A pilot trial to determine the effective dose of N-acetylcysteine for opioid reduction in patients undergoing spine surgery.

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PROTOCOL TITLE:

A pilot trial to determine the effective dose of N-acetylcysteine for opioid reduction in patients undergoing spine surgery.

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

- Objective: Determine the optimal dose of IV N-acetylcysteine (NAC) to produce opioid reduction following spine surgery and estimate the difference in opioid consumption between placebo and the selected optimal dose.
- The primary outcome will be 12-hour postoperative opioid consumption.
- The secondary outcomes will be 6-hour postoperative opioid consumption.
- Other exploratory outcomes will include intraoperative opioid consumption, postoperative anesthesia care unit (PACU) opioid consumption cumulative, non-opioid analgesic administration, postoperative opioid consumption at additional time points, and VAS pain scores. Patient demographic data, surgical data (procedure, operative duration), preoperative opioid consumption, time to hospital discharge will also be collected.

2.0 Background

As the opioid epidemic has gained notoriety, opioid sparing strategies have garnered more interest to provide analgesia without addictive potential, opioid related side effects, and elevated costs. Anesthesiologists and surgeons face the challenge of avoiding long term opioid use while still attempting to control the discomfort associated with invasive procedure. Additionally, postoperative opioids can lead to abuse by patients or others.[1]

N-acetylcysteine (NAC) has been an established drug since the 1960s. It is on the World Health Organization's List of 40 Essential Medicines)[a] and is FDA approved. NAC is a precursor to the amino acid L-cysteine and the antioxidant glutathione (GSH),[2] shown to promote homeostatic glutamate regulation by astrocytes. The sulfhydryl group (–SH) within the NAC molecule directly scavenges reactive oxygen species (ROS),[3] modulates the redox state of the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (neurotransmitter effect),[4] and inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) to modulate cytokine synthesis (anti/pro-inflammatory effect).[5]

NAC is probably best known as the treatment for hepatotoxicity from acetaminophen toxicity.[6b] However, NAC has also been utilized to treat psychiatric disorders (e.g, schizophrenia, obsessive compulsive disorders, addiction, compulsivity, anxiety), neurodegenerative disease symptoms (e.g., Alzheimer's disease, Parkinson's disease),

[a] World Health Organization. WHO Model List of Essential Medicines: 20th List. March 2017. Available online: http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1 (accessed February 24, 2020).

[b] FDA. Acetadote (acetylcysteine) Injection Package Insert. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-539_Acetadote.cfm (accessed on 22 February 24, 2020).

fertility, oral ulcers, chronic pain, hyperglycemia-induced oxidative damage, traumatic brain injury, and numerous other conditions.[7-16] There are also case reports of NAC helping with improving neurological status in patients comatose from carbon monoxide poisoning.[17] In the perioperative period, NAC has been primarily studied for its anti-inflammatory properties[18] and was noted to reduce the incidence of atrial fibrillation after coronary artery bypass graft surgery.[19] Although NAC has been used in outpatient studies for patients with chronic pain associated with sickle cell anemia[20] and diabetic neuropathy,[14,21] we are not aware of any studies examining NAC to enhance perioperative analgesia and decrease opioid administration.

3.0 Intervention to be studied

This study will involve administration of IV NAC or placebo (0.45% NaCl or 0.9% NaCl) in the perioperative period to patients scheduled for elective spine surgery and observation of postoperative opioid consumption. Our hypothesis is that NAC will reduce postoperative opioid consumption. This study will also examine the optimal dose of NAC to reduce opioid consumption.

NAC has a long history of safe administration and is frequently administered to critically ill patients.[6,17,19]

Medication information: NAC is FDA approved for multiple indications including an antidote to poisoning caused by acetaminophen overdose and prevention of acute hepatic injury.[b] It has been utilized to treat critically ill patients for over 60 years. It is generally well tolerated and has an excellent safety profile. Due to this excellent safety profile and with the approved dosing, this study will utilize NAC doses equal to the loading dose for acetaminophen treatment (150 mg/kg) or less (50 or 100 mg/kg).

Mechanism: NAC exerts its therapeutic effect through several mechanisms. NAC repletes glutathione reserves by providing cysteine, which is an essential precursor in glutathione production. NAC by itself also binds to toxic metabolites and scavenges free radicals. It also increases oxygen delivery to tissues, by increasing mitochondrial ATP production, and altering the microvascular tone to increase blood flow and oxygen delivery to the liver and other vital organs.

