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Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): a randomized, double blind, parallel-arm, placebo-controlled trial

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Keywords:	Delirium, Biomimetic sleep, Dexmedetomidine, Cardiac surgery < SURGERY, Patient reported outcomes

Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): a randomized, double blind, parallel-arm, placebo-controlled trial

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Public Title	Protocol for the Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) Trial
Scientific Title	Protocol for the Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) Trial: a Randomized, Double blind, Parallel-

	arm, Placebo-controlled Clinical Trial
Countries of Recruitment	United States
Health Condition(s) or Problem(s) Studied	Postoperative delirium, predictors of delirium
Intervention(s)	Trial arm 1: Dexmedetomidine-induced Sleep Group (primary intervention) Post cardiac surgical patients admitted to the cardiac surgical intensive care unit (CSICU) and extubated at least 30 minutes prior to 8:30 PM would receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes; maximum administered dose of 80mcg) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would receive a sleep induction dose of dexmedetomidine within 30 minutes of extubation. However, throughout the rest of the CSICU stay the dexmedetomidine administration time will be targeted for 9 PM. Trial patients admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU. Trial arm 2: Placebo Control Group. Post cardiac surgical patients admitted to the CSICU and extubated at least 30 minutes prior to 8:30 PM would receive placebo (intravenous normal saline over 40 minutes) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would receive the placebo infusion of normal saline within 30 minutes of extubation. However, throughout the rest of the CSICU stay the placebo administration time will be targeted for 9 PM. Trial patients who are admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU.
Key Inclusion, Exclusion and Objective Drop Criteria	Inclusion Criteria 1. Age ≥ 60

2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for ≥ 24 hours
3. Scheduled same day surgical admission

Exclusion Criteria

1. Blindness, deafness or the inability to speak English
2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure
3. Renal and liver failure requiring dialysis or Child-Pugh score > 5
4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness)
5. Previous cardiac surgery within 1 year of surgical procedure
6. Allergy to dexmedetomidine
7. Chronic therapy with benzodiazepines and/or antipsychotics
8. Severe neurological deficit due to structural or anoxic brain damage
9. Surgical procedures requiring total circulatory arrest

Objective Drop Criteria

1. Surgical procedure scheduled as second case of the day, and/or to be commenced after 12pm
2. Scheduled for a second surgical procedure during hospital stay
3. Post-operative intubation > 12 hours

Trial Type

Interventional
Allocation: Randomized
Intervention model: Parallel assignment
Blinding: Clinicians blinded to intervention, subject blinded to intervention, primary outcome assessor blinded to intervention
Assignment: Parallel
Primary purpose: Prevention

Date of First Enrollment

March, 2017

Target Sample Size

Recruiting until 300 patients receive the study

	intervention on Post Operative Day 0.
Recruitment Status	Enrolling
Primary Outcome(s)	Outcome name: Incidence of postoperative delirium Method of measurement: The Long Confusion Assessment Method Time points of interest: Postoperative day 1
Key Secondary Outcomes	Outcome name: ICU and hospital delirium/coma-free days Method of measurement: Delirium assessment with: The Long Confusion Assessment Method Time points of interest: Up until postoperative day 3, or up until postoperative day 7 or discharge for patients who are delirious beyond postoperative day 5 Outcome name: Severity of Delirium Method of measurement: The Long Confusion Assessment Method Time points of interest: Up until postoperative day 3 or up until postoperative day 7 for patients who are delirious beyond postoperative day 5 Outcome name: Date of Hospital Discharge / Length of Hospital Stay Method of measurement: Medical record review Time points of interest: Up till hospital discharge Outcome name: 30-day, 90-day, and 180-day mortality Method of measurement: Medical record review Time points of interest: 30 days, 90 days and 180 days postoperatively

Outcome name: Postoperative cognitive status

Method of measurement: Telephone Montreal Cognitive Assessment, 3D-CAM and PROMIS-29 applied cognition abilities questionnaire

Time points of interest: 30 days, 90 days and 180 days postoperatively

Outcome name: Postoperative health related quality of life

Method of measurement: PROMIS-29 physical function, global health, pain interference questionnaires, and sleep questionnaire

Time points of interest: 30 days, 90 days and 180 days postoperatively

Outcome name: Peri-operative EEG dynamics of delirium

Method of measurement: Intraoperative and post-operative EEG

Time points of interest: up to post-operative day 3

Authors' contributions: Authorship for this trial will be given to key personnel involved in trial design, recruitment, data collection, and data analysis. There are no publication restrictions and no professional writers will be involved in the generation of the manuscript. KTS, JQ, GC, HD, EYH, LEH, TTH, RI, KJP, and OA were responsible for conceptualizing trial design. JQ managed patient safety protocol. EYH, RI, and LH were responsible for recruitment, enrolment, and data collection. KTS, JQ, FB, ENB, GC, DAD, HD, AD, EYH, LEH, TTH, RI, ML, KJP, SS, GT, MBW, and OA have critically revised the MINDDS protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the MINDDS trial.

Conflict of interest statement: OA and ENB have a provisional patent application describing the use of alpha-2 agonists for promoting N3 sleep. All other authors have no interests to declare.

ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES

Principal Investigator:
Oluwaseun Akeju, M.D., M.M.Sc.

Responsibilities include: design and conduct of the MINDDS trial, preparation of protocol and revisions, organization of steering committee meetings, and publication of trial reports.

Steering Committee:
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Ken Shelton, M.D.
Brandon M Westover, M.D., Ph.D.

Responsibilities include: agreement of final protocol, reviewing progress of trial and if necessary, conducting changes to the protocol, coordinating with principal investigator, and communicating with trial management committee.

Trial Management Committee:
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Tim Houle, Ph.D.
Lauren E Hobbs, M.S.
Reine Ibala, B.S.
Eunice Hahm, B.S.
Kara Pavone, B.S.N, R.N.
Jason Qu, M.D.
Ken Shelton, M.D.

Responsibilities include: trial planning, organization of steering committee meetings, reporting SAEs (Serious Adverse Events) to Partners Healthcare IRB (Institutional Review Board), maintaining REDCap electronic database, reporting to steering committee, conducting data verification, recruitment, randomization, and follow-up of trial participants

Data Management Committee:
Hao Deng, M.D., M.P.H.
Tim Houle, Ph.D.

Responsibilities include: statistical design of trial, data verification.

Data Adjudication Committee:
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Responsibilities include: regularly reviewing delirium assessments, contacting trial management committee, retraining researchers if necessary.

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Responsibilities include: reviewing and evaluating the trial data to ensure participant safety, trial conduct, progress, and efficacy, and making recommendations regarding the continuation, modification, and termination of the trial.

Abstract

Introduction: Delirium, which is prevalent in post cardiac surgical patients, is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder. The pathophysiology of delirium remains poorly understood. However, basic science and clinical studies suggest that sleep disturbance may be a modifiable risk factor for the development of delirium. Dexmedetomidine is a α2a adrenergic receptor agonist medication that patterns the activity patterns of various arousal nuclei similar to sleep. A single nighttime loading dose of dexmedetomidine promotes non-rapid eye movement sleep stages N2 and N3 sleep. This trial hypothesizes dexmedetomidine-induced sleep as pre-emptive therapy for postoperative delirium.

Methods and Analysis: The MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial is a 300-patient block-randomized, placebo-controlled, double-blinded, single-site, parallel-arm superiority trial. Patients over 60 years old, undergoing cardiac surgery with planned cardiopulmonary bypass, will be randomized to receive a sleep inducing dose of dexmedetomidine or placebo. The primary outcome is the incidence of delirium on postoperative day 1, assessed with the Confusion Assessment Method by staff blinded to the treatment assignment. To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 300 patients receive the study intervention on post-operative day 0. Secondary outcomes will be evaluated by in-person assessments and medical record review for in-hospital end points, and by telephone interview for 30-day, 90-day, and 180-day end points. All trial outcomes will be evaluated using an intention-to-treat analysis plan. Hypothesis testing will be performed using a two-sided significance level (type I error) of α=0.05. Sensitivity analyses using the actual treatment received will be performed and compared with the intention-to-treat analysis results.

Additional sensitivity analyses will assess the potential impact of missing data due to loss of follow-up.

Ethics and dissemination: The Partners Human Research Committee approved the MINDDS trial. Recruitment began in March 2017. Dissemination plans include presentations at scientific conferences, scientific publications, and popular media.

Registration details: NCT02856594.

Strengths and limitations

- The MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) will study whether biomimetic sleep will reduce the incidence of delirium.
- The trial intervention is based on a polysomnography study confirming that a nighttime loading dose of dexmedetomidine induces biomimetic sleep.
- The treatment protocol is straightforward and will allow the results to be generalized to patients across a range of care settings.
- Collection of patient-centered outcomes data, including measures of functional independence, at up to 180-days will provide insight into the relationship between the trial intervention and meaningful patient end points.
- Delirium is a fluctuating disorder that may occasionally be missed despite rigorous and validated assessment methods.

Introduction

Delirium, which is prevalent in up to 48% of post cardiac surgical patients,[1] is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition that is not explained by a preexisting neurocognitive disorder.[2] It remains a leading cause of preventable morbidity and mortality in hospitalized elderly patients.[3] The morbidity associated with delirium is estimated to result in increased healthcare costs of approximately $16,000-$64,000 per patient annually. Increasing age and pre-existing cognitive impairment are key predisposing factors for delirium. Despite its impact, there are no definitive pharmacological preventative strategies for delirium. However, basic science and clinical studies suggest that sleep disturbances may be a modifiable risk factor for the development of delirium.

Sleep is a natural occurring state of decreased arousal that is crucial for normal cardiovascular, immune and cognitive function. Sleep deprivation, which is associated with increased pro-inflammatory cytokine levels including interleukin-6,[4-6] precedes the onset of delirium in patients.[7,8] A recent investigation linking brain activity of microglia, astrocytes, interleukin-6 and delirium in humans,[9] suggests a mechanistic link between sleep deprivation, brain inflammation, and delirium. Further, conditions associated with delirium are characterized by activation of the inflammatory cascade with acute release of inflammatory mediators.[10-24] Increasing age is a significant risk factor for the development of delirium. Notably, aging is associated with activated brain glia cell.[3,25] Following a systemic challenge such as critical illness, these activated glia have been suggested to facilitate an exaggerated neuroinflammatory state that predisposes to delirium.[3,25-27]

Sleep disturbance is a hallmark feature of the postoperative period,[28-32] and pharmacological induction of altered arousal states that are neurophysiologically indistinguishable from sleep, termed biomimetic sleep, may represent a preventative strategy for

the development of postoperative delirium. However, commonly administered sedative drugs, most of which modulate the γ amino butyric acid A ($GABA_A$) receptor induce altered arousal states that are neurophysiologically distinct from sleep. This neurophysiological distinction from sleep (i.e. frontal beta oscillations, frontal alpha oscillations, burst suppression, isoelectricity)[33-38] may explain why current sedative medications that modulate $GABA_A$ receptors are not delirium sparing. Rather, neural circuit dysfunction in sensory, memory encoding, and cognitive processing circuits may in part explain why these medications are independent risk factors for the development of delirium.[39]

Dexmedetomidine is a α2a adrenergic receptor agonist medication that patterns the activity patterns of various arousal nuclei similar to sleep.[40-44] Neurophysiologically, a continuous infusion of dexmedetomidine produces spindle and slow-delta oscillations.[36,45] This oscillatory dynamic shares features with non-rapid eye movement (REM) sleep stage N2 sleep.[36,46,47] Consistent with the hypothesis that the neurophysiological approximation of sleep may prevent delirium, the dexmedetomidine-infusion N2 sleep stage (with absent non-REM stages N1, N3 and REM sleep) has been associated with a reduced incidence of delirium in critically ill patients.[48-51] Instead of a continuous drug infusion, we recently found that a single nighttime dose of dexmedetomidine preserves normal sleep cycling. This drug administration paradigm promotes non-REM stage N3 sleep. Notably, N3 sleep is associated with improved cognition and synaptic plasticity.[52-60]

A neurophysiologically principled approach to pharmacologically promote sleep may reduce significantly the incidence of delirium in hospitalized patients. The MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial will evaluate dexmedetomidine-induced sleep as a pharmacological preventative strategy for delirium, and will characterize the impact of delirium prevention on patient-centered outcomes such as

functional recovery for up to 180-days. Risk factors and candidate mechanisms for the development of delirium such as intraoperative anesthetic management, perioperative electroencephalogram dynamics, and systemic inflammatory response will also be explored.

Trial objectives

Our primary hypothesis is that dexmedetomidine-induced sleep will result in a reduced incidence of delirium. Our intervention and control groups will be comprised of extubated cardiac surgical intensive care unit (CSICU) patients, because their relative homogeneity in terms of surgical procedures (i.e. cardiac surgery performed on cardiopulmonary bypass), anesthetic management, and systemic inflammatory response represents a unique opportunity to study the mechanisms underlying delirium, while limiting confounding factors that may otherwise be encountered in heterogeneous patients

Methods and analysis

Trial design

We will enroll 300 patients over a period of three years into a randomized, controlled, double-blinded, single-site, parallel-arm superiority trial. Our primary outcome is the incidence of delirium on postoperative day 1 upon administration of the study intervention. To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 300 patients receive the study intervention on post-operative day 0. Trial end points will be assessed via in-person interview (during hospitalization), medical record review, and telephone interview (after hospital discharge). The primary and secondary outcomes of delirium will be assessed via in-person interviews, which will be performed in the morning and afternoon with approximately 6 hours between interviews. All outcomes, including those obtained post discharge, will be assessed in a blinded fashion.

