HonorHealth John C. Lincoln Medical Center

Trauma Services

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Investigator Initiated Clinical Research Protocol

Protocol Title	Prospective Analysis of the Use of N-Acetylcysteine and Vitamins in the Treatment of TBI in Geriatric Patients
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Protocol Summary

Title	Prospective Analysis of the Use of N-Acetylcysteine and Vitamins in the Treatment of TBI in Geriatric Patients
Primary Objectives	Determine improvement in somatic, cognitive, and emotional post-concussion symptoms as measured by the Rivermeade Post-concussion Questionnaire (RPQ) in treatment group vs non-treatment group.
Secondary Objectives	Determine: 1. Glasgow Coma Scale (GCS) each day of admission and time of discharge. 2. Age and sex 3. Admission blood alcohol level 4. Alcohol Use Disorder 5. Admission systemic blood pressure (mm Hg) 6. Brain injury location and status as determined by computed tomography (CT) scans or magnetic resonance imaging (MRI) 7. Presence or absence of intracranial hemorrhage 8. Presence, frequency, and duration of seizures 9. Seizure medication and dose 10. Neurotrauma intervention type 11. Hospital Length of Stay 12. ICU Length of Stay 13. Ventilation Days 14. Complications associated with TBI 15. Discharge destination 16. Hemoglobin A1c level upon admission 17. Total mEq of carbonyl scavenger administered 18. Co-Morbidities 19. Injury Severity Score 20. Mechanism of Injury 21. Ethnicity/Race 22. Loss of consciousness

Study population	Inclusion: Patients age 60 years or older evaluated at HonorHealth John C. Lincoln North Mountain Medical Center or HonorHealth Deer Valley Medical Center by the trauma service, who have a diagnosis of head injury within three hours of presentation to the hospital. Exclusion: ● Patients without TBI ● Patient without clear history of head trauma ● Greater than 3 hours since head trauma event ● Patients with known asthma or atopic dermatitis ● Patients with known kidney disease ● Patient's under the age of 60 years old ● Currently enrolled in an ongoing research study ● Patients, who at baseline prior to the TBI, would not be able to participate in cognitive function testing (aphasia, severe dementia, non verbal; prior to TBI) ● Patients who are unable to tolerate PO medications within 3 hours of sustaining TBI.
Sample Size	60 patients per arm (total 120 patients)
Study Type	Prospective randomized pilot study
Study Design	Prospective analysis

Study Treatment Group	1) Hours 0-3 a. 4 grams PO loading dose of NAC (24.5 mEq carbonyl scavenger) b. Administration of oral multivitamin (Vitamin A 5,000 IU, Vitamin C 90mg, Vitamin D3 400 IU, Vitamin E 60 IU, Vitamin K 28mcg, Vitamin B1 3mg, Vitamin B2 3.4mg, Niacin 20mg, B6 6mg, Folic acid 400mcg, Vitamin B12 12mcg, Biotin 30mcg, Pantothenic acid 10mg, Calcium 40mg, Iron 9mg, Phosphorous 31mg, Iodine 150mcg, Magnesium 100mg, Zinc 15mg, Selenium 70mcg, Copper 2mg, Manganese 2mg, Chromium 50mcg, Molybdenum 75mcg, Chloride 7.5mg, Potassium 7.5mg, Boron 150mcg, Nickel 5mcg, Silicone 2mg, Tin 10mcg, Vanadium 10mcg) + additional 100mg thiamine tablet and 1mg folic acid tablet. c. Check admission magnesium level and replace per facility replacement protocol 2) Hours 18-24 after initial loading dose through post injury day 4 a. 2 grams NAC PO BID (12.25 mEq carbonyl scavenger BID) b. Daily oral multivitamin (if remaining in hospital) c. Check daily magnesium level and replace per facility replacement protocol (if remaining in hospital) 3) Day 5 - 7 a. 1.5 grams NAC PO BID (9.18 mEq carbonyl scavenger BID) b. Daily oral multivitamin (if remaining in hospital) c. Check daily magnesium level and replace per facility replacement protocol (if remaining in hospital) *N-acetyl Cysteine will be administered in liquid form either PO or via nasogastric tube (NGT) if patient has NGT in place for purposes other than delivery of study medications. The liquid NAC that will be used is a 20% solution that has been FDA approved. This liquid can be mixed with beverage of patient's choice in order the make the otherwise undesirable taste of the liquid medication, more palatable. ** This protocol has been adopted from *Amelioration of Acute Sequelae of Blast Induced Mild Traumatic Brain Injury by N-Acetyl cysteine: A Double-Blind, Placebo Controlled Study* published in Plos One on January 23, 2013; https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0054163 ** Enrolled patients will receive between a minimum of 26.34 mEq of carbonyl scavenger to a maximum of 158.96 mEq of carbonyl scavenger, depending on their length of hospitalization.

