Cognitive Outcomes and NeuroStimulants among the Cerebrally Injured & Obtunded in the United States: The CONSCIOUS Study

Background

Nearly 1.7 million Americans sustain a traumatic brain injury (TBI) each year.[1] While the majority of these injuries are mild and resolve without consequence,[1] some patients experience profound brain damage and become clinically obtunded. This spectrum of diminished consciousness includes a coma (no spontaneous eye opening or response to vigorous stimulation), vegetative state (no awareness of surroundings but demonstrating some spontaneous and stimulus-induced arousal), or minimally conscious state (some level of preservation of self-awareness).[2] Only 50% of patients in a vegetative state regain consciousness at 1 year and roughly 50% of minimally conscious TBI patients remain disabled at 1 year.[3] Fortunately, there is increasing evidence to suggest that consciousness and neurocognition after TBI can be improved by pharmacologic modulation of the dopaminergic, serotonergic, and noradrenergic pathways.[1]

Amantadine is one of the most commonly used medications to treat patients with disorders of consciousness.[3] It is believed to work by increasing extracellular dopamine levels via blocking reuptake and by facilitating synthesis; it is also an N-methyl-D-aspartate (NMDA) agonist.[4] In a single-center double-blinded randomized control trial among 76 patients with mild to severe TBI, amantadine was found to significantly reduce the frequency and severity of irritability (proxy for poor cognitive processing).[5] Giancino et al also prospectively evaluated 181 patients in a vegetative or minimally conscious state during their TBI rehabilitation phase. They found that in patients randomized to receive amantadine versus placebo, there was an accelerated rate of return to consciousness and cognitively mediated behaviors.[3]

Methylphenidate, another popular neurostimulant, inhibits dopamine and norepinephrine transport and reuptake.[6] Whyte et al demonstrated that methylphenidate use during the post-acute recovery phase of a moderate to severe TBI led to improved cognition speed in a small study of 34 patients.[7] Similarly, Willmott and Ponsford demonstrated that methylphenidate at a dose of 0.3 mg/kg twice daily improved cognitive functioning speeds during the inpatient rehabilitation phase among moderate to severe TBI patients.[8]

While these investigations substantiate the use of neurostimulants during rehabilitation or at a distant time following TBI, no pharmacologic intervention has been rigorously shown to augment neurocognition during the acute inpatient hospitalization for TBI.[3,9] Furthermore, there are no consistent guidelines to direct clinicians on medication dosing in TBI patients during the often tenuous time immediately following injury.[1] Therefore, the purpose of this study is to prospectively evaluate the impact of amantadine and methylphenidate on obtunded patients with TBIs when given during the acute phase of their initial hospitalization. We hypothesize that the early use of neurostimulants among TBI patients in a vegetative or minimally conscious state will be associated with greater improvement in neurocognitive outcomes.

Specific Aims

Primary aim: To assess the impact of neuropharmacologic agents administered to obtunded patients with TBIs during the acute, index hospitalization on cognitive outcomes and levels of consciousness.

Secondary aims: To identify a neuropharmacologic regimen (medication(s), dose, frequency, duration) associated with the greatest neurocognitive improvement.

Experimental Design/Methods

We will perform a prospective, observational cohort study of TBI patients who are vegetative or minimally conscious to evaluate the impact of neurostimulant therapy administration during the acute phase immediately following trauma. The critical care team member(s) at each institution will guide TBI care and decide whether to initiate neurostimulant therapy using clinical judgment.

Inclusion Criteria: any patient $\geq$ 18 years who presents with a GCS $\leq$ 8 and demonstrates radiographic evidence of a traumatic brain injury.

Exclusion Criteria: penetrating trauma; patients with any disability related to cognition that predates the TBI, pregnancy, known seizure disorder, prior treatment with a neurostimulant within 30 days, allergy or previous adverse reaction to a neurostimulant

Accordingly, it is possible that some patients will not receive neurostimulants during their admission. Therefore, each center will likely have two groups to observe:

1. Patients receiving neurostimulant therapy*
2. Patients not receiving neurostimulant therapy

*To be included in the neurostimulant therapy group, a patient must receive amantadine and/or methylphenidate and/or modafinil at least 7 days prior to discharge.

