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The effect of melatonin administration on sedation level as adjuvant to propofol in mechanically ventilated traumatic brain injury patients

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ABSTRACT

Background: Melatonin is a pineal gland neuro-hormone influencing the biological regulations of the circadian rhythm. Numerous investigations have revealed variable effects of melatonin in vivo, including anti-inflammatory, antioxidant, sedative, and anxiolytic effects. The effects of using exogenous melatonin as an adjuvant to propofol on the degree of sedation in patients were investigated.

Aim: We aimed to test the feasibility of melatonin as a sedative agent in traumatic brain injury patients.

Methods: This research was a double-blinded clinical trial conducted on 38 participants suffering from traumatic brain injuries necessitating sedation and mechanical ventilation. Participants were assigned randomly into two groups. Both groups were sedated by propofol infusion and monitored by bispectral index (BIS). Nineteen patients received 10 mg of melatonin, and 19 patients received a placebo (control). Propofol infusion rate and BIS values were recorded each 30 minutes for 12 hours.

Results: Exogenous melatonin administration led to a significant decrease in the amount of infused propofol necessary to attain the desired level of sedation. The propofol infusion rates were 4.87 ± 2.91 ml/h in the melatonin group and 6.37 ± 2.87 ml/h in the control group (P- values = 0.001).

Conclusion: Exogenous melatonin acts as an adjuvant to propofol in sedation, reducing the amount of propofol infusion needed.

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KEYWORDS
Sedation; traumatic brain injury; melatonin; bispectral index; intensive care

1. Introduction

In intensive care facilities, sedatives are used on a daily basis, especially for mechanically ventilated patients. Undesirable suboptimal sedation prolongs the mechanical ventilation

\ period and total critical care stay and worsens long-term cognitive functions and delirium, particularly in the acute phase after the initial injury [1].

Bispectral index (BIS) represents a decisive monitor for obtaining optimum sedation level and an independent method to give an objective, measurable scale rather than other subjective scales which depend on observer judgment [2,3]. Melatonin is valuable as a premedication owing to its sedative and anxiolytic effects [4,5]. Several investigations have demonstrated that premedication with exogenous melatonin resulted in sedation with the salvation of cognitive and psychomotor abilities without lengthening the recovery period [6,7].

No previous study has investigated the impact of melatonin administration on the dosage of propofol infusion in mechanically ventilated patients having traumatic brain injury who were monitored using an objective monitoring instrument such as the BIS.

Our hypothesis is that melatonin can reduce the dose of propofol when added as an adjuvant in brain trauma patients. The current research aimed to determine the extent of the sedation effect of exogenous melatonin as an adjuvant to propofol.

2. Methods

The current double-blinded, randomized controlled trial was performed at the Neurosurgical Intensive Care Unit, for six months (between January 2018 and July 2018), after the approval of the Institute's Ethics Committee. The procedure followed the guidelines in the seventh revision of the Declaration of Helsinki, 2008. The patient's relatives signed informed written consent. Clinical trial identifier: NCT04034771.

The sample size that detected a difference of 30% in propofol consumption was calculated. To achieve an alpha error of 0.05 and 80% research power, a sample size estimation was 36 patients (18 per group) was required according to MedCalc software. To account for probable dropouts, the number was increased to 38 participants (19 per group). The primary investigator

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created a computer-generated sequence utilizing an online random number generator to divide patients into two equal groups randomly. Participants' produced codes were placed in consecutively numbered opaque envelopes. The guidelines for making the medication bolus were included in each packet. A clinical pharmacist (who was not involved in patient management) opened the envelope and was in charge of preparing the medication.

