# Nighttime Dexmedetomidine for Delirium Prevention in Non-Mechanically Ventilated Patients after Cardiac Surgery: The MINDDS Randomized Controlled Trial *(Qu et al.)*

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**DETAILED STUDY PROTOCOL**

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

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## 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] Although the increased mortality rates ascribed to delirium remain debatable, delirium remains a leading cause of preventable morbidity in hospitalized elderly patients. It is also associated with 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 15% 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 power spectral analyses of intraoperative and CSICU electroencephalogram dynamics.

**Table 1** shows a proposed timeline.

| **Table 1: Planned Schedule** | | | | | | |
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| **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 metabolic profiling will be sensitive to detect early signatures of neurodegeneration that predisposes to the development of delirium.

**AIM 3:** Investigate power spectral analyses of intraoperative and CSICU electroencephalogram dynamics.

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 aim to enroll 530 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 postoperative day 0. Thus, 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; (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 deficit due to structural or anoxic brain damage; (9) surgical procedure requiring total circulatory arrest; (10) SARS-CoV-2 positive or SARS-CoV-2-like symptoms (i.e. fever, sore throat, new cough, new nasal congestion or runny nose, muscle aches, new loss of taste or smell, shortness of breath).

**Primary objective drop criteria for patients and controls:** (1) Scheduled for a second surgical procedure during hospital stay; (2) post-operative intubation > 12 hours**;** (3) SARS-CoV-2 positive or SARS-CoV-2-like symptoms (i.e. fever, sore throat, new cough, new nasal congestion or runny nose, muscle aches, new loss of taste or smell, shortness of breath).

**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 or D5W 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 or D5W 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 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 at any one instance. 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, abbreviated Montreal cognitive assessment and PROMIS-4A questionnaires scored at recruitment, 1 month, 3 months, 6 months. The 3-D CAM and TPS questionnaire will be administered at baseline. These questionnaires may be administered via email (RedCap), 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 0·05 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 15%, a type I error of 0·05, and power of 0·90, an n = 185 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 up to 370 patients total who receive the study intervention on postoperative day 0.

## 6. REMUNERATION

Patients will not be compensated for this study.

## 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.

## 10. SUPPLEMENTARY ANALYSIS

In a supplementary analysis data from the MINDDS study will be combined with data and specimens from the **M**aximizing tr**E**atment of **N**eurological **D**ysfunction using **IN**travenous **G**uanfacine (**MENDING**) study in an effort to help determine future routes of study of the alpha2 agonism on delirium and acquired-dementia/Alzheimer's disease and related dementias (ADRD). This collaboration will be established between MGH and Vanderbilt University Medical Center in order to share data and specimens for analysis.

Briefly, the MENDING trial leverages resources from three ongoing NIH-funded trials. Patients in the MENDING trial have been enrolled into one of the ongoing prospective studies through the Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center at Vanderbilt, all of which have daily delirium monitoring and 3- and 12-month cognitive assessments. These include the Illuminating Neuropsychological Dysfunction and Systemic Inflammatory Mechanisms Gleaned After Hospitalization in Trauma-ICU (INSIGHT-ICU) study (R01GM120484, PI: Patel), the Measuring Outcomes of Activity in Intensive Care (MOSAIC) study (K76AG054864, PI: Brummel); and the Bringing to light the Risk factors And Incidence of Neuropsychological dysfunction in ICU Survivors, 2nd (BRAIN-ICU-2) study (R01AG058639, PI: Ely). Patients enrolled into one of these parent observational studies will subsequently be consented for enrollment into the MENDING clinical trial, which evaluates the role of the alpha-2 agonist guanfacine. All study procedures for the MENDING trial at Vanderbilt are covered under their local IRB (Protocol 202000). Additionally, the consent for all MENDING studies includes approval to share data and specimens to evaluate mechanisms and associations with delirium, consistent with the aims of the MINDDS study. Thus, sharing of specimens and data will be consistent with future use described in the informed consent. Data collected from the MENDING study will be used in conjunction with neurocognitive data from the MINDDS study in interpreting the potential of alpha-2 agonism on delirium and ADRD.

All data shared between institutions will be coded so that the collaborating institution cannot identify individual participants. This limited dataset will only include dates (of neurocognitive assessments, admission/discharge) and ages over 89. All other identifiable aspects of data will be removed. No other identifiable information will be shared. If possible a completely deidentified data set will be shared between institutions. Data and specimen sharing will be bi-directional in order to study of the alpha2 agonism on delirium. Appropriate data and material transfer agreements will be obtained between sites prior to sharing of any data or specimens.

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