Eligibility criteria

Inclusion criteria

1. Age ≥ 60
2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for ≥ 24 hours
3. Scheduled same day surgical admission

Exclusion criteria

1. Blindness, deafness or the inability to speak English
2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure
3. Renal and liver failure requiring dialysis or Child-Pugh score > 5
4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness)
5. Previous cardiac surgery within 1 year of surgical procedure
6. Allergy to dexmedetomidine
7. Chronic therapy with benzodiazepines and/or antipsychotics
8. Severe neurological deficit
9. Surgical procedure requiring total circulatory arrest

Objective Drop Criteria

1. Surgical procedure scheduled as second case of the day, and/or to be commenced after 12pm
2. Scheduled for a second surgical procedure during hospital stay
3. Postoperative intubation > 12 hours

Baseline assessment

Patients will undergo a pre-randomization assessment that includes a brief medical record review, and evaluation the following:

1. Baseline cognitive function using the telephone Montreal Cognitive Assessment
2. Presence of delirium at the time of interview, as measured by the 3 min assessment for Confusion Assessment Method-defined delirium (3D-CAM)
3. Physical function with the PROMIS SF v1.2 -Physical function 8b
4. General health with the PROMIS SF v1.1- Global
5. Pain with the PROMIS SF v1.0- Pain Interference 8a
6. Applied cognition with the PROMIS v1.0- Applied Cognition Abilities SF 8a
7. Baseline sleep quality with the PROMIS-4A

Intervention

We will randomly allocate patients to receive placebo or dexmedetomidine nightly during their CSICU stay. All clinical care during preoperative, intraoperative and postoperative periods will follow normal standard of care. However, trial patients admitted to the CSICU and extubated at least 30 minutes prior to 8.30 PM would receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8.30 PM, but before 2 AM, would receive a sleep induction dose of dexmedetomidine within 30 minutes of extubation. However, throughout the rest of the CSICU stay the sleep induction time will be targeted for 9 PM. Trial patients who are admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU. The maximum dexmedetomidine dose that will be administered is 80 mcg. Clinicians will be asked to refrain

from routinely administering dexmedetomidine to patients in the operating room and in the CSICU. Otherwise, all other care decisions will be at the discretion of the clinical care team.

Outcomes

Primary outcome

The primary outcome measure for this trial is the incidence delirium in the CSICU on postoperative day 1. Delirium assessments will be conducted twice daily (AM and PM with at least 6 hours between tests) beginning on postoperative day 1 using the Long Confusion Assessment Method (CAM).[61,62] Trial staff blinded to treatment assignments will perform the delirium assessments. Delirium assessments for patients who are reintubated for clinical care or for further surgical management will be considered missing data.

Secondary outcomes (in-hospital)

Blinded trial staff will collect secondary outcomes during hospital admission. These outcomes include:

1. ICU and hospital delirium/coma-free days assessed twice daily through postoperative day 3, or up until postoperative day 7 or discharge for patients who are delirious beyond postoperative day 5
2. Severity of delirium scored using the CAM delirium severity scoring long form
3. Date of hospital discharge and length of hospital stay assessed by chart review
4. Inpatient mortality and major inpatient morbidity assessed by chart review
5. Peri-operative EEG dynamics of delirium

Secondary outcomes (post-discharge)

Blinded trial staff will collect secondary outcomes via telephone interviews and/or online questionnaires at 30-days, 90-days, and 180-days post procedure. These outcomes include:

1. Cognitive function using the telephone Montreal Cognitive Assessment
2. Physical function with the PROMIS SF v1.2 - Physical Function 8b

3. General health with the PROMIS SF v1.1 - Global
4. Pain with the PROMIS SF v1.0- Pain Interference 8a
5. Applied cognition with the PROMIS v1.0 - Applied Cognition Abilities SF 8a
6. Sleep quality with the PROMIS v1.0 - Sleep Disturbance 4A
7. Mortality

Sample size planning

The primary objective of this trial is to detect a difference in the incidence of delirium between the dexmedetomidine-induced sleep and normal care groups. Assuming a delirium event rate of 48%, a type I error of 0.05, and power of 0.80, an n = 150 patients per group will enable us to detect an absolute difference 15% (i.e., 48% versus 33%). With respect to decreased morbidity and healthcare costs, this change represents a clinically meaningful difference. Therefore, we will recruit up to 150 patients per group.

Recruitment

This study will be performed at the Massachusetts General Hospital in Boston, MA. Subjects will be recruited through the cardiac surgery preoperative clinic and all enrolled patients will provide written informed consent. Informed consent for this protocol will follow a two-part process. First, a verbal consent will be obtained at the pre-operative visit prior to administering pre-operative baseline questionnaires. During this visit, the trial protocol will be explained to potential participants. In addition, a flyer detailing an overview of the trial protocol, as well as a copy of the formal consent form, will be given to potential trial participants to take home. A study physician will obtain final, written consent on the day of surgery (typically within 14 days of the pre-operative visit). After written consent is obtained, the trial team will allocate a trial identification number to the subject based on the trial stratification schema. A clinical trial pharmacist will perform central allocation into study arms according to the randomization key

that is associated with each trial identification number.

Allocation

Eligible patients who provide written informed consent will be randomized to receive either dexmedetomidine or placebo with a 1:1 allocation as per a computer generated randomization schedule generated by an independent statistician, and stratified by cardiac surgery type (i.e. valvular repair versus non-valvular repair) using permuted blocks of random sizes. The block sizes will not be disclosed until the primary endpoint is analyzed to ensure concealment. Allocation concealment is further ensured by the fact that dexmedetomidine and placebo cannot be distinguished on the basis of appearance. The randomization key that is associated with each participant trial identification number will remain with the clinical trial pharmacist (AD) for the duration of the study. Thus, the clinical trial pharmacist will conduct randomization throughout the study in order to keep the data management and the statistician blind. All trial medications will be labeled as "dexmedetomidine or placebo," to preserve the integrity of randomization assignments. Thus, randomization into any study arm will be conducted without any influence of the study investigators, biostatisticians, and outcome assessors. The CSICU nurse taking care of the patient will administer the trial medication. If other medications are indicated for the treatment of delirium, the treating physician will prescribe this as part of standard clinical care.

Blinding

Assessors who are blind to treatment allocation will conduct all primary and secondary outcome assessments. To maintain the overall quality and legitimacy of the clinical trial, code breaks will occur only in exceptional circumstances when knowledge of the actual treatment is deemed essential by the treating physicians for further management of the patient. The treating physician will be directed to the clinical trial pharmacist to obtain the actual treatment code. The study investigators will maintain blindness and the treatment allocation. Additionally, the treating

physician will be directed to abstain from written or verbal disclosure of the code. The principal investigator (PI) will report all code breaks to the DSMB.

Criteria for patient discontinuation

Patients may be discontinued from trial treatment and assessments for several reasons. These include: voluntary discontinuation by the patient, safety reasons (i.e. active hemorrhage) as judged by the clinical and/or trial physicians, failure to maintain study eligibility during the hospital stay or non-compliance with the protocol as judged by the trial physician.

Data analysis

All trial outcomes will be evaluated using a modified intention-to-treat analysis plan. Hypothesis tests will be performed using a two-sided significance level (type I error) of α=0.05. Sensitivity analyses using the actual treatment received will also be performed and compared with the intention-to-treat analysis results. Additional sensitivity analyses will be performed to assess the potential impact of missing data due to follow-up losses. The primary outcome will be evaluated using logistic regression examining the presence or absence of delirium conditional on randomized group assignment. Any randomization imbalances, or other potential treatment effect modifiers will be further examined as covariates in sensitivity analyses. Secondary analyses will be evaluated using tests that are appropriate for the outcomes. We will use Pearson $\chi 2$ tests to compare categorical variables between the 2 trial groups and independent t-tests or Wilcoxon rank-sum tests to compare continuous variables. Time-to-event analyses will be used to compare the effects of dexmedetomidine-induced sleep and normal care on mortality, and CSICU and hospital lengths of stay. Kaplan-Meier survival curves will be used for graphical presentation of these time-to-event analyses, and log-rank statistics will be used to assess the effects of biomimetic sleep and normal care. For mortality analyses, patients will be censored at the time of last contact alive. Censoring for CSICU or hospital discharge readiness analyses will occur at time of death or trial withdrawal. Because missing data rarely

occur entirely at random, we will assess the associations between patient characteristics with respect to missing data. If patients with at least one missing outcome value are different from those with complete outcomes data, we will use multiple imputation to assign values to missing data risk factors and outcomes in regression modeling.

Heterogeneity of treatment effects

Subgroup comparisons will be conducted for heterogeneity of treatment–covariate interactions if the sample sizes and numbers of events within these subgroups are sufficient for analysis. If there is a treatment difference together with evidence of heterogeneity, relevant covariates and interaction terms will be added to the relevant regression models for formal significance testing. For the primary outcome, we plan for analyses of treatment effects within pre-specified subgroups potentially defined by:

1. Surgery type
2. Length of cardiopulmonary bypass
3. Presence of significant cardiac dysfunction (ejection fraction less than 35%)
4. Sedative administration in the ICU
5. Opioid administration in the ICU
6. Pain scores
7. Baseline cognitive status
8. Organ failure
9. Postoperative cerebrovascular disease
10. APACHE/EUROscore

Interim analyses

Interim efficacy data will be provided to the Data Safety Monitoring Board (DSMB) during yearly meetings to permit benefit-to-risk assessments. An independent statistician that is

unblinded to the treatment allocation will perform the interim-analysis. The statistician will report to the DSMB in a closed session. Thus, the DSMB will have unblinded access to all data to inform recommendations on study continuation. If at any time during the course of the study the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

Data management

All data collected for the MINDDS trial will be entered into the Massachusetts General Hospital Research Electronic Data Capture (REDCap) application.[63] Data entered into the database will be retrievable for viewing through the data entry applications. Data integrity will be enforced through referential data rules, valid values, range checks, and consistency checks against data already stored in the database. Programs designed to detect missing data or specific errors in the data will be implemented to detect additional errors. These errors will be summarized along with detailed descriptions for each specific problem in monthly Data Query Reports, which will be sent to the PI. The PI will respond by checking the original forms for inconsistency, checking other sources to determine the correction, modifying the original forms as necessary, and entering a response to the query. Data access will be restricted via password protection to only those individuals who are authorized to work on the trial. Specific privilege assignments within the database will also be employed to limit the types of data that authorized users may access to the minimum required by their role in the trial. Electronic audit trails will be used to capture and record changes to database contents automatically. Original study forms will also be kept in files. Participant files will be stored in numerical order in a secure and accessible place and manner. These files will be maintained in storage for a period of at least 5 years after study completion. Members of the adjudication committee will request a subset of these study forms later for quality control.

Site training

Trial team members have undergone a rigorous CAM training program led by a neuropsychologist and member of the team that created the Long-CAM.[62] The CAM is the most widely used delirium assessment tool in the research setting, with a high sensitivity and specificity when compared with formal psychiatric diagnosis.[61,62] The 3D-CAM is a three-minute assessment tool for delirium, which has good agreement with the CAM.[64] Those who attended this initial training will oversee the training of other team members. All trainees must demonstrate competence at conducting the structured interviews and in correctly scoring subjects. Trainees must first conduct at least two satisfactory CAM assessments in subjects not enrolled in the MINDDS trial in the presence of a trained team member. To establish competency in scoring the CAM, trainees will observe CAM interviews conducted by trained team members and will score the CAM independently. The trainee must agree with the trainer on the presence or absence of all cognitive features assessed by the CAM on a minimum of six interviews. After meeting the stipulations of training, the newly trained team member will conduct their first interview of a patient enrolled into the MINDDS trial in the presence of a previously trained team member. Independent of the training process, all MINDDS team members who are participating in CAM assessments must view and rate videos of CAM interviews of actors depicting delirious and non-delirious patients.

Data and safety monitoring

All unexpected adverse events that are related to the trial treatment will be recorded in the trial database and reported as required to the Partners Healthcare IRB. A data and safety monitoring board (DSMB) will also oversee the MINDDS trial. The DSMB will provide independent oversight of the MINDDS, and will review general conduct of the trial and trial data for participant safety. The DSMB is comprised of independent, multidisciplinary experts who will

make recommendations regarding the continuation, modification, or termination of the trial. The members will have the requisite expertise to examine accumulating data, to protect the integrity of the clinical experiments to which the patients have consented to participate, and to assure the regulatory bodies, the public and the National Institutes of Health that conflicts of interest do not compromise either patient safety or trial integrity. The DSMB will convene before trial initiation and annually to review safety events. Recommendations from the DSMB for protocol modifications or revisions will be communicated through a representative of the National Institutes on Aging to the PI.

The study operations committee will determine relatedness of an event to the study drug based on a temporal relationship to the study drug administration, whether the event is unexpected given the clinical course, previous medical conditions, and concomitant medications. Adverse events will also be communicated to members of the study steering committee for additional review. Expedited review will occur for all events meeting the FDA definition of SAEs – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, or event requiring or prolonging inpatient hospitalization. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. For purposes of this study, all SAEs will require reporting to the DSMB, regardless of their relatedness to the study drug. All relevant information will be reported to the DSMB for each SAE, including information about the event and its outcome, dosing history of all study drugs, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by e-mail of all related study forms shall be made to the DSMB within 2 days of the occurrence of any SAE. Information will be reviewed and a determination made of whether there was any possible relevance to the study drug. Additional reporting to the IRB will be done within 24 hours of the SAE. All patients that experience a SAE will be censored from the study at SAE occurrence.

Data Monitoring and Quality Assurance

Reflective of the state of the art in clinical trials, the MINNDS trial will employ a web-based portal for data quality and completeness. The portal will display in real time the following variables for all patients: sex, race, adverse events, study related data etc.

Trial risks

The risk of a breach of confidentiality is small and all possible efforts have been taken to ensure the security of trial data and minimize the risks of accidental disclosure of identifiable data elements. The risks associated with dexmedetomidine are related to drug induced reduction in sympathetic activity, resulting in hypotension and bradycardia. However, cardiovascular parameters are continuously monitored in the CSICU, ensuring that appropriate medical intervention can be instituted in a timely fashion for clinically significant hypotensive or bradycardic episodes. Thus, the risk of clinically significant hypotension or bradycardia in our patient study population is small.

Ethics and dissemination

The trial has been approved by the Partners Health Care IRB. The trial steering committee will be responsible for all major decisions regarding changes to the protocol. The committee will communicate these changes to the IRB and the DSMB. Electronic data and demographic information will be accessed only as necessary for completion of trial follow-up tasks. The PI has will have access to all data. The primary papers emanating from MINDDS will present primary and secondary outcome. Secondary analyses will also be conducted to construct predictive models for delirium occurrence and resource utilization. Mechanistic manuscripts on the pathophysiology, which will be based on biomarkers elicited from MINNDS study participants (i.e. perioperative electroencephalogram, serum, brain imaging) will also be published. Dissemination plans include presentations at local, national and international scientific conferences. Every effort will be made to publish results of the MINDDS trial in a peer-

reviewed journal. Dissemination of results to trial participants and their family members will be available upon request. Updates and results of the trial will be available to the public at clinicaltrials.gov.