Two physicians were aware of treatment allocations following the group assignment and monitored for potential side effects, as required by the Ethics Committee, but did not participate in clinical decisions concerning research treatment interruption or sedative delivery. The primary outcome was propofol consumption per hour for the first 6 hours after intubation. In a previous study [8], propofol consumption in intubated neuro-trauma patients was reported to be 39.3 ± 12.7 mg /kg/hr. Patients were assigned randomly to a group; Group (A) (n = 19) received oral melatonin of 10 mg during the propofol infusion, and Group (B) (n = 19) received placebo tablet filled with corn-starch powder (manufactured by pharmacology school) during the propofol infusion. The participants were chosen based on the following inclusion criteria: Age ≥ 18 years old, patients who needed intubation and mechanical ventilation due to traumatic brain injury (blunt non penetrating trauma) with an initial Glasgow Coma Scale from 6 to 8, patients who were vitally stable with baseline traumatic brain injury confirmed by computer tomography (CT) without an intracranial hemorrhage or brain edema necessitating surgical intervention. The patients with liver disease, severe renal insufficiency, hemodynamically instability with mean blood pressure below 60, and pregnant women were excluded. BIS probes were conducted on all patients, and EMG and EEG were evaluated using a forehead electrode. After intubation and initiation of mechanical ventilation, fentanyl (1 μg/kg/h) was continued at a fixed rate. A bolus of propofol 1 mg/Kg was administered intravenously through titration until the patient became sedated at (60–70) on the BIS. Subsequently, propofol infusion was maintained at 1 mg/Kg/h (each ml = 10 mg propofol). After that, 10 mg of melatonin (two tablets each of which is 5 mg) [9–12] was crushed and mixed with 20 ml of water, then given via the nasogastric tube, followed by a further 20 ml to group (A). Group (B) administered a placebo tablets in the same manner as Group (A). Follow-up on any changes in the BIS value was started 30 minutes just after melatonin administration and was continued for six hours [11,13]. The propofol infusion rate was modified to return the value of the BIS to (60–70) again, and this value was observed every thirty minutes by the intensive care physician, With the recording of the following: sex, age, APACHE-II, GCS score, the infusion rate of propofol required for keeping sedation value (60–70) guided by BIS monitor, and hemodynamics including heart rate and blood pressure. The amount of total consumed propofol was the primary. Secondary outcomes were hemodynamic parameters such as diastolic blood pressure, heart rate, systolic blood pressure.

Obtained data were processed by Statistical Package for Social Science (SPSS, version 25; SPSS Inc., Chicago, IL). Data were demonstrated, and appropriate analysis was performed for each parameter based on the data type. For parametric numerical data, mean ±SD and range were utilized.

In contrast, median and interquartile ranges (IQR) were utilized for non-parametric numerical data. Frequency and percentage were utilized for non-numerical data. The Student t-test was used to examine the statistical significance of the difference between the two research groups' means.

3. Results

Statistically, an insignificant difference was observed regarding population for gender, age, GCS, APACHE Ⅱ score, and initial hemodynamics ($P > 0.05$). With an average of 87% males, the research population was representative of any large, primarily trauma group (Table 1).

The experiment had 46 patients who were eligible to take part, and their relatives gave informed consent. Eight of them did not fulfill the inclusion criteria: one patient was suspected of intra-abdominal bleeding requiring surgical intervention, two patients were hemodynamically unstable with mean blood pressure lower than 60 mmHg and not responding to fluid resuscitation, and three patients experienced repeated

Table 1. Baseline hemodynamic characteristics and demographic data. Data were presented as mean (standard deviation).

	Melatonin group (n = 19)	Control group (n = 19)	PV
Age (year), mean ± SD*	35.2 ± 18.5	37.9 ± 12.5	0.81
Sex (male) *n* (%)	16(84)	17(89)	0.49
Glascow coma scale	7 [6–8]	6 [6–8]	0.82
Baseline HR (bpm)	87 ± 12.46	83 ± 7.07	0.2
Baseline SBP (mmHg)	127 ± 12.51	125 ± 13.86	0.6
Baseline DPB (mmHg)	78 ± 6.08	78 ± 6.50	1.0
APACHE Ⅱ †	7.65 ± 4.12	8.10 ± 3.95	0.35

*SD, standard deviation; †APACHE Acute Physiology and Chronic Health Evaluation.

convulsions. Finally, the study involved 38 patients distributed into two groups: melatonin and placebo, with 26 patients in every group (Figure 1).

The sedation target was achieved in both groups; BIS value (60 to 70). The mean of BIS in the melatonin group was 64.42 ± 2.63, and in the control group was 64.26 ± 2.45 (Figure 2).

