Title: The Effect of Guanfacine on Delirium in Critically Ill Patients

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Location of Study: Research will be conducted at the University of Alabama at Birmingham Hospital and University of Alabama at Birmingham Highlands Hospital. Patients will be recruited in the UAB Surgical Intensive Care Units.

Abstract

Delirium has been identified as a significant problem in the intensive care unit that has been shown to lead to increased hospital and ICU length of stay, increased hospital cost, increased ventilator days, and long-term cognitive disability. The etiology of delirium is multifactorial, however, the elderly critically ill remain at highest risk. Therapy is largely targeted at nonpharmacologic prevention as promising treatments have not been standardized.

One such pharmaceutical treatment is the medication dexmedetomidine. Originally designed as an antihypertensive, dexmedetomidine is a central acting alpha agonist used as a sedation adjunct and has shown to reduce the duration of delirium in the intensive care setting. Guanfacine, a medication with the same mechanism and within the same class as dexmedetomidine, has a more specific sight of action in the frontal lobe and therefore more behavior modification properties. For this reason, guanfacine has been shown to be an effective adjunct therapy in Attention Deficit Hyperactive Disorder and has a secondary FDA approval for its use in that behavior disorder.

One of the hallmark symptoms of delirium is inattention and hyperactive behavior. Given the similarities between delirium and hyperactive disorders, guanfacine has been identified as a potential medication that may be of therapeutic benefit in the treatment of delirium. It is the purpose of this study to investigate the effects of guanfacine on delirium in critically ill patients admitted to the ICU.

Null Hypothesis

The administration of guanfacine in ICU patients with delirium will not reduce the duration of delirium.

Hypothesis

The administration of guanfacine in ICU patients with delirium will reduce the duration of delirium.

Specific Aim

To quantify the duration of delirium in ICU patients treated with guanfacine or placebo.

Trial design

The study will be a prospective, single center, randomized, placebo-controlled, double- blind, intervention trial of guanfacine 2 mg versus placebo in critically ill patients admitted to the ICU with an expected LOS of at least 72 hours. (two arms, 1:1 enrollment, parallel design).

Methods

Inclusion criteria

- Patients admitted to the UAB hospital Surgical Intensive Care Unit (SICU)
- 18 years of age or older

- Expected total ICU length of stay of 72 hours or more per treating physician
- Diagnosed with delirium based on CAM-ICU assessment (see attached CAM-ICU assessment form)

Exclusion Criteria

- Patients younger than 18 years old
- Expected discharge from ICU within 72 hours of admission
- Expected or inevitable death with 48 hours of enrollment
- Pregnancy or breast feeding
- Non-English speaking
- Patients unable to be assessed by CAM-ICU due to neurologic illness
- Altered consciousness unable to participate in CAM-ICU assessment
- Patients with previous diagnosis of chronic, acute, subacute neurologic disease, or neurodegenerative disease
- Mental illness and/or psychosis
- Acute alcohol withdrawal
- No enteral route available for administration
- Treating physician refusal of enrollment based on severe hypotension (defined as requiring a vasopressor for longer than 24 hours) or bradycardia (Hr<50 bpm) at the time of screening
- Hepatic encephalopathy
- Blind or Hearing impaired
- Taking Guanfacine, for any reason
- On CYP3A inhibitor such as azole antifungals or clarithromycin
- On CYP3A inducers such as phenytoin or rifampin
- Severe xerostomia
- Enrolled in another interventional research trial

Intervention

-After patient or family member signs the informed consent

-Patients are enrolled within 48 hours of being diagnosed with delirium

-Randomization to placebo or study drug group on the day of enrollment

-Placebo group will receive pharmaceutical placebo.

-Guanfacine group will receive guanfacine 2 mg enterally via oral route or

nasogastric tube at 21:00 for 14 consecutive nights or until ICU discharge.

-CAM-ICU assessment will be conducted twice daily at am and pm. All data was deidentified and entered in secured RedCap database.

