Title page

Impact of oral melatonin on adult critically ill patients with ICU sleep deprivation: a study protocol and statistical analysis plan for a randomized controlled trial

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Abstract

**Background:** Sleep deprivation is common in critically ill patients in intensive care unit (ICU). It can result in delirium, difficult weaning, repeated nosocomial infections, prolonged ICU length of stay and increased ICU mortality. Melatonin, a physiological sleep regulator, is well known to benefit sleep quality of certain people, but evidence for effectiveness in ICU sleep disturbance is still limited.

**Methods/design:** The study is a prospective, randomized, double-blind, controlled, parallel-group design. Eligible patients are randomly assigned to one of the two treatment study groups, labeled ‘Melatonin group’ or ‘Placebo group’. Oral melatonin 3 mg or placebo is administered at 21:00 p.m. on four consecutive days. Earplugs and eye masks are made available for use of every participant. We plan to enroll 164 patients. The primary outcome is the objective sleep quality measured by the 24-hour polysomnography. The secondary outcomes are subjective sleep quality assessed by the Richards Campbell Sleep Questionnaire, anxiety level evaluated by the Visual Analogue Scale-Anxiety, delirium-free days in 8 days and 28 days, ventilation-free days in 28 days, antibiotic-free days, ICU length of stay, over all ICU mortality in 28 days and the incidence and severity of side effects of melatonin in ICU patients. Additionally, the body stress levels, oxidative stress level and inflammation level are obtained via measuring plasma melatonin, cortisone, norepinephrine, MDA, SOD, IL-6 and IL-8 concentration.

**Discussion:** The proposed study will be the first randomized controlled study to use the polysomnography, which is a gold standard of assessing sleep quality to evaluate
the effect of melatonin on the sleep quality and circadian rhythms of ICU patients. The results may provide a new treatment for ICU patients with sleep deprivation that is safe, effective and easily implementable in daily practice.

**Trial registration:** ClinicalTrials (NCT): ChiCTR-TRC-4004319.

**Keywords:** Melatonin, Sleep deprivation, Anxiety, Polysonmography

**Background**

Sleep deprivation is a major concern in critically ill patients in intensive care unit (ICU). Several studies have shown that poor sleep quality and the inability to sleep are the second largest stressors and rank among the top 3 major sources of anxiety during the ICU stay [1-3]. Sleep in ICU patients is characterized by frequent disruptions, loss of circadian rhythms and a paucity of time spent in restorative sleep stages. Typical findings described by polysomnography (PSG), a gold standard of assessing sleep quality, include increased latency, a higher proportion of non rapid eye movement (NREM) sleep stage 1 and 2 (or light sleep), and reduced restorative slow wave (SW) and rapid eye movement (REM) sleep, largely because of frequent arousals. Although patients in ICU may experience normal or near normal total sleep time (TST), they have about 50% sleep during the daytime [4, 5]. In a latest observational study using 24-hour PSG to evaluate the sleep quality in ICU by Elloit et al., despite improvements in ICU design, technology and health care personnel training, there has been no improvement in ICU sleep problem until now [5-7]. It has been found that there are many extrinsic and intrinsic factors of sleep deprivation in
the ICU setting, including noise, light, nursing procedures, the presence of existing
diseases, inflammatory mediator, anxiety, pain, sedative and opioid medications and
mechanical ventilator setting[8-12]. Further, the occurrence of ICU sleep deprivation
is associated with detrimental outcomes, including delirium, difficult weaning,
increased nosocomial infections, prolonged ICU length of stay (LOS) and increased
ICU mortality[13].

On the other hand, despite poor sleep quality disturbs almost ICU patients,
clinicians remain reluctant to administer traditional sedative-hypnotic drugs in
patients with sleep disorder. The major concerns are the side effects of these drugs,
mainly that they destroy the structure of sleep, reduce the clinician’s ability to monitor
the level of consciousness and that they induce respiratory depression and drop of
blood pressure[14].

