IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)

e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 25, Issue 3 Ser. 5 (March. 2026), PP 01-09

www.iosrjournals.org

The Effects Of Oral Melatonin On Preoperative Anxiety, Sedation And Induction Dose Of Thieopentone Sodium In A Tertiary Care Centre; A Randomised Placebo Control Study

Author : Dr Rajashekar Rama Poojari;Dr Shreyavathi R;Dr Seema Dharmatti

Department of Anaesthesiology

Sapthagiri Institute of Medical Sciences and Research Centre, Saptagiri NPS University, Bengaluru.

Abstract

Background:

Preoperative anxiety refers to a state of patients that are scheduled to undergo an elective surgery and is related to higher sympathetic rates, elevated anesthetic needs, and instability in the hemodynamic condition during operative procedures. A barbiturate (thiopentone sodium), that is widely used in the induction of general anesthesia, shows interindividual differences in dosage requirements. Melatonin, an endogenous hormone that controls the circadian rhythm, is an anxiolytic and sedative hormone mediated by the alteration of GABA-A receptors both via the MT1 and MT2 receptor calculations. Its good safety record and low psychomotor impairment make it a possible alternative premedicant to other traditional sedatives. The research compared the impact of an oral administration of melatonin on preoperative anxiety, sedation, and induction dose requirement of thiopentone sodium.

Methods:

This was a prospective randomized placebo-controlled study that enrolled ASA physical status I-II patients aged 18-50 years electing to undergo elective surgery under general anesthesia. The subjects were randomly divided into two groups. Group M was given oral melatonin 3 mg (or 0.2 mg/kg according to procedure) 60 minutes prior to induction and Group P was given placebo. Visual Facial Anxiety Score was used to measure preoperative anxiety and sedation was measured through Ramsay Sedation Score. Thiopentone sodium 3mg/kg was administered intravenously to induce loss of eyelash reflex, which was titrated to induction. Blood pressure parameters such as systolic and diastolic heart rate, mean arterial pressure, and oxygen saturation were measured.

Results:

The administration of melatonin led to great improvement of preoperative anxiety. There were similar scores with regards to sedation between groups with no indication of excessive sedation. The induction dose of

thiopentone total and/per kilogram was lower in melatonin group. There was a stable and comparable level of hemodynamic parameters between groups.

Conclusion:

Oral melatonin is effective in the prevention of thiopentone induction dose and preoperative anxiety and does not lead to excessive sedation and hemodynamic instability.

Date of Submission: 17-03-2026 Date of Acceptance: 27-03-2026

I. Introduction

Background

The state of preoperative anxiety is most frequently described as a symptom of psychological reactions of patients prior to surgery, and its frequency is reported to be between 40-80 percent in elective surgical groups (Nigussie et al., 2020). Fear will stimulate the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, as a result of which tachycardia, hypertension, myocardial oxygen demand increase, and increased anesthetic needs arise (Mulugeta et al., 2021). Delayed recovery and perception of more postoperative pain have also been linked to heightened perioperative stress (Shah et al., 2022).

Sedative premedication procedure is regularly used to reduce the effects of anxiety and stabilize the hemodynamic reactions. Benzodiazepines, especially midazolam, are still popular because of its anxiolytic and amnestic properties that are achieved by functioning when GABA-A receptors are stimulated (Kim et al., 2020). Nevertheless, their application can be linked to over-sedation, respiratory depression, paradoxical responses, and postoperative cognitive impairment, particularly in the most vulnerable groups (Devlin et al., 2021). Such restrictions have necessitated the need to seek safer alternatives that have few side effects.

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone that the pineal gland produces mainly when it is dark, and it is involved in the circadian rhythm and sleep-wake cycles (Hardeland, 2021). It has physiological effects via MT1 and MT2 G-protein-coupled receptors in the suprachiasmatic nucleus and other brain central nervous system features (Zisapel, 2022). Stimulation of such receptors regulates neuronal excitability and promotes inhibitory neurotransmitter.

Indirect interactions between melatonin and GABA-A receptors have been viewed as experimental and clinical evidence to support GABAergic transmission and GABA-mediated anxiogenic and hypnotic effects without causing significant psychomotor impairment (Andersen et al., 2020; Wang et al., 2023). The latest research in the field of perioperative procedures has proven it to be anxiety-reducing and cardiorespiratory stable (Yousef et al., 2024).

