Improving Sleep in Intensive Care Unit: An Overview of Diagnostic and Therapeutic Options

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Abstract

Good quality sleep is considered to be essential for healthy living and recovering from illness. It would be logical to think that good quality sleep is most required when a patient is critically ill in an intensive care unit (ICU). Several studies have demonstrated poor quality of sleep while the patients are in ICU. Subjective tools such as questionnaires while simple are unreliable to accurately assess sleep quality. Relatively few studies have used standardized polysomnography. The use of novel biological markers of sleep such as serum brain-derived neurotrophic factor concentrations may help in conjunction with polysomnography to assess sleep quality in critically ill patients. Attempts to improve sleep included nonpharmacological interventions including the use of earplugs, eye sleep masks, and pharmacological agents including ketamine, propofol, dexmedetomidine, and benzodiazepines. The evidence for these interventions remains unclear. Further research is needed to assess quality of sleep and improve the sleep quality in intensive care settings.

Keywords

sleep, critically ill patients, intensive care, polysomnography, sleep quality

Introduction

Some of the basic requirements for a healthy life is good nutrition, optimal exercise, and adequate restorative sleep. An average healthy human spends more than a third of their life in sleep. Yet the complete purpose of sleep is only partially known (1). Sleep is an important activity for ensuing health and recovery from illness (2). Sleep is dynamic with different stages, each with its own importance. Sleep may be broadly classified into rapid eye movement (REM) sleep and non-REM (NREM) sleep, with NREM further divided into light sleep (stage N1 and stage N2) and deep slow-wave sleep (stage N3).

The duration and frequency of stages of sleep depend on age, with slow-wave sleep and REM sleep reducing with aging; NREM stage 1 is about 15% to 25% of the total sleep time. This is the stage when transition from wakefulness to sleep occurs. An increased proportion of this stage is seen in patients with sleep disorders such as sleep apnea, parasomnia, and periodic limb movement disorder. The NREM stage 2 comprises the majority of normal sleep accounting to about 35% to 45% of the total nighttime sleep (3). The NREM stage 3 accounts for about 15% to 25% of the total sleep time (3) but was known to decrease with aging. This stage of sleep is considered to be most important phase in physiological recovery due to the release of growth hormone (4). REM sleep generally accounts for less than a quarter of total sleep time (3). The exact function of REM sleep is unknown but was thought to aid in memory consolidation, where important memories are retained and less important neural connections are omitted (5). Several sleep disorders are associated with abnormalities of REM sleep including obstructive sleep apnea, narcolepsy, parasomnia, restless legs

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syndrome, and worsening hypoxemia in chronic obstructive pulmonary disease patients (6).

Chronic sleep deprivation is known to be associated with several comorbidities, including obesity (7), diabetes (8), anxiety and depression (9,10), hypertension (11), heart disease and stroke (12), and increased risk of mortality (12). Sleep deprivation is also known to be associated with impaired cognition (13), impaired immune function (14), and increases unethical behavior (15). The exact mechanism that relates sleep to the development of aforementioned disorders is not clear, but it was postulated to be due to the possible effects of sleep loss in inducing acute and chronic inflammation (16). Studies including human volunteers who were sleep deprived or had sleep restriction showed changes in circulating pro-inflammatory and anti-inflammatory cytokines, soluble receptors, signaling pathways of inflammation, and innate immunity (16). Sleep is also considered to be an important component to aid in recovery from illness and injury (16,17).

While chronic sleep deprivation is associated with adverse outcomes, it appears that even shorter term sleep deprivation may have untoward consequences. This was well studied in health-care settings. Sleep in health-care settings are shown to be poor in several studies, and interventions including pharmacological and nonpharmacological were evaluated with variable success (18,19). Adverse effects of sleep in hospital settings are known to be associated with increased pain scores, poorer cardiorespiratory status, and the psychiatric health of acutely ill patients. Like vital signs, the patient sleep quality reveals much about patients' overall well-being and should be a routine part of medical evaluation (18).

Sleep in Intensive Care Unit

Sleep in critical care settings was shown to be of a poor quality, owing to artificial light, increased noise, a consequence of critical illness itself, and treatment interventions that disturb sleep. Sleep in intensive care unit (ICU) was shown to be significantly fragmented, with prolonged sleep latencies, frequent arousals, an increase in stage 2 NREM sleep, a reduction or absence of deep or slow-wave stage 3 NREM sleep, and a reduction or absence of REM sleep. The circadian rhythm is also very erratic in ICU which affects the metabolism of life-saving therapies such as antibiotics and nutrition (20).