Melatonin administration led to a significant reduction in the total infused dose of propofol in the melatonin group. The mean propofol infusion rate in the melatonin group was 4.87 ± 2.91 ml/h, while it was 6.37 ± 2.87 ml/h in the control group (p-value <0.05). Near the fourth hour after melatonin administration, the propofol infusion rate

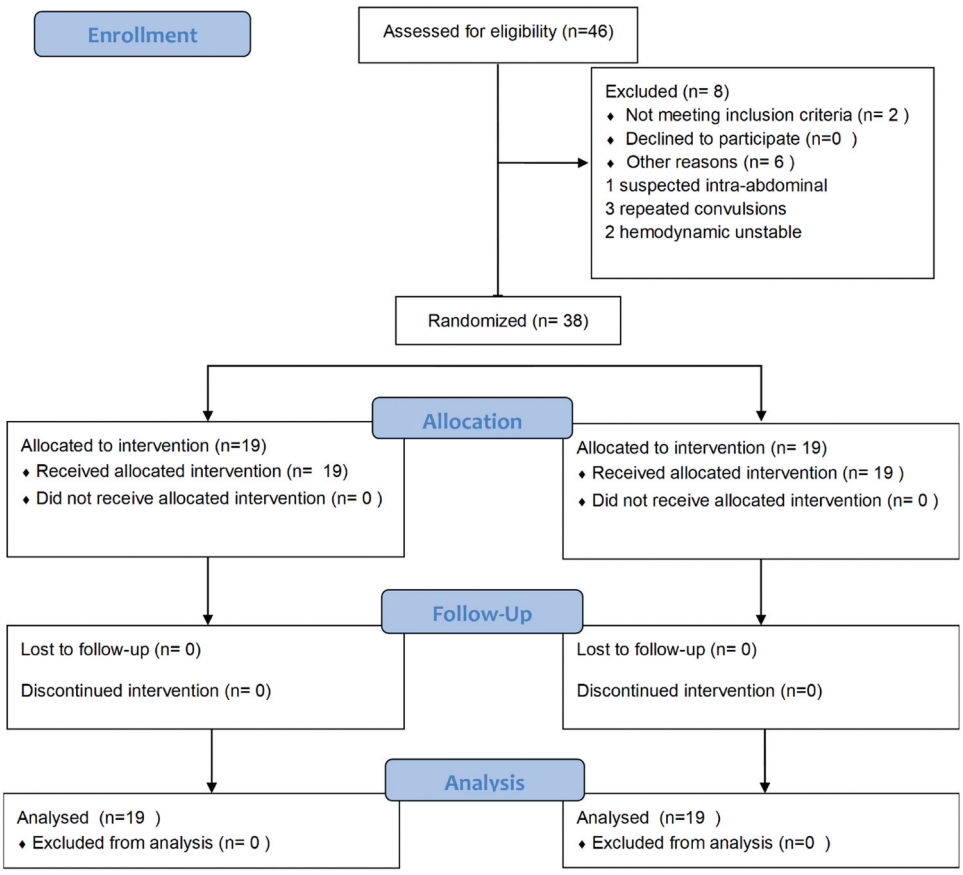

Figure 1. CONSORT flowchart showing the number of patients at each study phase.

