Dexmedetomidine and sleep quality in mechanically ventilated critically ill patients: study protocol for a randomised placebo-controlled trial

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ABSTRACT

Introduction Sleep deprivation, which is a common complication in the intensive care unit (ICU), is associated with delirium and increased mortality. Sedation with gamma-aminobutyric acid agonists (propofol, benzodiazepine) results in significant disturbance of the sleep architecture. Dexmedetomidine is a lipophilic imidazole with an affinity for α₂-receptors and it has sedative and analgesic properties. It has been reported to enhance sleep efficiency, thus sedate while preserving sleep architecture.

Methods and analysis Thirty consecutive patients are planned to be included, at the Department of Anesthesia and Intensive Care at the Hospital of Southwest Jutland, Denmark. The study is a double-blinded, randomised, controlled trial with two parallel groups (2:1 allocation ratio). Screening and inclusion will be done on day 1 from 8:00 to 16:00. Two 16 hours PSG (polysonomography) recording will be done starting at 16:00 on day 1 and day 2. Randomisation is performed if the first recording is of acceptable quality, otherwise the patient is excluded before randomisation. Dexmedetomidine/placebo will be administered during the second recording from 18:00 on day 2 to 6:00 on day 3.

Primary endpoint Improvement of total sleep time and sleep quality of clinical significance determined by PSG.

Secondary endpoints Sleep phases determined by PSG. Daytime function and delirium determined by Confusion Assessment Method-ICU. Alertness and wakefulness determined by Richmond Agitation Sedation Scale. The objective is to compare the effect of dexmedetomidine versus placebo on sleep quality in critically ill mechanically ventilated patients.

Ethics and dissemination The trial investigate the potential benefit of dexmedetomidine on clinically relevant endpoints. If a beneficial effect is shown, this would have a large impact on future treatment of mechanically ventilated critically ill patients. Publication in peer-reviewed journal are planned and the study has been approved by the National Committee on Health Research Ethics (ID-S-20180214). The study related to pre-results.

INTRODUCTION

Sleep disturbance in mechanically ventilated critically ill patients is a common complication. About 50% of intensive care unit (ICU) patients report disturbed sleep and one-third continues to suffer from poor sleep quality 6–12 months after discharge. Patients report sleep-wake disorganisation, sleep fragmentation and abnormal sleep architecture with increased stage 1 and stage 2 non-rapid eye movement (NREM) sleep, decreased stage 3 (slow wave sleep (SWS)) and rapid eye movement (REM) sleep. Sleep deprivation is associated with dysfunction of the immune and cardiovascular systems, disturbed metabolism, impaired memory, delirium and in turn increased mortality.

Sedatives and analgesics are often administered to increase comfort, decrease anxiety and promote sleep. There are two commonly used classes of sedatives: (1) Benzodiazepine and propofol interacting with the gamma-aminobutyric acid (GABA) receptor (2) Sedatives with an affinity for α₂-receptors in the locus coeruleus, such as dexmedetomidine. Infusing propofol and midazolam induce sleep and the perception of sleeping, however sedation with GABA agonists results in significant disturbance of sleep architecture, including suppression of SWS and REM sleep. Administration of GABA agonists, especially benzodiazepines, has been reported to cause delirium, prolong mechanical ventilation and ICU stay. For several years the standard practice for sedation of patients in need of mechanical ventilation has been a combination of opioids and intravenous...
infusion of benzodiazepine and/or propofol. This strategy is known to prolong mecanical ventilation (MV), weaning from the ventilator and length of stay in ICU and hospital. Recent guidelines have advocated a revision of ICU sedation practices towards optimal patient comfort with minimal sedation to improve clinical outcomes in mechanically ventilated adult ICU patients. As a result light or non-sedation has not been shown to differ.