Good quality sleep is considered to be essential to recover from illness (21). It would be logical to assume good quality sleep is most required when a patient is critically ill in an ICU. Several studies in critically ill patients have demonstrated poor quality of sleep while the patients are in ICU (22,23). In fact, sleep disruption is one of the commonest afflictions reported by survivors of critical illness (24).

Assessment of Sleep in ICU

The assessment of sleep in ICU patients has been performed using subjective and objective tools. Subjective tools include the Richard Campbell Sleep Questionnaire, self-reported sleep quality by patients and nurse, or clinician observations. These subjective tools, while they are simpler to use, are not reliable and can over- or underestimate the sleep quality and duration. Actigrapy, Bispectral Index (BIS), and polysomnography are the current available objective tools to measure sleep in critically ill patients. Polysomnography is considered to be gold standard (20). However, using polysomonography in ICU is fraught with challenges, including the skill, time, and resources to apply the instrumentation, capture, and analyze the data. The traditional polysomnography scoring systems used in sleep study reporting has been noted to be not as reliable in assessing sleep stages in patients who are in intensive care as compared to the non-ICU population due to the difficulties in voltage gain on signals and the influence of drugs such as benzodiazepines on electroencephalogram (EEG) signals (20). There is also compelling data to show that brain-derived neurotrophic factor (BDNF) is a blood biomarker of slow-wave sleep (25). Such novel biomarkers may help in conjunction with polysomnography in assessing sleep quality in critically ill patients.

Sleep quality in critical care settings are influenced by patient-related factors such as pain, stress, psychosis, circadian rhythm disturbances, and organ dysfunction as well as critical care environmental-related factors such as ambient noise, alarms from monitoring devices, lighting, patient care activities, monitoring, diagnostic, and therapeutic procedures (20). While the exact causal relation between sleep deprivation and adverse outcomes were not shown in critically ill patients, inadequate sleep was shown to be associated with mood changes including anxiety, depression, psychosis, and delirium (26); a reduced pain threshold (27); impaired immunity (28); hormonal imbalances (29); and an impairment of inspiratory muscle endurance (30). Furthermore, a strong association between sleep disruption and mortality was proposed (31). While the clinical studies thus far have not shown a direct causal relation between sleep and mortality in critically ill patients, sleep deprivation was shown to increase mortality in the mice model of sepsis (32).

Factors related to patient and environment were implicated in poor sleep quality in ICU studies. Of these factors, environmental factors account to only 30% of arousals and awakenings (33). It appears from these data that patient-related factors including the severity of illness, comorbidities, and the medication that the patients receive while in intensive care account to a large extent cause the sleep disturbances. Indeed, when healthy volunteers were studied with polysomnography in an ICU, the quality of sleep appears to have been well preserved irrespective of the sound and light disturbance that are routinely noted in ICUs (33).

Nonpharmacological Interventions to Improve Sleep in ICU

Several nonpharmacological interventions including different weaning mechanical ventilation modes, eye masks and/or earplugs, massage, foot baths, music interventions,

Table 1. Common Pharmacological Agents Used to Improve Quality of Sleep in ICU.

Agent	Sleep Mechanism of Action	Effect on Stages of Sleep	Specific Side Effects
Ketamine, Phencyclidine derivative	Noncompetitive NMDA receptor antagonist prolonging change in glutamatergic signaling downstream of the NMDA blockade	Increases slow-wave activity and high amplitude waves; increase in levels of BDNF; reduces REM sleep; no effect on nocturnal total sleep time	Psychological: Decreased awareness of environment, sedation, vivid dreams, amnesia, hallucinations, impaired thought processes and paranoia. Physiological: Tachycardia, increase in blood pressure
Dexmedetomidine, α-2 adrenoceptor agonist	Activates inwardly rectifying K^+ channel leading to cellular $K+$ efflux; inhibits voltage-gated Ca^{+2} channels causing membrane hyperpolarization and suppresses neuronal firing; inhibits NE release in locus coeruleus causing GABA output from VLPO nucleus and inhibiting neurotransmitters of wakefulness to produce NREM pattern; regulates arousal by inhibiting cholinergic neurotransmission	Mimics restorative deeper stages of natural sleep; increases sleep efficiency and stage 2; modifies the 24-hour sleep pattern by shifting it mainly to night	Sympatholytic effects resulting in bradycardia and hypotension
GABA agonists (Benzodiazepines and propofol)	Potentiate chloride ion channel activation in the hypothalamus leading to cellular hyperpolarization, prolonging postsynaptic inhibitory action of GABA; decrease orexin, histamine, and serotonin release; no effect on NE release from the locus coeruleus	Prolong stage 2 NREM sleep; decrease slow-wave sleep and REM sleep; Propofol may be superior to benzodiazepine	Sedation and risk of airway patency, hypotension (Propofol), tachyphylaxis (Benzodiazepines)
Melatonin	Neurohormone released from serotonin via activating the suprachiasmic nucleus in the hypothalamus in response to darkness	Reduce sleep latency	No robust data for serious side effects. Possible side effects although uncommon include nightmares, hypotension, abdominal pain