Conclusion

The MINDDS trial will evaluate a new preemptive therapeutic sleep strategy for the prevention of delirium, and may enable new insights into the pathophysiology of delirium.

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Authorship Eligibility and Contributorship

Authorship for this trial will be given to key personnel involved in trial design, recruitment, data collection, and data analysis. There are no publication restrictions and no professional writers will be involved in the generation of the manuscript. KTS, JQ, GC, HD, EYH, LEH, TTH, RI, KJP, and OA were responsible for conceptualizing trial design. JQ managed patient safety protocol. EYH, RI, and LH were responsible for recruitment, enrolment, and data collection. KTS, JQ, FB, ENB, GC, DAD, HD, AD, EYH, LEH, TTH, RI, ML, KJP, SS, GT, MBW, and OA have critically revised the MINDDS protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the MINDDS trial.

Minimizing ICU neurological dysfunction with dexmedetomidine-induced sleep (MINDDS): A randomized placebo-controlled trial

Principal Investigator: Oluwaseun Johnson-Akeju, M.D., M.M.Sc

1. BACKGROUND AND SIGNIFICANCE

Delirium is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder.[1] It is associated with increased mortality, prolonged hospitalization, prolonged institutionalization, and long-term cognitive deficits.[2-7] Patients with pre-existing dementia, such as Alzheimer's disease, are especially vulnerable to developing delirium.[8] The total healthcare cost attributable to delirium is estimated between $143 and $152 billion annually.[9] In the United States, delirium occurs in approximately 80% of critically ill patients admitted to medical/surgical intensive care units (ICU), [10] and 43% of patients admitted to cardiac surgical (CS) ICU.[11] Most patients diagnosed with delirium also present with multiple comorbidities (sepsis, multi-organ failure) that significantly confound our understanding of this disease.[2] Thus, to date, no pharmacological intervention to treat delirium has been identified.[2] The aging process has been identified as a risk factor for developing delirium.

Normal aging is associated with a morphological shift of glia (microglia, astrocytes) to an activated state. Following a systemic challenge such as critical illness, these activated glia aid a neuroinflammatory state that contributes to delirium. The aforementioned neuroinflammatory state is exacerbated by sleep disturbances.[15-17] Thus, sleep deprivation may be a modifiable risk factor for the development of delirium. Presently, pharmacological treatment with no current medication (benzodiazepines, antipsychotics) induces natural sleep or reliably reduces the incidence of delirium. **We have found that pharmacological induction of rapid eye movement sleep (REM) and non-REM I-III sleep states using dexmedetomidine, can now be safely achieved in humans**. Our overall objective is to evaluate the efficacy of dexmedetomidine-induced sleep in preventing delirium, investigate cellular and molecular mechanisms underlying delirium, and investigate whether recently described intraoperative electroencephalogram (EEG) signatures of the aging brain are associated with developing delirium.[18] Our central hypothesis is that nightly biomimetic sleep in elderly patients admitted to the CSICU for > 24hrs will reduce the incidence of ICU delirium.

Our intervention and control groups will be comprised of extubated CSICU patients, because their homogeneity in terms of surgical procedures, anesthetic management, and systemic inflammatory response represents a unique opportunity to study the mechanisms underlying delirium, while limiting confounding factors that may otherwise be encountered in heterogeneous patients found in the medical/surgical ICU. We will perform assessments of cognition (peri-operative), obtain EEG recordings (intra-operative, ICU) and blood samples (peri-operative).

At the conclusion of these studies, we will have expanded our knowledge of the pathophysiology of delirium, evaluated a new preemptive therapeutic strategy for delirium, suggest neurophysiologically based monitoring strategies to reduce significantly the amount of anesthetic administered to elderly patients – and possibly delirium – while being certain the patient is sufficiently unconscious for surgery (individualized anesthesia care), and enable continued investigation into the pathophysiology of this clinically important disorder.

2. SPECIFIC AIMS

We will pursue three aims. In the first aim, we will investigate the benefits of preemptive biomimetic sleep for reducing the risk of developing delirium in a randomized controlled trial; in the second aim, we will investigate the mechanisms of delirium using serum metabolic profiling; and in the third aim, we will investigate predictors of delirium from perioperative EEG recordings. **Table 1** shows a proposed timeline.

Table 1: Planned Schedule

Hypothesis	Short Name	Year 1	Year 2	Year 3	Year 4	Year 5
1.1	Nightly preemptive biomimetic sleep will reduce the incidence of delirium	..	..	..		
2.1	Serum metabolic profiling will be sensitive to detect neurodegeneration of preclinical delirium			..	..	
3.1	Absence of anesthesia-induced frontal alpha oscillations will be associated with delirium			..	..	..

3.2	Burst-suppression/anesthesia overdose will be associated with delirium		..	..	..

The specific aims of this study are:

AIM 1: Investigate the benefits of preemptive biomimetic sleep for reducing the risk of delirium in a Randomized Controlled Trial.

Hypothesis 1.1. Compared to standard treatments (benzodiazepines, antipsychotics), nightly preemptive biomimetic sleep will reduce the incidence of ICU delirium.

AIM 2: Investigate mechanisms of delirium using serum metabolic profiling.

Hypothesis 2.1. Unbiased serum metabolic profiling will be sensitive to detect early signatures of neurodegeneration that predisposes to the development of delirium.

AIM 3: Investigate predictors of delirium from perioperative EEG recordings.

Hypothesis 3.1. The relative absence of anesthesia-induced frontal alpha oscillations (a putative marker of brain vulnerability) is associated with delirium.

Hypothesis 3.2. Burst-suppression induced by the age-adjusted maintenance anesthetic (a putative marker of anesthetic overdose and brain vulnerability) is associated with the severity of delirium.

3. STUDY PROCEDURES

Subject Selection: We will enroll 300 patients over a period of three years into a randomized, controlled, double-blinded, single-site, parallel-arm superiority trial. Our primary outcome is the incidence of delirium on postoperative day 1 upon administration of the study intervention. Thus, in order to ensure that we are adequately powered, patients will be censored from the study if they do not receive dexmedetomidine or placebo on postoperative day 0. The cardiac surgical case volume at Massachusetts General Hospital (MGH) will enable us to meet our recruitment goals within our projected timeline. Cardiac surgeons, cardiac intensivists, and anesthesiologists at MGH will identify all potential study participants. This initial care provider-patient contact will ensure that eligible patients are comfortable with all study procedures. Once the potential participant confirms that he/she is comfortable with all study procedures, a copy of the consent form will be made available. Informed consent for this protocol will follow a two part process. First, a verbal consent will be obtained at the Department of Anesthesia, Critical Care and Pain Medicine pre-operative visit. This verbal consent is necessary to ensure that pre-operative baseline questionnaires can be administered. During this visit, the study protocol will also be explained to potential participants. In addition, a flyer detailing the study protocol will also be given to potential study participants. After verbal consent is obtained, the study team will allocate a study identification number, based on the study stratification schema, to the potential participant. Written consent will be obtained on the morning of surgery. The research pharmacy will allocate the participant into his/her assigned intervention group according to the randomization key associated with each study identification number. This key will be provided to the pharmacy by the study statisticians. All study team members, including the statisticians, and all clinical care providers will be blinded to the treatment group assignments. All subjects who provide verbal consent and complete the baseline assessment, but later decline participation in the study, or fail to give signed consent, will not be subject to any study-related follow-up or intervention. However their baseline assessment, which has already been acquired, may be used to identify factors that may predispose or bias patients toward enrollment. Patients who undergo secondary surgical procedures after admittance to the CSICU, and/or remain intubated longer than the 12 hours stipulated below, will not be subject to any further study procedures as they will no longer satisfy the primary inclusion and exclusion criteria.

Primary inclusion criteria for patients and controls: (1) age ≥ 60; (2) scheduled for a cardiac surgical procedure with planned post-operative admission to the CSICU for ≥ 24 hours; (3) scheduled same day surgical admission.

Primary exclusion criteria for patients and controls: (1) blind, deafness or the inability to speak English; (2) greater than 2 days of ICU admission in the month preceding the current surgical procedure; (3) renal and liver failure requiring dialysis or Child-Pugh score > 5; (3) follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness); (4) previous cardiac surgery within 1 year of surgical procedure; (5) allergy to dexmedetomidine; (6) post-operative intubation > 12 hours; (7) chronic therapy with benzodiazepines and/or

antipsychotics; (8) severe deficit due to structural or anoxic brain damage; (9) surgical procedure requiring total circulatory arrest.

Primary objective drop criteria for patients and controls: (1) Scheduled for a second surgical procedure during hospital stay.

Intervention (dexmedetomidine-induced sleep vs. placebo). After admission to the CSICU, rewarming, discontinuation of the sedative/anesthetic infusion and extubation of the airway, sedative medications will be administered as clinically indicated by the CSICU intensive care physician. Study patients admitted to the CSICU during the afternoon and extubated by 8:30 PM, would either receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes) or placebo (normal saline over 40 minutes) every night throughout their CSICU stay. A sustained infusion of dexmedetomidine would never be administered for study related purposes. The targeted sleep induction time will be 9 PM. For the second start or later surgical cases, study patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would either receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes) or placebo (normal saline over 40 minutes). The targeted sleep induction time will be within 30 minutes of extubation, with the earliest administration time being 9 PM. However, throughout the rest of the CSICU stay the sleep induction time will be targeted for 9 PM. In contrast, those patients who are admitted to the CSICU and remain intubated past past 2 AM will not begin study procedures until postoperative day 1, assuming they are extubated within 12 hours of admission to the CSICU. The maximum dose of dexmedetomidine that will be administered for any study participant will be 80mcg over a 40-minute period. Nighttime EEG may be obtained on all participants to enable sleep stage scoring in the spectral domain. The intraoperative EEG data acquisition system (Sedline) is a four-channel EEG device approved by MGH bioengineering. This device is currently used in all operating and procedural rooms at MGH for monitoring depth-of-anesthesia. For EEG monitoring in the ICU we will use the Compumedics Somte Portable PSG monitoring device.

Post cardiac surgical patients that are admitted to the CSICU have implanted temporary pacemakers and are also on a variety vasoactive medications (including but not limited to: norepinephrine, dobutamine, dopamine, and epinephrine) to maintain hemodynamic stability. Therefore, the administration of dexmedetomidine in these patients will not unduly compromise their cardiovascular status. However, patients with active bleeding necessitating surgical intervention will be excluded from the study.

Outcome measures and variables of interest. The primary outcome measure for this study is the incidence delirium in the CSICU on post-operative day 1. Secondary outcome measures include ICU- and hospital-delirium/coma-free days, length of hospital stay, 30-day mortality, 90-day mortality, and 180-day mortality. Variables of interest will include age, sex, years of formal education, race, ethnicity, marital status, , chronic disease burden (Charlson comorbidity index), cerebrovascular disease (Framingham Stroke Risk profile), physical function as assessed by NIH Patient Reported Outcomes Measurement Information System (PROMIS-29) questionnaires, organ failure (Sequential Organ Failure Assessment), length of cardiopulmonary bypass, presence of significant cardiac dysfunction (ejection fraction less than 35%), and sedative use in the ICU.

Cognitive testing. We will conduct delirium assessments twice daily (AM and PM with at least 6 hours between tests) beginning on post-operative day 1 using the Long- Confusion Assessment Method (CAM). Delirium assessments will be conducted up to day 3 or hospital discharge, whichever comes first. Patients who remain delirious past day 3 will be assessed until day 5 or hospital discharge, whichever comes first. For those patients who remain delirious past day 5, assessments will continue until day 7 or hospital discharge, whichever comes first.

Other Cognitive Testing: Cognitive decline will be estimated by taking into account the patient's baseline cognitive function and sleep quality before admission to the ICU, as assessed using the PROMIS-29, T-MOCA and PROMIS-4A questionnaires scored at recruitment, 1 month, 3 months, 6 months. The 3-D CAM will be administered at baseline. These questionnaires may be administered via email (RedCap) or regular mail, or phone call.

Blood Draws: For all patients, we will acquire peri-operative blood samples. This will enable us relate the serum metabolic/inflammatory profile to primary and secondary outcomes. For all study participants, blood sampling will be acquired as follows: (1) up to 40 ml of blood may be acquired at baseline on the day of surgery prior to the induction of general anesthesia (5-10ml for TSPO genetic profiling);(2) up to 20 ml of blood may be acquired at approximately 9 am of every ICU stay up to day 5. We may apply at least three distinct LC-

MS–based methods to study distinct plasma aliquots for each experimental sample.

Anesthetic management and EEG data acquisition: Intraoperatively, patients will receive standard anesthesia care in which the anesthesiologist uses age-adjusted drug dosing information, as well as heart rate, and blood pressure to set and titrate the anesthetic. This portion of the study will follow a strictly observational nature. EEG will be recorded per clinical practice in all patients using the 4-channel Sedline EEG machine that is installed in all operating rooms at MGH. In the ICU, EEG may be acquired through the Compumedics Portable PSG monitoring device.

Other data. A member of the study team will review the patient's bedside nursing log and clinical notes in the patient chart. A timeline of physiological data (obtained from continuously recorded clinical data in the CSICU), sedatives, analgesics, as well as any patient events will be recorded for later analysis in relation to outcome measures and nighttime spectral sleep stage scoring.