Outcomes

Primary

Duration of delirium

The primary outcome will be the number of days alive without delirium during the 14-day treatment period after randomization. Delirium assessments are measured by the Confusion Assessment Method- Intensive Care Unit (CAM-ICU). CAM-ICU measures a patient's fluctuations in mental status, inattention, disorganized thinking, and consciousness.

All assessors using the CAM-ICU will receive training in the assessment tool along with monitoring to ensure the reliable implementation. The CAM-ICU will be used twice daily with all patients while admitted until ICU discharge. Patients will be diagnosed as delirious when they have at least one positive CAM-ICU on the day of assessment up to ICU discharge or day 14 after enrollment if remaining in ICU. Patients will be diagnosed as delirium free when they have four (4) negative consecutive CAM-ICU assessments. Assessors will be blinded to treatment group.

Secondary

1. Type of delirium or Coma
   Based on patient RASS score, the participants will be categorized as having either hyperactive delirium (RASS >+1) or hypoactive delirium (RASS -3 to 0), Mixed (both hyperactive and hypoactive for the observation period), or Coma (RASS </= -4.
2. Duration of delirium
   Upon diagnosis of delirium, duration will be recorded as number of days of which the enrolled patient has a positive CAM-ICU until ICU discharge or day 14 after enrollment.
3. Delirium Severity
   Assessors will administer the CAM-ICU-7 Delirium Severity assessment.
   Indirect markers of delirium severity will also be recorded daily until ICU discharge or day 14 after enrollment. These markers are: 1) need for anti-psychotics or sedation (total daily doses will be calculated); 2) need for physical restraints; 3) patient removal of intravenous lines, drains or catheters.
4. ICU and hospital LOS
   Length of stay will be recorded using existing hospital data programs.
5. Morbidity and mortality
   Markers of morbidity and mortality will be recorded on a daily basis until ICU discharge or day 14 after enrollment. These include: 1) duration of mechanical ventilation measured as ventilator free days; 2) daily need for vasopressor use; 3)daily need for renal replacement therapy; 4) reintubation, delayed extubation or need for tracheostomy; 5) SOFA scores; In addition we will record 6) mortality at 30 and 90 days; and 7) destination after ICU and hospital discharge.

Analysis

Statistical Analysis. Demographics, such as gender, race, and age, as well as clinical characteristics (such as type of surgery, comorbidities) will be summarized using descriptive statistics. Continuous variables will be summarized using sample mean and sample variance whereas categorical variables will be summarized as proportions. The test of efficacy will follow the rejection region approach detailed in the Sample Size section using a Type I error rate of 0.05. 95% confidence intervals will be used to describe the incidence of delirium within the study population. Logistic regression models will examine whether age, gender, or comorbities associated with incidence of delirium when Guanfacine is administered.

Projected Sample Size. The primary outcome for statistical evaluation is delirium free days, defined as the number of days out of a 14-day period following enrollment. Power analyses are based on this outcome.

Based upon the historical evidence observed in the UAB Surgical ICU, delirium is experienced by approximately 24% of patients during their ICU stay.

All sample size and power estimates below assume a two-group, parallel design with 1:1 allocation ratio. In Table 1, we treat the primary outcome as number of delirium-free days during each patient's LOS.

We consider a range of detectable differences and desired levels of power in Table 1 below. The analysis consists of a two-sample t-test assuming equal variances and evaluation at a 0.05 level of significance. A mean difference of 10% is considered clinically meaningful, with larger differences indicating greater benefit. However, we do not have preliminary data providing reference values for the average and standard deviation of delirium free days in the control population. Thus, we express our detectable differences in terms of standard deviations between the two groups.

A sample size of 50 per group (100 total) will provide 85% power to detect an average proportion of delirium-free days in the treatment group that is at least 0.61 standard deviations different from the average proportion of delirium-free days in the control group.

Table 1. Detectable Δ (standard deviation) with new sample size.

Total(n)	Power	
	80%	85%
100	**0.57**	**0.61**
90	0.60	0.64
80	0.63	0.68