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Oral Melatonin as a Premedication and its Effect on Induction dose of Thiopentone Sodium: A Placebo Controlled Study

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Abstract

Context: Anxious patients require larger dosage of anaesthetics for induction of anaesthesia which leads to hemodynamic disturbances. Melatonin, as premedication decreases the required dose of induction agent and cause pre-operative anxiolysis. *Aims:* To compare effect of oral melatonin with placebo on required induction dose of thiopentone sodium, pre operative anxiety, orientation and sedation. *Materials and Methods:* This study was conducted on 80 ASA I & II patients scheduled for surgeries under general anaesthesia. Patients were randomised into two groups to receive melatonin (Group-M) and placebo (Group-P) as premedication. The required dose of thiopentone, anxiety score, sedation score and orientation score were studied at 0 min, 30 min and 60 min. Student t-test has been used to find the significance of study parameters on metric parameters and Mann–Whitney U test was used to find the significance of study parameters on ordinal between two groups. *Results:* The mean dose of thiopentone required for SE to reach 50 in group M is 3.69 mg/kg and in group P is 5.46 mg/kg. ($p<0.001$).The mean dose of thiopentone required for loss of eyelash reflex in group M is 3.56 mg/kg and 5.15 mg/kg in group P. ($p <0.001$) Patients were less anxious and more sedated at 30 and 60 min of premedication without any change in orientation. *Conclusion:* Melatonin 6 mg when compared to placebo given 60 minutes before surgery as a premedicant significantly reduced the induction dose of thiopentone sodium and provided better anxiolysis and sedation without affecting orientation.

Keywords: Melatonin; Premedication; Thiopentone Sodium; Placebo.

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Introduction

Anxious patients require larger dosage of anaesthetics for induction of anaesthesia which may lead to hemodynamic disturbances in the patient [1]. Many of the drugs have been investigated as premedicants to decrease the dosage of induction agent [2]. Melatonin causes pre-operative anxiolysis and increase in levels of sedation without impairing orientation [3]. It also decreases the intraoperative requirements of thiopentone and propofol [4].

Considering all these facts, a prospective randomized double blind placebo controlled study was planned to compare the effects of oral melatonin with placebo on required induction dose of thiopentone sodium, pre operative anxiety, orientation and sedation.

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Subjects and Methods

After taking hospital ethics committee approval and informed consent, adult patients (18-55yrs) of ASA physical status I & II scheduled for surgery under general anaesthesia from varied specialities of plastic surgery, surgical oncology, surgical gastroenterology, orthopedics, spine surgery were recruited for the study. Patients on chronic analgesic medication, antiepileptic drugs, antidepressant drugs, antipsychotic drugs, patients with sleep disorders, BMI>30 kg/m^2, pregnant and lactating females and patients with severe renal or hepatic dysfunction were excluded from the study. The estimated sample size required to get a 0.5 mg reduction of thiopentone dose is 36 in each group with alpha 0.01, power (1-beta) = 95, enrolment ratio 1. As dropout cases would be expected, a sample size of 40 in each group were selected for the study even though in the power analysis the sample size estimated was 36 in each group.

Preoperatively, at the time of preanesthetic evaluation, each patient was explained about the study and the premedication requirements with a short briefing on melatonin.

