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Feasibility of melatonin for prevention of delirium in critically ill patients: protocol for a multi-centre, randomized, placebo-controlled study

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ABSTRACT

Introduction Delirium is highly prevalent in the intensive care unit (ICU) and is associated with adverse clinical outcomes. At this time, there is no drug that effectively prevents delirium in critically ill patients. Alterations in melatonin secretion and metabolism may contribute to the development of delirium. Administration of exogenous melatonin has been shown to prevent delirium in non-critically ill surgical and medical patients. This trial will demonstrate the feasibility of a planned multicentre, randomized controlled trial to test the hypothesis that melatonin can prevent delirium in critically ill patients compared to placebo.

Methods and analysis This feasibility trial is a randomized, three-arm, placebo-controlled study of melatonin (2 mg vs. 0.5 mg vs. placebo, administered for a maximum of 14 days) for the prevention of delirium in critically ill patients. A total of 69 patients aged 18 and older with an expected ICU length of stay greater than 48 hours will be recruited from 3 Canadian ICUs. The primary outcome is protocol adherence (i.e., overall proportion of study drug doses administered in the prescribed administration window). Secondary outcomes include pharmacokinetic parameters, incidence, time to onset, and duration of delirium, number of delirium-free days, adverse events, self-reported sleep quality, rest-activity cycles measured by wrist actigraphy, duration of mechanical ventilation, ICU length of stay, and mortality. Data will be analyzed using an intention-to-treat approach.

Ethics and dissemination The study has been approved by Health Canada and the research ethics board of each study site. Trial results will be presented at international conferences and published in a peer-reviewed journal.

Trial registration clinicaltrials.gov NCT02615340

Strength: The incorporation of pharmacokinetic measurements into our planned analysis will inform dose selection of the planned future large scale randomized control trial.

Limitation: While a feasibility study is essential prior to the execution of a full-scale trial, this design does not permit the determination of delirium-related clinical outcomes.

INTRODUCTION

Delirium is a syndrome of acute brain dysfunction characterized by fluctuations in attention, mental status, disorganized thinking and altered level of consciousness.[1] Specific symptoms such as delusions and hallucinations, agitation, restlessness, and sleep disturbance are distressing for patients, families, and clinical staff.[2,3] Delirium is highly prevalent in the intensive care unit (ICU) where rates range from 40-90%.[4] Critically ill patients who develop delirium experience worse outcomes including increased mortality, prolonged mechanical ventilation, increased duration of ICU and hospital length of stay, functional and cognitive decline, and increased likelihood of placement in long-term care facilities.[5-10] These adverse clinical and systems level implications underscore the imperative of identifying safe and effective strategies for the prevention of delirium in critically ill patients. At this time however, no pharmacological agent has been shown to effectively prevent delirium or favourably alter related outcomes in this patient population.[4]

The pathophysiology of delirium is not fully understood. Current hypotheses include neuroinflammation, impaired cerebral oxidative metabolism, and disturbances of neuroendocrine and neurotransmitter systems.[11,12] In particular, there is considerable research on dopaminergic, cholinergic, gamma-aminobutyric acid, and serotonergic neurotransmitter pathways, as these modulate cognition, behaviour, mood, and sleep. Although disturbances of the sleep-wake cycle are not diagnostic of delirium, changes in sleep patterns are incorporated into delirium screening tools, and studies indicate sleep changes occur in over 75% of delirious patients.[13]

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone sequentially derived from tryptophan and serotonin in the pineal gland during hours of darkness.[14] It has multiple biological effects, most notably in the regulation and synchronization of circadian rhythms, where it works as a hypnotic in accelerating the initiation and improving the maintenance and efficiency of sleep.[14] Disturbances in circadian melatonin secretion have been described in a number of patient populations at high-risk of delirium, including general medicine, critically ill with sepsis, and post-operative.[15-21] Given these findings, the abnormal secretion and metabolism of melatonin may play a role in delirium pathogenesis.[13,15,16,18,22-24]

Unlike other hypnotics, melatonin causes no significant changes in sleep architecture and has no hangover effects or abuse potential.[25] The administration of exogenous melatonin may therefore prevent delirium through its effects on circadian rhythm and sleep.[19,20] Exogenous melatonin has also been shown to be sedative sparing,[26] an important factor in reducing delirium risk in the critically ill.[4,27,28]

The hypothesis that exogenous melatonin may prevent delirium has been explored in three randomized controlled trials.[29-31] In one study, hospitalized general medicine patients (N=145, aged 65 years and older) given low-dose melatonin (0.5 mg) at bedtime displayed significantly less delirium (3.6% vs. 19%, p=0.014) compared to placebo controls.[31] In a surgical population (N=222, aged 65 years and older) comparing melatonin (5 mg), midazolam (7.5 mg), and clonidine (0.1 mg) to no pre-medication administered the night prior to and again 90 minutes before surgery, patients receiving melatonin experienced significantly less delirium in the post-operative period compared to no pre-medication, midazolam, or clonidine (melatonin 9.4% vs. no pre-medication 32.7% vs. midazolam 44.0% vs. clonidine 37.3%, p <0.05).[29] In contrast, a large trial (N=444, aged 65 years and older) of hip fracture patients reported that a 3 mg dose of melatonin at bedtime did not reduce delirium compare to placebo (29.6% vs. 25.5% placebo, p=0.4); however, fewer patients treated with melatonin experienced long-lasting delirium, defined as more than two days (25.5% vs. 46.9%, p= 0.02).[30] Furthermore, a trial of ramelteon, a melatonin agonist, showed a significant reduction in delirium incidence compared to placebo (3% vs. 32%, p=0.003) when administered to a mix of ICU and acute ward patients (N=67).[32]

A recent systematic review found melatonin did not reduce delirium incidence (relative risk [RR] 0.41, 95% confidence interval [CI] 0.15 to 1.13; P =0.08).[33] However, in the subgroup of elderly patients treated in acute medical wards, melatonin decreased delirium incidence by 75% (RR 0.25, 95% CI 0.07 to 0.88; P = 0.03), but did not reduce sleep-wake disturbance (RR 1.24, 95% CI 0.51 to 3.00; P=0.64). Given the small number of melatonin studies for delirium prevention, more research is needed. This is particularly important in the critically ill population who are considered at highest risk and amongst the most burdened by delirium from both a clinical and resource utilization standpoint.

Study objectives

Exogenous melatonin may decrease delirium incidence in non-critically ill patients. However, there are no trials focused solely on the critically ill population. Based on the available evidence, we hypothesize exogenous melatonin, administered on a scheduled nightly basis, will be efficacious and safe in the prevention of delirium in critically ill adults.

This pilot study will serve to determine the feasibility of conducting a future large-scale, multi-centre, randomized placebo-controlled trial in critically ill patients at risk of delirium. Additionally we aim to determine appropriate melatonin dosing.

Specific study objectives are to:

1. Identify the proportion of administered doses of prescribed study drug (i.e. study protocol adherence);
2. Identify the proportion of screened study participants that meet inclusion criteria;
3. Identify the consent rate of eligible participants (i.e., feasibility and timeframe of enrolment: number screened, number excluded, number consented);
4. Describe, per patient, the time required to complete study enrolment and all data collection;
5. Describe the pharmacokinetic properties of enterally administered melatonin at a dose of 0.5 mg compared to 2 mg;
6. Describe the proportion of participants that experience adverse drug effects; and
7. Compare delirium incidence (Intensive Care Delirium Screening Checklist [ICDSC][34] score of 4 or more) and duration, self-reported sleep quality, rest-activity cycles (with wrist actigraphy), duration of mechanical ventilation, length of ICU and hospital stay, and ICU and hospital mortality.

METHODS AND ANALYSIS

This trial is funded by the Centre for Collaborative Drug Research at the University of Toronto, and will be conducted in accordance with the ethical principles outlined by the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans[35] and the Declaration of Helsinki. Health Canada (No Objection Letter, # 197507 November 7, 2016) and the research ethics board of each participating centre have approved the protocol (Sunnybrook Health Sciences Centre # 086-2016; Mount Sinai Hospital #16-0097-A; and Hôpital du Sacré-

Coeur de Montréal # 2017-1385). Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.[36]

Study design

We will conduct a three-arm, randomized, placebo-controlled feasibility trial comparing the safety and efficacy of two doses of melatonin (low dose = 0.5 mg and high dose = 2 mg) versus placebo for the prevention of delirium in patients with an anticipated ICU admission of >48 hours.

Study outcomes

Feasibility outcomes

1. Protocol adherence. We will calculate protocol adherence using the overall proportion of doses administered in the prescribed dose administration window divided by total number of study days. We will define adherence as administration of ≥85% of prescribed doses within the drug administration window qHS (*quaque hora somni* defined as 21:00 to 23:59 hours);
2. Trial recruitment. We will calculate the proportion of screened ICU patients meeting study inclusion criteria, the number of and reasons for patient exclusions, and the consent rate of eligible participants; and
3. Time-in-motion study. We will capture the amount of time required to screen for, consent, and enroll patients, to complete study procedures and data collection for the first ten patients at each site.

Pharmacokinetic outcomes

Plasma melatonin levels will be measured by mass spectrometry including:

1. Peak concentration (C_{max});
2. Time of peak concentration (T_{max});
3. Morning concentration (C_{9AM});
4. Half-life ($T_{½}$);
5. Mean apparent clearance (CL/F);

6. Mean apparent volume of distribution (V/F); and
7. Area under the concentration-time curve (AUC).

Clinical outcomes

1. Adverse events. We will screen for the following adverse events previously associated with melatonin: morning drowsiness (Sedation Agitation Scale (SAS)[37] scores < 3 or patient self-report of drowsiness between 07:00h and 12:00h), headache, vivid dreams;
2. Delirium incidence (ICDSC[34] score ≥4) and subsyndromal delirium (ICDSC score of 1 to 3);
3. Time to onset of delirium, delirium duration, and delirium-free days (at ICU discharge);
4. Self-reported sleep quality (Richards Campbell Sleep Questionnaire (RCSQ)[38,39] and rest-activity cycles with wrist actigraphy;
5. Duration of mechanical ventilation;
6. Length of stay (ICU and hospital); and
7. Mortality (ICU and hospital).

Location and setting

We will conduct the trial in three mixed-patient population ICUs in three university-affiliated hospitals (Sunnybrook Health Science Centre (Toronto), Mount Sinai Hospital (Toronto), and Hôpital du Sacré-Coeur de Montréal (Montreal). These ICUs have existing research infrastructure and extensive experience with clinical trial conduct, including studies related to delirium.

Participant selection and recruitment

The study subjects will be adult critically ill patients admitted to the ICU at any of the three study sites.

Inclusion criteria

1. Critically ill patients aged 18 years or older; and
2. Anticipated ICU stay >48 hours.

Exclusion criteria

1. ICU admission >48 hours at the time of screening;
2. Unable to assess for delirium (e.g., coma or deep sedation [SAS score 1 or 2 or 'No Response' score A or B on ICDSC]; receiving neuromuscular blocking drugs) at the time of screening;
3. Screened delirium positive (ICDSC score ≥4) prior to randomization;
4. Anticipated withdrawal of life sustaining therapy;
5. History of severe cognitive or neurodegenerative disease (e.g., dementia, Parkinson's disease) or severe structural brain injury (e.g., traumatic brain injury, intracranial hemorrhage) as the ICDSC assessment tool has not been validated in these patient populations
6. Unable to communicate in English or French (Montreal site) as we will be unable to assess for delirium using the ICDSC in non-English/French speaking patients
7. Absolute contraindication to enteral nutrition (e.g., gastrointestinal obstruction, perforation, recent gastrointestinal surgery, deemed strict nil by mouth, lack of enteral access)
8. Active seizures
9. Known pregnancy
10. Legally blind
11. Known allergy to melatonin

Eligible non-randomized criteria

1. Patient or substitute decision maker (SDM) declines consent
2. Patient unable to give consent and no SDM available
3. ICU physician declines consent
4. Consent not obtained due to another reason

Research personnel at each study site will screen for potential participants daily, Monday to Friday. Written informed consent will be sought from competent eligible participants, or substitute decision makers, if incompetent. Consent will be documented in the patient's medical record.

