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Effects of administration of melatonin on prevalence of delirium and duration of stay in patients admitted to neurosurgical intensive care unit – A prospective study

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ABSTRACT

Background: The occurrence of delirium in patients who undergo elective surgeries is a common occurrence. Multiple studies have assessed the effect of different drugs in various elective procedures to decrease the prevalence of postoperative delirium. The effect of melatonin to decrease the prevalence of delirium and duration of neurosurgical intensive care unit (NSICU) stay in patients undergoing neurosurgery has not been studied previously. The current study aimed to assess the same. **Aims and Objectives:** To assess the effect of preoperative and postoperative melatonin administration on the prevalence of delirium in patients undergoing elective ventilation in NSICU and to assess the effect of preoperative and postoperative melatonin administration on the duration of stay in NSICU. **Methods and Methods:** In this prospective observational study, 60 patients undergoing various neurosurgical procedures and admitted to NSICU were included. The patients were divided into two groups: one group received a placebo (Group P- tablet Sugarfree containing Aspartame) and another group received a tablet of melatonin 3 mg (Group M) in the preoperative and postoperative period. The effect of melatonin on the prevalence of delirium and duration of NSICU stay in these two groups was observed. **Results:** A decreasing trend of delirium was noted in both groups (Group M and Group P) with no statistical significance. A decreased prevalence of delirium was observed in patients of group M (33.3%) at the end of 12 h post-extubation compared to Group P (43.3%). The mean duration of stay for the patients in NSICU in Groups M and P were 2.7 and 3.2 days, with the range (1–14 Days) in Group M and Group P (1–20 days), respectively. **Conclusion:** Although there was a decreased prevalence of delirium and a decrease in the mean duration of the intensive care unit stay in patients who received oral melatonin, these beneficial effects did not show any statistical significance once compared with the control group.

Key words: Neurosurgery; Intensive care unit; Delirium; Length of stay

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INTRODUCTION

Delirium has been defined as an acute disturbance in attention and awareness with additional disturbances in cognition.[1] It may be characterized by hyperactive features (combative behavior), hypoactive (somnolent patient) delirium, or mixed delirium. Delirium is seen in nearly up to 80% of patients admitted to the intensive care units.[2] It may be caused by altered homeostasis, subtle sepsis, hypoxia, hypercarbia, or electrolyte imbalance. In

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a neurointensive care unit, delirium may be exacerbated by associated brain injury due to hemorrhage, stroke, or meningitis. Critically ill patients with delirium have increased morbidity and mortality, which may be associated with the persistence of cognitive impairment after discharge.[3] Non-pharmacological therapies such as early mobilization, eyeglasses/hearing optimization, correction of dehydration, and prevention of sleep deprivation and pharmacological therapies such as antipsychotic drugs (haloperidol, olanzapine, risperidone, quetiapine, or ziprasidone), cholinesterase inhibitors, and alpha-2 agonists are used to ameliorate delirium in the intensive care unit.[4-6]

Melatonin, crosses the blood–brain barrier easily, modulating the sleep and circadian rhythm. Its anti-inflammatory, anti-ischemic, antioxidant, and immunomodulatory activities offer neuroprotective effects in patients with neurological disorders. It has minimum potential for abuse, less cognitive impairment, and no extrapyramidal side effects, or respiratory depression.[7] Though its beneficial effects have been studied in heterogeneous population in the intensive care unit, the effects of melatonin administration for reducing delirium in the neurosurgical population are not well studied.

Aims and objectives

The primary aim of our study was to compare the effects of oral administration of melatonin on the prevalence of delirium in neurosurgical patient's with the control group in patients undergoing elective ventilation in the neurointensive care unit. The secondary aim was to compare the effect of oral administration of melatonin administration with the control group on the duration of stay in the neurointensive care unit.