Patients were demonstrated placards to understand the concept of VAS score to quantify their level of anxiety. Demographic profile such as height, weight, age and gender were noted. The extremes of the VAS anxiety scale were marked as "no anxiety" at the 0 end and "anxiety as bad as ever can be" at the 10 cm end. Sedation was assessed according to university of Michigan sedation scale (0 = alert, 1 = arousable to voice, 2 = arousable with gentle tactile stimulation, 3 = arousable with vigorous tactile stimulation, and 4 = lack of responsiveness) at baseline and after premedication. Orientation score was measured, with a three-point scale (0 = none, 1 = orientation in either time or place, and 2 = orientation in both). Approximately 60 min prior to surgery, each patient was taken to a quiet pre operative room. The drug was given to the patient in a sealed cover and asked to ingest it with sips of water. The identity of the tablet was not revealed to the patient or to the investigator. No other pre-medication was given. Anxiety, sedation, and orientation scores were assessed at baseline, 30 min and 60 min after giving premedication. After obtaining IV access, Ringer lactate was started at the rate of 100ml/hr. Intraoperatively electrocardiography, pulse oximetry (SpO_2), capnography ($EtCO_2$) and non-invasive blood pressure were continuously monitored. EEG entropy was used to measure the depth of anaesthesia (DOA) in both the groups. A special electrode with three elements was applied to the frontotemporal region as recommended by the manufacturer and connected to the monitor. Patients were premedicated with inj. fentanyl 2mcg/kg IV. All the patients were preoxygenated with 100% oxygen for 3 minutes followed by the induction by IV thiopentone. Thiopentone sodium 75mg was given within 10 seconds to all the patients initially.

Thereafter 25mg of IV thiopentone was given every 5 seconds until the induction endpoint of state entropy (SE) < 50 achieved. The total dose of thiopentone sodium required was recorded. The disappearance of the patient's ability to respond to commands like 'open your eyes' and the disappearance of the eyelash reflex was assessed by the investigator simultaneously. If there is no response, the thiopentone injection was stopped at that point and the facemask was applied firmly. If there is any response to the placement of mask, an additional dose of 25mg IV thiopentone was given every 5 seconds. The total dose of IV thiopentone that is required to abolish eye lash reflex and verbal response were also noted and correlated with entropy response. Heart rate, and mean arterial pressure were recorded until 10 minutes of induction. The study was considered to be complete at that point and further anaesthesia technique had no influence on the study.

The Statistical software SPSS 15.0 (Statistical Package for Social Sciences, Inc.) was used for the analysis of the data and Microsoft Excel was used to generate graphs and tables. Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous variables were presented as Mean (SD) and results on categorical measurements were presented in Numbers (%). Significance was assessed at 5% level of significance. Two tailed independent student t-test has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters and Mann–Whitney U test was used to find the significance of study parameters on ordinal between two groups.

Results

A comparative two group study (n=40 in each group) was performed to assess the effect of melatonin vs placebo as a premedication on induction doses of thiopentone, preoperative anxiety, sedation and orientation.

Observation of demographic variables in both the groups

Demographic data between 2 groups were comparable (Table 1).

Observation of changes in dose requirement of thiopentone sodium for induction

The mean dose of thiopentone sodium required for SE to reach 50 in melatonin group was 3.69 mg/kg and in placebo group was 5.46 mg/kg,this difference was statistically significant (p <0.001) (Table 2) (Fig.1).The mean dose of thiopentone required for loss of eyelash reflex in melatonin group was 3.56 mg/kg and 5.15 mg/kg in placebo group, and this difference was also statically significant (p <0.001). Patients in melatonin group required less dose of thiopentone for induction of anaesthesia when compared with patients in placebo group.

Haemodynamic parameters were comparable between both the groups during induction.

Observation of changes in VAS anxiety score

The baseline VAS anxiety scores were 7 (6-7.75) in melatonin group, and 6.5 (6-7) in placebo group, which were comparable (p=0.7) (Table 3). After 30 min of premedication there was statistically significant difference between two groups in VAS anxiety scores (p=0.017) i.e. patients in melatonin group are less anxious than patients in placebo group. 60 min after premedication, statistical difference between two groups was more than that at 30 min (p<0.001) i.e. more number of patients in melatonin had less anxiety after 60 min of premedication than placebo group.

Observation of changes in orientation score.