Outcomes Measures

A) Primary Outcome: change in cognition and/or consciousness as measured by:
   a. *Glasgow Outcome Score - Extended* (GOS-E)[10,11] — at 28-days or discharge (whichever is sooner); at 3-month follow-up
B) Secondary Outcomes:
   a. *Glasgow Coma Scale* (GCS) and *Disability Rating Scale* (DRS) scores
      i. Weekly until 28-days or discharge (whichever is sooner); at 3-month follow-up
   b. Discharge location, mortality, length of stay (LOS), adverse events

Variables

- Patient: age, gender, race/ethnicity, comorbidities
- Injury: mechanism (MVC, fall, etc.), injury severity score (ISS)
- Initial neurocognitive exam: GCS score, CT brain findings (Marshall classification)
- Hospital course: neurosurgical interventions (craniotomy, craniectomy, etc.), hospital LOS, ICU LOS, ventilator duration, tracheostomy placement, feeding tube placement
- Therapy (if applicable):

    - Neurostimulant(s): amantadine and/or methylphenidate and/or modafinil
    - Time elapsed from injury until administration of neurostimulant
    - Dosage, frequency, duration of neurostimulant (if stopped before discharge)
    - Therapeutic/prophylactic levetiracetam given? Yes/No
    - Use of additional neuromodulating agents? Yes/No
- Adverse events/complications:
    - Medication specific: cardiac arrhythmia, hypertension, tachycardia, seizure
    - In-hospital events: acute kidney injury (AKI), cardiopulmonary arrest, myocardial infarction (MI), pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), sepsis, unplanned admission to ICU, unplanned intubation, unplanned operative intervention, venous thromboembolic event (VTE)
- Outcomes:
    - GOS-E
    - Change in neurocognitive exam (Δ GCS, Δ DRS)
    - Discharge location, LOS, mortality, adverse events

Data Collection and Statistical Analysis

Chi-square tests will be used to compare categorical variables. Wilcoxon rank-sum tests (non-parametric) and Student's t-tests (parametric) will compare continuous variables. Neurostimulant therapy, as well as any confounding variable noted between groups, will be entered into a multivariable linear regression to determine associations with overall change in GCS, DRS, and GOS. Multivariable logistic regression will be used to determined correlations with categorical outcomes (i.e. discharge location, mortality). Data will be reported as adjusted beta coefficients or odds ratios with 95% confidence intervals. Statistical significance will be set at a $p < .05$.

For this study, we will determine the sample size based on change in Glasgow Coma Scale (GCS) score. The smallest improvement in GCS attributed to neurostimulant use that we believe to be clinically meaningful is 1-point. Using a standard deviation of 3 (to account for variability amongst multiple centers), a type I error of 0.05 and type II error of 0.2 (i.e. 80% power), our minimum sample size would need to be at least 71 patients. Nonetheless, we wish to further minimize our type I error to at least 0.025 and type II error to 0.1. With the same standard deviation of 3 and GCS improvement of 1-point, our sample size would increase to 130 patients (which also accounts for a 10% missing data and/or attrition rate).

Consent Procedures

This prospective observational study is designed to record data on patients who will be managed according to a critical care team's best clinical judgment. IRB approval will be obtained at all participating sites and Data Transfer Agreements will be completed when applicable. Data will be collected at each site, will be de-identified, and then entered into a secure RedCap database.

Risk/Benefit

The risk ascribed to this study is no greater than that of the current standard of care in which patients may or may not receive neurostimulant therapy based on a clinician's best judgment. However, if early neurostimulant therapy is identified as advantageous for obtunded patients with TBIs, then significant benefit could result in future evidence-based therapeutics.

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