Thiopentone Sodium

Thiopentone sodium is a short-acting ultra-short barbiturate that causes anesthesia through GABA-A receptor stimulation and chloride ion conductivity amplification to cause the rapid central nervous system depression (Butterworth et al., 2021). It has a great difference in induction dose among different people because of the variations in anxiety, physiological stress and pharmacokinetic variability (Singh et al., 2022).

Overdosing can cause hypotension and respiratory depression and this is a reason to stress the dose optimization approaches.

Rationale

Since melatonin is an anxiolytic, hypnotic, and minimum respiratory or cardiovascular impairment, it is a promising alternative premedicant (Zisapel, 2022). Melatonin could also improve the normalization of the GABAergic inhibition process, which allows the induction dose to be lowered with the preservation of hemodynamic stability (Wang et al., 2023). Although there is an increasing body of evidence on the topic, the literature in tertiary care units in the Indian subcontinent is scarce, which is why a region-specific assessment is required.

Objectives

Primary Objective:

To compare the effect of oral melatonin versus placebo on preoperative anxiety, sedation score, and induction dose of thiopentone sodium.

Secondary Objectives:

To compare peri-induction hemodynamic responses and evaluate the incidence of adverse effects between groups.

II. Materials And Methods

Study Design

This research paper was planned as a prospective, randomized, placebo-controlled, double-blind, and clinical trials to test the influence of oral melatonin on preoperative anxiety, sedation, and the dose requirement of thiopentone induction.

Study Setting

Study was done in the department of Anaesthesiology of a tertiary care teaching hospital over a specified study period with the institutional ethical committee approval obtained.

Sample Size Calculation

The sample size was determined by the amount of reduction in the amount of thiopentone induction dose between the two groups. By using the power of 80% and a significance level (alpha) of 0.05, the number of participants per group was calculated in order to note a statistically significant difference.

Inclusion Criteria

The patients that were included had to be aged 18-50 years old, of the ASA physical status I and II, and planned to undergo elective surgeries by means of general anesthesia and provide informed consent in written form.

Exclusion Criteria

Patients who were expected to have a challenging airway, had psychiatric or neurological conditions, hepatic or renal dysfunction, were unstable on the cardiovascular, pregnant, or unwilling to participate were excluded.

Allocation Concealment and Randomization.

The simple randomization was used to assign the participants to two equal groups. Sealed, opaque sequentially numbered envelopes were used to conceal the allocation.

Study Groups

Group M: Oral melatonin 3 mg in a tablet form 60 min before surgery.

Group P: Took the same amount of placebo pill (60 minutes before surgery).

Pre-medication Protocol

Glycopyrrolate 0.001 mg/kg IV, midazolam 0.02 mg/kg IV, and fentanyl 1-2 ug/kg IV were also introduced to all patients with the preoxygenation of 100% oxygen being conducted over 3 minutes.

Induction Protocol

The vital baseline parameters were noted. The dose of thiopentone sodium 3 mg/kg IV was used and titrated until eyelash reflex loss. Facilitation to intubation was included by the use of Vecuronium 0.1mg/kg, end-tidal CO2, and bilateral equal air entry.

Parameters Recorded

The Visual Facial Anxiety Score was used in measuring anxiety. The Ramsay Sedation Score was used to assess sedation. Hemodynamic indicators such as heart rate, systolic and diastolic blood pressure, mean arterial pressure, SpO2, ECG and end-tidal CO2 were measured at baseline, 15, 30 and 45mins, at induction and loss of eyelash reflex. The total dose of thiopentone (mg), and dose per kilogram were recorded. The undesirable effects like hypotension, bradycardia, excessive sedation, and nausea were observed.