4.0 Study Endpoints

- The primary outcome will be 12-hour postoperative opioid consumption.
- The secondary outcome will be 6-hour postoperative opioid pain score.
- Other exploratory outcomes will include intraoperative opioid consumption, postoperative anesthesia care unit (PACU) opioid consumption cumulative, non-opioid analgesic administration, postoperative opioid consumption at additional time points, and VAS pain scores at additional time points.
- Other collected data will include patient demographic data, surgical data (procedure, operative duration), preoperative opioid consumption, time to hospital discharge.

5.0 Inclusion and Exclusion Criteria/ Study Population

- **Inclusion**
    - Undergoing elective spine surgery involving 4 levels or less of the thoracic, lumbar, or sacral spine.
    - 18 years of age and older.
- **Exclusion**
    - Less than 40kg in weight.
    - Unable to provide written, informed consent.
    - History of an adverse or anaphylactoid reaction to acetylcysteine.
    - Active asthma, wheezing, or using inhaled bronchodilators.
    - Pregnant Women
    - Known blood clotting deficiency
    - Insulin dependent diabetes

6.0 Number of Subjects

Sample size: 70 subjects

First 20 subjects: We will initially randomize 5 patients to each dose group (placebo, 50, 100, and 150 mg/kg) to estimate the dose response curve and to identify the optimal dose. After enrollment of the first 20 patients, the study will undergo review by the study team and statistician.

- If the dose response curve is adequate and the optimal dose identified, 15 additional patients will be randomized to placebo and 15 to the optimal dose to estimate the difference in opioid consumption between patients on placebo vs. the optimal dose. (Total of 50 subjects with 20 from dose response curve and 30 to estimate the difference in opioid consumption.)
- If the dose response curve is not adequate after the initial 20 subjects 5 per each dose group, we will randomize and enroll an additional 5 patients to each dose group (placebo, 50, 100, and 150 mg/kg) to estimate the dose response curve and to identify the optimal dose. Once the optimal dose is identified with these initial 40 patients, 10 additional patients will be randomized to placebo and 10 to the optimal dose to estimate the difference in opioid consumption between patients on placebo vs. the optimal dose. (60 patients total with 40 to create the dose response curve and 20 more to estimate the difference in opioid consumption.)
- A sample size of 20 subjects per group (placebo and optimal dose) allows us to estimate a 95% confidence interval for the mean difference in opioid consumption with a width of $\pm$ 0.64 standard deviations from the mean. We will plan to consent 70 subjects to account for withdrawal but will complete the study once 50 or 60 subjects (based on the number of subjects required to create the dose response curve) have completed the protocol.

7.0 Setting

MUSC surgical clinics or preoperative anesthesia clinics

8.0 Recruitment Methods

- Potential subjects on the surgical schedule undergoing elective surgery of the spine involving 4 levels or less will be screened for eligibility.
- Information regarding the study will be presented to subject by a study team member in the surgical clinic or preoperative anesthesia clinic or in the preoperative period prior to sedation. On the day of surgery, subjects may then choose to provide written consent, decline to participate, or rescind their prior consent.

9.0 Consent Process

- Regardless of the preoperative location, the study team will present to the subject with risks and benefits of the study and the study medication (NAC). Subjects may provide written consent at that time or choose to consider the study until the day of surgery. Potential participants will be given time to read the consent and ask questions. Consent will be obtained from subjects by an IRB approved CITI certified study team member that has been trained on the protocol. Written consent will be completed once all questions are answered and exclusion and inclusion verified. Copies of all documents will be provided to the patients.

10.0 Study Design / Methods

Design: This prospective, double blinded clinical trial will randomize patient to receive placebo (0.45% NaCl or 0.9% NaCl) or NAC (50, 100, or 150 mg/kg). The randomization will be created by a statistician and shared with Investigational Drug Services (IDS) pharmacy prior to patient enrollment.

IDS pharmacy has planned to set up the study to be dispensed from the main OR pharmacy. IDS will prepare numbered kits containing NAC or placebo based on the randomization scheme. The kits will be stored in the OR pharmacy and dispensed based on the assigned subject number. This will allow enrollment any time of day that the OR pharmacy is open.

Groups: Patients will be randomized to receive NAC: 0 mg/kg (placebo; 0.45% NaCl or 0.9% NaCl), 50 mg/kg, 100 mg/kg, and 150 mg/kg (Max dose 15,000 mg). The maximum dose considered will be 150 mg/kg as this has been studied for safety in numerous patient populations including those with severe comorbidities. As NAC may be reconstituted in D5W or 0.45% NaCl, we will reconstitute all NAC doses in 250ml 0.45% NaCl or D5W. We will use 250ml 0.45% NaCl or 0.9% NaCl without NAC as our placebo.