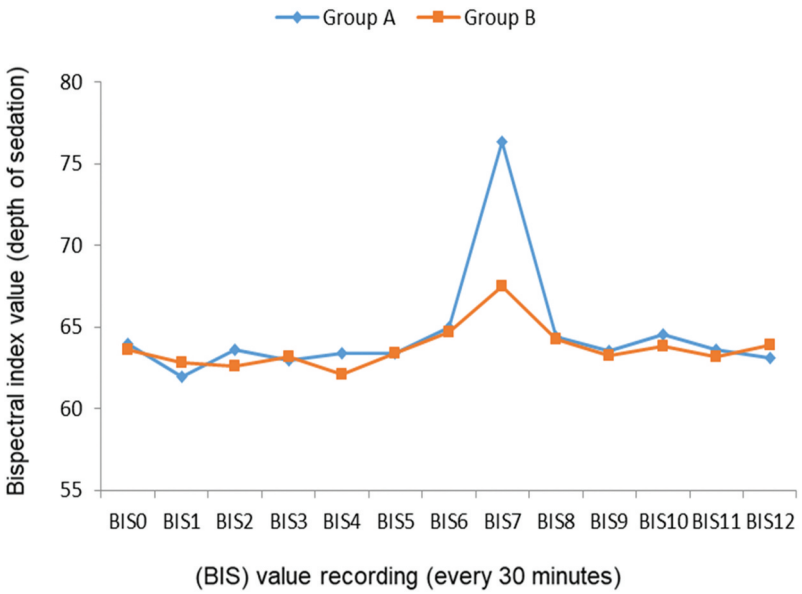

Figure 2. Comparison of Bispectral index values (BIS)between the two groups. Group A is the group of patients who received melatonin tablets, and group B is the group of patients who received placebo tablets.

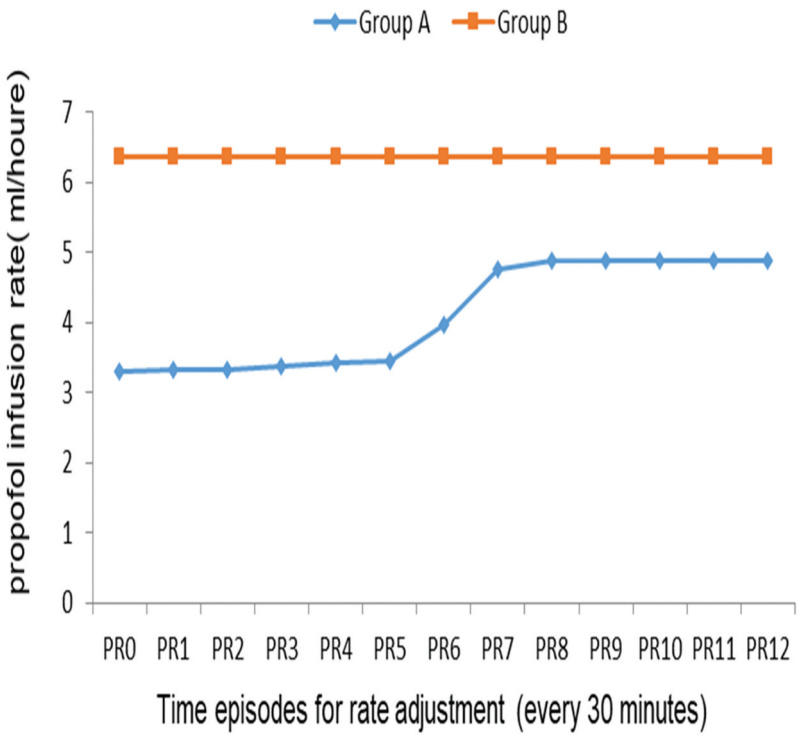

Figure 3. Comparison of Propofol infusion rate (PR) between both groups. Every 1 ml = 10 µg propofol. Group A is the group of patients who received melatonin tablets, and group B is the group of patients who received placebo tablets.

increased in the melatonin group, while the rate was constant in the control group. (Figure 3).

Systolic blood pressure did not vary throughout the study (Figure 4). The difference in diastolic blood pressure between the two groups was significant after propofol was added to restore sedation in melatonin group following 4.5 hours of sedation initiation (76.54 ± 5.158 in the melatonin group vs. 83.35 ± 4.511) ($P < 0.001$) (Figure 5).

4. Discussion

In the study, melatonin was found to have an adjuvant impact on propofol considering sedation, as evident by statistically significant descent in the required rate of propofol infused to achieve the desired sedation level (p-value < 0.05).

