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A study to evaluate the effect of oral melatonin on patient's anxiety scores and the dose requirement of propofol by bispectral index guided induction of general anaesthesia

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Abstract: Background: Preoperative anxiety is a common occurrence in patients undergoing surgery, and it can lead to a range of negative effects, including an increased requirement for anesthetic agents, hemodynamic instability, and delayed recovery. Melatonin has been shown to have an anxiolytic and hypnotic effect with fewer side effects. This study aimed to explore the potential of oral melatonin to reduce preoperative anxiety levels and the dose requirement of propofol for the induction of general anesthesia. **Aims and Objective:** To study the efficacy of oral melatonin on patient's anxiety score, the total dose required of inducing agent and the time required for first rescue analgesia postoperatively. **Materials and Methods:** 150 patients were equally divided into two groups, Group M and Group C. After written informed consent and the preoperative baseline parameters, oral Melatonin 6mg and vitamin B complex tablets were given with a sip of water to Group M and Group C respectively, 90 min before the surgery. Anxiety level was measured using VAS score preoperatively and 90 minutes after giving the drugs. Propofol was given till the BIS value was sustained for 1 min at 48 ± 2 and the total dose was measured in both the groups. Postoperative pain was assessed using VAS score just after extubation and in every 1hr for next 4 hrs. If score $\geq$ 4, Inj. Diclofenac was given and the time of first rescue analgesia was noted. **Results:**Group M had significantly reduced VAS score and the dose requirement of propofol for induction as compared to Group C $[p \leq 0.0001]$. The time of first rescue analgesia was also prolonged in Group M as compared to Group C $[p \leq 0.0001]$. **Conclusion:** Therefore, oral melatonin is an effective premedicant that reduces preoperative anxiety, the required induction dose of propofol, and provides postoperative analgesia.

Keywords: Melatonin; Propofol; Bispectral index monitoring (BIS); Visual facial anxiety score (VAS).

1. Introduction

Preoperative anxiety and stress are most commonly found in patients scheduled for surgical procedures under anesthesia. Anxiety can lead to an altered neuroendocrine response and other perioperative considerations like increased requirement of anaesthetic agents, hemodynamic instability, delayed recovery and prolonged hospital stay. It can affect both anaesthesia management and surgical outcomes. Thus, it is necessary to overcome preoperative anxiety for smooth induction, stable perioperative hemodynamics, and better postoperative outcomes [1,2].

Benzodiazepines and various other drugs such as opioids, gabapentin, clonidine, etc. are frequently used to reduce anxiety, but they have significant side effects such as amnesia, drowsiness, and cognitive impairment. So, there is an ongoing search for a drug that reduces preoperative anxiety with minimal side effects.

Melatonin is synthesized and secreted by the pineal gland and helps to maintain the circadian rhythm. Melatonin has a hypnotic effect due to modulation of the GABAergic system in the brain through its action on melatonin receptors (MT1 and MT2) which probably leads to reduction in the required dose of induction agents [3]. The analgesic effect of melatonin is most likely mediated by GABA receptors and opioid receptors [4,5] and it also increases β-endorphin levels in the spinal cord by acting on MT2 receptors [6]. In some studies, melatonin has been proven to reduce blood pressure and catecholamine levels within 90 minutes of administration and has the potential to blunt the sympathetic response in the cardiovascular system. Thus, melatonin is an effective preoperative drug due to its sedative, hypnotic, analgesic, anti-inflammatory, anti-oxidative, and chronobiotic properties [7,8].

Among the various induction agents, propofol is the most commonly used induction agent for general anesthesia. The usual recommended intravenous induction dose of propofol produces unconsciousness in most of the patients. However, the major side effect at this dose is hypotension. Several studies have shown that using the bispectral index as an adjunct to monitoring the depth of anaesthesia can reduce requirement of the inducing agent, side effects and improving postoperative outcomes [9].

Melatonin is currently being used primarily for sleep regulation and has also been evaluated for sedation in the ICU. We aim to explore the effects of pre-operative oral melatonin on the patient's anxiety level and the total dose of propofol required for induction by using bispectral index monitoring.

