ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 05 | May - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EFFECT OF MELATONIN ON DOSE RESPONSE OF PROPOFOL FOR INDUCTION OF GENERAL ANAESTHESIA USING BISPECTRAL INDEX MONITOR

Anaesthesiology

Prasad M Senior Resident, Department of Anaesthesiology, Chettinad Hospital and Research Institute

Mathews L Professor, Department of Anaesthesiology, Chettinad Hospital and Research Institute

Ravindran K Professor, Department of Anaesthesiology, Chettinad Hospital and Research Institute

ABSTRACT

Background and Aims: Anaesthesia is a balance between anaesthetic drug requirement and state of arousal of patient. Premedication has been found to decrease the requirement of intravenous anaesthetic agents like propofol for induction of anaesthesia. This study was designed to study the effect of oral melatonin on dose response of propofol used for induction of general anaesthesia, using Bispectral Index(BIS). **Material and Methods:** The study included 54 patients who were admitted for elective surgeries under general anaesthesia. Patients were randomized into two groups to receive tablet melatonin 6 mg or placebo 100 minutes prior to induction. At 100 minutes all the patients were induced with intravenous propofol at the rate of 4ml (40 mg/min) with Bispectral Index monitoring. Induction was stopped when BIS score reached 45. The total dose of propofol required to achieve BIS score of 45 was recorded. Heart rate and blood pressure were compared between two groups. **Results:** The parameters obtained was analysed using chi-square test, shapirowik test, unpaired sample t test and pearson correlation. The total propofol dose to achieve BIS score of 45 and heart rate (HR) and mean arterial pressure (MAP) were comparable. The total dose of propofol to achieve BIS of 45 was less in melatonin group with a statistical significance ($P<0.05$). There was a minimal change in hemodynamic parameters in the two groups without statistical significance ($P>0.05$). **Conclusion:** Melatonin premedication decreases the dose requirement of propofol required for induction without affecting haemodynamic stability.

KEYWORDS

Melatonin, Propofol, Bispectral Index, Hemodynamic parameters.

INTRODUCTION

Anaesthesia is a balance between anaesthetic drug requirement and state of arousal of patient. Inadequate doses lead to increased incidence of awareness, while generous administration of drugs leads to hemodynamic instability, delayed recovery, and increase other complications.[1] The primary goal of premedication is to relieve anxiety and produce sedation. Melatonin is a hormone secreted by pineal gland and has sleep promoting functions in humans.[2] Melatonin has been used a premedication to relive anxiety. decrease delirium, attenuation of hemodynamic response to laryngoscopy and tracheal intubation. Melatonin premedication has been helpful in the reduction of induction dose of intravenous anaesthetic agent.[2,3,4,5,6,7,8] In the absence of central nervous system monitoring, hypnotic agents are traditionally administered on the basis of fixed dose regimen adjusted to the response of patient judged by clinical parameters including loss of verbal response.[1]Bispectral index (BIS) monitor is used to monitor hypnosis and depth of anaesthesia. The BIS monitor processes a single frontal electroencephalographic signal to calculate a dimensionless number that provides a measure of patient's level of consciousness. BIS values range from 100 to 0, reflecting the awake state and the absence of brain activity.

Targeting a range of BIS values between 40 and 60 is advocated to prevent anaesthesia awareness while allowing a reduction in the administration of anaesthetic agents.[9]The primary objective was to evaluate the effect of oral melatonin on induction dose requirement of Propofol during induction of anaesthesia by means of Bispectral Index and compare with the placebo group. The secondary objective was to compare heart rate and blood pressure between two groups melatonin and placebo group.

METHODOLOGY

After Institutional Human Ethics Committee and written informed consent, 54 patients undergoing elective surgeries were included in the study. Patients assessed as American society of Anaesthesiologist (ASA) grade III & IV, cardiac, renal, hepatic, neurological disorders or any serious medical condition that would interfere with the electroencephalogram (EEG) interpretation, known hypersensitivity to Propofol or melatonin, pregnant women and body weight below 50 kg or above 90 kg were excluded. The sample size was calculated based on a previous observation made by A. Turkistani et al, by taking 95% confident interval (alpha=0.05, 80% power) and by using a software (Ref: Clinical software version 2018, by clinical LLC. available from Clinical com) the sample size derived was 27 per group. Selected 54 patients were randomly divided into two groups (27 in each group) using a computer-generated randomization code.

Group I ~ (n=27) Premedication with oral melatonin 6mg (3mg x 2 tablets), induction with intravenous anaesthetic agent Propofol (1% w/v, Baxter) with titration according to Bispectral index.

