Oxidative Stress and Surgical Recovery

NCT04732000

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1. PURPOSE OF THE STUDY

a. Brief Summary

Chronic pain, functional impairment and slow rates of recovery are key issues for patients after surgery and trauma. Most approaches designed to limit chronic pain or enhance functional recovery focus on modulating peripheral or CNS responses and not on preventative strategieSs. Recent research suggests limiting oxidative stress in the perioperative period might limit tissue damage, organ dysfunction and immune system activation. These factors in turn may preemptively decrease pain and increase function post op. This study is designed to help determine the effectiveness of this strategy for improving postop recovery.

b. Objectives

Our central hypothesis is that perioperative administration of N-acetyl cysteine will reduce perioperative oxidative stress, limit immune system activation and improve key indices of surgical recovery. Although the planned work will not comprehensively address this hypothesis, it will solidify the required collaborations, identify the most useful tools and help the team estimate the required sample sizes for more definitive externally funded efforts.

Note: N-acetyl cysteine (NAC) is an antioxidant well-studied in the perioperative period; it is safe, relatively inexpensive and widely available.

c. Rationale for Research in Humans

This is a study on oxidative stress and it's influence on surgical recovery in humans, necessitating human participants be involved.

2. STUDY PROCEDURES

a. Procedures

Participants will be consented prior to the initiation of any study procedures.

Participants will be recruited from the Stanford orthopedic population scheduled to undergo total hip replacement surgery. The anesthetic and perioperative management of patients will be standardized according to ERAS-based recommendations as outlined by the Stanford Anesthesia Department.

Participants will be randomized to be in 1 of 2 treatment groups.

Group 1: An N-Acetylcysteine infusion will be administered to 50% of the participants during surgery as follows: IV infusion of 50 mg/kg over 1 hour followed by an additional 50 mg/kg over 3 hours, making the total dose 100 mg/kg.

Group 2: A placebo (Normal Saline) infusion will be given to in blinded fashion to the other 50% of patients

1) Assessments of pain, physical function and analgesic medication use will be made before surgery, daily on postoperative days 1-3, and then twice a week through post-op week 6. Validated surveys and a patient diary will be used to collect this data. The surveys include the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) adapted for patients undergoing lower extremity joint surgery, the Brief Pain Inventory (BPI), and the Surgical Recovery Scale (SRS).

2) Delirium will be measured using the Confusion Assessment Method (CAM) days 1-3 while in-house.

3) Additional data will be collected including demographics, surgical/anesthesia data (e.g. duration), and medical/medication history. 4) Peripheral blood samples will be collected before surgery and 1hr and 24hr after surgery based on our prior study showing that monocyte activation early after surgery strongly correlates with delayed pain resolution and functional impairment. addition 2/8/2021: We will collect blood for genomic analysis once, at the time of the preop sample collection.

5) Exhaled breath samples will be collected intraoperatively prior to incision and at wound closure as well as at 1 and 24 hours after surgery to be analyzed for aldehydes including formaldehyde, crotenaldehyde, and benzaldehyde.

We will also collect clinical information including demographics, medical and medication history, medical/clinical course from surgery through 6 weeks post op.

b. Procedure Risks

N-acetyl cysteine is a powerful anti-oxidant used safely for a variety of conditions including acetaminophen overdose. While not without potential ill effects the dose chosen is low and considered safe given in the context of surgery.

All other measures are safe and with only the risk of loss of confidentiality, or in the case of blood draws a very small risk of infection.

c. Use of Deception in the Study

Deception will not be used.

d. Use of Audio and Video Recordings

No audio or video recordings will be made.

e. Alternative Procedures or Courses of Treatment

There is no alternative procedure beyond not participating. Standard care will not be altered if participants enroll in this project.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

NA

g. Study Endpoint(s)

We are not comparing treatments. The study will end when all participants have completed all study related procedures.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Chronic pain, functional impairment and slow rates of recovery are key issues for patients after surgery and trauma. Chronic pain after surgery, for example, affects 10-80% of all those having operations, while commonly performed hip and knee joint replacement surgeries have an approximately 25% rate of chronic pain and functional limitation [1]. No preventative strategy in current use unequivocally modifies these rates, and few novel approaches have been tested. Furthermore, persistent postsurgical pain is a major route to chronic opioid use, opioid use disorder and, regrettably, opioid overdose. Most strategies designed to limit chronic pain or enhance functional recovery after surgery are directed at modulating peripheral and central nervous system activity and do not strongly modify the underlying tissue pathophysiology or fundamental systemic responses. Strategies limiting oxidative stress in the perioperative period, on the other hand, might limit tissue damage, organ dysfunction and immune system activation. Within our department, the Gross lab has established expertise in pain and organ damage related to reactive aldehyde production, a measure of oxidative stress, and recently expanded their repertoire of assays to quantify reactive aldehydes in breath samples in volunteers although surgical patients have not been studied [2]. Likewise, the Clark lab has demonstrated the ability of antioxidants to reduce post-injury pain behaviors as well as reduce innate and adaptive immune system activation in laboratory animals [3]. This work has not been translated to human populations. On the other hand, Dr. Gaudilliere has developed leading edge techniques for the analysis of immune activation in human patients proven useful for understanding the cellular correlates of postoperative pain and recovery [4]. One cell type strongly linked to pain and delayed recovery from orthopedic surgery, monocytes, are strongly activated by oxidative stress [5], suggesting that oxidative stress may be a critical early mechanism having persistent impact on surgical recovery.

