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REVIEW

Good night and good luck: sleep in the ICU

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Abstract

Sleep in the ICU is poor and improving sleep proves to be challenging. However, clinical trials on the use of pharmacological and non-pharmacological interventions to improve sleep in the ICU are scarce. The few clinical trials that have been performed are hampered by difficulty in obtaining reliable objective sleep measurements in the ICU environment. Therefore, firm evidence on the effect of all commonly used interventions is limited. Strategies to decrease noise and light exposure seem promising, since pilot studies and small clinical trials suggest that implementation is feasible and most interventions are low-cost. Standardisation of sleep-promoting protocols might lead to a possibility of performing multicentre trials that can provide much needed evidence on the efficacy of non-pharmacological interventions to improve sleep in the ICU. Although many different medications are used to improve sleep in the ICU, there is insufficient evidence in the literature to support the use of any of them to effectively improve sleep. The use of benzodiazepines is not recommended based on the lack of evidence for their efficacy and the association with increased risk of delirium. Emphasis on non-pharmacological sleep-promoting measures before prescribing medication is warranted, as it is currently not clear to what extent prescribing sleep-promoting medications is actually beneficial to ICU patients. Clinical trials on existing pharmacological options and expanding treatment options by considering sodium oxybate or suvorexant are logical future directions to improve the treatment of sleep problems in the ICU.

Introduction

Humans spend approximately one-third of their life sleeping: a physiological state of reversible unconsciousness that is still one of the greatest mysteries in biology. Sleeping behaviour is highly conserved through evolution and shared among many species, indicating its great importance for optimal health.[1] So what happens if you do not sleep well? Most knowledge on sleep and the lack of it is derived from sleep deprivation studies. These studies underscore the importance of sufficient sleep for a variety of important processes such as neurocognitive functioning, memory consolidation, respiratory function and immune/host defence functions.[2-4]

It is widely documented that patients in the intensive care unit (ICU) suffer from poor sleep,[5] with up to 61% of patients reporting sleeping problems.[6] Also, when asked to report on their ICU experience, patients rank poor sleep second on the list of most bothersome experiences just behind having experienced pain.[7] Several studies that evaluate sleep on the ICU objectively using polysomnography exemplified sleep is also poor on an electroencephalographic level.[8] Sleep architecture changes drastically: even though total sleep duration over the 24 hours of the day appears unaffected, sleep becomes highly fragmented. The number of arousals increases and half of sleeping time is spent during the daytime hours.[3, 9, 10] The time spent in REM and deep sleep is severely shortened. Deep sleep plays a critical role in restorative processes, energy conservation, tissue repair and consolidation of memories.[11, 12] On the other hand, time spent in light sleep is significantly increased. In severely ill patients, poor sleep could have major consequences for overall well-being. Even though the consequences on clinical outcome remain partly unknown, strong correlations between ICU sleep disruption and increased incidence of systemic illness, poor recovery, delayed wound healing and increased mortality

have been reported.[13, 14] Furthermore, poor sleep is associated with ICU post-traumatic stress, depression, delirium[15-17] and persistent sleep disturbances after ICU stay.[18]

The underlying cause of sleep disturbances on the ICU is multifactorial. The primary illness and its pathophysiology play a significant role in patients' sleep disruption. Next to consider is the ICU environment itself. Constant close monitoring, diagnostic testing, medical support such as mechanical ventilation or medication, together with environmental factors such as excessive noise and light exposure, contribute to an unfavourable sleep environment.[8,19] Disentangling the contribution of each of these aetiological factors on ICU patients' sleep is complex and aetiological research is limited. Therefore, this narrative review provides a concise overview of intervention studies aiming to improve sleep in the ICU by focusing on environmental factors influencing ICU patients' sleep, mainly light and noise exposure. Additionally, both non-pharmacological and pharmacological treatment options are addressed, and new options to improve sleep in the ICU are discussed.

