Title:
Platelet-rich plasma versus Corticosteroid injection for the treatment of femoroacetabular Impingement

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Platelet-rich plasma versus Corticosteroid injection for the treatment of femoroacetabular Impingement

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Study Personnel
Ranae Hoeft, MS; Clinical Research Coordinator
Elizabeth Sibilsky Enselman, MEd, ATC, CCRP; *Clinical Research Coordinator*
Christopher Robbins, PhD; *Research Area Specialist Senior II*
Jaimee Gauthier, BS, CCRP; *Department Clinical Research Coordinator*

Background/Significance:
Femoroacetabular impingement (FAI) is a condition first described by Ganz et al. in 2003 characterized by bony abnormalities of the femoral head and acetabulum[1]. FAI can be divided into two groups based on this anatomic deformity—those that involve the femoral head-neck junction (cam impingement) or acetabulum (pincer impingement)[3]. Because of these morphological alterations, contact can occur between the femur and acetabulum at normal ranges of motion.[10] Repetitive contact because the femoral head and acetabulum can result in damage to the labrum and adjacent articular cartilage[1]. FAI can give rise to pain and is widely regarded as the initiating factor for the onset of hip osteoarthritis[11]. At this point changing the bony abnormality and its effect of the natural history of FAI is unknown. As a result the initial treatment of FAI is non-surgical and includes activity modification, physical therapy, and anti-inflammatory drugs[13]. Corticosteroid injections are commonly used in orthopedics to treat the pain and inflammation of joint and soft tissue conditions[14]. Despite the current use of corticosteroid for the treatment of musculoskeletal conditions and the increased role of platelet rich plasma (PRP), there are no available studies evaluating their role in the treatment of FAI.

More recent treatment efforts have focused on cellular based therapies such as platelet rich plasma (PRP) for the treatment of joint and soft tissue conditions. PRP is defined as a volume of plasma fraction from autologous blood with platelet concentrations above baseline. Platelets contain many bioactive proteins and growth factors that could potentially accelerate healing and stimulate anti-inflammatory properties[21-22]. Recent studies show promising clinical results with intra-articular PRP injections for symptomatic knee osteoarthritis[15-18]. Animal studies have also shown positive effects in stimulating cartilage matrix metabolism in osteoarthritis affected animal joints[19,20].

Purpose:
The purpose of this double-blinded study is to compare the clinical response of intra-articular platelet rich plasma (PRP) versus corticosteroid injection in patients affected by femoroacetabular impingement (FAI).

Specific Aims:
Specific Aim 1: To assess the effect of PRP treatment of FAI symptoms compared to standard corticosteroid treatment.

Hypothesis 1: We hypothesize that compared to corticosteroids, patients with FAI that are treated with PRP will have (i) lower pain scores (ii) improved Hip Disability and Osteoarthritis Outcome Score (HOOS), Patient Reported Outcome Measurement Information System (PROMIS) Global Health Scale scores and (iii) increased hip stability scores as measured by BioDex stability station functional testing.

Specific Aim 2: To determine if PRP treatment of FAI reduces (i) radiographic and (ii) biochemical markers of joint inflammation and cartilage degradation.

Hypothesis 2: We hypothesize that compared to corticosteroids, patients with FAI that are treated with PRP will have (i) a diminished change in Kellgren-Lawrence radiographic scores and (ii) reduced levels of circulating biomarkers C-reactive protein, cartilage oligomeric matrix protein and type II collagen propeptide levels in circulation.

Primary Outcome:
- Pain as measured by Visual Analog Scale (VAS)

Secondary Outcome(s):
- Patient reported function and symptoms
- Evaluate performance of serum biomarkers
- Change in Kellgren-Lawrence classification scores calculated from anterior-posterior (AP) pelvis radiographs between pre-treatment and 1 year post-treatment

Plan for measurement of these outcomes:
- The Primary outcome measures will be:
    - Change in 7 point pain Visual Analogue Scale (VAS)
- Secondary outcome measures include:
    - Hip Disability and Osteoarthritis Outcome Score (HOOS)
        - Western Ontario and McMaster Universities Arthritis Index (WOMAC), calculated as a subscore of the HOOS
    - Patient Reported Outcome Measurement Information System (PROMIS) Global Health Scale
    - Serum Biomarker analysis: IFN-g, IL-6, MCP-1, MIP-1b, IL-1b, TNF-alpha, high-sensitivity CRP, COMP
    - Change in Kellgren-Lawrence classification scores calculated from AP pelvis radiographs between pre-treatment and 1 year post-treatment

Methods:

Inclusion Criteria:

- Patients with symptomatic FAI with duration of symptoms for at least 6 weeks
- Clinical and radiographic evidence of FAI defined as the presence of a cam, pincer or combined lesion apparent from radiographs
- Mild to moderate osteoarthritis (Kellgren-Lawrence grade ≤ 2)
- Patients able to provide consent to study participation
- VAS pain level of ≥ 5

Exclusion Criteria:

