Title: Does early platelet rich plasma injection decrease the risk of post-traumatic arthritis in pilon fractures undergoing two-staged open reduction with internal fixation?

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A) Scientific Aims

Specific Aim 1: Determine the effects of a single intra-articular injection of platelet rich plasma (PRP) for mitigating the development of post-traumatic arthritis (PTA) in patients being surgically treated for pilon fractures in one ankle.

Null hypothesis: A single intra-articular injection of platelet rich plasma (PRP) will not be associated with significant improvements in outcome based on patient-reported measures of pain and function, as well as diagnostic imaging findings of PTA in patients being surgically treated for pilon fractures in one ankle.

Specific Aim 2: Assess the discriminatory potential of a synovial fluid biomarker panel for categorizing presence and severity of PTA based on patient-reported outcome measures of pain and function, as well as diagnostic imaging findings in patients being treated for pilon fractures in one ankle.

Null hypothesis: Synovial fluid biomarkers will not have high discriminatory capabilities for categorizing presence and severity of PTA in patients being treated for pilon fractures in one ankle.

B) Background and Significance

Pilon fractures are common and are associated with a 75% chance for symptomatic post-traumatic arthritis (PTA).[1] Although the mechanisms for initiation and progression of PTA after pilon fracture are incompletely understood, articular fracture is known to induce pro-inflammatory cytokines and degradative enzymes, which can result in chondrocyte death, accelerate cartilage degradation, and drive synovitis after injury. These pathologic processes appear to be especially important in the early phases of disease.[2-4] Current treatments for articular fractures are focused on biomechanical issues: anatomic reduction, rigid stability, and limb alignment. These are critical issues to address for optimal healing, early limb use, and joint function. However, the biologic components of articular fracture are likely as, or even more important, with respect to development of PTA. As such, research efforts also need to focus on these important aspects in order to mitigate the development and progression of joint pathology after articular fracture.

In an in vitro study, antioxidant treatment delivered hours after articular cartilage injury was reported to prevent progression of PTA-related pathology.[5] Using canine models of PTA, our group has noted significant benefits after intra-articular injection of platelet rich plasma (PRP) in decreasing pain, improving limb use, maintaining joint range of motion, and mitigating progression of osteoarthritis. Beneficial results associated with PRP treatment of OA have also been reported in clinical veterinary patients.[6] Based on this translational evidence in conjunction with the regulatory status and availability of PRP for clinical use in trauma patients, this orthobiologic therapy appears to have strong potential for providing a practical means of mitigating development of PTA in patients suffering ankle fracture. Importantly, we will be able to use a synovial fluid biomarker panel that has been shown to have high discriminatory potential for categorizing presence and severity of OA in dogs[9], to assess patients for PTA after pilon fracture – which provides critical data regarding disease mechanisms[7,8] – and treatment monitoring for development and assessment for novel therapeutic strategies for this pervasive problem.

C) Previous Work on the Study

There has been little published work on this particular treatment strategy for post traumatic arthritis of the ankle

D) Methods

With IRB approval and informed consent, patients (n=40) will be included who sustain closed pilon fracture of one ankle and are undergoing initial reduction with spanning external fixation, followed by open reduction with internal fixation (ORIF). Up to 50 patients will be enrolled in order to account for expected attrition in this patient population. Patients will be randomized to one of two treatment groups:

- PRP (n=20): single intra-articular injection of 5 ml of a leukocyte-reduced platelet rich plasma (ACP, Arthrex, Naples, FL) at the time of closed reduction and initial stabilization using ankle-spanning external fixation

- Control (n=20): single intra-articular injection of 5 ml of sterile 0.9% saline at the time of closed reduction and initial stabilization using ankle-spanning external fixation

