

Scope of Melatonin in Critically Ill Patients Admitted to Intensive Care Unit (ICU): Need for an Integrated Intervention Care Bundle

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Abstract

Lack of quality sleep is a major concern in severely ill patients admitted to intensive care units (ICU) across the world. They are regularly under influence of sedatives to tolerate invasive ventilation. These patients experience altered sleep circadian rhythm, minimal sleep in restorative phase, marked by frequent disruptions caused by nursing and medical interventions and ambient noise during the night.

Interestingly, approximately 50% have switched their sleep pattern to day time. Melatonin's primary physiological function is to convey to human body daily circadian variation in of day light and darkness of night.

In view of high safety profile and benefits, melatonin has a crucial part in improving sleep in these critically ill patients. Whilst further multi-center clinical trials to address efficacy and efficiency of melatonin are needed, we explore role of an 'INTEGRATED' intervention sleep care bundle in an ICU setting.

Keywords: Melatonin; Critically Ill Patients; ICU

Introduction

Lack of quality sleep is a major concern in critically ill patients admitted to an ICUs across the world. Lack of quality sleep and latency in onset of sleep were amongst the top sources of anxiety experienced by these patients during their ICU stay [1-3]. They experience altered sleep circadian rhythm, minimal sleep in restorative phase, marked by frequent disruptions. Even though ICU patients may experience near normal total sleep time (TST), interestingly more than half of that sleep occurs during the daytime [4,5].

Despite several advancements in health care technology, design and allied and nursing personnel training, it has not translated into better sleep patterns for ICU patients [5-7]. Factors contribution to poor quality sleep in the ICU setting including ambient noise, artificial lighting, nursing and medical interventions, presence of co-existing diseases, sedative and opioid agents and both non-invasive and invasive ventilation [8-12].

Furthermore, ICU sleep deprivation is associated with detrimental outcomes, including delirium, difficulty weaning from invasive mechanical ventilation, increased nosocomial infections, prolonged ICU length of stay (LOS) and increased ICU mortality [13]. Sleep goals

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for ICU patients are to get enough sleep, reset disordered circadian rhythms, adjust abnormal sleep structure, reduce sleep interruption, overcome fatigue and anxiety, facilitate nursing care and treat disease.

At present, there is no ideal effective treatment in use to improve ICU sleep that covers all of these ideal properties. Recently melatonin, a physiological sleep aid, has gained interest among ICU scholars. Melatonin could be effective for insomnia and daytime sleepiness caused by time zone changes [14] and work shifts [15] that induce the malfunctioning of biological clocks. It maintains synchronisation in situations where the circadian rhythms are jeopardized and resynchronize after a period of free-run release.

It could also improve the sleep quality of non-ICU critically ill patients with dialysis [16], moderate to severe COPD [17] and asthma [18]. In addition, Yousaf F, *et al.* highlighted perioperative use of melatonin is effective in reducing preoperative anxiety [19]. Al-Aama T, *et al.* found melatonin decreases delirium in the elderly patients; suggested it has a role in the prevention of postoperative delirium [20], as well as possessing certain analgesic qualities, and may reduce concomitant opioid use in the postoperative period with a corresponding reduction in opioid-associated side effects [21,22].

Melatonin Physiology Melatonin (N-acetyl-methoxytryptamine) is a neuro-hormone mainly secreted by the pineal gland. Light signals play the most important role in the synthesis and secretion of melatonin in organisms. Increased light intensity decreases the quantity of endogenous melatonin produced and shifts the pattern of release throughout the circadian clock.

Endogenous melatonin is released at night, beginning at approximately 9:00 pm with a peak release at between 2:00 and 4:00. Melatonin release is typically inhibited between 7:00 and 9:00, coinciding with the peak of endogenous cortisol [23]. This secretion pattern makes the physiological activities in the human body, such as the sleep-wake cycle, synchronised with the circadian rhythm.

In addition, melatonin might act as a mood stabilizer, relieve stress, act as an anti-oxidation and anti-inflammation agent, suppress pathogens and protect the functioning of multiple organs [21,22], which are undoubtedly helpful to the recovery of ICU patients, and thereby might improve sleep. It is a methoxy-indole synthesized and secreted principally by the pineal gland at night under normal light/dark conditions.