2. Aim and Objectives:

To evaluate the effect of oral melatonin on patients' anxiety scores and the dose requirement of propofol using bispectral index guided induction of general anaesthesia.

Our primary objectives were to compare the effect of oral melatonin on patients' anxiety level using VAS and to measure the total dose requirement of propofol for induction using bispectral index monitoring (BIS). Our secondary objectives were to compare hemodynamic changes like HR, MAP, and SpO2 intraoperatively (every 20 minutes until the end of surgery) and postoperatively (at the time of extubation and every hourly for the next 4 hours). Also, to compare the time required for the first rescue analgesia (measured by VAS score) and any other side effects (if any).

3. Materials and Method:

This double blinded, randomized, prospective and controlled study was conducted in Department of Anaesthesiology, M.G.M. Medical College and M.Y. Hospital, Indore, [M.P.] over a period of 12 months, from 1 July 2021 to 30 June 2022, after approval from Ethics and Scientific Review Committee. 150 patients of ASA I and II either gender between 18 to 60 years, undergoing elective surgeries under general anesthesia were randomized into two groups. Inclusion criteria were (1) Age between 18-60 years of either sex (2) Weight between 40-65 kgs (3) ASA I, II (4) Mallampati class I, II (5) Patients planned for elective surgeries under GA of time duration till 2 hours. Exclusion criteria were (1) Refusal to informed written consent (2) Known hypersensitivity to Melatonin and diclofenac (3) Pregnancy and lactation (4) Patient on neuroleptic medications, alcohol abuse and immunosuppressants. Patients admitted in the Department of Surgery, planned for elective surgery under general anaesthesia fulfilling the inclusion criteria were included in the study. The day before surgery, all patients were visited for pre-anaesthetic assessment, the study protocol was explained and written informed consent was taken. Randomisation was done by closed envelope method using computer generated randomised numbers. On the day of surgery, patients were kept nil orally for six hours. In preoperative room, all the multipara-monitor were attached and preoperative hemodynamic parameters and an anxiety score were measured using the Visual Anxiety Score. [A VAS score of 2 was considered significant.]

The patients were randomly divided into 2 groups by using simple randomisation method: Group M and Group C. Patients in Group M received oral melatonin tablets (6 mg) with a single sip of water in the preoperative room, while those in Group C received oral vitamin B complex tablets 90 minutes before surgery, and were monitored until they were shifted to the operating room. IV ringer's lactate was administered as maintenance fluid through a peripheral venous cannula and patients were premedicated. Before induction (90 minutes after drug administration) hemodynamic parameters such as heart rate, MAP and oxygen saturation

were recorded. Anxiety score was measured just before induction(baseline) in both the groups by using Visual Anxiety score.

All the patients were preoxygenated for 3 minutes with 100% oxygen, then induced with a propofol infusion of 50 mcg/kg/min and injection fentanyl 2 mcg/kg intravenously. Propofol infusion was continued till the end point of hypnosis, when the BIS value was sustained for 1 minute at 48±2. Laryngoscopy and intubation were facilitated with injection succinylcholine 1.5 mg/kg intravenously. Anaesthesia was maintained with 60% nitrous oxide in oxygen, isoflurane, and injection atracurium intravenously (0.5 mg/kg loading dose and 0.1 mg/kg maintenance dose) while the patient was mechanically ventilated. At the end of surgery, residual blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg and extubation was done on meeting extubation criteria.

The intraoperative hemodynamic parameters such as heart rate, MAP and SpO2 were recorded every 20 minutes till the end of surgery. The following hemodynamic parameters were also recorded at the time of extubation till the first four hours postoperatively.

The VAS score for pain was used to assess postoperative pain immediately after extubation and every 1 hour until the first 4 hours after surgery. When the VAS score was 4 or higher, Inj. Diclofenac 1.5mg/kg was administered as a rescue analgesic, and the time was recorded. Any intraoperative and postoperative adverse effects were noted and treated by standard medical care.

4. Statistical Analysis:

Statistical Package of Social Science (SPSS Version 20; Chicago Inc. USA) used for Statistical analysis. Mini tab version 17.0 was used for calculating the P values. Kolmogorov-Smirnov test was applied for testing the normality. Comparison of means between the two groups was done using unpaired 't' test & ANOVA test. Numbers and percentages were used to present descriptive statistics. P value of <0.05 was taken as statistically significant. The final data was presented in the form of tables, graphs and bar diagrams.