4. DATA ANALYSIS PLAN

Data will be analyzed using an intention-to-treat approach defined as all randomized patients who receive an intervention. Continuous data will be described using median and interquartile range, and categorical data using frequencies and proportions. The primary outcome will be evaluated using logistic regression examining the presence or absence of delirium conditional on randomized group assignment. Any randomization imbalances, or other potential treatment effect modifiers will be further examined as covariates in sensitivity analyses. Secondary analyses will be evaluated using tests that are appropriate for the outcomes. We will use Pearson $\chi 2$ tests to compare categorical variables between the 2 study groups and independent t-tests or Wilcoxon rank-sum tests to compare continuous variables. Time-to-event analyses will be used to compare the effects of dexmedetomidine-induced sleep and normal care on mortality, CSICU and hospital lengths of stay, CSICU and hospital readmission rates. Kaplan-Meier survival curves will be used for graphical presentation of these time-to-event analyses and log-rank statistics to assess the effects of biomimetic sleep and normal care. For mortality analyses, patients will be censored at the time of last contact alive or days from enrollment, whichever was first. Censoring for CSICU or hospital discharge readiness analyses will occur time of death or study withdrawal. Two-sided *P* values of .05 or less were considered to indicate statistical significance. Because missing data rarely occur entirely at random, we will assess the associations between patient characteristics with respect to missing data. If patients with at least one missing outcome value are different from those with complete outcomes data, we will use multiple imputation to assign values to missing risk factors and outcomes in regression modeling.

Metabolite concentrations will be log transformed to reduce heteroscedasticity of case-control differences. Metabolite levels will be compared in persons who developed delirium versus those who did not using two-tailed t tests. To screen these associations in the context of the balance of type-I and type-II errors, we will consider both FDR adjusted and Bonferroni-corrected P value thresholds. For metabolites meeting the less conservative FDR P value threshold, logistic regression analyses to estimate the OR of developing cognitive deficits will be performed at different metabolite values. Metabolites will be analyzed as continuous variables (log transformed and scaled to SD of 1), and regressions adjusted for age, sex, delirium assessment, CT-ICU length of stay, and surgical duration. To examine the unique predictive ability of these metabolites, we will conduct an exploratory stepwise logistic model including all metabolites meeting our threshold, and conduct cross-validation procedures to examine the internal consistency of these estimates. We will then construct a multimarker score based on the regression coefficients of the metabolites that were significant and consistent in our multivariable model, and then assess whether a model including clinical risk factors plus the multimarker panel improves delirium prediction compared with the model including clinical risk factors only.

All EEG data will be downloaded for off-line computational analysis. Data will be visualized and analyzed using signal processing and statistical algorithms available in MatLab, and using algorithms developed in house by the study investigators. To address hypothesis 3.1, we will employ multitaper power spectral analysis,[21] multitaper bivariate coherence analysis.[18] We will also perform phase-amplitude modulation between low and high frequency EEG components.[21] To address hypothesis 3.2, Segmentation of EEG recordings into burst and suppression periods will be performed in a semi-automated manner using an adaptation of previously described methods.[22-24] We will quantify the depth of burst suppression using the burst suppression probability (BSP), a number between 0 and 1, which describes the instantaneous probability of the EEG being in a state of suppression. A BSP value of 0 corresponds to a continuously active EEG with no

suppression, whereas a value of 1 corresponds to a completely isoelectric or suppressed EEG.

5. POWER ANALYSIS

The primary objective of this study is to detect a difference in the incidence of ICU delirium between the dexmedetomdine-induced sleep and normal care groups. Assuming a delirium event rate of 48%, a type I error of 0.05, and power of 0.80, an n = 150 patients per group will enable us to detect an absolute difference 15% (i.e., 48% versus 33%). With respect to decreased morbidity and healthcare costs, this change represents a clinically meaningful difference. Therefore, we will recruit up to 150 patients per group.

6. REMUNERATION

Patients will be paid by check at the completion of the study for their participation as follows:

- $15 for completion of questionnaires at each time-point (1, 3 and 6 months). Remuneration for all questionnaires completed by study participants will be processed 6 months after their surgery date. Thus, 1 check will be issued for all study questionnaires that are completed (i.e. $45 for 3, $30 for 2, and $15 for 1 questionnaire).
    - Everyone who completes all questionnaire time-points will be enrolled in a raffle to win 1 of 3 iPads.

7. RISK AND DISCOMFORT

Dexmedetomidine risks: The risks involved in the administration of dexmedetomidine include nausea, xerostomia, atrial fibrillation, and transient hypertension during drug loading. The significant risks involved are directly related to a drug induced reduction in sympathetic activity, resulting in hypotension and bradycardia. Rare case reports of sinus arrest in instances of rapid drug administration and in patients with a high resting vagal tone have also been described. Drug discontinuation, dose reduction, or the use of vasoactive substances causes a return of these hemodynamic parameters to baseline. All subject hemodynamic parameters will be continuously monitored to ensure that appropriate medical intervention will be instituted for any clinically significant hypotensive or bradycardic episodes. In addition, most of our study subjects will have temporary pacemakers in place for routine post surgical heart-rate management. Since dexmedetomidine maintains the respiratory rate and we are only administering a one-time dose (similar to our recently completed proof of concept study in healthy volunteers; NCT01485393), there is no concern for respiratory compromise.

EEG risks: The risks associated with EEG electrodes are redness and irritation at placement site.

Psychological risks: Psychological risks include the possibility of claustrophobia within the scanner.

Questionnaire risks: Minimal risks associated with completing questionnaires are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning.

Data risks: Procedures are in place to reduce the likelihood of a breach of confidentiality including the de-identification of data and storage of data only on partners approved devices/portals. However, there is a small risk that people outside of this study may be exposed to information about study subjects.

8. POTENTIAL BENEFITS

Subjects will have no direct benefit from taking part in this study. Findings from these studies will help advance our understanding of the pathophysiology of delirium. In particular, this project will assess the role of sleep induction and neuroinflammation in the establishment and/or maintenance of delirium. As such, we envision that in the future the information obtained from the proposed research will enhance the diagnosis and management of delirium.

9. MONITORING AND QUALITY ASSURANCE

No identifiers other than study ID's will be included in the dataset. Thus, all data will be deidentified and data will be stored on password protected partners computers and cluster for off-line analysis. The proposed study will be monitored for safety, with monthly staff meetings reviewing adverse events and treatment outcomes and directly reporting any adverse events. The PI will also routinely monitor and assure the validity and integrity of collected data and adherence to the IRB-approved protocol. The trained staff members who carry out the procedures will also carefully monitor the study throughout its duration. The team will evaluate the progress of the study, verify that the rights and well being of the subjects are protected, verify that the reported

study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments. Outcome monitoring and adverse events will all be reported through appropriate channels of the Human Studies Committee. A DSMB will also oversee this study.

Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines, as well as the RDRC within 5 days.

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Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial

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Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial

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Countries of Recruitment	United States
Health Condition(s) or Problem(s) Studied	Postoperative delirium, predictors of delirium
Intervention(s)	Trial arm 1: Dexmedetomidine-induced Sleep Group (primary intervention) Post cardiac surgical patients admitted to the cardiac surgical intensive care unit (CSICU) and extubated at least 30 minutes prior to 8:30 PM would receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes; maximum administered dose of 80mcg at any one instance) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would receive a sleep induction dose of dexmedetomidine within 30 minutes of extubation. However, throughout the rest of the CSICU stay the dexmedetomidine administration time will be targeted for 9 PM. Trial patients admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU. Trial arm 2: Placebo Control Group. Post cardiac surgical patients admitted to the CSICU and extubated at least 30 minutes prior to 8:30 PM would receive placebo (intravenous normal saline over 40 minutes) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would receive the placebo infusion of normal saline within 30 minutes of extubation. However, throughout the rest of

	the CSICU stay the placebo administration time will be targeted for 9 PM. Trial patients who are admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU.
Key Inclusion, Exclusion and Objective Drop Criteria	Inclusion Criteria 1. Age ≥ 60 2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for ≥ 24 hours 3. Scheduled same day surgical admission Exclusion Criteria 1. Blindness, deafness or the inability to speak English 2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure 3. Renal and liver failure requiring dialysis or Child-Pugh score > 5 4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness) 5. Previous cardiac surgery within 1 year of surgical procedure 6. Allergy to dexmedetomidine 7. Chronic therapy with benzodiazepines and/or antipsychotics 8. Severe neurological deficit due to structural or anoxic brain damage 9. Surgical procedures requiring total circulatory arrest Objective Drop Criteria 1. Scheduled for a second surgical procedure during hospital stay 2. Post-operative intubation > 12 hours
Trial Type	Interventional Allocation: Randomized Intervention model: Parallel assignment Blinding: Clinicians blinded to intervention, subject blinded to intervention, primary outcome assessor blinded to intervention Assignment: Parallel

	Primary purpose: Prevention
Date of First Enrollment	March, 2017
Target Sample Size	Recruiting until 370 patients receive the study intervention on Post Operative Day 0.
Recruitment Status	Enrolling
Primary Outcome(s)	Outcome name: Incidence of postoperative delirium Method of measurement: The Long Confusion Assessment Method Time points of interest: Postoperative day 1
Key Secondary Outcomes	Outcome name: ICU and hospital delirium/coma-free days Method of measurement: Delirium assessment with: The Long Confusion Assessment Method Time points of interest: Up until postoperative day 3 if no delirium. Up until postoperative day 5 if delirium exhibited but resolved. Up until postoperative day 7 or discharge if delirium unresolved by postoperative day 5. Outcome name: Severity of Delirium Method of measurement: The Long Confusion Assessment Method Time points of interest: Up until postoperative day 3 if no delirium. Up until postoperative day 5 if delirium exhibited but resolved. Up until postoperative day 7 or discharge if delirium unresolved by postoperative day 5. Outcome name: Date of Hospital Discharge / Length of Hospital Stay Method of measurement: Medical record review

Time points of interest: Up until hospital discharge

Outcome name: 30-day, 90-day, and 180-day mortality

Method of measurement: Medical record review

Time points of interest: 30 days, 90 days and 180 days postoperatively

Outcome name: Postoperative cognitive status

Method of measurement: Abbreviated Montreal Cognitive Assessment, 3D-CAM and PROMIS-29 applied cognition abilities questionnaire

Time points of interest: 30 days, 90 days and 180 days postoperatively

Outcome name: Postoperative health related quality of life

Method of measurement: PROMIS-29 physical function, global health, pain interference questionnaires, and sleep questionnaire

Time points of interest: 30 days, 90 days and 180 days postoperatively

Authors' contributions: Authorship for this trial will be given to key personnel involved in trial design, recruitment, data collection, and data analysis. There are no publication restrictions and no professional writers will be involved in the generation of the manuscript. KTS, JQ, GC, HD, JAG, EYH, LEH, TTH, RI, KJP, and OA were responsible for conceptualizing trial design. JQ managed patient safety protocol. EYH, JAG, RI, and LH were responsible for recruitment, enrolment, and data collection. KTS, JQ, FB, ENB, GC, DAD, HD, AD, JAG, EYH, LEH, TTH, RI, ML, KJP, SS, GT, MBW, and OA have critically revised the MINDDS protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the MINDDS trial.

Conflict of interest statement: OA and ENB have a provisional patent application describing the use of alpha-2 agonists for promoting N3 sleep. All other authors have no interests to declare.

ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES

Principal Investigator:
Oluwaseun Akeju, M.D., M.M.Sc.

Responsibilities include: design and conduct of the MINDDS trial, preparation of protocol and revisions, organization of steering committee meetings, and publication of trial reports.

Steering Committee:

Oluwaseun Akeju, M.D., MMSc
Federico Bilotta, MD
Alan DiBiasio, Pharm.D
Tim Houle, Ph.D
Gaston Cudemus, M.D.
Marco L Loggia, Ph.D.
Kara Pavone, B.SN., R.N
Jason Qu, M.D.
Shahzad Shaefi, M.D., MPH
Ken Shelton, M.D.
Brandon M Westover, M.D., Ph.D.

Responsibilities include: agreement of final protocol, reviewing progress of trial and if necessary, conducting changes to the protocol, coordinating with principal investigator, and communicating with trial management committee.

Trial Management Committee:
Oluwaseun Akeju, M.D, M.M.Sc.
Tim Houle, Ph.D.
Lauren E Hobbs, M.S.
Reine Ibala, B.S.
Eunice Hahm, B.S.
Jacob Gitlin, B.S.
Kara Pavone, B.S.N, R.N.
Jason Qu, M.D.
Ken Shelton, M.D.

Responsibilities include: trial planning, organization of steering committee meetings, reporting SAEs (Serious Adverse Events) to Partners Healthcare IRB (Institutional Review Board), maintaining REDCap electronic database, reporting to steering committee, conducting data verification, recruitment, randomization, and follow-up of trial participants

Data Management Committee:
Hao Deng, M.D., M.P.H.
Tim Houle, Ph.D.

Responsibilities include: statistical design of trial, data verification.

Data Adjudication Committee:
Oluwaseun Akeju, M.D., M.M.Sc.
Shahzad Shaefi, M.D., MPH

Brandon M Westover, M.D., Ph.D.

Responsibilities include: regularly reviewing delirium assessments, contacting trial management committee, retraining researchers if necessary.

Data and Safety Monitoring Committee:
Wie Chao, M.D., Ph.D. - University of Maryland School of Medicine
Jesse Ehrenfeld, M.D.,M.P.H. -Vanderbilt University Medical Center
Michael Gropper, M.D., Ph.D. - University of California San Francisco
Keith A. Jones, M.D. - The University of Alabama at Birmingham

Responsibilities include: reviewing and evaluating the trial data to ensure participant safety, trial conduct, progress, and efficacy, and making recommendations regarding the continuation, modification, and termination of the trial.

Abstract

Introduction: Delirium, which is prevalent in post cardiac surgical patients, is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder. The pathophysiology of delirium remains poorly understood. However, basic science and clinical studies suggest that sleep disturbance may be a modifiable risk factor for the development of delirium. Dexmedetomidine is a α2a adrenergic receptor agonist medication that patterns the activity of various arousal nuclei similar to sleep. A single nighttime loading dose of dexmedetomidine promotes non-rapid eye movement sleep stages N2 and N3 sleep. This trial hypothesizes dexmedetomidine-induced sleep as pre-emptive therapy for postoperative delirium.

Methods and Analysis: The MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial is a 370-patient block-randomized, placebo-controlled, double-blinded, single-site, parallel-arm superiority trial. Patients over 60 years old, undergoing cardiac surgery with planned cardiopulmonary bypass, will be randomized to receive a sleep inducing dose of dexmedetomidine or placebo. The primary outcome is the incidence of delirium on postoperative day 1, assessed with the Confusion Assessment Method by staff blinded to the treatment assignment. To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 370 patients receive the study intervention on post-operative day 0. Secondary outcomes will be evaluated by in-person assessments and medical record review for in-hospital end points, and by telephone interview for 30-day, 90-day, and 180-day end points. All trial outcomes will be evaluated using an intention-to-treat analysis plan. Hypothesis testing will be performed using a two-sided significance level (type I error) of α=0.05. Sensitivity analyses using the actual treatment received will be performed and compared with the intention-to-treat analysis results.

