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Original Research Article

Adjuvant effect of melatonin on anesthesia induced by thiopental sodium in human subjects

Sengottaian Sivakumar*, Bhavya Krishna

Department of Anesthesiology, Sri Ramachandra University, Chennai, Tamil Nadu, India

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***Correspondence:**
Dr. Sengottaian Sivakumar,
E-mail: sengottaian@yahoo.com

ABSTRACT

Background: Melatonin has unique properties of anxiolysis, hypnosis, and analgesia without impairing psychomotor skills. We studied the dose requirements of thiopentone for induction of general anesthesia following administration of oral melatonin compared to that of placebo.
Methods: The study is a prospective randomized double-blinded study conducted at Sri Ramachandra Medical College, which included 44 patients of ASA status I and II in the age group of 16 to 55 years who underwent elective surgical procedures under general anesthesia. Patients were randomly allocated to 2 groups by drawing lots. Group A received T. Melatonin 0.2mg/kg and Group B received placebo 120 minutes prior to induction of anesthesia. The baseline heart rate, blood pressure, Spo2 and Ramsay sedation score were noted down. After adequate preoxygenation, all patients received Injection Fentanyl 2 mcg/kg followed by Inj. Thiopentone 2.5% which was titrated to loss of eyelash reflex. The dose of thiopentone required was noted down in both the groups. Hemodynamic parameters (HR, Systolic and diastolic BP) were monitored prior to induction and every 3 minutes for the first 10 minutes.
Results: Both the groups were comparable with regard to age, weight and ASA status. Ramsay sedation score prior to induction of anesthesia was not significantly different in both the groups.
The mean dose of Thiopentone required in Group A (Melatonin) was 138.64±6.3 mg and 223.86±5.3 mg in Group B (Placebo) with P value 0.000. The mean per Kg dose requirement of Thiopentone in Group A was 2.54±0.64mg and 4.56±0.67mg in Group B (placebo) with P value 0.000. Hemodynamic parameters were similar in both the groups.
Conclusions: Administration of melatonin 0.2mg/kg body weight significantly reduced the induction dose of Thiopentone.

Keywords: Adults, General anesthesia, Melatonin, Surgery, Thiopentone

INTRODUCTION

Melatonin, a hormone involved in the diurnal rhythm of sleep, is a potentially useful oral natural-sleep agent and is available commercially.[1,2] In humans, melatonin ((5-methoxy-N-acetyltryptamine) is produced mainly by the pineal gland and, to a lesser extent, by the gastrointestinal tract and retina. These sites synthesize melatonin from the amino acid tryptophan, via the 5-hydroxyindole-O-methyl transferase enzyme pathway.[3] It is classed as a 'dietary supplement' by the United States Food and Drug Administration.[4]

Melatonin is a secretory product produced in the pineal gland and in several extra pineal sites, which has a wide variety of functions.[5,6] Exogenous melatonin has been used as a chronobiotic (to shift circadian phase), as an antioxidant, and as an unlike oncostatic agent. most

hypnotic medications, melatonin has minimal effects on psychomotor function.[7-11] Several different oral melatonin formulations have been developed, including immediate release, controlled (sustained) release and surge-sustained release.[12-17]

A large range of doses have been used in clinical trials, with considerable debate regarding the role of low dose (0.1-0.5 mg) and high dose (2-10 mg) melatonin. Past studies have found bioavailability of exogenous melatonin to be highly variable, ranging from 1 to 74%, though this broad range may indicate formulation and/or dose input dependence.[18-22] Endogenous melatonin is primarily metabolized in the liver by hydroxylation (approximately 90%) to 6-hydroxymelatonin and excreted in the urine following conjugation with sulfuric or glucuronic acid.[23,24] We designed a study to find the dose reductions of Thiopentone during induction of general anesthesia.

METHODS

With the Institute Ethics Committee's approval and informed consent from all patients, this prospective randomized parallel group study was carried out. The procedures followed were in accordance with the ethical standards of the Institutional Research Ethics Committee standards and with that of the Helsinki Declaration of 1975, as revised in 2000. Present study included 44 patients who underwent elective surgical procedures under general anesthesia. Patients were randomly allocated to 2 groups by drawing lots. Group A received oral Melatonin 0.2mg/kg and group B received placebo. Both the groups received medications 120 minutes prior to induction of anesthesia. The person who administered the drug did not participate in the preparation of the drug, thereby maintaining double blinding. Subjects who underwent elective surgeries under GA, ASA grade I & II status and 16-55 years of age were included in the study. Subjects who were ASA III or greater, age more than 55 years and less than 16 years, pregnant and lactating females, BMI >30, on any antipsychotic drugs, sleep disorders and/or severe renal or hepatic derangement were excluded from the study.

Hemodynamic parameters (HR, Systolic and diastolic BP) were monitored prior to administration of the drug, upon induction and every 3 minutes for the first 10 minutes. Ramsay sedation score was monitored before administering melatonin and before induction of anesthesia. After adequate preoxygenation, all patients received Inj. Fentanyl 2 mcg/kg followed by Inj. Thiopentone 2.5% which was titrated to loss of eyelash reflex. The dose of Thiopentone required was noted in both the groups.

Statistical analysis

The collected data were analyzed with SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). To describe about the data descriptive statistics, mean and SD were used.

RESULTS

Both the groups were comparable with regard to age, weight, height and ASA status. The mean dose of Thiopentone required for loss of eye lash reflex was 138.64±6.3 mg in Melatonin group and 223.86±5.3 mgs in placebo group respectively, with p value 0.000 (Table 1).

