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Effects of administration of melatonin on agitation and duration of stay in patients of traumatic brain injury admitted to neurosurgical intensive care unit – A retrospective study

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ABSTRACT

Background: Agitation is frequently encountered in patients recovering from traumatic brain injury (TBI) in the intensive care unit (ICU). The etiopathology for agitation is multifactorial. Melatonin has been widely used to study the effects of delirium in ICU, however, its effect on agitation is not well studied. **Aims and Objectives:** The aim of this study was to assess the effect of melatonin administration on the prevalence of agitation and length of stay in patients with severe TBI, managed conservatively, or undergoing decompressive craniectomy. **Materials and Methods:** A retrospective observational study with 70 patients undergoing various decompressive craniotomy or managed conservatively, and admitted to neurosurgical ICU was included in the study. Thirty-six patients were recruited from the control group and 34 patients received melatonin during their stay in the ICU. In this study, records of 70 patients who had suffered isolated TBI with no associated injuries were analyzed. The patients had a Glasgow coma score of 3–14 on admission to ICU. The patients were managed as per the standard protocols, as per the existing guidelines, and based on TBI guidelines. **Results:** A non-significant decreasing trend of agitation and reduced duration of ICU stay was noted in patients who received melatonin compared with the control group. The prevalence of agitation observed on modified Ramsay scale (Mean ± SD) in patients who received melatonin on Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, and Day 9 were −1.67 ± 3.01; −1.61 ± 2.82; −1.2 ± 2.55; −1.23 ± 2.51; −1.23 ± 2.11; −1.05 ± 2.09; and 0.76 ± 2.03, respectively. These scores were slightly lower than observed in the control group on Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, and Day 9 as −1.58 ± 3.16; −1.33 ± 2.72; −1.08 ± 2.46; −1.13 ± 2.25; −0.94 ± 1.87; −0.52 ± 1.7; and 0.52 ± 1.36, respectively. The mean ± SD duration of stay in ICU of patients receiving melatonin (13.14 ± 3.37) and not receiving melatonin (14.52 ± 3.73) was comparable (P = 0.1). **Conclusion:** Although there was a decreased prevalence of agitation and a decrease in the mean duration of the ICU 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; Agitation; Length of stay; Melatonin

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INTRODUCTION

Patients with traumatic brain injury (TBI) present with loss of consciousness and aberrant motor behaviors associated with agitation and combativeness. The prevalence of agitation in hospitalized patients with TBI ranges from 10% and 90%.[1] Post-traumatic agitation may be caused by altered brain metabolism, dysregulation of dopaminergic

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transmission, and remodeling of neural network.[2] Sufficient pain relief, regulation of the light-dark cycle simulation, adequate hydration, and electrolyte balance may be the initial approaches taken to reduce agitation. Antipsychotics (typical and atypical) are used widely for prophylaxis and treatment of agitation in head injury patients. However, their efficacy and safety are questionable. Due to the dopaminergic suppression associated with antipsychotics, impaired cognitive recovery may be seen. Retrospective clinical studies have shown that using antipsychotics to treat post-traumatic delirium can impair cognitive recovery and consequently recovery of consciousness.[3] Prospective animal studies suggest that both typical and atypical antipsychotics may hinder recovery from TBI-related deficits.[4-6] These results suggest that dopaminergic suppression interferes with arousal and consequently recovery of consciousness.

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.[7] It has minimum potential for abuse, less cognitive impairment, no extrapyramidal side effects, or respiratory depression.[7] Melatonin has neuroprotective effects in head injury and may not lead to adverse effects associated with the use of antipsychotics.

Aims and objectives

The primary aim of our study was to compare the effects of oral administration of melatonin on the prevalence of agitation in TBI patients with the control group. 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 retrospective, observational study was conducted in the Neurointensive care unit at a tertiary care hospital in Northern India from January 2020 to December 2023 after obtaining clearance from the Institutional Ethics Committee (IEC/SKIMS Protocol #RP 20-2019). The records of all adult patients above the age of 18 years admitted with moderate to severe head injury were reviewed by the authors.

Inclusion criteria

The patients who were incorporated in the study were patients who had suffered isolated TBI with no associated injuries. The patients had a Glasgow coma scale (GCS) score of 3–14 on admission to the intensive care unit (ICU). The patients were managed as per the standard protocols as per the existing guidelines for the management of TBI based on TBI guidelines.