Sleep goals for ICU patients are to get enough sleep, reset the disordered
circadian rhythms, adjust the abnormal sleep structure, reduce sleep interruption,
overcome fatigue and anxiety, facilitate nursing care and resumption of disease. An
ideal therapy for improving sleep in ICU should be economical, feasible, rapid in
onset and offset and without local and systemic adverse effects. At present, there is
little effective treatment in use that has all these ideal properties to improve ICU sleep.
Current studies are mainly focused on the non-drug treatment such as earplugs/eye
mask[10, 15], imagery and relaxation[16], etc. They are relatively safe but do not
guarantee efficacy. Among them, the clinical researches on earplugs/eye masks have a
bit of maturity[15]. Some domestic and international experts and scholars
recommended that ICU incorporate earplugs/eye mask into the routine nursing care[17]. However Bourne[18] and Gabor[7] et al. showed environmental factors to be responsible for a fraction of arousal and awakenings, and Perras et al. indicated that the physiological regulation of melatonin secretion by darkness and light was abolished in severely ill patients in ICU. Therefore, the treatment based environmental factors might have limited effect. Recently, melatonin, a physiological sleep aid, has raised ICU scholars’ concerns.

Melatonin (N-acetyl-methoxytryptamine) is a neurohormone mainly secreted by the pineal gland. Light signal plays most important role in synthesis and secretion of melatonin in the organism. So the environmental cues that regulate an organism’s biological clock are predominantly the daily alternation of light and darkness acting via the retina and retina-hypothalamic pathways directly on the suprachiasmatic nuclei (SCN). Melatonin secretion increases directly with the length of darkness. 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 around 21:00 with peak release between 2:00 and 4:00. Melatonin release is inhibited typically between 7:00 and 9:00, coinciding with the peak of endogenous cortisol[19]. This secretion pattern makes the physiological activities in human body, such as sleep-wake cycle synchronized with circadian rhythm. So melatonin is a good sleep aid. In addition, the current experiments in vitro and in vivo suggested that melatonin might stabilize mood, relieve stress, anti-oxidation, anti-inflammation, suppress pathogens and protect multiple organ
function[19], which are undoubtedly helpful to ICU patients’ recovery, thereby might improve sleep.

Prolonged-release melatonin (Circadin®), an oral medication of the physiological sleep and circadian rhythm regulator, designed to mimic the endogenous pattern of melatonin production, is licensed for primary insomnia in patients aged 55 years and over. It results in significant and clinically meaningful improvements in sleep quality, morning alertness, sleep onset latency and quality of life and without withdrawal symptoms upon discontinuation[20]. Recently, extensive clinical trials also pointed out that melatonin could be beneficial in the different populations with sleep disorders, such as, (1) melatonin might be effective for insomnia and daytime sleepiness caused by time zone changes[21] and work shifts[22] inducing malfunctioning biological clocks. Maybe melatonin maintains synchronization in situations where the circadian rhythms are jeopardized and resynchronizes subjects after a period of free-run release; (2) melatonin might improve the sleep quality of non-ICU critically patients with dialysis[23], moderate to severe COPD [24] and asthma[25]. In addition, available clinical data shows that perioperative use of melatonin is effective in reducing preoperative anxiety[26] and has a role in prevention of postoperative delirium[27], as well as has analgesic qualities and may reduce concomitant opioid use in the postoperative period with a corresponding reduction in opioid-associated side effects[28].

Melatonin has been given safely to humans in doses of 1-15 mg. Although treatment results in plasma levels up to 10-100 times the normal peak night
concentration about 1 hour after ingestion, it has a wide safety margin[29]. Buscemi et al. in a meta-analysis concluded that melatonin is safe for short-term use[30]. They found that most common side-effects of melatonin used were headache, dizziness, nausea, and drowsiness[30]. Most importantly, although melatonin has the hypnotic, sedative and antalgic properties, it has few respiratory and hemodynamic effect.

