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Study protocol for a prospective randomised double-blind placebo-controlled clinical trial investigating a Better Outcome with Melatonin compared to Placebo Administered to normalize sleep–wake cycle and treat hypoactive ICU Delirium: the Basel BOMP-AID study

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ABSTRACT

Introduction Delirium is frequently observed in the intensive care unit (ICU) population, in particular. Until today, there is no evidence for any reliable pharmacological intervention to treat delirium. The Basel BOMP-AID (**B**etter **O**utcome with **M**elatonin compared to **P**lacebo **A**dministered to normalize sleep-wake cycle and treat hypoactive **I**CU **D**elirium) randomised trial targets improvement of hypoactive delirium therapy in critically ill patients and will be conducted as a counterpart to the Basel ProDex Study (Study Protocol, BMJ Open, July 2017) on hyperactive and mixed delirium. The aim of the BOMP-AID trial is to assess the superiority of melatonin to placebo for the treatment of hypoactive delirium in the ICU. The study hypothesis is based on the assumption that melatonin administered at night restores a normal circadian rhythm, and that restoration of a normal circadian rhythm will cure delirium.

Methods and analysis The Basel BOMP-AID study is an investigator-initiated, single-centre, randomised controlled clinical trial for the treatment of hypoactive delirium with the once daily oral administration of melatonin 4 mg versus placebo in 190 critically ill patients. The primary outcome measure is delirium duration in 8-hour shifts. Secondary outcome measures include delirium-free days and death at 28 days after study inclusion, number of ventilator days, length of ICU and hospital stay, and sleep quality. Patients will be followed after 3 and 12 months for activities of daily living and mortality assessment. Sample size was calculated to demonstrate superiority of melatonin compared with placebo regarding the duration of delirium. Results will be presented using an intention-to-treat approach.

Ethics and dissemination This study has been approved by the Ethics Committee of Northwestern and Central Switzerland and will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use; Good Clinical Practice (GCP) or ISO EN 14155 (as far as applicable), as well as all national legal and regulatory requirements. Study results will be presented in international conferences and published in a peer-reviewed journal.

Trial registration number NCT03438526.

Protocol version Clinical Study Protocol Version 3, 10.03.2019.

Strengths and limitations of the study

- The study's main strength is the implementation of a promising and secure therapy approach for hypoactive delirium.
- This is a prospective, randomised, double-blind, placebo-controlled clinical trial for data of high quality of evidence.
- A competing risk analysis with end of delirium and in-hospital death as competing risks will be performed if deaths during delirium are observed.
- The study is further limited by the heterogeneity of critically ill patients. However, development of disturbed circadian rhythm is considered to develop independently of the underlying disease leading to intensive care unit admission and may be a trigger in many cases.

BACKGROUND AND RATIONALE

Delirium is a neurobehavioural syndrome that frequently develops in the postoperative and/or intensive care unit (ICU) setting. The incidence of older patients who develop delirium syndrome (further named simply 'delirium') during their hospital stay ranges from 10% to 80%.[1 2] Cardiac surgery[3] and ICU patients[4] belong to a population with high risk for delirium development. Delirium may be accompanied by serious complications such as prolonged ICU and hospital stay, reduced quality of life and increased mortality. Furthermore, the duration of delirium is associated with worse long-term cognitive function in the general ICU population.[5]

The aforementioned consequences of delirium are observed in all of three subtypes: hypoactive, hyperactive and mixed. However, pharmacological options to manage delirium usually address hyperactive and mixed delirium in standard operating procedures targeting agitation specifically, whereas pharmacological options to favourably influence hypoactive delirium are lacking and currently not recommended according to international guidelines (eg, American Geriatrics Society, The American Geriatrics Society Expert Panel, JAGS 2015[6]; Pain, Agitation/sedation, Delirium, Immobility, and Sleep disruption (PADIS) guideline, last update 2018.[7]

Overall, disturbed circadian rhythm is considered to play a crucial role in all three subtypes of delirium,[8] including the hypoactive form.[9] Particularly in disorders associated with diminished or misaligned melatonin rhythms (eg, circadian rhythm-related sleep disorders, jet lag and shiftwork, insomnia in children with neurodevelopmental disorders, Alzheimer's disease) clinically meaningful effects of melatonin treatment have been demonstrated in placebo-controlled trials.[10] Previous investigations have confirmed loss of circadian rhythm in patients who had developed delirium, laying the basis for our study hypothesis.[11] However, limited evidence of the connection between circadian health and delirium was found recently in a meta-analysis of 13 trials, but the trials investigated were of great heterogeneity.[12] The potential of chronotherapy to reduce delirium incidence has been suggested in a recently published article.[13] Moreover, melatonin is to be investigated for ICU delirium prevention in an Australian study,[14] and a feasibility trial of melatonin for prevention of delirium in critically ill patients has just been terminated.[15]

The Basel BOMP-AID (**B**etter **O**utcome with **M**elatonin compared to **P**lacebo **A**dministered to normalize sleep-wakecycle and treat hypoactive **I**CU **D**elirium) prospective randomised clinical study will investigate if the administration of melatonin targeting reinstitution of a normal circadian rhythm will lead to shorter duration of hypoactive ICU delirium compared with placebo.