Exclusion criteria

The exclusion criteria were (a) patients who had a poor neurological recovery with no purposeful responses (no eye-opening and/or extensor or no motor response), (b) patients who had associated chest/lung injuries, abdominal trauma or long bone fractures; (c) patients on antipsychotic medication; (d) history of any substance abuse; (e) expected death within next 48 h; (f) chronic renal failure, hepatic impairment with Child-Pugh class B and C; (g) receiving massive blood transfusion in the intraoperative period, or with coagulopathy. The case records and the treatment charts were analyzed for the administration of the medicines received in the ICU, the presence or absence of melatonin for sedation, the neurological status of the patient during the course of ICU stay, duration of stay in the neurointensive care unit, modified Ramsay sedation score, presence or absence of sedation that needed restraint, need for sedative agents/antipsychotics for controlling the agitation. 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 agitation and delirium in control group (not receiving melatonin) as 85% a total sample size of 60 was needed with 30 patients in each group. A total of 90 patients were included in the study. Out of these 90 patients, 20 patients were excluded from the final analysis due to a poor neurological recovery. (34 Patients receiving melatonin and 36 who did not receive melatonin).

As a standard institutional protocol, all patients with severe TBI received, Injection midazolam (0.01 mg/kg/h) and injection fentanyl (1–2 μg/kg/h) until tracheal extubation was planned. Once tracheal extubation was planned, the infusions of injection fentanyl and injection midazolam for sedation were stopped. Once the patients regained consciousness, responded to verbal commands, and had adequate recovery of neuromuscular power, the tracheal extubation was done. In patients who were not found to be meeting the criteria for tracheal extubation, a planned tracheostomy was done. Data were noted on the modified Ramsay sedation scores after extubation or after tracheostomy for 5 days.

The data were 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 were 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. P<0.05 was considered statistically significant. All P-values were two-tailed.

RESULTS

On reviewing the records of patients admitted from January 2020 to December 2023, a total of 90 patients were incorporated in the study. Out of these 90 patients, 20 patients were excluded from the final analysis due to poor neurological recovery (GCS 3, brain dead or death) in these patients. All the patients enrolled had severe TBI with a GCS score of <8 and a need for tracheal intubation and mechanical ventilation. The patients who died, during the course of the study or failed to show any purposeful response were excluded from the final analysis. The patients included in the study, had acute subdural hematomas, acute extradural hematomas, and multiple brain contusions.

It was observed that out of these, 34 patients received melatonin (Group M), and 36 did not receive melatonin (Group C). 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). In Group M five patients were managed conservatively while as twenty-nine patients underwent decompressive craniectomy. In Group C, six patients were managed conservatively while as 29 patients underwent decompressive craniectomy. The nature of the surgical procedure, duration of the surgical procedure, and duration of mechanical ventilation in the ICU, between the two groups were comparable (Table 1).

At the end of the surgical procedure, none of the patients could be extubated, due to a low GCS score. All the patients in both groups needed mechanical ventilation in the post-operative period due to a low GCS score. In our study, out of 34 patients in group M receiving melatonin 24 patients were hemodynamically unstable at the end of surgery and in need of inotropic support. Twenty patients were having metabolic acidosis at the end of the surgical procedure in group M receiving melatonin. In the control group (Group C), 25 patients out of 36 patients were hemodynamically unstable at the end of surgery with 21 patients in need of inotropic support.

The mean duration of mechanical ventilation in the ICU was comparable (P=0.98) in patients receiving Melatonin (mean of 66.83 h with an SD of 26.39 h) and control group (mean of 67.05 h with an SD of 29.85 h) (Table 2).

Figure 1 depicts the incidence of agitation in Group M and Group P on various days for the initial 1 week from 72 h after initiation of mechanical ventilation. The average RAS scores in the group receiving melatonin on all days were lower once compared with the control group. There was no significant statistical difference in the modified RAS scores between the two groups.

