Correlation between intraoperative tourniquet use and limb pH, functional measures and patient-reported outcomes after ankle fracture surgery

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Protocol

1) **Protocol Title**
Correlation between intraoperative tourniquet use and limb pH, functional measures and patient-reported outcomes after ankle fracture surgery

2) **Objectives**
This study aims to 1) **characterize skeletal muscle pH during/after tourniquet use** and 2) **investigate any relationship between intraoperative tourniquet use and postoperative functional measures/patient-reported outcomes.**

3) **Background**
Cushing first described a pneumatic tourniquet 1904, normalizing its use in optimizing intraoperative visualization and decreasing blood loss.[1] Tourniquets are widely accepted as "safe" for up to two hours of continued use, despite known risks and a paucity of literature supporting this duration. The two-hour limit comes from a 1971 paper by Shaw Wilgis using pH, PO2, and PCO2, in which he suggested that tourniquet ischemia longer than two hours approached a "critical point" where the fatiguability of muscle and further acidosis "produce irreversible changes" (pH ≈ 7.0).[2] Complications of tourniquets include tourniquet site pain, increased surgical site pain and swelling from reperfusion, neuropraxia, vascular injury, functional weakness, and decreased muscle endurance. Similar to compartment syndrome, tourniquets eliminate the tissue perfusion gradient necessary for oxygen, glucose, and lactic acid exchange. Lack of molecular exchange within the tissue is thought to result in tissue anoxia and acidosis, leading to cellular death of skeletal muscle and nerves.

The clinical outcomes of tourniquet use have been studied more recently, but these studies were small and did not use robust physical exam measures or patient reported outcomes. In 1997, Ömeroğlu et al. randomized 32 patients undergoing ankle fracture surgery to no-tourniquet and tourniquet groups and found increased pain scores in the tourniquet cohort at 24 and 48 hours postoperatively.[3] More recently, a 2004 randomized, controlled study by Konrad et al. assigned 54 patients with operative ankle fractures to no-tourniquet and tourniquet groups; findings included no difference in intraoperative time between the groups and significantly increased postoperative swelling and pain (measured via malleolar circumference and VAS) in the tourniquet cohort at 5 days and 6 weeks postoperatively.[4]

Surveys of foot and ankle surgeons in the US and Canada in 2005 revealed that tourniquet inflation pressure and duration of use has wide variability as there are currently few evidence-backed recommendations informing proper tourniquet use.[5] We found no available literature synthesizing clinical outcomes of tourniquet use with its metabolic effects, particularly intramuscular pH. The use of intraoperative tissue pH monitoring remains experimental but is already being utilized at OHSU by our trauma surgeons, who insert a pH catheter into leg musculature to measure real-time tissue metabolism during reamed intramedullary nailing for tibia fractures in order to understand metabolic markers of compartment syndrome.

4) **Study Design**

This randomized, prospective study will include ankle fracture patients undergoing surgical treatment at Oregon Health and Science University. The study includes only two arms, tourniquet and no-tourniquet (control).

This study will utilize the same research material and process as current IRB approved protocol STUDY00017959 "Correlation of compartment syndrome diagnosis and pH measurement" under PI, Jung Yoo.

Preliminary data was collected to determine the accuracy of our intended pH catheter, the VersaFlex® pH catheter, in recording muscle tissue pH. The catheter's measurements were compared to a standard USDA approved meat pH meter, the HANNA Instruments meat pH meter, and found to be 99.7% accurate at measuring the pH of living and dead (to simulate compartment syndrome) rat muscle tissue. The preliminary results suggest the VersaFlex® pH catheter as an appropriate choice for this study. To date, we have performed pH recording using protocol from STUDY0017959 on 20 patients without any complications or adverse effects.