5. Results

All the demographic parameters like age, sex and weight were comparable in both the groups. The mean anxiety score was significantly lower in Group M [1.93 ±0.49] in comparison to Group C [2.85±0.62] and difference was found to be statistically significant (P<0.0001). (Table 1).

The mean dose of propofol required for induction was lower in Group M (91 ± 7.80) in comparison to Group C (99 ± 2.94) and was found to be statistically significant (P<0.0001) (Table 2).

All hemodynamic parameters such as heart rate and MAP were reduced and stable in Group M as compared to Group C intraoperatively and postoperatively after 90 minutes of melatonin administration.

Intraoperative heart rate the mean heart rate was 83.03 ± 7.36 per minute for Group M and 83.55 ± 3.86 in Group C (P>0.05). There was reduction in mean heart rate after 90 minutes in Group M (81.84 ± 3.92) while in Group C there was an increase in mean heart rate (88.43 ± 3.42). At all the other time intervals intraoperatively, the mean heart rate was lower in Group M in comparison to the Group C but statistical insignificant (P >0.05). Intraoperative blood pressure-the mean MAP was preoperatively was 95.74 ± 4.61mm Hg for Group M and 95.54 ± 9.43 mmHg in Group C (P>0.05). There was a reduction in mean MAP after 90 minutes in Group M (92.53 ± 4.35) while in Group C there was an increase in MAP (96.19 ± 7.33). At all the other time intervals intraoperatively, the MAP was lower in Group M as compared to Group C but statistically insignificant (P>0.05).

Postoperative heart rate - On extubation the mean heart rate was lower in Group M (86.45 ± 5.76) as compared to Group C (99.30 ± 4.79). Also, the mean heart rate was lower in Group M as compared to Group C at all the time intervals after extubation. There were statistically significant differences seen in mean heart rate between the two groups (P < 0.05) at the time of extubation, first hour and the third hour.

In Group M and Group C, the mean SpO2 remained stable throughout the study period. The mean SpO2 was comparable between the two groups at all the time intervals (P>0.05).

The mean VAS score was significantly lower at all the time intervals after extubation in Group M in comparison to Group C (Table 3) (P<0.05). The VAS score in melatonin Group increased sequentially from extubation till 2nd hour for which rescue analgesia was given. The mean time of first rescue analgesia in

Group M was 114.86 ± 19.98 minutes and in Group C was 30.05 ± 8.34 minutes. The mean time of first rescue analgesia was significantly prolonged in Group M in comparison to Group C (Table 4) (P<0.0001).

The incidence of adverse effects such as bradycardia, hypotension, nausea/vomiting, headache and others like raised blood pressure were lower in Group M in comparison to Group C and were found to be statistically not significant (P=1.000)

Table 1. Visual facial anxiety score

Anxiety score	Group C [Mean±SD]	Group M [Mean±SD]	P value
Preoperative [before giving melatonin/Vit-B]	2.85±0.61	2.85 ±0.63	1.00
90 mins after 6mg oral melatonin/Vit-B given [baseline]	2.85±0.62	1.93 ±0.49	<0.0001

Unpaired 't' test applied. P value = 0.001, Significant

Table 2. Bispectral index monitoring for depth of anaesthesia

Bis index (48±2)	Group C	Group M	P value
Dose of propofol required for induction (in mg)	99 ± 2.94	91 ± 7.80	<0.0001

Unpaired 't' test applied. P value = 0.001, Significant

Table 3. Post operative pain analysis by vas score

VAS score	Group C	Group M	P value
Just after Extubation	3.85 ± 0.52	2.10 ± 0.40	0.0001
1 hour	3.24 ± 0.35	2.90 ± 0.54	0.0001
2 hours	2.90 ± 0.11	3.72 ± 0.29	0.0001
3 hours	2.82 ± 0.16	3.04 ± 0.15	0.0001
4 hours	2.90 ± 0.16	2.50 ± 0.44	0.0001

Unpaired 't' test applied. P value < 0.05 was taken as statistically significant

Graph 01: Bar diagram showing comparison of mean VAS score between the two groups at different time intervals

Table 4. Comparison of mean time of first rescue analgesia

Parameter	Group M [Mean±SD]	Group C [Mean±SD]	P value
Time of first rescue analgesia[mins]	114.65± 19.98	30.05± 8.34	<0.0001

Unpaired 't' test applied. P value<0.05 is Significant

6. Discussion

In our prospective, randomised, and double blinded study. Group M received 6 mg of oral melatonin and Group C received a vitamin B-complex tablet 90 min before induction of general anaesthesia.