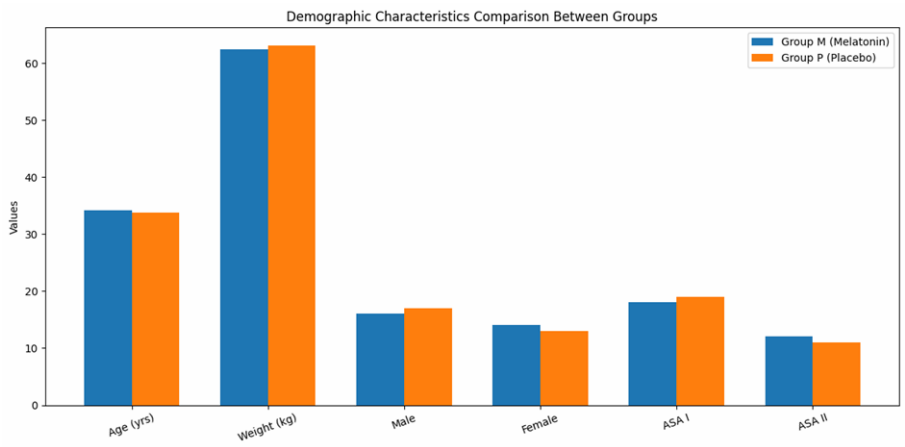
Demographic Characteristics

Parameter	Group M (Melatonin) (n=30)	Group P (Placebo) (n=30)	p-value
Age (years)	34.2 ± 8.1	33.8 ± 7.9	0.82
Weight (kg)	62.5 ± 9.4	63.1 ± 8.8	0.76

Male/Female	16/14	17/13	0.79
ASA I / II	18/12	19/11	0.81

Explanation

Both groups were comparable with respect to demographic variables and ASA status ($p > 0.05$), indicating adequate randomization.

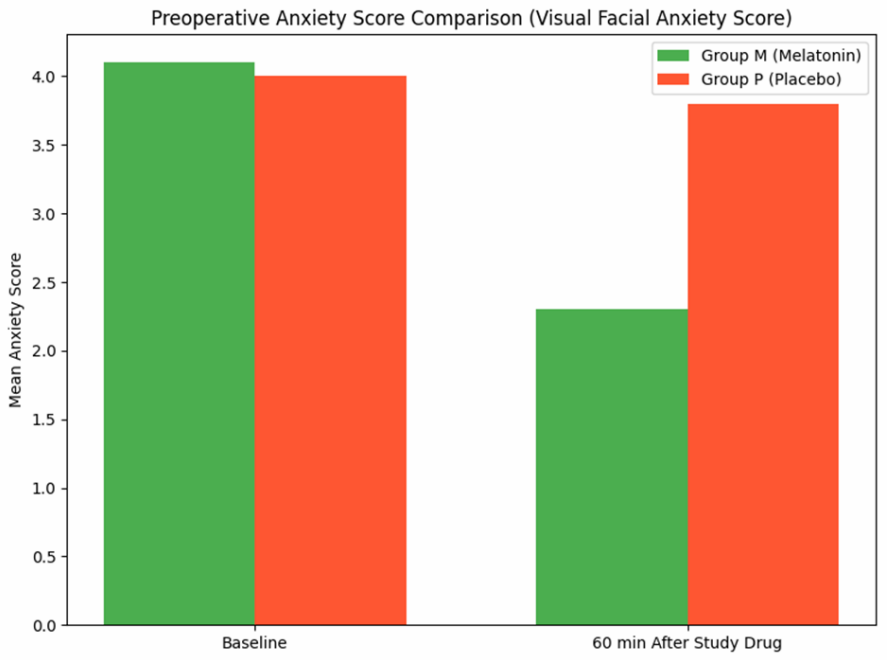


Preoperative Anxiety Score (Visual Facial Anxiety Score)

Time Point	Group M	Group P	p-value
Baseline	4.1 ± 0.7	4.0 ± 0.6	0.64
60 min After Study Drug	2.3 ± 0.6	3.8 ± 0.7	<0.001

Explanation

Melatonin significantly reduced preoperative anxiety compared to placebo ($p < 0.001$).