Study candidates will be identified as they present to the University Hospital emergency room or clinics and will be recruited for enrollment. Informed consent will be obtained as per IRB protocol. The patients will be approached by an orthopedic resident physicians, attending, or study staff to present the current study. Patients will be told of the details of the study and what is required of them if they chose to participate. The patients will be randomized by envelop to one of two groups, the PRP or control group. The patients will be blinded to which treatment they receive. Patients will be treated according to current standard of care, Following initial reduction and placement of ankle-spanning external fixation, synovial fluid will be aseptically obtained via arthrocentesis from both ankles and saved for subsequent biomarker analysis at the Comparative Orthopedic Laboratory. For the injured ankle, the PRP injection will be performed through the same needle used for arthrocentesis. PRP will be isolated from venous blood drawn from a peripheral vein. When appropriate, ORIF will be performed for definitive fracture treatment likely 7-14 days following external fixator placement. Prior to capsulotomy for ORIF, synovial fluid will again be aseptically obtained via arthrocentesis from both ankles and saved for subsequent biomarker analysis.

Follow-up assessments will be performed at 3 weeks, 6 weeks, 12 weeks, 6 months, 12 months, and 18 months after surgery for all patients. Radiographs will be obtained at 6 weeks and each subsequent visit. Patient reported outcomes (PRO) including AOFAS, SF 12 and VAS for pain and level of function will be recorded at all follow-up assessments starting at 3 weeks. At 18 months, MRI of the affected ankle will be performed and used for whole-joint assessment of OA.[10]

Number of patients per group was determined from a pre-study power analysis using previously published data on prevalence of PTA after pilon fracture – the assumption being that a 10% reduction in percentage of patients experiencing symptomatic PTA would be clinically significant. Patients and all patient evaluators will be kept blinded to treatment until all data are collected and analyzed by the co-investigator responsible for

all data analyses. For data analysis, PTA presence will be defined based on a diagnosis of OA, or findings consistent with OA, reported for either imaging modality at any assessment time point. PTA severity will be determined from whole-joint MRI scoring and patient reported outcomes at 18 months after surgery and categorized as mild, moderate or severe. To test the first hypothesis, we will compare treatment groups for statistically significant ($p<0.05$) differences in proportions with PTA, proportions within each severity category, and PRO scores using Fisher's exact tests, t-Tests, and rank sum tests. To test the second hypothesis, we will perform receiver operator characteristic curve analyses to determine the discriminatory capabilities (area under the curve (AUC)) of the panel for distinguishing the presence and severity of PTA. The injured ankle will be compared to the normal, contralateral ankle and AUC>0.8 will be considered to represent high and clinically useful discriminatory capability. In addition, patient age, gender, BMI, tobacco use, and co-morbidities, as well as the CT scan injury severity score[11] will be assessed as variables for predicting likelihood of presence and severity of PTA using Fisher's exact test and odd's ratios.
Based on its mechanisms of action and preliminary data, we expect to reject our null hypotheses and show that a single injection of PRP is associated with significant improvements in outcomes. We also expect that our synovial fluid OA biomarker panel will have high discriminatory capabilities for categorizing presence and severity of PTA in patients being treated for pilon fractures in one ankle.

Subject Selection

Inclusion criteria:

-Patients with closed unilateral pilon fractures
-Patients undergoing staged pilon procedures with an external fixator index procedure

Exclusion criteria:

- Patients who are younger than 18 years of age
- Open pilon fracture
- Patients with contralateral lower extremity injury
- Patients unable to comply with the follow-up appointments
- Patients who had previous ankle injury to the currently injured ankle
- Patients who are pregnant
- Prisoners

E) Re-consent of previously incompetent subjects

Subjects who are consented while in an incompetent state will be approached after the procedure if and when they become competent. During the re-consent process, the subject will again be informed of the study details and be given as much time as needed to make their decision to continue enrollment in the study.

F) Quality Assurance of Data Collection:

Patient confidentiality will be maintained by adherence to the rules of HIPAA and the University of Missouri IRB. All patients will have a de-identified Patient Study ID

number and the data will be maintained in a secured environment within the Department of Orthopaedic Surgery. Additionally, copies of study documents will be maintained in a secured location in a locked suite in the Department of Orthopaedic Surgery, with access granted only to the designated research personnel.

References

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