Study evaluations	Effectiveness of intervention on somatic, cognitive, and emotional post-concussion symptoms as determined by the Rivermeade Post-concussion Questionnaire (RPQ), within 24 hours of admission, post injury day 7, and post injury day 30. Patients who have been discharged prior to post injury day 7 will receive a phone call from a blinded member of the staff who will conduct RPQ-3, and RPQ-13 testing over the phone.
Study period	November 1, 2019- March 31, 2020

1. OBJECTIVE

The primary objective of this study is to determine the effect of supplemental N-acetyl cysteine and additional vitamin therapy on somatic, cognitive, and emotional post-concussion symptoms as determined by the Rivermeade Post-concussion Questionnaire (RPQ) (2,3), within 24 hours of admission, post injury day 7, and post injury day 30. The RPQ questionnaires will be given to patients older than 60 years, who have been evaluated by the HonorHealth John C. Lincoln Medical Center or Deer Valley Medical Center trauma service within 3 hours of sustaining a traumatic brain injury (TBI). Secondary objectives are: (a) correlations with sex, age, presence or absence of intracranial hemorrhage, initial blood alcohol levels, presence to absence of an Alcohol Use Disorder (AUD); (b) correlations with brain injury location and clinical status within 24 hours of admission, post injury day 7, and post injury day 30; (c) presence, frequency, and duration of seizures; (d) Glasgow Coma Scale (GCS) (4) during hospitalization; (5) at discharge; (f) neurotrauma intervention type, (g) hospital length of stay, (h) ICU length of stay, (i) ventilation days, (j) complications associated with TBI, and (k) discharge destination and (l) admission hemoglobin A1c level (m) presenting blood alcohol level and (o) total mEq of carbonyl scavenger administered throughout the patient's enrollment in the study as well as (p) co-morbidities, (q) injury severity score, (r) mechanism of injury,(s) and ethnicity/race,(t) Loss of consciousness

The prospective pilot study will be a randomized, parallel group trial.

2. BACKGROUND/SCIENTIFIC RATIONALE

Traumatic brain injury remains a challenging and complicated disease process to treat, despite the advance of technology used to monitor and guide treatment. Currently the mainstay of treatment is aimed at limiting secondary brain injury by providing interventions targeted at eliminating secondary insults to the already injured neurons, through the help of multiple specialties in the ambulatory, observation, admitted, and critical care settings (6). There is no single drug that can treat secondary brain injury (7), which involves very complex and interdependent biochemical mechanisms. At present, the field is moving in the direction of polypharmacy.

A recent review of the literature reveals that one of the most damaging secondary injury mechanisms is oxidative stress (8,9). During injury, reactive oxygen species (ROS) are generated, particularly in the presence of Fe^{3+} released during hemorrhaging and related hemoglobin degradation mechanisms (10). ROS are not a good target of intervention because ROS are very short-lived, less than milliseconds. However, the secondary products of ROS are longer lived, making them ideal targets for intervention and attenuation of further injury. ROS attack the lipid membrane of cells and their mitochondria via lipid peroxidation mechanisms, readily generating very toxic lipid aldehydes, which can exist for days causing damage to, not only the original injured cell, but neighboring cells as well (11, 12). These lipid aldehydes contain very reactive carbonyl groups, which overwhelm the natural antioxidant

defense mechanisms and form adducts with small and large biomolecules containing accessible nucleophilic atoms, such as N and S (13). These small target biomolecules include many B vitamins, which under oxidative stress such as in TBI, cannot act in their normal role as enzymatic cofactors, but only as carbonyl scavengers, thus resulting in cellular depletion of these key enzymatic cofactors, propagating further cellular dysfunction. Furthermore, the lipidic carbonyl adducts formed with the small biomolecules are excreted from the injured cells, thereby creating cell-localized deficiencies in micronutrients, such as B_2, B_3, B_6, and folic acid, serving to further compound post-injury cellular dysfunction and TBI sequela (14).