Table 1: Demographic parameters in both groups

Demographic parameters	Group M	Group P	p Value
No of cases	40	40	
Age (years) Mean (SD)*	39 (13)	39.6 (12.98)	0.52
Weight (Kg) Mean (SD)	57.6 (10.2)	54.6 (9.0)	0.32
Height (cm) Mean (SD)	161.5 (8.59)	161.5 (7.87)	0.21
Sex (M: F) (N) (%)	25:15 (63:37)	20:20 (50:50)	0.25
BMI (kg/cm^2) Mean (SD)	22.0 (2.42)	20.8 (2.91)	0.15
ASA physical status* (I:II)(N)(%)	32:8 (80:20)	30:10 (75:25)	0.5

*SD: Standard deviation
*American society of anaesthesiologist

Table 2: Comparison of dose of thiopentone required for induction of general anesthesia in both groups

Parameter	Group M Mean (S.D)	Group P Mean (S.D)	P
Dose SE-50 mg/kg	3.69(0.56)	5.46(0.6).	<0.001
Dose LOE mg/kg	3.56(0.66)	5.15(0.764)	<0.001

SE:State entropy LOE: Loss of eyelash reflex M: melatonin P: Placebo

Table 3: Comparison of two groups with respect to VAS anxiety score before premedication, 30 min and 60 min after premedication

Parameter	Group M Median [25% - 75%]	Group P Median [25% - 75%]	P value
AS-0	7(6-7.75)	6.5(6-7)	0.07
AS-30	5(4-5)	5[5- 6]	0.017
AS-60	4(4-5)	5(4.25-6)	<0.001

AS: anxiety score

Patients in both groups were fully oriented after the administration of premedication study drug up to the time of induction (Table 4).

Observation of changes in sedation scores

Baseline sedation scores were comparable in both the groups. More number of patients were asleep (arousable to gentle tactile stimulation) at the end of 60 min. The sedation scores were found to be statistically significant at 30 and 60 min interval (Table 5).

Discussion

The result of present study suggests that premedication with oral Melatonin 6 mg given 60 min prior to surgery caused statistically significant reduction in pre-operative anxiety, provided adequate sedation and decreased the required dose of thiopentone sodium for induction. Melatonin as oral premedication can be used as a general anaesthetic adjuvant. It produces significant dose dependent increase in GABA concentration in the central nervous system [5]. In our study, we found

Table 4: Comparison of two groups with respect to orientation scores before premedication, 30 min and 60 min after premedication

Parameter	Group M Median [25% - 75%]	Group P Median [25% - 75%]	P value
OS-0	2(2-2)	2(2-2)	1.0
OS-30	2(2-2)	2(2-2)	1.0
OS-60	2(2-2)	2(2-2)	1.0

OS: Orientation score

Table 5: Comparison of two groups with respect to sedation scores before premedication, 30 min and 60 min after premedication

Parameter	Group M Median [25% -75%]	Group P Median [25% - 75%]	P value
SS-0	0(0-0)	0(0-0)	0.139
SS-30	1(0-1)	0(0-0)	<0.001
SS-60	1(1-1)	0.5(0-1)	<0.001