We propose a randomized, prospective trial to further characterize muscular pH and postoperative characteristics in patients undergoing ankle fracture surgery with or without use of intraoperative tourniquet. Participants will be randomized prospectively to a tourniquet versus no-tourniquet group. All participants will have a continuous intramuscular pH probe placed in the anterior compartment of the leg prior to start of surgery. Intraoperatively and for two hours postoperatively, we will continuously measure intramuscular pH. We will measure tourniquet duration, as well as lactate and venous blood gas pre-tourniquet and at the time of tourniquet release. We will collect functional outcomes including postoperative pain, range of motion, swelling, and strength/fatiguability; patient reported outcomes via validated surveys; as well as adverse outcomes including falls and venous thrombosis. We hypothesize that tourniquet use results in altered metabolic markers including intramuscular pH and poorer patient reported and functional outcomes measured at our follow-up periods of 2 hours, 2 days, 3 weeks, 6 weeks and 3 months. We plan to assess our patient reported outcomes by utilizing the Foot and Ankle Ability Measure (FAAM) and PROMIS physical function (PF) and pain interference (PI) modules, as these are validated and widely used measures of patient reported outcomes.[6] Information gleaned from this study will help us further understand the relationship between tourniquet use, intramuscular and venous pH and patient outcomes after ankle fracture surgery, and may help formulate evidence-based guidelines for duration and use of tourniquets intraoperatively.

Patients will be screened in the emergency department, clinic or preop area day of surgery. Patients can also be screened/recruited via telephone but consent for all patients will occur via email in REDCap or on paper. Following consent of subjects via email or on paper, REDCap, a secure web application designed for research use and for building and maintaining clinical databases, will be used to document data..

PROMIS surveys and VAS pain scale will be administered at postoperative follow-up appointments to track participants over time. The follow-up appointments will take place:

- New patient
- 3 weeks
- 6 weeks
- 3 months

VAS pain scale will also be asked at 2 hours and 2 days postoperatively.

Determining tissue pH and understanding its relationship to tourniquet use, the patient's physical function, clinical outcome, and physiologic changes will provide important information about the relationship between tissue pH and tourniquet use and current determinants of tissue protection and function.

5) **Study Population**

a) **Number of Subjects**

We estimate that 290 patients will meet the eligibility criteria to be included in our study over a three-year period.

Inclusion and Exclusion Criteria

Adult patients (18 years to 89 years) undergoing surgical ankle fracture fixation at OHSU will be eligible for this study. Patients with sepsis, other significant long bone or internal injuries will be excluded from the study (including ipsilateral limb injuries). Patient medical records and specific procedural information will be pre-reviewed by the research staff to determine eligibility. In the event of a screen failure, all data already collected will be destroyed immediately.

b) **Vulnerable Populations**

We will not include children, pregnant women, neonates, decisionally impaired adults, or prisoners in this study.

c) **Setting**

All procedures will be performed at OHSU by OHSU personnel. Determination of eligibility will occur in Sam Jackson Hall. Study surgical procedures will take place in the South OR or Center for Health and Healing outpatient surgery center (participants will be either inpatients or outpatients). Consent will take place in the emergency room, the Orthopaedic clinic, or in inpatient areas. Patients can be contacted by telephone for recruitment and collection of email address but all consents will be obtained on paper or electronically via email in REDCap. Research administrative tasks along with data management and analysis will be conducted in Sam Jackson Hall at OHSU using the web application, REDCap. PROMIS Surveys will be collected in REDCap and administered via email.

d) **Recruitment Methods**

Patient medical records and specific procedural information will be pre-reviewed by the research staff to determine eligibility. No additional advertising or recruitment will be conducted. Subjects will not receive compensation.

e) **Consent Process**

Once identified by the pre-review discussed above, which can include a telephone conversation to discuss the study, patients will be consented via RedCap. Research staff and/or the care team will emphasize that participating in this study is optional and that patients can continue their care without participation. This fact will be reiterated throughout the consent discussion. Research staff and/or the care team will also emphasize that patients can withdraw their consent at any time. Participants will be continuously reminded of their ability to withdraw consent throughout the consent discussion and treatment period. They can also elect to not participate in the pH probe portion of the study and just have their outcomes tracked as a randomized tourniquet or non-tourniquet patient.

Modifications to the Consent Process

Patient medical records and specific procedural information will be pre-reviewed by the research staff to determine eligibility. This information is necessary to identify potential subjects. Every effort will be taken to protect subject privacy both before and after consent.

Non-English Speaking Subjects

Non-English speaking subjects will be enrolled in this study. Short forms will be used with the use of an interpreter. The interpreter will assist with the initial consent process and subsequent study visits. The interpreter may be in person or on the phone. If using a short consent form, an interpreter present by phone may sign the interpreter box on the full English form via secure email, fax or mail. The interpreter may not be the subject's friend or family member except in urgent circumstances. A subject who chooses to use his or her own interpreter must sign a waiver. OHSU Interpreter services will be contacted to obtain this document.