The administration of dexmedetomidine compared with propofol to treat disturbed circadian rhythm in the other two types of delirium—hyperactive and mixed—is being investigated in our counterpart study: The Basel ProDex clinical study—Comparison of propofol and dexmedetomidine infused overnight to treat hyperactive and mixed ICU delirium (Study Protocol, BMJ Open, July 2017).[16]

HYPOTHESIS

In our randomised study, we aim to test the hypothesis that once daily oral administration of melatonin compared with placebo at 20:00 (ie, after completion of scheduled nursing procedures, usually around 20:00[17]), beginning at the day of diagnosis of hypoactive delirium may reinstitute normal circadian rhythm thus decreasing the duration of delirium. It will further be investigated whether the improved circadian rhythm might reduce the likelihood of conversion to agitated delirium in patients with primary diagnosis of hypoactive delirium. Melatonin/placebo will be repeated daily until delirium resolution as assessed with the Intensive Care Delirium Screening Checklist (ICDSC).

METHODS

Study design

The Basel BOMP-AID study is an investigator-initiated, single-centre, prospective, randomised, double-blind, placebo-controlled clinical trial of patients suffering from hypoactive delirium.

Approvals

Approval to conduct this study was granted by the Ethics Committee of Northwestern and Central Switzerland (EKNZ 2018-00161) in April 2018. This study will be registered at the Swiss National Clinical Trial Portal (SNCPT) and is registered at ClinicalTrials.gov (Identifier: NCT03438526).

Study setting

Adult ICU at a Swiss academic tertiary medical care centre treating medical or surgical patients.

Study population

Inclusion criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Adult patients (aged 55 years or older).
- Current delirium (hypoactive type) detected by a specialised assessment method: ICDSC score ≥3[18] in combination with a Richmond Agitation Sedation Scale (RASS) score ≤0.

Exclusion criteria

Participants meeting the following criteria are excluded from the study:

- Delirium prior to ICU admission.
- Sleep disorder not caused by hypoactive delirium.
- Sedation in the ICU.
- Hypersensitivity to the studied substances (ie, melatonin, placebo content).
- Age <55 years.

- Terminal state.
- Status epilepticus or postictal states following seizures on electroencephalogram (EEG).
- Active psychosis.
- Substance abuse in current medical history.
- Dementia.
- Pregnancy.

STUDY MEDICATION

The first oral administration of melatonin at the beginning of the night (20:00) is scheduled at the end of the period in which hypoactive delirium is diagnosed (ie, 24 hours prior first administration of melatonin). Patients enrolled in the trial will be randomised to receive either melatonin (Circadin, tablets of 2 mg for oral administration, Neurim Pharmaceuticals AG, Zug, Switzerland) or placebo (lactose monohydrate, cellulose powder, magnesium stearate (Ph. Eur.), microcrystalline cellulose, provided by the hospital pharmacy of the University Hospital Basel, Switzerland), administered orally at 20:00 (ground and diluted to change pharmacokinetics from slow release to rapid action). The first dose of oral melatonin will be administered after study inclusion (ie, study allocation). Rapid melatonin action (ie, high melatonin level in a short period of time) corresponds to the physiological path of melatonin regulation within the body.

During the consecutive nights, the randomised study drug will be administered again and at the same time if indicated. The latter will allow us to clearly detect the suggested shortening of delirium duration in the cohort receiving melatonin.

After randomisation, the physician in charge will prescribe the study drug and the nurse caring for the patient will then prepare and administer the study drug as prescribed at 20:00 or after the last invasive nursing activity:

- Melatonin (Circadin): two 2 mg tablets (equals 4 mg total in one dose).
- Placebo: 2 tablets; galenic, colour and texture equal to Circadin.

OUTCOME MEASURES

Primary outcome measure

Delirium duration in number of 8-hour shifts.

Secondary outcome measures

- Delirium-free days at 28 days after study inclusion.
- Death until day 28, day 90 and day 365 from ICU admission.
- Number of ventilator days.
- Length of ICU stay (hours).
- Length of hospital stay (days).
- Sleep quality, assessed by the Richards-Campbell Sleep Questionnaire (RCSQ; total score).

Other outcome measures

The following outcomes are measured by smartwatches. The smartwatches will be attached half an hour before the administration of the drug (19:30) and left attached as long as possible, but at least until 06:00 of every day of the study period. Therefore, the smartwatch will be taken off only if the patient can be transferred to the ward or during specific procedures (eg, surgery) for hygienic reasons.