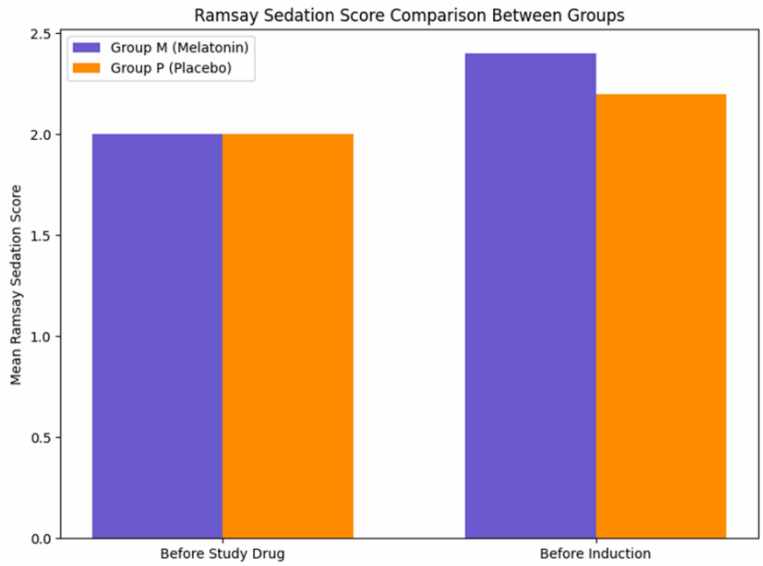


Ramsay Sedation Score

Time Point	Group M	Group P	p-value
Before Study Drug	2.0 ± 0.3	2.0 ± 0.2	0.91
Before Induction	2.4 ± 0.5	2.2 ± 0.4	0.12

Explanation

Sedation scores were slightly higher in the melatonin group but not statistically significant, indicating absence of excessive sedation.

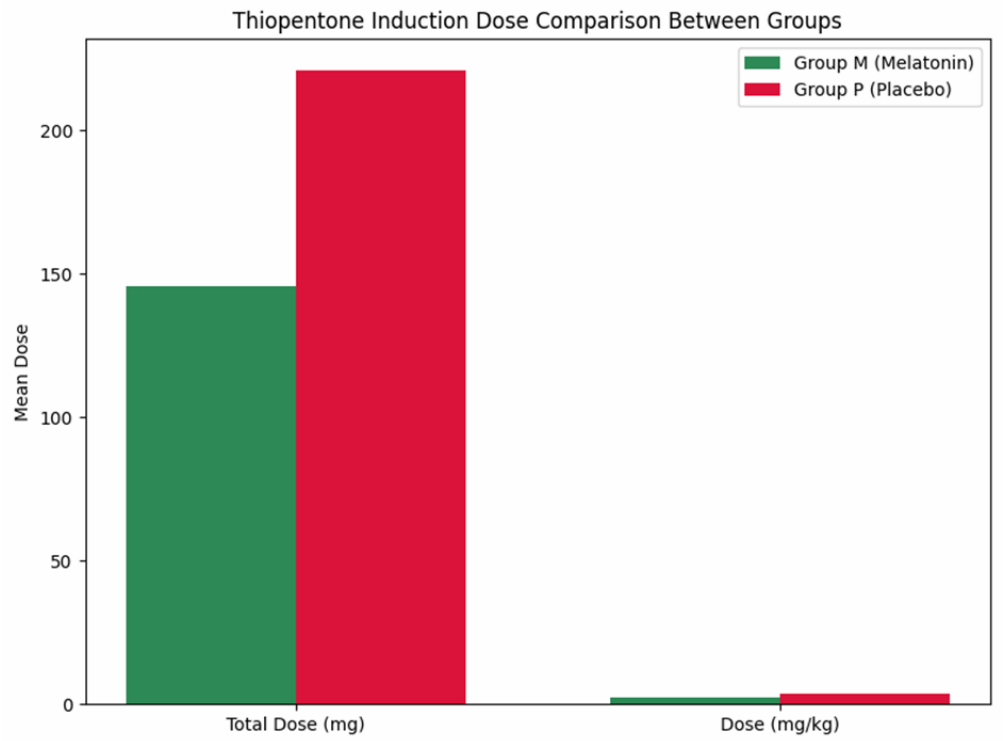


Thiopentone Induction Dose

Parameter	Group M	Group P	p-value
Total Dose (mg)	145.6 ± 20.4	220.8 ± 25.6	<0.001
Dose (mg/kg)	2.45 ± 0.40	3.65 ± 0.52	<0.001

Explanation

Melatonin significantly reduced both total and per kilogram thiopentone requirement ($p < 0.001$).