The design of clinical trials useful for understanding the efficacy of perioperative treatments for enhancement of recovery is a focus of Dr. Angst's, while the analysis of

complex datasets and incorporation of innovative statistical approaches in the forte of Dr. Aghaeepour [4, 6, 7]. The skills of these two investigators will assure that the study is well designed and that the analysis will yield the maximum quantity of data.

N-acetyl cysteine (NAC) is an antioxidant well-studied in the perioperative period; it is very safe, relatively inexpensive and widely available. Our central hypothesis is, therefore, that perioperative administration of NAC will reduce perioperative oxidative stress, limit immune system activation and improve key indices of surgical recovery. Although the planned work will not comprehensively address this hypothesis, it will solidify the required collaborations, identify the most useful tools and help the team estimate the required sample sizes for more definitive externally funded efforts.

References

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b. Findings from Past Animal Experiments

Excerpt from above: ...the Clark lab has demonstrated the ability of antioxidants to reduce post-injury pain behaviors as well as reduce innate and adaptive immune system activation in laboratory animals [3]. This work has not been translated to human populations.

4. RADIOISOTOPES OR RADIATION MACHINES

a. Standard of Care (SOC) Procedures

Identify Week/Month of Study	Name of Exam	Identify if SOC or Research
NA	NA	NA

b. Radioisotopes

i. Radionuclide(s) and chemical form(s)

NA

ii. Total number of times the radioisotope and activity will be administered (mCi) and the route of administration for a typical study participant

NA

iii. If not FDA approved: dosimetry information and source documents (package insert, Medical Internal Radiation Dose [MIRD] calculation, and peer reviewed literature)

NA

c. Radiation Machines – Diagnostic Procedures

i. Examination description (well-established procedures)

NA

ii. Total number of times each procedure will be performed (typical study participant)

NA

iii. Setup and techniques to support dose modeling

NA

iv. FDA status of the machine and information on dose modeling (if procedure is not well-established)

NA

d. Radiation Machines – Therapeutic Procedures

i. Area treated, dose per fraction/number of fractions, performed as part of normal clinical management or due to research participation (well-established procedures)

NA

ii. FDA status of the machine, basis for dosimetry, area treated, dose per fraction and number of fractions (if procedure is not well-established)

NA

5. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Investigational Drugs, Biologics, Reagents, or Chemicals

N/A

b. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	N-Acetyl Cysteine
Dosage:	100 mg/kg total dose
Administration Route	IV administration 50mg/kg over 1 hour then 50 mg/kg over 3 hours.
New and different use? (Y/N)	Y
Commercial Product 2	
Name:	NA
Dosage:	NA
Administration Route	NA
New and different use? (Y/N)	NA
Commercial Product 3	
Name:	NA
Dosage:	NA
Administration Route	NA
New and different use? (Y/N)	NA

6. PARTICIPANT POPULATION

a. Planned Enrollment

i) 30 participants enrolled with an expected 20 to complete all study procedures.
ii) 30
iii) Orthopedic surgery patients undergoing clinically indicated total hip arthroplasty.

b. Age, Gender, and Ethnic Background

18 years of age or older
Both men and women
All ethnic backgrounds

c. Vulnerable Populations

Vulnerable subjects will not be enrolled.

d. Rationale for Exclusion of Certain Populations

Pregnant women and children will not be enrolled. THA surgeries are not performed on pregnant women. Children will not be included as THA surgery would only be done in extremely rare cases.

e. Stanford Populations

Participants who are laboratory personnel, employees, and/or students will not be targeted for enrollment but will not be excluded. All participants will undergo the same evaluation for inclusion.

f. Healthy Volunteers

There will be no healthy volunteers enrolled.

g. Recruitment Details

Participants will be consented in the clinic after a clinician in either the orthopedic or pre anesthesia clinic has gained permission from the patient to discuss this research project with the research team. We will gather PHI from the electronic medical record prior to consenting patients to ensure basic inclusion criteria are met prior to engaging individual patients. A request for a waiver of authorization for recruitment is included in this application.

In some cases when we are not able to meet patients in the clinic as described above we will contact them by phone or secure zoom call to present the study. Participants can choose to either schedule an appointment for in person consent or consent using a secure REDCap consent form.

A telephone screen is attached to section 16 for use when appropriate.

In all cases patients will not be cold-called and will only be contacted by someone with a treating relationship, or called if someone with a treating relationship gets the patients approval for the call.