Abbreviations: BDNF, brain-derived neurotrophic factor; Ca^{+2}, calcium ion; K^+, potassium ion; GABA, gamma-aminobutyric acid; ICU, intensive care unit; NE, norepinephrine; NMDA, N-methyl-D-aspartate receptor antagonist; NREM, non-rapid eye movement; REM, rapid eye movement; VLPO, ventrolateral preoptic nucleus.

nursing interventions, valerian acupressure, aromatherapy, and sound masking were tried to improve to the quality of sleep in ICU (34). Of these interventions, the use of earplugs or eye masks or a combination of both was shown to be somewhat beneficial in improving the sleep quality in ICU (34). There is also now a move to introduce the so-called chronobundle in intensive care which is backed by a great deal of basic science (35).

Pharmacological Interventions to Improve Sleep in ICU

Various pharmacological interventions have been tested in several studies, aiming to improve sleep quality and circadian rhythm in ICU. A summary of these agents is presented in Table 1. Despite their current use, the evidence for individual intervention remains unclear, where no pharmacological agents were shown to consistently ensure good sleep quality in ICU. In general, some agents induce sleep by inhibiting the excitatory pathway such as N-methyl-d-aspartate (NMDA) receptor antagonists, for example, ketamine, whereas others potentiate inhibitory synaptic receptors such as agents that enhance or mimic gamma-aminobutyric acid (GABA) neurotransmitter such as barbiturates, propofol, benzodiazepine, or benzodiazepine analogues. In ICU, agents such as propofol, benzodiazepines, ketamine, dexmedetomidine, and melatonin have been evaluated. Propofol and benzodiazepines for instance are used in ICU to replicate normal sleep. These agents exert their main effect on the hypothalamus via potentiating GABA-mediated chloride channel activation thereby cellular hyperpolarization, prolonging postsynaptic inhibitory action of GABA, and inducing sleep. The role of propofol in enhancing good quality and quantity of sleep, however, remains debatable (36).

Ketamine, a phencyclidine derivative, is unique for inducing a state of dissociative anesthesia. It is a mixture of

central depressants by acting at multiple receptors including NMDA, opioid, nicotinic, muscarinic, and monoaminergic receptors (37). Ketamine induces hypnosis by noncompetitive inhibitory effect on NMDA-mediated glutaminergic input to the GABAergic system. It reduces presynaptic glutamate release, therefore inhibiting the excitatory activity of the limbic system. The NMDA inhibitory pathway leads to slow-wave sleep (38), and it causes unconsciousness at higher doses. It is unclear whether ketamine's analgesic advantage has an impact on sleep. Ketamine preserves airway tone and respiration although increases the sympathetic activity via enhancing central and peripheral monoaminergic transmission and anticholinergic inhibition. Further, inhibition of the central cholinergic transmission may also contribute to induction of anesthetic and hallucination state.

Ketamine increases total sleep with slow-wave activity. Acutely, ketamine increases early night slow-wave and high-amplitude slow-wave activity. It elevates the BDNF levels, a peripheral surrogate marker of plasticity. However, ketamine is possibly associated with altered sleep architecture as evidenced by a reduction in REM sleep (39). There are some data that ketamine boluses adjunct to propofol infusion in noncritically ill patients achieved end points of hypnosis. However, the combined drug approach did not depress EEG variables in proportion to its hypnotic effect when compared to propofol alone (38,40). Despite the hypnotic impact of ketamine, there are no strong data to prove or refute its clinical effect on sleep in the critically ill patients.