The rationale for the study is to use the safe carbonyl scavenger, N-acetylcysteine (NAC) and other water soluble vitamins, to neutralize the reactive carbonyl groups on the lipid aldehydes and effectively replace water soluble micronutrients that are depleted since the moment TBI first occurs. NAC has been selected as the carbonyl scavenger of choice for two reasons. First, NAC is well known to physicians and is well tolerated by patients in the treatment of acetaminophen (paracetamol) toxicity (15). Second, NAC has been shown to be effective in treating symptoms of blast TBI in humans in a 2013 study conducted by the United States Military (16).

For the treatment group, the initial loading dose and subsequent doses of PO NAC has been selected to be the same as the dosage used in the military study published in 2013 titled *Amelioration of Acute Sequelae of Blast Induced Mild Traumatic Brain Injury by N-Acetyl cysteine: A Double Blind, Placebo Controlled Study* over the first 3 hours, when oxidative stress due to the TBI is maximal (16).

It is insufficient to treat oxidative stress in TBI by just neutralizing reactive carbonyl groups found in lipid aldehydes. By the time a patient receives treatment, it is highly likely that the oxidative stress has already caused excretion of essential micronutrients from the injured cells via the formation of adducts, described above, propagating cellular dysfunction. These will have to be replaced. In this particular setting this will be done by daily parenteral administration of an oral multivitamin, a safe preparation of essential B vitamins (described further below) that is familiar to physicians.

Specific B vitamins have been shown to act as carbonyl scavengers under high oxidative stress (14) as a common survival strategy, which is best documented for B_6 vitamers in fungus (Bilski 2000), yeast (Chumnantana, 2005), plants (Chen, 2005), and animals (17). However, the doses used to neutralize all reactive carbonyl groups in animal studies are much higher than the upper tolerable levels for humans for some B vitamins. For example, an estimate of lost B_6 after TBI has been calculated from the amount of a B_6 shown to make a significant difference in specific markers in TBI trials with animals (17-20). The optimal B_6 doses in animal studies range from 300 mg/kg (1.77 mEq/kg, equivalent to 124 mEq for 70 kg patient) to 600 mg/kg (3.54 mEq/kg, equivalent to 248 mEq for 70 kg patient), suggesting that significant amounts of B_6 are acting as carbonyl scavengers before they can resume their normal role as enzymatic cofactors. The high range of mEq of B_6 and other B vitamins (14) needed to improve TBI markers has two implications 1) that physicians have been underestimating the amount of B vitamins lost to oxidative damage caused by TBIs and 2) that an alternative carbonyl scavenger will need to be employed in order to achieve sufficient cellular concentrations to neutralize reactive carbonyl groups formed after TBI without subjecting patients to previously untested high levels of B vitamins, while still allowing standard doses of B vitamins to achieve sufficient cellular concentrations to allow for normal cellular function, even in the face of the massive oxidative insult caused by TBI. Thus, the study opts to fill this void by using NAC, not B vitamins, as the carbonyl scavenger, while simultaneously replacing the B vitamins that are likely to have been lost as a result of the initial injury via daily administrations of an oral multivitamin. If the B vitamins were given in the absence of NAC, the extra B vitamins would likely be “used up” only as carbonyl scavengers and thus not be available for enzymatic cofactor functions. Although it is unusual to test the

efficacy of more than one therapeutic agent at one time, replacement of the lost B vitamins is necessary because the B vitamins serve as enzymatic cofactors in cellular repair mechanisms and in the synthesis of neurotransmitters, such as acetylcholine, GABA, and dopamine, critical for memory, higher seizure threshold, cognition, and other neurological functions. Because the objective of the proposal is to determine the effect of the treatment on somatic, cognitive, and emotional post-concussion symptoms, it is essential to replenish the lost B vitamins by including B vitamins in the treatment.