Noise and light in the ICU

Over the past decade, there has been a growing interest in investigating the impact of environmental factors, such as noise and light, on ICU patients' sleep as these factors are potentially modifiable.

Patients admitted to the ICU need continuous observation and clinical support. Intensive monitoring by the nursing staff and thus frequently waking patients to perform vital and diagnostic tests and administer medication is inevitable in clinical practice in these critically ill patients. Besides that, monitoring machines that track and support the patient's physiological condition, such as mechanical ventilators, constitute a continuous source of noise. Noise levels in ICUs commonly average above 50 dB, far exceeding the recommended levels published by the World Health Organisation: 35 to 45 dB during the day and 30 to 35 dB at night.[9, 20, 21] Short noise peaks, often surpassing levels of 80 dB, are no exception in the ICU.[22, 23] One study detected peak sound levels of over 85 dB occurring at least once every hour during the night.[20]

Another important factor to consider is light exposure. Light is essential for synchronising and maintaining the circadian rhythm, which regulates processes such as our sleep-wake rhythm and many other processes in the body.[24] A light intensity higher than 100 lux is sufficient to suppress melatonin production, the pineal hormone that is increased in the evening and night and facilitates sleep.[25] During the night, even dim light can already adversely affect sleep structure by increasing the number of awakenings.[26] Consequentially, ICU patients' sleep is disrupted by excessive light exposure during the night.[27, 28] Further disruption of the circadian rhythm is caused by insufficient light exposure during the daytime period in the ICU, since light intensity rarely exceeds 150 lux during the daytime period.[29]

If excessive light and noise exposure complicate sleep in the ICU, the solution seems straightforward: implement direct changes to the environment itself or simply diminish exposure to these stimuli. Hence, numerous trials have tried to explore the clinical efficacy of non-pharmacological interventions on sleep quality and length of ICU stay. These studies investigate non-pharmacological interventions alone or combinations of them, including usage of eye masks and earplugs and methods to reduce environmental noise and light pollution.

Several studies assess the effect of wearing eye masks and earplugs to improve subjective or objective sleep parameters.[30, 31] In general, subjective sleep parameters improve after the introduction of eye masks and earplugs, even though comparison of different studies is difficult due to high variability in inclusion criteria, interventions and outcome parameters.[32-34] The few studies that focus on objective sleep parameters describe small decreases in REM sleep latency and the number of arousals during the night.[35, 36] However, these results were based on healthy subjects. Assessments were done in an environment that mimics the ICU, but may not fully reflect the true situation. One reason for the lack of studies using the gold standard for objective sleep measurement, polysomnography, might be that it has proved to be impractical, labour intensive and expensive in the context of an ICU setting.[37] This was also illustrated by another study in the ICU that aimed to evaluate the effect of noise cancelling headphones and eye masks on objective sleep parameters as measured by polysomnography, but failed in their aim due to profound difficulties to score sleep according to the American Academy of Sleep Medicine (AASM) criteria that is used in all other patient populations.[38]

Another approach to decreasing light and noise exposure is intervening in the environment that is producing these sleep-disrupting elements. A few studies investigate 'quiet time' in the ICU. Interventions during periods of quiet time include dimmed lights, minimal nursing activity, quiet staff conversations and prohibition of visits.[39] These interventions were feasible to significantly lower sound and light levels during quiet time hours, although sometimes impossible in case of emergency alarms. Besides that, adherence to the interventions to achieve a quieter environment proved to be difficult, because some of them interfered with regular clinical practice. The outcome parameter of both studies was whether or not the patients were observed sleeping during quiet versus control periods.[39, 40] This outcome parameter makes interpretation and comparison of the results of these studies challenging. Two other studies showed a significant improvement in subjective sleep quality after introducing a bundle of light and noise reducing interventions

in the ICU.[41, 42] However, one of those studies had a very low sample size, while in the other study only a small subset of included patients completed the sleep questionnaire that was the primary outcome measure. Again, the influence of these interventions on frequently used subjective sleep parameters was limited, and unknown for objective sleep parameters, as no sleep was objectively assessed.