It was observed that the mean duration of stay for the patients in the ICU was lower in the group receiving melatonin (Group M) once compared with the group (Group) which

Table 1: Demographic characteristics of the study population

Variable	Group M n=34 (%)	Group P n=36 (%)	P-valve (CI)
Age	43.50±13.5	44.72±13.81	0.71 (−5.29–7.73)
Gender: Male	19 (55.9)	23 (63.9)	
Female	15 (44.1)	13 (36.1)	0.49 (−14.31–29.34)
Comorbidities			
HTN	5 (14.7)	3 (8.3)	0.40 (−9.40–22.75)
Hypothyroidism	2 (5.9)	4 (11.1)	0.44 (−9.61–20.02)
DM	2 (5.9)	1 (2.7)	0.51 (−8.92–16.60)
Seizure disorder	1 (2.9)	1 (2.7)	0.95 (−1.40–12.36)
CAD	1 (2.9)	1 (2.7)	0.95 (−1.40–12.36)
COPD	1 (2.9)	0	1.0 (−7.03–14.85)
Total	12 (35.2)	10 (27.7)	0.50 (−13.78–28.08)
Type of surgery			
Extradural hematoma	10 (29.4)	11 (30.5)	0.92 (−19.82–21.68)
Subdural Hematoma	9 (26.4)	11 (30.5)	0.70 (−16.73–24.25)
Cerebral contusions	12 (35.2)	9 (25.0)	0.35 (−10.97–30.41)
Diffuse Axonal injury	3 (8.8)	5 (13.8)	0.51 (−11.12–20.84)
Duration of Surgery (minutes)	144.11±63.87	143.33±59.32	0.95 (−30.16–28.60)

Demographic profile of the patients: Group M- Group Melatonin, Group P- Group Placebo, HTN: Hypertension, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease

Table 2: Patient characteristics of the study population

Variable	Group M n=34 (%)	Group P n=36 (%)	P-value (CI)
Pre-operative vitals			
HR	79.91±10.73	84.13±10.59	0.10 (−0.86–9.30)
SBP	133.05±15.04	133.83±12.71	0.81 (−5.84–7.40)
DBP	78.97±8.92	80.19±9.61	0.58 (−3.20–5.64)
MAP	97.32±9.38	98.38±8.25	0.61 (−3.14–5.26)
Duration of MV	5.6±4.11	7.5±8.32	0.23 (−1.25–5.05)
Inotropic support			
Yes	24 (70.5)	25 (69.4)	0.92 (−9.84–21.70)
No	10 (29.4)	11 (30.5)	
Metabolic acidosis			
Yes	20 (58.8)	21 (58.3)	0.96 (−1.56–22.40)
No	14 (41.1)	15 (41.6)	
Anisocoria			
Yes	3 (8.8)	4 (11.1)	0.75 (13.33–17.62)
No	31 (91.1)	30 (83.3)	0.33 (8.87–24.10)
Duration of stay in NSICU (Days)	13.14±3.37	14.52±3.73	0.1096 (−0.31–3.07)

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, MV: Mechanical ventilation

