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A. Study Purpose and Rationale

Sedation is integral in caring for critically ill patients. Sedation helps to alleviate the pain and discomfort associated with the ICU including necessary but potentially painful invasive procedures, monitoring devices, catheters and tubing, routine nursing care and prolonged immobility. It helps patients tolerate mechanical ventilation and treats the pain that is associated with the varying illnesses that brought the patient into the ICU (Novaes et al). Currently, the standard recommended sedatives used for the purposes described include lorazepam, a benzodiazepine and fentanyl, an opioid (Jacobi et al). These intravenous medications work by producing anxiolysis, analgesia and sedation (Ostermann et al). However, sedation is not without its disadvantages including the possibility of accumulating doses over time and prolonging ICU stay and thereby contributing to rising health care costs (Koleff et al). Sedating medications have also been shown to contribute to delirium which has been shown to have long term side effects and increased mortality (Ely et al). Many patients, perhaps due to the nature of their disease, their baseline mental status and cerebral function or the intensity of the ICU environment require prolonged or high doses of sedation. In addition to these drawbacks, lorazepam and fentanyl have the potential to cause addiction and physical dependence. In our cognitively intact patients on the wards or in our clinics, we can readily observe the addictive potential of these medications. Many patients ill enough to require ICU level care also require mechanical ventilation. The duration and quantity of the sedation necessary to enable patients to tolerate mechanical ventilation is such that a possible contributor to the difficulty in these patients to wean from sedation may be opioid and benzodiazepine withdrawal. Those patients at highest risk for opioid and benzodiazepine withdrawal include patients whom have been maintained on continuous IV infusion >7 days, received >35 mg lorazepam daily or >5 mg fentanyl daily (Jacobi et al). In fact, during a rotation in the MICU, a relevant observation was made. A patient, whom had suffered a long and protracted course and required multiple medications for sedation including a new medication with a novel mechanism of action called dexmedetomidine, was deemed clinically stable to begin weaning sedation. The first medication titrated off was dexmedetomidine, an IV central alpha2 agonist. Within hours the pt appeared to develop overt signs of opioid withdrawal such as tachycardia, agitation, yawning, piloerection, pupillary dilation, nausea and vomiting. Given the similar mechanism of action of dexmedetomidine to clonidine, it appeared that the patients' opioid withdrawal was being treated with dexmedetomidine or was masking the opioid withdrawal all along. The medication was promptly restarted and pt was eventually successfully weaned from her sedation. This observation prompted the hypothesis that during active weaning of sedation patients may suffer varying degrees of opioid withdrawal. Furthermore, the novel agent dexmedetomidine by its agonist action on alpha2 receptor induces a state of

diminished agitation, analgesia without compromising arousal and respiratory drive and may treat opioid withdrawal. Studies of dexmedetomidine appear to demonstrate a trend toward fewer days on mechanical ventilation but have yet to demonstrate fewer days in ICU (Pandharipande et al). Regardless of this weakness, decreasing days on the ventilator would mean fewer days exposed to mechanical ventilation and its associated risks such as barotrauma with possible pneumothorax and ventilator associated pneumonia. As such, I propose a study to test this medication in patients being weaned from sedation while mechanically ventilated. I predict that patients will be able to be more rapidly weaned from standard sedation medications such as lorazepam and fentanyl with the addition of low dose continuous dexmedetomidine vs. absence of adjunctive dexmedetomidine.

