Pain, Agitation and Delirium (PAD) Protocol in the Duke CICU

NCT02903407

Version dated 10/4/2017 Reviewed by IRB

1. **Protocol Title:**
   Pain, Agitation and Delirium Protocol in Ventilated Patients in the Duke CICU

2. **Purpose of the Study:**
   This study aims to examine the use of protocol directed sedation using the Duke PAD (pain, agitation and delirium) protocol with the current sedation medications of propofol or dexmedetomidine compared to the PAD protocol with midazolam, per CICU usual care, as an initial step toward understanding the best management of sedation in these patients.

   Project Aims
   a. Examine the efficacy of the PAD protocol using propofol or dexmedetomidine versus midazolam with regard to goal sedation, pain control and level of delirium in intubated Duke CICU patients.
   b. Determine differences in duration of ventilator days, CICU stay and total hospital stay with the PAD protocol using propofol or dexmedetomidine compared to midazolam in the Duke CICU.
   c. Compare the rates of adverse effects of the current PAD protocol with propofol or dexmedetomidine versus midazolam for sedation in the Duke CICU, including hypotension, bradycardia, difficulty with ventilator weaning due to sedation, and delirium.

3. **Background and Significance:**
   The optimal approach to management of sedation in the ICU has become a topic of increasing interest. The most recent guidelines outline the pharmacologic mechanisms of commonly used medications as well as scales on which to measure goals of pain, sedation, agitation and delirium in the critically ill patient.[1] This guideline is based on a cadre of randomized controlled trials examining the medications in the medical intensive care unit and post cardiac surgery patients.[2-7] Notably, in each of the trials, patients presenting with acute myocardial infarction, heart failure or cardiogenic shock have been excluded or largely underrepresented.

   Using the current guidelines as a foundation, a new pain, agitation and delirium (PAD) protocol, which prioritizes the use of propofol or dexmedetomidine for sedation, was developed and instituted at Duke University Hospital. However, use of this protocol in the CICU has raised important considerations. Some of these stem from the specific hemodynamic characteristics of the population, including significant bradycardia and hypotension, which can be worsened due to known side effects of propofol and dexmedetomidine. It remains unclear whether the benefits of these medications outweigh the risks in CICU patients as the use of these medications has not been studied previously in this specific population. This study aims to examine the use of protocol directed sedation using the Duke PAD protocol with the current sedation medications of propofol or dexmedetomidine compared to the PAD protocol with midazolam, per CICU usual care, as an initial step toward understanding the best management of sedation in these patients.

4. **Design and Procedures**

   Design
   All patients requiring mechanical ventilation, except for those post cardiac arrest, will be randomized 1:1 in an open label trial design to PAD management under the current Duke PAD protocol (propofol or dexmedetomidine as first line for sedation) versus use of midazolam for

sedation within the PAD protocol. Choice between propofol or dexmedetomidine will be per physician discretion. Each of the medications – propofol, dexmedetomidine and midazolam – are already approved for sedation in patients who are intubated and receiving ICU level care. Both groups may be treated, as needed, with an opiate medication chosen by the provider for analgesia. Patients will be monitored per standard of care in the CICU using the Richmond Agitation and Sedation Scale (RASS) with a set goal sedation level of RASS 0 to -2. Pain will be monitored based on the Critical-Care Pain Observation Tool (CPOT) assessment with goal less than or equal to 2. Delirium will be evaluated based on the Confusion Assessment Method for the ICU (CAM-ICU) with goal of negative or patient's baseline.

Setting
The trial will take place in the Duke Cardiac Intensive Care Unit

Outcomes and Measures
The primary outcome measure will be CICU length of stay. In an open label design, we believe this endpoint will be least subject to biases within the constraints of sample size and budget.

Patients will be monitored for hemodynamic instability, defined as the requirement for up-titration or addition of vasopressor support or transition to an alternative sedation regimen due to hemodynamic intolerance with bradycardia or hypotension. Necessity of vasopressor support and titration of these medications will be documented as will cause for crossover between groups. Heart rate and blood pressure at baseline and use and dose of vasopressor agents prior to starting the randomized treatment assigned will be documented, as will these parameters as collected per CICU protocol.

Secondary end points will include demographics, in-hospital mortality, total hospital length of stay, number of ventilator days, time from decision to extubate to actual extubation, time from withdrawal of sedation to ICU discharge, days alive without delirium or coma, percent of time at goal sedation, occurrence or worsening of delirium, including severity and duration following extubation and need for reintubation.

Data will also be collected for severity of illness stratification using the APACHEII score; interval doses and cumulative amounts of both opioid and sedation medication will be recorded.

