The Effect of Early Saline Lavage on Synovial Fluid Composition Following Human Intra-Articular Ankle Fracture

Document Date: 12/12/2024

NCT05465382

Purpose of the Study

The purpose of this study is to examine the effect of early, percutaneous, intra-articular saline lavage on the undiluted synovial fluid microenvironment during the acute phase following intra-articular fracture of the human ankle. We hypothesize that early intervention with percutaneous joint lavage in the first 0-48 hours after injury will attenuate the production of pro-inflammatory cytokines, MMP's and cartilage breakdown products compared to non-lavaged control subjects at the time of surgical fixation.

Background & Significance

Post traumatic osteoarthritis (PTOA) is a frequent cause of disability in orthopaedic trauma patients. Post-traumatic etiologies represent a disproportionately high percentage of clinically significant osteoarthritis of the ankle (65-80%) as compared to the knee and hip (2-10%). Compared to other forms of arthritis, PTOA is unique in that the timing of onset is known. As a result, there is an opportunity for studying the underlying pathogenesis at the time of injury and targeting interventions aimed at treating early disease and preventing disease progression.

Traditionally, the intraoperative restoration of anatomic joint congruity and balanced articular loading were thought to be the main factors involved in preventing the development of PTOA. However, even after anatomic reduction, intra-articular fractures of the lower extremity are still susceptible to the development of PTOA. Furthermore, the relationship between residual articular surface displacement and the development of PTOA is inconsistent in the literature. While the mechanical components of intra-articular fracture treatment have been well studied, more recent work has focused on better understanding the biological response within the joint that likely contributes to cartilage damage and the progression of PTOA.

At the time of intra-articular ankle fracture, chondrocyte death and apoptosis occur locally along the fracture edges. However, immediately thereafter, the entire joint is exposed to the inflammatory environment created by injury to the periarticular soft tissues and fractured bone edges. This gives rise to the so-called "innocent bystander" phenomenon, whereby uninjured cartilage throughout the joint is subjected to the deleterious effects of the inflammatory burden created by the healing fracture site. In 2015, Adams et al. sought to better define this inflammatory environment, and demonstrated the presence of significantly elevated levels of pro-inflammatory cytokines and extracellular matrix-degrading mediators present in the synovial fluid after intra-articular ankle fracture, which could play a role in the development of PTOA. Followup study here at Duke has demonstrated that the intra-articular composition of these inflammatory cytokines and matrix metalloproteinases (MMP's) changes over time, with evidence of in-vivo cartilage degeneration present by 10 days post-injury. Furthermore, in-vitro study has demonstrated the clear deleterious effect of synovial fluid fracture hematoma (SFFH) on chondrocyte viability on a time-based scale, with SFFH collected from 0-2 days post-injury demonstrating the greatest potential for cartilage damage.

These studies suggest that early intervention to alter the composition of the intra-articular environment may attenuate the inflammatory response, diminishing the potential for "innocent bystander" cartilage

damage and the subsequent development of PTOA. Currently, there are no therapeutics approved for the treatment of PTOA. Commercially available anti-inflammatory cytokine agents and metalloproteinase inhibitors have been shown to increase chondrocyte viability in animal and in-vitro models, however, their use is not yet approved for the treatment of PTOA in human subjects.

Saline joint lavage represents a potentially simple, low-risk and minimal-cost intervention which has not been previously studied for this purpose in human subjects. Open joint lavage at the time of definitive surgical fixation is within the standard of care, but typically occurs greater than 10 days after injury by which time cartilage degradation has already begun. Early, saline lavage during initial presentation to the clinic or emergency department may theoretically alter the progression of the intra-articular inflammatory response by evacuating the bulk of the developing synovial-fluid fracture hematoma.

The vast majority of ankle fractures present to the ER or urgent care within a day of fracture. Moreover, a large subset of these fractures require reduction (fracture setting) that is painful. It is our standard of care to perform an intra-articular lidocaine injection before reduction. We will take advantage of this standard of care needle insertion to the fractured ankle to perform saline joint lavage to diminish this early inflammatory burden.