Additional sensitivity analyses will assess the potential impact of missing data due to loss of follow-up.

Ethics and dissemination: The Partners Human Research Committee approved the MINDDS trial. Recruitment began in March 2017. Dissemination plans include presentations at scientific conferences, scientific publications, and popular media.

Registration details: NCT02856594.

Strengths and limitations

- The treatment protocol is based on a plausible biological mechanism suggesting that biomimetic sleep may reduce the incidence of delirium.
- The treatment protocol is straightforward and will allow the results to be generalized to patients across a range of care settings.
- Collection of patient-centered outcomes data, including measures of functional independence, at up to 180-days will provide insight into the relationship between the trial intervention and meaningful patient end points.
- Risk factors and pathophysiological mechanisms of delirium will be explored in separate sub-studies.
- Delirium is a fluctuating disorder that may occasionally be missed despite rigorous and validated assessment methods.

Introduction

Delirium, which is prevalent in post cardiac surgical patients,[1] is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition that is not explained by a preexisting neurocognitive disorder.[2] Although previously reported associations between delirium and increased mortality are debatable,[3] delirium remains a leading cause of preventable morbidity in hospitalized elderly patients.[3 4] The morbidity associated with delirium is estimated to result in increased healthcare costs of approximately $16,000-$64,000 per patient annually. Increasing age and pre-existing cognitive impairment are key predisposing factors for delirium. Despite its impact, there are no definitive pharmacological preventative strategies for delirium. However, basic science and clinical studies suggest that sleep disturbances may be a modifiable risk factor for the development of delirium.

Sleep is a natural occurring state of decreased arousal that is crucial for normal cardiovascular, immune and cognitive function. Sleep deprivation, which is associated with increased pro-inflammatory cytokine levels including interleukin-6,[5-7] precedes the onset of delirium in some patients.[8 9] A recent investigation linking brain activity of microglia, astrocytes, interleukin-6 and delirium in humans,[10] suggests a mechanistic link between sleep deprivation, brain inflammation, and delirium. Further, conditions associated with delirium are characterized by activation of the inflammatory cascade with acute release of inflammatory mediators.[11-25] Increasing age is a significant risk factor for the development of delirium. Notably, aging is associated with activated brain glia cell.[4 26] Following a systemic challenge such as critical illness, these activated glia have been suggested to facilitate an exaggerated neuroinflammatory state that predisposes to delirium.[4 26-28]

Sleep disturbance is a hallmark feature of the postoperative period,[29-33] and pharmacological induction of altered arousal states that are neurophysiologically

indistinguishable from sleep, termed biomimetic sleep, may represent a preventative strategy for the development of postoperative delirium.[34 35] However, commonly administered sedative drugs, most of which modulate the γ amino butyric acid A ($GABA_A$) receptor induce altered arousal states that are neurophysiologically distinct from sleep.[34 35] This neurophysiological distinction from sleep (i.e. frontal beta oscillations, frontal alpha oscillations, burst suppression, isoelectricity)[34-41] may explain why current sedative medications that modulate $GABA_A$ receptors are not delirium sparing. Rather, neural circuit dysfunction in sensory, memory encoding, and cognitive processing circuits may in part explain why these medications are independent risk factors for the development of delirium.[34 42]

Dexmedetomidine is a α2a adrenergic receptor agonist medication that patterns the activity of various arousal nuclei similar to sleep.[43-47] Neurophysiologically, a continuous infusion of dexmedetomidine produces spindle and slow-delta oscillations.[34 39 48] This oscillatory dynamic shares features with non-rapid eye movement (REM) sleep stage N2 sleep.[34 39 49 50] Consistent with the hypothesis that the neurophysiological approximation of sleep may prevent delirium, the dexmedetomidine-infusion N2 sleep stage (with absent non-REM stages N1, N3 and REM sleep) has been associated with a reduced incidence of delirium in critically ill patients.[51-54] Instead of a continuous drug infusion, we recently found that a single nighttime dose of dexmedetomidine preserves normal sleep cycling.[35] This drug administration paradigm promotes non-REM stage N3 sleep. Notably, N3 sleep is associated with improved cognition and synaptic plasticity.[55-63]

A neurophysiologically principled approach to pharmacologically promote sleep may reduce significantly the incidence of delirium in hospitalized patients. The primary objective of the MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial is to evaluate dexmedetomidine-induced sleep as a pharmacological preventative strategy

for delirium, and to characterize the impact of delirium prevention on patient-centered outcomes such as functional recovery. In separate sub-studies, risk factors and pathophysiological mechanisms of delirium will be explored using: 1) unbiased serum metabolic, proteomic, and extracellular vesicular profiling; 2) power spectral analyses of intraoperative and CSICU electroencephalogram dynamics; and, 3) integrated positron emission tomography/magnetic resonance imaging of [^{11}C] PBR28.

Trial objectives

Our primary hypothesis is that dexmedetomidine-induced sleep will result in a reduced incidence of delirium. Our intervention and control groups will be comprised of extubated cardiac surgical intensive care unit (CSICU) patients, because their relative homogeneity in terms of surgical procedures (i.e. cardiac surgery performed on cardiopulmonary bypass), anesthetic management, and systemic inflammatory response represents a unique opportunity to study the mechanisms underlying delirium, while limiting confounding factors that may otherwise be encountered in heterogeneous patients

Methods and analysis

Trial design

We will enroll 370 patients over a period of three years into a randomized, controlled, double-blinded, single-site, parallel-arm superiority trial. Our primary outcome is the incidence of delirium on postoperative day 1 upon administration of the study intervention. To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 370 patients receive the study intervention on post-operative day 0. Trial end points will be assessed via in-person interview (during hospitalization), medical record review, and telephone interview (after hospital discharge). The primary and secondary outcomes of delirium will be assessed via in-person interviews, which will be performed in the

morning and afternoon with approximately 6 hours between interviews. All outcomes, including those obtained post discharge, will be assessed in a blinded fashion.

Eligibility criteria

Inclusion criteria

1. Age ≥ 60
2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for ≥ 24 hours
3. Scheduled same day surgical admission

Exclusion criteria

1. Blindness, deafness or the inability to speak English
2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure
3. Renal and liver failure requiring dialysis or Child-Pugh score > 5
4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness)
5. Previous cardiac surgery within 1 year of surgical procedure
6. Allergy to dexmedetomidine
7. Chronic therapy with benzodiazepines and/or antipsychotics
8. Severe neurological deficit
9. Surgical procedure requiring total circulatory arrest

Objective Drop Criteria

1. Scheduled for a second surgical procedure during hospital stay
2. Postoperative intubation > 12 hours

Baseline assessment

Patients will undergo a pre-randomization assessment that includes a brief medical record review, and evaluation the following:

1. Baseline cognitive function using the abbreviated Montreal Cognitive Assessment
2. Presence of delirium at the time of interview, as measured by the 3-min assessment for Confusion Assessment Method-defined delirium (3D-CAM)
3. Physical function with the PROMIS SF v1.2 -Physical function 8b
4. General health with the PROMIS SF v1.1- Global
5. Pain with the PROMIS SF v1.0- Pain Interference 8a
6. Applied cognition with the PROMIS v1.0- Applied Cognition Abilities SF 8a
7. Baseline sleep quality with the PROMIS-4A

Intervention

We will randomly allocate patients to receive placebo or dexmedetomidine nightly during their CSICU stay. All clinical care during preoperative, intraoperative and postoperative periods will follow normal standard of care. However, trial patients admitted to the CSICU and extubated at least 30 minutes prior to 8.30 PM would receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8.30 PM, but before 2 AM, would receive a sleep induction dose of dexmedetomidine within 30 minutes of extubation. However, throughout the rest of the CSICU stay the sleep induction time will be targeted for 9 PM. Trial patients who are admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU. The maximum dexmedetomidine dose that will be administered at any one instance is 80 mcg. Clinicians will be asked to refrain from routinely administering dexmedetomidine to patients in the operating

room and in the CSICU. Otherwise, all other care decisions will be at the discretion of the clinical care team.

Outcomes

Primary outcome

The primary outcome measure for this trial is the incidence delirium in the CSICU on postoperative day 1. Delirium assessments will be conducted twice daily (AM and PM with at least 6 hours between tests) beginning on postoperative day 1 using the Long Confusion Assessment Method (CAM).[64 65] Trial staff blinded to treatment assignments will perform the delirium assessments. A combination of the 3D-CAM and the abbreviated Montreal cognitive assessment conducted at baseline includes all the cognitive domains that are captured by the long-CAM. Thus, long-CAM results will be benchmarked against these baseline data for delirium scoring (i.e. change from baseline). Patients who elect to withdraw from the study during their hospital stay will be re-approached by the study team within 8-24 hours of study withdrawal. The study team member will elicit the reason for study discontinuation and confirm the withdrawal decision. This visit serves to ensure that the withdrawal decision was made during an informed and non-delirious cognitive state. In the event that a patient finds it difficult to complete an assessment (i.e. pain, clinical intervention), only the long-CAM domains necessary to dispel the presence of delirium will be assessed (i.e. acute onset, inattention, disorganized thinking and altered level of consciousness). Patients who cannot complete this shortened assessment will be re-approached several hours later. Long-CAM assessments for patients who are reintubated for clinical care or for further surgical management will be considered missing data.

Secondary outcomes (in-hospital)

Blinded trial staff will collect secondary outcomes during hospital admission. These outcomes include:

1. ICU and hospital delirium/coma-free days assessed twice daily until postoperative day 3. Delirious patients will be assessed until postoperative day 5. In the event that delirium does not resolve by postoperative day 5, assessments will continue until postoperative day 7 or hospital discharge.
2. Severity of delirium scored using the CAM delirium severity scoring long form
3. Date of hospital discharge and length of hospital stay assessed by chart review
4. Inpatient mortality and major inpatient morbidity assessed by chart review

Secondary outcomes (post-discharge)

Blinded trial staff will collect secondary outcomes via telephone interviews and/or online questionnaires at 30-days, 90-days, and 180-days post procedure. These outcomes include:

1. Cognitive function using the abbreviated Montreal Cognitive Assessment
2. Physical function with the PROMIS SF v1.2 - Physical Function 8b
3. General health with the PROMIS SF v1.1 - Global
4. Pain with the PROMIS SF v1.0- Pain Interference 8a
5. Applied cognition with the PROMIS v1.0 - Applied Cognition Abilities SF 8a
6. Sleep quality with the PROMIS v1.0 - Sleep Disturbance 4A
7. Mortality assessed by chart review, and/or elicited from family member during follow-up calls

Sample size planning

The primary objective of this trial is to detect a difference in the incidence of delirium between the dexmedetomidine-induced sleep and normal care groups. Assuming a delirium event rate of 15%, a type I error of 0.05, and power of 0.90, an n = 184 patients per group will enable us to detect an absolute difference 10% (i.e., 15% versus 5%). With respect to decreased morbidity and healthcare costs, this change represents a clinically meaningful difference. Therefore, we will recruit 370 patients.

Recruitment

This study will be performed at the Massachusetts General Hospital in Boston, MA. Subjects will be recruited through the cardiac surgery preoperative clinic and all enrolled patients will provide written informed consent. Informed consent for this protocol will follow a two-part process. First, a verbal consent will be obtained at the pre-operative visit prior to administering pre-operative baseline questionnaires. During this visit, the trial protocol will be explained to potential participants. In addition, a flyer detailing an overview of the trial protocol, as well as a copy of the formal consent form, will be given to potential trial participants to take home. A study physician will obtain final, written consent on the day of surgery (typically within 14 days of the pre-operative visit). After written consent is obtained, the trial team will allocate a trial identification number to the subject based on the trial stratification schema. A clinical trial pharmacist will perform central allocation into study arms according to the randomization key that is associated with each trial identification number.

Allocation

Eligible patients who provide written informed consent will be randomized to receive either dexmedetomidine or placebo with a 1:1 allocation as per a computer-generated randomization schedule generated by an independent statistician, and stratified by cardiac surgery type (i.e. valvular repair versus non-valvular repair) using permuted blocks of random sizes. The block sizes will not be disclosed until the primary endpoint is analyzed to ensure concealment. Allocation concealment is further ensured by the fact that dexmedetomidine and placebo cannot be distinguished on the basis of appearance. The randomization key that is associated with each participant trial identification number will remain with the clinical trial pharmacist (AD) for the duration of the study. Thus, the clinical trial pharmacist will conduct randomization throughout the study in order to keep the data management team and the statistician blind. All trial medications will be labeled as “dexmedetomidine or placebo,” to

preserve the integrity of randomization assignments. Thus, randomization into any study arm will be conducted without any influence of the study investigators, biostatisticians, and outcome assessors. The CSICU nurse taking care of the patient will administer the trial medication. If other medications are indicated for the treatment of delirium, the treating physician will prescribe this as part of standard clinical care.

Blinding

Assessors who are blind to treatment allocation will conduct all primary and secondary outcome assessments. To maintain the overall quality and legitimacy of the clinical trial, code breaks will occur only in exceptional circumstances when knowledge of the actual treatment is deemed essential by the treating physicians for further management of the patient. The treating physician will be directed to the clinical trial pharmacist to obtain the actual treatment code. The study investigators will maintain blindness and the treatment allocation. Additionally, the treating physician will be directed to abstain from written or verbal disclosure of the code. The principal investigator (PI) will report all code breaks to the DSMB.

Criteria for patient discontinuation

Patients may be discontinued from trial treatment and assessments for several reasons. These include: voluntary discontinuation by the patient, safety reasons (i.e. active hemorrhage) as judged by the clinical and/or trial physicians, failure to maintain study eligibility during the hospital stay or non-compliance with the protocol as judged by the trial physician.