Randomization and blinding

Following informed consent, subjects will be randomly assigned in a 1:1:1 manner to one of the three study arms using a computer-generated, permuted-block randomization schedule, stratified according to site and concealed in sealed, sequentially numbered, opaque envelopes. The clinical trial pharmacists and/or trial pharmacy technician at each site will randomize patients to treatment groups by drawing sequentially sealed, opaque envelop from a box containing an allocation code. Study personnel, the ICU team, participants and family members will be blind to study group allocation, except in an emergency and only after unblinding is approved by the principal investigator. In this instance, the principal investigator and attending physician will discuss whether unblinding is necessary to provide medical care to the patient.

A target sample of 15 participants (five from each study arm) from the Mount Sinai Hospital site will be recruited for inclusion in the pharmacokinetic analysis. There are no additional inclusion or exclusion criteria for participation in the pharmacokinetic analysis.

Interventions

After randomization, a pre-printed study medication order will be placed in the patient's medical chart. Study subjects will receive study drug (melatonin 0.5 mg, melatonin 2 mg, or placebo) once daily qHS, between 21:00 and 23:59. Study medication will be administered by mouth (po or *per os*) or if necessary, by feeding tube (nasogastric, orogastric, jejunal or percutaneous endoscopic gastrostomy (PEG)) with subsequent flushing with 20mL of sterile water. All study drugs will be administered commencing the day of study enrolment and continued until ICU discharge, death, or up to a maximum of 14 days, whichever occurs first. This maximum duration of study drug administration was selected because critically ill patients are at greatest risk of developing delirium within the first two weeks of ICU admission.[8]

The optimal dose of melatonin for the prevention of delirium has yet to be determined. Published trials for delirium prevention in hospitalized, non-critically ill adults have administered oral nightly doses of melatonin ranging from 0.5 to 3 mg.[29-31] Trials of melatonin for sleep disorders have used higher doses, up to 10 mg.[40-43] A small study evaluating melatonin for sleep in mechanically ventilated adults (N=24) found a 10 mg nightly dose excessively increased plasma concentrations and resulted in morning drowsiness. The

authors therefore suggested doses of 1 to 2 mg may be more appropriate in critically ill patients.[44] For jetlag in non-clinical populations, melatonin doses between 0.5 and 5 mg have been shown to be similarly effective; however, doses above 5 mg were not found to be more effective than lower doses.[45] Given the relatively sparse data on melatonin for delirium prevention and the lack of trials in ICU patients, we have chosen doses we feel are reasonable given the available data, while also ensuring sufficient difference to identify an effective dose.

We will not protocolize administration of any co-interventions in this study. The clinical team will remain responsible for all other aspects of patient care, including any pharmacological or non-pharmacological interventions for delirium prevention and treatment, or interventions that may be associated with delirium development. As such, the management of pain, agitation, sedation, delirium, and sleep will be performed according to local practice, the details of which will be captured through study data collection. The use of open-label melatonin will not be permitted in this study.

Study medication

The clinical trial pharmacist and/or pharmacy trial technician at each site will compound melatonin 1 mg/mL oral suspension in accordance with Good Manufacturing Procedures (GMP) guidelines. All sites will use a non-animal synthetic source of melatonin (Jamieson Laboratories, NPN 80015041 immediate release) to compound doses. The compounded 1 mg/mL solution will be further diluted with a 1:1 mixture of Ora-Plus and Oral-Sweet (Paddock Laboratories Inc., NDC 054-0304-16) to prepare study doses identical in appearance (milky white colour and identical final volume). Each 5 mL dose will be dispensed in amber oral syringes labeled as “melatonin/placebo study drug.” Only the clinical trial pharmacist and/or pharmacy trial technician specified on the delegation of responsibility log will prepare and dispense the study drug.

The study drug will be stored, tracked, and counted in accordance with standard pharmacy dispensing practices by the clinical trial pharmacist and/or pharmacy trial technician. The pharmacy department at each site will maintain a dispensing list kept in the study operations binder that records the identity of participants for each study randomization number. The randomization number will be indicated on the prescription in the subject’s chart and on the

dispensing label, allowing the bedside nurse to verify that the patient receives the appropriate study medication. The nurse will record the administration of study drug in the medication administration record (MAR), in accordance with standard ICU practice, in addition to signing the study preparation and administration log.

Data collection

To ensure consistency and optimization of the data collection process, case report forms and standard operating procedures will be included in each site's study resource binder. Study training sessions will be held at each site, and attendance of research staff will be documented. Only trained and qualified research staff will be permitted to collect study data.

Protocol adherence and feasibility assessment

Each morning, the research team will review the medication profile of study subjects to ascertain if study drug was administered and, where applicable, identify the reasons for late (i.e. protocol deviation) or missed (i.e. protocol violation) doses. Each site will maintain a screening log documenting patients: 1) screened, 2) ineligible, 3) eligible, 4) consented and enrolled, and 5) declined. Using a time-in-motion template[46] from by the Canadian Critical Care Trials Research Coordinator Group, the time required to complete patient screening, maintain the study log, and complete all consent and study-related procedures, including data capture, will be recorded on a daily basis for the first ten patients enrolled at each site.

Pharmacokinetics

A pharmacokinetic analysis of plasma melatonin concentration will be conducted at the Mount Sinai Hospital site in participants that consent to the required blood samples. A target sample of 15 subjects (five from each study arm) will be enrolled. On the first study day, research personnel will collect eight blood samples of 4 mL each using BD vacutainer tubes (K2 EDTA 7.2 mg, DB Franklin Lakes, NJ, USA). The first sample will be taken prior to the first dose of study drug, and subsequent samples will be collected throughout the night at pre-defined intervals ($t_{0\ (baseline)}$, $t_{0.5hr}$, t_{1hr}, t_{2hr}, t_{4hr}, t_{6hr}, t_{8hr}, t_{12hr}) terminating 12 hours later (i.e. the next morning). Specimens will be screened for hemolysis and redrawn if needed. All samples will be centrifuged and stored at -80°C until assays are performed by Mount Sinai Hospital

Services Laboratory. Plasma melatonin concentration will be measured using mass spectrometry, and sample dilution to within the linear range of the assay will be performed as necessary. Non-compartmental pharmacokinetic analysis (PKSolution 2.0; Summit Research Services, Montrose, CO, USA) will be used to compare the three study doses. The timing of the blood samples was chosen based on pharmacokinetic studies using similar methodology, in critically and non-critically ill patients.[47-49]

Because melatonin release is regulated by the presence of light, research personnel will also measure light intensity at the time (i.e. in the 5 minutes prior) of each blood sample. Light intensity will be measured near the head of the patient's bed at eye level using a lux-meter (Environment Meter SHSEHY002, Shimana, Digital Measurement Metrology, Brampton, Ontario, Canada).

Clinical outcomes

Delirium The ICDSC[34] is an 8-item checklist that requires initial evaluation of the patient's level of consciousness, with subsequent delirium screening if the patient is neither comatose nor stuporous. Using a cutoff score of 4, the ICDSC has 99% sensitivity and 75% specificity when compared to psychiatric assessment using DSM[1] criteria. Clinical staff will screen for delirium once daily until the patient is discharged from the ICU. If bedside staff have not complete the ICDSC, research staff will prompt the completion of the assessment. All ICDSC scores will be recorded on the case report form for the duration of the patient's ICU admission, enabling the determination of both the incidence and duration of delirium and subsyndromal delirium.[50]

Sleep The RCSQ is a simple, validated survey instrument used to evaluate perceived depth, latency, efficiency, and quality of sleep in intensive care patients.[38,39] Patients will be asked to complete the RCSQ each morning of study participation, independently or with the assistance of their bedside nurse. If the patient is unable to complete the RCSQ, no sleep data will be collected for that day because of poor correlation between patient and nursing scores.[51] Although polysomnography[52,53] is the reference standard for measuring sleep, its requirement for specialized technology and expert staff for interpretation render it logistically challenging in the ICU setting. Polysomnograms are also particularly difficult to interpret in ICU

patients because of considerable polypharmacy and pathophysiology associated with their critical illness.

Patients enrolled at the Hôpital du Sacré-Coeur de Montréal site (n target = 21) will have rest-activity cycles measured using wrist actigraphy. The actigraph is a small, watch-like device that contains an accelerometer, which records physical motion in all directions with a sensitivity of 0.05 g. Motion is converted into an electric signal, which is digitally integrated to derive an activity count per 1-minute epoch. The rest-activity cycle consolidation will be estimated with the ratio of daytime activity to total 24-hour activity. For each 24-hour day and for each participant, the activity counts will be summed separately for daytime (07:00-21:59 hours) and night-time (22:00-6:59 hours) periods. Night-time is defined according to the schedule of the hospital unit, and is characterized by lower levels of activity and light. The percentage of activity occurring in the daytime will be divided by the total 24-hour activity to obtain the daytime activity ratio. According to previously published data,[54] a daytime activity ratio of 80% will be chosen to designate an adequate consolidation of the rest-activity cycle, synchronized to the day-night cycle.

Adverse events We will adhere to published guidelines[55,56] for reporting serious adverse events in academic drug trials in critical care. As such, the only adverse events recorded will be those reasonably thought to be a consequence of study participation, and judged by investigators to be unrelated to the patient's underlying disease or an unexpected complication of critical illness.

Other data Other data recorded daily will include Glascow Coma Scale (GCS)[57] and SAS[37] scores, psychoactive drug exposure (i.e., type and dose of sedative, analgesic, anti-anxiety, and antipsychotic medications), sedation protocols or sedation interruption; mobilization out of bed; physical restraint; accidental device removal; presence of a visible clock or window, use of a television, computer, or iPad; single versus shared room; isolation precautions; and strategies to preserve day-night orientation including light and noise reduction (i.e., earplugs and eye masks). Patient demographics (age, sex), comorbidities, use of visual and auditory aids, severity of illness score (Sequential Organ Failure Assessment (SOFA)[58]), admission diagnosis, best possible medication history[59], duration of mechanical ventilation, ICU and hospital length of stay, and ICU and hospital mortality will also be recorded.

Statistical considerations

Sample size

The sample size for this pilot study has been determined to measure adherence to prescribed study drug, with adherence defined as administration of ≥85% of prescribed doses within the administration window using a margin of error of +/- 5%. For an average daily drug administration lasting 4 days and an intra-cluster correlation (ICC) of 0.115 (adjusting for the clustering effect of repeated drug administration within the same subject), 69 patients (or 276 drug administration adherence opportunities) will enable determination of successful adherence (rate 85%; margin of error of +/- 5% at a 95% confidence level).

Statistical analysis

Data will be analyzed using an intention-to-treat approach. Simple descriptive statistics will be used to report feasibility outcomes, pharmacokinetics, as well as baseline demographic and clinical variables. Continuous variables will be described using measures of central tendency and spread (means and standard deviations or medians and interquartile ranges, dependent on data distribution). Frequencies, proportions and their 95% confidence intervals will be used to describe categorical variables. Except for analyses of repeated measures, Kruskal-Wallis tests will be used to compare continuous variables, and chi-square tests to compare categorical variables. Methods that account for clustering will be used when analyzing repeated observations from the same subject. Time-to-event analyses will be used to compare the effects of study drug on the onset of delirium, duration of mechanical ventilation, ICU and hospital length of stay.

Analyses will be considered significant when $p \leq 0.05$ (two-tailed). All analyses will be performed by an independent statistician using SAS 9.3.

Ethics and dissemination

Ethical considerations

The trial will be conducted in accordance with Good Clinical Practice following published tri-council guidelines,[35] the Canada Natural Health Products Regulations, The Canadian

Personal Health Information Protection Act (PHIPA), and the International Conference on Harmonization Good Clinical Practice (ICH GCP). All data will be de-identified and will be presented in summary form to preserve the anonymity of individual subjects.

All patients or their substitute decision maker will sign an informed consent form before trial participation and will be given a copy for their records. Research staff will provide an appropriate lay explanation of the proposed aims, methods, objectives and possible harms of the study. A specific section outlining the acquisition and storage of blood samples is included in the informed consent form. We will complete routine quality control to ensure that the study is being conducted according to protocol. This routine quality control will include verification of 1) inclusion and exclusion criteria; 2) source data checks, to ensure accuracy of data collection; 3) adverse events checks to confirm these are recorded, assessed, and reported according to protocol; and 4) case report form review, to ensure completion according to protocol.