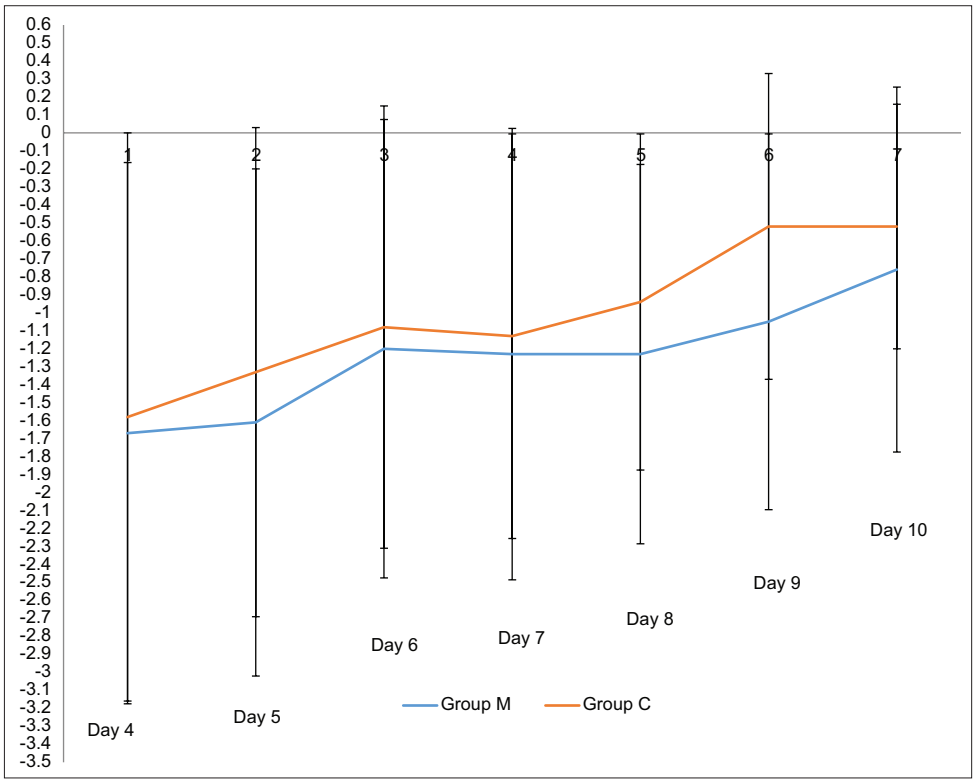

Figure 1: Prevalence of agitation (Modified RAS score) in Group M and Group C at various intervals of time (Day 4 to Day 10). Group M- Group Melatonin, Group C- Control Group. The data points are chronologically arranged from day 4 to day 10 from left to right

did not receive it. The mean duration of stay in ICU was 13.14 days (in patients receiving melatonin and 17.51 days in patients who did not receive melatonin (Group C).

DISCUSSION

Agitation and aggressiveness are major issues in the neuro-ICU in patients who are recovering from TBI. These patients are difficult to manage and their recovery, mobilization, and liberation from mechanical ventilation get impaired.[9] The patients in our study suffered a severe head injury and were either managed conservatively or operated for the same. Most of these patients have a severe degree of brain dysfunction due to severe trauma.[7] The present study was aimed to evaluate the effect of melatonin on the amelioration of agitation and the duration of stay in the neurointensive care unit.

Low serum melatonin levels are associated with delirium and agitation in adult patients.[10] Melatonin has the advantages of having anti-inflammatory, anxiolytic, and analgesic properties, which may lead to a reduction in the incidence of delirium and agitation.[11,12] It was observed in our study that though the administration of melatonin reduced the incidence of agitation and the duration of stay in ICU, these effects were not significant. This may have been a result of the multifactorial pathology leading to agitation in our patient population.

Zhang et al., observed that there was a significant decrease in the incidence of emergence agitation with the administration of melatonin compared with placebos and midazolam.[13] Similarly melatonin at doses of melatonin 0.1 mg/kg in children was found to be effective in reducing the incidence of emergence agitation in children after sevoflurane anesthesia.[14] Gehrman et al., observed that there were no significant differences ($P>0.05$) in treatment effects, between the melatonin and placebo-treated groups in the observed agitated behavior rating scale (physical or verbal agitation) in patients with Alzheimer disease.[15] It was observed by You et al., that melatonin reduced the rate of delirium in medical patients, while the role of melatonin in reducing the incidence of delirium in surgical patients and critical care unit patients was variable and required further study.[16] The results of our study were different from these studies. The administration of melatonin may have reduced the agitation due to pharmacological actions of the drug; however, the reduction in agitation may not be 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 produces opposite effects to that of melatonin in preventing delirium, and other confounding factors such as sepsis, hypoxia, metabolic disturbances, pain, and infusions of multiple sedative drugs. The presence of very high light intensity and noise levels in the ICU, with a lack of proper sleep hygienically environment may have additionally reduced the beneficial effects of melatonin. Our patients were a cohort of patients with severe TBI, where the effects of melatonin on suprachiasmatic nucleus of the hypothalamus (on MT_1 and MT_2 receptors) would have been offset by cerebral edema. A higher dose of a drug or reducing the interval for drug administration may result in a better response in future studies.