Data analysis

All trial outcomes will be evaluated using a modified intention-to-treat analysis plan. Hypothesis tests will be performed using a two-sided significance level (type I error) of $\alpha=0.05$. Sensitivity analyses using the actual treatment received will also be performed and compared with the intention-to-treat analysis results. Additional sensitivity analyses will be performed to assess the potential impact of missing data due to follow-up losses. The primary outcome will

be evaluated using logistic regression examining the presence or absence of delirium conditional on randomized group assignment. Any randomization imbalances, or other potential treatment effect modifiers will be further examined as covariates in sensitivity analyses. Secondary analyses will be evaluated using tests that are appropriate for the outcomes. We will use Pearson $\chi 2$ tests to compare categorical variables between the 2 trial groups and independent t-tests or Wilcoxon rank-sum tests to compare continuous variables. Time-to-event analyses will be used to compare the effects of dexmedetomidine-induced sleep and normal care on mortality, and CSICU and hospital lengths of stay. Kaplan-Meier survival curves will be used for graphical presentation of these time-to-event analyses, and log-rank statistics will be used to assess the effects of biomimetic sleep and normal care. For mortality analyses, patients will be censored at the time of last contact alive. Censoring for CSICU or hospital discharge readiness analyses will occur at time of death or trial withdrawal. Because missing data rarely occur entirely at random, we will assess the associations between patient characteristics with respect to missing data. If patients with at least one missing outcome value are different from those with complete outcomes data, we will use multiple imputation to assign values to missing data risk factors and outcomes in regression modeling.

Heterogeneity of treatment effects

Subgroup comparisons will be conducted for heterogeneity of treatment–covariate interactions if the sample sizes and numbers of events within these subgroups are sufficient for analysis. If there is a treatment difference together with evidence of heterogeneity, relevant covariates and interaction terms will be added to the relevant regression models for formal significance testing. For the primary outcome, we plan for analyses of treatment effects within pre-specified subgroups potentially defined by:

1. Surgery type

2. Length of cardiopulmonary bypass
3. Presence of significant cardiac dysfunction (ejection fraction less than 35%)
4. Sedative administration in the ICU
5. Opioid administration in the ICU
6. Pain scores
7. Baseline cognitive status
8. Organ failure
9. Postoperative cerebrovascular disease
10. APACHE/EUROscore

Interim analyses

Interim efficacy data will be provided to the Data Safety Monitoring Board (DSMB) during yearly meetings to permit benefit-to-risk assessments. An independent statistician that is unblinded to the treatment allocation will perform the interim-analysis. The statistician will report to the DSMB in a closed session. Thus, the DSMB will have unblinded access to all data to inform recommendations. If at any time during the course of the study the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

Data management

All data collected for the MINDDS trial will be entered into the Massachusetts General Hospital Research Electronic Data Capture (REDCap) application.[66] Data entered into the database will be retrievable for viewing through the data entry applications. Data integrity will be enforced through referential data rules, valid values, range checks, and consistency checks against data already stored in the database. Programs designed to detect missing data or specific errors in the data will be implemented to detect additional errors. These errors will be

summarized along with detailed descriptions for each specific problem in monthly Data Query Reports, which will be sent to the PI. The PI will respond by checking the original forms for inconsistency, checking other sources to determine the correction, modifying the original forms as necessary, and entering a response to the query. Data access will be restricted via password protection to only those individuals who are authorized to work on the trial. Specific privilege assignments within the database will also be employed to limit the types of data that authorized users may access to the minimum required by their role in the trial. Electronic audit trails will be used to capture and record changes to database contents automatically. Original study forms will also be kept in files. Participant files will be stored in numerical order in a secure and accessible place and manner. These files will be maintained in storage for a period of at least 5 years after study completion. Members of the adjudication committee will request a subset of these study forms later for quality control.

Site training

Trial team members have undergone a rigorous CAM training program led by a neuropsychologist and member of the team that created the Long-CAM.[65] The CAM is the most widely used delirium assessment tool in the research setting, with a high sensitivity and specificity when compared with formal psychiatric diagnosis.[64 65] The 3D-CAM is a three-minute assessment tool for delirium, which has good agreement with the CAM.[67] Those who attended this initial training will oversee the training of other team members. All trainees must demonstrate competence at conducting the structured interviews and in correctly scoring subjects. Trainees must first conduct at least two satisfactory CAM assessments in subjects not enrolled in the MINDDS trial in the presence of a trained team member. To establish competency in scoring the CAM, trainees will observe CAM interviews conducted by trained team members and will score the CAM independently. The trainee must agree with the trainer

on the presence or absence of all cognitive features assessed by the CAM on a minimum of six interviews. After meeting the stipulations of training, the newly trained team member will conduct their first interview of a patient enrolled into the MINDDS trial in the presence of a previously trained team member. Independent of the training process, all MINDDS team members who are participating in CAM assessments must view and rate videos of CAM interviews of actors depicting delirious and non-delirious patients.

Data and safety monitoring

All unexpected adverse events that are related to the trial treatment will be recorded in the trial database and reported as required to the Partners Healthcare IRB. A data and safety monitoring board (DSMB) will also oversee the MINDDS trial. The DSMB will provide independent oversight of the MINDDS, and will review general conduct of the trial and trial data for participant safety. The DSMB is comprised of independent, multidisciplinary experts who will make recommendations regarding the continuation, modification, or termination of the trial for harm from intervention. The members will have the requisite expertise to examine accumulating data, to protect the integrity of the clinical experiments to which the patients have consented to participate, and to assure the regulatory bodies, the public and the National Institutes of Health that conflicts of interest do not compromise either patient safety or trial integrity. The DSMB will convene before trial initiation and annually to review safety events. Recommendations from the DSMB for protocol modifications or revisions will be communicated through a representative of the National Institutes on Aging to the PI.

The study operations committee will determine relatedness of an event to the study drug based on a temporal relationship to the study drug administration, whether the event is unexpected given the clinical course, previous medical conditions, and concomitant medications. Adverse events will also be communicated to members of the study steering committee for additional review. Expedited review will occur for all events meeting the FDA

definition of SAEs – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, or event requiring or prolonging inpatient hospitalization. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. For purposes of this study, all SAEs will require reporting to the DSMB. All relevant information will be reported to the DSMB for each SAE, including information about the event and its outcome, dosing history of all study drugs, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by e-mail of all related study forms shall be made to the DSMB within 2 days of the occurrence of any SAE. Information will be reviewed and a determination made of whether there was any possible relevance to the study drug. Additional reporting to the IRB will be done within 24 hours of the SAE. All patients that experience a SAE will be censored from the study at SAE occurrence.

Data Monitoring and Quality Assurance

Reflective of the state of the art in clinical trials, the MINDDS trial will employ a web-based portal for data quality and completeness. The portal will display in real time the following variables for all patients: sex, race, adverse events, study related data etc.

Trial risks

The risk of a breach of confidentiality is small and all possible efforts have been taken to ensure the security of trial data and minimize the risks of accidental disclosure of identifiable data elements. The risks associated with dexmedetomidine are related to drug induced reduction in sympathetic activity, resulting in hypotension and bradycardia. However, cardiovascular parameters are continuously monitored in the CSICU, ensuring that appropriate medical intervention can be instituted in a timely fashion for clinically significant hypotensive or bradycardic episodes. Thus, the risk of clinically significant hypotension or bradycardia in our patient study population is small.

Ethics and dissemination

The Partners Health Care IRB has approved the trial. The trial steering committee will be responsible for all major decisions regarding changes to the protocol. The committee will communicate these changes to the IRB and the DSMB. Electronic data and demographic information will be accessed only as necessary for completion of trial follow-up tasks. The PI has will have access to all data. The primary papers emanating from MINDDS will present primary and secondary outcome. Secondary analyses will also be conducted to construct predictive models for delirium occurrence and resource utilization. Mechanistic manuscripts on the pathophysiology of delirium from sub-studies (i.e. electroencephalogram dynamics, biomarker discovery, brain imaging) will also be published. Dissemination plans include presentations at local, national and international scientific conferences. Every effort will be made to publish results of the MINDDS trial in a peer-reviewed journal. Dissemination of results to trial participants and their family members will be available upon request. Updates and results of the trial will be available to the public at clinicaltrials.gov.

In summary, the MINDDS trial will evaluate a new preemptive therapeutic sleep strategy for the prevention of delirium, and may enable new insights into the pathophysiology of delirium.

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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	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1, 6
	2b	All items from the World Health Organization Trial Registration Data Set	Page 1, 6
Protocol version	3	Date and version identifier	Page 1
Funding	4	Sources and types of financial, material, and other support	Page 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pages 1-6 and 10, 11, 35
	5b	Name and contact information for the trial sponsor	Page 6
	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	N/A
	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)	Pages 10-12, 35

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	Pages 15-17
	6b	Explanation for choice of comparators	Pages 16-17?
Objectives	7	Specific objectives or hypotheses	Page 17
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)	Page 17
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	Page 19, 22
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)	Page 18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 19
	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)	Page 18, 20, 23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 20, 22
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 19-20, 23, 28
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	Pages 20-21
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)	Pages 19-22

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	Page 13,17, 21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 22
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	Pages 19, 22-24
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	Page 22, 23
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 22
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pages 22-23
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 23, 25
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	Pages 19-22, 25-26
	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	Pages 20-21

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	Page 25-26, 28
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	Pages 23-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pages 24-25
	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)	Pages 23-24
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	Pages 27-28
	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	Page 25
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	Pages 27-28
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Pages 27-28
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 29
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)	Pages 27-29

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 22
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 22
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	Page 17, 19, 21, 26, 28
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10
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	Page 29
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	Page 28
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	Page 29
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 10, 35
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 29
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	N/A

*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.

BMJ Open

Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial

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Primary Subject	Intensive care

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Keywords:	Delirium, Biomimetic sleep, Dexmedetomidine, Cardiac surgery < SURGERY, Patient reported outcomes

Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial

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Authors' contributions: Authorship for this trial will be given to key personnel involved in trial design, recruitment, data collection, and data analysis. There are no publication restrictions and no professional writers will be involved in the generation of the manuscript. KTS, JQ, GC, HD, JG, EYH, LEH, TTH, RI, KJP, and OA were responsible for conceptualizing trial design. JQ managed patient safety protocol. EYH, JG RI, and LH were responsible for recruitment, enrolment, and data collection. KTS, JQ, FB, ENB, GC, DAD, HD, AD, JG EYH, LEH, TTH, RI, ML, KJP, SS, GT, MBW, and OA have critically revised the MINDDS protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the MINDDS trial.

Conflict of interest statement: OA and ENB have a provisional patent application describing the use of alpha-2 agonists for promoting N3 sleep. All other authors have no interests to declare.

Abstract

Introduction: Delirium, which is prevalent in post cardiac surgical patients, is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder. The pathophysiology of delirium remains poorly understood. However, basic science and clinical studies suggest that sleep disturbance may be a modifiable risk factor for the development of delirium. Dexmedetomidine is a α2a adrenergic receptor agonist medication that patterns the activity of various arousal nuclei similar to sleep. A single nighttime loading dose of dexmedetomidine promotes non-rapid eye movement sleep stages N2 and N3 sleep. This trial hypothesizes dexmedetomidine-induced sleep as pre-emptive therapy for postoperative delirium.

Methods and Analysis: The MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial is a 370-patient block-randomized, placebo-controlled, double-blinded, single-site, parallel-arm superiority trial. Patients over 60 years old, undergoing cardiac surgery with planned cardiopulmonary bypass, will be randomized to receive a sleep inducing dose of dexmedetomidine or placebo. The primary outcome is the incidence of delirium on postoperative day 1, assessed with the Confusion Assessment Method by staff blinded to the treatment assignment. To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 370 patients receive the study intervention on post-operative day 0. Secondary outcomes will be evaluated by in-person assessments and medical record review for in-hospital end points, and by telephone interview for 30-day, 90-day, and 180-day end points. All trial outcomes will be evaluated using an intention-to-treat analysis plan. Hypothesis testing will be performed using a two-sided significance level (type I error) of $\alpha=0.05$. Sensitivity analyses using the actual treatment received will be performed and compared with the intention-to-treat analysis results. Additional sensitivity analyses will assess the potential impact of missing data due to loss of follow-up.

Ethics and dissemination: The Partners Human Research Committee approved the MINDDS trial. Recruitment began in March 2017. Dissemination plans include presentations at scientific conferences, scientific publications, and popular media.

Registration details: NCT02856594.

Strengths and limitations

- The treatment protocol is based on a plausible biological mechanism suggesting that biomimetic sleep may reduce the incidence of delirium.
- The treatment protocol is straightforward and will allow the results to be generalized to patients across a range of care settings.
- Collection of patient-centered outcomes data, including measures of functional independence, at up to 180-days will provide insight into the relationship between the trial intervention and meaningful patient end points.
- Risk factors and pathophysiological mechanisms of delirium will be explored in separate sub-studies.
- Delirium is a fluctuating disorder that may occasionally be missed despite rigorous and validated assessment methods.

Introduction

Delirium, which is prevalent in post cardiac surgical patients,[1] is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition that is not explained by a preexisting neurocognitive disorder.[2] Although previously reported associations between delirium and increased mortality are debatable,[3] delirium remains a leading cause of preventable morbidity in hospitalized elderly patients.[3 4] The morbidity associated with delirium is estimated to result in increased healthcare costs of approximately $16,000-$64,000 per patient annually. Increasing age and pre-existing cognitive impairment are key predisposing factors for delirium. Despite its impact, there are no definitive pharmacological preventative strategies for delirium. However, basic science and clinical studies suggest that sleep disturbances may be a modifiable risk factor for the development of delirium.