CONCLUSION

Delirium is a common syndrome in critically ill patients and is associated with numerous adverse clinical outcomes.[5-10] At this time, no effective drug treatment exists for delirium,[4] making the identification of a safe and effective prevention therapy a clinical imperative. Exogenous melatonin is inexpensive to administer and demonstrates a wide safety margin across adult and paediatric clinical populations. This feasibility trial is the first to explore the effect and pharmacokinetics of both high and low dose melatonin against placebo in critically ill adults. The results of this study are expected in 2018 and if feasibility is proven, we plan to conduct an adequately powered pragmatic randomized controlled trial of similar design.

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Author contributions

LB, DS, DW, JF, SM, MG, EF, MD, AA, FB, and LR made substantial contributions to the conception and/or design of the study protocol. LB, DS, DW, and LR conceived of the overall study and wrote the first draft of the protocol and this manuscript. LB, DS, DW, AA, and LR provided critical input pertaining to the design of the study interventions, procedures, and outcomes. LB, DS, MG, AA, and LR designed the data analysis and management plan. LB, DS, DW, JF, SM, EF, MD, FB, and LR critically revised the protocol for important intellectual content and approved the final version to be published. LB, DS, DW, JF, SM, MG, EF, MD, AA, FB, and LR agree to be accountable for all aspects of the work, ensuring its accuracy and integrity.

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Michael Christian MD, MSc; Heather Boon, PhD; Wei Xiong, MSc; Elizabeth Wilcox, MD; Catherine Duclos BA, PhD (candidate); Nadia Gosselin PhD; Salmaan Kanji, PharmD; Michelle Rodrigues, BSc; Hilde Vandenberghe PhD

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Competing interests statement

None declared.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-2
	6b	Explanation for choice of comparators	10-11
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7,10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8, 12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12-14

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15-16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9,12,16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15-16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	If requested by BMJ Open
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	12

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Feasibility of melatonin for prevention of delirium in critically ill patients: A multi-centre, randomized, placebo-controlled study

Date of version: May 27, 2016

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PROTOCOL SIGNATURE PAGE

Feasibility of melatonin for prevention of delirium in critically ill patients:
A multi-centre, randomized, placebo-controlled study

Version #1: January 30, 2016
Version # 2: May 27, 2016

My signature below confirms that I have generated the protocol with the listed co-investigator team, and agree that it contains all of the necessary details for conducting the study as described. We will conduct this protocol as outlined therein, and according to Good Clinical Practice and all applicable local and national regulations.

_____ Date: _____
Damon Scales, M.D., Ph.D

_____ Date: _____
Louise Rose, Ph.D.

_____ Date: _____
Lisa Burry, BScPharm, Pharm.D.

Table of Contents

1.0 ABBREVIATIONS

AA-NAT	N-acetyltransferase
AUC	area under the concentration-time curve
C_{max}	peak concentration
C_{9AM}	morning concentration
CRF	case report form
CI	confidence interval
CL/F	mean apparent clearance
ENR	Eligible non-randomized
EUR	Euro
GABA	gamma-aminobutyric acid
ICU	Intensive Care Unit
ICDSC	Intensive Care Delirium Screening Checklist
mcg	microgram
mg	milligrams
mL	milliliters
MT6	6-sulphatoxymelatonin
NA	Refers to a data point that was not available from the patient's paper or electronic chart to be copied onto the CRF
pg	picograms
PK	pharmacokinetics
qHS	*quaque hora somni* or every night at bedtime; administration of drug between 21:00-23:59
RCSQ	Richard Campbell Sleep Questionnaire
RCT	randomized controlled trial
SAS	Sedation Agitation Scale
$T_{½}$	half-life
T_{max}	time of peak concentration
USD	U.S. dollars
V/F	mean apparent volume of distribution

2.0 OVERVIEW

Delirium is an acute brain dysfunction affecting 40-90% of the approximately 13 million critically ill patients admitted to ICUs annually worldwide. Delirium is characterized by fluctuating changes in mental status, including inattention, disorganized thinking, and altered level of consciousness, with numerous risk factors identified in critically ill patients. Delirium is associated with deleterious effects on patient outcomes, including increased mortality, prolonged duration of mechanical ventilation and length of ICU and hospital stay, poor cognitive outcomes, and increased resource utilization. To date, no pharmacologic agent has been shown to prevent or treat delirium in critically ill patients.

While delirium prevalence is high and risk factors have been clearly identified, the pathophysiology of ICU delirium is not fully understood. Current hypotheses focus on neuroinflammation, neuroendocrine disturbances, and imbalances of neurotransmitters modulating cognition as well as behavior and mood, including serotonin, the precursor to melatonin. Disturbances of the circadian sleep-wake cycle represent one of the core features of delirium, and patients with delirium demonstrate altered serum melatonin concentrations and metabolite production. Additionally, melatonin metabolism has been shown to be disturbed after surgery, sleep deprivation, insomnia, and in critical illness, all of which are associated with delirium.

In clinical trials of hospitalized patients, melatonin has been shown to prevent delirium or shorten the duration of delirium in elderly medical and peri-operative populations, with doses ranging from 0.5 mg to 10 mg. At this time, the efficacy of melatonin for preventing delirium in critically ill patients, and the optimal dose to achieve this potential effect, are unknown. Thus, a large scale randomized controlled trial is needed to determine if melatonin is a safe and effective therapy to prevent delirium in this vulnerable population. Before this trial can be conducted, study protocol feasibility and dosing need to be determined. The aim of this study is to assess the feasibility of conducting a future, large scale randomized controlled trial designed to evaluate the efficacy of enterally administered melatonin for prevention of delirium in critically ill adults.

3.0 BACKGROUND

3.1 Delirium in the intensive care unit

Delirium is characterized by acute onset of fluctuations in attention, mental status, organized thinking, and level of consciousness.[1] It is highly prevalent in the intensive care unit (ICU) population, where reported rates range from 40-90%.[2] Substantive literature shows that critically ill patients with delirium experience significantly more adverse outcomes compared to those who do not develop delirium, including increased mortality, longer durations of mechanical ventilation, ICU and hospital stay, functional decline, and placement in long-term care facilities.[3-8] Delirium poses a significant economic burden: the annual cost of delirium has been estimated to be USD >164 billion, and EUR >182 billion in 18 European countries.[9, 10] These negative clinical and healthcare system implications underscore the imperative to identify effective and safe delirium prevention and treatment strategies for the critically ill.

The pathophysiology of delirium is not fully understood. Current hypotheses include neuroinflammation, impaired cerebral oxidative metabolism, disturbances of the neuroendocrine system, and alterations of various neurotransmitters.[11, 12] There has been much research focus on studying the alterations in the cholinergic, dopaminergic, gamma-aminobutyric acid (GABA), and serotonergic neurotransmitter pathways, as these pathways modulate cognition, behavior, mood, and sleep. Numerous pharmacological agents that target various identified pathways have been investigated for delirium prevention and treatment in both critically ill and non-critically ill patient populations. To date, no pharmacological agent has been shown to prevent delirium in critically ill patients or successfully alter delirium outcomes of those who develop delirium.[2]

3.2 Melatonin and its role in delirium pathophysiology

Melatonin is a neurohormone produced by the pineal gland during the hours of darkness. Melatonin has multiple biological effects but most notably melatonin plays a pivotal role in the regulation and synchronization of circadian rhythms.[13] It works as a hypnotic by accelerating sleep initiation and improving sleep maintenance and efficiency. Unlike other hypnotics, melatonin causes no significant changes in sleep architecture, nor does it have hangover effects or abuse potential, nor has it been associated with delirium.

Disturbances in the circadian pattern of melatonin secretion have been described in hospitalized medical patients, critically ill patients with sepsis, and those with post-operative delirium.[14-20] Although disturbances in sleep-wake cycle are not a diagnostic criterion for delirium, it is incorporated into delirium assessment tools with studies indicating sleep changes occur in > 75% of delirious patients.[21] Therefore melatonin and changes in its metabolism are likely part of the pathogenesis of delirium.

3.3 Data for melatonin in prevention of delirium

There is a growing body of evidence to support the use of melatonin for many indications including the treatment of jet lag, sleep disturbances in adults and children, and behavioral aspects of dementia. Three randomized controlled trials have specifically evaluated melatonin for prevention of delirium in hospitalized patients. However, these trials did not include critically ill

patients (Appendix 1).[22-24] In a double blind, randomized controlled trial, low-dose melatonin (0.5 mg) versus placebo was shown to reduce delirium incidence (3.6% vs. 19%, p=0.014) in 122 hospitalized general medical patients aged >65 years.[22] However, there were no differences between groups in delirium severity, length of hospital stay, use of psychotropic drugs, or mortality. Sultan and colleagues compared the effect of melatonin (5mg) to midazolam (7.5 mg), or clonidine (0.1 mg), or no pre-medication (control) given the night before surgery and repeated 90 minutes pre-operatively on post-operative delirium incidence in 222 patients ≥ 65 years receiving hip arthroplasty.[23] Melatonin was associated with decreased delirium incidence compared to all other groups (melatonin 9.4% vs. control 32.7% vs. midazolam 44.0% vs. clonidine 37.3%, p <0.05). In contrast, in 444 hip fracture patients 65 years and older, there was no difference in delirium incidence when melatonin at 3 mg was compared to placebo (melatonin 29.6% vs. placebo 25.5%, p=0.4), though fewer melatonin treated patients experienced delirium beyond two days (melatonin 25.5% vs. placebo 46.9%, p=0.02).[24]

3.4 Pharmacological and pharmacokinetic considerations of melatonin

3.4.1 Pharmacology

Melatonin, N-acetyl-5-methoxytryptamine, is a neurohormone derived sequentially from tryptophan and serotonin in the pinealocytes.[13] The rate-limiting enzyme is N-acetyltransferase (AA-NAT) whose synthesis is promoted by darkness with its activity modulated by multiple neuronal interactions based in the suprachiasmatic nuclei. Clock-genes control the synthesis of melatonin by controlling the production of two proteins, which in turn provide negative feedback for gene suppression. Light induces AA-NAT proteolysis resulting in a prompt decline in melatonin synthesis.[13, 25, 26] The decline in circulating levels of the clock-proteins triggers gene transcription and a new cycle of melatonin synthesis with peak activation at night. Increased light intensity both increases the quantity of endogenous melatonin produced and shifts the pattern of release throughout the circadian clock (known as melatonin synchronization). Of note, there is no synchronization of melatonin release in blind people (known as free-running state).[27]

Animal studies and *ex vivo* experiments suggest melatonin has multiple biological effects besides regulation and synchronization of circadian rhythms. Melatonin exerts many regulatory functions by modulating cellular behavior via binding to specific receptors and intra-cellular targets.[13, 25] It acts as an effector of the inflammatory cell compartment, able to alter leukocyte function and reduce the oxidative environment of chronic inflammation. Melatonin inhibits the expression of the isoforms of inducible nitric oxide synthase and cyclo-oxygenase and limits the production of excessive amounts of nitric oxide, leukotrienes, and other mediators of the inflammatory process.[28-33] Melatonin has been shown to have anti-oxidant properties in brain tissue; it slows the degenerative changes and clinical progression of Alzheimer's disease, inhibits excitotoxic damage, and prevents ischemic-reperfusion injury associated with traumatic brain injury.[30, 32, 33] Although melatonin has anti-oxidant effects, it has been shown to have pro-oxidative properties. These oxidative effects are considered to be responsible for its anti-microbial properties.[34-36] Melatonin has been shown in animal studies to have oncostatic effects on hormone-dependent cancers although the precise mechanisms are not clear.[37-39]

3.4.2 Pharmacokinetics (PK)

The circadian pacemaker within the suprachiasmatic nucleus triggers the pineal gland to produce melatonin with the onset of darkness.[13] Melatonin secretion increases directly with the length of darkness. Endogenous plasma concentrations begin to rise around 21:00 hours, peak at approximately 100 pg/mL between 02:00 to 04:00 hours, and return to usual low daytime levels by 09:00 hours.[13] The peak of melatonin release correlates with the nadir of core temperature and alertness.[40] The total production of endogenous melatonin is approximately 30 mcg/day. However, plasma concentrations vary greatly between individuals and are reduced with age, cognitive impairment, and in critical illness.[13, 18, 41-43]