Design & Procedures

This is a prospective randomized control trial which will be performed exclusively at Duke University Hospital (DUH). We plan to enroll 60 patients with the hopes to have 40 evaluable subjects.

After informed consent is obtained, subjects will be randomized into one of two groups as listed below.
Group 1: intra-articular saline lavage (n=30)
Group 2: no intra-articular saline lavage (n=30)

Randomization will occur by the opening of pre-prepared envelopes which will be stored in the orthopaedic resident office (HAFS Building, Room 1661). Envelopes will be labeled #1-#60. Thirty envelopes will contain a note card labeled “Group 1” and Thirty envelopes will contain a note card labeled “Group 2”. Envelopes will be pre-prepared by key study personnel not involved in the consent or randomization process.

Upon informed consent, subjects will undergo physical examination, medical history assessment, vital sign measurements, and x-rays of the injured and/or contralateral ankle as part of their standard clinical care. After initial evaluation, subjects will undergo aspiration of the injured ankle joint via the standard anteromedial arthroscopy portal approach. This will be performed with sterile technique using a 16-guage needle attached to a 10cc syringe. As previously mentioned, this standard of care needle insertion is used independent of the current study for the administration of intra-articular lidocaine for patient pain relief. The aspirate will be immediately transported to Dr. Adam’s lab (LSRC Building, Room B331) aliquoted and stored at -80 degrees Celsius for batch analysis.

Subjects in Group 1 will then undergo saline joint lavage as follows:
Three 10cc syringes will be filled with 10cc of sterile 0.9% normal saline.

One 10cc normal saline syringe will be injected into the ankle joint through the previously placed anteromedial 16-gauge needle.
Saline will be withdrawn from the joint into the attached 10cc syringe.
The needle will be left in place, the syringe detached, and the lavage repeated with the remaining two 10cc normal saline syringes.
After three rounds of lavage, 10cc of 1% lidocaine without epinephrine will be injected into the joint via the existing anteromedial 16-gauge needle. This will serve as an intra-articular hematoma block for patient comfort during fracture reduction and splinting.
This intra-articular lidocaine block is routinely performed as standard of care for ankle fractures presenting to the emergency department. As described, only one needle stick will be performed which will facilitate sample aspiration, lavage and lidocaine block, thus causing minimal to no additional discomfort to the patient.

Subjects in group 2 will not undergo normal saline lavage. After synovial fluid aspiration as described above, they will undergo intra-articular injection of 10cc of 1% lidocaine without epinephrine via the existing anteromedial 16-gauge needle. This will serve as an intra-articular hematoma block for patient comfort during fracture reduction and splinting.

The aspiration and lavage protocol as described above will take place in the DUH ED and be performed only by approved key study personnel.

After the initial aspiration +/- lavage and stabilization of the ankle joint, subjects will undergo a period of soft tissue rest to allow for the resolution of soft tissue swelling. This is standard of care in the treatment of periarticular lower extremity fractures. Subjects will then undergo surgical fixation when it is deemed appropriate by the Orthopaedic Trauma team, independent of this study. At the time of surgery, after tourniquet inflation, all subjects will again undergo intra-articular aspiration of the injured ankle joint. This will be performed using a 16-gauge needle attached to a 10cc syringe via a standard anteromedial arthroscopy portal approach. The aspirate will be immediately aliquoted, transported to Dr. Adam's lab (LSRC building B331) and stored at -80 degrees Celsius for batch analysis.

Selection of Subjects

Adult subjects (over 18 years of age) presenting to the DUH Emergency Department with an intra-articular fracture of the ankle joint between 0-48 hours from the time of injury will be eligible for inclusion. Intra articular fracture (IAF) is defined as any fracture of the fibula or tibia in which the fracture line(s) exit into the cartilage surface of the ankle joint. Exclusion criteria include: 1) age <18yo, 2) open fracture, 3) subjects presenting >48 hours from the time of injury, 4) nonoperatively treated fractures.

