups

There was no significant difference between the two groups in view of their age (Table 1, 2), sex (Table 1, 3) and weight (Table 1, 4) characteristics. Several studies have used extremes of ages like young children [18] or patients older than 60 years [20] but, this study was conducted on an age group between 18-55 yrs.

Patients belonging to ASA physical status I and II were comparable between the two groups (Table 5).The types of elective surgeries (Table 6) and also, the duration of surgery and anaesthesia (Table 7) were all comparable between the groups.

### Analysis of data related to anxiety (Table 8)

Three studies, two by Naguib *et al.* [12, 21] and one by Caumo *et al.* [22] compared the effects of melatonin with that of a placebo. 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.

The mechanism of melatonin for anxiolysis seems to be related to both receptor and non-receptor mediated actions. Specific melatonin G-protein coupled receptors (MT1, MT2) are distributed widely throughout the body and at the suprachiasmatic nucleus. Non-receptor mediated actions of melatonin are a more recent discovery [23].

In the present study there was decrease in anxiety scores in both the groups from baseline, but the decrease in anxiety score was more in melatonin than in placebo group. The decrease in anxiety score was noted as early as 15 minutes and maximum decrease in anxiety score was seen at 60 min. When melatonin was compared with placebo, the VAS-A score on the day before surgery, before premedication and at 0 min was comparable. There was strongly significant difference ($P$<0.001) in VAS anxiety score at 15, 30, 45, 60 mins after premedication and before induction which was comparable the above mentioned three studies.

### Analysis of data related to sedation (Table 9a & 9b)

Many studies compared sedation levels after premedication with melatonin, midazolam or placebo [7, 9, 12, 14, 15, 19, 21]. 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.* [19, 21].

This study showed that Melatonin produced enough sedation which would calm the patient and induce a natural sleep which is very much desirable against the deep sedation produced by benzodiazepines. Hence patients sedated with melatonin would require less pre-operative monitoring.

### Analysis of data related to orientation (Table 10)

At least five studies assessed the orientation scores with

respect to time and place at multiple times during the study period among the melatonin and placebo groups [7, 9, 12, 14, 21].
In present study it is found that there was no change in orientation scores in melatonin and placebo group before and at 0 min, 15 min, 30 min, 45 min, 60 min after premedication and at induction. Thus, it showed that melatonin did not produce any change in orientation.

**Analysis of data related to oxygen saturation ($SpO_2$) (Table 11)**

The level of oxygen saturation ($SpO_2$) was assessed to determine if melatonin had any impact on oxygen saturation over time if used as a premedication.
In the melatonin group, the difference in SpO2 from baseline (97.83±0.96%) and at 0, 15, 30, 45, 60 minutes were 97.85%, 96.43%, 96.80%, 95.60%, 96.43% respectively. In the placebo group, the baseline $SpO_2$ value was 97.73±0.64% and the difference in baseline SpO2 and that at 0,15,30,45, and 60minutes were not significant.
Evagelidis P *et al.* [24] also showed that melatonin premedication did not have any significant effect on oxygen saturation levels. Therefore, it appears that the use of melatonin as an oral premedication did not affect the oxygen saturation levels clinically.