Another justification for the administration of an oral multivitamin is that prior studies have shown (21), alcohol use is a significant contributing factor to a TBI. Some, but not necessarily all TBI patients may be diagnosed as suffering from Alcohol Use Disorder (AUD) and will typically receive an oral multivitamin upon admission, which includes, 0.84 mEq of total B vitamins. In addition, the treatment group will be supplemented with an oral multivitamin on a daily basis to replenish lost nutrients due to oxidative stress from admission through post injury day 7 or hospital discharge, whichever comes first.

A similar argument is made for magnesium, which has been repeatedly demonstrated to be rapidly excreted after a TBI (27-29). Magnesium is an essential cofactor in neurologic enzymatic reactions that either activate or utilize most B vitamins. Without magnesium, it is pointless to administer B vitamins. Many clinical trials have been carried out using magnesium as the sole therapeutic treatment for TBI with mixed success (30-32), most likely due to the fact that the magnesium is given in the absence of additional B vitamins or other carbonyl scavengers, resulting in lack of cellular ability to utilize available magnesium. To ensure that each TBI patient, in the treatment as well as the non-treatment group, is getting sufficient magnesium, levels will be kept within normal limits per the hospital protocol for magnesium replacement.

In TBI, the most important tools used to assess degree of brain injury and prognosis are exam findings, with the Glasgow Coma Scale (GCS) being the most commonly used synopsis of exam results (3, 4, 33). GCS uses findings of three exam components: eye, verbal, and motor responses, to quantify level of consciousness following TBI, with 3 being the worst defined as deep coma or death, and 15 being the best, a fully awake person. The GCS is computed daily throughout the hospital stay. Another scoring algorithm, the Glasgow Outcome Scale (GOS), divides patients into five categories regarding their likely outcome, with the worse score of 1 for death and the best score of 5 indicating low disability (5). Biligin and colleagues (34) have shown that the GCS is a meaningful predictor of GOS in TBI patients. The outcome assessments of somatic, cognitive, and emotional post-concussion symptoms will be measured by the questionnaire RPQ. RPQ consists of 16 questions, with three that address initial early symptoms of TBI, including headache, dizziness, and nausea, and are termed RPQ-3. Another 13 questions, termed RPQ-13, address the presence or absence of later symptoms, such as depression, poor concentration, and restlessness. Investigators have found that better reliability is achieved by summating the scores into RPQ-3 and RPQ-13, because the questions measure somewhat different constructs (2). Computed tomography (CT) scans or magnetic resonance imaging (MRI) will be used to determine the location and status of the brain injury.

3. EXPERIMENTAL DESIGN AND METHODS

3.1 Study Design

Patients who meet the inclusion and exclusion criteria with be stratified into two groups:

1. Patients who will be offered intervention; These patients include those who are age 60 years or older who present to the John C. Lincoln North Mountain Emergency Department and undergo evaluation by the John C. Lincoln trauma service within 3 hours of obtaining a documented TBI, between the dates of September 1, 2019 and January 1, 2020.
2. Patients who will not be offered intervention.

The study will be a two center, prospective pilot, randomized, parallel-group trial. Patients will be randomized according to the facility to which they present. All patients presenting to HonorHealth John C. Lincoln Medical Center will be offered voluntary enrollment in the treatment group. All patients presenting to HonorHealth Deer Valley will be offered voluntary enrollment in the control group.

Of note, Deer Valley Medical Center is a state level 1 trauma center whereas North Mountain is both a state and ACS level 1 trauma center. Despite these small administrative differences, both North Mountain and Deer Valley are staffed and run by the same group of trauma surgeons and neurointensivists both who employ identical treatment strategies and protocols.

All patients in the treatment group will be given an oral multivitamin upon admission and will be given magnesium per the hospital magnesium replacement protocol for up to 7 days or hospital discharge, whichever comes first.