Interest in melatonin as a potential therapeutic or prophylactic agent in management of sleep disturbance in the ICU derives from demonstrated low plasma concentrations and altered secretion patterns of melatonin in the critically ill patients. Shilo et al. has studied day secretion of melatonin in a group of patients in ICU compared to a group of patients in ordinary medical wards. He found a missing nocturnal peak of melatonin in most ICU patients[31]. Mundigler et al. found disturbed circadian secretion of melatonin in ICU patients with sepsis (16 out of 17 patients) but preserved circadian rhythm in ICU patients who didn’t have sepsis (6 out of 7 patients)[32]. Olofsson et al. found that abolished circadian rhythm of melatonin secretion in mechanically ventilated patients in ICU[33]. Perras suggested that nocturnal melatonin concentration in ICU patients was negative correlated with illness severity[34]. In addition, various drugs commonly used in ICU also reported alter melatonin secretion and decrease plasma levels of melatonin[35], such as benzodiazepines, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and beta-blockers and so on. Therefore, low melatonin level, poor sleep quality and illness are in the reciprocal causation and form a vicious circle. Supplementation of exogenous melatonin to remodel the melatonin level in human body which
approaches to the physiological state might be one of most effective strategies for improving sleep.

Both melatonin and cortisol are biological markers of circadian rhythm. Some previous studies have showed that there is hypo-secretion of melatonin and an overall high cortisol excretion in most patients in ICU. Cortisol is an important stress hormone which would be invoked by ICU noise, light and other stressors and leads to anxiety and sleep disturbance. It is known that melatonin can reduce the adrenocortical response to stress and down-regulate the synthesis and release of cortisol. Moreover, in addition to reducing the stress, the role of melatonin as an anti-oxidant, anti-inflammatory agent or part of the sepsis treatment is wildly discussed. So melatonin administration might benefit ICU patients a lot.

Recently, Mistraletti et al. studied pharmacokinetics of melatonin given orally in ICU patients and found a good oral bioavailability of the drug[36]. Also, a few works suggest it can take up to 3 days to achieve sufficient effect of melatonin on sleep quality[13]. Until now, there are only three studies investigating the influence of melatonin treatment on sleep quality in critically ill patients. Shilo et al.[37] and Bourne et al.[18] showed melatonin improved sleep quality and sleep length in critically ill patients in ICU, but Ibrahim et al.[29] showed a negative result in their study. There are some inconsistency such as inclusion criteria, drug allowed, sound and light control and monitoring method in the three studies, specifically as follows:

(1) Ibrahim’s study included patients who were not limit the use of sedative and analgesic that might affect serum melatonin level; (2) there is no uniformity for the
control of patient exposure to noise and light among the three studies, which may have a more powerful effect on observed sleep than even the pharmacological levels of melatonin achieved; (3) most of all, they didn’t use the PSG, a gold standard for assessing sleep, to evaluate the sleep quality, and ignored the importance of monitoring the all-day sleep, likely because it is very difficult to perform 24-hour PSG in severely ill patients in ICU.

The aim of present work is to evaluate the efficacy and safety of melatonin for ICU sleep deprivation. Our hypothesis is that melatonin will improve the sleep quality in ICU patients.

**Methods/Design**

**Study design and outcomes**

The present study is a prospective, single-center, randomized, double-blind, placebo-controlled, two-arm trial in patients with sleep deprivation in ICU. All eligible patients in ICU will be 1:1 randomized to the treatment intervention with melatonin or placebo. The objective of the trial is to evaluate the efficacy and safety of melatonin for ICU sleep deprivation. Definitions of variables in objectives are reported in Table 1.

**Primary outcome is:**

To determine the effect of melatonin administration on 24-hour a day sleep-wake cycle and subjective sleep quality, including nightly /daytime sleep time, TST, percentages of NREM stage 1/2, SWS and REM, the incidence of arousals per hour, duration of sleep without waking and number of sleep periods.
Secondary outcomes are:

1. Objective sleep quality assessed by the Richards Campbell Sleep Questionnaire (RCSQ)
2. Anxiety level measured by the Visual Analogue Scale-Anxiety (VAS-A)
3. Stress level
4. Level of oxidative stress
5. Level of inflammation
6. Delirium-free days in 8 days and 28 days
7. Ventilator-free days in 28 days
8. Antibiotic-free days in 8 days and 28 days
9. ICU length of stay
10. Over all ICU mortality at 28 days
11. The incidence and severity of side effects of melatonin in ICU patients

Study setting and population

The study setting is the comprehensive ICU, Fuxing Hospital, Capital Medical University, Beijing, China.