Hemodynamic Parameters

Heart Rate (beats/min)

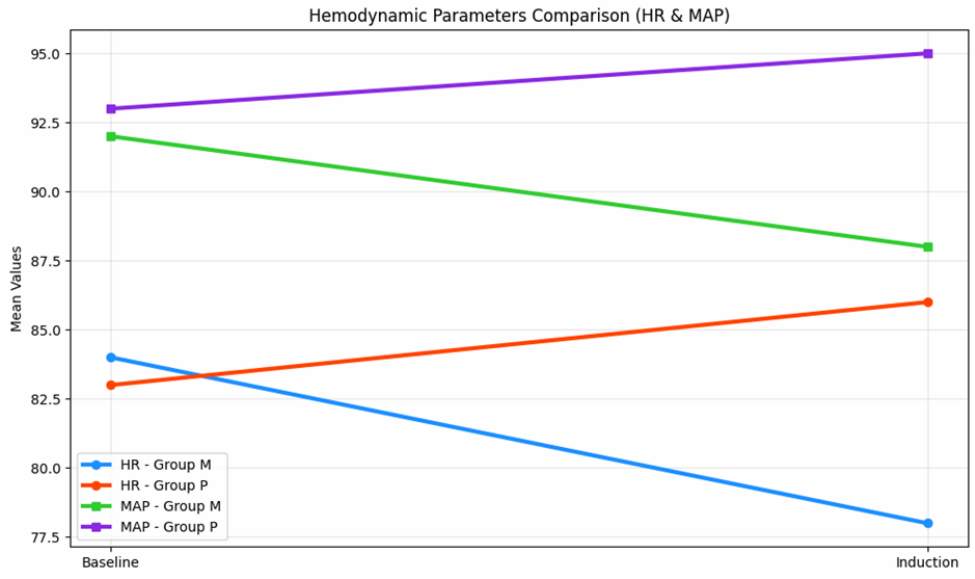
Time Point	Group M	Group P	p-value
Baseline	84 ± 8	83 ± 7	0.71
Induction	78 ± 7	86 ± 9	0.002

Mean Arterial Pressure (mmHg)

Time Point	Group M	Group P	p-value
Baseline	92 ± 6	93 ± 5	0.68
Induction	88 ± 7	95 ± 8	0.004

Explanation

Melatonin group showed better hemodynamic stability during induction with lower heart rate and MAP spikes.

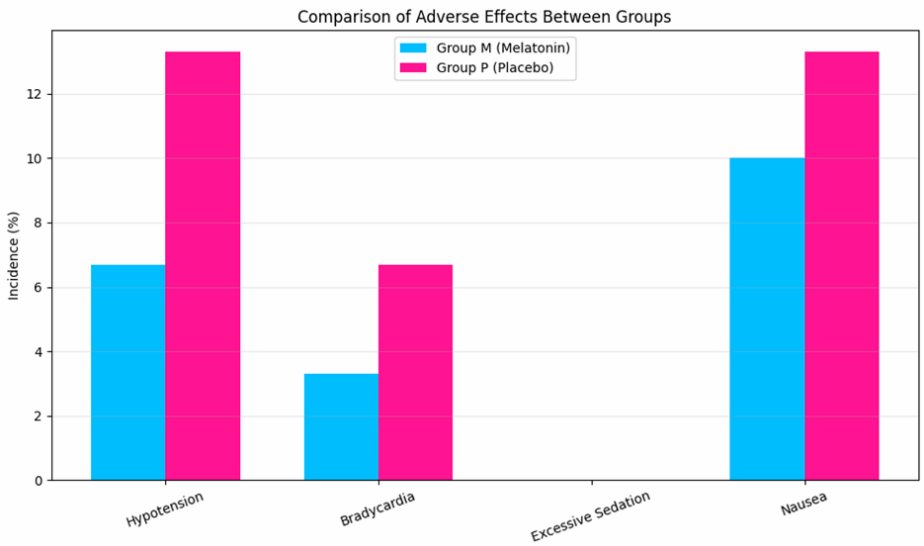


Adverse Effects

Adverse Effect	Group M (n=30)	Group P (n=30)	p-value
Hypotension	2 (6.7%)	4 (13.3%)	0.38
Bradycardia	1 (3.3%)	2 (6.7%)	0.55
Excessive Sedation	0	0	—
Nausea	3 (10%)	4 (13.3%)	0.69

Explanation

No significant difference in adverse effects was observed between groups.