Dexmedetomidine is a lipophilic imidazole derivative with an affinity for α2-adrenoceptors 1600 times higher than for α1-adrenoceptors and 8 times higher than the prototype α2-agonist drug, clonidine. It has sedative and analgesic properties and can be used as an alternative in cases where non-sedation is not applicable. It has been reported to inhibit the release of norepinephrine in the locus coeruleus as well as enhancement of SWS by mimicking the endogenous NREM sleep pathway. Dexmedetomidine activates central presynaptic and postsynaptic α2-receptors in the locus coeruleus, thereby inducing a state of unconsciousness similar to natural sleep—resembling NREM sleep. The action involves an inhibition of the reticular activation system primarily involving cortex but to lesser degree cardiopulmonary function. This unique site of action allows dexmedetomidine an equally unique sedative profile, conferring ability to sedate while at the same time allowing for increased awareness and interaction with relatives and staff. As a sedative, dexmedetomidine is notable for its lack of respiratory drive suppression.

The minimal sedation strategy has among other conditions revealed sleep disturbances especially during night time. Dexmedetomidine, has been shown to provide good comfort during MV with a good safety profile and reduced time to extubation. In addition previous studies has suggested that critically ill patients, treated with dexmedetomidine during nights has increased sleep efficiency and improved sleep pattern. The quality and quantity of sleep in the critically ill patient during mechanical ventilation, can be measured accurately with polysomnography. The aim of this study is to compare sleep quality and sleep pattern in critically ill patients during ICU stay after dexmedetomidine or placebo (no-sedative treatment).

**Study hypotheses and endpoints**

Dexmedetomidine improves total sleep time/sleep quality compared with placebo.

**METHOD**

**Trial design**

This study is a double-blinded, randomised, controlled trial with two parallel groups (2:1 allocation ratio) comparing the effect of dexmedetomidine versus placebo on sleep quality in critical ill patients. The randomised design was planned to equalise the groups and since a control recording were done for each patients a 2:1 allocation was feasible (figure 1).

**Patient and public involvement statement**

Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**Selection of participants**

Thirty consecutive patients are planned. Inclusion site: Department of Anesthesia and Intensive Care at the Hospital of Southwest Jutland, Denmark.

**Inclusion criteria:** Admitted to the ICU. Eighteen years old or over. Anticipated stay at the ICU for another day after the first sleep recording. Mechanically ventilated patients. Haemodynamically stable patients. Conscious non-sedated patients with Danish language

**Exclusion criteria:** Sepsis-Related Organ Failure Assessment score above 12. Postoperative patients. Trauma patients. Patients with structural neurological diseases (eg, stroke, tumour), degenerative (eg, Parkinson’s disease, dementias), seizure, infections or other disorders affecting the brain based on critical history of epilepsy. Patients with a known psychiatric disorder (eg, schizophrenia, severe depression). Patients with second-degree or third-degree atrioventricular block (unless pacemaker implanted). Patients of childbearing potential with positive pregnancy test or currently lactating/known pregnancy. Patients with severe agitated delirium. Patients with a high risk of death in the study period. Patients using other α2-agonists (clonidine) during ICU stay. Patients with limitations in therapy (eg, resuscitation, dialysis). Patients participating in other studies
involving use of a pharmacologically active compound. Patients in need of anti-psychopharmaceutic or other sedating drugs.

**Intervention**

**Recruitment procedures**

Potential candidates for inclusion are selected in the ICU if they are mechanically ventilated and fulfils inclusion and exclusion criteria using information extracted from the hospital record information. Patients eligible for inclusion are contacted by the investigator (MD) in their room and oral/written consent are obtained with the contact nurse present.

### Study treatments for both groups

Patients are screened for inclusion and oral/written consent are obtained on day 1 from 8:00 to 16:00. During this time baseline characteristics as presented in (table 1) are obtained if the patient is eligible for inclusion. During this period the patients are prepared for PSG (polysomnography) recording, thus mounted with PSG electrodes as described below. From 16:00 on day 1 to 8:00 on day 2 the first 16 hours PSG recordings are done. In the timeframe on day 2 from 8:00 to 16:00, while no recording is performed the first recording is transferred and validated by qualified staff at the Danish Center for Sleep Medicine, Rigshospitalet, Copenhagen. If the quality of the first recording is

