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COMPARISON OF EFFICACY OF MELATONIN VS OLANZAPINE IN TREATING DELIRIUM IN CRITICALLY ILL PATIENTS: A PROSPECTIVE RANDOMIZED CONTROL STUDY

Anaesthesiology

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ABSTRACT

Delirium is very common in patients admitted to intensive care units (ICU) and leads to increased morbidity. It has multi-factorial aetiology and sleep deprivation as well as sleep quality play important role. The anti-psychotic drug olanzapine is established for treatment but has limitation of prolongation of Qtc interval. Melatonin, a sleep modulating compound, is devoid of major side effects in therapeutic doses and has been used in prevention of delirium. This study was aimed at comparing the effectiveness of melatonin vs olanzapine in treating delirium in critically ill patients. **Methods:** This prospective randomized double blind comparative study was conducted after approval from institutional ethical committee and registration with CTRI (CTRI/2021/05/033908). All ICU patients were assessed daily for the development of delirium, using CAM-ICU (Confusion Assessment Method) score. Those diagnosed with delirium and fulfilling inclusion criteria, were randomly allocated in three groups of 50 each, by computer generated tables. Group M: receiving melatonin 9mg; Group O: receiving olanzapine5mg; Group C: receiving haloperidol 2.5mg, as daily oral doses. The participants were tested daily using revised delirium rating scale (DRS-R-98) scores and the duration and severity of delirium was noted. The side effects were also noted. The data was analysed using independent t test, p value <0.05 was considered statistically significant. **Results:** There was no significant difference between the olanzapine and melatonin group in terms of DRS -R98 score from baseline to all the 5 consecutive days. **Conclusion:** Melatonin is as effective as olanzapine in the treatment of delirium

KEYWORDS

critical illness, delirium, effectiveness, melatonin, olanzapine, sleep deprivation.

INTRODUCTION

Delirium is a neuropsychiatric syndrome incorporating disturbances in consciousness, attention, cognition and perception and is frequently observed in patients admitted to intensive care units (ICU). The closed environment preventing sunlight, noises of monitors, indwelling catheters, tubbings, minimum interaction with family members are important factors which precipitate delirium in ICU patients. It has an acute onset and a fluctuating course that is usually developed within hours and continued from several days to several weeks, or even months.

Its incidence being 11% to 80% and is associated with increased suffering of patient and family, lengthened ICU stay as well as overall hospital stay and increased cost of treatment[1]. Recognizing delirium and establishing its diagnosis remains a challenge even in the expert hands. It can be evaluated through reliable tools such as Confusion Assessment Method for the Intensive Care Unit (CAM- ICU score) and Intensive Care Delirium Screening Checklist (ICDSC score). CAM- ICU rating indicated a high sensitivity (93%) and specificity (89%) for diagnosing delirium, while the ICDSC scoring showed a higher sensitivity (99%) but a lower specificity (64%)than CAM- ICU score[2]. As a protocol, all ICU patients should be continuously monitored and assessed daily for any sign of delirium and the treatment should be initiated as early as possible so as to have a better prognosis.

Clinical management and pharmacologic treatment of delirium requires more exploration. Haloperidol is most commonly used in treating delirium but cognitive numbness, dysphoria, extrapyramidal side effects such as akathisia and oropharyngeal dysfunction; neuroleptic malignant syndrome and dystonic reactions, including laryngospasm and trismus are very disturbing[3]. Newer antipsychotics such as quetiapine and olanzapine are used in treatment of delirium but prolongation of Q Tc interval is the major limitation to their use[4].

Among the various hypotheses, its aetiology of delirium is attributed to alteration in the 24-hour circadian rhythm, resulting in the alteration in normal sleep cycle; as well as the quality of sleep[5]. Since melatonin, a naturally occurring pineal hormone, is established in maintaining normal sleep cycle as well as sleep quality, we hypothesized that it can be a useful medication in treating the delirium. Moreover, it is hypothesized that melatonin secretion is delayed or low in older individuals with delirium, thereby increasing the incidence of delirium. The available data also indicates that there is a suppression of the nocturnal peak level of melatonin and a decline in the circadian amplitude of the melatonin rhythm in older adults. Various studies have established the use of melatonin in preventing delirium but literature is scarce regarding its use in treating delirium. Literature regarding comparison of olanzapine and melatonin is very scarce, hence the appropriateness of the study.

METHODS

This hospital based, prospective, randomized, double blind, comparative study was conducted at intensive care unit of a tertiary care hospital. Before commencing the study, permission was obtained from institutional ethical committee. It was registered with CTRI (Clinical Trials Registry of India): CTRI/2021/05/033908 on 30/05/2021. The period of study was from June 2021 till September 2022. Written informed consent was obtained from the patient or attendant mainly parent/spouse /adult child before enrolling them for the study. The person giving consent knew that he/she has the right to refuse to be a part of the study. The procedures were conducted in accordance with the Helsinki declaration-2013.All patients admitted to the intensive care unit were assessed daily for the development of delirium, using CAM- ICU (Confusion Assessment Method) score as a routine protocol[2].