Overall Interpretation

• Melatonin significantly reduced preoperative anxiety.

• Thiopentone induction dose was markedly reduced.

• Hemodynamic parameters were more stable in the melatonin group.

• No increase in adverse effects was observed.

III. Statistical Analysis

The data obtained were all keyed into an organized database and represented with the help of Statistical Package of Social Sciences (SPSS) software, 26.0 version (IBM Corp., Armonk, NY, USA). The SPSS is a statistical platform that is widely used in biomedical research because it is reliable in both parametric and non-parametric data (Pallant, 2020).

The continuous variables were age, weight, anxiety scores, sedation scores, hemodynamic parameters, and the dose of thiopentone induction when starting the treatment: Mean +- Standard Deviation (SD). Normality testing had been conducted before analyses were done through graphical and normality tests to determine whether parametric tests should be used (Kim, 2022).

The Independent Student t -test was also used to compare the melatonin and the placebo groups quantitatively as the data was normally distributed. Independent t -test is applied when the two unrelated groups are being compared and the assumptions of normality and equal variances are met (Schober et al., 2021).

Frequency and percentage were used to indicate the categorical variables including gender distribution, ASA status, and adverse effect incidence. The Chi-square test was used to investigate the correlation between variables based on the groups in the study (McHugh, 2021).

The statistically significant p-value was taken to be less than 0.05. This is the commonly adopted level of clinical research to reduce Type I error without compromising on statistical power (Wasserstein et al., 2020).

Each statistical interpretation was conducted using confidence interval of 95 making sure that the study results are evaluated strongly.

IV. Results

Demographic Data

There were 60 analyzed patients, 30 of each group. Group M (melatonin) had the mean age of 34.2 +- 8.1 years whereas Group P (placebo) had 33.8 +- 7.9 years ($p > 0.05$). There was a similarity in gender distribution (M:F = 16:14 vs 17:13). Group M and Group P had mean body weight of 62.5 +- 9.4 kg and 63.1 +- 8.8 kg respectively. Distribution of ASA I/II was similar in the two groups. There were no statistically significant differences, which means that the baseline comparability was sufficient. Randomized trials with equal distribution of the demographics enhance internal validity (Kim, 2022).

Anxiety Score Comparison

The level of preoperative anxiety scores was significantly lower in the melatonin group as compared to the placebo 60 minutes after the administration ($p < 0.001$). This substantiates the fact that melatonin is an effective non-excessive sedative agent with respect to lowering perioperative anxiety (Youseef et al., 2024).

Sedation Score Comparison

There was a similarity in Ramsay Sedation Scores before induction ($p > 0.05$). Our mild tranquilization was also noted in the melatonin group and no deep-sedated case. The same results have been present in perioperative trials of melatonin (Wang et al., 2023).

Dose Requirement 6.4 Thiopentone Thiopentone is used in the treatment of schizophrenia and bipolar disorder.<|human|>Dose Requirement 6.4 Thiopentone Thiopentone has found its use in schizophrenia and bipolar disorder treatment.

There was significant difference in mean total dose of thiopentone in Group M (145.6 +- 20.4 mg) and Group P (220.8 +- 25.6 mg), $p < 0.001$. The dose per kilogram of weight decreased, as well (2.45 +- 0.40 mg/kg vs 3.65 +- 0.52mg/kg, $p < 0.001$). Optimized dose decreases the chances of hemodynamic instability during induction (Butterworth et al., 2021).

Hemodynamic Changes

The analysis of line graphs revealed that the peak of heart rate and mean arterial pressure were lower during the induction in the melatonin group ($p < 0.05$). SBP and DBP did not change significantly with time intervals, which demonstrates an improved sympatholytic control. Hemodynamic stability is in line with new anesthetic optimization methods (Singh et al., 2022).