The following smartwatch assessments are based on activity (counts/min):

- Sleep duration per night (minutes) defined as the period from lights off to lights on.
- Number of sleep interruptions (number of consecutive 5 min bouts of >0 activity).
- The relative amplitude (RA) calculated from the ratio of the most active 10 hours period (M10) to the least active 5-hour period (L5) across the averaged 24-hour profile (assessment depends on patient cooperation during the day with keeping the smartwatch attached).
- Interdaily stability (IS), which quantifies the invariability day by day, that is, how well the sleep–wake cycle is synchronised to supposedly stable environmental cues. Timing information comes from determining the onset of the 5 hours with least activity (L5 onset) and onset of the 10 hours with most activity (M10 onset).

In addition, wrist/skin temperature (degrees/min) will be registered to assess degree of relaxation (ie, difference in degrees Celsius per minute between distal skin regions (finger, feet and so on) and proximal skin regions (clavicular, sternum and so on)).

DEFINITIONS/CONDITIONS

Inclusion criteria

Hyperactive delirium presents with restlessness, agitation and hypervigilance and is often accompanied by hallucinations and delusions. Patients showing lethargy and who seem to be slowed down (eg, speech, spontaneous movements) raise suspicion for development of hypoactive delirium. Mixed delirium shows features of both conditions.[19]

Normally, an ICDSC of ≥4 is warranted to diagnose delirium. Due to difficult diagnosis of hypoactive delirium and the overlap with mixed delirium, the investigators will consider those with an ICDSC score ≥3 (subsyndromal delirium, ie, ICDSC=3 in this study[20]) and Richmond Agitation Sedation Scale (RASS) score ≤0 in the absence of drug-induced coma as eligible for study inclusion. If patients reveal an ICDSC score ≥3 and a RASS score ≤0, a member of the study team will assess the patient according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) delirium criteria[21] for definite study inclusion.

Patients suffering from mixed delirium before randomisation (primary diagnosis) will explicitly not be included in the study. In case of hyperactivity after the first nightly melatonin dose, sedatives administered for this reason will be recorded.

Exclusion criteria

Sleep disorder not caused by hypoactive delirium

Patients suffering from sleep disorders (eg, restless legs syndrome, narcolepsy) or showing signs of sleep disorder (eg, insomnia, agitation during the night, sleep fragmentation) will not be included. Known sleep apnoea with or without treatment will not lead to study exclusion of the patient. Newly diagnosed sleep apnoea or sleep apnoea arising under melatonin treatment will lead to study exclusion.

Sedation in the ICU

Patients in need of sedation in the ICU will not be included. Unsedated patients with diagnosed hypoactive delirium will be included also if they are intubated or tracheotomised.

Hypersensitivity to the active substances

Hypersensitivity to the active substances is defined as a known allergy to melatonin or a substance contained in the placebo.

Age <55 years

We will only include patients aged 55 and older in our study in accordance with the melatonin instructions for intake in Switzerland.

Terminal state

Patients suffering from an incurable disease and who have a terminal illness with very short-term life expectancy (48 hours) will not be included in our study.

Status epilepticus or postictal states following seizures on EEG

Patients admitted with status epilepticus or postictal states without confirmed resolution of epileptic activity on EEG will not be included. An unexplained unconscious state will be evaluated with EEG prior to study enrolment. This may include a systematic search for other causes (eg, hypothyroidism, hypothermia, hypercapnia, opioid overdose) including encephalitis.

Active psychosis

Patients with known psychiatric disorder possibly revealing psychotic symptoms (eg, schizophrenia) will be excluded from the study.

Substance abuse in current medical history

Depending on the substance (ie, benzodiazepines, antipsychotics), patients might be excluded during the screening procedure. If the study participant raises suspicion for substance withdrawal (eg, completion of patient history by next of kin), he or she will be withdrawn from the study. Toxicity screening will be performed following a case-by-case basis risk assessment.

Dementia

Patients suffering from dementia will not be included.

Pregnancy

Pregnant women will not be included due to lack of data for or against melatonin in pregnancy.

Primary outcome measure

Duration of delirium in number of shifts

The onset of delirium will be defined as the start of the first of a minimum of two subsequent shifts with an ICDSC score ≥3 and a RASS score ≤0. The end of the delirium will be defined as the end of the last shift with an ICDSC score ≥3 and RASS score ≤0 that precedes a minimum of two subsequent shifts with an ICDSC score <3 and RASS 0 without delirium symptoms according to the DSM-V criteria.

On account of its long-time use in our institution and its high sensitivity and specificity, as described later, the ICDSC represents the preferred assessment tool in our study.