Table 1: Mean dose of thiopentone needed for loss of eye lash reflex.

Group	N	Mean	SD	Std. Error of Mean
Melatonin	22	138.64	29.608	6.312
Placebo	22	223.86	24.973	5.324

The mean per kg dose requirement of Thiopentone was 2.54±0.64 mgs in Melatonin group and 4.56±0.67 mgs in placebo group respectively, with p value 0.000 (Table 2).

Table 2: Mean Per Kg Dose requirement of thiopentone for loss of eye lash reflex.

Group	N	Mean	SD	Std. Error of Mean
Melatonin	22	2.548	0.65616	0.13989
Placebo	22	4.566	0.67904	0.14477

Ramsay sedation scores prior to induction of anesthesia and prior to administering melatonin were not significantly different in both the groups. Hemodynamic parameters were similar in both the groups during different time intervals except pre induction mean heart rate which was significantly less in melatonin group (Figure 1).

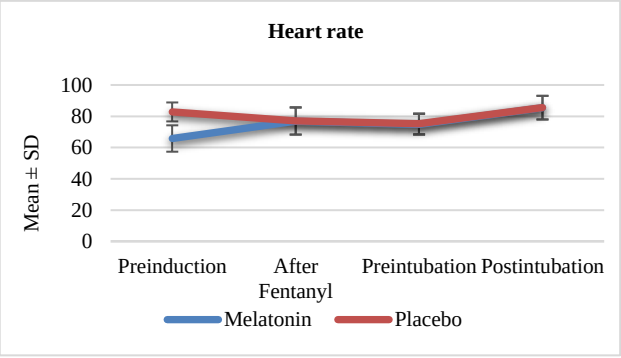

Figure 1: Differences in Mean heart rate in both the groups during various intervals during procedure.

DISCUSSION

Melatonin has a hypnotic/sedative effect when administered orally. The sedative effect of melatonin is

due to modulation of gamma-aminobutyric acid (GABA-A) receptors in the brain through its action on melatonin receptors (MT1 and MT2). Binding of melatonin to the MT1 receptor appears to affect the GABA A receptor through the G-coupled protein pathway. This enhances the binding of GABA to the GABA A receptor, which is similar to how other anesthetic drug such as Propofol and benzodiazepines exert their anesthetic effects.[25-28]

Miyoshi H et al showed intraperitoneal injection of 100 mg/kg melatonin significantly reduces MAC for isoflurane in rats by 24% when compared with control subjects.[28] We assumed that its inhibitory actions on central nervous system responsible for sedation and anxiolysis may have a role in reductions of anaesthesia induction doses. The peak effect of exogenous melatonin ranges from 60 to 150 min.[31] Based on this, we made a hypothesis that melatonin can provide maximum effect when given 120 minutes and was administered 120 minutes before induction of anesthesia.

Kain et al safely used oral melatonin in children with the maximum dose of 0.4 mg/kg without any major side-effects.[29] In present study we used 0.2 mg/kg and found significant dose reductions in the study group. This is because Kain et al studied the effect in pediatric age group which might have needed increased dosage of the drug. Naguib et al showed I.V. melatonin can exert hypnotic effects similar to those observed with thiopental and Propofol.[25] Studies done by Ionescu et al, Naguib et al and Samarkandi et al and Acil et al compared the effects of melatonin and midazolam with that of a placebo, where they found that anxiolysis in the melatonin group was comparable to that produced by midazolam group.[25-27,30] This was in contrast to capuzzo et al.[32] wherein, they did not find any significant anxiolytic effect of melatonin when compared to either midazolam or placebo. The above authors could not find the anxiolytic effect of oral melatonin probably the study group patients were elderly, which may be a contributory factor towards the insignificant effect. Even in our study pre induction heart rate was lower, indicating patients in melatonin group were less anxious when compared to placebo group. Ramsay sedation score was measured prior to induction and found to be similar in both the groups indicating that there was no untoward sedation effect of the drug.

In a study conducted by Naguib et al Melatonin premedication significantly enhanced the effects of both Propofol and thiopental, resulting in significantly lower ED50 and ED90 values.[25] Similarly in present study, oral premedication with 0.2 mg/kg melatonin approximately 120 minutes before induction of anesthesia, reduced the mean total dose of thiopentone. The mean total dose of thiopentone for loss of eye lash reflex in Group A (Melatonin) was 138.64±6.3 mg and in Group B (Placebo) was 223.86±5.3 mg with P value 0.000. The mean per Kg dose requirement of Thiopentone in Group A (Melatonin) 2.54±0.64 mgs and Group B (placebo) 4.56±0.67 mgs with P value 0.000, indicating significant reductions in the dose requirements for thiopentone at end points commonly used for induction of anesthesia without causing any sedative untoward effects in the preoperative period. Which is probably due to interplay between the melatonergic and GABAnergic systems, and it has been demonstrated that melatonin administration produces significant, dose-dependent increases in GABA concentrations in the central nervous system, which is proposed to be the cause of reduction of doses of induction agents.

CONCLUSION

In present study, administration of melatonin 0.2mg/kg body weight significantly reduced the induction dose of Thiopentone in patients undergoing surgery under general anesthesia. At the molecular level, we are just scratching the surface of understanding how melatonin works as an anesthetic. The issue is further complicated by our incomplete understanding of the molecular and cellular mechanism(s) of anesthesia induced by other intravenous and inhalational drugs and of the relation between anesthesia and sleep circuitry in the brain.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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