For the treatment group, the initial loading dose and subsequent doses of PO NAC has been selected to be the same as the dosage used in the military study published in 2013 titled *Amelioration of Acute Sequelae of Blast Induced Mild Traumatic Brain Injury by N-Acetyl cysteine: A Double-Blind, Placebo Controlled Study* over the first 3 hours, when oxidative stress due to the TBI is maximal; Within the first 3 hours of TBI patients will be administered a loading dose of 4g of PO NAC. Days 2-4 patients will be given 2g PO NAC BID, and then days 5-7 patients will be given 1.5g PO NAC BID. Patients will be administered NAC only while they remain in patient status. Administration of NAC will expire on post injury day 7 or discharge, whichever comes first. In addition to an oral multivitamin, given upon admission to all enrolled patients, the treatment group will also receive, for up to 7 days or until hospital discharge, whichever comes first, an oral multivitamin.

To assess the effectiveness of supplemental NAC and extra vitamin therapy on somatic, cognitive, and emotional post-concussion symptoms, and RPQ will be given to the treatment and non-treatment groups by a member of the study personnel within 24 hours of admission, post injury day 7, and post injury day 30, either in the hospital or via telephone if the patient has been discharged.

Members of the RPQ team will receive training on the protocol and study instruments. The RPQ questionnaire will be administered by trained study personnel.
The scores for RPQ-3, RPQ-13 and individual RPQ questions regarding headache, nausea, sleep disturbance, poor concentration, and forgetfulness/poor memory of the treatment group will be compared to the non-treatment group and to similar, normal populations per the literature, using a 95% confidence interval. The effect of supplemental NAC and extra vitamin therapy on other parameters, such as GCS; GOS; presence, frequency, and duration of seizures; length of hospital stay; ICU length of days; and complications associated with TBI, will also be determined by a comparison with the non-treatment group, as a secondary objective of the study.

3.2 Statistical Plan

- We will enlist a statistician to assist in employing the appropriate data analysis.

3.3 Study Outcome Measures

Primary Endpoints:

1. Somatic, cognitive, and emotional post-concussion symptoms as measured by, RPQ-3, and RPQ-13 scores within 24 hours of admission, post injury day 7, and post injury day 30. Patients who have been discharged prior to post injury day 7 will

receive a phone call from a blinded member of the staff who will conduct RPQ-3, and RPQ-13 testing over the phone.

2. The severity of the five most common post TBI symptoms, including headache, nausea, sleep disturbance, poor concentration and forgetfulness/poor memory as measured by the scores of individual questions in the RPQ within 24 hours of admission, post injury day 7, and post injury day 30. In patients who have been discharged prior to the day 7 evaluation will receive a phone call from a blinded member of the staff who will conduct identical questionnaire as the patient would receive if they were still hospitalized.

Secondary Endpoints:

1. Glasgow Coma Scale (GCS) each day of admission and time of discharge.
2. Age and sex
3. Admission blood alcohol level
4. Alcohol Use Disorder
5. Admission systemic blood pressure (mm Hg)
6. Brain injury location and status as determined by computed tomography (CT) scans or magnetic resonance imaging (MRI)
7. Presence or absence of intracranial hemorrhage
8. Presence, frequency, and duration of seizures
9. Seizure medication and dose
10. Neurotrauma intervention type
11. Hospital Length of Stay
12. ICU Length of Stay
13. Ventilation Days
14. Complications associated with TBI
15. Discharge destination
16. Hemoglobin A1c level upon admission
17. Total mEq of carbonyl scavenger administered
18. Co-Morbidities
19. Injury Severity Score
20. Mechanism of Injury
21. Ethnicity/Race
22. Loss of consciousness

3.4 Data Management

All data will be entered into a central database using an electronic case report form. The database is a secure, web-based informatics system that is password protected. Only the research team will have access to the raw data.

3.5 Provisions to Protect the Privacy Interests of Subjects

All data will be collected only after obtaining informed consent from the study participant. Collected data will then be entered into a central database using an electronic case report form. The database is a secure, web-based informatics system that is password protected. Only the research team will have access to the raw data.

3.6 Provisions to Maintain the Confidentiality of Data

All extracted data from the medical record will be de-identified. A study number will be used when referring to patients. A separate correlation tool will be kept that links protected health information with study number. This will be stored in a password protected electronic database and only the research team will have access. Specific information that will be accessed include: history of present illness, physical examination findings, neurologic scale scores, laboratory findings, radiographic studies, and progress notes.