Secondary outcome measures

Delirium-free days at 28 days after study inclusion

Delirium will be assessed during 28 days after study inclusion if the patient is in the ICU. In case of re-transfer to the ICU within this period because of delirium or other reasons, delirium of any kind (hypoactive, hyperactive, mixed) will be recorded.

Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 1.2). AEs are therefore difficult to detect in critically ill patients since the physical state leading to ICU admission itself may already lead to severe complications and further deterioration of physical and mental health.

Serious adverse event

Serious adverse events (SAEs) are classified as any medical occurrence that results in death, is life-threatening, requires prolongation of existing hospitalisation, or results in persistent or significant disability/incapacity. SAE reporting is required from the responsible Swiss authorities. The third criterion from the SAE definition will be excluded in our trial, as the occurrence of delirium generally leads to prolongation of ICU and/or hospital stay.

Serious unexpected adverse drug reaction

A serious unexpected adverse drug reaction (SUSAR) indicates an adverse drug reaction that is of a nature or a severity inconsistent with the applicable product information.

Table 1 Study period overview

Study period	Enrolment	Allocation	Post-allocation			Closeout	Follow-up
Time point (hours)	–t1	t_0=0	t1=24	t2=48	t3=72	t4=XX	3/12 months
Enrolment	X						
Eligibility screening	X						
Informed consent	X						
Assessments							
Vital signs		X	X	X	X	X	
Delirium screening tools	X	X	X	X	X	X	
ADLQ		X					X
Drug therapy							
Oral melatonin or placebo		X	(X)	(X)	(X)		

ADLQ, Activities of Daily Living Questionnaire.

Since melatonin has no known major side effects, no AEs/SAEs/SUSARs are expected by its use in delirious patients after careful enrolment following our exclusion criteria. In addition, much higher doses have been used in investigations on melatonin as an anaesthetic adjuvant without reported major side effects (animal model).[22]

STUDY PERIOD OVERVIEW

The study period consists of enrolment, allocation, post-allocation and closeout (table 1). Allocation has been defined as the first day of melatonin or placebo administration at 20:00 after delirium has been diagnosed. Closeout has been defined as point of time of recovery from delirium.

Screening

Following the delirium assessment part of the Asses and treat pain, Awakening and Breathing trials, Coordination of care and Choice of sedative, Delirium monitoring and management, and Early mobility (ABCDE) bundle[23] representing the core of the institutional Pain, Agitation and Delirium (PAD) guidelines,[24] we will screen every patient admitted to the ICU for ongoing delirium to evaluate eligibility for study recruitment.

Delirium assessments

Every patient admitted to the study site will be screened for study eligibility according to the inclusion and exclusion criteria. Patients meeting study participation criteria are those who fulfil the inclusion criteria and none of the exclusion criteria. Eligibility screening data will be stored using the electronic case report form (eCRF) established by the Clinical Trial Unit (CTU, part of Department of Clinical Research), Basel.

For screening and for the whole duration of the delirium, we will perform the ICDSC during every shift. The ICDSC and the CAM-ICU are the most well-studied and widely implemented adult ICU delirium screening tools worldwide; both are recommended by regularly updated clinical practice guidelines. The Intensive Care Unit of the University Hospital Basel routinely uses the ICDSC for assessment of delirium. The ICDSC is an 8-item checklist of delirium symptoms evaluated over an 8–24 hour period (table 2).[25] Detailed information has been given in the publication of the study protocol of the Basel ProDex Study.[16]

Nursing interventions

Nursing interventions (eg, position changes; diuresis; administration of pain medicine; administration of sedatives for nursing procedures and other interventions) will be registered.

Three-month and 12-month follow-up

To assess long-term follow-up of patients who received melatonin and compare it with those who received placebo, we will perform a follow-up at 3 and 12 months after the prevailing hospital case has been officially closed (discharge date). With this follow-up, we will assess the following information equally at 3 and 12 months (information either given by the patient or his/her family/contact person):

- Death after hospital discharge.
- Hospital readmission.
- Activities of Daily Living Questionnaire (ADLQ).
- Additional episodes of delirium after study closeout.

ASSESSMENTS

Assessment of delirium

Delirium will be assessed by the ICDSC as explained above.

Assessment of sedation and pain level

Level of sedation will be assessed according to the RASS. Pain will be assessed using the Critical Care Pain Observational Tool (C-POT) and/or Visual Analogue Scale/Numeric Rating Scale (VAS/NRS) scales.