MATERIALS AND METHODS

This prospective, observational study was conducted in the neurointensive care unit at a tertiary care hospital in Northern India from January 2020 to January 2023. After obtaining approval from the institutional ethical committee and informed written consent from the patient or their immediate relatives, all adult patients above the age of 18 years (who were oriented and responding to verbal commands with a Glasgow coma score of 15) scheduled for elective neurosurgical procedures were incorporated into the study. The patients were randomized to receive melatonin or placebo (tablet Sugar-free containing Aspartame) in the pre-operative period at 8 am in the morning. All patients were shifted to the operating room, and the basic essential monitors (electrocardiogram, pulse oximeter, non-invasive blood pressure) were attached. After pre-oxygenation, general anesthesia was induced with fentanyl 2 μg/kg, preservative-free lidocaine hydrochloride (1.5 mg/kg), and propofol 2 mg/kg (in increments of 20 mg) till there was the loss of verbal response. Tracheal intubation was facilitated with an injection of rocuronium 1 mg/kg. A mixture of oxygen, nitrous oxide, and isoflurane was used for the maintenance of anesthesia. At the end of the procedure, all patients were accessed for tracheal extubation. Patients whose trachea was not extubated in the operating room were shifted for elective mechanical ventilation to the neurosurgical intensive care unit (NSICU). During their course stay in the intensive care unit, the patients were sedated with an injection of fentanyl 2 μg/kg body weight and injection of midazolam (0.1 mg/kg body weight). In all patients, continuous monitoring of heart rate, systolic and diastolic blood pressure, electrocardiogram, and oxygen saturation was done during the stay in the intensive care unit. In the intensive care unit, depending on the initial randomization (done before surgery), the patients received either oral melatonin 3 mg eight hourly (group M) or tablet Sugarfree through nasogastric tube. All patients received adequate fluid (70–100 mL/h) to maintain euvolemia and electrolytes to maintain hemostasis. After 12–18 h of mechanical ventilation, the patient's neurological, respiratory, and cardiovascular status were assessed for tracheal extubation. Tracheal extubation was planned in all patients with a physiologically stable cardiovascular, respiratory and neurological parameters. A total of 60 patients were enrolled in the study. Group M consisted of 30 patients that received tablet melatonin 3 mg orally and Group P consisted of 30 patients (control group) that received tablet Sugarfree. Sample size was calculated using open Epi software, based on the study done by Vijayakumar et al.,[8] based on this study, assuming a two-sided significance level (1-alpha) of 95 with a power of 80% and a prevalence of delirium in patients receiving melatonin as 51%; and prevalence of delirium in the control group (not receiving melatonin) as 85% a total sample size of 60 was needed with 30 patients in each group.

Injection midazolam and injection fentanyl were continued till a plan was made for tracheal extubation. Once a plan for tracheal extubation was made, injection of fentanyl and injection midazolam was stopped. Once the patients regained consciousness, responded to verbal commands and had adequate recovery of neuromuscular power, the tracheal extubation was done.

Inclusion criteria

All the patients undergoing neurosurgical procedures and admitted to NSICU were included in the study.

Exclusion criteria

Patients <18 years of age, receiving melatonin before intensive care unit (ICU), altered sensorium (Glasgow

coma score of <15), known psychiatric disorders, expected death within the next 48 h, chronic renal failure, hepatic impairment with Child-Pugh class B and C, and patients on anti-coagulant medication, receiving massive blood transfusion in the intraoperative period, or with coagulopathy were excluded from the study.

Delirium was assessed using the Confusion Assessment Method for ICU (CAM-ICU score immediately after tracheal extubation and at hourly intervals for the next 24 h. If the patients were agitated, it was treated by a bolus of injection midazolam 1–2 mg IV or/and injection of fentanyl 50 μg IV bolus in a titrated dose.

The data was recorded and compiled in a spreadsheet (Microsoft Excel) and then exported to the data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD, and categorical variables expressed as frequencies and percentages. Student's independent t-test was used for comparing continuous variables. The Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. A P<0.05 was considered statistically significant. All P-values were two-tailed.

