Research Proposal: w/ drug

Title: A Randomized Double Blinded Placebo Controlled Trial of Transdermal Clonidine for Adjuvant Sedation in Ventilated Trauma Patients Experiencing Delirium.

Authors:

Resident:

Attending:

Pharmacist:

Medical Student:

Introduction:

Obtaining the appropriate level of sedation and analgesia in severely injured trauma patients admitted to the intensive care unit (ICU) can be challenging due the diversity of injuries as well as the breadth of comorbidities present in this population. Injured patients may have neurologic, soft tissue, visceral, vascular, orthopedic or various combinations of these injuries and consequently experience a severe stress and pain response.[1] The multitude of comorbid conditions can range from diabetes, heart disease and hypertension to psychological problems such as depression, anxiety and substance abuse, all of which can affect outcomes.

Clonidine, an antihypertensive medication, is useful for many medical applications due to its sympatholytic properties. Clonidine is a selective alpha-2 agonist that acts on the brain and spinal cord to produce sedation and analgesia.[1] These properties make clonidine a useful adjuvant to traditional analgesics such as opiods and sedatives such as benzodiazepines and propofol.

Multiple prospective randomized trials demonstrate clonidine's physiologic effects and support its clinical efficacy as a sympatholytic agent. Clonidine decreases serum epinephrine, norepinephrine and cortisol as well as heart rate and mean arterial pressure.[2-4] Clonidine effectively blocks the sympathetic response during the treatment of drug withdrawal.[5] Pretreating surgical patients with clonidine decreases myocardial ischemia as well as cardiac lactate production intraoperatively and can reduce postoperative mortality related to cardiac ischemia.[3, 6-8] Preoperative Clonidine administration also decreases the deterioration of renal function postoperatively.[9]

Clonidine's use as an adjuvant to traditional analgesia is also well supported. Preoperative clonidine decreases the narcotic dose required to achieve appropriate surgical analgesia intraoperatively as well as postoperatively.[3, 7, 10] Clonidine also demonstrates analgesic and sedative properties.[11] Clonidine decreases the dose of propofol and anesthetic required for

surgical procedures.[3, 12-16] Although clonidine is not an anxiolytic, clonidine decreased the level of observed anxiety in patients undergoing outpatient surgery in one study.[17]

Clonidine's most prominent adverse effects are bradycardia and hypotension. In the above mentioned studies, no life-threatening hypotension occurred, and all minor hypotensive episodes responded to interventions. Multiple studies have assessed the safety profile of clonidine. Clonidine in a dose of 5mg/kg is safe for elderly patients undergoing sedation.[18] Clonidine has been found safe in head injury patients, with no significant effect on ICPs or CPPs.[19] Clonidine is frequently dosed in transdermal form and this form of clonidine is safe perioperatively.[10, 14]

Dexmedetomidine is an intravenous alpha-2 agonist similar to clonidine available for sedation in the ICU. Dexmedetomidine is well studied in ventilated patients and is both safe and effective for sedation in this population.[20-22] Patients sedated with dexmedetomidine experience less delirium, develop less tachycardia and hypertension and spend less time on the ventilator than those sedated with midazolam.[21] ICU sedation with dexmedetomidine also resulted in less medication induced coma and ICU delirium compared to sedation with lorazepam.[22]

Clonidine has been used in ICUs worldwide as well as our own institution, MUMC Savannah, GA. to achieve appropriate anxiolysis, sedation and sympatholysis in a variety of clinical situations.[23] Delirium is prevalent in the ICU and is a significant source of patient morbidity.[24, 25] Delirium is a treatable condition that responds to medical intervention.[26] A recent study showed a reduction the severity of delirium, improvement in respiratory function, shortened weaning duration and ICU length of stay by treating postoperative aortic surgery patients with intravenous clonidine.[27] Delirium can be accurately assessed by the CAM-ICU scale in ventilated patients in the ICU.[28]

In our experience, ventilator dependant trauma patients frequently fail extubation trials secondary to inappropriate sedation, inadequate analgesia or undertreated delirium. Patients that fail extubation for these reasons have a potentially preventable prolonged ventilator, ICU and hospital course. Clonidine may prove to be effective in decreasing failed extubation trials in these patients. To date, there are no published studies examining the effect of clonidine on extubation efforts in ventilated trauma patients.