Table 2 Suggestions for assessing delirium with the Intensive Care Delirium Screening Checklist (ICDSC)

1. Altered level of consciousness choose one from A–E		
A. Exaggerated response to normal stimulation	RASS=+1 to +4	(1 point)
B. Normal wakefulness	RASS=0	(0 points)
C. Response to mild or moderate stimulation (follows commands)	RASS −1 to −3	(0 points)
D. Response only to intense and repeated stimulation (eg, loud voice and pain)	RASS −4	*Stop assessment
E. No response	RASS −5	*Stop assessment
2. Inattention		(1 point if any present)
A. Difficulty in following commands OR		
B. Easily distracted by external stimuli OR		
C. Difficulty in shifting focus		
Does the patient follow you with their eyes?		
3. Disorientation		(1 point if any abnormality)
A. Mistake in either time, place or person		
Does the patient recognise ICU caregivers who have cared for him/her and not recognise those that have not? What kind of place are you in? (list examples)		
4. Hallucinations or delusions		(1 point if any abnormality)
A. Equivocal evidence of hallucinations or a behaviour due to hallucinations (Hallucination=perception of something that is not there with NO stimulus) OR		
B. Delusions or gross impairment of reality testing (Delusion=false belief that is fixed/unchanging)		
Any hallucinations now or over past 24 hours? Are you afraid of the people or things around you? (fear that is inappropriate to the clinical situation)		
5. Psychomotor agitation or delay		(1 point for either)
A. Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential danger (eg, pulling out IV lines or hitting staff) OR		
B. Hypoactive or clinically noticeable psychomotor slowing or delay		
Based on documentation and observation during shift by primary caregiver		
6. Inappropriate speech or mood		(1 point for either)
A. Inappropriate, disorganised or incoherent speech OR		
B. Inappropriate mood related to events or situation		
Is the patient apathetic to current clinical situation (ie, lack of emotion)? Any gross abnormalities in speech or mood? Is patient inappropriately demanding?		
7. Sleep/wake cycle disturbance		(1 point for any abnormality)
A. Sleeping less than 4 hours at night OR		
B. Waking frequently at night (does not include wakefulness initiated by medical staff or due to loud environment) OR		
C. Sleep≥4 hours during the day		
Based on primary caregiver assessment		
8. Symptom fluctuation		(1 point for any)
Fluctuation of any of the above items (ie, 1–7) over 24 hours (eg, from one hospital shift to another)		
Based on primary caregiver assessment		
Total ICSDC score (add 1–8)		

ICSDC, Intensive Care Delirium Screening Checklist; ICU, intensive care unit ; RASS, Richmond Agitation Sedation Scale.

All scores (ie, ICDSC, RASS/SAS, CPOT, VAS/NRS) will be assessed by nurses responsible for the treatment of the study patient. Advanced nurse practitioners coach the nursing staff and verify the agitation and delirium assessments in the study patients in regular intervals.

Assessment of study drug side effects

We will not administer melatonin in a dose to exert sedative effects or other potential side effects. The chosen dose of 4 mg has been determined after consulting a chronobiologist of the University of Basel.

Assessments documented on the case report form

On our eCRF, we will document the following information concerning our study participants (sequential order):

- Patient information including socioeconomic status.
- Study group.
- Study eligibility.
- Results of the planned assessment tools.
- Cardiovascular parameters.
- Laboratory values.
- Drugs administered.
- Nursing interventions.
- Outcome overview.
- Follow-up at 3 and 12 months.

RANDOMISATION

Trial staff will have permanent access to the eCRF where patients are screened and randomised to one of the study arms. Randomisation will be performed via the eCRF after checking the eligibility of the patient. A unique patient identification code will be assigned to every screened patient without possible inference to patient identity.

Stratified block randomisation will be performed with stratification for type of admission (medical or surgical) and sepsis (yes or no).

All patients with hypoactive delirium, except for those meeting one or more of the exclusion criteria, will be randomised to our study.

BLINDING

The treating medical team (ie, responsible nurse and physician) and the patient will be blinded for the treatment arm (placebo vs active comparator). Daily assessment of mental state will be documented by the treating medical team. Study allocation/termination and outcome assessment including follow-up will be coordinated by a member of the study team.

PATIENT INFORMATION AND INFORMED CONSENT

Because all study participants are delirious, they do not have the capacity to give their consent for the study. For this reason, an independent auditing physician, acting as the patient's representative, will declare each patient's suitability for study participation in the patient's name. The signed document of the independent physician is the prevailing condition for inclusion of the patient in our study.

If possible, depending on the general condition of the delirious participants, the investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits, and any discomfort it may entail. Each participant (depending on constitution) or their next of kin will be informed that participation in the study is voluntary, that withdrawal from the study is possible any time and that withdrawal of consent will not affect the subsequent medical assistance and treatment.

If at all possible, the participant or the next of kin will be informed that the medical record may be examined by authorised individuals other than their treating physician.

All participants in the study will be provided a participant information sheet describing the study and providing sufficient information for the participant and his/her next of kin to make an informed decision about their participation in the study. We will also provide a consent form to be signed by participant's next of kin.

