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ORIGINAL ARTICLE

Sleep medication and sedative use in Dutch intensive care units: a nationwide survey

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Abstract

Background: Intensive care patients often suffer from short, fragmented and low-quality sleep. Poor sleep can cause prolonged mechanical ventilation, delirium and deranged metabolic function. Sound scientific evidence for sleep-promoting treatments is lacking. Benzodiazepines, which are frequently used to treat sleep disturbances, may themselves have a disruptive effect on sleep. This survey describes the current practice of treating sleep disturbances in Dutch intensive care units (ICUs).

Methods: For this retrospective cross-sectional survey, we visited Dutch ICUs and used a structured case report form. The primary outcome was the frequency of use of sleep-promoting medication. Secondary outcomes were: type of sleep medication, non-pharmacological treatments, exposure to environmental factors and the presence of protocols on the promotion of sleep.

Results: 279 patients from 21 ICUs where included. Of 225 patients who did not receive continuous deep sedation at night, 76 (33.8%) received sleep-promoting medication. Benzodiazepines and zopiclone were most commonly used (60/225, 26.7%). Men received more sleep medication than women. Exposure to mechanical ventilation, noise, patient age and access to an entertainment system did not influence the likelihood of receiving sleep medication. Of the 21 ICUs, 16 had a protocol on sleep disturbances of which 13 advised benzodiazepines.

Conclusion: 33.8% of the patients in our survey received at least one sleep-promoting drug, most commonly a benzodiazepine. Nearly all evaluated ICU protocols on sleep promotion advised the use of benzodiazepines. More research on optimal sleep-promoting therapies is needed.

Introduction

Patients admitted to the intensive care unit (ICU) often suffer from sleep disturbances.[1-4]

Patients typically suffer from shorter, more fragmented sleep and sleep quality is often poor.[5-9] In the existing literature, the term sleep quality is often used to describe both sleep architecture and subjective sleep quality reports from patients. Sleep architecture describes the time spent in the different sleep stages. The sleep stages can be divided into non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep can be further divided into three stages: N1, N2 and N3 (also called slow-wave) sleep.[10] The REM and slow-wave stages are thought to be the most important contributors to the restorative function of sleep.[3,7,8] Hence, sleep quality may largely be determined by the time spent in these stages.

Sleep in ICU patients is affected by a variety of environmental, disease-related and psychological factors. Environmental factors include those inherent to intensive care such as alarms, noisy equipment, mechanical ventilation, permanent light and nightly examinations or interventions.[1,3,7,8] Disease-related aspects include organ dysfunction, pain and adrenergic stress,[7,8] as well as certain frequently prescribed medication such as opioids, catecholamines and steroids.[1,3,9,11] And finally, psychological factors such as stress, anxiety and fear may also induce sleep disturbances.[8]

Sleep disturbances cause emotional and psychological distress for patients[3] and may lead to prolonged mechanical ventilation,[1,9,11,12] deranged immune function,[1,3,9,11] catabolism and reduced glucose tolerance,[1,9] and cognitive impairment.[3,7,11]

The current literature describes many tactics to improve sleep in ICU patients, both non-pharmacological and pharmacological. However, most of these interventions

lack the sound scientific evidence required to support their effectiveness. This makes an evidence-based approach to improve sleep on the ICU difficult. In daily practice, sleep disturbances in ICU patients are often treated with benzodiazepines. Although they provide effective treatment of stress and anxiety, they have a disruptive effect on the architecture of sleep. Benzodiazepines, in particular, reduce the time spent in the restorative phases of slow-wave and REM sleep and in addition to that may induce or prolong delirium in ICU patients.[1,3,9,13,14]