**Analysis of data related to hemodynamics (Tables 12, 13, 14 & 15)**

In this study**,** each subject's heart rate, blood pressures (SBP, DBP and MAP) was measured on the day before surgery, before premedication and at 0, 15, 30, 45, 60 minutes after premedication and just before induction.
The mean basal heart rate on day before surgery and on the day of surgery were comparable between the two group (P=0.203 and P=0.359 respectively). Inter group comparison shows statistically highly significant difference in the heart rate measured at15, 30, 45 and 60 minutes and even before induction. Within the melatonin group the maximum change in the heart rate was seen at 15 min from baseline and maximum decrease was seen at 60 minutes. Within the placebo group there was no significant change in heart rate. Both the group showed increase in heart rate just before induction, in the melatonin group the increase was below the baseline heart rate whereas, in the placebo group the increase in heart rate was more than baseline heart rate.
There was statistically significant difference ($P$<0.001) in SBP, DBP and MAP at 15, 30, 45, 60 minutes and before induction in between the group. In melatonin group, the decrease in blood pressures from baseline was seen at 15 min and the maximum decrease was at 60 minute. In the placebo group the decrease in blood pressure from the baseline was seen at different time interval after premedication, but was not clinically significant as seen in melatonin group. It was noted that there was increase in blood pressures just before induction in both the group. This could be due to shifting of patient from quite premedication room to noisier operating room and the operating room environment. However, in melatonin group the increase in blood pressures was well below the baseline blood pressures and in placebo group, the increase in blood pressures was well above the base line blood pressures.
Observation shows that melatonin, by decreasing anxiety and inducing sedation has an impact on the heart rate and blood pressures significantly compared to placebo [14, 25, 26].
The mechanism of action on the circulation and heart rate is complex. Melatonin may bind to specific melatonin receptors in the blood vessels, interfering with the vascular response to catecholamines [25, 27]. It may interfere with the peripheral and central autonomic system, causing a reduction in adrenergic outflow and catecholamine levels causing an effect on heart rate [28, 29]. It may induce relaxation of the smooth muscle of the arterial walls by increasing nitric oxide availability thus having a mild hypotensive effect [30].

**Analysis of data related to dose requirement of propofol for induction (Table 16)**

Several premedicants can cause decrease in dose requirements of propofol. Some of them are α2-adrenergic agonists like clonidine and dexmedetomidine and benzodiazepines like midazolam [31, 32]. Melatonin also has been evaluated for its capabilities of having synergistic action on anaesthetic agents [12, 16, 17].
In this study the dose of propofol required for loss of response to verbal commands and loss of eye lash reflex were 54.25±13.18mgs/0.93±0.21mg/kgand 57.75±14.59mgs /1.00±0.24mg/kg respectively in the melatonin group and 79.00±11.50mgs/1.35±0.21mg/kg and 88.50±13.31mgs /1.51±0.24mg/kg respectively in the placebo group. The difference in mean required dose of propofol in mgs and also per kg body weight was statistically strongly significant ($p$<0.001) between the two groups at all stages of induction.
Naguib M, *et al.* [12] concluded that Melatonin premedication significantly decreased the dose of propofol required to induce anesthesia and Turkistani A, *et al.* [33] showed that Melatonin premedication, in an oral dose of either 3 or 5 mg, reduced the required dose of propofol.
This study finding is in concordance with above cited studies findings and confirm that melatonin decreases the dose requirement of propofol for induction.

**Adverse effects of melatonin**

There were no adverse effects of melatonin seen with the dosage of 3mg used during the study. Melatonin is reported to have a high and an excellent safety profile [13, 24].

**Analysis of data related to recovery (Table 17)**

Naguib M *et al.* [19] concluded that premedication with melatonin was associated with preoperative anxiolysis and sedation without affecting the quality of recovery. Samarkandi A *et al.* [35] stated that melatonin was not only as effective as midazolam in alleviating preoperative anxiety but, it was also associated with a tendency towards faster recovery.
In this study, it was observed that the mean average time taken for recovery using Modified Aldrete Scoring System was 5.88±1.88 minutes in the melatonin group and 6.25±1.37 minutes in the placebo group which was not statistically significant (P value=0.194). Thus, showing that melatonin has no effect on recovery similar to the above mentioned studies?

**Conclusion**

**From the present study it can be concluded that**

1. Oral melatonin 3mggiven60 minutes before surgery can provide adequate anxiolysis and sedation when compared to placebo.
2. Oral melatonin did not affect the orientation of the patient.

3. Oral melatonin decreased the dose requirement of Propofol for induction when compared to placebo.
4. Oral melatonin had significant impact on heart rate and blood pressure and an excellent safety profile devoid of any major side effects.
5. Oral melatonin did not delay the time to recovery from anaesthesia comparable to placebo.

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**Conflict of interest**
None

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Nil

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