6) **Procedures**

Patient medical records and specific procedural information will be reviewed by the research staff. Participants will be subject to retrospective evaluation of their charts. We will collect the following information from our chart review: age, sex, comorbidities, current medications, substance use, occupation, height, weight, BMI, physical examination results, fracture type, and nature of the surgical procedure. Standard preoperative laboratory evaluation will take place with basic metabolic panel, complete blood count, 25(OH)D level and hemoglobin A1c. Preoperative radiographic evaluation includes x-rays of the ankle and tibia/fibula. Co-morbidities will be assessed with American Society of Anesthesiologists (ASA) Physical Status Classification System. Fractures will be categorized into three groups: isolated fibular, bimalleolar and bimalleolar equivalent, and trimalleolar and trimalleolar equivalent fractures. All study data is to be uploaded to REDCap data managed by the coordinating site.

The patient will be randomized to tourniquet or no tourniquet based on a computerized randomization with a random number generator, which will be queried and communicated to the surgeon by the research assistant. For each patient, calf girth will be measured at its greatest dimension bilaterally. A pneumatic tourniquet will be placed with the center of the tourniquet halfway between the ASIS and the patella for all patients, but only the participants randomized to the "tourniquet" group will have the tourniquet inflated. The tourniquet will be deflated after the splint is complete or at the 2 hour mark, whichever is sooner. Length of surgery will be recorded, in addition to length of tourniquet use (and elevation/deflation times relative to surgery stop/start times). The surgeons' current practice of using/not using regional anesthesia will not change and methods will be documented. However, surgeons' preferred practice of using/not using tourniquets will be randomized to control for surgeon skill level and average surgical time.

For all patients, a VersaFlex® pH catheter from the Covidien pH monitoring kit will be placed in the anterior compartment of the operative leg via small incision and the Digitrapper® Recorder will measure and record continuous intramuscular pH. Recording will start immediately after placement of the probe and will continue intraoperatively and for 2 hours postoperatively. The probe will be removed in PACU prior to patient discharge.

In the tourniquet arm, the operative limb will be exsanguinated with esmarch bandage and all tourniquets will be inflated to 250 mm Hg. The tourniquet will be inflated from prior to incision through wound closure and placement of sterile dressings, or up to, and never longer than, 120 minutes intraoperatively. For all patients, venous blood gas and lactate will be collected after induction of anesthesia and at the time of tourniquet release for the tourniquet arm and at the conclusion of surgery for the no-tourniquet arm. If a surgeon determines that use of a tourniquet is required for optimal fracture reduction in the "no tourniquet" group, then the limb will be exsanguinated and the tourniquet will be inflated intraoperatively. The patient will remain in their assigned arm of the study and an intention to treat analysis will be done.

Malleolar circumference (swelling), calf girth, quadricep strength (via timed up and go), ankle range of motion, fatigability (via biodex), proximal and distal lower extremity strength (via handheld dynamometer), and balance measures (single-limb stance time and Y-balance test scores) will be measured by blinded physical therapists at 6 weeks and 12 weeks. VAS pain score will be collected electronically prior to surgery, 2 hours after procedure stop time, 2 days after surgery, and then at each visit using the aforementioned schedule. The FAAM and PROMIS PI and PF modules will be collected at the time of 3-week, 6-week, and 3-month postoperative followup appointments electronically via Redcap. Other relevant variables including number of postoperative PT sessions and adverse events, including number of postoperative falls, DVT or PE and wound complications, will be collected at postoperative PT and clinic visits.