The information sheet and the consent forms for participants and next of kin have been submitted to the competent ethics committee for revision and have been approved. The formal consent from a participant's next of kin, using the approved consent form, must be obtained before the participant is subjected to any study procedure.

The next of kin should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee). The signed form will be retained as part of the study records. Participant's for whom consent cannot be obtained will be excluded from the study.

After recovery, the patient will be informed about his/her participation in the study and he/she will have the possibility to withdraw their data from the study. In case of ex-post study withdrawal, patient data will be destroyed on the study participant's wish.

SAFETY

No SAEs are expected to result from the administration of melatonin in delirious patients after careful enrolment following our exclusion criteria.[26] Melatonin appears to be safe when used short term.[27]

An individual subject will be excluded from the study in case of the following:

- Withdrawal of consent by the independent physician or next of kin.
- An AE that in the opinion of the sponsor contraindicates further measuring (emergency setting).

Serious adverse reactions

The occurrence of SAEs will be assessed during every shift based on the bedside visit and results of vital and laboratory parameters and will be recorded daily on the eCRF.

All changes in research activity and unanticipated problems will be reported to the competent Ethics Committee by the sponsor and the principal investigator. An SAE or a SUSAR must be reported within 7 days if fatal, otherwise within 15 days. The sponsor will provide an annual safety report.

Melatonin

No serious adverse reactions are specified in the product characteristics of melatonin (Swissmedic Journal 09-2011;

www.compendium.ch). Impact on renal/hepatic impairment has not been investigated.

PATIENT WITHDRAWAL

Patients withdrawn (excluding ex-post study withdrawal) from the study and subjects who could not be followed over the intended period and for all designated points of assessments, regardless of reason will be included in the intention-to-treat (ITT) analysis. Unless consent for follow-up is withdrawn, subjects discontinued before closeout will be followed for the full study period, and all laboratory and clinical evaluations will occur as defined in the protocol. We can guarantee that the measurements will by no means delay therapy.

STATISTICS

Detailed methodology for summaries and statistical analyses of the data collected in this study will be documented in a statistical analysis plan, which will be finalised before database closure and will be under version control by the Clinical Trial Unit, University Hospital of Basel.

Hypothesis

For the primary outcome, the null hypothesis to be tested is that ICU patients in a state of hypoactive delirium treated with melatonin or placebo do not differ regarding the duration of the delirium.

The corresponding alternative hypothesis is that ICU patients in a state of hypoactive delirium treated with melatonin or placebo will differ regarding the duration of the delirium.

Determination of sample size

Sample size was estimated to be able to show the superiority of melatonin compared with placebo regarding the duration of delirium (in number of shifts).

The sample size calculation was based on an expected duration of delirium of 15 shifts (5 days) for patients treated with placebo (in line with findings of Page *et al*,[28] a reduction of the duration of delirium by δ=3 shifts (1 day), and an SD in both arms of 6 shifts (2 days).

Sample size was calculated with a resampling method. Each sample size, $n_{i=1,\ldots,49}=10,\ldots, 298$, was evaluated by sampling 999 times $n_i/2$ individual patients from a normal distribution with a mean of 15 (placebo arm) and $n_i/2$ with a mean of 12 (melatonin arm), both with an SD of 6. In addition, different effect sizes for melatonin versus placebo, ranging from 1 to 6 shifts were applied to assess the sensitivity of the sample size with regard to the expected effect size. Because the number of shifts can only be positive negative simulated values (which rarely occurred) were replaced by zero. A Wilcoxon rank-sum test was used to test for a difference between trial arms. Sample size was set to ensure at least 90% power (1–β=0.9) at a significance level of 5% (α=0.05).

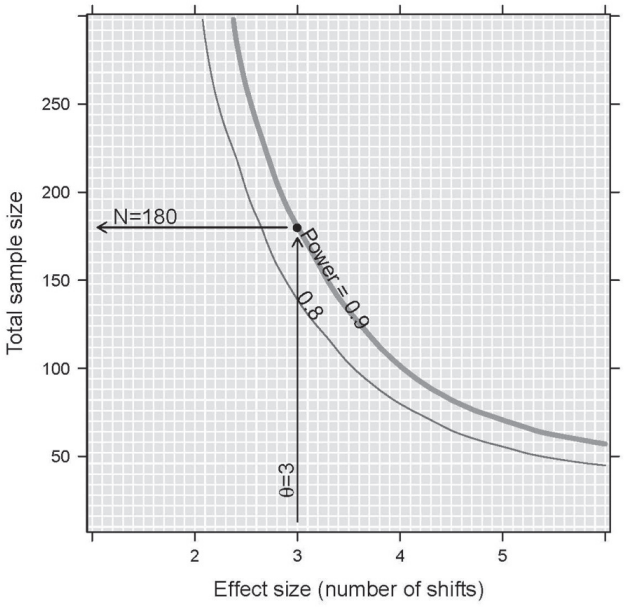

Figure 1 Total sample size (number of patients, not including dropouts) needed to be able to show the superiority of melatonin to placebo with respect to delirium duration (number of shifts), assuming an SD of 6 shifts, depending on the expected effect size. The numbers on the curves show the corresponding power. An example is shown for an effect size of 3 shifts and a power of 90%. The curves are smoothed and for illustration only.