Circadian secretion of melatonin is suppressed in critically ill patients admitted to ICU. Low melatonin levels, poor sleep quality and illness have a reciprocal causation interaction and form a vicious circle. Pharmacokinetics and Safety Profile Melatonin has been given safely to humans in doses of 1 to 15 mg.

Although treatment results in plasma levels up to 100 times the normal peak night concentration approximately 1 hour after ingestion, it has a wide safety margin [23] and safe for short-term use [24]. Most common side effects of melatonin use were headache, dizziness, nausea and drowsiness [32]. Most importantly, although melatonin has hypnotic, sedative and analgesic properties, it has few respiratory and hemodynamic effects.

However, melatonin has good oral bioavailability in ICU patients [37] and take up to three days to achieve the desired effect of melatonin on sleep quality [13,23,25,26].

Current Evidence

The interest in melatonin as a potential therapeutic or prophylactic agent in the management of sleep disturbance in the ICU derives from the demonstrated low plasma concentrations and altered secretion patterns of melatonin in critically ill patients. Shilo, *et al.* studied the day secretions of melatonin in a group of ICU patients compared to a group of patients in ordinary medical wards. They found that the nocturnal peak of melatonin was missing in most ICU patients [27]. Mundigler, *et al.* described a disturbed pattern of circadian secretion

of melatonin in ICU patients with sepsis (16 out of 17 patients) but a preserved circadian rhythm in ICU patients who did not have sepsis (six out of seven patients) [28].

Olofsson, *et al.* found that the circadian rhythm of melatonin secretion was abolished in mechanically ventilated patients in the ICU [29]. Perras, *et al.* suggested that the nocturnal melatonin concentrations in ICU patients were negatively correlated with illness severity [30]. In addition, various drugs commonly used in the ICU have been reported to alter melatonin secretion and to decrease the plasma levels of melatonin [31] including benzodiazepines, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and beta-blockers.

Therefore, low melatonin levels, poor sleep quality and illness have a reciprocal causation interaction and form a vicious circle. The supplementation of exogenous melatonin to remodel the melatonin level in the human body that approaches the physiological state might be one of most effective strategies for improving sleep.

Moreover, in addition to reducing the stress, the role of melatonin as an antioxidant and anti-inflammatory agent or part of sepsis treatment is widely discussed. Claustrat B, *et al.* suggested the circadian organisation of other physiological functions depend also on the melatonin signal, for instance immune, antioxidant defenses, haemostasis and glucose regulation [32]. Thus, administration of melatonin might significantly benefit ICU patients.

Melatonin should be considered in all patient aged = 18-years-old with Glasgow Coma Scale (GCS) score = 10. Inpatients requiring prolonged invasive ventilation, melatonin could be complimentary to sedative agents. It should be considered in all the patients needing invasive ventilation for more than five days. Sagrillo-Fagundes L, *et al.* have highlighted maternal melatonin provides the first circadian signal to the fetus. They concluded melatonin has neuro-protective effects of during pregnancy and on fetal brain development [33]. However, Melatonin is contraindicated in patients with a history of convulsions, neurological disease, sleep apnoea, deafness or blindness; It is not indicated in patients with alcohol consumption = 50 units per week or drug use as sleep disturbance could be multifactorial.

Other exclusion criteria include liver insufficiency (child-Pugh class C), renal insufficiency (requires dialysis), severe heart failure (the New York Heart Association classification III/IV) and known allergy to melatonin. Intestinal obstruction, paralytic ileus, gastroparesis or other conditions are likely to affect the enteral absorption of melatonin.

Moreover, use of drugs that might alter melatonin secretion and decrease plasma levels of melatonin such as benzodiazepines, NSAIDs, corticosteroids, beta-blockers, haloperidol and amiodarone should be reviewed regularly. Critically ill patient cohort Lack of quality sleep has a significant impact on signs and symptoms of delirium. These critically ill patients usually begin to experience delirium over a few hours or a few days.