RESULTS

A total of 60 patients undergoing elective neurosurgical procedures were enrolled in the study. Thirty patients received Melatonin 3 mg (Group M), while 30 patients received tablet of sucrose (control group) in a randomized fashion. It was observed that the demographic profile was comparable for both groups with respect to age, gender, comorbidities, duration, and type of surgery (Table 1). There was no significant difference in heart rate, mean arterial blood pressure and oxygen saturation before induction and at the time of extubation between the groups receiving melatonin and the control group. The patients enrolled in the study underwent craniotomy for aneurysmal clipping for subarachnoid hemorrhage, intracranial tumor decompression, and transnasal transsphenoidal decompression for pituitary tumors. The nature of the surgical procedure, duration of the surgical procedure, and duration of mechanical ventilation in the intensive care unit between the two groups were comparable. It was observed that 36.7% of patients who received melatonin and 46.7% in the control group needed mechanical ventilation, respectively, in the postoperative period (P=0.432). In our study, 11 patients (36.7%) in the melatonin group and 14 patients (46.7%) in the placebo group could not be extubated in the operation theater due to various reasons such as unstable hemodynamics, the requirement of vasopressors, the requirement of ventilator support, and acidotic ABG's.

Table 1: Demographic profile of the patients

Variable	Group M	Group P	P-value
Age	42.3±13.63	41.6±12.21	0.819
Gender	Male-40% Female-60%	Male-33.3% Female-66.7%	0.592
Comorbidities (%)			
HTN	16.7	6.7	0.421
Hypothyroidism	6.7	10	0.64
Seizure disorder	3.3	3.3	1.000
Type of surgery (%)			
Aneurysmal clipping	16.7	20.2	0.475
ICSOL	53.3	63.3	
TNTS resection of PT	30	16.7	
Duration of surgery	5.4±1.89	5.6±1.69	0.667

Group M: Group Melatonin, Group P: Group placebo, ICSOL: Intracranial space-occupying lesions, HTN: Hypertension, TNTS: Transnasal transspenoidal, PT: Pituitary tumors

The mean duration of mechanical ventilation in the intensive care unit was comparable (P=0.488) in patients receiving melatonin (mean of 5.6 h with a range of 2–15 h) and control group (mean of 7.5 h with a range of 2–27 h) (Table 2). In patients receiving melatonin and the control group, 11 and 14 patients could not be extubated, respectively, at the end of surgery. Prolonged duration of surgery (>8 h), excessive blood loss (>600 mL), metabolic acidosis, hypothermia, need for inotropes, and metabolic acidosis were associated with the need for postoperative mechanical ventilation.

Figure 1 depicts the incidence of delirium in group M and group P at various intervals of time post extubation up to 12 h after extubation. A decreasing trend of delirium at hourly intervals was noted in both groups with no statistical significance. However, a decreased incidence of delirium was observed in patients receiving tablet melatonin (Group M) at induction (33.3%) at the end of 12 h post-extubation as compared to patients who did not (Group P) receive melatonin (43.3%).

Figure 2 depicts the incidence of delirium in Group M and Group P at various intervals of time, 12 h after extubation. A decreasing trend of delirium was observed in both the groups of patients, those receiving melatonin (Group M) and those receiving a placebo (Group P). The patients receiving melatonin had a decreased incidence (13.3%) of delirium at different time intervals compared to the group that did not receive melatonin (23.3%), though this was not statistically significant.

It was observed that the mean duration of stay for the patients in the intensive care unit was lower in the group receiving melatonin (Group M) once compared with the group (Group) which did not receive it.The mean duration of stay in intensive care unit was 2.7 days (range