Oral exogenous melatonin undergoes extensive first-pass metabolism, with a wide variation in its bioavailability.[13, 25] Melatonin is predominantly metabolized by CYP1A2 of the hepatic cytochrome P450 enzyme system, and following subsequent conjugation with sulphuric or glucuronic acid is excreted in the urine.[44] The principal metabolite is 6-sulphatoxymelatonin (MT6) with plasma concentrations of melatonin correlating closely with urinary MT6 concentrations. The elimination half-life ($t_{½}$) of melatonin is 30-45 minutes, though this is increased to up to 100 minutes in patients with end stage liver disease.[44] Appendix 1 summarizes available PK information for both critically ill and non-critically ill hospitalized patients. In a small series of 12 ICU patients, Mistraletti *et al* found peak serum values were reached quickly, approximately 15 minutes, following a 3 mg dose of oral melatonin, with high pharmacological melatonin concentrations observed for a further 10 hours.[43]

Many medications are known to affect melatonin secretion or excretion. The majority of these reduce melatonin serum concentrations and include: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, benzodiazepines, local anaesthetics, beta-blockers, calcium channel blockers, clonidine, caffeine, tobacco, alcohol, and sodium valproate.[44] Opioids may either increase or decrease melatonin serum concentrations by modulating N-acetyltransferase, which converts serotonin to N-acetylserotonin, a precursor to melatonin.[44-46] Melatonin concentrations are reduced by the antidepressant fluoxetine, but increased by other antidepressants including fluvoxamine, desipramine, and monoamine oxidase inhibitors.[47]

3.4.3 Dosing and administration

The physiological dose of melatonin is believed to be 0.3 mg/day.[48-50] However, various doses (0.5-100 mg) have been used in clinical trials in a variety of populations. The optimal dose for delirium prevention has yet to be determined. Published delirium prevention trials in hospitalized, but non-critically ill patients have administered between 0.5-3 mg orally every night (qHS)[22-24] while trials for sleep disorders in hospitalized patients have used between 0.5-10 mg orally qHS.[50-53] In trials evaluating melatonin for jetlag, doses between 0.5mg and 5 mg orally once daily were similarly effective. However, higher doses caused participants to fall asleep faster. Doses above 5 mg were not found to be more effective than doses less than 5 mg.[54] A small study evaluating melatonin for sleep in mechanically ventilated adults in the ICU (n = 24) found that 10 mg orally qHS increased normal plasma concentrations excessively resulting in morning drowsiness.[55] These authors suggested doses of < 3 mg would likely be most appropriate for critically ill patients. In addition to the optimal dose, the timing of melatonin

administration needs to be considered. Melatonin was administered around bedtime (i.e. between 20:00 and 22:00 hours), matching the circadian pattern of melatonin release.

3.4.4 Safety

Exogenous melatonin has a very wide safety margin and is well tolerated with few side effects reported for all adult and pediatric populations studied.[52-54, 56, 57] It has been safely administered to humans in doses of up to 100 mg per day for prolonged study periods. A meta-analysis of 17 randomized controlled trials including 651 participants with sleep disorders showed no difference in adverse effects compared with placebo.[53] The most commonly reported side effects in the context of these studies were headache, dizziness, nausea, and drowsiness. Melatonin has demonstrated antiepileptic activity in both *in vitro* and *in vivo* studies;[58] however, an increase in seizure activity was reported in four children with severe epilepsy.[54] In a Cochrane review of 10 trials reporting on melatonin for jet lag, the only other reported side effect was of fixed drug skin eruption occurring in 2 males.[54] Ongoing trials of melatonin in oncology patients attest to the drug's low toxicity, and to date there are no empirical data demonstrating harmful risk in this population.[57, 59]

Melatonin has been evaluated in critically ill patients in four studies: three trials evaluated impact on sleep compared to placebo[42, 44, 60] and one trial evaluated pharmacokinetics.[43] Doses in the trials ranged from 3mg to 10 mg. At 10 mg qHS patients reported excessive morning sedation compared to placebo and the authors suggested a dose of 1 or 2 mg qHS would avoid the carry-over effect based on their pharmacokinetic analysis.[44] In all of these trials, only one patient reported a headache on a single night (responded to acetaminophen).[44]

4.0 HYPOTHESIS AND OBJECTIVES

The available evidence indicates melatonin may decrease the incidence of delirium in non-critically ill patient populations; however, trials in the critically ill are lacking. We hypothesize that melatonin, administered on a scheduled nightly basis during ICU admission, will be efficacious and safe for the prevention of delirium in critically ill adults. The null hypothesis is that there is no difference in delirium incidence between placebo and melatonin. Prior to conducting an adequately powered multi-centre, blinded randomized, placebo-controlled trial in critically ill patients, we need a better understanding of melatonin pharmacokinetics (PK) in critically ill patients. This will help to determine appropriate dosing, drug administration issues (specifically protocol adherence), adverse drug effects, and recruitment rates based on our inclusion and exclusion criteria.

Our specific aim is to conduct a phase II triple blind, placebo-controlled randomized trial comparing two doses of melatonin (low dose = 0.5mg and high dose = 2mg) to assess the feasibility of a future full-scale RCT. Feasibility of the larger trial will be based on protocol adherence and participant recruitment rates. Data on PK properties of melatonin will be assessed to determine dosing for future studies of melatonin in the critically ill.

Our specific objectives are to:

1. Identify the proportion of prescribed study drug doses administered to participants (i.e. adherence to study protocol);
2. Identify the proportion of screened participants meeting study inclusion criteria;
3. Identify the consent rate of eligible participants (i.e. feasibility of enrolment - # screened, # excluded, # consented)
4. Describe the time required to complete enrolment and data collection per patient;
5. Describe the PK properties of enterally administered melatonin at a dose of 0.5mg compared to a dose of 2mg;
6. Describe the proportion of participants administered melatonin 0.5mg, melatonin 2mg, or placebo that experience adverse drug effects;
7. Compare the delirium rates (Intensive Care Delirium Screening Checklist (ICDSC)[61] score of ≥4), delirium duration, sleep quality, rest-activity cycles (with actingraphy), mechanical ventilation duration, length of ICU and hospital stay, and ICU and hospital mortality for patients receiving enterally administered melatonin at a dose of 0.5 mg, 2 mg, and placebo.

5.0 RESEARCH DESIGN AND METHODOLOGY

5.1. Study design

We will conduct a blinded, placebo-controlled pilot RCT and pharmacokinetic study comparing two doses of melatonin (low dose = 0.5 mg and high dose = 2 mg) in critically ill patients.

5.1.1 Outcomes

Feasibility outcomes

1. Adherence to study protocol. We will calculate protocol adherence as the overall proportion of administered doses in the prescribed qHS administration window (between 21:00 and to 23:59 hours) divided by total number of eligible study days. This will be our primary outcome.
2. Trial recruitment. We will calculate the proportion of ICU patients screened that meet study inclusion criteria, the number of patients excluded and reasons for exclusion, and the consent rate of eligible participants.
3. Time in motion. Research coordinators at each site will capture the amount of time it takes to screen, consent, enroll patients, complete study procedures, and collect data.

PK outcomes

1. Plasma melatonin concentrations measured by mass spectrometry to evaluate the two doses of melatonin compared to placebo:
   a. peak concentration (C_{max})
   b. time of peak concentration (T_{max})
   c. morning concentration (C_{9AM})
   d. half-life ($T_{½}$)
   e. mean apparent clearance (CL/F)
   f. mean apparent volume of distribution (V/F)
   g. area under the concentration-time curve (AUC). We will measure eight plasma melatonin concentrations on Day 1 of the study to calculate the above parameters.

Clinical outcomes

1. Adverse events. As this is a feasibility study and adverse drug events as expected to be very low based on the published literature we will look for the following specific events: morning drowsiness (Sedation Agitation Scale (SAS) [Appendix 2][62] scores < 3 or patient's self report of drowsiness between 07:00h and 12:00h), headache, vivid dreams.
2. Delirium (ICDSC score of ≥4) [Appendix 3] incidence
3. Time to onset of delirium and delirium duration
4. Sleep (Richards Campbell Sleep Questionnaire,[63, 64] [Appendix 4] self-reported sleep quality by patient and/or assisted by nurse on a Likert scale, and rest-activity cycles with actigraphy)
5. Duration of mechanical ventilation

6. Length of stay - ICU and hospital
7. Mortality - ICU and hospital

5.2 Setting and participants

5.2.1 Study setting

We will conduct the study at three academic hospitals: Mount Sinai Hospital (Medical surgical ICU, Toronto), Sunnybrook Health Science Centre (Medical surgical trauma level 2 and 3 ICUs, Toronto), and Hôpital du Sacré-Cœur, (medical surgical trauma level 2 and 3 ICUs, Montréal). These ICUs have strong research infrastructure to support trial conduct including past experience with sedation and delirium trials.

5.2.2 Inclusion criteria

1. Critically ill patients ≥18 years of age (in level 2 and level 3 ICUs)
2. anticipated ICU stay of >48 hours.

5.2.3 Exclusion criteria

1. ICU admission of > 48 hours prior to screening
2. unable to assess for delirium (e.g. comatose defined as SAS 1 or 2 or either 'No Response' Score A or B on ICDSC, chemically paralyzed with neuromuscular blocking drugs) at the time of screening
3. screened delirium positive prior to randomization (ICDSC score ≥4 out of 8)
4. anticipated withdrawal of care in next 48 hours
5. known history of severe cognitive or neurodegenerative disease (e.g. dementia, Parkinson's disease) or severe structural brain injury (e.g. traumatic brain injury, intracranial hemorrhage) as the ICDSC assessment tool has not been validated in these patient populations
6. unable to communicate in English or French (Montréal site)
7. contraindications to receiving any enteral medication (defined as absolute contraindication to enteral nutrition such as gastrointestinal obstruction, perforation, recent upper GI surgery, no enteral access)
8. active seizures
9. known pregnancy
10. legally blind
11. known allergy to melatonin.

5.2.4 Eligible non-randomized (ENR) criteria

1. Patient or SDM declines consent
2. Patient unable to give consent and no SDM available
3. ICU physician declines consent
4. Consent not obtained due to other reason

5.3 Study procedures

The study procedures will be performed only by the authorized study staff at each site as specified on the delegation of responsibility log. [Appendix 5]

5.3.1 Screening and randomization

Research personnel at each site will screen for potential participants once daily Monday to Friday. [Appendix 6, 7]. Written informed consent will be sought from eligible participants, if competent, or their substitute decision maker when the potential participant is not competent. Consent will be document in the patient's medical record. See Appendix 8 for consent form. Following informed consent, the study coordinator will notify the Clinical Trials Pharmacist in the Department of Pharmacy. Participants will be randomly assigned in a 1:1:1 manner to one of three study arms using a computer-generated, permuted-blocked randomization scheme stratified according to site (block size: 6; generated by biostatistician). We will use opaque sealed numbered envelopes for allocation concealment that will be opened and viewed by only the Department of Pharmacy Clinical Trials Pharmacist and Trials Technician.

5.3.2 Intervention

Participants will be randomized to one of three study arms: melatonin 0.5 mg, melatonin 2 mg, or placebo. A pre-printed study medication prescription order will be placed in the participant's medical chart [Appendix 9] by the research coordinator.

Study arm # 1: Enteral melatonin 0.5 mg;
Study arm # 2: Enteral melatonin 2 mg;
Study arm # 3: Enteral matched placebo.

Study drug will be given daily at qHS (*quaque hora somni* or every night at bedtime with administration of drug between 21:00-23:59H), starting on the day of enrollment until ICU discharge, death, or up to 14 days, as most critically ill patients are at greatest risk of delirium in the first two weeks of admission. The study medication will be given by mouth (po or *per os*) or if needed, it can be administered via the feeding tube followed by a flush with 20mL water.

Study drug preparation: The Clinical Trials Pharmacist and/or Pharmacy Trials Technician at each site will compound melatonin 1 mg/mL oral suspension to prepare the appropriate dosage for each study arm [Appendix 10]. Only authorized site staff, the Clinical Trials Pharmacist and/or Pharmacy Trials Technician as specified on the delegation of responsibility log may prepare and dispense the study drug [Appendix 5]. All sites will use a synthetic source of melatonin (non-animal, non-human) (Jamieson Laboratories, NPN 80015041 immediate release) to compound doses. Participants will receive one of three translucent, milky white solutions dispensed in amber oral syringes identified as "Melatonin/Placebo Study Drug." Solutions will appear identical in color and volume.