In 2018, the Society of Critical Care Medicine (SCCM) published the Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (the PADIS guideline).[8] The guideline gives several recommendations on how to treat or prevent sleep disruption. Non-pharmacological recommendations are selecting a certain ventilator mode (assist control instead of pressure support), reducing the amount of noise and light, and using a dedicated sleep promotion protocol. However, the position of pharmacological options in this guideline remains uncertain. A recommendation on use of benzodiazepines is absent, although it does state that they may increase disturbance of sleep. The guideline does advise against the use of propofol to treat sleep disturbances because of REM sleep suppression. The effect of melatonin and dexmedetomidine remains uncertain due to a lack of underpinning scientific evidence. In other studies, however, dexmedetomidine is shown to promote a more natural sleep architecture and hence appears to be a promising alternative for sleep-promoting treatment.[1,2]

To investigate the current approach to the treatment of sleep disturbances in the Dutch ICU, we conducted a nationwide survey. The objective was to describe the current practice of prevention and treatment of sleep disturbances. We aimed to describe the type and frequency of sleep-promoting medication use, as well as application of non-pharmacological interventions and the presence of specific protocols for the prevention and treatment of sleep disturbances.

Methods

This was a retrospective, cross-sectional study of the current practices of sedation, use of sleep-promoting medication and environmental factors in Dutch ICUs and it was carried out between May 2019 and July 2020. To achieve a representative sample of Dutch intensive care practices, tertiary academic ICUs, major non-academic hospitals and smaller local hospitals were approached. The study was coordinated by the Haga Teaching Hospital in The Hague, the Netherlands. Because of the retrospective and anonymous cross-sectional database study approach, the regional ethical review board (METC Leiden, The Hague and Delft) waived the requirement for an individually informed consent procedure for the study.

Participating hospitals were visited by single investigators. Using a pre-defined, structured case-record form, we extracted data about the use of sedatives, opioids, sleep medication, environmental information and anonymous demographic data from the previous 24 hours of patients' digital records. Patients were eligible for inclusion when they had been treated for at least one full night in the ICU. If a participating ICU facilitated medium or high care beds under the medical supervision of the intensivist, these patients were also included. Coronary care unit patients admitted to combined units were not included. Patients admitted after 18:00 hours in the evening before data collection or were discharged or had died before 06:00 in the morning of data collection were excluded. There were no other exclusion criteria.
If patients were deeply sedated during the night of data collection, they were considered not to be 'at risk' of receiving sleep medication. A patient was considered to be deeply sedated with a Richmond Agitation and Sedation Scale (RASS) of -3 or lower and the presence of continuous sedation. We recorded information on the presence of noise-generating medical devices, such as mechanical ventilation, without discriminating whether it had or had not been present during the entire 24-hour observation period.

The primary outcome of this study was the frequency of administration of sleep-promoting medication during the night section of the 24-hour observation period (22:00-06:00 hours). For all sedative drugs administered during the night, we reviewed the nurses' and doctors' notes for information about the indication of the prescription. Medication that was considered likely to be prescribed primarily for anxiety, such as a three-times daily oxazepam prescription, was not counted as sleep-promoting medication, even if the evening dose was administered during the night section of the observation period. Secondary outcomes were type of sleep medication, daytime use of sedatives, non-pharmacological treatments, exposure to environmental factors and the presence of ICU protocols on sleep-promoting treatments. We also intended to study the effect of demographic and environmental predictors on the likelihood of receiving sleep medication during the observation period. Predictors were selected based on the available literature, the feasibility of assessing them during a visit and the probability they were documented by the participating ICUs.