All patients admitted to our ICU with acute respiratory failure requiring mechanical ventilation and tracheotomy to assist weaning are screened daily for study eligibility.

Inclusion criteria are:

1. Age ≥18-years-old
2. Glasgow Coma Scale(GCS) ≥10
Sedation has been discontinued for a minimum of 36 hrs for propofol, morphine, alfentanil and dexmedetomidine and 48 hrs for lorazepam and midazolam;

expected mechanical ventilation days≥ 5 days

Patients are clinically and biologically stable, and pass the weaning screening, and therefore ready to be weaned from mechanical ventilation.

**Exclusion criteria are:**

- Pregnant or breast-feeding women
- Preadmission treatment of sleep disturbances
- A history of convulsions, psychiatric or neurological disease, sleep apnea, deafness and blindness
- Alcohol consumption of greater than or equal to 50 unit per week or drug use
- Liver insufficiency (child-pugh C)
- Renal insufficiency (need dialysis)
- Severe heart failure (New York Heart Association classification III/IV)
- Intestinal obstruction, ileus, gastroparesis or other conditions likely to affect enteral absorption of melatonin
- Using drugs which might alter melatonin secretion and decrease plasma levels of melatonin, such as benzodiazepines, NSAIDs, Corticosteroids, beta-blockers, haloperidol, amiodarone[42, 43].
- Known allergy to melatonin
- Readmitted to ICU after randomization to the study
- Enrolled in another trial
Ethical aspects and informed consent

When a patient is identified as eligible for the study, immediate contact will be made with the 24-hour on-call study coordinator, who will confirm eligibility. The attending physician will introduce the patient and his/her family to the study coordinator. The physician will make sure the patient and family knows the credentials of the study coordinator, and say that this person is going to discuss a study program that is being conducted, and that this person is qualified to do so. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand.

The study coordinator will explain that there is a possibility that the patient may suffer from poor sleep quality, if so, the patient could become worse. The coordinator will say that there is a physiological sleep aid that provides good sleep quality without respiratory depression, while facilitating patient’s condition. Also, he will explain that in a small percentage of patients, melatonin could cause headache, dizziness, nausea, and drowsiness. The potential advantages of using or not using melatonin will be described. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study coordinator, local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

A register is kept of all patients evaluated for inclusion and of patients who
withdraw from the study. The latter are clinically followed up without their data being analyzed in the study.

The study protocol and consent forms were approved by the Institutional Review Board of Fuxing Hospital Affiliated to Capital Medical University (approval number KY2014-22) and by the Chinese Clinical Trial Registry (ChiCTR-TRC-4004319). The Fuxing Hospitals’ Institutional Review Board gave positive advice for the addition of their ICU as the study site.

**Randomization, double-blind and allocation concealment**

The study has a prospective, randomized, double-blind, placebo-controlled, parallel-group design. Eligible patients are randomly assigned to one of the two treatment study groups, labeled ‘MT group’ or ‘placebo group.’ Randomization is based on a computer generated random digits table and follows a concealed process using sealed and numbered envelopes that allocate the patient to either of the two arms of the study. Patients may be randomized into this study only once unless they were discharged from the hospital and were re-admitted beyond 180 days of the first enrollment. The study does not allow cross-over and, if any occur, they will be reported as protocol violations.

Experimental drug and placebo with the same character are prepared by a pharmacist. Patients and all study personnel except the investigative pharmacist are blind to treatment assignment. The details of the series are unknown to any of the investigators and are contained in a set of opaque and sealed envelopes, each bearing on the outside only the number.
Trial interventions

All patients are randomized 1:1 to oral melatonin or placebo. Time zero (T0) is defined by randomization and the study treatment and relevant inspections are started just after. Baseline data about sleeping state of patients needs to be recorded on day 1 after enrollment, so interventions are not on this day and begin on day 2. Melatonin group patients oral or tube feed melatonin 3 mg at 9:00 PM for four consecutive nights (from day 2 to 5) once they have enrolled in the research. If melatonin is administered by nasogastric (or naso-jejunal) tube, the tablet should be crushed and mixed with 20 ml of water, followed by another 20 ml to flush out the remnants inside the tube. Placebo group patients oral or tube feed placebo with the identical method at the same time as melatonin group.