5. Selection of Subjects:
All patients admitted to the CICU, who require intubation and sedation for mechanical ventilation that is expected to be >24 hours in duration will be included, unless they meet the specified exclusion criteria. Patients intubated within one hour prior to care transition to the CICU will also be screened for inclusion.

Exclusion criteria include patients following resuscitation from cardiac arrest, patients who have suffered a neurologic event (seizure, stroke) or who have baseline dementia, both of which could limit delirium assessment, patients with child class B and C liver disease, and patients with known allergy to study medications. Patients known to be pregnant, whether by medical record review or knowledge of care team, will not be enrolled.

6. Subject Recruitment and Compensation:
Each patient admitted to the CICU who meets study inclusion criteria will be recruited for participation. The study will be introduced by a member of the participant's health care team and

only once that participant or their next of kin agree to be contacted by the research team will the research team approach the participant about participating in this study. Once agreed, informed consent may obtained by a member of the study team. After informed consent, patients will be randomized to either sedation under the current Duke PAD protocol (propofol or dexmedetomidine as first line for sedation) or to midazolam for sedation within the PAD protocol. The study statistician will generate the randomization sequence using SAS version 9.2 statistical package (SAS Institute, Cary, NC) so that randomization is assigned 1:1 to either arm of the study. Approximately 250 participants will take part in this study at Duke.

Subjects will receive no compensation for participation in the proposed study.

7. **Consent Process**:
   Consent will be obtained from the patient or a legally authorized representative (LAR) if the patient is unable to consent. Informed consent will be completed in a private location and all questions will be answered. Risks and benefits of participation will be outlined. If patient or LAR chooses not to participate, they will continue to receive treatment as per standard of care.

8. **Subject's Capacity to Give Legally Effective Consent:**
   Given our patient population, it is likely that the subject will not have the capacity to give legally effective consent. If the subject is not able to give legally effective consent, study personnel will approach available next of kin for study consent. If next of kin is not available, the potential subject will be excluded from the pool of potential subjects. Subject or next of kin will be provided with study consent, and informed of risks and benefits of study. Subjects who regain cognition during the study will be re-consented if a legally authorized representative originally consented for the subject.

9. **Study Interventions:**
   As a part of this study, patients will be randomized to receive treatment with either the current sedation medications included in the Duke PAD protocol (propofol or dexmedetomidine) versus sedation with midazolam, per CICU usual care. Choice between propofol or dexmedetomidine will be per physician discretion. Each of these medications is already in use clinically for the purpose of sedation in patients who are intubated in the intensive care unit. Thus, none are investigational in nature. However, they have not been compared to each other in this specific treatment group previously. Treatment otherwise will be per usual care. Electronic medical records will be used during the course of the patient's hospitalization to obtain data necessary for secondary outcomes listed above. Participation in study will end when patient is discharged from the hospital and data beyond the index hospitalization will not be utilized for the purpose of this study.

10. **Risk/Benefit Assessment:**
    There are known side effects and risks to the medications to be used in this study. In order to minimize these risks, doses of each medication will be reduced as possible while meeting appropriate sedation based on RASS score.

    It is expected that each of the medications may cause hypotension, respiratory depression and that midazolam may worsen delirium. Standard of care with use of volume management or pressor support will be employed should an individual develop hypotension. All patients participating in

the study will be mechanically ventilated. Delirium precautions and strategies to minimize ICU delirium per usual care will be utilized for all patients.

On rare occasion dexmedetomidine and propofol may also cause bradycardia. Dose reduction strategies will be utilized but in rare cases it may be necessary to support the patient with cardiac pacing, either by transcutaneous or temporary venous pacing. These events will be carefully monitored and will be recorded as 'expected' but reportable adverse events, as they are considered to be anticipated events that may occur during the course of treatment.

Other events that may occur such as that are not routinely associated with treatment with dexmedetomidine, propofol or midazolam, will also be recorded on the Subject Adverse Event Case Report Form and be followed to satisfactory resolution. Both anticipated and unanticipated severe adverse events will be reported to the IRB within 10 working days.

If an individual chooses not to participate in the study, he or she will be treated as per standard of care in the Duke CICU.

Our study represents the first randomized controlled trial between these particular sedation medications in our described patient population. It is possible that we may find that length of time on a ventilator or in the ICU or hospital is shorter with one treatment or the other and that may reflect a clinical benefit to a participant. There are no other known or expected benefits from participating in this study. We hope to obtain data towards the impact of the two sedation regimens on this patient population to better inform treatment decisions in the future.

11. Costs to the Subject:

There will be no costs incurred by the subject related to participation in this study.