Patients who were diagnosed with delirium through CAM- ICU score, were randomly allocated in three groups of 50 patients each by computer generated randomization tables.

Group M: Patients receiving melatonin 9mg orally as a daily dose
Group O: Patients receiving olanzapine5mg orally as a daily dose
Group C: Patients receiving haloperidol 2.5mg orally as a daily dose

Critically ill patients aged 18-65 years, of either gender, having delirium, verbally responsive and not having dementia were included in the study. Patients who had previous history of seizure or active seizure, severe pre-existing cognitive or neuron-degenerative disease or any absolute contraindication to enteral nutrition were not included in the study. Likewise, those having less than 5 days of ICU stay, on neuromuscular blocking agents for mechanical ventilation, comatose and deeply sedated patients; those with history of drug allergy, pregnant or lactating females and those not giving consent, were excluded from the study.

The study participants were randomized into one of the study groups, using computer generated randomization tables. After randomization, the intensivist prescribed the study drug orally or via enteral tube within 5h of the diagnosis of delirium. The drugs were supplied in sealed envelopes by the hospital pharmacy and were administered by the critical care nurse unaware of the study. Patients were also unaware of the drug administered. These measures were taken so as to minimize observer's bias. The study drugs were administered as single daily doses orally or through nasogastric tube, within 5 hours of the diagnosis of delirium, preferably in the evening hours. The participants were tested every 24 hours using the DRS-98 score. The duration and severity of delirium was noted based on this score. We also observed for complications like drowsiness, respiratory depression, headache, drug dependence, carry-over effect and nightmares. If the patients did not respond to treatment, they were excluded from the study and alternative drugs used for treatment of delirium as per advice of the psychiatrist.

The primary end point was to assess the severity and duration of delirium as measured with the modified delirium rating scale (DRS-R-98) scores. The secondary end point was the duration of ICU stay.

Delirium Rating Scale-Revised-98 (DRS-R-98)

3 ITEMS FOR DIAGNOSIS: (scored from 0-2 or 0-3)
(1) Temporal onset of items
(2) Fluctuation of symptom severity
(3) Physical disorder

13 ITEMS FOR SEVERITY: (scored from 0-3)
(1) Sleep-wake cycle disturbance
(2) Perceptual disturbances
(3) Delusions
(4) Lability of affect
(5) Language
(6) Thought process abnormalities
(7) Motor agitation
(8) Motor retardation
(9) Orientation
(10) Attention.
(11) Short
(12) Long
(13) Visuospatial ability.

The details were recorded in the prescribed proforma. The sample size was estimated based on the method of one-way ANOVA. By anticipating the effect size of 0.26 across the three groups, the final sample size was estimated to be 147 overall i.e., 49 subjects in each group with 5% level of significance and 80% power. Hence, we rounded off to 50 patients in each group.

All the readings were noted in a prescribed patient proforma. The data were analysed using IBM (International Business Machines) statistical software SPSS (Statistical Package for Social Sciences) version 25.0. Qualitative data were represented as frequency and proportion. Quantitative data were represented as mean and standard deviation. For comparison of continuous parametric data independent t-test was used and for categorical data Pearson's chi-square test was used. P value <0.05 was considered as statistically significant.

RESULTS

The study groups were demographically identical. [Table 1] The baseline DRS-R-98 score at the start of treatment was around 30 and was comparable in all the groups. Mean age was around 45-65 years in all the groups, those above 65 were lesser in percentage. Moreover, male patients outnumbered female ones in both groups.

Table 1: Comparison of demographic profiles

Variables	Group C	Group O	Group M	P value
Age(years) (Mean±S.D.)	52.76±17.96	51.19±15.29	52.17±13.26	0.835
<65 years	19 (63.33%)	21(70%)	23(76.67%)	0.530
≥ 65 years	11± (36.67%)	9(30%)	7(23.33%)	
Male	35(70%)	30(60%)	28(56.67%)	0.541
Female	15(40%)	20(40%)	12(43.33%)	

Group O(olanzapine) and group M(melatonin) patients had significantly lower DRS-R-98scores than group C at day 4, day 5 and day 6; however, there was no significant difference between the olanzapine and melatonin groups. [Table 2]. (p<0.05).