SS: Sedation score

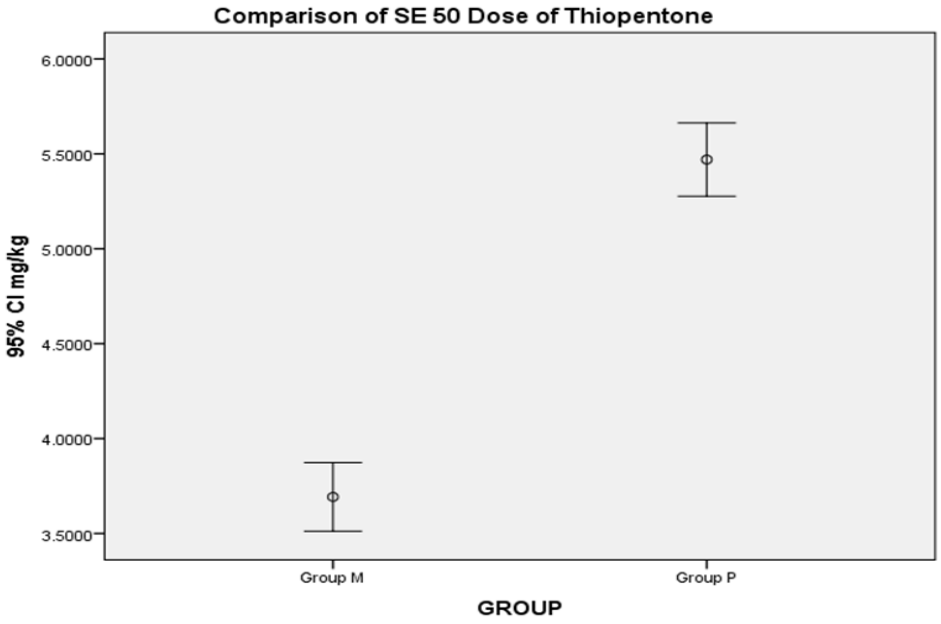

Fig. 1: Error bar showing comparison of SE-50 dose of thiopentone in both groups

that there was a decrease in dose requirement of thiopentone in patients who were premedicated with melatonin when compared to placebo group. The mean dose requirement in melatonin group is 3.69mg/kg and in placebo group is 5.46 mg/kg, which shows statistically significant difference between two groups ($p<0.05$). Melatonin group required 1.4 times less thiopentone dose compared to placebo group. Our findings are in accordance to the findings seen in studies done by Naguib et al. [3] and Turkistani et al.[6].

A recent study has shown the mean per kg dose requirement of thiopentone in melatonin group is 2.54 ±0.64mg and in placebo group is 4.56±0.67mg with p value of 0.000 showing a significant difference [7]. We considered state entropy (SE) 50 as the end point of induction. Several studies have reported that BIS is a reliable predictor of the level of sedation, loss of consciousness and recall [8-10]. Glass and colleagues concluded that BIS values less than 50 indicated an adequate depth of anaesthesia with a variety of clinically used anaesthetic agents [11]. So, we decided the target of SE value 50 as reference to adequate hypnosis. In our study the required dose to reach SE 50 were 3.69mg and 5.46 mg per kg in melatonin and placebo group respectively.

Melatonin also has been evaluated for its capabilities of having synergistic action on IV anesthetic agents. Turkistani et al. found that propofol dose required to achieve loss of eye lash reflex and loss of response to verbal commands was more on the placebo group when compared to melatonin group [6]. Naguib M et al. [8] conducted a study to assess the effects of melatonin premedication on propofol and thipentone induction dose response curves [4]. They found that propofol ED_{50} values decreased from 1.5 mg/kg (1.4-1.6mg/kg) and 1.6 mg/kg (1.5-1.7 mg/kg) to 0.9 mg/kg(0.8-0.96) and 0.9 mg/kg (0.8-0.95 mg/kg) respectively. They concluded that melatonin premedication significantly decreases the dose of both propofol and thiopentone required to induce anaesthesia. This can be explained by another study of Naguib, where it has shown that the relative potency of thiopental following melatonin premedication was 1.3-1.4 times greater than that of thiopentone after placebo [12]. In rats, it has been shown that orally administered melatonin potentiated the anaesthetic effect of thiopentone and ketamine [13]. It has a wide range of safety margin. It has been used at a dose of 0.4 mg/kg in children safely [14]. Naguib and coworkers used melatonin dosage ranging from 3-10 mg P.O for anxiolysis and sedation in adults and children without impairment of psychomotor skills. We chose 6mg of melatonin instead of 5 mg as in other studies [6], because the preparation available in India is 3 mg of melatonin so that patient can be given two tablets as premedication. In our study we used modified VAS which was used by Naguib et al. for measuring anxiety [3]. There is significant difference between two groups at 30 min ($p=0.017$) and also at 60 min ($p <0.001$). The mechanism of melatonin for anxiolysis related to both melatonin receptor activation and effect on GABA transmission [16]. The inference of present study is oral melatonin is more effective in producing anxiolysis. Similar studies done by Samarkandi et al., Ionescu et al., and Acil et al. compared the effects of melatonin, midazolam with placebo, found that anxiolysis is better in melatonin and midazolam group when compared with placebo [12,15,16]. Naguib et al. and Caumo et al. compared the effects of melatonin that of a placebo [3,5,17]. These studies also showed good anxiolytic effect of melatonin preoperatively when compared to placebo. The timing of anxiety assessment varied among the trials but a statistically significant difference in anxiety score was evident at different points of time in the melatonin group. Several other studies reported that melatonin was useful for reducing anxiety prior to surgery, presumably due to its sedative effect [14,18,19]. However, other studies were unable to confirm these results. Similarly, in anxious children oral 0.5 mg/kg melatonin premedication was similar to placebo for sedation during dental treatment [20]. In a more recent study it was shown that oral melatonin given to children before surgery in doses up to 0.4mg/kg was less effective than oral midazolam in reducing preoperative anxiety [21]. Methodological variability may have limited the validity of these studies. These include discrepancies in the time of day in which the studies were performed, the lack of valid evaluative tools for anxiety and variability in the bioavailability of the formulations used. However, when compared to placebo, melatonin given as premedication can reduce preoperative anxiety in adults when measured 50 to 100 mins after administration [22].