Soltani et al., showed that morphine consumption and mechanical ventilation time were significantly lower in the melatonin group than in the control.[17] There was a reduction in the ICU stay and a better GCS in the melatonin group within a shorter period seen with the administration of melatonin once compared with the control group. These results were not similar to our study, where it was observed that the administration of melatonin did not reduce significantly, the duration of stay in ICU compared with the control group. This may be due to multiple factors such as age, comorbidities, sepsis, electrolyte imbalance, and involvement of other organ systems of the patients in our study population. Delirium may be caused by multiple factors as neuroinflammation, hypoxia, alterations in energy metabolism, and imbalances in multiple neurotransmitter pathways. The use of melatonin may target only a few of these potential mechanisms and may be the reason for the limited efficacy of melatonin in our study.[18] A systematic review comparing medications used for management of delirium symptoms (antipsychotics, alpha-2 agonists, benzodiazepines, antidepressants, acetylcholinesterase inhibitors, melatonin, opioids, and antiemetics has found variable results due to multifactorial pathology.[19] A combination of dexmedetomidine, oral melatonin, or other alpha-2 agonists may show better results.[20] The introduction of prolonged-release preparations of melatonin or longer-acting analogs may also show better results in the clinical practice.[21]

However, the salient feature of our study was an attempt to explore the promising results of melatonin, in a homogenous population of TBI patients and to see whether the administration of melatonin could reduce the incidence of agitation in this patient population. Future studies aimed at studying the effects of melatonin on mild, moderate, and severe head injury may help to give better results.

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. A lack of proper stratification depending on the intensity of TBI was not possible. We could not study the need for decreased requirement non-pharmacological maneuvers (restraint) or the use of pharmacological interventions (antipsychotics) to reduce the prevalence of agitation.

CONCLUSION

Our study observed that oral administration of melatonin in the intraoperative period in the ICU do not decrease the incidence of agitation and stay in NSICU. Although there was a reduction in the prevalence of delirium, however, it was not of any clinical significance. Other factors as severity of the head injury, other comorbid functions, age, and sepsis could be contributory to the agitation in the neurointensive care unit. A higher dose

of melatonin and the use of more potent analogs of melatonin may be investigated in the future to achieve better results.