Hypothesis:

Primary research hypothesis: Treating ventilated trauma patients in the ICU with the transdermal Clonidine protocol (0.3 mg) will result in a mean reduction of 12 hours (0.5 days) of ventilator support time.

$$H_o: \mu_{\text{Clonidine Vent-Time}} = \mu_{\text{Placebo Vent-time}}$$

Sample Size Estimate:

Samples size was estimated at 60 patients per group, will achieve 90% power to detect a mean difference of 12.0 hours between the null hypothesis that both group means are 264 hours and the alternative hypothesis that the mean of the clonidine group is 252 hours, with an estimated standard deviation of 20 hours (SEE: Devlin, et al. 2010) a significance level (alpha) of 0.05000 using a two-sided two-sample t-test. Interval analysis will be conducted when a total of 50 patients are obtained.

Secondary research hypothesis: Treatment with transdermal clonidine will decrease delirium in trauma patients during their ICU stay.

Methods:

All adult trauma patients admitted to the ICU requiring mechanical ventilation will be evaluated on a daily basis for possible enrollment into the study throughout their ICU course. Only ventilated trauma patients that posses the below inclusion criteria and do not meet any exclusion criteria will be enrolled into the study after informed consent is obtained (see protocol flow chart). Patients requiring mechanical ventilation will not be considered ready for extubation until they meet the institution's criteria for starting a spontaneous breathing trial (SBT). Patients must meet criteria for the institutions SBT protocol, have a documented failed SBT and the diagnosis of delirium as assessed by the CAM-ICU assessment tool to be eligible for the study. Patients must also be considered stable from a neurologic, respiratory and cardiovascular standpoint to potentially receive clonidine as assessed by the attending MD. Patients will then be consented for the study by the PI, sub-PI or a designated MD who is familiar with all study protocols.

Upon enrollment, patients will be randomized using a computer generated program. Drug administration will be the responsibility of the ICU research pharmacist who will remain unblinded. On the days the ICU research pharmacist is unable to administer the drug she will designate an informed substitute who is familiar with the study protocol. Patients enrolled in the treatment group will receive an oral loading dose of clonidine 0.3 mg and placement of a clonidine transdermal system at a dose of 0.3-mg/day (Catapres TTS-3) which will be covered by the supplied overlay patch which will provide blinding. In 12 hours the patient will receive a second and final oral dose of clonidine 0.3mg. The placebo group will receive a placebo oral tablet and the overlay patch only. In 12 hours they will receive a second and final placebo tablet. Physicians and staff will remain blinded with the aid of the transdermal overlay present on both the treatment and placebo groups. A total of 120 patients will be enrolled, 60 patients in each group. An interval analysis will be conducted when a total of 50 patients are obtained. The patients will remain enrolled for a minimum of 7 days and will continue in the study for 14 days if the patient has required mechanical ventilatory support within 24 hours of the 7 day mark. All

patients will be disenrolled in the study after 14 days or upon discharge from the hospital, whichever comes sooner.

Patients will be removed from the study at any point if the attending physician feels that treatment with clonidine may be inappropriate to that patient's care at that time or they develop any of the exclusion criteria. In the event that a patient experiences a known, non-life-threatening reaction or side effect that could relate to the study or study medication, the PI will decide if the patient should be disenrolled from the study or if the patient should continue in the based on the clinical situation and potential harm to the patient. The patient will be treated for any potential reactions. If a patient enrolled in the study should have an adverse event not typically associated with the study drug and the reaction is severe or life-threatening, then the investigator or the attending physician may choose to withdraw the patient from the study. If this occurs, the patient will be withdrawn and unblinded and the IRB notified of the occurrence. If the patient was receiving clonidine and the adverse effect is felt to be caused by this medication then the FDA will be notified of the adverse event. In the event that a physician or staff accidentally becomes unblinded, the PI will decide if the person or persons that have become unblinded will have a significant impact on that patient's management, and if so, the patient will be disenrolled in the study.