For this study, assuming a difference in duration of delirium of 3 shifts and a SD of 6 shifts, 190 patients should be recruited to ensure 180 evaluable patients, considering a dropout rate of 5%. Figure 1 shows the sensitivity of the sample size is with respect to the expected effect size.

Planned analyses

Datasets to be analysed, analysis populations

We will conduct an ITT and a per protocol (PP) analysis.

The ITT set will include all patients randomised to melatonin or placebo excluding cases of ex-post study withdrawal. According to the ITT principle, patients will be analysed according to the randomised treatment.

The PP set will include all patients from the ITT set who met the inclusion criteria, did not meet any of the exclusion criteria and did not have a major protocol violation. Patients not receiving the randomised treatment will be analysed according to the received treatment.

Primary analysis

The primary outcome, duration of the delirium, will be compared between trial arms using a generalised linear model with duration of delirium as dependent variable. Since delirium duration (number of shifts) corresponds to a count variable, we will use a Poisson or negative binomial error distribution (depending on the dispersion). Type of admission (medical or surgical), sepsis (yes/no) and treatment (melatonin vs placebo) will be used as explanatory factors. This analysis will be applied to the

ITT set and is further referred to as the 'main analysis'. We will estimate effect sizes together with 95% CI.

To assess the sensitivity of the result with respect to the analysis method used, we will conduct the following sensitivity analyses on the ITT set:

S1—Comparison of trial arms using a Wilcoxon rank-sum test (also called Mann-Whitney test).

S2—As the'main analysis', but adjusting the treatment effect by including additional covariates in the model that might also affect the duration of delirium.

S3—If we observe any deaths during delirium, we will perform a competing risk analysis with end of delirium and in-hospital death as competing risks.

To assess the sensitivity of the result with respect to the analysis set used, we will also apply all analyses described above (main and sensitivity analyses) to the PP set.

Secondary analyses

Secondary outcomes will be compared between trial arms using statistical models with type of admission, sepsis and the treatment as explanatory factors. The number of delirium free days at day 28 and the number of ventilator days (counts) will be analysed by a generalised linear model with Poisson (or quasipoisson) error distribution and log link. Hospital and ICU length of stay will be analysed as counts using a generalised linear model or, in case of deaths during ICU/hospital stay, as time to ICU/hospital discharge using a competing risk analysis with end of ICU/hospital stay and in-hospital death as competing risks. Mortality within 28, 90 and 365 days (binary outcome) will be analysed using a generalised linear model with binomial error distribution and logit link, or depending on the number of deaths, as time to death with a Cox proportional hazards model. Sleep quality (total score of the RCSQ will be analysed using a linear or a generalised linear model. Outcomes listed as 'other outcomes' will be analysed descriptively.

In addition, the effect of melatonin versus placebo on the primary outcome will be compared among the following patient subgroups:

- Type of admission (surgical vs medical).
- Sepsis (yes/no).
- Cardiac surgery (yes vs no).
- Gender.
- Age (>65 years vs <=65 years).

For each subgroup variable, we will use a statistical model similar to the one described as the 'main analysis', including the subgroup variable, the treatment and the interaction between subgroup and treatment. A significant interaction will indicate that the treatment effect differs among subgroups. We will also estimate the treatment effect (with a 95% CI) separately in each subgroup to be able to graphically display the separate effect sizes together with the overall effect.

The statistical models for the secondary analyses will be applied to the ITT and to the PP set.

Deviation(s) from the original statistical plan

If substantial deviations of the analysis as outlined in these sections are needed for whatever reason, the protocol will be amended. All deviations of the analysis from the protocol or from the detailed analysis plan will be listed and justified in a separate section of the final statistical report.

Handling of missing data and dropouts

Missing values on the primary endpoint will be imputed for the ITT analyses. A detailed description of the imputation methods and corresponding sensitivity will be specified in the detailed analysis plan. Missing values on secondary endpoints will not be imputed (complete case analyses).

DATA REGISTRATION

Data will be entered into a web-based eCRF established by the CTU Basel. Paper case report forms will be used in parallel in case of possible technical difficulties.

DATA HANDLING AND MANAGEMENT

All data from this study will be kept within the Investigator Site File, and only the study team will have access. In case of a patient's ex-post denial of study participation, the data collected will not be used for publication involving either the corresponding trial or future trials. In such cases, the data will be destroyed. If the patient does not disagree, data collected until the time point of withdrawal will be used for analysis, but no further data will be collected.