12. Data Analysis & Statistical Considerations:

Calculations were performed in order to determine sample size necessary to achieve adequate power for the study based on our primary endpoint of CICU length of stay. From prior literature regarding sedation and length of stay in the ICU with midazolam as the agent for sedation, we estimated a standard deviation of 0.51.[6] Prior studies have used a clinically significant reduction in time of sedation of 15-20%[3,8] and we felt a similar difference in total length of ICU stay was also clinically significant. Using a power of 80% with an alpha of 0.05 and a two-sided test, sample sizes were calculated for a range of relative differences between groups, as seen in Table 1 below. Additionally, we have calculated an estimated duration of enrollment based on average number of intubated and sedated patients who are admitted to our CICU in a given month (Table 1).

Table 1. Sample Sizes to Detect Relative Difference between Groups

Relative difference in ICU LOS between groups	**10%**	**15%**	**20%**	**25%**
Sample Size Required	408	182	102	66
Estimated Duration of	53	24	13	9

Enrollment (months)				

Based on feasibility using these calculations, we propose sample sizes to detect a 20% relative difference between groups and thus a goal of 102 patients per group with estimated duration of enrollment of 13 months. We will reassess sample size and timeline at 6 months and 1 year with the input of our medical safety monitor.

13. Data & Safety Monitoring:

Study endpoints as well as patient demographics, clinical/laboratory characteristics and socioeconomic variables, as well as additional patient clinical information, including but not exclusive to ejection fraction, hemodynamic measurements and in-hospital complications, will be collected. Data will be stored on password-protected computers in a RedCap database with access limited to the PI, designated Key Personnel, and study statistician. With the exception of the study statistician, these individuals will be blinded to treatment assignment.

Dr. Wang (a cardiology faculty member who is not involved in the study) will review interim data for adverse events after 25% and 50% of patients are recruited and have completed assessment of the primary endpoint. Data will be reviewed by group without knowledge of treatment assignment. Dr. Lokhnygina, the unblinded study statistician, will prepare the reports and participate in the review.

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)). The PI will review and sign off on all adverse events and problems and will report them to the IRB in accordance with HRPP policies: within 5 business days for severe AEs and within 24 hours if the AE involves a subject death.

14. Privacy, Data Storage & Confidentiality:

All paper data will be kept secured in a locked cabinet in Dr. Newby's office. The data will be retained until the conclusion of the data analysis, and then destroyed per IRB guidelines. Only the PI and the personnel listed on KP will have access to the paper data.

Data stored in electronic format will be housed in a secure server behind the Duke University Medical Center firewall. Subject data will be extracted and entered into a password-protected and encrypted REDCap database. Only study staff listed as key personnel with the IRB will have access to the REDCap database.

REDCap accounts are stored within the DTMI LDAP server hosted by the Duke Office of Information Technology (OIT). Authentication occurs via the OIT implementation of Kerberos. All connections to the system, both external and internal, occur over encrypted channels. Access to components of the system is role-based and can only be granted by administrators of the system. All collected information is stored on a database server hosted by Duke Health Technology Services (DHTS). The database server resides behind the DHTS internal firewall and

access to the server is controlled via firewall rules. All collected data are backed up daily, both on the local server and by the DHTS enterprise backup system. During data collection, subject identifiers and relevant data elements will be recorded in the database. Then, study-specific identification numbers will be assigned to each subject. Prior to dissemination of any information in this database beyond the DUMC's secure servers or firewall, all identifiers will be stripped from the database and data will only be referenced by the study-specific identification numbers. A master log, which links the study-specific identification number to the study subject, will be generated. The master log will be stored on the same secure network server mentioned in the above paragraph. The database will be destroyed 12 months after analysis of all data and completion of the project.

The adequacy of the Research Data Security Plan (RDSP) will be evaluated and approved by the Cardiology CRU prior to study conduct.

Any publications or presentations that result from this research will not identify any subjects individually and will present data in aggregate form only.

15. References:

1. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013;41(1):263-306.
2. Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med.* 2006;34(5):1326-1332.
3. Hall RI, Sandham D, Cardinal P, et al. Propofol vs midazolam for ICU sedation : a Canadian multicenter randomized trial. *Chest.* 2001;119(4):1151-1159.
4. Huey-Ling L, Chun-Che S, Jen-Jen T, Shau-Ting L, Hsing IC. Comparison of the effect of protocol-directed sedation with propofol vs. midazolam by nurses in intensive care: efficacy, haemodynamic stability and patient satisfaction. *J Clin Nurs.* 2008;17(11):1510-1517.
5. Pandharipande PP, Sanders RD, Girard TD, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. *Crit Care.* 2010;14(2):R38.
6. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA.* 2009;301(5):489-499.
7. Searle NR, Cote S, Taillefer J, et al. Propofol or midazolam for sedation and early extubation following cardiac surgery. *Can J Anaesth.* 1997;44(6):629-635.
8. Jakob, Stephan M., et al. "Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials." *Jama* 307.11 (2012): 1151-1160.