After randomization, given the possible powerful effect of high level of noise, turning on of light, or intensive routine care and procedures on patients sleep in ICU, we will offer earplugs and eye masks to the patients and dimming the main light at night (from 21:00 PM to 7:00 AM). Meanwhile, meetings and posters were employed to encourage staff to minimize environmental, nursing, and clinical disturbances such as clustering patient care activities during the nocturnal study periods. Also, nurses should select time periods to promote sleep by avoiding routine ICU care activities (such as the daily bath), reducing ambient noise, and turning down the lights during these periods. Other therapy and nursing project should follow clinical guidelines and nursing criterion.

In particular, during the sleep evaluation and intervention period (T0 time - 21:00
PM on days 6), analgesia, delirium and agitation will be managed in accordance with local guidelines. If the patients will need to use sedatives, analgesics and antipsychotic drug which can influence the effectiveness of melatonin and sleep structure, they are regarded as the protocol violation and should drop out. To help manage particular complex cases, three flowcharts are proposed, for pain, sedation, and delirium (Figures 1, 2 and 3). They stress the importance of considering all those factors (that is, organic and metabolic causes, noise/light, anxiety, presence of invasive tools, pain, and so on) that could contribute to agitation, delirium and pain, and should be corrected before administering any neuroactive drug. Analgesics (particularly opiates) must be used only in case of pain (Verbal Numeric Rating (VNR) > 3; or Behavioral Pain Scale (BPS) > 6)[44]. If delirium (CAM-ICU+) and agitation (RASS>0) appears, after correcting underlying causes, the non-pharmacological protocol will be applied and potential deliriogenic therapies stopped; only after these interventions may physicians prescribe haloperidol or any other antipsychotic drug, according to local guidelines and remove these participants.

**End of participation in the study**

The patients leave the study when the following occurs:

1. He(she) refuses to participate to the study
2. An exclusion criterion appears during the intervention
3. Severe adverse event occurs
4. Patient’s condition gets worse
5. ICU discharge or die
Data collection and management

Trained staff record data and fill in the web-based collection forms. At the moment of patient inclusion the data on demographic characteristics and the history of past illnesses of the patients are obtained: age, sex, height and weight, APACHE II score, SOFA score, GCS score, diagnosis, comorbidities. Clinical, physiological and analytical variables such as vital signs (T, BP, HR, RR, etc.), routine ICU laboratory tests (WBC, SCr, BUN, ALT, AST, etc.) will be recorded at the moment of inclusion as well as the duration time of ventilation, ventilation mode, the number of delirium, ICU length of stay and the names, dose, duration of use and time of last use of sedative, analgesic medication and vasopressor drug prior to study inclusion.

Furthermore, sleep related baseline data including objective and subjective sleep quality and anxiety level should be recorded. The definite measures are as follows:

Subjective sleep quality, including TST, the length of sleep at night (21:00 PM-7:00 AM)/in daytime (7:00AM-21:00 PM), sleep architecture (NREM stage 1/2, SWS, REM), sleep disruption (the numbers of arousals and duration of sleep), which will be monitored for one 24-hour period using a portable PSG device from day 1 21:00 PM to day 2 21:00 PM. PSG remains the gold standard for sleep quality assessment. Electroencephalograph (EEG) (O1/M2, C4/M1), electromyograph (EMG), electrooculograph (EOG) (right and left) and electrocardiograph (ECG) (lead II) will be recorded. Patients’ skin will be prepared according to standard techniques. Gold cup EEG electrodes were placed at O1/M2 and C4/M1 according to the International 10-20 System. Two EOG electrodes were used for right and left eye movements. The
EMG electrodes were located over the right and left masseter (facial) muscles. Electrode application will be performed by the specialist.