Group II~ (n=27) Premedication with placebo (2 multi vitamin tablets) and induction with intravenous anaesthetic agent Propofol (1% w/v, Baxter) with titration according to Bispectral index.

The study was registered in clinical trials registry – India (CTRI) on 02-07-2019. CTRI Registration no: CTRI/2019/07/019998 The study duration was 1 year from 10-7-2019 to 05-06-2020. The study was conducted in Chennai, Tamilnadu.

The study drug Melatonin 6mg (3mg x2) tablets and placebo (2 multivitamin tablets) were packed into similar looking sealed packets labelled with randomisation code generated by the software. The study drug was administered by the ward nurse.

All patients underwent routine pre-operative assessment in the preanesthetic clinic on the day before surgery. The patients enrolled in the study were premedicated with Tab Ranitidine 150 mg and Tab Alprazolam 0.5 mg on the night before surgery. They were advised fasting of eight hours for solid foods and 2 hours for oral clear fluids prior to surgery.

On the day of surgery, the study tablet was opened from the sealed packing and given 100 mins before induction by the ward nurse. Patient was asked to take the drug with a few sips of water. On arrival to the operating room, an intravenous line was established. Standard monitoring included electrocardiogram (ECG), non-invasive blood pressure (NIBP) measurement, heart rate (HR), pulse oximetry (SaO2) and capnography (ETCO2). In addition bispectral index (BIS) monitor (BIS version 3.2, Aspect Medical Systems Inc., Newton, MA, USA) was placed before induction of anaesthesia.

After preoxygenation, at the start of induction heart rate, blood pressure, SaO2 and BIS was noted. An anaesthesiologist who was blinded to the study injected Propofol (1% w/v, Baxter)10mg (1ml) over 5seconds every 15seconds at the rate of 40 mg (4ml) per minute until the BIS score reached 45.

The total dose of propofol required was recorded. Heart rate and blood pressure was recorded when the BIS value reached 45. Loss of response to verbal commands was also recorded before administration of opioids or neuromuscular blocking agents. At the end of procedure the patients were shifted to the post anaesthesia care unit (PACU) with

stable vitals, where they received standard care of monitoring for twenty-four hours and then shifted to ward in a stable hemodynamic condition.

Statistical Analysis

A total of 54 patients were included in analysis. They were divided in 2 groups of 54 each. The statistical data was entered in MS-Excel and imported to SPSS 20.0 version for statistical analysis. Chi-square test/Fisher's exact test was used to find out the difference between two groups' proportionate values. Shapiro wilk test and box-whisker plot were used to find whether the empirical data followed normal distribution or not as parametric statistical tests are considered valid if the data followed normal distribution. Unpaired sample t test was used to compare the two-group data which was collected from different individuals. Paired sample t test was used to compare the two-group data which was collected from same individuals at two different states. Pearson correlation analysis was used to find the linear relationship between two continuous data. 5% level of significance was considered statistically significant.

Table 1 show the demographic details of patients. The statistical significance value of gender vs. treatment group (P=0.413>0.05), reveals that there was no significant difference in the male and female proportions among melatonin group and placebo group. The patients age and their weight were not different in both treatment groups. i.e.on an average patients' age was around 36 years old and weight around 65 kg.

Table 1: Demographic details of patients in Melatonin group and placebo group (orginal)

Demographic variables	Melatonin group (n=27)	Placebo group (n=27)	P-value
Gender			
Male	14 (52%)	11 (41%)	0.413
Female	13 (48%)	16 (59%)	
Age (yr) Mean±SD	35.89±12.03	37.81±12.78	0.571
Weight (kg) Mean±SD	65.11±9.08	65.15±9.67	0.988

***P>0.05, SD – standard deviation**

From the table 2, it is observed that no statistically significant difference was noticed in the heart rate among Melatonin group and Placebo group at the baseline (P>0.05). After induction of propofol to the patients in both groups, their heart rates were monitored at some time intervals. As per the 5% level of significance, there was no statistically significant difference in the heart rates among the Melatonin group patients and placebo group patients at 15 sec. to 210 sec. after the induction of Propofol.