B. Study Design and Statistical Analysis

This is a randomized double blind placebo controlled clinical trial comparing dexmedetomidine as an adjunct for sedation weaning and the existing standard of care for weaning sedation in the medical intensive care unit. In order to explore the possibility that dexmedetomidine in low dose as an adjunct to sedation during sedation weaning will allow for more rapid weaning, each group would need 26 persons to power the study appropriately. Previous studies conducted in this field have looked at various interventions to minimize the duration of time intubated and total time in the ICU. Kress et al published a NEJM study comparing daily interruption of sedation at 48 hours vs. standard of care. The intervention in this study was able to improve the time to extubation from 7.3 to 4.9 days with a RR 1.9. After its publication in 2000, daily interruption of continuous sedative infusions has become standard of care. Therefore the power calculation for the proposed study is based on the number of days to extubation observed in the intervention group of Kress' study, 4.9, with range from 2.5 to 8.6. Based on the unpaired t-test for 80% power, 26 participants in each arm would be required to power this study for a $p=0.05$ to detect statistical significance. At the specified time point of 48 hours, intubated and sedated patients will be randomized to either the intervention group (low dose continuous infusion dexmedetomidine) or the control group (normal saline or placebo). Patients would remain on the low dose dexmedetomidine as other sedatives are weaned as deemed appropriate, not including daily interruption of sedation which would include all continuous infusions in both intervention and treatment arms. When standard sedative infusions are weaned to off and remain off for 1 hour and patient deemed to tolerate this by a RASS score 0 dexmedetomidine infusions can be terminated. Time to extubation, time to ICU discharge, coma-free and delirium-free days during following 12 days would be calculated based on RASS level and CAM-ICU score and compared between groups. The recruitment of 52 ICU patients would likely take 6-12 months. Our medical ICU has 24 beds. Usually at least half of patients in the ICU at a given time point require mechanical ventilation and sedation. Therefore 6-12 months would likely be plenty of time to recruit the appropriate number of patients to detect a significant difference.

C. Study Drug- Dexmedetomidine or Precedex ®

Dexmedetomidine works as a central alpha2 agonist. It is approved for sedation in mechanically ventilated patients. This medication mediates its sedative effects via its actions at the locus ceruleus. It has been studied mostly in post-operative patients and has been shown to spare the respiratory depression that is present with use of other sedatives such as benzodiazepines. I propose that this medication in addition to its use as a sedative, effectively treats or masks opioid withdrawal and therefore may decrease total sedation weaning time, intubation time and ICU length of stay. This medication is a continuous IV infusion. Unlike previous studies that have compared its efficacy as a sedative to other medications, this study will examine its effects on agitation and delirium as an adjunct to standard sedative mediations. For this, I intend to use a low dose infusion such as 0.2- 0.5 mcg/kg/hr. Standard use includes an initial bolus dose 1 mcg/kg/hr with a titration from 0.2 mcg/kg/hr to desired effect, not to exceed 1.5 mcg/kg/hr (Prandharipande et al). Adverse effects include concentration dependent decreases in heart rate, cardiac output and cerebral blood flow. Given the short half life of this medication, resolution of these effects is observed rapidly after the discontinuation of this medication. No known long term side effects have been described.

D. Study Subjects

Inclusion criteria- ICU, intubated and mechanically ventilated for at least 48 hours, maintained on continuous IV sedation up to 48 hours, suitable to be weaned from sedation (off pressors, minimal ventilatory settings)
Exclusion criteria- age <18, hr < 50, acute heart failure, acute coronary event within last 30 days, no plan to wean from sedation for palliative purposes

E. Recruitment of Subjects

Potential study participants will be identified by ICU staff. Health care proxy of potential study participant will be identified and approached by principal invesitgator for inclusion in this study.

F. Confidentiality

Each study participant will be given unique, nondescript identifiers. All identifying patient data will be blinded to investigators and kept confidential and secure. Only research pharmacists will be unblended to patient's treatment arm

G. Potential Conflict of Interest

At this time no industry sponsorship exists and as the sole investigator I have no vested interest in the success of the study drug.

H. Location of Study

In order to abide New York state law, prohibiting research conducted on patients unable to consent themselves, I plan to engage New Jersey Intensivists in this study to avoid my consent difficulties.

I. Potential Risks

Bradycardia has been observed with use of this study drug. In order to minimize this risk, continuous blood pressure, pulse monitoring will continue throughout entirety of sedation wean and discontinuation of study drug will occur for pulse <50. Patients in the treatment arm may be at risk for longer duration on ventilator or longer duration in ICU.

J. Potential Benefits

Treatment of opioid withdrawal and subsequent decreased agitation and improved cognition may lead to decreased time on ventilator or total time in ICU thereby reducing ventilator associated risks such as pneumothorax, ventilator associated pneumonia or ICU associated delirium and other nosocomial infections. In addition to potential benefits for the patient, decreasing ICU length of stay will have more far reaching effects on health care cost and will increase availability of ICU beds.

K. Compensation

At this time no compensation is available to participants

L. Costs

There are no anticipated costs to patients.

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