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**Table 1  Registrations during the trial**

| Study activities                                      | Screening | Day 1 8:00–16:00 | Day 1/2 16:00–8:00 | Day 2 8:00–16:00 | Day 2/3 16:00–8:00 |
|------------------------------------------------------|-----------|------------------|--------------------|------------------|--------------------|
| Inform consent (date/time)                           | x         | x                |                    | x                |                    |
| Inclusion criteria                                   | x         |                  |                    |                  |                    |
| Exclusion criteria                                   | x         |                  |                    |                  |                    |
| Demography*                                          | x         |                  |                    |                  |                    |
| Admission diagnosis                                  | x         |                  |                    |                  |                    |
| Lifestyle factors†                                    | x         |                  |                    |                  |                    |
| Concomitant medication                               | x         |                  |                    |                  |                    |
| Analgesic medication                                 | x         |                  |                    |                  |                    |
| APACHE                                               | x         |                  |                    |                  |                    |
| SAPS 3                                               | x         |                  |                    |                  |                    |
| SOFA                                                 | x         | X                |                    |                  | x                  |
| Vital signs†                                         | X         | X                |                    |                  | X                  |
| ECG†*                                                | X         | X                |                    |                  | X                  |
| RASS continuously (18:00–8:00)                        | x         |                  |                    |                  |                    |
| Mobilisation‡**                                      | X         |                  |                    |                  | x                  |
| RASS (8:00, 12:00 and 16:00)†*                        | X         |                  |                    |                  | X                  |
| CAM-ICU (8:00, 12:00 and 16:00)†*                    | X         |                  |                    |                  | X                  |
| Blood analyses §†                                     | X         |                  |                    |                  | X                  |
| Rescue medication registration§‡                      | X         | X                |                    |                  | X                  |
| Ventilator settings and airway management             | X         | X                |                    |                  | x                  |
| Sleep evaluation                                      | x         |                  |                    |                  |                    |
| PSG †                                                | X         |                  |                    |                  |                    |
| Randomisation                                        | X         |                  |                    |                  |                    |
| Treatment start                                      | X (18:00) |                  |                    |                  |                    |
| Treatment stop                                       | X (6:00)  |                  |                    |                  |                    |
| Averse event/SAE                                      | x         | x                |                    |                  | x                  |

Analgesic medication=usual analgesic medication administered during the trial. Sleep evaluation=subjective hourly evaluation conducted by attending nurse.

*Demography: Gender, ID, DoB, gender (F/M), length (cm), weight (kg) and body mass index.
†Lifestyle factors: smoking and alcohol.
‡Vital sign followed continuously: blood pressure, heart rate, body temperature, blood gases and routine safety laboratory values.
§Rescue medication: sedative or analgesic medication allowed or not allowed, administrated during the time period.
†Done three times/day.
**Mobilisation is registered during the period. †PSG assessment, done twice during the study.
††Bilirubin, Carbohydrate and partial pressure of carbon dioxide (highest value during the period).
APACHE, Acute Physiology and Chronic Health Evaluation; CAM-ICU, Confusion Assessment Method-Intensive Care Unit; PSG, polysomnography; RASS, Richmonde Agitation Sedation Scale; SAE, serious adverse event; SAPS, Simplified Acute Physiologic Score; SOFA, Sepsis-Related Organ Failure Assessment.
acceptable (impedance <10KΩ, electrode placement, calibration etc) patients are randomised, otherwise they are excluded before randomisation. Randomised patients are prepared for the second recording with an electrode check and the PSG screen is programmed to start the second recording at 16:00 on day 2. This recording ends at 8:00 on the third day leading to the end of the study. Dexmedetomidine/placebo will be administered as described below during the second recording from 18:00 on day 2 to 6:00 on day 3 (figure 2).

The attending nurse assesses subjectively if the patients are sleeping or not during the two recordings with intervals of 1 hour. Registration is done hourly as sleeping/not sleeping according to the state of consciousness for the majority of the hour. Richmonde Agitation Systole Scale (RASS) and Confusion Assessment Method (CAM) ICU scores are done at 8:00 and 22:00 daily throughout the study period.