Study arm # 1: Melatonin 0.5 mg from the 1mg/mL oral suspension *qs* to 5 mL with 1:1 mixture of Ora-Plus and Ora-Sweet (final concentration of 0.1 mg/mL; final volume in the oral syringe will be 5 mL)

Study arm # 2: Melatonin 2 mg from the 1mg/mL oral suspension *qs* to 5 mL with 1:1 mixture of Ora-Plus and Ora-Sweet (final concentration 0.4 mg/mL; final volume in the oral syringe will be 5 mL)

Study arm #3: Melatonin 0 mg *qs* to 5 mL with 1:1 mixture of Ora-Plus and Ora-Sweet (final concentration 0 mg/mL; final volume in the oral syringe will be 5 mL)

For participants who receive the study medication by feeding tube, the feeding tube will be flushed with 20mL water following dose administration (Note: This is standard practice for administering medications through a feeding tube).

5.3.3 Co-interventions

The ICU clinical team will be responsible for all other pharmacological and non-pharmacological interventions including management of pain, agitation, sedation, delirium, and sleep according to local practice.

5.4 Blinding, unblinding, and study product accountability

Study drug assignment will be accessible *only* to the Clinical Trials Pharmacist and Trials Pharmacy Technician. The Clinical Trials Pharmacist will open the opaque sealed envelope prepared by the biostatistician for each participant enrolled once consent has been obtained. The Clinical Trials Pharmacist will attach the randomization code contained within the envelop to the Randomization Form [Appendix 7]. Study group assignment will be inaccessible to the study personnel, ICU clinicians, and participants/families except in an emergency, only after the unblinding is approved by the principal investigators, who will discuss with the attending physician as to whether unblinding is necessary for the proper medical management of the participant.

The Clinical Trials Pharmacist and/or Pharmacy Trials Technician will dispense study drug in amber BD oral syringes daily, identified as "Melatonin/Placebo Study Drug". Study medication will be stored, tracked, and counted in accordance with standard pharmacy dispensing practices by the Clinical Trials Pharmacists and/or Pharmacy Trials Technician. A Dispensing List will be maintained in the pharmacy department in the melatonin study operations binder that records the identity of participants for each randomization number [Appendix 11]. The randomization number will be indicated on the prescription in the participant's chart and the dispensing label to enable the participant's nurse administering the study drug to verify the right participant is receiving the right drug. The participant's nurse will record study dose administration on the Medication Administration Record in accordance with standard ICU practice and sign on the Preparation and Administration Log [Appendix 7].

5.5 Pharmacokinetic (PK) analysis

We will conduct a PK analysis of plasma melatonin concentrations. The PK analysis will only be conducted at Mount Sinai Hospital with participants that consent to the required blood samples. We will enroll 15 participants, five from each study arm using stratified randomization On the first day of the study only, eight blood samples (4 mL each) will be collected in BD vacutainer lavender top tubes (K2 EDTA 7.2 mg, by DB Franklin Lakes, NJ, U.S.A.) in the following intervals, from the time of first study drug dose to the following morning (t_0, $t_{0.5}$, t_1, t_2, t_4, t_6, t_8, t_{12}) [see preprinted prescription order Appendix 9]. These sample times were chosen based on pharmacokinetic studies using similar methodology in critically ill and non-critically ill patients.[43, 44, 65] As melatonin release is regulated by light we will also measure light intensity to coincide with each plasma sample (t_0, $t_{0.5}$, t_1, t_2, t_4, t_6, t_8, t_{12}) (0-5 minutes before each blood draw). Light intensity will be measured near the head of the patient's bed, at the patient's eye level, using a lux-meter (Environmental Meter SHSEHY002, Shimana). Specimens will be screened for hemolysis, and redrawn if present. All samples taken will be centrifuged, and stored at -80°C until the assay is performed by Mount Sinai Hospital Services laboratory.

Plasma melatonin concentrations will be measured using mass spectrometry. Sample dilution to within the linear range of the assay will be undertaken as necessary. Plasma concentrations will be corrected for endogenous plasma melatonin concentrations by subtracting the t_0 hour baseline value. Non-compartmental pharmacokinetic analysis will be undertaken (PKSolution 2.0; Summit Research Services, Montrose, CO, USA) to compare the three study groups.

5.6 Rest-activity analysis

We will conduct a study of rest-activity cycles using actigraphy[66] for all participants at Sacré-Coeur Hospital. All patients recruited at this site (21 patients) will wear a wrist actigraph (Actiwatch-L, Philips Healthcare, Andover, MA) on a non-paralyzed, non-restrained arm from study enrolment to the end of the study participation (maximum of 14 days). For study days where a patient has both arms restrained, data will not be captured by the actigraph but not analyzed.

The actigraph is a small, watch-like device that contains an accelerometer, which records physical motion in all directions with a sensitivity of 0.05g. Motion is then converted to an electric signal, which is digitally integrated to derive an activity count per 1-minute epoch. Data will be uploaded into dedicated software (Actiware 5.0) approximately every 7 days or at the end of study participation if shorter than 7 days. The rest-activity cycle consolidation will be estimated with the ratio of daytime activity to total 24-hour activity. For each 24-hour day and for each participant, the activity counts will be summed separately for daytime (07:00-21:59 hours) and night-time (22:00-6:59 hours) periods. Night-time is defined according to the schedule of the hospital unit, and is characterized by lower levels of activity and light. Total 24-hour activity (07:00-06:59 hours) is the sum of the daytime and night-time periods. The percentage of total 24-hour activity occurring in the daytime will be calculated to obtain the daytime activity ratio: daytime activity ratio = (daytime activity/24-hour activity) Å~ 100. A ratio of 50% indicates a level of activity evenly distributed across daytime and night-time

periods, whereas a ratio of 100% indicates that all activity occurred during the daytime. According to previously published data, a daytime activity ratio of 80% will be chosen to designate an adequate consolidation of the rest-activity cycle, synchronized to the day-night cycle.

5.7 Data capture and measurements

***Data capture*:** To ensure consistency and to optimize data collection, we will provide standard operating procedures in the study binder as well as study orientation sessions to each site documenting attendance [Appendix 12]. Research personnel at each site will maintain a screening log documenting all patients: 1) screened, 2) ineligible (and reasons), 3) eligible, 4) consented and enrolled, and 5) declined. Research personnel will also record the time to complete participant screening and maintenance of the participant log, consent procedures, and data capture using a time and motion template developed and validated by the Canadian Critical Care Trials Group Research Coordinators for the first ten patients at each site [Appendix 13]. Completion of the time in motion data capture will help estimate future workload and personnel costs for our planned future large scale RCT.

Using the standardized case report form (CRF) [Appendix 7] research personnel will collect from the paper and electronic chart the patient demographics on study enrolment (e.g., age, sex, comorbidities, severity of illness score [Sequential Organ Failure Assessment (SOFA) score],[70] admission diagnosis, and best possible medication history [BMPH][71]. A patient's medication history is routinely collected by pharmacy staff at each site as part of the Accreditation Canada Medication Reconciliation process.

We will also collect the following from the chart for each day if the clinical team has ordered it as part of clinical care/or patient assessment: psychoactive drug exposure (i.e., any formulation of sedative, analgesic, anti-anxiety, hypnotic, antipsychotic), SOFA score variables, use of physical restraint, devices (e.g. intravenous catheter) and accidental device removal, mobilization (e.g. sitting at edge of bed, ambulation), strategies to preserve day-night orientation (e.g. clock, television), and SAS and GCS scores. A patient's level of sedation and agitation is routinely assessed by bedside nurses using the SAS in each ICU every 1 to 4 hours.[62] The CRF for daily data collection will run on the following time window to match nursing shift change and ICU daily flowsheet - 08:00H to 0759H. The research team will review the medication profile daily to determine if study doses were administered and reasons for late or non-administration and complete a protocol violation form if needed. We will also collect outcomes from the chart: duration of mechanical ventilation, length of ICU and hospital stay, and ICU and hospital mortality.

For data not available from the patient's paper or electronic chart will be marked as 'not available' (NA) in the CRF.

Measurements (Measured for feasibility not safety):
***i) Delirium*:** Each of the study ICUs already use the ICDSC tool as part of routine daily nursing assessment. The ICDSC is an 8-item checklist that requires initial evaluation of level of consciousness with a sedation agitation assessment tool followed by delirium screening if the

patient is not comatose or stuporous. The ICDSC with a cut-off of a score of 4 demonstrated 99% sensitivity and 75% specificity compared to psychiatric assessment using DSM-IV criteria.[61] As ICDSC is part of routine ICU assessment, the ICDSC will be used to assess all patients for the presence of delirium in the study. The study personnel will collect the ICDSC scores once daily (between 1400 -1700H) from the bedside chart. If the ICDSC has not been completed by the bedside staff, the research staff will prompt the bedside clinical staff to complete the assessment. We will collect this measurement for feasibility purposes and not safety.

***ii) Sleep*:** Sleep in the ICU is characterized by frequent arousals, loss of the restorative sleep stages, and an even distribution of sleep throughout the day and night (rather than night alone). Only recently have outcomes related to ICU-associated sleep disruption gained attention, primarily because of its potential association with ICU delirium.[67, 68] Currently there is no method of evaluating sleep that is acceptable and feasible for widespread use in the ICU. Although polysomnography is the reference standard for measuring sleep, its requirement for specialized technology not readily available in the ICU, and expert staff for interpretation render it logistically challenging. Also, polysomnograms are particularly difficult to interpret in the setting of drugs commonly prescribed for the critically ill as well as pathophysiology associated with critical illness (e.g. sepsis, hepatic encephalopathy, renal failure). For patients enrolled at the Sacré-Coeur Hospital rest-activity cycles will be measured using actigraphy as described in Section 5.6. We will collect this measurement for feasibility purposes and not safety.

We will also use the Richards-Campbell Sleep Questionnaire (RCSQ) for patients at all three sites. RCSQ is a simple, validated survey instrument to evaluate perceived sleep depth, sleep latency (time to fall asleep), number of awakenings, efficiency (percentage of time awake) and sleep quality in intensive care patients.[63, 64, 69] Patients with or without the assistance of their nurse will be asked to complete the questions of the RCSQ each morning and the results will be transcribed on the CRF (the CRF will become the source document). We will not ask the nurses to complete the RCSQ if the patient is unable to participate as poor correlation has been shown between patient and nursing scores. We will collect this measurement for feasibility purposes and not safety.

iii) Melatonin plasma concentrations and Light Intensity: A sample of 15 participants from Mount Sinai Hospital, five participants from each study arm, will complete the PK assessment of melatonin plasma concentrations and room light intensity with the first study dose as described in Section 5.5. These samples will be taken by the research staff at Mount Sinai Hospital for feasibility purposes, not safety.

5.8 Criteria for removal from the protocol

In addition to the planned study drug discontinuation timeframe, treatment may be stopped in the following instances:

1. An adverse event that, in the judgment of the principal investigator(s) or attending physician, would require discontinuation of the study drug;

2. When requested by the participant or their legally authorized representative (consent withdrawal);
3. The principal investigator, the institutional research ethics board, or a government agency such as Health Canada terminates the study.

6.0 STATISTICS

6.1 Sample size calculation

We have determined our sample size according to adherence to prescribed study drug with adherence defined as ≥85% of doses administered using a margin of error of +/- 5%. We have adjusted our sample size estimation for the clustering effect of repeated drug administration within the same participant using intra-cluster correlation (ICC). For an average of daily drug administration for 4 days, with a total of 69 patients (or 276 drug administration adherence monitoring) and ICC=0.115, we can determine our successful adherence rate of 85% within a margin of error of +/- 5% (i.e. actual protocol adherence rate = 80% to 90%) at 95% confidence level.