Table 2: Hemodynamic and respiratory variables between the two groups

Variable	Group M	Group P	P-value
Pre-operative vitals			
HR	81.07±10.94	84.07±11.31	0.301
SBP	134.03±15.81	134.37±13.30	0.930
DBP	79.57±9.36	80.83±9.40	0.603
MAP	97.72±9.98	98.68±8.56	0.689
Vitals at extubation			
HR	90.43±14.46	84.43±12.35	0.089
SBP	135.13±16.97	134.67±16.20	0.914
DBP	81.03±9.01	78.87±7.84	0.326
MAP	99.06±9.74	97.46±8.25	0.127
Extubated	63.3%	53.3%	
Not extubated	36.7%	46.7%	0.432
Requirement of Mechanical ventilation in NSICU			
Yes	36.7%	46.7%	0.432
No	63.3%	53.3%	
Duration of mechanical ventilation	5.6±4.11	7.5±8.32	0.488
Re-intubation			
Yes	6.7%	10%	0.641
No	93.3%	90%	
Duration of stay in NSICU	2.7±2.49	3.2±3.87	0.478

Group M: Group melatonin, Group P: Group placebo, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial blood pressure, NSICU: Neurosurgical intensive care unit

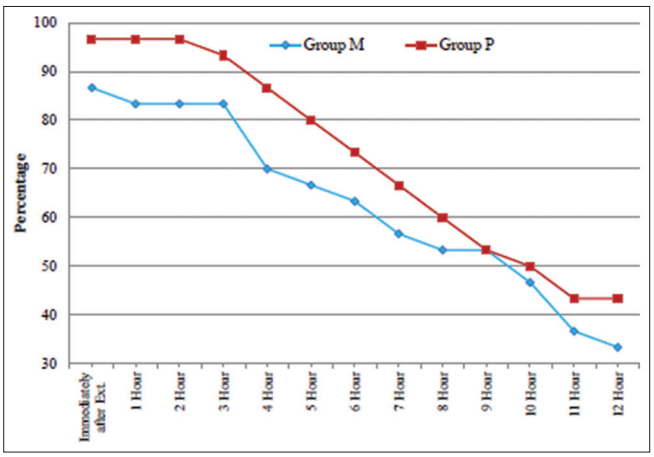

Figure 1: Line diagram showing prevalence of delirium (CAM ICU score) in two groups at various intervals of time (post-extubation to 12 h). Group M: Group Melatonin, Group P: Group Placebo

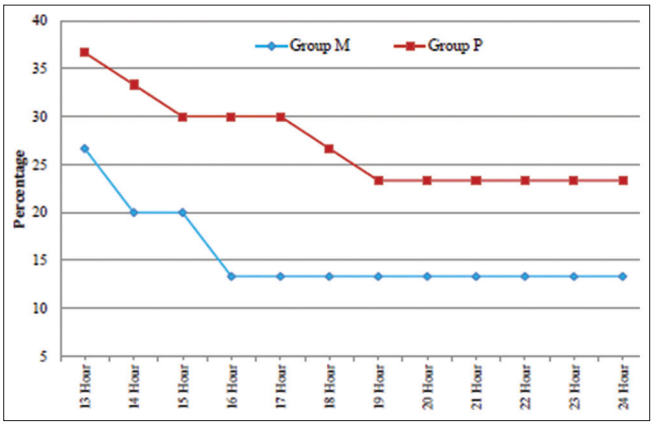

Figure 2: Line diagram depicting prevalence of delirium (CAM ICU score) in two groups at various intervals of time (12 h–24 h). Group M: Group Melatonin, Group P: Group Placebo

of 1–14 Days) in patients receiving melatonin and 3.2 days (1–20 days) in patients who did not receive melatonin (group P).

DISCUSSION

Delirium is a challenging condition in most of the patients admitted in NSICU. Many of these patients have a variable degree of brain dysfunction due to underlying illness such as the intracranial tumor, subarachnoid hemorrhage or intracerebral or intraventricular bleeding. The current study aimed to evaluate the effect of melatonin on the prevalence of delirium and the duration of ICU stay. The patients enrolled in the study underwent a variety of neurosurgical procedures such as aneurysmal clipping, craniotomy with decompression, and transnasal transsphenoidal.