The subjective sleep quality refers to subjective feelings of nightly sleep status of patient. Baseline nightly sleep perceptive quality (day 1 21:00 PM to day 2 7:00 AM) will be evaluated by using RCSQ at 9:00 AM on day 2. The RCSQ contains five 100mm visual analogue scales (VAS): sleep depth, latency, awakenings, time awake and quality of sleep (higher scores indicate better sleep). The RCSQ was pilot tested in a medical ICU and validated with overnight PSG in medical ICU patients. In our study, patients who are unable to write were assisted; the patient use their current communication strategy to indicate where the investigator should mark the VAS.

Anxiety is defined as a state marked by apprehension, agitation, increased motor activity, arousal, and fearful withdrawal. The baseline anxiety level are assessed on day 2 9:00 AM via self-report using the 100-mm VAS-A which is presented to patients with a vertical orientation like a thermometer. The bottom of the scale is anchored by the statement “not anxious at all” and the top was anchored by “most anxious ever.” Patients indicate their current level of anxiety in response to “How are you feeling today?” The VAS-A score is the number of millimeters from the bottom edge of the line anchor to the patient’s mark. The VAS-A and the Spielberger State Anxiety Inventory are correlated (r=0.4916 to r=0.8219), demonstrating concurrent validity.

During the intervention period (days 2-5), outcomes related data such as objective and subjective sleep quality and anxiety level should be recorded. Analyses
are limited to the fourth day (day 5 21:00 PM - day 6 21:00 AM) since potential chronophypnotic benefits of melatonin are not immediate and may take at least 3 days to be released. Therefore, objective sleep quality should be monitored for one 24-hour period using the PSG from day 5 21:00 PM to day 6 21:00 PM and associated parameters and methods see as proclaimed in the preceding article. Meanwhile, subjective sleep quality and anxiety level should be evaluated at 9:00 AM on days 6 and related methods are also shown before. In addition, daily information including vital signs and lab parameters, SOFA score, neurological monitoring (RASS, CAM-ICU, GCS), as well as the mode, parameter and duration of mechanical ventilation should be recorded.

Sound and illuminance levels are recorded from day 1 to day 6 using the integrated sound pressure level meter and illuminance level meter. Continuous equivalent sound pressure levels (Leq) in ‘A’ weighted decibels and peak sound pressure levels (Lpeak) in ‘C’ weighted decibels are logged every second. Illuminance level (in lux) is recorded, using a sensor placed close to the patient’s head, once per minute. The bedside nurse should be requested to log an event whenever the patient received treatment or care. The event log contained the following items: clinical assessment; tracheal suctioning; pressure area care; physiotherapy; mouth/eye care; blood test (sampling); wash; non-invasive blood pressure; eating and drinking; dressing; pain; line insertion; X-ray; etc. Drug records are compiled daily for drugs known to adversely affect sleep or melatonin pharmacokinetics.

At ICU discharge, patients’ data and vital status, length of mechanical
ventilation, days of antibiotics use, delirium-free days, length of ICU stay and ICU mortality will be recorded.

To investigated the enteral absorption and metabolism of orally administered melatonin in critically ill patients during their ICU stay and evaluate the serum melatonin levels and their circadian variations in these patients, melatonin levels are measured in blood samples taken on days 1-2 (before intervention) and days 5-6 (4 days after intervention) at 20:45 (before administration), 21:10, 21:30, 24:00, 03:00, 06:00, 14:00 and 20:00 hr in 20 patients each group. Plasma levels of norepinephrine and cortisol are also measured at the same time points. In addition, plasma levels of SOD, MDA, CAT, IL-6 and IL-8 are measured at 7:00AM on day 2 and day 6.

**Current sample size justification**

Primarily, we expect an increase time of the patient’s night sleep after melatonin administration in ICU patients with sleep deprivation. In the previous studies, the median TST during the 24-hour period was 5 hours and the median percentage of TST from the nightly sleep was 59%. In order to observe a 20% difference in the nightly sleep time between the two study arms: such a difference is considered clinically relevant and likely to influence practice. Using the Power and Sample Size Calculation program, we will need to study 82 experimental subjects and 82 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The Type I error probability with testing this null hypothesis is 0.05.