Symptoms tend to be worse during the night when it's dark and things look less familiar. They experience reduced awareness of the environment resulting in being easily distracted/withdrawn, with little or no activity or little response to the environment. They develop an inability to stay focused on a topic or switch topics. They usually get stuck on an idea.

Their cognitive impairment results in poor memory, disorientation; and difficulty speaking or recalling words and understanding speech. They may find it difficult to read or write. They frequently develop hallucinations, restlessness, agitation or combative behaviour and bradykinesia or lethargy. However, elderly patient in this cohort are likely to withdrawn.

'INTEGRA TED' Intervention Care Bundle

It is a matter of debate if melatonin should be replaced in patients who do not have nocturnal surge or should be supplemented in all critically ill patients. In view of high dose safety profile and benefits including decreases sleep onset latency, increases total sleep time and

improves overall sleep quality; melatonin has a role in improving sleep quality in these critically ill patients admitted to ICU. Therefore, an integrated intervention care bundle which includes melatonin is an acceptable practical option.

Patel, *et al.* [34] demonstrated a reducing environmental noise and lighting in the ICU was effective in improving sleep and reducing incidence of delirium.

Care bundles have been used in clinical medicine in improve standard of care and patient outcome by promoting the consistent implementation of a group of effective interventions.

An 'INTEGRA^TED' sleep care bundle that includes mitigation of drugs that alter melatonin secretion, regular monitoring of sleep quality, proactive use of melatonin and non-pharmaceutical interventions like mimicking day-night pattern and noise monitoring devices could prove instrumental in restoring sleep rhythm in these critically ill patients.

		Active interventions	Risk mitigation
Interventions (Pharmacological)	I	Melatonin	1. Competitive Inhibitors of Melatonin 2. Choice of Sedatives: Morphine, midazolam and Renal dose titrate if needed
Testing	T	Richards Campbell Sleep Questionnaire during ICU Ward round	
Examination (CNS)	E	Daily Sedation Score RASS SCORE -2	>-3-Assess for ICU delirium
goal directed non-pharmacological interventions	g	Nursing interventions restricted to 23.00 hours Switch monitoring equipment to night mode Reducing telephone volumes at night, Earplugs to patients.	Minimise interventions to minimum after 23.00 and drug administrations
Re-orientation MDT protocol	R	Regular reorientation of patient whilst on ICU by doctors and other health care workers proactively	
Environmental Adaptations	A	Closing doors, Decibel meters Day-night light adjustments	Avoid bright lighting after 23.00 hrs
ICU delirium	uni T ED approach	'CRUMBLED' during ward round	

Table 1: Sleep care bundle for critically ill patients admitted to ICU.

CNS pathology	Abscess, hydrocephalus, subdural hematoma, Infection, seizures, stroke, tumors, metastases, vasculitis, Encephalitis, meningitis, syphilis and IC hemorrhage,
Respiratory	Consider respiratory failure type 1 and 2. Other causes such as COPD, ARDS, PE*
Urinary/fecal retention	Consider urinary retention or fecal impaction, especially in elderly and in postoperative patients
Myocardial	Consider myocardial causes: myocardial infarction, acute heart failure, arrhythmia
Biochemistry abnormalities	Especially hyponatremia, azotemia, hyperbilirubinemia, hypocalcemia and metabolic acidosis
Low intracranial pressures	Consider presence of hypertension or hypotension-low cerebral perfusion
Elderly	Evaluate patients older than 65 years with greater attention
Drugs	Evaluate the use of sedatives (e.g. benzodiazepines or opiates) and medications with anticholinergic activity. Cessation of smoking or alcohol; Withdrawal from chronic sedative drugs

Table 2: ICU DELIRIUM: THINK 'CRUMBLED':

Conclusion

Although, future multicenter clinical trials to address individualized therapeutic efficiency of melatonin, its anti-inflammatory, antioxidant and neuroprotective effects in the critically ill patients were much needed.

An 'INTEGRATED' sleep care bundle in the critically ill patient cohort is an acceptable approach in the current clinical setting.

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