Kurdi and Muthukalai reported that oral melatonin (0.4 mg/Kg) given 60-min in pre-operative population provided satisfactory sedative and anxiolytic effects

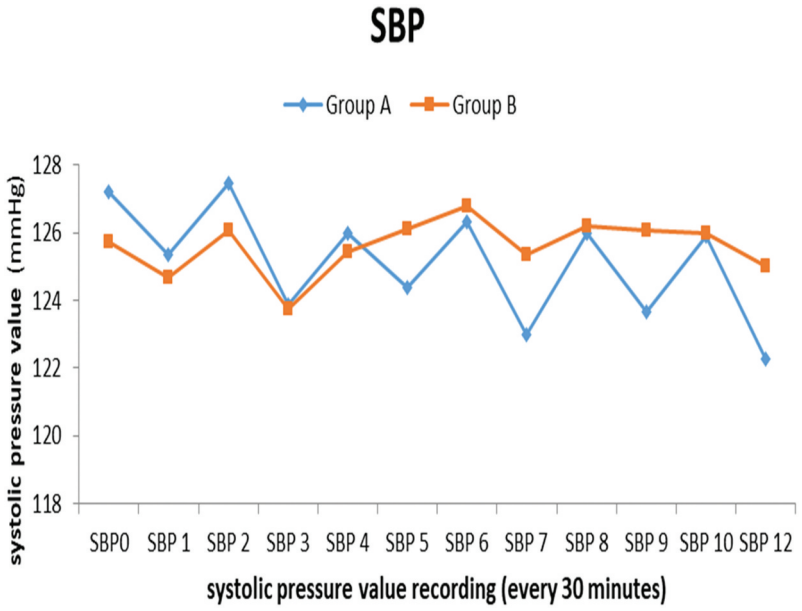

Figure 4. Comparison of SBP between both groups. SBP: Systolic blood pressure. Group A is the group of patients who received melatonin tablets, and group B is the group of patients who received placebo tablets.

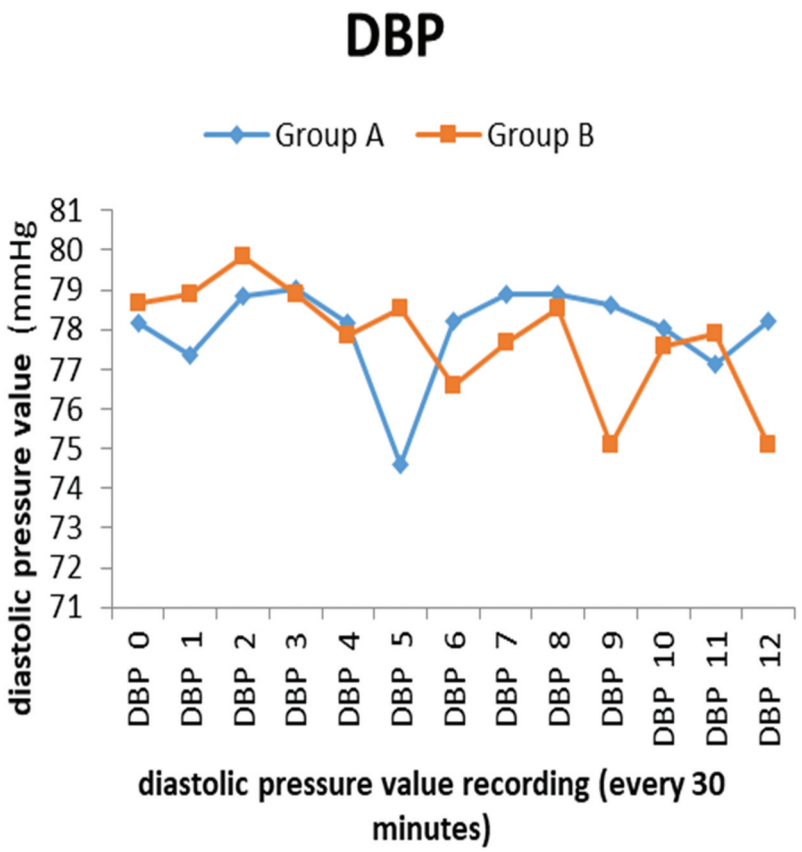

Figure 5. Comparison of DBP between both groups. DBP: Diastolic blood pressure. Group A is the group of patients who received melatonin tablets, and group B is the group of patients who received placebo tablets.