Enrollment:

Following confirmation of informed written consent, patients will be assigned an enrollment number and randomized using the randomization, created by a statistician, to one of four IV NAC groups: 0 mg/kg (placebo; 0.45% NaCl or 0.9% NaCl), 50 mg/kg, 100 mg/kg, or 150 mg/kg. Patients will proceed to the operating room where they will receive general anesthesia for their planned, elective surgical procedure. Intraoperatively, the designated IV NAC or placebo infusion will be initiated and completed by a clinical care team member. Patients will only receive NAC once as a single dose that will run over 60

minutes. Patients will be monitored in the operating room while receiving NAC and in the PACU postoperatively consistent with our standard perioperative care at MUSC.

The recorded anesthesia stop will mark time zero. The primary end point will be 12-hour postoperative opioid consumption.

Patient and procedural characteristic will be recorded throughout the perioperative period. Demographic data (age, gender, race, weight, height, body mass index) and preoperative opioid consumption will be collected after completion of informed consent (yes or no; and consumption quantified if applicable). Surgical data (operative procedure and surgical duration) will be collected after surgery. Time of hospital discharge will be collected after the patient is discharged from the hospital.

Other exploratory outcomes will be collected as long as the patient is still in the hospital and able to self-report up to 48 hours post-operatively. Data will be collected from subject self-reporting their VAS score and using the electronic medical record. These data include intraoperative opioid consumption, postoperative anesthesia care unit (PACU) opioid consumption cumulative, non-opioid analgesic administration, postoperative opioid consumption up to 48 hours or discharge. VAS pain scores will be recorded pre-operatively, post operatively and at 24 hours unless discharged prior to 24 hours post operatively.

In order to identify the optimal IV NAC dose for perioperative opioid reduction and estimate the difference in opioid consumption between placebo and the selected optimal dose, the study will progress in two phases.

- In the first phase (20 subjects), we will attempt to identify the optimal dose. The optimal dose is defined as the dose or doses of NAC for which a $\geq$20% reduction in opioid consumption relative to placebo is expected based on the dose response curve. If 20% reduction is not achieved, the optimal dose will be the maximum dose (150 mg/kg) administered during the study.
- In the second phase, after finding the optimal dose, 15 additional patients will be randomized to placebo and 15 to the optimal dose to estimate the difference in opioid consumption between patients on placebo vs. the optimal dose (30 subjects). A sample size of 20 subjects per group (5 from phase 1 and 15 from phase 2) allows us to estimate a 95% confidence interval for the mean difference in opioid consumption with a width of $\pm$ 0.64 standard deviations from the mean.
- If we are unable to create a dose response curve following the enrollment of the first 20 subject, an additional 20 subjects (5 per group) will be enrolled to create the dose response curve prior to starting the second phase.

Research procedures: The IV NAC dose [0 mg/kg (placebo; 0.45% NaCl or 0.9% NaCl), 50 mg/kg, 100 mg/kg, or 150 mg/kg] will be the only research procedure.

All other aspects of preoperative (e.g., clinic visits, labs, imaging) intraoperative (e.g, surgical procedures, anesthesia medications or procedures), and postoperative care (e.g., hospital admission and care, clinic follow-up, labs, imaging) will not be research procedures but consistent with planned patient care for a patient having elective spine surgery. The patient will be responsible for all charges related to the surgery and perioperative care excluding the NAC medication.

11.0 Data Management

Research data will be coded. Upon enrollment, subjects will be assigned a randomized numerical identifier for the remainder of the study. This number will be used to label research charts and paperwork associated with the subject. An electronic enrollment log will link patient name and MRN with his/her study ID number. This log will be kept separate from all research data. All paper information will be kept in a locked cabinet in a locked office. All electronic data will be kept on MUSC's password protected server.

Electronic data will be kept on a password protected MUSC server and a redcap database. All paper documents will be kept in a locked cabinet, in a locked office. Only IRB approved, CITI trained study team members will have access to the data. All data will be kept for 6 years per MUSC policy.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

Any adverse events related to NAC will be treated according to MUSC Hospital policy and procedures and the practice of the Department of Anesthesia.

The Department of Anesthesia's DSMB will review the study on an annual basis. Any adverse events will be reported and reviewed by the DSMB. Adverse events will be reported to MUSC's IRB per policy.

All data will be kept in a locked office, in a locked cabinet, and electronic data will be stored on a password protected MUSC server or redcap database. Only CITI certified, IRB approved study team members will have access to data.

14.0 Withdrawal of Subjects (if applicable)

- Circumstances under which subjects will be withdrawn from the research without their consent include severe allergy/intolerance to NAC.
- Subjects may withdraw from the study at any time. If patients voluntarily withdraw from the research study, they will receive our institutional standard of care for perioperative pain management.