6.2 Statistical analysis

We will analyze data using the intention-to-treat principle. Simple descriptive statistics will be used to report feasibility outcomes, pharmacokinetics, as well as baseline demographics and clinical outcomes. Continuous variables will be described using measures of central tendency and spread (means and SDs or medians and interquartile ranges dependent on data distribution). Frequencies, proportions and their 95% confidence intervals (CI) will be used to describe categorical variables. Except for analyses of repeated measures, we will use the Kruskal-Wallis test to compare continuous variables between the three treatment groups and chi-square tests to compare categorical variables. We will use methods that account for data clustering when analyzing repeated observations from the same participant. We will use time-to-event methods (Kaplan-Meier) to compare ICU and hospital length of stay between treatment arms. We will use log-rank tests to assess differences between groups. We will use a Markov regression modelling and generalized estimating equations to analyze the probability of being delirious on each day after receipt of study drug according to assigned treatment group. No subgroup analyses will be performed on this sample.

All tests will be two-tailed testing with a significance level of $p \leq 0.05$. All data analyses will be performed using SAS 9.3 by an independent statistician.

7.0 SAFETY REPORTING

Before launching into an adequately powered RCT testing whether melatonin confers benefit, harm, or has no impact on prevention of delirium in critically ill patients we must successfully complete this feasibility study. Melatonin is a non-prescription medication commonly used in the community and hospital setting (including the ICU) to aid sleep and is established in the published literature in both non-critically and critically ill patients to be well tolerated with few adverse effects [Appendix 14]. The most likely adverse events associated with melatonin in hospitalized or acutely ill patients include morning drowsiness, headache, and vivid dreams. The doses we have selected for this trial are at the lowest end of the published dose range and are unlikely to be associated with serious adverse events based on the published literature. As well the design of this trial seeks to protect participants from harm by careful participant selection, choice of intervention, and appropriate monitoring. Through our exclusion criteria we will seek to exclude those patients potentially at risk of adverse effects.

The extensive monitoring in the ICU will allow the detection and management of adverse effects. In general, critically ill patients are at high risk of serious adverse events and the usual approach of reporting all serious adverse events to the REB would result in large numbers of reports not actually related to the study intervention, but rather reflect the underlying disease process or expected complications of critical illness.[72] Our approach to serious adverse events (SAE) will be in accord with the published guidelines for academic drug trials in critical care[72] [Appendix 15] and 'The Initiative to Streamline Clinical Trials [http://n2canada.ca/isct/ - Appendix 16]. As such, only adverse events that might reasonably be a consequence of participation in this trial and are judged by the investigators not due to the underlying disease or expected complications of critical illness will be recorded.

7.1 Definition

Adverse events are defined as: any unfavourable and unintended sign, or any symptom or disease temporally associated with the use of the study drug and not more likely explained by an alternative cause (e.g. change in ICU clinical condition, alternative drug causing the adverse event). As melatonin is a drug commonly used for sleep and rarely associated with adverse events we have incorporated the most likely adverse events - morning drowsiness, headache, and vivid dreams – into our outcomes to be collected daily as part of the CRF.

Serious adverse events (SAE) are defined as events that: result in death; are life threatening; require prolongation of existing hospitalization; and result in persistent or significant disability/incapacity. Information about all serious adverse events, whether volunteered by the study participant, discovered by the clinical team, investigator questioning, or other means will be recorded and followed up on as appropriate. The investigating team will assess the causal relationship of the adverse event to the study drug (causality) as follows:

- Unrelated: There is not a reasonable possibility that the adverse event may have been caused by the study drug.
- Possibly related: The study drug may have caused the adverse event, however there is insufficient information to determine the likelihood of this possibility.

- Related: There is a reasonable possibility that the adverse event may have been caused by the study drug.

7. 2 Expectedness

Adverse events will be assessed according to the following categories:

- Expected (anticipated): the event is identified in nature, severity, or frequency in the applicable product information (i.e. investigator's brochure or product monograph).
- Unexpected (unanticipated): the event is not identified in nature, severity, or frequency in the applicable product information (i.e. investigator's brochure or product monograph)
- More prevalent: the event occurs more frequently than anticipated or at a higher prevalence than expected

The critically ill patient population is relatively unique in that virtually all are admitted to the ICU for life-sustaining therapies (e.g. mechanical ventilation, vasopressors, renal replacement therapy). Many of the potential subjects will be admitted with the expectation of receiving end-of-life care and dying in the ICU. Published critical care literature suggests 20% of patients are expected to die in the ICU. Furthermore, a multiplicity of medical complications is likely to occur in this population, consistent with the nature of their progressive illness (e.g. nosocomial infections; septic shock; multiorgan failure; need for vasopressors; acute lung injury; acute renal failure and the need for renal replacement therapy; arrhythmias; cardiac arrest; coma; gastrointestinal bleeding; aspiration; venous thromboembolism) [Appendix 15]. To be mindful of these relatively unique morbidity and mortality expectations in the critical ill patient population and the study drug's low risk of toxicity, adverse events will be considered in this context.

7.3 Adverse event recording and reporting

Investigations into potential adverse events should be done during each contact with a participant. Investigations may be done through specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded promptly in the source document, and assessed by an investigator in a timely manner allowing sufficient time to meet required reporting timelines for SAEs and SUADRs (serious unexpected adverse drug reactions) if needed. Adverse event CRFs should be completed using source documents by a delegated research team member in a timely manner. All clearly related signs, symptoms, and abnormal diagnostic procedures should be recorded in the source document, though should be grouped under one diagnosis.

The following are not considered AEs and therefore do not require recording:

- Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the investigator, the disease or condition worsens in severity or frequency
- At the discretion of the investigator, events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of IP exposure

- Elective medical or surgical procedures

Serious adverse events will be reported to the Research Ethics Board at each site as per their reporting guidelines and institutional Standard Operating Procedures (SOPs). Serious adverse events (SAE) that are both unexpected and related/possible related to the study drug will be subject to expedited reporting to Health Canada by the Sponsor according to the regulations below. A report will be filed in the cases:

1. where the SAE is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
2. where it is fatal or life-threatening, as soon as possible, but no later than 7 days after becoming aware of the information; within 8 days after having informed Health Canada of the fatal or life-threatening SUADR, the Sponsor will submit as complete as possible, a report to Health Canada which includes an assessment of the importance and implication of any findings.

SAEs that are expected or that are unrelated to the study drug are not reportable. Each SAE subject to expedited reporting will be reported. Any updated follow up information that becomes available regarding the SUADR will be reported in a follow up report.

8.0 ETHICAL CONSIDERATIONS and quality management

8.1 Applicable laws and standards

We will obtain approval of the Research Ethics Board (REB) at each site and Health Canada. The trial will be conducted in accordance with Good Clinical Practice following the Tri-council Guidelines, the Canada Natural Health Products Regulations, The Canadian Personal Health Information protection Act (PHIPA), and the International Conference on Harmonization Good Clinical Practice (ICH GCP).

8.2 Ethics

The investigator team will only initiate this trial after written approval of the protocol and any amendments (if applicable) is provided, by the REBs and Health Canada. If required, protocol amendments will be submitted to each REB for approval. Reports on, and reviews of, the trial, its progress, and its safety aspects will be submitted to each Research Ethics Board at intervals according to their respective guidelines.

Initial contact with a potential participant or their substitute decision maker will be made as per institutional practice (i.e. either directly by the research team or by a member of the clinical team (primary circle of care) who may inform the potential participant or their substitute decision maker that there is an ongoing study and inquire about his/her agreement to be contacted by a member of the study team). In the event that the investigators are part of the patient's clinical team, they will neither be recruiting participants nor obtaining consent. A Study Investigator or another authorized person from the research team will explain to each participant or their substitute decision maker the aims, methods, reasonably anticipated benefits and potential hazards of the trial and any discomfort in written form and by verbal explanation in non-technical terms. An assessment will be made by the study team as to the patient's capacity to understand the risks and benefits of participation in the trial. Potential participants or their substitute decision maker will be given opportunity to ask questions and sufficient time to make their decision. We will inform consenting persons that their care will not be affected in any other way than study drug administration and that should they decide to refuse participation or withdraw from the study their care will not change other than study drug will no longer be administered.

Patients or substitute decision makers will provide written informed consent prior to any trial related activity. We will not use deferred consent. Both the participant or substitute decision maker and the investigator or designee will sign and date the form. If the participant or substitute decision maker requires assistance during the consent discussion, an impartial witness will also sign and date the consent form. The participant or substitute decision maker will receive a copy of the completed informed consent form and a copy will be placed in the participant's medical chart. Participants who lack capacity at enrollment and later regain capacity will be asked to choose continuation from the study.

8.3 Data management and quality assurance

We will protect participants' privacy. All data will be de-identified, and a unique study identifier will be assigned for each participant. The research assistants at each site will record data on a paper case report form (CRF) in accordance with study procedures. De-identified CRFs with only the randomization number will be sent to the Coordinating Center, Sunnybrook Hospital Clinical Trial Services (signature required). Data will be entered into an electronic database, which will be stored on a password-protected computer. All data will be presented in summary form to preserve the anonymity of individuals.

The principal investigators will cooperate with all sponsor and REB monitoring processes. The principal investigators will complete routine quality control to ensure that the study is being conducted according to protocol. This routine monitoring of the study will include:

- Verification of inclusion and exclusion criteria to confirm that only eligible participants are participating in the trial;
- Verification of source data to ensure accuracy of study data;
- Verification that adverse events are recorded, assessed, and reported according to protocol;
- Verification of the CRFs to ensure that they are being completed according to protocol.

It is the responsibility of the REB, qualified investigator and regulatory sponsor to retain study essential documents as per local regulatory requirements and GCP Guidelines.

Study essential documents must be maintained in a secure and confidential manner for participating Canadian sites for a period of 25 years. For the purposes of this study, the start date of the retention period is the date of issue of the final report of the trial. Exceptions may be made for sites which close prematurely, wherein the start date for the retention period will be the date of notification to Health Canada of the sites closure. All study records are then to be destroyed according to local and national policy and requirements. It is the responsibility of each site to request authorization for destruction at the completion of the retention period and/or for the sponsor to inform the investigator/institution when these documents may be destroyed.

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10.0 APPENDICES

Appendix 1	Table 1: Studies evaluating melatonin for the prevention of delirium in non–critically ill patients
	Table 2: Studies evaluating melatonin in critically ill patients for any indication
	Table 3: Pharmacokinetic studies in either critically ill or hospitalized non-critically ill patients
Appendix 2	Sedation Agitation Scale (SAS)
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BMJ Open

Feasibility of melatonin for prevention of delirium in critically ill patients: protocol for a multi-centre, randomized, placebo-controlled study

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Feasibility of melatonin for prevention of delirium in critically ill patients: protocol for a multi-centre, randomized, placebo-controlled study

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ABSTRACT

Introduction Delirium is highly prevalent in the intensive care unit (ICU) and is associated with adverse clinical outcomes. At this time, there is no drug that effectively prevents delirium in critically ill patients. Alterations in melatonin secretion and metabolism may contribute to the development of delirium. Administration of exogenous melatonin has been shown to prevent delirium in non-critically ill surgical and medical patients. This trial will demonstrate the feasibility of a planned multicentre, randomized controlled trial to test the hypothesis that melatonin can prevent delirium in critically ill patients compared to placebo.

Methods and analysis This feasibility trial is a randomized, three-arm, placebo-controlled study of melatonin (2 mg vs. 0.5 mg vs. placebo, administered for a maximum of 14 days) for the prevention of delirium in critically ill patients. A total of 69 patients aged 18 and older with an expected ICU length of stay greater than 48 hours will be recruited from 3 Canadian ICUs. The primary outcome is protocol adherence (i.e., overall proportion of study drug doses administered in the prescribed administration window). Secondary outcomes include pharmacokinetic parameters, incidence, time to onset, and duration of delirium, number of delirium-free days, adverse events, self-reported sleep quality, rest-activity cycles measured by wrist actigraphy, duration of mechanical ventilation, ICU length of stay, and mortality. Data will be analyzed using an intention-to-treat approach.

Ethics and dissemination The study has been approved by Health Canada and the research ethics board of each study site. Trial results will be presented at international conferences and published in a peer-reviewed journal.

Trial registration clinicaltrials.gov NCT02615340

Strengths and limitations

- The incorporation of pharmacokinetic measurements into our planned analysis will inform dose selection of the planned future large-scale randomized control trial.
- Inclusion of baseline plasma melatonin concentrations will add to the limited literature of melatonin metabolism in critically patients.