All data being collected for use in this study is part of the MHUMC nurse and respiratory therapist charting requirements and no additional physical exams, blood tests or labor is required by MHUMC staff. Ventilator time will be recorded and will be defined by the number of hours the patient must be supported by any type of mechanical ventilator whether it is through an endotracheal tube or through a tracheostomy tube. Successful extubation will be defined as the point a patient is off mechanical ventilation for a period of greater than 24 hours. All patients will be ventilated on the Servo I brand mechanical ventilator and ventilator weaning will be per institution protocol. The prevalence of delirium will be measured by the amount of positive CAM-ICU scores. The ICU staff responsible for assessing and documenting CAM-ICU assessments will each undergo a brief refresher session conducted by the PIs and sub-PIs prior to starting the study. Patients will not receive the CAM-ICU evaluation if their RASS score is -4 to -5. The patient's sedation will be held until the patient reaches a RASS of -3 or greater and then it will be performed. Patients may be treated with as needed with intravenous and oral antipsychotic class medications for delirium as deeded appropriate by the responsible ICU team. The medication and the total daily dose in milligrams of each antipsychotic medication will be recorded. Clonidine, dexmedetomidine or any other alph-2 agonist medications cannot be used in study patients regardless of indication unless that patient is disenrolled from the study to prevent potential drug interactions and overdosing. Mean MAP and heart rate will be recorded twice daily between 0300-0500 and 1500-1700. Hypotension will be defined as a systolic blood pressure (SBP) < 90 or diastolic blood pressure (DBP) < 60 or requirement for vasoactive medications. Bradycardia will be defined as a heart rate (HR) < 60. An interval analysis will be

performed and the study will be terminated if interval analysis of data shows a significant benefit or harm to subjects in the treatment group.

Inclusion Criteria:

1. Ventilated trauma patients 18 years of age or older admitted to the ICU >24h
2. Patients must meet minimal medical criteria for potential extubation (meet criteria for being placed on spontaneous breathing trials per established MUMC SBT protocol)
3. Patients must exhibit delirium as assessed by the CAM-ICU assessment tool
4. Patients must be declared stable from a neurologic, respiratory and cardiovascular standpoint to potentially receive clonidine by the attending MD
5. Consent must be obtainable and fully obtained prior to being entered in the study

Exclusion Criteria:

1. Patients under 18
2. Bradycardia (HR<60)
3. Presence of an active pacemaker
4. Hypotension (<90/60) or active treatment of hypotension with vasoactive medications
5. Patients actively being treated with Clonidine or dexmedetomidine
6. Presence of an allergy to Clonidine
7. Pregnancy

Statistical Analysis:

Primary outcome will be comparison of mean hours of mechanical ventilation times, compared by Student's T-test, and secondary outcomes, with Bonferroni Correction. Multivariate analysis will be used for consideration of factors that may be potential confounders.

Trial Stopping Rules:

The study will be terminated if interim analysis at 50% accrual shows a significant benefit exceeding 15 hours mean decrease in mechanical ventilation time.

Endpoints:

Primary Endpoint: Duration of mechanical ventilation following administration of first dose of clonidine or placebo (days)

Secondary Endpoints:

1. Incidence and duration in hours of delirium (as assessed by the CAM-ICU score currently used)
2. ICU length of stay (days)
3. Time to pass first SBT following administration of first dose of clonidine or placebo(hours)
4. Amount of aniphyscotic class medications used
5. Amount of analgesia required (as morphine equivalent units)
6. Amount of sedation required (as total sedatives given)
7. Mean incidence and duration of delirium (as assessed by daily CAM score currently used)
8. MAP (in mmHg)
9. HR (beats per minute)
10. Anti-hypertensive use
11. Adverse effects (hypotension and bradycardia)

Budget:

1. Cost of placebo pill, clonidine pill, clonidine transdermal system and covers

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