Table 2: Test of normality for heart rate (original)

Heart Rate	Shapiro-Wilk		
	Statistic	df	P-value
HR-0 sec	.929	8	0.509
HR-15 sec	.926	8	0.483
HR-30 sec	.941	8	0.622
HR-45 sec	.952	8	0.733
HR-60 sec	.925	8	0.475
HR-75 sec	.837	8	0.070
HR-90 sec	.942	8	0.626
HR-105 sec	.885	8	0.210
HR-120 sec	.921	8	0.442
HR-135 sec	.923	8	0.458
HR-150 sec	.933	8	0.544
HR-165 sec	.906	8	0.326
HR-180 sec	.927	8	0.487
HR-195 sec	.930	8	0.518

***P>0.05, df – degrees of freedom, HR- heart rate,**

Based on Shapiro-wilk normality test, the empirical data of SBP, DBP and MAP were normally distributed (Refer Fig1). Since, almost all the statistical significance (P>0.05) values were more than 5% level of significance. Therefore, we could apply parametric statistical test to compare the blood pressure among Melatonin group and placebo group. Here, paired sample t test was used to compare the blood pressure of same individuals at different states in melatonin group as well as in the Placebo group. From the output of unpaired sample t test (table 3), it is concluded that both melatonin group and placebo group patients had the same level of SBP, DBP and MAP at the baseline (P>0.05). After the induction of propofol dose to reach BIS 45, patients' blood pressure were again observed. SBP, DBP and MAP of melatonin group patients had the similar level of blood pressures of placebo group patients.

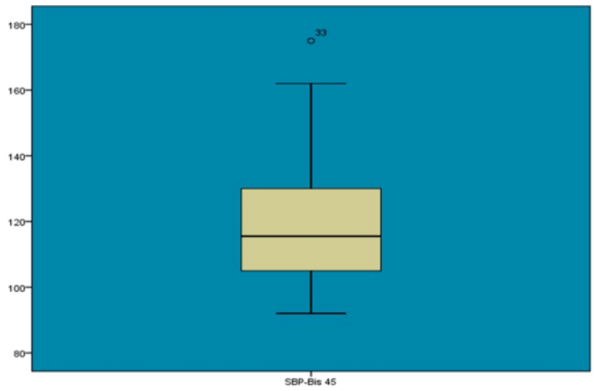

Figure 1- Box-whisker plot for SBP –BIS 45

Table 3: Difference in the Blood Pressure among Melatonin group and placebo group (original)

Blood pressure (mm hg)	Melatonin	placebo	t-value	P-value
	Mean±SD			
SBP - 0 sec	132.11±15.63	135.30±19.52	-0.662	0.511
SBP-BIS 45	120.93±16.82	116.15±17.49	1.023	0.311
DBP-0 sec	84.11±12.57	81.33±12.41	0.817	0.418
DBP-BIS 45	75.78±11.60	71.89±10.55	1.288	0.203
MAP-0 sec	101.30±11.86	99.56±13.84	0.496	0.622
MAP-BIS 45	91.15±11.73	86.78±12.31	1.335	0.188

***P>0.05, SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure.**

From the table 4 Propofol dose (mg) requirement to reach BIS 45 was compared between Melatonin group patients and Placebo group patients through unpaired t test. As per the 5% level of significance, there was a significant difference (p value- 0.001) in the required propofol dose to reach BIS 45 among melatonin group and placebo group. i.e., on an average, around 103 mg propofol dose was required to reach BIS 45 in melatonin group patients while 123 mg level was required in placebo group patients.

Table 4: Difference in the Propofol dose level between Melatonin group subjects and placebo group subjects (original)

	Melatonin	Placebo	t-value	P-value
	Mean±SD			
Propofol Dose (mg)	102.59±18.52	122.96±19.96	-3.887	0.001*

***P value – 0.001, SD - Standard deviation.**

Response to the verbal commands was compared between Melatonin group patients and placebo group patients using chi-square test / Fisher's exact test. After induction of propofol to the patients in both groups, their response to the verbal commands monitored frequently. All Melatonin group patients and placebo group patients had responded to the verbal commands from baseline to 75 sec after the induction of Propofol (table 5). As per the 5% level of significance, there was no statistically significant difference in the response to the verbal commands among the Melatonin group patients and placebo group patients at 90 sec. after the induction of Propofol (P>0.05). But, there was a significant changes in the proportions of response to the verbal commands among the melatonin group patients compared with the placebo group patients at 105 sec. after the induction of Propofol (P<0.05). ie., The majority of the melatonin group patients did not response to the verbal commands after the Propofol induction.

In addition, all the melatonin group patients did not response to the verbal commands within 135 sec after the Propofol induction while 27% placebo group patients responded to the verbal commands. Therefore, Propofol along with melatonin significantly reduces the

response to the verbal commands compared with propofol with placebo.