- Pilot study with multi-centre participation supporting will bolster the ability to determine the feasibility of conducting a future large-scale randomized control trial.
- While a feasibility study is essential prior to the execution of a full-scale trial, this design does not permit the determination of delirium-related clinical outcomes.
- Plasma melatonin will be measured on day 1 of the study intervention; therefore, this study will not provide data on melatonin kinetics in the context of the delirium status.

INTRODUCTION

Delirium is a syndrome of acute brain dysfunction characterized by fluctuations in attention, mental status, disorganized thinking and altered level of consciousness.[1] Specific symptoms such as delusions and hallucinations, agitation, restlessness, and sleep disturbance are distressing for patients, families, and clinical staff.[2,3] Delirium is highly prevalent in the intensive care unit (ICU) where rates range from 40-90%.[4] Critically ill patients who develop delirium experience worse outcomes including increased mortality, prolonged mechanical ventilation, increased duration of ICU and hospital length of stay, functional and cognitive decline, and increased likelihood of placement in long-term care facilities.[5-10] These adverse clinical and systems level implications underscore the imperative of identifying safe and effective strategies for the prevention of delirium in critically ill patients. At this time however, no pharmacological agent has been shown to effectively prevent delirium or favourably alter related outcomes in this patient population.[4]

The pathophysiology of delirium is not fully understood. Current hypotheses include neuroinflammation, impaired cerebral oxidative metabolism, and disturbances of neuroendocrine and neurotransmitter systems.[11,12] In particular, there is considerable research on dopaminergic, cholinergic, gamma-aminobutyric acid, and serotonergic neurotransmitter pathways, as these modulate cognition, behaviour, mood, and sleep. Although disturbances of the sleep-wake cycle are not diagnostic of delirium, changes in sleep patterns are incorporated into delirium screening tools, and studies indicate sleep changes occur in over 75% of delirious patients.[13]

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone sequentially derived from tryptophan and serotonin in the pineal gland during hours of darkness.[14] It has multiple biological effects, most notably in the regulation and synchronization of circadian rhythms, where it works as a hypnotic in accelerating the initiation and improving the maintenance and efficiency of sleep.[14] Disturbances in circadian melatonin secretion have been described in a number of patient populations at high-risk of delirium, including general medicine, critically ill with sepsis, and post-operative.[15-21] Given these findings, the abnormal secretion and metabolism of melatonin may play a role in delirium pathogenesis.[13,15,16,18,22-24]

Unlike other hypnotics, melatonin causes no significant changes in sleep architecture and has no hangover effects or abuse potential.[25] The administration of exogenous melatonin may therefore prevent delirium through its effects on circadian rhythm and sleep.[19,20] Exogenous melatonin has also been shown to be sedative sparing,[26] an important factor in reducing delirium risk in the critically ill.[4,27,28]

The hypothesis that exogenous melatonin may prevent delirium has been explored in three randomized controlled trials.[29-31] In one study, hospitalized general medicine patients (N=145, aged 65 years and older) given low-dose melatonin (0.5 mg) at bedtime displayed significantly less delirium (3.6% vs. 19%, p=0.014) compared to placebo controls.[31] In a surgical population (N=222, aged 65 years and older) comparing melatonin (5 mg), midazolam (7.5 mg), and clonidine (0.1 mg) to no pre-medication administered the night prior to and again 90 minutes before surgery, patients receiving melatonin experienced significantly less delirium in the post-operative period compared to no pre-medication, midazolam, or clonidine (melatonin 9.4% vs. no pre-medication 32.7% vs. midazolam 44.0% vs. clonidine 37.3%, p <0.05).[29] In contrast, a large trial (N=444, aged 65 years and older) of hip fracture patients reported that a 3 mg dose of melatonin at bedtime did not reduce delirium compare to placebo (29.6% vs. 25.5% placebo, p=0.4); however, fewer patients treated with melatonin experienced long-lasting delirium, defined as more than two days (25.5% vs. 46.9%, p= 0.02).[30] Furthermore, a trial of ramelteon, a melatonin agonist, showed a significant reduction in delirium incidence compared to placebo (3% vs. 32%, p=0.003) when administered to a mix of ICU and acute ward patients (N=67).[32]

A recent systematic review found melatonin did not reduce delirium incidence (relative risk [RR] 0.41, 95% confidence interval [CI] 0.15 to 1.13; P =0.08).[33] However, in the subgroup of elderly patients treated in acute medical wards, melatonin decreased delirium incidence by 75% (RR 0.25, 95% CI 0.07 to 0.88; P = 0.03), but did not reduce sleep-wake disturbance (RR 1.24, 95% CI 0.51 to 3.00; P=0.64). Given the small number of melatonin studies for delirium prevention, more research is needed. This is particularly important in the critically ill population who are considered at highest risk and amongst the most burdened by delirium from both a clinical and resource utilization standpoint.

Study objectives

Exogenous melatonin may decrease delirium incidence in non-critically ill patients. However, there are no trials focused solely on the critically ill population. Based on the available evidence, we hypothesize exogenous melatonin, administered on a scheduled nightly basis, will be efficacious and safe in the prevention of delirium in critically ill adults.

This pilot study will serve to determine the feasibility of conducting a future large-scale, multi-centre, randomized placebo-controlled trial in critically ill patients at risk of delirium. Additionally we aim to determine appropriate melatonin dosing.

Specific study objectives are to:

1. Identify the proportion of administered doses of prescribed study drug (i.e. study protocol adherence);
2. Identify the proportion of screened study participants that meet inclusion criteria;
3. Identify the consent rate of eligible participants (i.e., feasibility and timeframe of enrolment: number screened, number excluded, number consented);
4. Describe, per patient, the time required to complete study enrolment and all data collection;
5. Describe the pharmacokinetic properties of enterally administered melatonin at a dose of 0.5 mg compared to 2 mg;
6. Describe the proportion of participants that experience adverse drug effects; and
7. Compare delirium incidence (Intensive Care Delirium Screening Checklist [ICDSC][34] score of 4 or more) and duration, self-reported sleep quality, rest-activity cycles (with wrist actigraphy), duration of mechanical ventilation, length of ICU and hospital stay, and ICU and hospital mortality.

METHODS AND ANALYSIS

Study design

We will conduct a three-arm, randomized, placebo-controlled feasibility trial comparing the safety and efficacy of two doses of melatonin (low dose = 0.5 mg and high dose = 2 mg) versus placebo for the prevention of delirium in patients with an anticipated ICU admission of >48 hours.

Study outcomes

Feasibility outcomes

1. Protocol adherence. We will calculate protocol adherence using the overall proportion of doses administered in the prescribed dose administration window divided by total number of study days. We will define adherence as administration of ≥85% of prescribed doses within the drug administration window qHS (*quaque hora somni* defined as 21:00 to 23:59 hours);
2. Trial recruitment. We will calculate the proportion of screened ICU patients meeting study inclusion criteria, the number of and reasons for patient exclusions, and the consent rate of eligible participants; and
3. Time-in-motion study. We will capture the amount of time required to screen for, consent, and enroll patients, to complete study procedures and data collection for the first ten patients at each site.

Pharmacokinetic outcomes

Plasma melatonin levels will be measured by mass spectrometry including:

1. Peak concentration (C_{max});
2. Time of peak concentration (T_{max});
3. Morning concentration (C_{9AM});
4. Half-life ($T_{½}$);
5. Mean apparent clearance (CL/F);
6. Mean apparent volume of distribution (V/F); and
7. Area under the concentration-time curve (AUC).

Clinical outcomes

1. Adverse events. We will screen for the following adverse events previously associated with melatonin: morning drowsiness (Sedation Agitation Scale (SAS)[35] scores < 3 or patient self-report of drowsiness between 07:00h and 12:00h), headache, vivid dreams;
2. Delirium incidence (ICDSC[34] score ≥4) and subsyndromal delirium (ICDSC score of 1 to 3);

3. Time to onset of delirium, delirium duration, and delirium-free days (at ICU discharge);
4. Self-reported sleep quality (Richards Campbell Sleep Questionnaire (RCSQ)[36,37] and rest-activity cycles with wrist actigraphy;
5. Duration of mechanical ventilation;
6. Length of stay (ICU and hospital); and
7. Mortality (ICU and hospital).

Location and setting

We will conduct the trial in three mixed-patient population ICUs in three university-affiliated hospitals (Sunnybrook Health Science Centre (Toronto), Mount Sinai Hospital (Toronto), and Hôpital du Sacré-Coeur de Montréal (Montreal). These ICUs have existing research infrastructure and extensive experience with clinical trial conduct, including studies related to delirium.

Participant selection and recruitment

The study subjects will be adult critically ill patients admitted to the ICU at any of the three study sites.

Inclusion criteria

1. Critically ill patients aged 18 years or older; and
2. Anticipated ICU stay >48 hours.

Exclusion criteria

1. ICU admission >48 hours at the time of screening;
2. Unable to assess for delirium (e.g., coma or deep sedation [SAS score 1 or 2 or 'No Response' score A or B on ICDSC]; receiving neuromuscular blocking drugs) at the time of screening;
3. Screened delirium positive (ICDSC score ≥4) prior to randomization;
4. Anticipated withdrawal of life sustaining therapy;
5. History of severe cognitive or neurodegenerative disease (e.g., dementia, Parkinson's disease) or severe structural brain injury (e.g., traumatic brain injury, intracranial

hemorrhage) as the ICDSC assessment tool has not been validated in these patient populations

6. Unable to communicate in English or French (Montreal site) as we will be unable to assess for delirium using the ICDSC in non-English/French speaking patients
7. Absolute contraindication to enteral nutrition (e.g., gastrointestinal obstruction, perforation, recent gastrointestinal surgery, deemed strict nil by mouth, lack of enteral access)
8. Active seizures
9. Known pregnancy
10. Legally blind
11. Known allergy to melatonin

Eligible non-randomized criteria

1. Patient or substitute decision maker (SDM) declines consent
2. Patient unable to give consent and no SDM available
3. ICU physician declines consent
4. Consent not obtained due to another reason

Research personnel at each study site will screen for potential participants daily, Monday to Friday. Written informed consent will be sought from competent eligible participants, or substitute decision makers, if incompetent. Consent will be documented in the patient's medical record.

Randomization and blinding

Following informed consent, subjects will be randomly assigned in a 1:1:1 manner to one of the three study arms using a computer-generated, permuted-block randomization schedule, stratified according to site. The clinical trial pharmacists and/or trial pharmacy technician at each site will randomize patients to treatment groups using the REDCap interactive randomization technology. Study personnel, the ICU team, participants and family members will be blind to study group allocation, except in an emergency and only after unblinding is approved by the principal investigator. In this instance, the principal investigator and attending physician will discuss whether unblinding is necessary to provide medical care to the patient.

A target sample of 15 participants (five from each study arm) from the Mount Sinai Hospital site will be recruited for inclusion in the pharmacokinetic analysis. There are no additional inclusion or exclusion criteria for participation in the pharmacokinetic analysis.

Interventions

After randomization, a pre-printed study medication order will be placed in the patient's medical chart. Study subjects will receive study drug (melatonin 0.5 mg, melatonin 2 mg, or placebo) once daily qHS, between 21:00 and 23:59. Study medication will be administered by mouth (po or *per os*) or if necessary, by feeding tube (nasogastric, orogastric, jejunal or percutaneous endoscopic gastrostomy (PEG)) with subsequent flushing with 20mL of sterile water. All study drugs will be administered commencing the day of study enrolment and continued until ICU discharge, death, or up to a maximum of 14 days, whichever occurs first. This maximum duration of study drug administration was selected because critically ill patients are at greatest risk of developing delirium within the first two weeks of ICU admission.[8]

The optimal dose of melatonin for the prevention of delirium has yet to be determined. Published trials for delirium prevention in hospitalized, non-critically ill adults have administered oral nightly doses of melatonin ranging from 0.5 to 3 mg.[29-31] Trials of melatonin for sleep disorders have used higher doses, up to 10 mg.[38-41] A small study evaluating melatonin for sleep in mechanically ventilated adults (N=24) found a 10 mg nightly dose excessively increased plasma concentrations and resulted in morning drowsiness. The authors therefore suggested doses of 1 to 2 mg may be more appropriate in critically ill patients.[42] For jetlag in non-clinical populations, melatonin doses between 0.5 and 5 mg have been shown to be similarly effective; however, doses above 5 mg were not found to be more effective than lower doses.[43] Given the relatively sparse data on melatonin for delirium prevention and the lack of trials in ICU patients, we have chosen doses we feel are reasonable given the available data, while also ensuring sufficient difference to identify an effective dose.