Statistical analyses

SPSS Statistics v 26 was used for all analyses. A p-value of <0.05 was considered statistically significant. Logistic regression modelling was used to detect relationships between

Table 1. Population characteristics (n=279)

Age (median, IQR)	**66 years (52-73)**
Male sex	**54.8%**
Length of ICU admission at time of inclusion (days, median, IQR)	**5 (2-12)**
Type of ICU (n, %)	
University	**113 (40.5)**
Non-university, ≥12 beds	**131 (47.0)**
Non-university, <12 beds	**35 (12.5)**
Type of admission (n, %)	
Elective	**58 (20.8)**
Non-elective	**221 (79.2)**
Admission category (n, %)	
Medicine	**114 (40.9)**
Surgery	**77 (27.6)**
Cardiology / Cardiothoracic surgery	**54 (19.4)**
Neurology / Neurosurgery	31 (11.1)
Other	1 (0.4)

IQR = interquartile range; ICU = intensive care unit

Table 2. Sleep promoting medication use in non-sedated patients (n=225)

Bolus medication	
Zopiclon	**14 (6.2)**
Combination of benzodiazepines*	**14 (6.2)**
Oxazepam	**12 (5.3)**
Temazepam	**10 (4.4)**
Lorazepam	**5 (2.2)**
Midazolam	**4 (1.8)**
Melatonin	**2 (0.9)**
Promethazine	**3 (1.3)**
Continuous infusions	
Propofol	**4 (1.8)**
Dexmedetomidine	**4 (1.8)**
Clonidine	**2 (0.9)**
Midazolam	1 (0.4)
Other	**4 (1.8)**

All values presented as n, %. *Combinations of different benzodiazepines or a benzodiazepine with another agent

environmental and demographic factors and the use of sleep medication. Univariable logistic regression was used to identify potential factors associated with a higher likelihood of receiving sleep medication. Factors with a univariable p-value of 0.10 or below were selected for stepwise backward modelling strategy.

Results

Between May 2019 and July 2020, 325 patients from 21 ICUs were screened for inclusion. Of these, 279 patients fulfilled the inclusion criteria. The study was stopped early due to logistical difficulties relating to the COVID-19 outbreak in the Netherlands. It caused a significant change in patient characteristics and sedation practices. Site visits had to be stopped because of government policy, which further hindered on-site data collection. The sample presented in this study does not include relevant numbers of COVID-19 patients.

Characteristics of the patients included in the analysis are presented in *table 1*. The characteristics mostly match the average Dutch ICU population when compared with data from the Netherlands Intensive Care Evaluation (NICE) database, the only difference being an overrepresentation of university hospitals in our survey.

Table 3. Environmental factors (n=279)

Noise exposure (n, %)	
One factor	**121 (43.4)**
Two or more factors	**41 (14.7)**
Factors (n, %)	
Mechanical ventilation	**129 (46.2)**
Chest drainage	**32 (11.5)**
Continuous renal replacement therapy	**25 (9.0)**
High flow nasal oxygen	14 (5.0)
Extracorporeal life support	7 (2.5)
Room type (n, %)	
Single room, doors open	**103 (36.9)**
Single room, doors closed*	60 (21.5)
Multiple patient room**	116 (41.6)

*Room doors could be closed as a standard policy or because of isolation; **this included curtain areas, two bedrooms, 'islands' and other forms of care environments with several patients in the same room

Table 4. Univariable logistic regression analysis of risk factors for sleep medication administration in patients not receiving deep sedation during the observation night (n=225)

				Univariate logistic regression		
		Sleep medication (n=76)	**No sleep medication (n=149)**	**B**	**OR**	**P-value**
Age*	**Median, IQR**	67 (51-74)	66 (53-73)	0,006	1,006	0,58
Sex	**Male (%)**	71.6	56.7	0,657	1,930	0,04
Access to entertainment	Median, IQR	8 (4-21)	5 (2-12)	0,024	1,025	0,006
Hospital type**	**Academic (%)**	43.4	36.9			0,504
Admission type	**Unplanned (%)**	82.9	73.8	0,541	1,718	0,13
Type of room (single/multi)	**Single room (%)**	60.5	54.4	0,253	1,287	0,378
Exposure to mechanical ventilation	% on mechanical ventilation	34.2	34.9	0,030	1,031	0,918
Exposure to any noise generating device	% exposed to at least one device	52.6	45.6	-0,280	0,756	0,321
Access to entertainment	% with access to entertainment	59.2	46.3	-0,521	0,594	0,068