Table 2: Comparison of Total DRS-R-98 score

Day after diagnosing delirium	Group C	Group O	Group M	P-value		
				Group C v/s Group O	Group C v/s Group M	Group M v/s Group O
Baseline	29.46± 1.89	30.23± 2.33	30.28± 2.72	0.235	0.334	0.319
Day 1	24.30± 1.71	24.95 ±1.87	26.55 ±2.89	0.226	0.323	0.412
Day 2	20.34 ±3.16	17.89 ±3.34	17.65 ±5.63	0.032	0.002	0.0542
Day 3	13.45 ±7.35	11.63 ±2.97	10.58 ±6.98	0.022	0.021	0.762
Day 4	12.42 ±6.45	9.22 ±3.16	10.32 ±7.12	0.001	0.023	0.569
Day 5	9.95 ±5.56	5.25 ±2.64	6.73 ±7.53	<0.001	<0.001	0.629
Day 6	7.23 ±3.57	3.63 ±1.56	5.35 ±7.59	<0.001	<0.001	0.051
Independent t-test						

Also; both olanzapine and melatonin group patients had significantly lower score at day 3, day 4 and day 5 than haloperidol arm (Group C) (p>0.05). There was no significant difference between the Group O, Group M and Group C (haloperidol group) in terms of CAM- ICU score at the time of inclusion in the study. The duration of stay was significantly shorter in olanzapine and melatonin arm as compared to haloperidol (p<0.05). But there was no significant difference in olanzapine and melatonin in term of duration of stay(p>0.05). [Table3]

Table 3: Baseline CAM-ICU score and duration of stay in hospital

Variable	Group C	Group O	Group M	P-value		
				Group C v/s Group O	Group C v/s Group M	Group M v/s Group O
Baseline CAM-ICU score	4.33± 0.79	4.63± 0.53	4.58± 0.62	0.352	0.237	0.359
Duration of stay (days)	7.33± 3.79	5.63±2.33	5.58±2.62	<0.001	<0.001	0.592

There were no significant complications observed in the study groups. Two patients in group C had dizziness and one in group O had restlessness. There were no complications in the group M.

DISCUSSION

Delirium is frequently related to disruption of normal sleep. The sleep disturbances in delirium include sleep fragmentation, poor night time sleep and frequent short day time naps. Thus, there is disrupted sleep cycle overall sleep quality is poor[6]. Various factors that have been linked with poor sleep quality in critically ill patients include severity of the critical illness, lack of natural sun light, ambient noise, multiple tubing, pain, use of polypharmacy and mechanical ventilation[7,8]. From the sleep perspective, earlier, it was believed that sedation could be useful in preventing delirium. However, with more research, it has been emphasized that not only total sleep duration, but also the preservation of sleep architecture is essential for prevention and management of delirium. Melatonin is a routine drug for managing jet lag. It is established in maintaining sleep- wake cycle as well as preserving normal quality of sleep[5]. Accordingly, it is hypothesized that melatonin, which has an important role in regulating circadian rhythm, may be of some benefit in preventing and managing delirium. Further, melatonin is considered to have a benign side effect profile and is considered to have no influence on QTc interval[9]. Due to this, it can be considered as a safer option among patients with prolonged QTc interval.

At present, some studies are available regarding use of melatonin in preventing delirium, but there is limited information on the role of melatonin in the management of delirium. A study compared melatonin with ramelteon suggests that their use is associated with reduction in severity of delirium and reduction in agitation[10].

The literature regarding the use of melatonin in treatment of delirium in critically ill patients is very scarce. It has been stated that melatonin may have some benefit in the prevention and management of delirium in older adults. However, there is no evidence that melatonin reduces the severity of delirium or has any effect on behaviour or functions in individuals. Anti-psychotics are considered as the preferred agents in treating patients with delirium. However, a major concern with their use of is QTc prolongation. However, melatonin is not known to be associated with prolongation of QTc interval. A retrospective study compared the effectiveness of melatonin versus antipsychotics drug quetiapine in treating critically ill patients diagnosed with delirium. They assessed the severity of delirium using DRS-R-98 and MMSE (Mini Mental State Examination) scores and observed that melatonin is as effective as quetiapine in the management of delirium. They concluded that melatonin may be another pharmacological option for the treatment of delirium, especially among patients with prolonged QTc interval[11].

These observations are consistent with our study. We compared the effectiveness of melatonin with anti-psychotic drug, olanzapine for treating delirium in ICU patients. To the best of our search of literature, we did not find a similar study. Findings of the present study suggest that melatonin is as effective as haloperidol and olanzapine in the management of delirium. It suggests that melatonin may be a good alternative for the management of delirium.

The doses of melatonin used for treatment of delirium varies within a wide range from 3mg up to 10 mg daily oral dose[12]. Hence, we conducted a pilot study comparing 3 mg, 6mg and 9 mg daily oral dosing of melatonin. We observed that 9 mg dose was effective in treating delirium in majority of patients. Thus, the justification of dose used in our study. Regarding the dose of haloperidol and olanzapine, a group of researchers have compared 2.5 mg haloperidol and 5 mg olanzapine were equally effective in treating delirium[3]. Hence the doses of these drugs used in our study.

CONCLUSION

Thus, we conclude that melatonin is as effective as haloperidol and olanzapine in management of delirium. Since it is devoid of major side effects, it can be a better drug for treatment of delirium.

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