7) **Data and Specimens**

a) **Handling of Data and Specimens**

We will collect the following information from our chart review: age, sex, comorbidities, current medications, height, weight, BMI, physical examination results, fracture type, nature of the surgical procedure, and results of lab draws, including comprehensive metabolic panel, blood gas and complete blood count. We will also collect fracture classification information from CT and/or X-ray radiographs. A VersaFlex® pH catheter from the Covidien pH monitoring kit will be placed in the anterior compartment of the leg. Intramuscular pH will be measured and recorded using the Digitrapper® Recorder for the duration of surgery and for 2 hours postoperatively, then deidentified and uploaded to a secure location on the OHSU x:drive. Data will be coded with unique identifiers and stored in a secure, password protected location on the OHSU x:drive. Data will be stored indefinitely.

b) **Sharing of Results with Subjects**

Results will not be shared with subjects.

c) **Data and Specimen Banking**

Data to be collected from study subjects by OHSU research personnel and entered into REDCap data registry. PROMIS surveys will be administered electronically via email, and will be entered directly into REDCap database. All other data to be collected by study coordinator directly from subject's medical record via Epic.

HIPAA identifiers will only be visible to the site that contributed them. In other words, HIPAA identifiers of OHSU subjects will only be visible to OHSU study personnel and the data administrator at the primary site. These identifiers are not for the purpose of research but simply to ease data collection at each site. Identifiers will be flagged in the REDcap database so that they cannot be exported. De-identified data will be available to other members of the consortium after an application process with a proposed study.

8) **Data Analysis**

Use of tourniquet and tourniquet time will be our independent variables. Intramuscular pH, venous blood gas and lactate are dependent physiologic variables. Objective functional outcomes will be malleolar circumference (swelling), calf girth, quadricep strength (via timed up and go), ankle range of motion, fatigability/total work (via biodex), proximal and distal lower extremity strength (via biodex), balance measures (single-limb stance time and Y-balance test scores), and fall frequency. Patient-reported outcomes will be assessed via validated PROMIS and FAAM surveys. Covariates, including age, sex, comorbidities, current medications, height, weight, BMI, physical examination results, fracture type, lab values, and nature of the surgical procedure, as well as our dependent variables will be compared, using chi-squared, fisher's exact, ANOVAs, and t-tests, between patients that did and did not use a tourniquet. Regression analysis will be conducted to determine the relationship between the dependent and independent variables. All analyses will be completed using SAS statistical software (SAS Institute, Cary NC).

9) **Privacy, Confidentiality and Data Security**

Only IRB approved research staff will be collecting data from the chart review. Access to data will be restricted to the principal investigator and the study team with password protection. Every effort will be taken to protect subject privacy. After complete collection, data will be completely unidentified and stored on OHSU's x:drive, a secure, password protected location. and/or REDCap. During collection, data will be password protected and stored on OHSU's x:drive. Standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Data Security is ensured.

1. **Project Level Security in REDCap:** Data groups will be created in REDCap to restrict the data access. Sites can only see the data entered by personnel that belongs to the specific site. Cross site data access is restricted.
2. **Data Storage Security:** All the REDCap data is stored on an Oregon Health and Science University server that is protected inside a firewall. The access to the server is restricted and tightly controlled by the server administrators.

10) **Risks and Benefits**

a) **Risks to Subjects**

This study presents only minimal risk to subjects as tourniquet use for duration under 2 hours is considered "safe." There will be minimal risk of loss of confidentiality to subjects. Only IRB approved research staff and the care team will be able to contact patients and collect data from the chart review. Every effort will be taken to protect subject privacy.

b) **Potential Benefits to Subjects**

Potential benefits are limited to the generation of data that could help care of future patients.

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[1] Cushing H. *Pneumatic tourniquets: with especial reference to their use in craniotomies:* Medical news; 1904.
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[3] Ömeroğlu H, Günel U, Biçimoğlu A, Tabak AY, Uçaner A, Güney Ö. The Relationship Between the Use of Tourniquet and the Intensity of Postoperative Pain in Surgically Treated Malleolar Fractures. *Foot Ankle Int*. 1997;18(12):798-802. doi:10.1177/107110079701801208
[4] Konrad G, Markmiller M, Lenich A, Mayr E, Ruter A. Tourniquets May Increase Postoperative Swelling and Pain after Internal Fixation of Ankle Fractures: *Clinical Orthopaedics and Related Research*. 2005;NA;(433):189-194. doi:10.1097/01.blo.0000151849.37260.0a
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[6] Hung M, Baumhauer JF, Licari FW, Voss MW, Bounsanga J, Saltzman CL. PROMIS and FAAM Minimal Clinically Important Differences in Foot and Ankle Orthopedics. Foot Ankle Int. 2019;40(1):65-73. doi:10.1177/1071100718800304