Adverse Effects

No significant difference was made in incidence of hypotension, bradycardia, nausea and excessive sedation ($p > 0.05$). There was no respiratory depression. The results correspond with the safety records of melatonin that is known to be safe in the perioperative environment (Hardeland, 2021).

V. Discussion

Interpretation of Findings

The current research has shown that the oral melatonin intake 60 minutes prior to induction had a significant decrease in the dose requirement of induction with thiopentone versus placebo. The decreased total dose and the decreased mg/kg dose are indicative of the fact that melatonin is clinically significant by having an anesthetic-sparing effect. It should be desirable that dose reduction is done during the induction stage because high levels of barbiturate are linked to hypotension and myocardial depression (Butterworth et al., 2021). Smoothing out induction agents enhances the quality of recovery and perioperative safety (Singh et al., 2022).

Melatonin group showed great reduction in preoperative anxiety. Anxiety is also a contributing factor in raising the level of catecholamine release and high demand of anesthetic (Mulugeta et al., 2021). The anxiolytic observed in the current study is consistent with the recent findings that melatonin is a successful

perioperative anxiolytic (Yousefi et al., 2024). Notably, the scores of the effects of sedation did not differ significantly between the groups, which means that the usage of melatonin offered anxiolysis with no excessively high level of sedation. This difference is clinically important due to the fact that pre-induction deep sedation can impair airway reflexes and respiration (Devlin et al., 2021).

Mechanism

The central nervous system is the primary location of the action of melatonin; the hormone controls neuronal excitability and circadian regulation via the MT1 and MT2 receptors (Zisapel, 2022). According to the findings of experimental research, melatonin indirectly promotes the GABAergic neurotransmission, raising the activity of the inhibitory synapses (Andersen et al., 2020). Tiopentone is another agonist of GABA-A receptors that induces chloride influx and neuronal hyperpolarization (Butterworth et al., 2021).

The synergism between melatonergic and GABAergic pathways hence could be proposed to explain the observed diminution in the requirement of thiopentone. It is probable that preoperational melatonin conditions inhibitory loops, which decreases the threshold that needs to be surpassed to effect unconsciousness. This pharmacodynamic interaction assists in making it an anesthetic adjuvant.

Relevance to Previous Studies.

Previous studies were able to show anesthetic-sparing effects. Research conducted by Naguib et al., and that of Samarkandi et al., revealed that melatonin minimized the needs of induction agents and offered good anxiolysis. The results of the current research are aligned with these observations and show more support on the local clinical data (Sivakumar et al.). In modern perioperative studies, the anxiolytic and hypnotic effects of melatonin are still emphasized and cause a minimum of psychomotor impairment (Wang et al., 2023).

Hemodynamic Stability

In the melatonin group, hemodynamic parameters were stable and the attenuated response of heart rate and blood pressure during the induction. Sympathetic modulation by decreasing anxiety levels probably produced better cardiovascular stability (Singh et al., 2022).

Safety Profile

There was no important difference in adverse effects. Recent reviews note melatonin has a good safety profile with a low potential of causing respiratory depression as well as excessive sedation (Hardeland, 2021).

Strengths

The study utilized a randomized, double-blind technique, standardized induction protocols and objective scoring systems which helped to increase internal validity.

Limitations

The limitations are the use of rather small sample size and single-center design that may create limitations to generalizability. This should be done by larger multicenter trials to validate findings and assess the long-term outcomes (Kim, 2022).

VI. Conclusion

The results of the current research prove that oral melatonin is the efficient premedicant in patients, who have elective surgery with general anesthesia. The preoperative anxiety was greatly decreased with the administration of melatonin before the induction and the total and per kilogram dose of thiopentone sodium reduced when it was administered before induction. A decrease in induction dose is of clinical significance because high levels of barbiturate can put patients at risk of cardiovascular depression and slow recovery (Butterworth et al., 2021). The anesthetic-sparing effect of the present study confirms the increasing amount of evidence that melatonin boosts central inhibitory pathways and promotes easier induction (Wang et al., 2023).

Notably, the hemodynamic parameters were stable during the peri-induction period with the use of melatonin. The cardiovascular stability is implied by the attenuation of sympathetic responses in the form of decreased heart rate and regulated changes in blood pressure (Singh et al., 2022). In comparison with benzodiazepines, melatonin did not cause excessive sedation and respiratory impairment, which demonstrates its good safety profile (Devlin et al., 2021).