**Statistical analysis**
All analyses will be according to the intention-to-treat principle, that is, all randomized patients will be analyzed in the groups to which they were originally allocated and will be blinded to treatment assignment. Baseline characteristics will be summarized by carrying out univariate analyses. Categorical variables will be presented as numbers and percents, percentages, and analyzed by the $\chi^2$-test. Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and interquartile range as appropriate. Comparison of continuous variables will be performed using Student’s t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Plasma levels of melatonin, cortisol and norepinephrine will be analyzed by repeated measure analysis of variance (ANOVA). All tests of significance will be at the 5% significance level and two-sided. Analyses will be conducted using SPSS 17.0.

Discussion

A significant difference in the safety and/or efficacy endpoints will provide important evidence for improving ICU patient sleep quality. Also, a neutral result will provide important insight, as this would mean that more studies are needed to evaluate the safety and efficacy of melatonin for ICU sleep deprivation.

Trial status

The study has been initiated as planned in February 2014. One interim analysis advised continuation of the trial. The study will be completed in February 2015.

Abbreviations

APACHE II: Acute Physiology and Chronic Health Evaluation II score; BP: blood
pressure; BPS: Behavioral Pain Scale; CAM-ICU: The Confusion Assessment Method for The Intensive Care Unit; COPD: chronic obstructive pulmonary disease; ECG: electrocardiograph; EEG: Electroencephalograph; EMG: electromyograph; EOG: electrooculograph; GCS: Glasgow Coma Scale; HR: heart rate; ICU: intensive care unit; MDA: malonaldehyde; NREM: none rapid eye movement; NSAIDs: non-steroidal anti-inflammatory drugs; PSG: polysomnography; RASS: Richmond Agitation Sedation Scale; RCSQ: Richards Campbell Sleep Questionnaire; REM: rapid eye movement; RR: respiratory rate; SCN: suprachiasmatic nuclei; SOD: Superoxide dismutase; SOFA: sequential organ failure assessment; SpO2: peripheral oxygen saturation; TST: total sleep time; SWS: slow wave sleep; VAS-A: Visual Analogue Scale-Anxiety; VNR: Verbal Numeric Rating;

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

HWH, LJ and XMX participated in the design of the study and drafted the manuscript. BZ and JJC participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

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Table 1 Definition of study objectives

<table>
<thead>
<tr>
<th>Objective</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective sleep quality</td>
<td>It contains total sleep time, the length of sleep at night (21:00 PM-7:00 AM)/in daytime (7:00 AM-21:00 PM), sleep architecture(NREM stage1/2, SWS, REM), sleep disruption (the numbers of arousals and duration of sleep), which will be monitored for one 24-hour period using a portable PSG device.</td>
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<tr>
<td>Subjective sleep quality</td>
<td>It is the subjective feelings of nightly sleep status of patient, including sleep depth, wake time after sleep onset, number of awakenings after sleep on set, latency to sleep onset, and sleep quality. It will be evaluated using RCSQ[38, 39].</td>
</tr>
<tr>
<td>Anxiety level</td>
<td>ICU anxiety is defined as a state marked by apprehension, agitation, increased motor activity, arousal, and fearful withdrawal during the ICU stay[40]. It will be assessed by VAS-A.</td>
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<tr>
<td>Delirium-free days in 8 days and 28 days</td>
<td>Number of days that the patient is alive and not delirious over 8 and 28 days starting from the day of inclusion. Patients are diagnosed as delirious when they have at least one positive CAM-ICU screening during their ICU stay. A delirium-free day is defined as a negative CAM-ICU screening during a day. In case a delirious patient is discharge to the ward, a delirium-free day is defined as a delirium observation scale score of less than 3 during a complete day[41].</td>
</tr>
<tr>
<td>Ventilator-free days in 8 days and 28 days</td>
<td>Time in days that the patient is not on the mechanical ventilator. If the patient is ventilated mechanically, including invasive and non-invasive ventilation several times during one ICU admission, then the non-ventilator times are added. Ventilator-free days (in 28 days) will be calculated.</td>
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<tr>
<td>Antibiotic-free days in 8 days and 28 days</td>
<td>Number of days that patient needn’t use any antibiotic during within 8/28 days from randomization will be calculated.</td>
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<tr>
<td>ICU length of stay</td>
<td>Days of admission in ICU.</td>
</tr>
<tr>
<td>Over all ICU mortality at 28 days</td>
<td>Survival time will be assessed. Patients will be classified as either “alive at study day 28” or, if dead, “dead at study day 28”. Differences between the two strategies in mortality rates will be evaluated using the assumption of asymptotic normality. Estimates of relative risks and odds ratios and the corresponding 95% interval of confidence intervals will be presented.</td>
</tr>
<tr>
<td>Side effects</td>
<td>Headache, dizziness, nausea, and drowsiness, determined daily by physical examination by the intensivist, and withdrawal symptoms upon discontinuation evaluated after the drugs are stopped.</td>
</tr>
</tbody>
</table>
Figure 1 Bedside flowchart for pain management in ICU patients.