Table 5-Comparing the response to verbal commands among Melatonin group and placebo group

Time	Verbal commands	Melatonin	placebo	Fisher's exact P-value
0 sec	Present	27 (100%)	27 (100%)	-
15 sec	Present	27 (100%)	27 (100%)	-
30 sec	Present	27 (100%)	27 (100%)	-
45 sec	Present	27 (100%)	27 (100%)	-
60 sec	Present	27 (100%)	27 (100%)	-
75 sec	Present	27 (100%)	27 (100%)	-
90 sec	Present	25 (93%)	26 (96%)	1.000
	Absent	2 (7%)	1 (4%)	
105 sec	Present	15 (60%)	23 (88%)	0.020*
	Absent	10 (40%)	3 (12%)	
120 sec	Present	5 (33%)	14 (61%)	0.097
	Absent	10 (67%)	9 (39%)	
135 sec	Present	0 (0%)	3 (27%)	0.214
	Absent	5 (100%)	11 (73%)	
150 sec	Present	-	1 (33%)	-
	Absent	-	2 (67%)	
165 sec	Absent	-	1 (100%)	-

On the basis of Fig.2, the empirical propofol dose for loss of verbal commands data was approximately normally distributed. Since, the middle line which is in the box-whisker plot, segregate the entire Propofol data into approximately two equal portions. Hence, we applied parametric statistical test to find the difference in the level of propofol dose for loss of verbal commands between Melatonin group subjects and placebo group subjects. Propofol dose (mg) requirement to loss verbal commands was compared between Melatonin group patients and placebo group patients through unpaired t test. As per the 5% level of significance (table 6), there was a significant difference in the required propofol dose to loss verbal commands among melatonin group and placebo group. i.e., on an average, around 77 mg propofol dose was required to loss verbal commands in melatonin group patients while 85 mg level was required in placebo group patients.

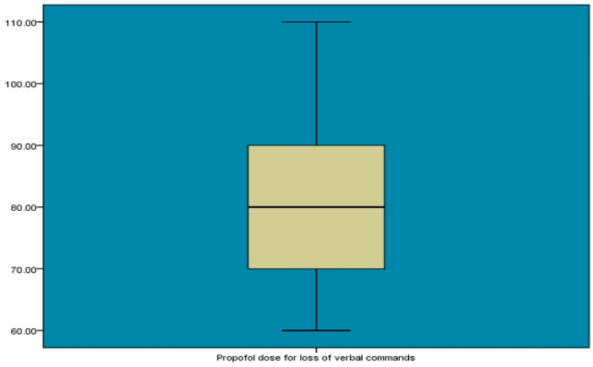

Figure 2- Box-whisker plot for Propofol dose level for loss of verbal commands

Table 6 - Difference in the Propofol dose level for loss of verbal commands between Melatonin group subjects and placebo group subjects

	Melatonin	Placebo	t-value	P-value
	Mean±SD			
Propofol dose level for loss of verbal commands (mg)	76.67±8.77	84.81±10.51	-3.092	0.003

*P<0.003, SD – standard deviation, mg - milligram

DISCUSSION

Many studies have been conducted to evaluate the effect of premedication on the induction and maintenance dose of propofol in both animals and humans using different endpoints.[10,11,12] Our present study aimed at assessing the role of melatonin as premedication and its effects on intravenous propofol used for induction of anaesthesia using bispectral index.

Melatonin when administered orally has sedative and hypnotic effects. Through its action on melatonin receptors (MT1 and MT2) it modulates gamma-aminobutyric acid (GABA-A) receptors in the brain and cause sedative effects. Melatonin by binding to MT1 receptor appears to affect the GABA A receptor through G-coupled protein pathway and enhance the binding of GABA to GABA-A receptor similar to other anaesthetic drugs such as propofol and benzodiazepines.[13,14,15,16]

The demographic data of both the groups were comparable in terms of mean values of age, gender and weight. The hemodynamic parameters such as heart rate, blood pressure and mean arterial pressure were comparable in between two groups.