In general, clinical trials on the use of non-pharmacological interventions to improve sleep on the ICU generally provide low quality evidence. The results of studies that assess objective sleep are difficult to compare due to low sample sizes and the use of different inclusion criteria and outcome measurements.[31] Strategies to decrease noise and light exposure on the ICU mostly appear to subjectively improve sleep. In combination with the low costs and the feasibility of introducing most non-pharmacological interventions, more attention to the effect of noise and light exposure seems worthwhile. A recent survey study highlights that few ICUs use sleep assessment questionnaires or sleep promoting protocols.[19] More research focusing on objective sleep parameters is warranted to draw firm conclusions on the value of non-pharmacological interventions to improve both objective and subjective sleep in the ICU.

Pharmacological interventions to enhance sleep

Implementing non-pharmacological interventions seems to be an important step in the right direction to improve sleep in the ICU, but has not yet shown to be able to effectively resolve the problem of suboptimal sleep in the ICU. Therefore, pharmacological interventions are often used to promote sleep in the ICU. Light sedation with drugs such as benzodiazepines or propofol helps patients to relieve stress and discomfort. Counterintuitively, instead of restoring a healthy sleep architecture the use of these drugs can further contribute to sleep problems.[43]

Even though a wide variety of pharmaceutical options are employed in this manner, there is no standard agent for promoting sleep in the ICU. The compounds used to improve sleep all have in common that they decrease the time spent awake. There is, however, a distinct biological difference between physiological sleep and drug-induced sleep, in which the mechanism of action of the administered drug plays a vital role.

The largest group of prescribed medications are the benzodiazepines. No randomised clinical trials investigating the effect of this medication group on sleep in the ICU have been published. The main difference between the different benzodiazepines concerns their half-life in the body. They should therefore be chosen carefully to comply with the physician's goal of improving sleep. Because of its short half-life, temazepam is one of the most commonly used benzodiazepines for promoting sleep. However, there are strong arguments to be made against benzodiazepine use for promoting sleep in the ICU. First of all, electroencephalography studies in non-ICU populations show that benzodiazepines increase patients' total sleep time but do so through the promotion of light sleep.[44, 45] As deep sleep and REM sleep are linked to restorative processes, benzodiazepines might increase sleep time, but do not create optimal sleep that aids in restoring bodily functions.[2, 4, 46, 47] Secondly, benzodiazepine prescription in the ICU is strongly linked to the occurrence of delirium and they often have long-lasting effects during the day, such as drowsiness. These effects negatively influence patients' circadian rhythm.[17, 48-51] This lack of diurnal rhythm contributes to decreased sleep efficiency in the following night and increases the chance of developing delirium. Lastly, benzodiazepines are known to have a rebound effect once stopped.[52]

Propofol is most often used in the sedation of patients undergoing medical procedures. It is suggested that the state of unconsciousness created by propofol is similar, yet not identical to physiological sleep, as it shows many features atypical for physiological sleep when measured by polysomnography.[53, 54] Patients do not progress through regular sleep cycles as in physiological sleep and have less deep sleep and REM sleep. Furthermore, it requires constant administration through an intravenous line and has several possible side effects, including haemodynamic instability and the propofol infusion syndrome.[55] Although it has proved to be an effective compound for sedating patients, there is insufficient evidence to support it as a pharmacological option for promoting physiological sleep.[56, 57]

Dexmedetomidine is an α2-receptor agonist and is being employed at an increasing rate in the ICU. Its primary use is sedation and several trials show promising results such as reduced time until extubation and decreased occurrence of delirium.[58-61] Although it might be recommended for sedation, it does not promote optimal sleep. It increases light sleep phases at the cost of deep sleep and REM sleep.[60, 62] Furthermore, it is currently rather expensive compared with alternatives whilst also requiring continuous intravenous administration. Lastly, dexmedetomidine is associated with haemodynamic side effects.[61]

Non-benzodiazepines, also called Z-drugs, have been suggested to have comparable efficacy to benzodiazepines but with less side effects. Other studies, however, describe a side effect profile that is comparable with that of benzodiazepines.[63-65] Very little research has been done on their use in the ICU and thus evidence to recommend their use is insufficient.