9/14/21: We will use the new part 11 compliant Adobe Sign process for remote consent when appropriate.

5/11/22: We will partner with the Research Participation team for Honest Broker outreach. Potential participants are identified via STARR and invited by Research Participation team (honest broker) on behalf of study team. See Section 16 for Honest Broker study invitation letters. We will be using MyHealth. Epic MyChart, study team receives only the interested responses via Epic MyChart In Basket.

h. Eligibility Criteria

i. Inclusion Criteria

1) Over 18
2) Male of female
3) Planning to undergo primary total hip arthroplasty
4) Fluent in English
5) Willing and able to sign an informed consent form and HIPAA authorization and to comply with study procedures

ii. Exclusion Criteria

1) Infectious disease within the last month
2) Immune-suppressant therapy within the last 2 months (e.g., azathioprine or cyclosporine)
3) Chronic medication with potential immune-modulatory effects (e.g., daily oral morphine-equivalent intake > 30 mg)
4) Major surgery within the last 3 months or minor surgery within the last month.
5) History of substance abuse (e.g., alcoholism, drug dependency)
6) Pregnancy
7) Autoimmune disease interfering with data interpretation (e.g. lupus)
8) Renal, hepatic, cardiovascular, or respiratory diseases resulting in clinically relevant impaired function
9) Active malignancy
10) Participation in another clinical trial of an investigational drug or device within the last month that, in the investigator's opinion, would create an increased risk to the participant or compromise the integrity of the study
11) Other conditions compromising a participant's safety or the integrity of the study
12) History of anaphylaxis

i. Screening Procedures

Patients will be prescreened by reviewing the e-medical record for documented exclusion criteria. At the time of consent participants will be interviewed to confirm eligibility criteria is met.

j. Participation in Multiple Protocols

We will ask participants if they are engaged in other research projects at the time of enrollment.

Participants will not be enrolled if they are currently engaged in another trial if their safety or the integrity or either study would be at risk.

k. Payments to Participants

Participants will be paid $150; $75 following hospitalization, and $75 at the completion of the 6-week post op follow up.

l. Costs to Participants

There will be no cost to the participant.

m. Planned Duration of the Study

1) Screening per participant will take approx. 15 minutes.
2) Active participation will take approx. 7 weeks from consent through 6 week follow up.
3) Data analysis will take approx. 6 months.

Overall recruitment and completion of participant involvement in the trial will take approximately 1 year.

7. RISKS

a. Potential Risks

i. Investigational devices

NA

ii. Investigational drugs

NA

iii. Commercially available drugs, biologics, reagents or chemicals

In the literature the most frequently reported adverse events attributed to I.V. acetylcysteine administration were rash, urticaria, and pruritus. The frequency of adverse events has been reported to be between 0.2% and 20.8%, and they most commonly occur during the initial loading dose of acetylcysteine.

Adverse effects reported following acetylcysteine infusion given to treat acetaminophen overdose include:
Tachycardia
Ear pain
Nausea and vomiting
Chest tightness/feeling hot
Anaphylactoid reaction ~ 10% mild to moderate / 1% severe reaction
Rhonchi/throat tightness
Rash/flushing/pruritis

iv. Procedures

Blood draws carry a small risk of bleeding, bruising, pain and infection.

Breath analysis carries no calculable risk.

Completion of surveys carries the risk of loss of confidentiality.

v. Radioisotopes/radiation-producing machines

NA

vi. Physical well-being

As mentioned above.

vii. Psychological well-being

None known

viii. Economic well-being

None

ix. Social well-being

None known

x. Overall evaluation of risk

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

b. International Research Risk Procedures

NA

c. Procedures to Minimize Risk

Blood draws: Blood will be drawn using sterile supplies and aseptic technique. All Stanford policies regarding blood draws will be followed.

Loss of confidentiality: All PHI/confidential information will be kept from casual view, and managed and stored by trained research staff following all HIPAA and Stanford policies.

N-acetylcysteine infusion: Infusions will take place in the operating room and PACU where trained medical staff will be in attendance and available to intervene in the unlikely event of an adverse event requiring medical intervention.

d. Study Conclusion

The experiment will terminate when all study participants have concluded all study procedures

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

This study does not fall into the category of those requiring DSMPs as describe in the guidance provided above. Data and study procedures will be continually evaluated as the study progresses. Research team meetings are held weekly and problems associated with study conduct are discussed as needed (daily if necessary) with the PI.

ii. Person(s) responsible for Data and Safety Monitoring

NA

iii. Frequency of DSMB meetings

NA

iv. Specific triggers or stopping rules

NA

v. DSMB Reporting

NA

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Y

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

N

f. Risks to Special Populations

NA

8. BENEFITS

There is some hope that participants recovery will be positively affected by the infusion of N-acetylcysteine though this is not guaranteed. Acquisition of knowledge regarding oxidative stress, and use of antioxidants in the context of surgery and trauma may impact medical practice and significantly benefit patients in the future.

9. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.