Sleep is a natural occurring state of decreased arousal that is crucial for normal cardiovascular, immune and cognitive function. Sleep deprivation, which is associated with increased pro-inflammatory cytokine levels including interleukin-6,[5-7] precedes the onset of delirium in some patients.[8 9] A recent investigation linking brain activity of microglia, astrocytes, interleukin-6 and delirium in humans,[10] suggests a mechanistic link between sleep deprivation, brain inflammation, and delirium. Further, conditions associated with delirium are characterized by activation of the inflammatory cascade with acute release of inflammatory mediators.[11-25] Increasing age is a significant risk factor for the development of delirium. Notably, aging is associated with activated brain glia cell.[4 26] Following a systemic challenge such as critical illness, these activated glia have been suggested to facilitate an exaggerated neuroinflammatory state that predisposes to delirium.[4 26-28]

Sleep disturbance is a hallmark feature of the postoperative period,[29-33] and pharmacological induction of altered arousal states that are neurophysiologically indistinguishable from sleep, termed biomimetic sleep, may represent a preventative strategy for

the development of postoperative delirium.[34 35] However, commonly administered sedative drugs, most of which modulate the γ amino butyric acid A ($GABA_A$) receptor induce altered arousal states that are neurophysiologically distinct from sleep.[34 35] This neurophysiological distinction from sleep (i.e. frontal beta oscillations, frontal alpha oscillations, burst suppression, isoelectricity)[34-41] may explain why current sedative medications that modulate $GABA_A$ receptors are not delirium sparing. Rather, neural circuit dysfunction in sensory, memory encoding, and cognitive processing circuits may in part explain why these medications are independent risk factors for the development of delirium.[34 42]

Dexmedetomidine is a α2a adrenergic receptor agonist medication that patterns the activity of various arousal nuclei similar to sleep.[43-47] Neurophysiologically, a continuous infusion of dexmedetomidine produces spindle and slow-delta oscillations.[34 39 48] This oscillatory dynamic shares features with non-rapid eye movement (REM) sleep stage N2 sleep.[34 39 49 50] Consistent with the hypothesis that the neurophysiological approximation of sleep may prevent delirium, the dexmedetomidine-infusion N2 sleep stage (with absent non-REM stages N1, N3 and REM sleep) has been associated with a reduced incidence of delirium in critically ill patients.[51-54] Instead of a continuous drug infusion, we recently found that a single nighttime dose of dexmedetomidine preserves normal sleep cycling.[35] This drug administration paradigm promotes non-REM stage N3 sleep. Notably, N3 sleep is associated with improved cognition and synaptic plasticity.[55-63]

A neurophysiologically principled approach to pharmacologically promote sleep may reduce significantly the incidence of delirium in hospitalized patients. The primary objective of the MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial is to evaluate dexmedetomidine-induced sleep as a pharmacological preventative strategy for delirium, and to characterize the impact of delirium prevention on patient-centered outcomes such as functional recovery. In separate sub-studies, risk factors and pathophysiological

mechanisms of delirium will be explored using: 1) unbiased serum metabolic, proteomic, and extracellular vesicular profiling; 2) power spectral analyses of intraoperative and CSICU electroencephalogram dynamics; and, 3) integrated positron emission tomography/magnetic resonance imaging of [^{11}C] PBR28.

Trial objectives

Our primary hypothesis is that dexmedetomidine-induced sleep will result in a reduced incidence of delirium. Our intervention and control groups will be comprised of extubated cardiac surgical intensive care unit (CSICU) patients, because their relative homogeneity in terms of surgical procedures (i.e. cardiac surgery performed on cardiopulmonary bypass), anesthetic management, and systemic inflammatory response represents a unique opportunity to study the mechanisms underlying delirium, while limiting confounding factors that may otherwise be encountered in heterogeneous patients

Methods and analysis

Trial design

Study details including study team roster, organizational structure and responsibilities, are included in the supplementary file. We will enroll 370 patients over a period of three years into a randomized, controlled, double-blinded, single-site, parallel-arm superiority trial. Our primary outcome is the incidence of delirium on postoperative day 1 upon administration of the study intervention. To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 370 patients receive the study intervention on post-operative day 0. Trial end points will be assessed via in-person interview (during hospitalization), medical record review, and telephone interview (after hospital discharge). The primary and secondary outcomes of delirium will be assessed via in-person interviews, which will be performed in the morning and afternoon with approximately 6 hours between interviews. All outcomes, including those obtained post discharge, will be assessed in a blinded fashion.

Eligibility criteria

Inclusion criteria

1. Age ≥ 60
2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for ≥ 24 hours
3. Scheduled same day surgical admission

Exclusion criteria

1. Blindness, deafness or the inability to speak English
2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure
3. Renal and liver failure requiring dialysis or Child-Pugh score > 5
4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness)
5. Previous cardiac surgery within 1 year of surgical procedure
6. Allergy to dexmedetomidine
7. Chronic therapy with benzodiazepines and/or antipsychotics
8. Severe neurological deficit
9. Surgical procedure requiring total circulatory arrest

Objective Drop Criteria

1. Scheduled for a second surgical procedure during hospital stay
2. Postoperative intubation > 12 hours

Baseline assessment

Patients will undergo a pre-randomization assessment that includes a brief medical record review, and evaluation the following:

1. Baseline cognitive function using the abbreviated Montreal Cognitive Assessment
2. Presence of delirium at the time of interview, as measured by the 3-min assessment for Confusion Assessment Method-defined delirium (3D-CAM)
3. Physical function with the PROMIS SF v1.2 -Physical function 8b
4. General health with the PROMIS SF v1.1- Global
5. Pain with the PROMIS SF v1.0- Pain Interference 8a
6. Applied cognition with the PROMIS v1.0- Applied Cognition Abilities SF 8a
7. Baseline sleep quality with the PROMIS-4A

Intervention

We will randomly allocate patients to receive placebo or dexmedetomidine nightly during their CSICU stay. All clinical care during preoperative, intraoperative and postoperative periods will follow normal standard of care. However, trial patients admitted to the CSICU and extubated at least 30 minutes prior to 8.30 PM would receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8.30 PM, but before 2 AM, would receive a sleep induction dose of dexmedetomidine within 30 minutes of extubation. However, throughout the rest of the CSICU stay the sleep induction time will be targeted for 9 PM. Trial patients who are admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU. The maximum dexmedetomidine dose that will be administered at any one instance is 80 mcg. Clinicians will be asked to refrain from routinely administering dexmedetomidine to patients in the operating room and in the CSICU. Otherwise, all other care decisions will be at the discretion of the clinical care team.

Outcomes

Primary outcome

The primary outcome measure for this trial is the incidence delirium in the CSICU on postoperative day 1. Delirium assessments will be conducted twice daily (AM and PM with at least 6 hours between tests) beginning on postoperative day 1 using the Long Confusion Assessment Method (CAM).[64 65] Trial staff blinded to treatment assignments will perform the delirium assessments. A combination of the 3D-CAM and the abbreviated Montreal cognitive assessment conducted at baseline includes all the cognitive domains that are captured by the long-CAM. Thus, long-CAM results will be benchmarked against these baseline data for delirium scoring (i.e. change from baseline). Patients who elect to withdraw from the study during their hospital stay will be re-approached by the study team within 8-24 hours of study withdrawal. The study team member will elicit the reason for study discontinuation and confirm the withdrawal decision. This visit serves to ensure that the withdrawal decision was made during an informed and non-delirious cognitive state. In the event that a patient finds it difficult to complete an assessment (i.e. pain, clinical intervention), only the long-CAM domains necessary to dispel the presence of delirium will be assessed (i.e. acute onset, inattention, disorganized thinking and altered level of consciousness). Patients who cannot complete this shortened assessment will be re-approached several hours later. Long-CAM assessments for patients who are reintubated for clinical care or for further surgical management will be considered missing data.

Secondary outcomes (in-hospital)

Blinded trial staff will collect secondary outcomes during hospital admission. These outcomes include:

1. ICU and hospital delirium/coma-free days assessed twice daily until postoperative day 3. Delirious patients will be assessed until postoperative day 5. In the event that delirium does not resolve by postoperative day 5, assessments will continue until postoperative day 7 or hospital discharge.
2. Severity of delirium scored using the CAM delirium severity scoring long form
3. Date of hospital discharge and length of hospital stay assessed by chart review

4. Inpatient mortality and major inpatient morbidity assessed by chart review

Secondary outcomes (post-discharge)

Blinded trial staff will collect secondary outcomes via telephone interviews and/or online questionnaires at 30-days, 90-days, and 180-days post procedure. These outcomes include:

1. Cognitive function using the abbreviated Montreal Cognitive Assessment
2. Physical function with the PROMIS SF v1.2 - Physical Function 8b
3. General health with the PROMIS SF v1.1 - Global
4. Pain with the PROMIS SF v1.0- Pain Interference 8a
5. Applied cognition with the PROMIS v1.0 - Applied Cognition Abilities SF 8a
6. Sleep quality with the PROMIS v1.0 - Sleep Disturbance 4A
7. Mortality assessed by chart review, and/or elicited from family member during follow-up calls

Sample size planning

The primary objective of this trial is to detect a difference in the incidence of delirium between the dexmedetomidine-induced sleep and normal care groups. Assuming a delirium event rate of 15%, a type I error of 0.05, and power of 0.90, an n = 184 patients per group will enable us to detect an absolute difference 10% (i.e., 15% versus 5%; Table 1). With respect to morbidity and healthcare costs, any observable decrease in delirium rates is clinically meaningful. Therefore, we will recruit 370 patients.

Recruitment

This study will be performed at the Massachusetts General Hospital in Boston, MA. Subjects will be recruited through the cardiac surgery preoperative clinic and all enrolled patients will provide written informed consent. Informed consent for this protocol will follow a two-part process. First, a verbal consent will be obtained at the pre-operative visit prior to administering pre-operative baseline questionnaires. During this visit, the trial protocol will be

explained to potential participants. In addition, a flyer detailing an overview of the trial protocol, as well as a copy of the formal consent form, will be given to potential trial participants to take home. A study physician will obtain final, written consent on the day of surgery (typically within 14 days of the pre-operative visit). After written consent is obtained, the trial team will allocate a trial identification number to the subject based on the trial stratification schema. A clinical trial pharmacist will perform central allocation into study arms according to the randomization key that is associated with each trial identification number.

Allocation

Eligible patients who provide written informed consent will be randomized to receive either dexmedetomidine or placebo with a 1:1 allocation as per a computer-generated randomization schedule generated by an independent statistician, and stratified by cardiac surgery type (i.e. valvular repair versus non-valvular repair) using permuted blocks of random sizes. The block sizes will not be disclosed until the primary endpoint is analyzed to ensure concealment. Allocation concealment is further ensured by the fact that dexmedetomidine and placebo cannot be distinguished on the basis of appearance. The randomization key that is associated with each participant trial identification number will remain with the clinical trial pharmacist (AD) for the duration of the study. Thus, the clinical trial pharmacist will conduct randomization throughout the study in order to keep the data management team and the statistician blind. All trial medications will be labeled as “dexmedetomidine or placebo,” to preserve the integrity of randomization assignments. Thus, randomization into any study arm will be conducted without any influence of the study investigators, biostatisticians, and outcome assessors. The CSICU nurse taking care of the patient will administer the trial medication. If other medications are indicated for the treatment of delirium, the treating physician will prescribe this as part of standard clinical care.

Blinding

Assessors who are blind to treatment allocation will conduct all primary and secondary outcome assessments. To maintain the overall quality and legitimacy of the clinical trial, code breaks will occur only in exceptional circumstances when knowledge of the actual treatment is deemed essential by the treating physicians for further management of the patient. The treating physician will be directed to the clinical trial pharmacist to obtain the actual treatment code. The study investigators will maintain blindness and the treatment allocation. Additionally, the treating physician will be directed to abstain from written or verbal disclosure of the code. The principal investigator (PI) will report all code breaks to the DSMB.

Criteria for patient discontinuation

Patients may be discontinued from trial treatment and assessments for several reasons. These include: voluntary discontinuation by the patient, safety reasons (i.e. active hemorrhage) as judged by the clinical and/or trial physicians, failure to maintain study eligibility during the hospital stay or non-compliance with the protocol as judged by the trial physician.

Data analysis

All trial outcomes will be evaluated using a modified intention-to-treat analysis plan. Hypothesis tests will be performed using a two-sided significance level (type I error) of $\alpha=0.05$. Sensitivity analyses using the actual treatment received will also be performed and compared with the intention-to-treat analysis results. Additional sensitivity analyses will be performed to assess the potential impact of missing data due to follow-up losses. The primary outcome will be evaluated using logistic regression examining the presence or absence of delirium conditional on randomized group assignment. Any randomization imbalances, or other potential treatment effect modifiers will be further examined as covariates in sensitivity analyses. Secondary analyses will be evaluated using tests that are appropriate for the outcomes. We will use Pearson $\chi 2$ tests to compare categorical variables between the 2 trial groups and independent t-tests or Wilcoxon rank-sum tests to compare continuous variables. Time-to-event analyses will be used to compare the effects of dexmedetomidine-induced sleep and normal

care on mortality, and CSICU and hospital lengths of stay. Kaplan-Meier survival curves will be used for graphical presentation of these time-to-event analyses, and log-rank statistics will be used to assess the effects of biomimetic sleep and normal care. For mortality analyses, patients will be censored at the time of last contact alive. Censoring for CSICU or hospital discharge readiness analyses will occur at time of death or trial withdrawal. Because missing data rarely occur entirely at random, we will assess the associations between patient characteristics with respect to missing data. If patients with at least one missing outcome value are different from those with complete outcomes data, we will use multiple imputation to assign values to missing data risk factors and outcomes in regression modeling.

Heterogeneity of treatment effects

Subgroup comparisons will be conducted for heterogeneity of treatment–covariate interactions if the sample sizes and numbers of events within these subgroups are sufficient for analysis. If there is a treatment difference together with evidence of heterogeneity, relevant covariates and interaction terms will be added to the relevant regression models for formal significance testing. For the primary outcome, we plan for analyses of treatment effects within pre-specified subgroups potentially defined by:

1. Surgery type
2. Length of cardiopulmonary bypass
3. Presence of significant cardiac dysfunction (ejection fraction less than 35%)
4. Sedative administration in the ICU
5. Opioid administration in the ICU
6. Pain scores
7. Baseline cognitive status
8. Organ failure
9. Postoperative cerebrovascular disease

10. APACHE/EUROscore

Interim analyses

Interim efficacy data will be provided to the Data Safety Monitoring Board (DSMB) during yearly meetings to permit benefit-to-risk assessments. An independent statistician that is unblinded to the treatment allocation will perform the interim-analysis. The statistician will report to the DSMB in a closed session. Thus, the DSMB will have unblinded access to all data to inform recommendations. If at any time during the course of the study the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

Data management

All data collected for the MINDDS trial will be entered into the Massachusetts General Hospital Research Electronic Data Capture (REDCap) application.[66] Data entered into the database will be retrievable for viewing through the data entry applications. Data integrity will be enforced through referential data rules, valid values, range checks, and consistency checks against data already stored in the database. Programs designed to detect missing data or specific errors in the data will be implemented to detect additional errors. These errors will be summarized along with detailed descriptions for each specific problem in monthly Data Query Reports, which will be sent to the PI. The PI will respond by checking the original forms for inconsistency, checking other sources to determine the correction, modifying the original forms as necessary, and entering a response to the query. Data access will be restricted via password protection to only those individuals who are authorized to work on the trial. Specific privilege assignments within the database will also be employed to limit the types of data that authorized users may access to the minimum required by their role in the trial. Electronic audit trails will be used to capture and record changes to database contents automatically. Original study forms will also be kept in files. Participant files will be stored in numerical order in a secure and

accessible place and manner. These files will be maintained in storage for a period of at least 5 years after study completion. Members of the adjudication committee will request a subset of these study forms later for quality control.