3.7 Research Setting

HonorHealth John C. Lincoln Medical Center

HonorHealth Deer Valley Medical Center

3.8 Consent Process

All patients who will be enrolled in this study will give written informed consent. The consent is an ongoing process throughout the entire study. These patients include those who are age 60 years or older who present to HonorHealth John C. Lincoln or Deer Valley emergency department and undergone evaluation by the HonorHealth trauma service within 3 hours of obtaining a documented TBI, between the dates of September 1, 2019 and January 1, 2020 who are able to provide informed consent for themselves or who have a Legally Authorized Representative (LAR) available to provide consent for them.

4. STUDY POPULATION

4.1 Patient Identification

Patients meeting inclusion/exclusion criteria will be identified and offered participation in our study. Those meeting inclusion/exclusion criteria who opt for participation in our study will be either offered the supplemental treatment (Honorhealth John C Lincoln Medical Center) and subjects at Honorhealth Deer Valley Medical Center will comprise the control group and will be treated with standard care for TBI without NAC/vitamins.

2. Sample Size

60 subjects at Honorhealth John C L Lincoln Medical Center and 60 subjects at Honorhealth Deer Valley

3. Inclusion Criteria

Patients who will be offered NAC/Vitamin intervention; These patients include those who are age 60 years or older who present to the John C. Lincoln North Mountain emergency department and undergone evaluation by the John C. Lincoln trauma service within 3 hours of obtaining a documented TBI, between the dates of September 1, 2019 and January 1, 2020.

Patients who will not be offered intervention but treated with standard of care for TBI; These patients include those who are age 60 years or older who present to the Deer Valley emergency department and undergone evaluation by the trauma service within 3 hours of obtaining a documented TBI, between the dates of September 1, 2019 and January 1, 2020.

4. Exclusion Criteria

- Patients without TBI
- Patients with a history of TBI greater than 3 hours prior to presentation
- Patient's under the age of 60 years old
- Currently enrolled in an ongoing research study
- Patients who at baseline prior to the TBI, cannot participate in cognitive function testing (aphasia, severe dementia, non verbal; prior to TBI)
- Patients who are unable to tolerate PO medications within 3 hours of sustaining TBI.

5. Withdrawal of Subjects

- Those who have been previously included in the study who later wish to opt out of the study.
- Patients in whom their primary medical team feels has developed an adverse reaction to any of the medications being administered in the study will be immediately withdrawn (with documentation and inclusion in later statistical analysis as having to have been withdrawn for adverse reaction) and all potentially offending medications discontinued. At the investigators discretion, any subject can be withdrawn for any reason.

6. Resources Available

- Pharmacy support – for the preparation and administration of supplemental therapy (NAC, vitamin B complex, oral multivitamin, magnesium replacement protocol)

5. RISK/BENEFIT ASSESSMENT

5.1 Potential Risks

For the Acetadote oral N-acetylcysteine Formulation, the potential risks for the treatment group are the same as those risks associated with NAC treatment for acetaminophen toxicity. The most common, albeit rare, adverse effect is an anaphylactoid reaction,

usually manifested by rash, wheeze, or mild hypotension. (35,36) Rarely, severe life-threatening reactions may occur in predisposed individuals, such as patients with asthma or atopic dermatitis, and may be characterized by respiratory distress, facial swelling, and even death (37). Most adverse reactions occur within the first 15 minutes of NAC administration; thus, all patients will be monitored carefully during this time period.

For the extra vitamins in the treatment group, rare cases of anaphylaxis may be seen, as with any medication; therefore, appropriate precautions will be taken

5.2 Potential Benefits

The potential benefits to the subjects who received the study medications include a decrease in somatic, cognitive, and emotional post-concussion symptoms as determined by RPQ, a decrease in seizure activity, a shorter ICU length of stay, and a shorter hospital stay. However because of the research setting, these potential benefits cannot be guaranteed. Study participants who did not receive the study medical may benefit from the health effects accrued from standard care for TBI.

6. COST AND COMPENSATION

There will be no additional costs to study participants. There are no funds set aside by Honorhealth to compensate study participants.

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