Subject Recruitment and Compensation

Upon evaluation by the orthopaedic surgery team in the Duke University Hospital Emergency Department, subject eligibility will be confirmed and the study will be introduced to the subject by their treating physician. Key personnel with role of "Collaborator" will review the study in detail with the subject. Paper consent forms will be signed and stored in a key-locked file cabinet within the study coordinators office (Duke Orthopaedics Arringdon, 3rd Floor, Room 3262).

We plan to enroll 60 subjects to capture 40 participants as determined by our power analysis which is detailed below. All patients who meet the above inclusion criteria will be eligible for the study. In this way, enrollment will be equitable across all demographic groups.

Risk/Benefit Assessment

As described above, this study represents minimal risk and discomfort to subjects. It is standard of care to administer an intra-articular lidocaine injection during the emergency department management of ankle fractures. We will utilize this standard of care needle insertion to the fractured ankle to perform our study related aspiration and saline lavage. In this way, no additional risk or discomfort will be incurred by the subject as a result of participation. Patients choosing not to participate will receive the normal standard of care for treatment of their injury independent of this study. Furthermore, consenting to participate in this study in no way obligates subjects to undergo surgical fixation of their ankle fracture. This decision will be made in consultation with their treating surgeon.

Risk is involved to the extent that privacy and confidentiality may be compromised. However, every reasonable effort will be made to limit breaches of privacy and confidentiality.

Subjects will not benefit directly from this study. However, data and conclusions derived from this study may improve the current understanding of post traumatic arthritis and possibly influence future patient care or study designs.

Data Analysis & Statistical Considerations

Sample Size Estimate

The study was powered (a-priori) for randomized between group differences in the primary outcome measures of Cytokines and Matrix Metalloproteinase levels collected during standardized aspirations. The study will involve two independent groups: 1) individuals with intra-articular fractures of the ankle who receive saline lavage (experimental) and 2) individuals with intra-articular fractures of the ankle who do not receive lavage (control). Differences between groups will be evaluated with a fixed effects repeated measures, analysis of covariance (RM-ANCOVA) with three dedicated time points ([1.] baseline, [2.] in the OR after anesthesia is induced (generally within 24 hours of lavage), and [3] 1 to 2 weeks post-injury). Baseline cytokines and Matrix Metalloproteinase levels will be used as a covariate control. Assuming a normal distribution for the cytokines and Matrix Metalloproteinase levels and assuming a partial theta squared effect size of 0.40 (large effect*, primarily occurring at the second time

point), we constructed a sample size estimation estimating for between groups' comparisons. With an expected 80% power, 2 time intervals*, 1 control interval, two independent groups, and a standard error of probability of 0.05, we estimated the need for a minimum sample size of 40 for statistical significance (~20 per group). We will employ intention to treat and chains equation imputation and will not oversample each group for drop outs.

Statistical Analyses

The primary outcome measure will be cytokines and Matrix Metalloproteinase levels measured at two distinct time points after injury. We will use a between groups, repeated measures Analysis of Covariance (RM-ANCOVA) to measure differences between the two designated groups. A RM-ANCOVA is used in examining the differences in the mean values of the dependent variables that are related to the effect of the controlled independent variables while taking into account the influence of the uncontrolled independent variables (baseline) over more than one time point. A p value of 0.05 will be used to measure statistical significance.

*Medium effect size required a sample size of 98
+Three time intervals would only require a sample size of 36.

Data & Safety Monitoring

The only major risk involved is the loss of confidentiality and every effort will be made to ensure this does not happen by the research staff. No followup contact with subjects will be necessary after their ankle aspirations. The results of this research will not be placed in their medical record. No PHI will leave Duke. It will not be necessary to specifically provide the subjects with any additional information, as their involvement ends with their ankle joint aspiration at the time of surgery and does not influence their longitudinal care. Furthermore, any research findings will be made available through publication. Research records containing MRN will be kept in an electronic spreadsheet on the Duke server of which access is limited to the PI and his research staff. Any electronic information will be stored on a computer that is password protected. After data collection and prior to statistical analysis, a case number will be assigned to the data and the medical record number (the only identifying data collected) will be stripped from the database. After the review is complete, publication has been accepted and all revisions have been made to the manuscript, then the study will be closed in the eIRB.