Melatonin has been studied in different doses and its peak duration of action is from 60 to 150 minutes after oral administration. Turkistani *et al.*, [10] compared two doses of oral melatonin (3 mg and 6 mg) given 100 minutes before induction on preoperative anxiety and the required dose of propofol for induction. He found that the melatonin was equally effective in both doses (3 mg and 6 mg) and time durations ranging from 80 to 100 minutes. In our study we also used similar dose of melatonin(6mg) which was administered 90 minutes before induction.

6.1. Preoperative anxiety

The anxiolytic effect of melatonin in our study was consistent with Afsaneh Norouzi *et al.*, [11] study in which oral melatonin (3mg) significantly reduced the anxiety level as compared to placebo Group. Arvind

Khare *et al*., [12] in their study found that premedication using oral melatonin (6 mg) is an effective alternative to alprazolam for providing better anxiolysis, lesser sedation with maintenance of cognitive and psychomotor function. Ismail SA and Mowafi HA *et al*., [7] had also documented that the melatonin Group significantly reduced the anxiety scores from 5 to 3 after premedication.

Our findings were contradicting to study done by Isik *et al*., [13] in which he compared melatonin and midazolam premedication on child anxiety undergoing dental treatment and found that melatonin (3mg) had no effect on the anxiety. This could be due to small sample size in study groups and while the target group was children whereas, adults (> 15 and < 55 years) were targeted in our study. Melatonin is shown to be effective in reducing the anxiety level probably by modulating MT1 and MT2 receptors of brain. The analgesic effect of melatonin is most likely mediated by GABA receptors and opioid receptors. It was found that melatonin also increases β-endorphin levels in the spinal cord by acting on MT2 receptors.

6.2. Dose of propofol

The required induction dose of propofol was lower in the melatonin Group as compared to the control Group. To avoid any human error, we administered propofol as an infusion rather than a bolus in an incremental dose fashion. The BIS monitor is validated for measuring the depth of anesthesia. We randomly used values of 48 $\pm$ 2 for our study. There was statistical difference ($P < 0.001$) (Table 2). in the mean dose requirement of propofol in Group C (99 $\pm$ 2.94 mg) as compared to Group M (91 $\pm$ 7.80 mg).

Our findings were comparable to several studies; M Naguib & AH Samarkandi *et al*., [14], found that oral premedication with 0.2 mg/kg melatonin significantly reduces the propofol and thiopental doses required for loss of responses to verbal commands and eyelash stimulation. Afsaneh Norouzi *et al*., [11] in their study found that oral melatonin at the dose of 3 mg effectively reduced the required dose of propofol for induction with statistically significant difference in propofol dose between the two groups. Turkistani *et al*., [10], found that the mean induction dose of propofol producing a BIS score of 45 was 134 mg in the placebo Group vs. 115 and 114 mg in the M3 and M5 Groups, respectively. They documented that oral melatonin 3 or 5 mg is recommended to reduce propofol induction dose to achieve bispectral index (BIS) 45.

The hypnotic action of melatonin is probably due to modulation of the MT1 receptor, which appears to enhance the binding of GABA to the GABA A receptor leading to hyperpolarization of the chloride channel through the G-coupled protein pathway. This mechanism of action is similar to how other anaesthetic drugs, such as propofol and benzodiazepines exert their anaesthetic effects.

6.3. Haemodynamic parameters

In our study, after 90 minutes of melatonin administration, all hemodynamic parameters such as heart rate, SBP, DBP, and MAP were reduced in Group M, whereas all of these parameters slightly increased in Group C, but the difference was found to be insignificant.