*A separate analysis also showed no effect of age on sleep medication use when age is processed as a variable with 3 age categories; **Treated as categorical variable with dummy variables. Categories: Academic hospital, non-academic major (>12 beds), non-academic minor (12 beds or smaller) Multivariable Nagelkerke R^2: 0.102; IQR = interquartile range B = regression beta; OR = odds ratio

Use of sleep-promoting medication

During the night section of the 24-hour observation period, 54 (19.4%) patients were deeply sedated with a continuous infusion of sedatives. Of the 225 patients without deep sedation, 76 (33.8%) received at least one sleep-promoting drug. There was considerable variety in the type of sleep-promoting medication used (*table 2*). Benzodiazepines and zopiclone where the most commonly used agents (60/225, 26.7%). Combinations of benzodiazepines and other agents, such as melatonin, were also common.

Exposure to noise and environmental factors

Table 3 shows the environmental factors that patients were exposed to during the 24-hour observation period. We noticed that non-pharmacological sleep-promoting interventions, such as earplugs, were not consistently documented in the medical or nursing notes and could therefore not be studied reliably. We were able to analyse the number of patients who had access to an entertainment system provided by the hospital. The devices we found ranged from a television on a roller stand to ceiling arm-mounted multimedia entertainment systems. In our sample, 127 (45.5%) patients had access to an entertainment system during the observation period.

Daytime sedation and oral benzodiazepine use

During the 24-hour observation period, 115/279 (41.2%) of the patients were treated with continuous infusions of sedatives. Continuous infusions of opioids were administered to 110/279 (39.4%) of the patients. Propofol was the most commonly administered continuous sedative (83/115, 72.2%), and remifentanil the most commonly administered continuous opioid (41/110, 37.3%). A total of 164 (58.8%) patients did not receive any continuous sedatives. Of note, some patients with continuous sedative infusions also received oral benzodiazepines during the observation period. Of the 153 patients who did not receive any continuous sedatives during the day, 11 (6.7%) patients received an oral benzodiazepine.

Logistic regression analysis of factors associated with sleep medication administration

Table 4 shows the results of the univariable analysis of risk factors associated with the administration of sleep medication. In general, none of the factors analysed explained a relevant proportion of variance within the data. Patients treated with sleep medication were more likely to be men (71.6% vs 56.7%, OR 1.9, 95% CI 1.02 to 3.65). Patients treated with sleep medication had been admitted to the ICU for longer compared with those not treated with sleep medication (median, IQR 8 (4 to 21) vs 5 (2 to 12) days). With each extra day of ICU treatment, the probability of being treated with sleep medication increased by 2.5% (OR 1.025, p=0.006). An unplanned admission was more common in patients who were treated with sleep medication (82.9% vs 73.8%), but this difference was not statistically significant (OR 1.718, p=0.13). The presence of three factors in the analysis with a

relevant univariable effect (sex, admission duration and access to entertainment) indicated that a multivariable model would be appropriate. However, the amount of variation in the data explained by this model was too small to be of relevance.

Of the 21 ICUs in our survey, 16 had a protocol designed to treat sleep disturbances. All protocols had non-pharmacological recommendations and 13 protocols contained pharmacological recommendations to treat sleep disturbances. The most used non-pharmacological recommendations included lighting at night, nightly activities (such as vital controls, nursing activities or blood sampling), the possibility to use a personal entertainment system and the use of an eye mask and/or ear plugs.

All protocols that advised pharmacological interventions recommended benzodiazepines. Of these protocols, five also recommended the use of clonidine, four recommended melatonin, three recommended dexmedetomidine, one recommended propofol and another protocol recommended the use of gamma hydroxybutyric acid.