Sivakumar S et al in a study found that oral melatonin 0.2 mg/kg given as premedication reduced the induction dose of thiopentone.[8] Hence we presumed that melatonin may have a role in reducing the dose requirement of propofol. The peak effect of exogenous melatonin ranges from 60-150 min.[17]Turkistani.A et al, in a study gave oral melatonin 100 minutes before induction of anaesthesia and found to have effects on anaesthetic dose[7]. Gupta P in a study found that oral melatonin at a dose of 6 mg given 120 min before induction of induction of anaesthesia was found effective in attenuating cardiovascular responses to laryngoscopy and endotracheal intubation[18] Hence, we presumed that administrating melatonin orally 100 min before induction might reduce the dose requirement of propofol. Kain et al used oral melatonin in a maximum dose of 0.4 mg/kg without any major side effects.[19] In a study conducted by Sivakumar et al oral melatonin 6 mg was given 120 min before induction safely without any side effects and it also attenuated cardiovascular responses to laryngoscopy and intubation.[8]Turkistani A premedicated patients with either 3mg or 5 mg oral melatonin without any reported side effects. However in patients who received 5 mg the requirement of induction dose was much lesser when compared with the group that received 3mg.[7] As melatonin was available in a dose of 3 mg, we decided to administer oral melatonin at a dose of 6 mg (2 tablets) 100 minutes before induction of anaesthesia.

The Bispectral index (BIS) monitor is a proprietary algorithm that translates electroencephalographic data into a numerical value, 100 (awake) to 0 (isoelectric encephalogram). BIS has been a reliable indicator for assessing level of sedation, loss of consciousness and recall.[20,21,22] Glass and colleagues concluded that BIS values less than 50 indicated an adequate depth of anaesthesia for clinically used anaesthetic agents.[23] Lallemand and colleagues in a study used etomidate for induction to see BIS changes to orotracheal intubation and found out that a BIS value less than 50 was associated with the absence of purposeful movements.[24]In a study conducted by Turkistani A end point of induction was correlated to BIS value of 45.[7] Hence we used BIS value of 45 as a reference point for end of induction of anaesthesia.

Propofol is the most used intravenous anaesthetic agent for induction. Propofol has a lag time to full effect of 90s, which can become shorter when propofol is administered slowly. In humans the optimal rate of injection was suggested as 50 mg/min.[25]Shah K N in a study found that when propofol was given as a bolus dose of 2 mg/kg I V, it caused a decrease in mean arterial pressure by 19% and 17% when compare with the titration group which was 5% and 4%. They also found that titration of propofol reduces hemodynamic changes, dose requirement and achieve same level of BIS as bolus dose.[26]In a study conducted by Turkistani A propofol administered intravenously at the rate of 30 mg/min achieved BIS value of 45. In our study propofol was a administered at the rate of 40 mg/min till the BIS score was 45.

The primary outcome in our study were effect of oral melatonin (6mg) in the dose requirement of propofol for induction of general anaesthesia using bispectral index. In our study propofol was a administered at the rate of 40 mg/min till the BIS score was 45. We found that mean ± SD induction dose of propofol to achieve BIS score of 45 was102.59 ±18.52 in the group that received oral melatonin(6 mg) whereas in the placebo group it was 122.96±19.96 (p<0.01). We also found that the dose requirement of propofol to achieve loss of

verbal response was less in melatonin group when compared with the placebo group which was statistically significant ($p<0.01$). Our study findings was similar to the study conducted by Turkistani A, where they found that oral melatonin when given at a dose of 3 mg or 5 mg reduced the required dose of propofol to achieve a BIS score of 45 when compared with the placebo and also the dose of propofol that resulted in loss of response to verbal commands was less in melatonin group when compared with the placebo group.[7] However in our study we did not compare two different doses of melatonin.

The secondary outcome in our study were to compare the hemodynamic parameters such as heart rate and blood pressure in between melatonin and the placebo group at the end of induction. We found no significant difference in heart rate between two groups. However, we found that the even though the decrease in MAP was less in melatonin group compared with the placebo, it was not statistically significant ($p>0.05$).

The limitations in our study were that we used standard dose of oral melatonin (6 mg) for all patients. We were not able to compare with a large sample size. Further we did not compare the two different doses of melatonin. We also did not assess the anxiety score in these patients. Our study also did not include paediatric population. Further studies should consider these limitations. Future studies are required to assess the different doses of melatonin on requirement of intravenous anaesthetic patients.

CONCLUSION:

The main finding of the study was that melatonin premedication reduced the dose requirement of propofol to achieve BIS score of 45 ensuring adequate hypnosis. It also helped in reducing the dose of propofol to achieve loss of verbal response. Melatonin premedication helped in reducing the induction dose requirement of propofol without significantly changing the haemodynamic parameters. Therefore, melatonin premedication along with titration of propofol with BIS monitoring reduces the dose requirement of Propofol to achieve adequate depth of anaesthesia

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