The hypothesis that admission to the ICU causes disruption of the circadian rhythm and thus that administration of melatonin improves patients' sleep appears sound.[66] Administration of

melatonin is simple with few known side effects whilst there is some evidence that it reduces the incidence of delirium.[67, 68] However, there is no evidence that melatonin administration is improving or even influencing sleep. The use of melatonin as a useful intervention to improve sleep in the ICU is therefore not recommended.[38, 69, 70]

Suvorexant, a selective dual orexin receptor antagonist, has recently shown its efficacy in primary insomnia.[71] First results of the use of suvorexant in the ICU setting show a decrease in delirium incidence upon treatment.[72] No studies on the effect on sleep problems in the ICU setting have been published.

Sodium oxybate has been administered for over a decade to adult and paediatric populations of narcolepsy. Even though ICU physicians might have reservations regarding this compound due to the misuse of gamma hydroxybutyrate, a similar compound frequently leading to ICU admission, its use in therapeutic doses for improving subjective and objective sleep quality has proven to be safe, with a very low addictive rate.[73] In randomised clinical trials in patients with narcolepsy, sodium oxybate was shown to promote not only light, but also deep sleep.[74-77] However, no studies have been performed that evaluate the use of sodium oxybate in the ICU and thus there is currently no evidence to recommend its use. It could, however, prove to play a valuable role in the future considering the promising results in narcolepsy patients. A randomised clinical trial evaluating the effect of sodium oxybate in ICU is currently including patients (Netherlands Trial Register no. NL7983).

Although many different medications are used to promote sleep in the ICU, evidence to support any of them to effectively improve sleep is lacking. Relevant and valid arguments can be made against the use of the most commonly prescribed medications, such as benzodiazepines, as sleep promoting medication. Exploring alternative non-pharmacological sleep-promoting measures before prescribing medication seems worthwhile, as it is currently not clear to what extent prescribing sleep promoting medication is actually beneficial to ICU patients.

General conclusion

Sleep quality in the ICU is poor, but improving sleep proves to be challenging. Clinical trials on the use of pharmalogical and non-pharmacological interventions to improve sleep in the ICU are scarce. The few clinical trials that have been performed are hampered by the difficulty of obtaining reliable objective sleep measurements in the ICU environment. Therefore, firm evidence on the effect of all commonly used interventions is limited. Strategies to decrease noise and light exposure seem promising, since implementation proves to be feasible and most interventions are low-cost. Standardisation of sleep-promoting protocols might lead to a possibility of performing multicentre trials that can provide much needed evidence on the efficacy of non-pharmacological interventions to improve sleep in the ICU.

Although many different medications are used to promote sleep in the ICU, there is insufficient evidence in the literature to support the use of any of them to effectively improve sleep. Emphasis on non-pharmacological sleep-promoting measures and addressing patient-specific factors negatively influencing sleep before prescribing medication is warranted, as it is currently not clear to what extent prescribing sleep-promoting medications is actually beneficial to ICU patients. Clinical trials on existing pharmacological options and expanding treatment options by considering sodium oxybate or suvorexant are logical future directions to improve the treatment of sleep problems in the ICU. These clinical trials aiming to improve the treatment of sleep problems seem most feasible and relevant in the subgroup of ICU patients who are able to provide feedback on subjective sleep. It is expected that this subgroup is most influenced by environmental factors and would benefit most from interventions aiming to reduce this influence.

Disclosures

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