15.0 Risks to Subjects

- IV NAC can cause rate related anaphylactoid reactions in 0.2-18% of patients.[22,23c] Most of the anaphylactoid reactions are mild (6%) or moderate (10%) with severe reactions (i.e., bronchospasm and hypotension) rare at 1% or less. Bronchospasm more commonly occurs in patients with pre-existing reactive airway diseases, like asthma. Bronchodilating agents are effective in treating these patients. To minimize this risk, patients with asthma, wheezing, or prescribed bronchodilators will be excluded from the study. Similarly, patients with a history of a prior anaphylactoid reactions to acetylcysteine will also be excluded.

  If an anaphylactoid events occurs, patients will be treated as described by FDA guidelines.[b] IV NAC will be stopped immediately and the patient treated with antihistamine medication (e.g., diphenhydramine) and IV fluids if required. Vasopressors are not typically necessary. NAC therapy may be restarted at a slower rate after resolution of any possible reaction. However, if an anaphylactoid reaction or

similar symptoms return upon reinitiating NAC treatment or increases in severity, IV NAC will be discontinued. Additionally, all possible medication reactions will be reported to the Anesthesia DSMB and MUSC IRB.

There is also a risk of loss of confidentiality.

16.0 Potential Benefits to Subjects or Others

- IV NAC may provide analgesia with reduced postoperative opioid consumption. This may help reduce postoperative opioid administration for numerous patients undergoing various types of invasive surgical procedures. Because opioid administration is associated with numerous negative side effects, including nausea, vomiting, pruritus, constipation, sedation, and respiratory suppression, reduction in opioid consumption may, in turn, reduce the frequency/severity of these side effects.
- Patients receiving the placebo may receive no direct benefit from participating but will receive current standard care for their surgical procedure.

17.0 Sharing of Results with Subjects

N/A

18.0 Drugs or Devices (if applicable)

N-acetylcysteine (NAC): N-acetylcysteine (NAC) has been an established drug since the 1960s. It is on the World Health Organization's List of 40 Essential Medicines)[a] and is an FDA approved medication. NAC is a precursor to the amino acid L-cysteine and the antioxidant glutathione (GSH),[2] shown to promote homeostatic glutamate regulation by astrocytes. The sulfhydryl group (–SH) within the NAC molecule directly scavenges reactive oxygen species (ROS),[3] modulates the redox state of the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (neurotransmitter effect),[4] and inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) to modulate cytokine synthesis (anti/pro-inflammatory effect).[5]

NAC is probably best known as the treatment for hepatotoxicity from acetaminophen toxicity.[6b] However, NAC has also been utilized to treat psychiatric disorders (e.g, schizophrenia, obsessive compulsive disorders, addiction, compulsivity, anxiety), neurodegenerative disease symptoms (e.g., Alzheimer's disease, Parkinson's disease), fertility, oral ulcers, chronic pain, hyperglycemia-induced oxidative damage, traumatic brain injury, and numerous other conditions.[7-16] There are also case reports of NAC helping with improving neurological status in patients comatose with carbon monoxide poisoning.[17] In the perioperative period, NAC has been primarily studied for its anti-inflammatory properties[18] and was noted to reduce the incidence of atrial fibrillation after coronary artery bypass graft surgery.[19] Although NAC has been used in outpatient studies for patients with chronic pain associated with sickle cell anemia[20] and diabetic neuropathy,[14,21] we are not aware of any studies examining NAC to enhance perioperative analgesia and minimize opioid administration.

[a] World Health Organization. WHO Model List of Essential Medicines: 20th List. March 2017. Available online: http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1 (accessed February 24, 2020).

[b] FDA. Acetadote (acetylcysteine) Injection Package Insert. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-539_Acetadote.cfm (accessed on 22 February 24, 2020).

An IND in not required for this study. First, NAC is FDA approved for IV administration. Next, the doses studied do not exceed the FDA approved doses. Further, this study does not and will not seek to change the FDA labeling. Last, NAC has an over 60-year history of efficacious and safe use. The history or NAC use at the proposed dosages does not suggested a substantial risk or harm to patients.

Pharmacy: NAC is currently stored in the MUSC OR and inpatient pharmacies. It is easily prepared by reconstituting in D5W or 0.45% NaCl. We will reconstitute in 250 ml of D5W or 0.45% NaCl, and 0.45% or 0.9% NaCl will also serve as our placebo. NAC is FDA approved and can currently be ordered by any physician for administration if indicated. Study related NAC will be ordered and administered perioperatively following enrollment. NAC is stable once prepared for 24 hours.

IDS pharmacy has planned to set up the study to be dispensed from the main OR pharmacy. IDS will prepare numbered kits containing NAC or placebo based on the randomization scheme. The kits will be stored in the OR pharmacy and dispensed based on the assigned subject number. This will allow enrollment any time of day that the OR pharmacy is open.

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