Previous studies have shown that the beneficial effect of exogenous melatonin for sleep and delirium management in ICU patients did not show a consistent pattern.[9-11] The delirium may be caused in the intensive care unit due to abnormal levels of melatonin and loss of circadian rhythms. Previous studies also have the limitations of small sample size, heterogeneous patient populations with various pathologies leading to imbalance of the study variables, and different drug dosage/duration regimens of melatonin administered.

In our study we did not observe remarkable effects of melatonin in reducing the delirium in homogenous cohort of neurosurgical population. This may be as a result of lack of efficacy of melatonin in surgical population once

it is compared with surgical population. Similar findings have been observed by Chen et al., with a limited use of melatonin in reducing the delirium in patients admitted to surgical ICU patients.[12]

In our study, it was observed that the administration of melatonin reduced the prevalence of delirium; however, the reduction in delirium was not significant once compared with the control group. It may be due to the imbalance of other neurotransmitters and hormones related to the stress of surgical procedures such as cortisol, which produce opposite effects to that of melatonin in preventing delirium. It was observed by Coppola et al., delirium may be caused by disturbances in melatonin and cortisol in the postoperative period.[13] The sole supplementation of melatonin may not lead to an appreciable decrease in delirium due to the prevalence of high levels of cortisol in the postoperative period.[14,15] The residual effects of anesthesia may be contributory to delirium in the immediate postoperative period. Hence, the effects of melatonin administration may hence be not profound and efficacious, once compared with the administration of melatonin in medical populations associated with delirium.[16]

One of the main outcomes of our study was to measure the prevalence of ICU-related delirium measured CAM ICU scales. We presumed that melatonin will improve sleep quality and, hence, patients would develop significantly less delirium. However, the presence of very high light and noise levels in the intensive care unit may have mitigated the beneficial effects of melatonin. Melatonin administration, along with augmentation of sleep hygiene and environmental conditions, may have resulted in better results in the reduction of delirium.[17]

Also, from a pharmacological perspective, neurosurgical patients may have an unpredictable effect due to the altered intracranial hemodynamics, as the receptors (MT_1 and MT_2 receptors) for melatonin (MT) are found in the suprachiasmatic nucleus of the hypothalamus. Diffuse cerebral edema, intraventricular bleeds, and subarachnoid hemorrhage, or surgical manipulation may lead to unpredictable effects affecting the efficacy of the melatonin, making the response variable.[18,19] A higher dose of drug or reducing the interval for drug administration may produce better responses, which needs to be confirmed by future studies. The administration of more potent melatonin analogies may also be helpful in reducing delirium in the neurointensive care unit.[20,21]

Limitations of the study

Our study had several limitations. The sample size in our study population was small. We could not ascertain the levels of melatonin in the blood. Increasing age could have caused variable prevalence of delirium and a proper stratification of age between the two groups in our study was not possible.

However, the salient feature of our study was an attempt to explore the promising results of melatonin in a homogeneous population of injured brains and to see whether the administration of melatonin could modulate these effects on delirium. We feel more robust and well-planned randomized controlled trials could answer these questions in a better way in the future.

CONCLUSION

Our study observed that oral administration of melatonin in the pre-operative and intraoperative period in the intensive care unit (in patients who could not be extubated at the end of surgery) decreases the prevalence of delirium and stay in NSICU. However, our study observed that significant beneficial effects could not be achieved. This could be due to multiple other factors (underlying neurological disease, elevated levels of other stress hormones, diffuse cerebral edema, high light, and noise levels in the intensive care unit), which could influence the outcome. A higher dose of melatonin and the use of more potent analogs of melatonin may achieve better results and could be the subject of investigation for future studies.

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Author's Contribution:
AH- Initial data collection, data analysis, prepared first draft of manuscript; **ZA-** Definition of intellectual content, literature survey, implementation of study protocol; **IN-** Concept, design, clinical protocol, manuscript preparation; **AM-** Editing, and manuscript revision; **ZS-** Data collection; **MM-** Design of study, statistical analysis and interpretation; **SAM-** Data collection, data analysis; **IN-** manuscript preparation.

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