Dexmedetomidine is a relatively selective α-adrenergic agonist, sedative, hypnotic, and an analgesic agent. Dexmedetomidine is increasingly used in ICU setting. Although it is sympatholytic, dexmedetomidine has mostly a cardiovascular stabilizing effect, and it preserves the respiratory function. Its site of action is mainly located in the pontine locus coeruleus. At the cellular level, dexmedetomidine couples with G-protein inhibiting adenylyl cyclase enzyme. This process results in activation of inwardly rectifying potassium channel, K-efflux, and inhibition of voltage-gated Ca channels causing hyperpolarization, thereby inhibiting cholinergic neurotransmission in brain regions that regulate arousal. Unlike conventional hypnotic agents, dexmedetomidine hypnotic effect mimics natural sleep, particularly the restorative deeper stages of sleep. In a recent study by Alexopoulou et al (41), nocturnal dexmedetomidine infusion was administered to 13 highly selected critically ill patients. Sleep was evaluated by polysomnography for 57 consecutive hours. Dexmedetomidine increased sleep efficiency and modified 24-hour sleep patterns by promoting sleep during nighttime. Conversely, nocturnal dexmedetomidine did not aid in a better sleep quality when compared to placebo in a more recent randomized control trial of 100 critically ill patients (42). Although it was a bigger study, sleep quality was only assessed subjectively using a Leeds Sleep Evaluation Questionnaire score. Wu et al (43) investigated low dose dexmedetomidine to improve sleep in nonmechanically ventilated elderly patients in ICU after noncardiac surgery. In this study, they found dexmedetomidine to improve overall sleep quality.

Melatonin is a neurohormone that is synthesized and secreted from the pineal gland, which is located in the posterodorsal aspect of the diencephalon, just above the cerebellum. Melatonin is released from serotonin by activating the suprachiasmic nucleus in the hypothalamus in response to darkness, which then undergoes a cascade of enzymatic reactions. Exposure to external light inhibits this mechanism (44). Melatonin may have a modest sleep-promoting effect by correcting the circadian phase derangement. It has been found to reduce sleep latency; however, it had no effects on other sleep measures such as total sleep time, sleep fragmentation, and sleep efficiency when compared to placebo (45,46). Melatonin has a low side effect profile and low residual daily drowsiness even in large doses. It has no risk of drug dependence when compared to benzodiazepine. Theoretically, melatonin alters sleep phase shifting in patients with melatonin deficiency or patients with circadian rhythm dysfunction such as critically ill patients. However, a recent systematic review specifically focusing on the usefulness of melatonin on the quantity and quality of sleep in adult patients in ICUs found that the evidence was insufficient to determine the role of melatonin in improving the quality and quantity of sleep in critically ill patients (47).

However, the results for its effectiveness to entrain circadian sleep in critically ill patients are mixed. Pharmacological interventions are important and may not only improve the quality of sleep in critically ill patients in future but also has the potential to outperform the gains of the environmental interventions. Nevertheless, the currently available and used pharmacological agents used for sleep in ICU are not ideal (31). Newer pharmacological agents or novel uses of older agents may need to be tried in carefully conducted clinical trials with objective assessment of sleep using polysomnography.

Conclusions

There is a significant body of evidence that indicates sleep in ICUS are of poor quality. Assessment of sleep in critically ill patients in ICU is very different to assessment of sleep in a sleep laboratory. Measurement of sleep in ICU is technically challenging, given the limitations in skill set, resources, and agreed upon criteria. The subjective tools, while they are simpler to use, are not reliable and can over- or underestimate the sleep quality and duration. The current objective tools are not widely available and require significant experience to record and interpret the data. These include actigraphy, BIS, and polysomnography each with their own merit and drawbacks. Polysomnography is considered to be the gold standard. Biomarkers such as BDNF may prove to help us evaluate sleep in conjunction with objective sleep evaluation tools.

To improve our understanding of the implications of poor sleep quality in intensive care, we need to have clear and

consistent way of reporting sleep in ICU, analyzing circadian rhythm in ICU, evaluation of the effects of poor sleep on clinically important outcomes in patients, and a multi-pronged approach that includes both nonpharmacological and pharmacological measure to ensure optimal sleep. Pharmacological agents that promote stage 3 NREM sleep and or REM sleep are required to improve sleep quality and hopefully improve patient outcomes in critically ill patients.

Authors' Note

R.T. and J.M. contributed to conception and design of the study. R.T., J.M., and K.H. contributed in drafting the article or making critical revisions related to important intellectual content of the manuscript and final approval of the version of the article to be published.

Declaration of Conflicting Interests

Funding

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