Discussion

This study aimed to describe current practices in the treatment of sleep disturbances in Dutch ICUs. We found that approximately one third of patients without deep sedation received at least one sleep-promoting drug. Zopiclone and the short-acting oral benzodiazepines temazepam and oxazepam were the most commonly used drugs. Combinations of different types of benzodiazepines and combinations of benzodiazepines with other sedatives were also commonly used.

Our results illustrate that Dutch ICU patients are highly exposed to sleep disturbing factors. However, none of the noise-generating factors we studied had a statistically significant effect on the probability of receiving sleep medication. We expected patients in single rooms or patients with access to an entertainment system to have a lower likelihood of receiving sleep medication, though our results show that these factors had no significant effect. However, this study was designed to map the frequency with which pharmacological and non-pharmacological treatments of sleep disturbances were used, not to investigate the effect of a particular intervention on sleep disruption.

Our survey showed a discrepancy between the daily practice of treating sleep disturbances and the advice given by the PADIS guideline and the current literature. Our survey shows that benzodiazepines are still the most commonly used treatment of disturbed sleep, and that even continuous infusions with either propofol or benzodiazepines are still used. The current literature advises against these forms of treatment.

One explanation for this discrepancy may be that it is quick and easy to prescribe medication to treat sleep disturbances and patients often appear to be sound asleep after admission. This makes these medications logical first choice for many physicians and nurses. However, whilst patients often appear to be asleep, the actual quality of sleep cannot be determined from this observation alone. Hence it follows that the use of benzodiazepines is counterintuitive: rather than promoting sleep, they disrupt the slow-wave and REM sleep and thus reduce the restorative function of sleep.[1,3,9] In our opinion they should therefore be avoided in the treatment of sleep disturbances in the ICU.

Our survey found that four patients were treated with dexmedetomidine. According to the PADIS guideline, the effects of dexmedetomidine on the quality of sleep remain unclear as underpinning scientific evidence is absent. However, current literature indicates that dexmedetomidine promotes a more natural sleep architecture and thus appears to be a promising alternative for benzodiazepines.[1,2] Further research is needed to confirm these results.

Our results also showed a considerable difference between the daytime sedation (115 of 279 patients) and night-time sedation (54 of 279 patients). We believe this difference is caused by postoperative patients who had sedation right after surgery, which was stopped on the same day, but after admission to the ICU.

This study had some limitations. The study was stopped prior to reaching the predetermined thresholds for inclusion. Although we included a variety of larger and smaller hospitals in locations across the Netherlands, hospitals from the provinces of Zeeland, Limburg and Gelderland are underrepresented in the sample. Also, our survey had an over-representation of university hospitals when we compare our results with the Netherlands Intensive Care Evaluation (NICE) database. This may be due to a higher willingness to participate in medical research of these facilities. We do not think that this had a large influence on our results, since the hospital type did not increase the likelihood of receiving sleep medication. The cross-sectional design of the study allowed us to study a large sample consisting of different hospitals and their practices. However, the results should be interpreted with caution, considering the dynamic nature of ICU treatment. An advantage of the cross-sectional study design is that it minimises the influence the study had on daily practice and is therefore more likely to yield a realistic and representative impression of a regular day in Dutch ICUs. We were limited in our ability to reliably observe the application of non-pharmacological sleep-promoting treatments as their use was rarely documented in the medical or nursing records. Hence in most cases we were unable to assess whether an entertainment system was actually used, and how many nightly interventions a patient was subjected to.

Conclusion

In our survey 33.8% of the patients received at least one sleep-promoting drug. A patient's likelihood of receiving sleep-promoting drugs increased with the length of ICU stay. Exposure to noise-generating equipment was not associated with an increased likelihood of being treated with sleep-promoting drugs. Benzodiazepines were the most commonly used drugs to treat sleep disturbances. Nearly all evaluated ICU protocols on sleep promotion advised the use of benzodiazepines. More research on optimal sleep-promoting strategies is needed and should focus on non-pharmacological and benzodiazepine-sparing strategies.

Disclosures

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