Site training

Trial team members have undergone a rigorous CAM training program led by a neuropsychologist and member of the team that created the Long-CAM.[65] The CAM is the most widely used delirium assessment tool in the research setting, with a high sensitivity and specificity when compared with formal psychiatric diagnosis.[64 65] The 3D-CAM is a three-minute assessment tool for delirium, which has good agreement with the CAM.[67] All CAM assessors will be required to score CAM interview videos depicting delirious and non-delirious patients. Team members that attended the initial CAM training program will oversee the training of new team members. Trainees will be required to observe CAM interviews conducted by previously trained team members, and to agree with the trainer on the presence or absence of cognitive features assessed by the CAM on a minimum of six interviews. Newly trained team members will be required to conduct their first CAM assessment of a MINDDS trial patient in the presence of a previously trained team member.

Data and safety monitoring

All unexpected adverse events that are related to the trial treatment will be recorded in the trial database and reported as required to the Partners Healthcare IRB. A data and safety monitoring board (DSMB) will also oversee the MINDDS trial. The DSMB will provide independent oversight of the MINDDS, and will review general conduct of the trial and trial data for participant safety. The DSMB is comprised of independent, multidisciplinary experts who will make recommendations regarding the continuation, modification, or termination of the trial for harm from intervention. The members will have the requisite expertise to examine accumulating data, to protect the integrity of the clinical experiments to which the patients have consented to

participate, and to assure the regulatory bodies, the public and the National Institutes of Health that conflicts of interest do not compromise either patient safety or trial integrity. The DSMB will convene before trial initiation and annually to review safety events. Recommendations from the DSMB for protocol modifications or revisions will be communicated through a representative of the National Institutes on Aging to the PI.

The study operations committee will determine relatedness of an event to the study drug based on a temporal relationship to the study drug administration, whether the event is unexpected given the clinical course, previous medical conditions, and concomitant medications. They will communicate to adverse events to members of the study steering committee for additional review. The study steering committee will perform expedited reviews for all events that meet the FDAs definition of SAEs. They will also perform expedited reviews for any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, or side effect. All SAEs will be reported to the DSMB along with all relevant event and outcome information. The DSMB will be notified by e-mail within 2 days of the occurrence of any SAE and a formal review will be performed to determine relatedness to the study. Additional reporting to the IRB will be done within 24 hours of the SAE. All patients that experience a SAE will be censored from the study at SAE occurrence.

Data Monitoring and Quality Assurance

Reflective of the state of the art in clinical trials, the MINDDS trial will employ a web-based portal for data quality and completeness. The portal will display in real time the following variables for all patients: sex, race, adverse events, study related data etc.

Trial risks

The risk of a breach of confidentiality is small and all possible efforts have been taken to ensure the security of trial data and minimize the risks of accidental disclosure of identifiable data elements. The risks associated with dexmedetomidine are related to drug induced reduction in sympathetic activity, resulting in hypotension and bradycardia. However,

cardiovascular parameters are continuously monitored in the CSICU, ensuring that appropriate medical intervention can be instituted in a timely fashion for clinically significant hypotensive or bradycardic episodes. Thus, the risk of clinically significant hypotension or bradycardia in our patient study population is small.

Ethics and dissemination

The Partners Health Care IRB has approved the trial. The trial steering committee will be responsible for all major decisions regarding changes to the protocol. The committee will communicate these changes to the IRB and the DSMB. Electronic data and demographic information will be accessed only as necessary for completion of trial follow-up tasks. The PI has will have access to all data. The primary papers emanating from MINDDS will present primary and secondary outcome. Secondary analyses will also be conducted to construct predictive models for delirium occurrence and resource utilization. Mechanistic manuscripts on the pathophysiology of delirium from sub-studies (i.e. electroencephalogram dynamics, biomarker discovery, brain imaging) will also be published. Dissemination plans include presentations at local, national and international scientific conferences. Every effort will be made to publish results of the MINDDS trial in a peer-reviewed journal. Dissemination of results to trial participants and their family members will be available upon request. Updates and results of the trial will be available to the public at clinicaltrials.gov.

In summary, the MINDDS trial will evaluate a new preemptive therapeutic sleep strategy for the prevention of delirium, and may enable new insights into the pathophysiology of delirium.

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Table 1. Numeric Results for Testing Two Proportions using the Z-Test with Unpooled Variance

Target Power	Actual Power	Sample size group 1	Sample size group 2	Total sample size	Proportion group 1	Proportion group 2	Difference between proportions	Alpha
0.80	0.80687	56	56	112	0.01	0.15	0.14	0.05
0.90	0.90131	74	74	148	0.01	0.15	0.14	0.05
0.80	0.80388	69	69	138	0.02	0.15	0.13	0.05
0.90	0.90167	92	92	184	0.02	0.15	0.13	0.05
0.80	0.80183	138	138	276	0.05	0.15	0.10	0.05
0.90	0.90019	184	184	368	0.05	0.15	0.10	0.05
0.80	0.80009	683	683	1366	0.10	0.15	0.05	0.05
0.90	0.90027	915	915	1830	0.10	0.15	0.05	0.05
0.80	0.80010	1106	1106	2212	0.11	0.15	0.04	0.05
0.90	0.90015	1481	1481	2962	0.11	0.15	0.04	0.05
0.80	0.80003	2033	2033	4066	0.12	0.15	0.03	0.05
0.90	0.90006	2722	2722	5444	0.12	0.15	0.03	0.05
0.80	0.80008	4722	4722	9444	0.13	0.15	0.02	0.05
0.90	0.90004	6321	6321	12642	0.13	0.15	0.02	0.05
0.80	0.80001	19458	19458	38916	0.14	0.15	0.01	0.05
0.90	0.90000	26048	26048	52096	0.14	0.15	0.01	0.05

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Primary Registry and Trial Identifying Number	**ClinicalTrials: NCT02856594**
Date of Registration	July 29 2016
Secondary Identifying Numbers	IRB ID#: 2016 P000742
Source(s) of Monetary Support	National Institute on Aging Grant (Award Reference Number R01 AG053582-01)
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Public Title	Protocol for the Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) Trial
Scientific Title	Protocol for the Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) Trial: a Randomized, Double blind, Parallel-arm, Placebo-controlled Clinical Trial

Countries of Recruitment	United States
Health Condition(s) or Problem(s) Studied	Postoperative delirium, predictors of delirium
Intervention(s)	Trial arm 1: Dexmedetomidine-induced Sleep Group (primary intervention) Post cardiac surgical patients admitted to the cardiac surgical intensive care unit (CSICU) and extubated at least 30 minutes prior to 8:30 PM would receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes; maximum administered dose of 80mcg at any one instance) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would receive a sleep induction dose of dexmedetomidine within 30 minutes of extubation. However, throughout the rest of the CSICU stay the dexmedetomidine administration time will be targeted for 9 PM. Trial patients admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU. Trial arm 2: Placebo Control Group. Post cardiac surgical patients admitted to the CSICU and extubated at least 30 minutes prior to 8:30 PM would receive placebo (intravenous normal saline over 40 minutes) at 9 PM every night throughout their CSICU stay. Trial patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would receive the placebo infusion of normal saline within 30 minutes of extubation. However, throughout the rest of the CSICU stay the placebo administration time will be targeted for 9 PM. Trial patients who are admitted to the CSICU and remain intubated past 2 AM will begin trial procedures the following day, assuming they are extubated within 12 hours of admission to the CSICU.
Key Inclusion, Exclusion and Objective Drop Criteria	Inclusion Criteria 1. Age ≥ 60 2. Scheduled for a cardiac surgical procedure with planned postoperative admission to the CSICU for ≥ 24 hours 3. Scheduled same day surgical admission

	Exclusion Criteria 1. Blindness, deafness or the inability to speak English 2. Greater than 2 days of ICU admission in the month preceding the current surgical procedure 3. Renal and liver failure requiring dialysis or Child-Pugh score > 5 4. Follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness) 5. Previous cardiac surgery within 1 year of surgical procedure 6. Allergy to dexmedetomidine 7. Chronic therapy with benzodiazepines and/or antipsychotics 8. Severe neurological deficit due to structural or anoxic brain damage 9. Surgical procedures requiring total circulatory arrest Objective Drop Criteria 1. Scheduled for a second surgical procedure during hospital stay 2. Post-operative intubation > 12 hours
Trial Type	Interventional Allocation: Randomized Intervention model: Parallel assignment Blinding: Clinicians blinded to intervention, subject blinded to intervention, primary outcome assessor blinded to intervention Assignment: Parallel Primary purpose: Prevention
Date of First Enrollment	March, 2017
Target Sample Size	Recruiting until 370 patients receive the study intervention on Post Operative Day 0.
Recruitment Status	Enrolling
Primary Outcome(s)	Outcome name: Incidence of postoperative delirium Method of measurement: The Long Confusion

Key Secondary Outcomes	Assessment Method Time points of interest: Postoperative day 1 Outcome name: ICU and hospital delirium/coma-free days Method of measurement: Delirium assessment with: The Long Confusion Assessment Method Time points of interest: Up until postoperative day 3 if no delirium. Up until postoperative day 5 if delirium exhibited but resolved. Up until postoperative day 7 or discharge if delirium unresolved by postoperative day 5. Outcome name: Severity of Delirium Method of measurement: The Long Confusion Assessment Method Time points of interest: Up until postoperative day 3 if no delirium. Up until postoperative day 5 if delirium exhibited but resolved. Up until postoperative day 7 or discharge if delirium unresolved by postoperative day 5. Outcome name: Date of Hospital Discharge / Length of Hospital Stay Method of measurement: Medical record review Time points of interest: Up until hospital discharge Outcome name: 30-day, 90-day, and 180-day mortality Method of measurement: Medical record review Time points of interest: 30 days, 90 days and 180 days postoperatively Outcome name: Postoperative cognitive status Method of measurement: Abbreviated Montreal Cognitive Assessment, 3D-CAM and PROMIS-29 applied cognition abilities questionnaire Time points of interest: 30 days, 90 days and 180

days postoperatively

Outcome name: Postoperative health related quality of life

Method of measurement: PROMIS-29 physical function, global health, pain interference questionnaires, and sleep questionnaire

Time points of interest: 30 days, 90 days and 180 days postoperatively

ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES

Principal Investigator:
Oluwaseun Akeju, M.D., M.M.Sc.

Responsibilities include: design and conduct of the MINDDS trial, preparation of protocol and revisions, organization of steering committee meetings, and publication of trial reports.

Steering Committee:
Oluwaseun Akeju, M.D., MMSc
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Ken Shelton, M.D.
Brandon M Westover, M.D., Ph.D.

Responsibilities include: agreement of final protocol, reviewing progress of trial and if necessary, conducting changes to the protocol, coordinating with principal investigator, and communicating with trial management committee.

Trial Management Committee:
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Kara Pavone, B.S.N, R.N.
Jason Qu, M.D.
Ken Shelton, M.D.

Responsibilities include: trial planning, organization of steering committee meetings, reporting SAEs (Serious Adverse Events) to Partners Healthcare IRB (Institutional Review Board), maintaining REDCap electronic database, reporting to steering committee, conducting data verification, recruitment, randomization, and follow-up of trial participants

Data Management Committee:
Hao Deng, M.D., M.P.H.
Tim Houle, Ph.D.

Responsibilities include: statistical design of trial, data verification.

Data Adjudication Committee:
Oluwaseun Akeju, M.D., M.M.Sc.
Shahzad Shaefi, M.D., MPH

Brandon M Westover, M.D., Ph.D.

Responsibilities include: regularly reviewing delirium assessments, contacting trial management committee, retraining researchers if necessary.

Data and Safety Monitoring Committee:
Wie Chao, M.D., Ph.D. - University of Maryland School of Medicine
Jesse Ehrenfeld, M.D.,M.P.H. -Vanderbilt University Medical Center
Michael Gropper, M.D., Ph.D. - University of California San Francisco
Keith A. Jones, M.D. - The University of Alabama at Birmingham

Responsibilities include: reviewing and evaluating the trial data to ensure participant safety, trial conduct, progress, and efficacy, and making recommendations regarding the continuation, modification, and termination of the trial.

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	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1, 6
	2b	All items from the World Health Organization Trial Registration Data Set	Page 1, 6
Protocol version	3	Date and version identifier	Page 1
Funding	4	Sources and types of financial, material, and other support	Page 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pages 1-6 and 10, 11, 35
	5b	Name and contact information for the trial sponsor	Page 6
	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	N/A
	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)	Pages 10-12, 35

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	Pages 15-17
	6b	Explanation for choice of comparators	Pages 16-17?
Objectives	7	Specific objectives or hypotheses	Page 17
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)	Page 17
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	Page 19, 22
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)	Page 18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 19
	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)	Page 18, 20, 23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 20, 22
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 19-20, 23, 28
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	Pages 20-21
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)	Pages 19-22

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	Page 13,17, 21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 22
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	Pages 19, 22-24
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	Page 22, 23
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 22
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pages 22-23
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 23, 25
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	Pages 19-22, 25-26
	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	Pages 20-21

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	Page 25-26, 28
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	Pages 23-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pages 24-25
	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)	Pages 23-24
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	Pages 27-28
	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	Page 25
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	Pages 27-28
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Pages 27-28
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 29
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)	Pages 27-29

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 22
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 22
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	Page 17, 19, 21, 26, 28
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10
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	Page 29
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	Page 28
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	Page 29
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 10, 35
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 29
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	N/A

*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.