All study data will be archived in a designated place on our Surgical Intensive Care Unit at the University Hospital of Basel for a minimum of 10 years after study termination or premature termination of the clinical study. We plan to store the data also within an anonymised and password-protected eCRF.

MONITORING

We have appointed an experienced study nurse of the University Hospital of Basel to be responsible for study monitoring focusing on data entry.

The sponsor plans no regular monitoring visits at the investigator's site prior to the start of the study. Monitoring will commence with the study initiation visit, followed by regular monitoring visits within timeframes that will have to be determined and stated above. A member of the study team will conduct daily monitoring of eCRF performance.

The source data/documents are accessible to monitors, and questions are answered during possible monitoring.

ETHICAL JUSTIFICATION

Due to the nature of delirium, patients eligible for study participation are not able to give their consent.

As described above, we will seek the patient's approval for use of collected data for our publication after the delirium has resolved.

Delirium is a serious condition calling for immediate diagnosis and therapy. Because ICU length of stay is associated with patient morbidity and mortality, we chose to investigate a therapeutic approach that might reduce the duration of delirium, thus, leading to shorter ICU and hospital stays.

By achieving our goal, we may positively influence patient well-being and enhance satisfaction after severe medical conditions and, most importantly, promote a reduction in patient morbidity and mortality. This, in turn, would have a positive impact on our society and on the economy.

ENROLMENT

Patients from the Intensive Care Unit of the University Hospital of Basel are primarily scheduled for study participation. The study is planned to begin in December 2019 and will continue for a 3-year period.

STUDY MANAGEMENT AND ORGANISATION

The study will be organised and managed by the research team of the Intensive Care Unit, University Hospital of Basel. An experienced study nurse who is not a member of the research team will provide monitoring. The CTU Basel will ensure the statistical research plan and statistical analysis. An eCRF will be established.

Co-enrolment of study participants in other clinical trials is basically allowed but will have to be discussed among the competing research teams prior to randomisation.

INSURANCE

Insurance will be provided by the Sponsor through the liability insurance of the University Hospital of Basel.

DATA SHARING AND PUBLICATION

Study results will be communicated to the individual patient when he or she regains capacity to give study consent. During the ongoing study and until publication, there will be no public access to the data. We plan to publish the data in an open source major peer-reviewed clinical journal.

A public description of the study in German will soon be available on the Swiss National Clinical Trial Portal (SNCTP).

FINANCES

Funding

This research is not currently supported by any funding agency. We have applied for financial support at the ICU Research Foundation of the University of Basel (submission until December 2019; decision expected February 2020).

- Study drug/personnel/laboratory will be financed by the above-mentioned grant approved by the ICU Research Foundation of the University Hospital of Basel.
- All other drugs used during the study are part of the routine treatment of patients with delirium. No additional costs will arise.

The design and planned conduct of this trial have not been and will not be influenced by any funding sources.

DISCUSSION

Study rationale

We hypothesise that oral administration of melatonin compared with placebo at the beginning of the night (20:00) will lead to a shorter duration and diminished severity of delirium. The results of this study may lead to better algorithms for the treatment of delirium, which could improve clinical care for patients, reduce the burden of family members and protect the patient's long-term autonomy and health.

Population

We will include patients admitted to the ICU suffering from hypoactive delirium.

Intervention

There is limited but promising evidence that restoration of circadian rhythm by melatonin shortens the duration of hypoactive delirium. In our study, we aim to confirm the superiority of melatonin over placebo for the delirium treatment. Melatonin reveals no known frequent side effects. As such, it is an innovative approach for a delirium type that until today lacks the possibility of drug treatment.

Comparator

Since there is no pharmacological approach for treatment of hypoactive delirium, we have chosen a placebo as a comparator to melatonin to be able to truly confirm or refute melatonin as an option.

Outcome

Based on the hypothesis that melatonin shortens the duration of delirium, we have decided to evaluate the duration of delirium in 8-hour shifts.

Sample size

As described above, sample size was estimated to be able to show the superiority of melatonin compared with placebo regarding the duration of delirium in hours.

Perspective

The Basel BOMP-AID study aims to improve quality of delirium treatment by implementation of melatonin into the treatment regime of hypoactive delirium based on high-quality data.

Study status

The ethics committee granted approval of this study in April 2018. Inclusion of first patient planned for April 2020.

ETHICS AND DISSEMINATION

This study has been approved by the Ethics Committee of Northwestern and Central Switzerland and will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use; Good Clinical Practice (GCP) or ISO EN14155 (as far as applicable), as well as all national legal and regulatory requirements. Study results will be presented in international conferences and published in a peer-reviewed journal.

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