To assess the degree of sedation between the melatonin and placebo group, we used the sedation scale similar to the scale which was used by Naguib et al and Acil et al. We found that the sedation scores in two groups i.e. melatonin and placebo group before and after premedication were statistically significant at 30 min ($p < 0.001$) and 60 min ($p <0.001$) after premedication [3,16]. This outcome was in contrast to studies by Isik et al. where they did not find any significant sedative effect of melatonin when compared to placebo [20]. Radwan et al. compared the impact of premedication of melatonin and

gabapentin on postoperative pain and analgesic requirements found that sedation scores were significantly higher in melatonin group compared to both gabapentin and control groups up to 20 hours postoperatively [23].

Our study showed that melatonin produced enough sedation which would calm the patient and induce a natural sleep. Similar studies compared sedation levels after premedication with melatonin, midazolam, or placebo. Increased levels of sedation in the melatonin and midazolam group versus 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 [4]. In a study done by Acil et al., 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 [21].

In our study, we used a similar scale for orientation score which was used by Naguib et al. [4] We found that there was no change in orientation scores in melatonin and placebo group before and after giving premedication. Four studies assessed the orientation scores with respect to time and place at multiple times during the study period among the intervention and placebo groups. In two studies, i.e. Naguib et al. and Acil et al. the orientation scores were similar in the melatonin, midazolam, and placebo groups except at 30 min after premedication when the midazolam group exhibited significant disorientation ($p<0.05$) [4,20]. In another study by Naguib et al., all patients remained oriented in time and place at all times except at 15 min after surgery when both intervention groups illustrated significant disorientation compared with the placebo group [14]. However, no statistically significant difference was observed in the orientation score between the melatonin and placebo group. Since patients knew that they were receiving a medication to allay anxiety preoperatively there would have been a possible effect. To eliminate this confounding factor we included a control group which received a placebo.

The limitation of our study are, cases done under general anesthesia for all types of surgeries have been included leading to probability of bias. Plasma levels of melatonin were not measured. Psychomotor and cognitive functions were not assessed in the postoperative period; quality of recovery could have helped in suggesting its use in ambulatory or day care surgeries.

Conclusion

From the present study conducted on 80 patients under general anaesthesia, we conclude that compared to placebo, melatonin 6 mg given 60 min before surgery as a premedicant significantly reduced the induction dose of thiopentone sodium and provided better anxiolysis and sedation without affecting orientation.

Key Messages

Melatonin 6mg used as a premedication decreases the requirement of thiopentone sodium and provided better anxiolysis, sedation without affecting orientation.

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