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REFERENCES

1. Rahmani E, Lemelle T, Sharp H, Smarbafzadeh E and Kablinger A. A descriptive analysis of pharmacological management of aggression and/or agitation in patients with traumatic brain injury in a Southwest Virginia inpatient population. J Clin Pharm Ther. 2022;47(12):2083-2090.
   https://doi.org/10.1111/jcpt.13754
2. Ganau M, Lavinio A and Prisco L. Delirium and agitation in traumatic brain injury patients: An update on pathological hypotheses and treatment options. Minerva Anestesiol. 2018;84(5):632-640.
   https://doi.org/10.23736/S0375-9393.18.12294-2
3. Nikooie R, Neufeld KJ, Oh ES, Wilson LM, Zhang A, Robinson KA, et al. Antipsychotics for treating delirium in hospitalized adults: A systematic review. Ann Intern Med. 2019;171(7):485-495.
   https://doi.org/10.7326/M19-1860
4. Hoffman AN, Cheng JP, Zafonte RD and Kline AE. Administration of haloperidol and risperidone after neurobehavioral testing hinders the recovery of traumatic brain injury-induced deficits. Life Sci. 2008;83(17-18):602-607.
   https://doi.org/10.1016/j.lfs.2008.08.007
5. Wilson MS, Gibson CJ and Hamm RJ. Haloperidol, but not olanzapine, impairs cognitive performance after traumatic brain injury in rats. Am J Phys Med Rehabil. 2003;82(1):871-879.
   https://doi.org/10.1097/01.PHM.0000091982.33232.CB
6. Folweiler KA, Bondi CO, Ogunsanya EA, Laporte MJ, Leary JB, Radabaugh HL, et al. Combining the antipsychotic drug haloperidol and environmental enrichment after traumatic brain injury is a double-edged sword. J Neurotrauma. 2017;34(2):451-458.
   https://doi.org/10.1089/neu.2016.4417
7. Lewandowska K, Małkiewicz MA, Siemiński M, Cubała WJ, Winklewski PJ and Mędrzycka-Dąbrowska WA. The role of melatonin and melatonin receptor agonist in the prevention of sleep disturbances and delirium in intensive care unit - a clinical review. Sleep Med. 2020;69:127-134.
   https://doi.org/10.1016/j.sleep.2020.01.019
8. Vijayakumar HN, Ramya K, Duggappa DR, Gowda KV, Sudheesh K, Nethra SS, et al. Effect of melatonin on duration of delirium in organophosphorus compound poisoning patients: A double-blind randomised placebo controlled trial. Indian J Anaesth. 2016;60(11):814-820.
   https://doi.org/10.4103/0019-5049.193664
9. Reznik ME, Schmidt JM, Mahta A, Agarwal S, Roh DJ, Park S, et al. Agitation after subarachnoid hemorrhage: A frequent omen of hospital complications associated with worse outcomes. Neurocrit Care. 2017;26(3):428-435.
   https://doi.org/10.1007/s12028-016-0331-1
10. Shen QH, Li HF, Zhou XY, Lu YP and Yuan XZ. Relation of serum melatonin levels to postoperative delirium in older patients undergoing major abdominal surgery. J Int Med Res. 2020;48(3):300060520910642.
    https://doi.org/10.1177/0300060520910642
11. Won E, Na KS and Kim YK. Associations between melatonin, neuroinflammation, and brain alterations in depression. Int J Mol Sci. 2021;23(1):305.
    https://doi.org/10.3390/ijms23010305
12. Samarkandi A, Naguib M, Riad W, Thalaj A, Alotibi W, Aldammas F, et al. Melatonin vs. midazolam premedication in children: A double-blind, placebo-controlled study. Eur J Anaesthesiol. 2005;22(3):189-196.
    https://doi.org/10.1097/00003643-200503000-00005
13. Zhang D, Jia X, Lin D and Ma J. Melatonin or its analogs as premedication to prevent emergence agitation in children: A systematic review and meta-analysis. BMC Anesthesiol. 2023;23(1):392.
    https://doi.org/10.1186/s12871-023-02356-x
14. Özcengiz D, Gunes Y and Ozmete O. Oral melatonin, dexmedetomidine, and midazolam for prevention of postoperative agitation in children. J Anesth. 2011;25(2):184-188.
    https://doi.org/10.1007/s00540-011-1099-2
15. Gehrman PR, Connor DJ, Martin JL, Shochat T, Corey-Bloom J and Ancoli-Israel S. Melatonin fails to improve sleep or agitation in double-blind randomized placebo-controlled trial of institutionalized patients with Alzheimer disease. Am J Geriatr Psychiatry. 2009;17(2):166-169.
    https://doi.org/10.1097/JGP.0b013e318187de18
16. You W, Fan XY, Lei C, Nie CC, Chen Y and Wang XL. Melatonin intervention to prevent delirium in hospitalized patients: A meta-analysis. World J Clin Cases. 2022;10(12):3773-3786.
    https://doi.org/10.12998/wjcc.v10.i12.3773
17. Soltani F, Salari A, Javaherforooshzadeh F, Nassajjian N and Kalantari F. The effect of melatonin on reduction in the need for sedative agents and duration of mechanical ventilation in traumatic intracranial hemorrhage patients: A randomized controlled trial. Eur J Trauma Emerg Surg. 2022;48(1):545-551.
    https://doi.org/10.1007/s00068-020-01449-3
18. Prendergast NT, Tiberio PJ and Girard TD. Treatment of delirium during critical illness. Annu Rev Med. 2022;73:407-421.
    https://doi.org/10.1146/annurev-med-042220-013015
19. Sadlonova M, Duque L, Smith D, Madva EN, Amonoo HL, Vogelsang J, et al. Pharmacologic treatment of delirium symptoms: A systematic review. Gen Hosp Psychiatry. 2022;79:60-75.
    https://doi.org/10.1016/j.genhosppsych.2022.10.010
20. Daou M, Telias I, Younes M, Brochard L and Wilcox ME. Abnormal sleep, circadian rhythm disruption, and delirium in the ICU: Are they related? Front Neurol. 2020;11:549908.
    https://doi.org/10.3389/fneur.2020.549908
21. Wade AG, Ford I, Crawford G, McMahon AD, Nir T, LaudonM, et al. Efficacy of prolonged release melatonin in insomnia patients aged 55 - 80 years: Quality of sleep and next-day alertness outcomes. Curr Med Res Opin. 2007;23(10):2597-2605.
    https://doi.org/10.1185/030079907X233098

Authors' Contribution:
ZA- Initial data collection, data analysis, prepared first draft of manuscript; **IN-** Clinical protocol, manuscript preparation; **SAM-** Editing, and manuscript revision; **ZS-** Data collection, data analysis; **AM-** Statistical analysis and interpretation; **EA-** Data collection, data analysis; and **MR-** Coordination and manuscript revision.

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