comparable to oral midazolam (0.2 mg/Kg) and better than placebo. Oral melatonin, unlike midazolam, did not affect psychomotor functions or cognition [14]. Intriguingly, Kurdi and Muthukalai showed that the sedation scores for the last three groups before and after premedication showed statistical significance ($p < 0.05$). They favored the melatonin and midazolam groups, in any case. Midazolam generated the most sedation compared to melatonin or placebo, according to an intergroup study of sedation scores. However, they assessed sedation via a sedation scale where (0 = alert), (1 = arouses to voice), (2 = arouses with gentle tactile stimulation), (3 = arouses with vigorous tactile stimulation), and (4 = lack of responsiveness), which was a subjective scale. In the present study, there was an advantage of using a BIS as an objective method to evaluate the real effect of melatonin as an adjuvant to the main sedative agent during the stay period in intensive care. BIS is dependable and more valuable than RASS in being objective and continuous, at least in mechanically ventilated patients under propofol sedation [15]. In addition, in patients with TBI, interpretation remained relatively subjective and challenging. These findings indicated that the BIS could be an excellent objective tool for evaluating propofol sedation in the ICU [16].

In addition, the difference between the scale grades in the previous study was not uniform, i.e., the relation between the scale and the level of consciousness and the degree of impairment was not linear.

In the current study, the effect of melatonin administration appeared within 30 to 60 minutes. Patients required a higher (propofol rate of infusion) after 240 minutes to 300 minutes, which meant that the melatonin effects started to wear off after around 4 hours from the onset of administration. This difference in propofol dose between both groups was significant (p-value <0.05).

In general, critically ill patients' elimination half-life of melatonin (3 mg via nasogastric tube) was protracted at 1 hour and 34 minutes with a Tmax that occurred only 16 minutes after administration. However, serum melatonin levels declined significantly within 4 hours [17].

Besides Tmax, another essential physiologic parameter that affected the period of raised melatonin levels was the initial given dose. At higher doses, there was a greater possibility of extended periods of supraphysiologic melatonin levels [18,19]. This was consistent with our findings (we used a larger dose of 10 mg) [12]. The onset of sedation appeared approximately before the first 30 min after melatonin administration, and the sedation effect decreased considerably within 5 hours.

The present study showed that melatonin decreased significantly the needed dose of propofol infusion ($p < 0.05$). Compared to the current results,

Turkistani et al. [20] performed a study on 45 adult patients undergoing different surgical procedures where melatonin was used as a premedication in an oral dose of either 3 or 5 mg. It decreased the propofol needed to achieve a BIS score of 45, with enough hypnosis for tracheal intubation without extending the postoperative recovery period [20].

In the present study, BIS was used to monitor sedation levels during propofol infusion as an ideal method for sedation titration, agreeing with our choice for monitoring. Park et al. published a meta-analysis that included 1039 patients, 526 of whom were in a BIS group and 513 of whom were not in a BIS group, and looked into BIS monitoring during endoscopic procedures. According to the study, the overall dosage of propofol was significantly lower with BIS monitoring than under non-BIS monitoring [21]. The researchers mentioned that BIS-guided sedation could be valuable in enhancing the number of analgesics or adjuvants used and the amount of main sedative drugs used.

In critical care practice, normal circadian rhythm is affected by many factors related either to the patient's critical condition or the surrounding environmental factors. Particular clinical studies have revealed the supportive role of melatonin administered during the whole ICU stay. The broad spectrum of melatonin's effects varies from antimicrobial properties, antioxidant activity, immunomodulatory effects, and neuroprotective role to even oncostatin actions [22].

There were some limitations to the current research: It was a single-center study with a sedative medication guideline that may differ from other ICUs. Furthermore, the differences in recovery across study groups were not assessed. Finally, a gap in our knowledge was found concerning the severity of head trauma, such as AIS and ICP. This should be evaluated in future investigations.

5. Conclusion

Exogenous enteral melatonin can be used as an adjuvant to the sedative effect of propofol, aiming at lowering the needed propofol infusion dose.

Acknowledgments

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Disclosure statement

No potential conflict of interest was reported by the authors.

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