Our findings were comparable to several studies; Marzieh Beigom Khezri [15] in which sublingual melatonin [3mg] showed reduction in the mean heart rate before induction and intraoperatively as compare to control Group, but there was no statistically significant difference in mean heart rate. Also, the mean SBP, DBP and MAP were lower in the melatonin Group as compare to control Group with no statistically significant difference. Afsaneh Norouzi [11] given oral melatonin (3mg), 50 minutes before induction. They also found that the mean heart rate and the mean blood pressure were lower in melatonin Group at all the time interval after premedication, but there was no statistically significant difference in mean heart rate in comparison to placebo Group.

The heart rate lowering effect of melatonin may be attributed to its anxiolytic actions. The underlying mechanism is probably the synergy between melatonergic and GABAergic systems and the blood pressure lowering effect can be explained by two main mechanisms. It acts on specific melatonin receptors present on blood vessels and interferes with the action of catecholamines and hence vascular response to sympathetic stimulation is reduced. It increases the availability of nitric oxide leading to relaxation of smooth muscles of arterials walls leading to vasodilation and reduced blood pressure.

6.4. Postoperative analgesia

In our study, the mean VAS score swas significantly lower at all the time intervals after extubation in Group M in comparison to Group C (P<0.05). The VAS score in melatonin Group increased sequentially from extubation till 2nd hour for which rescue analgesia was given. (Table 3)

The mean time of first rescue analgesia in Group M was 114.86± 19.98 minutes and in Group C was 30.05± 8.34 minutes. The mean time of first rescue analgesia was significantly prolonged in Group M in comparison to Group C (Table 4) (P<0.0001)

Our findings were similar to the study done by Hale Borazan & Seema Tuncer *et al.,* [16] in which they administered 6 mg melatonin one night before and one hour before the surgery and concluded that post operatively VAS score was significantly lower in melatonin group than control group at 1,2,4,6,12,18 and 24 hours after surgery ($p < 0.05$). Salah A Ismail & Hany A Mowafi [7] in which they administered 10 mg oral melatonin 90 min before cataract surgery. They found that perioperative verbal pain scores were significantly lower in the melatonin group with less intraoperative fentanyl requirement as compared with the control group (P=0.007).

Our findings were comparable to the study done by Marzieh Beigom Khezri [15] in which two doses of oral melatonin (3 mg and 6 mg) compared with placebo. The mean time to first analgesic request was also longer in Group M3 than in Groups M6 and P Group, but the difference between three groups were not significant. F. H. kiabi & S. A. Emadi *et al*., [17] in which the effect of two different doses of oral melatonin (5mg and 10mg) were compared with placebo for postoperative pain. The post operative pain scores were assessed at 2 h,6 h, 12 h and 24 h and there was a significant pain reduction in both melatonin groups and duration of rescue analgesia was prolonged (10 mg> 6 mg) in comparison to control group.

It was found that melatonin exerts its antinociceptive effects through MT1 and MT2 melatonergic receptors located in the dorsal region of the spinal cord and also in different parts of the brain involved in pain modulation.

6.5. Adverse effect

In our study the incidence of adverse effects such as bradycardia, hypotension, nausea/vomiting, headache and others like raised blood pressure were minimal in Group M with no significant difference between the two groups.

Our findings were similar to study done by Tushar Patel & Madhuri S. Kurdi [18] and Marzieh Beigom Khezri [15] in which no significant differences were found in the three groups in terms of intraoperative and postoperative side effects including nausea, vomiting, vertigo and respiratory depression. But the incidence of headache was more in Group M6 compare to Group M3 and placebo

7. Limitation

We assessed the effects of single dose of melatonin given 90 min prior to induction. It would have given more clarity regarding the function of melatonin if different doses given at different time intervals were assessed. Secondly, the catecholamine level was not measured, which would have been a better and appropriate criterion than hemodynamic parameters to assess sympathetic stimulation.

8. Conclusion

Overall, we can conclude that the administration of oral melatonin effectively reduces the preoperative anxiety, required induction dose of propofol and provides postoperative analgesia. Oral melatonin maintains stable hemodynamics intraoperatively as well as postoperatively with lesser adverse effects.

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