We will not protocolize administration of any co-interventions in this study. The clinical team will remain responsible for all other aspects of patient care, including any pharmacological or non-pharmacological interventions for delirium prevention and treatment, or interventions that may be associated with delirium development. As such, the management of pain, agitation,

sedation, delirium, and sleep will be performed according to local practice, the details of which will be captured through study data collection. The use of open-label melatonin will not be permitted in this study.

Study medication

The clinical trial pharmacist and/or pharmacy trial technician at each site will compound melatonin 1 mg/mL oral suspension in accordance with Good Manufacturing Procedures (GMP) guidelines. All sites will use a non-animal synthetic source of melatonin (Jamieson Laboratories, NPN 80015041 immediate release) to compound doses. The compounded 1 mg/mL solution will be further diluted with a 1:1 mixture of Ora-Plus and Oral-Sweet (Paddock Laboratories Inc., NDC 054-0304-16) to prepare study doses identical in appearance (milky white colour and identical final volume). Each 5 mL dose will be dispensed in amber oral syringes labeled as “melatonin/placebo study drug.” Only the clinical trial pharmacist and/or pharmacy trial technician specified on the delegation of responsibility log will prepare and dispense the study drug.

The study drug will be stored, tracked, and counted in accordance with standard pharmacy dispensing practices by the clinical trial pharmacist and/or pharmacy trial technician. The pharmacy department at each site will maintain a dispensing list kept in the study operations binder that records the identity of participants for each study randomization number. The randomization number will be indicated on the prescription in the subject’s chart and on the dispensing label, allowing the bedside nurse to verify that the patient receives the appropriate study medication. The nurse will record the administration of study drug in the medication administration record (MAR), in accordance with standard ICU practice, in addition to signing the study preparation and administration log.

Data collection

To ensure consistency and optimization of the data collection process, case report forms and standard operating procedures will be included in each site’s study resource binder. Study training sessions will be held at each site, and attendance of research staff will be documented. Only trained and qualified research staff will be permitted to collect study data.

Protocol adherence and feasibility assessment

Each morning, the research team will review the medication profile of study subjects to ascertain if study drug was administered and, where applicable, identify the reasons for late (i.e. protocol deviation) or missed (i.e. protocol violation) doses. Each site will maintain a screening log documenting patients: 1) screened, 2) ineligible, 3) eligible, 4) consented and enrolled, and 5) declined. Using a time-in-motion template[44] from by the Canadian Critical Care Trials Research Coordinator Group, the time required to complete patient screening, maintain the study log, and complete all consent and study-related procedures, including data capture, will be recorded on a daily basis for the first ten patients enrolled at each site.

Pharmacokinetics

A pharmacokinetic analysis of plasma melatonin concentration will be conducted at the Mount Sinai Hospital site in participants that consent to the required blood samples. A target sample of 15 subjects (five from each study arm) will be enrolled. On the first study day, research personnel will collect eight blood samples of 4 mL each using BD vacutainer tubes (K2 EDTA 7.2 mg, DB Franklin Lakes, NJ, USA). The first sample will be taken prior to the first dose of study drug, and subsequent samples will be collected throughout the night at pre-defined intervals ($t_{0\ (baseline)}$, $t_{0.5hr}$, t_{1hr}, t_{2hr}, t_{4hr}, t_{6hr}, t_{8hr}, t_{12hr}) terminating 12 hours later (i.e. the next morning). Specimens will be screened for hemolysis and redrawn if needed. All samples will be centrifuged and stored at -80°C until assays are performed by Mount Sinai Hospital Services Laboratory. Plasma melatonin concentration will be measured using mass spectrometry, and sample dilution to within the linear range of the assay will be performed as necessary. Non-compartmental pharmacokinetic analysis (PKSolution 2.0; Summit Research Services, Montrose, CO, USA) will be used to compare the three study doses. The timing of the blood samples was chosen based on pharmacokinetic studies using similar methodology, in critically and non-critically ill patients.[45-47]

Because melatonin release is regulated by the presence of light, research personnel will also measure light intensity at the time (i.e. in the 5 minutes prior) of each blood sample. Light intensity will be measured near the head of the patient's bed at eye level using a lux-meter

(Environment Meter SHSEHY002, Shimana, Digital Measurement Metrology, Brampton, Ontario, Canada).

Clinical outcomes

Delirium The ICDSC[34] is an 8-item checklist that requires initial evaluation of the patient's level of consciousness, with subsequent delirium screening if the patient is neither comatose nor stuporous. The ICDSC has been shown to have a pooled sensitivity of 74% and specificity of 82%.[48] Clinical staff will screen for delirium once daily until the patient is discharged from the ICU. If bedside staff have not complete the ICDSC, research staff will prompt the completion of the assessment. All ICDSC scores will be recorded on the case report form for the duration of the patient's ICU admission, enabling the determination of both the incidence and duration of delirium and subsyndromal delirium.[49]

Sleep The RCSQ is a simple, validated survey instrument used to evaluate perceived depth, latency, efficiency, and quality of sleep in intensive care patients.[36,37] Patients will be asked to complete the RCSQ each morning of study participation, independently or with the assistance of their bedside nurse. If the patient is unable to complete the RCSQ, no sleep data will be collected for that day because of poor correlation between patient and nursing scores.[50] Although polysomnography[51,52] is the reference standard for measuring sleep, its requirement for specialized technology and expert staff for interpretation render it logistically challenging in the ICU setting. Polysomnograms are also particularly difficult to interpret in ICU patients because of considerable polypharmacy and pathophysiology associated with their critical illness.

Patients enrolled at the Hôpital du Sacré-Coeur de Montréal site (n target = 21) will have rest-activity cycles measured using wrist actigraphy. The actigraph is a small, watch-like device that contains an accelerometer, which records physical motion in all directions with a sensitivity of 0.05 g. Motion is converted into an electric signal, which is digitally integrated to derive an activity count per 1-minute epoch. The rest-activity cycle consolidation will be estimated with the ratio of daytime activity to total 24-hour activity. For each 24-hour day and for each participant, the activity counts will be summed separately for daytime (07:00-21:59 hours) and night-time (22:00-6:59 hours) periods. Night-time is defined according to the schedule of the

hospital unit, and is characterized by lower levels of activity and light. The percentage of activity occurring in the daytime will be divided by the total 24-hour activity to obtain the daytime activity ratio. According to previously published data,[53] a daytime activity ratio of 80% will be chosen to designate an adequate consolidation of the rest-activity cycle, synchronized to the day-night cycle.

Adverse events We will adhere to published guidelines[54,55] for reporting serious adverse events in academic drug trials in critical care. As such, the only adverse events recorded will be those reasonably thought to be a consequence of study participation, and judged by investigators to be unrelated to the patient's underlying disease or an unexpected complication of critical illness.

Other data Other data recorded daily will include Glascow Coma Scale (GCS)[56] and SAS[35] scores, psychoactive drug exposure (i.e., type and dose of sedative, analgesic, anti-anxiety, and antipsychotic medications), sedation protocols or sedation interruption; mobilization out of bed; physical restraint; accidental device removal; presence of a visible clock or window, use of a television, computer, or iPad; single versus shared room; isolation precautions; and strategies to preserve day-night orientation including light and noise reduction (i.e., earplugs and eye masks). Patient demographics (age, sex), comorbidities, use of visual and auditory aids, severity of illness score (Sequential Organ Failure Assessment (SOFA)[57]), admission diagnosis, best possible medication history[58], duration of mechanical ventilation, ICU and hospital length of stay, and ICU and hospital mortality will also be recorded.

Statistical considerations

Sample size

The sample size for this pilot study has been determined to measure adherence to prescribed study drug, with adherence defined as administration of ≥85% of prescribed doses within the administration window using a margin of error of +/- 5%. For an average daily drug administration lasting 4 days and an intra-cluster correlation (ICC) of 0.115 (adjusting for the clustering effect of repeated drug administration within the same subject), 69 patients (or 276 drug administration adherence opportunities) will enable determination of successful adherence (rate 85%; margin of error of +/- 5% at a 95% confidence level).

Statistical analysis

Data will be analyzed using an intention-to-treat approach. Simple descriptive statistics will be used to report feasibility outcomes, pharmacokinetics, as well as baseline demographic and clinical variables. Continuous variables will be described using measures of central tendency and spread (means and standard deviations or medians and interquartile ranges, dependent on data distribution). Frequencies, proportions and their 95% confidence intervals will be used to describe categorical variables. Except for analyses of repeated measures, Kruskal-Wallis tests will be used to compare continuous variables, and chi-square tests to compare categorical variables. Methods that account for clustering will be used when analyzing repeated observations from the same subject. Time-to-event analyses will be used to compare the effects of study drug on the onset of delirium, duration of mechanical ventilation, ICU and hospital length of stay.

Analyses will be considered significant when $p \leq 0.05$ (two-tailed). All analyses will be performed by an independent statistician using SAS 9.3.

Ethics and dissemination

This trial is funded by the Centre for Collaborative Drug Research at the University of Toronto, and will be conducted in accordance with the ethical principles outlined by the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans[59] and the Declaration of Helsinki. Health Canada (No Objection Letter, # 197507 November 7, 2016) and the research ethics board of each participating centre have approved the protocol (Sunnybrook Health Sciences Centre # 086-2016; Mount Sinai Hospital #16-0097-A; and Hôpital du Sacré-Coeur de Montréal # 2017-1385). Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.[60]

Ethical considerations

The trial will be conducted in accordance with Good Clinical Practice following published tri-council guidelines,[59] the Canada Natural Health Products Regulations, The Canadian Personal Health Information Protection Act (PHIPA), and the International Conference on

Harmonization Good Clinical Practice (ICH GCP). All data will be de-identified and will be presented in summary form to preserve the anonymity of individual subjects.

All patients or their substitute decision maker will sign an informed consent form before trial participation and will be given a copy for their records. Research staff will provide an appropriate lay explanation of the proposed aims, methods, objectives and possible harms of the study. A specific section outlining the acquisition and storage of blood samples is included in the informed consent form. We will complete routine quality control to ensure that the study is being conducted according to protocol. This routine quality control will include verification of 1) inclusion and exclusion criteria; 2) source data checks, to ensure accuracy of data collection; 3) adverse events checks to confirm these are recorded, assessed, and reported according to protocol; and 4) case report form review, to ensure completion according to protocol.

CONCLUSION

Delirium is a common syndrome in critically ill patients and is associated with numerous adverse clinical outcomes.[5-10] At this time, no effective drug treatment exists for delirium,[4] making the identification of a safe and effective prevention therapy a clinical imperative. Exogenous melatonin is inexpensive to administer and demonstrates a wide safety margin across adult and paediatric clinical populations. This feasibility trial is the first to explore the effect and pharmacokinetics of both high and low dose melatonin against placebo in critically ill adults. The results of this study are expected in 2018 and if feasibility is proven, we plan to conduct an adequately powered pragmatic randomized controlled trial of similar design.

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Author contributions

LB, DS, DW, JF, SM, MG, EF, MD, AA, FB, and LR made substantial contributions to the conception and/or design of the study protocol. LB, DS, DW, and LR conceived of the overall study and wrote the first draft of the protocol and this manuscript. LB, DS, DW, AA, and LR provided critical input pertaining to the design of the study interventions, procedures, and outcomes. LB, DS, MG, AA, and LR designed the data analysis and management plan. LB, DS, DW, JF, SM, EF, MD, FB, and LR critically revised the protocol for important intellectual content and approved the final version to be published. LB, DS, DW, JF, SM, MG, EF, MD, AA, FB, and LR agree to be accountable for all aspects of the work, ensuring its accuracy and integrity.

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Competing interests statement

None declared.

Data sharing statement

Because this is a prospective protocol, the data are not gathered or published at this time. The final dataset will be available to the primary investigators (LB, LR, DS) only. Data sharing contracts between the participating institutions are in negotiations.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-2
	6b	Explanation for choice of comparators	10-11
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7,10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8, 12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12-14

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15-16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9,12,16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15-16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	If requested by BMJ Open
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	12

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.