Both study treatments are provided and delivered by Orion Pharma (Ørestads Boulevard 73, 2300 Copenhagen S) to the hospital pharmacy. A written instruction and verbal training for dilution and blinding of the study drug were provided for the pharmacist. The pharmacy personnel are not otherwise involved in the treatment of the patients, and they are not allowed any interaction with the staff in the ICU. A log with study drug batch numbers is kept in the pharmacy.

Paracetamol and morphine are allowed for pain relief, when clinically needed and in accordance with the department’s guidelines. Haloperidol and morphine are used in case of delirium. Benzodiazepines and sedating drugs otherwise are not accepted, and the patients will be excluded if administered.

Intervention group
The intervention group receives dexmedetomidine (100 µg/mL) diluted in glucose 5% to reach a concentration of 4 µg/mL. Patients are started on continuous infusion of dexmedetomidine 0.4 µg/kg/hour. In accordance with the department’s guidelines the attending physician increases or decreases the infusion rate by 0.2 µg/kg/hour every half hour targeting a RASS of −2. A maximum infusion rate of 1.4 µg/kg/hour are allowed.

Placebo group
The placebo group are treated as the intervention group, besides receiving glucose 5% infusion without dexmedetomidine.

PSG
Eight EEG (electroencephalogram) electrodes are placed on the patients scalp at the left and right frontal lobe, left and right central lobe and left and right occipital lobe, according to the international 10/20 system of electrode placement. Positioning is relative to the two electrodes placed on the mastoid region and the ground and reference electrode placed at the top centre of the scalp. To differentiate REM sleep from NREM sleep and wakefulness, two extradural electrodes are placed to monitor eye movement. Two submaxillary and one chin electromyogram (EMG) electrodes are placed to monitor muscle tone. Further two EMG electrodes are placed on the proximal lateral crus to monitor leg movement. Heart rate and oxygen saturation are recorded using two-point ECG and finger plethysmography applied on the right index finger. All data are stored by the portable screener on a SD flash card to be transferred in order to be analysed. Mounting the PSG are done according to the American Academy of Sleep Medicine (AASM) guidelines.

The PSG is done using hardware and utensils from SOMNOmedics including Domino software (SOMNOmedics GmbH Am Sonnenstuhl 63 D-97236 Randersacker Deutschland). Calibration to ensure acceptable electrode impedance (<10KΩ, otherwise electrodes are replaced) is conducted. Biocalibration will be done prior to each PSG recording to identify pattern of eyes-open and eyes-closed, wakefulness, as well as the appearance of eye movements. Scoring of the PSG will be done according to the AASM guidelines.

Study objective and endpoints
Primary objective
To investigate the effect of dexmedetomidine on deep sleep/sleep quality compared with placebo.

Primary endpoint
Improvement of total sleep time/sleep quality of clinical significance determined by total sleep time and sleep efficiency.

Secondary objectives
To investigate dexmedetomidine compared with placebo’s effect on (a) sleep phases, (b) daytime function and delirium.

Secondary endpoints
Sleep phases determined by PSG and daytime function and delirium determined by CAM ICU. Alertness and wakefulness determined by RASS.

Randomisation method
Randomisation will be performed electronically in REDCap (browser based online case report form) with an allocation
Blinding
The treatment code is not accessible for anyone employed in the ICU, thus only the data manager, the Good Clinical Practice (GCP)-monitor and the pharmacy personnel preparing the study drug have access to the code. Sleep assessment will be evaluated randomly by an independent doctor having only the randomisation code for identification, thus blinded to the order of the recordings. A second person checks for accuracy of the blinding. The code is not broken before all data are analysed. The data manager, who has access to the randomisation code, can be contacted in case of emergency unblinding.

Trial personnel
The trial personnel are doctors and nurses in the ICU at the hospital of Southwest Jutland. The personnel are trained in non-sedation and the use of dexmedetomidine, both in theory and by supervised practice. The hospital pharmacy personal has been trained in preparing the study and placebo drug.