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Consider the patient not cooperative if: RASS≤-2/CAM-ICU+ /communication or linguistic barriers.

2 Verbal Numeric Rating(VNR) 0 = no pain, 10 = maximal conceivable pain.
   Ask: “Can you quantify your pain between 0 and 10?”
   Consider at rest and breakthrough pain(e.g. =coughing, tracheo-bronchial aspiration,…).

3 Consider the evaluation as reliable if it takes into account the subjective parameters the patients use to evaluate their pain: cultural, religious and familial aspects, expectation for secondary benefits.

4 Behavioral Pain Scale (BPS)= absence of pain, 12 = maximal pain.
   - Compliance to ventilation: 1. Tolerance movement/2. Coughing but tolerating ventilation for most of the time/3. Fighting ventilator/4. Unable to control ventilation
AGITATION MANAGEMENT IN ICU

1. Is the patient agitated? Actual RASS > target (AGITATED)
   - Correct organic/metabolic causes
     - Correct problems due to invasive tools / physical restriction/mental stress, etc.
     - Non pharmacological protocol (relax, comfort, etc.)

2. Dose agitation improve? (Actual RASS = 0/-1)
   - YES
     - Re-evaluate every shift
   - NO
     - Is the patient in pain?
       - YES
         - Follow the pain management in ICU (see Figure 1)
       - NO
         - Administer sedative until RASS target is reach

Figure 2 Bedside flowchart for agitation management in ICU patients.

1. Always aim for RASS target = 0/-1 (patient awake and tranquil, well adapted despite invasive tool and critical condition). RASS target may be between -2 to -4 if required by clinical conditions.
2. Sepsis, hypoperfusion, hypo/hyperglycemia, hypoxia, fever, electrolyte imbalance, alkalosis/acidosis, etc.
3. Mode of ventilation; bladder catheter positioning; bronchial aspiration;
Figure 3 Bedside flowchart for delirium management in ICU patients.

1Sepsis, hypoperfusion, hypo/hyperglycemia, hypoxia, fever, electrolyte imbalance, alkalosis/acidosis,…

2None pharmacological protocol
   Orientation
   Use patient’s visual and auditory aids.
   Encourage communication calling the patient by name.
   Availability of patient’s personal belongings.
   Coherence between physicians and staff intervention.
   Use music or TV during the daytime

3Consider to stop or decrease delirigenic therapy:
   anticholinergic drug, metoclopramide, inhibitor of protonic pump, promethazine, etc.

Environment
   Lights off during the night, on during the daytime.
   Orient patients’ beds to allow vision of sunlight.
   Discourage sleep during the daytime.
   Patient mobilization and physiotherapy during the daytime.
   Control excessive noise during the daytime.
   Avoid medical and nursing procedures during the night.
Figure 4 Trial procedures flow sheet.