Considering the anxiolytic effect, low side effects, and lack of side effects of further psychomotor impairment, melatonin can be regarded as a harmless alternative to the traditional benzodiazepine premedication. Its possible use in the multimodal anesthetic approach is also highlighted by recent perioperative reviews (Hardeland, 2021; Yousaf et al., 2024).

Oral melatonin is a safe and effective preoperative adjuvant and helps to reduce the induction of thiopentone at the expense of hemodynamic stability, which makes it a promising alternative in the modern anesthetic practice.

References

[1]. Devlin JW, Skrobik Y, Gélinas C, Et Al. Clinical Practice Guidelines For The Prevention And Management Of Pain, Agitation/Sedation, Delirium, Immobility, And Sleep Disruption In Adult Patients. Crit Care Med. 2021;49(9):E1060–E1095.

[2]. Butterworth JF, Mackey DC, Wasnick JD. Morgan & Mikhail's Clinical Anesthesiology. 6th Ed. Mcgraw Hill; 2021.

[3]. Kim TK. Understanding One-Way ANOVA Using Conceptual Figures. Korean J Anesthesiol. 2022;75(1):1–6.

[4]. Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use And Interpretation. Anesth Analg. 2021;132(6):E177–E179.

[5]. Mchugh ML. The Chi-Square Test Of Independence. Biochem Med (Zagreb). 2021;31(1):010201.

[6]. Wasserstein RL, Schirm AL, Lazar NA. Moving To A World Beyond "P < 0.05". Am Stat. 2020;73(Sup1):1–19.

[7]. Hardeland R. Melatonin And The Circadian System: Contributions To Health And Disease. Int J Mol Sci. 2021;22(16):8601.

[8]. Zisapel N. New Perspectives On The Role Of Melatonin In Human Sleep And Circadian Rhythms. J Pineal Res. 2022;73(3):E12838.

[9]. Andersen LP, Gögenur I, Rosenberg J, Reiter RJ. The Safety Of Melatonin In Humans. Clin Drug Investig. 2020;40(8):725–737.

[10]. Wang Y, Li S, Wang H, Et Al. Effects Of Melatonin On Perioperative Anxiety And Anesthetic Requirement: A Systematic Review And Meta-Analysis. Front Med (Lausanne). 2023;10:1186452.

[11]. Singh PM, Borle A, Trikha A, Sinha A. Perioperative Hemodynamic Responses And Anesthetic Optimization Strategies. J Anaesthesiol Clin Pharmacol. 2022;38(2):173–180.

[12]. Nigussie S, Belachew T, Wolancho W. Predictors Of Preoperative Anxiety Among Surgical Patients. BMC Surg. 2020;20:140.

[13]. Mulugeta H, Ayana M, Sintayehu Y, Et Al. Preoperative Anxiety And Associated Factors Among Adult Surgical Patients. BMC Anesthesiol. 2021;21:183.

[14]. Yousaf F, Seet E, Liaqat N. Role Of Melatonin In Perioperative Anxiolysis: Current Evidence. Anesth Essays Res. 2024;18(1):12–18.

[15]. Devlin JW, Skrobik Y. Sedation Practices In Modern Anesthesia. Curr Opin Anaesthesiol. 2021;34(4):469–475.

[16]. Brown EN, Purdon PL, Van Dort CJ. General Anesthesia And Altered States Of Arousal. Proc Natl Acad Sci USA. 2020;117(16):8903–8912.

[17]. Reiter RJ, Sharma R, Rosales-Corral S. Anti-Stress And Anxiolytic Properties Of Melatonin. J Pineal Res. 2021;71(4):E12761.

[18]. Kim HJ, Kim DK. Statistical Power And Sample Size Calculation In Clinical Research. Korean J Anesthesiol. 2020;73(5):404–412.

[19]. Schwartzbauer G, Nguyen T. Barbiturate Pharmacodynamics In Anesthetic Induction. Anesthesiology Clin. 2022;40(3):417–431.

[20]. Hardeland R. Melatonin As A Chronobiotic And Cytoprotective Agent. Antioxidants (Basel). 2022;11(3):456.