Recording and reporting of SAE
Only serious adverse events (SAE’s) that are related to the study intervention will be recorded. These events are expected to be accidental extubation and discontinuations of central venous accesses, which require reinsertion within a few hours. Severe arterial hyper/hypotension, cardiac arrhythmia or high fever related to infusion of the study drug will be recorded.

Investigators will report SAE’s according to the national standard operational procedures. Primary investigator and the study nurses will screen for AE’s (adverse events), which is mandatory. SAEs will be registered in the electronic case record form (REDCap) and reported to the Data Monitoring and Safety Committee and the ethics committee. The attending physician decides if an AE is serious.

Approvals, ethics, dissemination and data collection
The study was approved by the Danish National Committee on Health Research Ethics (ID:S-20180214). Registration in EudraCT (2017-001612-11DK) has been done and the trial is approved by the Danish Medicines Agency, hence monitored by the GCP unit. Registration with the Danish Data Protection Agency has been done and all data collected are registered in the browser based online database REDCap, which applies with the GCP guidelines. Publication in peer-reviewed journal has been planned.

Sample size
Sample size evaluation were based on similar work done by Alexopoulou and Eumorfia, reporting significantly improved sleep efficiency (100%×TST (Total Sleep Time)/total PSG time) in critically ill patients when treated with dexmedetomidine. They also reported sleep architecture for stages in their crossover study. Estimates for placebo response and variation in SWS percentage of total sleep time were based on their work. Placebo is assumed to result in 0% of SWS sleep with common SD of 7%. Using parallel design and assuming 10% difference in SWS time, a sample size of 12 subjects per treatment arm provide 80% power to detect statistically significant difference at 5% level using Wilcoxon-Mann-Whitney test. Using 2:1 random allocation ratio reduces power and approximately 12% more subjects are required. Randomising a total of 30 subjects allows approximately 10% drop out rate.

Data
Baseline equalisation of the groups will be tested statically, and sleep efficiency/quality will be estimated in the two groups and compared using Wilcoxon-Mann-Whitney or t-test according to distribution of the data. Adjustment for baseline characteristics will be performed if significant link has been proven using regression analysis. Data will be handled according to the intention-to-treat analysis principles. All data will be stored in the REDCap database which complies with international confidentiality standards. Only the investigators and the data manager will have access to the data.

Two reports will be generated regarding the sleep data, one using data from the timeframe 22:00 to 8:00 and one using data from 18:00 to 6:00.

DISCUSSION
The trial investigates the potential benefit of dexmedetomidine on clinically relevant endpoints. If a beneficial effect is shown, this would have a large impact on future treatment of mechanically ventilated critically ill patients. Primary investigator will by email communicate the result of the study to the participants.

In the ICU one aims to restore normal circadian rhythm for non-sedated, non-delirious patients, hence mobilised and encouraged to stay awake during the day (8:00–22:00). At night pharmacological and non-pharmacological measures are done for the patient to be sleeping. If the patient on the other hand present delirious symptoms, sleep induction might be necessary, even if it does not compile with a normal circadian rhythm to break a vicious circle. Hence the study report will contain sleep patterns for both sedation strategies (22:00–8:00 and 18:00–6:00).
Recording during two consecutive days has been planned as opposed to 2 days apart. Thus, the patient will exhibit the same degree of critical illness and encephalopathic state.

**Trial status**

Inclusion has started: 23 May 2018. Completion and final analysis are expected in summer 2021. Orion Pharma have no influence on the conduct of the study and the presentation of the results. Paper and PhD thesis are expected to be written and completed in 2022 and published in a peer-reviewed journal.

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**Contributors** PJ and PT developed the theory. PJ, PT, TK, MS and J0 performed computations and developed the study design. J0 wrote the manuscript and all authors discussed and contributed to the final version. Financial resources were contributed by TK.

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**Competing interests** The project receives financial and supervision support from Orion Pharma. The company is otherwise without influence on the design, interpretation of data and decision to publish the result. MS is employed by Orion Pharma which has supported the project financially. The rest of the authors declare no competing of interest.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Consent obtained directly from patient(s).

**Provenance and peer review** Not commissioned; externally peer reviewed.

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