- High grade osteoarthritis (Kellgren-Lawrence ≥ 3)
- Minimum joint space < 2 mm as measured on AP radiograph
- Hip dysplasia (center edge angle < 20° on AP radiograph)
- Patients with clinically significant cardiovascular, renal, hepatic, endocrine disease, cancer or diabetes
- Patients with ongoing infection including Tuberculosis, HIV and Hepatitis
- Patient with history of osteomyelitis/septic arthritis or active infections near the joint
- Anticoagulation therapy
- Patients who are pregnant or breast feeding
- Patients with systemic, rheumatic or inflammatory disease of the knee or chondrocalcinosis, hemochromatosis, inflammatory arthritis, arthropathy of the knee associated with juxta-articular Paget's disease of the femur or tibia, hemophilic arthropathy, infectious arthritis, Charcot's knee joint, villonodular synovitis, and synovial chondromatosis
- Patients taking immunosuppressant medication
- Patients with a recent history of abnormal hematology or serum chemistry lab results which is interpreted by investigation team as clinically significant
- Patients receiving any injectable treatment to affected hip within 2 months of study enrollment
- BMI greater than 35 or less than 20
- Known hypersensitivity to kenalog, or lidocaine or any of the components

Minimum Age: 18
Maximum Age: 45

Number of Subjects to be included in study: N = 40 (n = 20 per arm)

Proposed Study Start Date: 7/1/16
Proposed Study End Date: 6/30/18

Summary of Human Subject Involvement:

Patients with symptomatic femoroacetabular impingement (FAI) identified from our MedSport clinic will be potential candidates for this study. The diagnosis of FAI is based on the guidelines described by Ganz[25]. Exclusion/inclusion criteria are described above. Baseline data will include radiographs, serum biomarkers, pregnancy test, and clinical data regarding hip pain. Patients

will be randomized to one of 2 treatment arms: A) ultrasound guided hip intra-articular corticosteroid injection; or B) ultrasound guided hip intra-articular platelet rich plasma injection.

Follow-up will be obtained at 6 weeks, 3 months, 6 months and 12 months. At each follow-up visit, the following will be collected:

1. 7-point visual analog pain scale;
2. The WOMAC, the HOOS, and the PROMIS Global Health scale;
3. Radiographs (initial encounter and 12 months only);
4. Serum biomarkers (IFN-g, IL-6, MCP-1, MIP-1b, IL-1b, TNF-alpha, highly sensitive CRP, COMP) at all time points.

Screening:
X days prior to randomization, potential subjects will have the following tests done as part of screening for eligibility:

- A history and physical examination, including height and weight and BMI calculation;
- Clinical assessment of hip pain; including history, physical exam and subjective patient reporting.
- Radiographs; including standing AP pelvis, Dunn lateral views and false profile view
- Blood will be drawn for serum biomarkers;
- Serum or urine pregnancy test for females of child bearing potential

Patient Selection:
Dr. Awan and Dr Bedi see patients with hip pain as part of their routine clinical practice. They will do all the screening of potential patients. Once a patient has been enrolled in the study, he/she will be rescheduled and that subsequent visit will serve as their initial study visit. During that initial study visit the patient will be randomized to one of the two treatment arms and the injection will be performed.

Randomization Technique
Patients who meet the eligibility criteria will be assigned to steroid or PRP treatment using randomly assigned permuted blocks of 5, created with the random number generator function within STATA, to maintain equal group sizes.

Blood Draws and Serum Preparation
Serum used for biomarkers analysis will be prepared from 4-5mL of blood drawn from an antecubital vein using standard clinical techniques. Serum will be aliquoted and stored in a de-identified fashion at -80ºC until analyzed. CBC with Diff with also be done. This is being done one time to help evaluate patient's overall health.

PRP Preparation
To maintain blinding, all patients will have approximately 125 mL of blood drawn from an antecubital vein. For those individuals who are in the PRP treatment group, PRP will be prepared by Ms. Enselman who is trained in preparing PRP and who is unblinded to the treatment assignment. PRP will be prepared using a commercially available processing unit (Arthrex Angel system; Naples, FL). The Arthrex Angel unit is a FDA cleared system (510k

number BK110046), and the PRP will be prepared using the manufacturers guidelines. Patients will remain in the treatment room while the PRP is being prepared. Once the blood is drawn from the patient, PRP is prepared using density gradient centrifugation with the processing unit mentioned above. Centrifugation takes approximately 20 minutes. Of the PRP that was collected small sample will be sent to the lab for CBC and diff analysis.

Sterile Technique

For ultrasound guided procedures, a sterile probe cover will be used in addition to routine sterile techniques using Chloroprep cleansing solution and sterile drapes.

Hip Intra-articular Corticosteroid

A 22-gauge spinal needle will be advanced from distal to proximal under ultrasound guidance towards the head-neck junction of the hip joint. Approximately 10 ml of 1% Lidocaine will be used for anesthesia of the skin and subcutaneous tissue. Once the hip joint has been reached, the injectate will consist of 4 ml of 10 mg/ml Kenalog for a total dose of 40 mg.

Hip Intra-articular PRP

The hematocrit will be set at 2% to obtain a final product that is approximately 6-8 times higher than baseline in terms of platelet concentration. This approach will also produce a leukocyte-reduced preparation. Final product will be approximately 6-8 ml of platelet rich plasma.

A 22-gauge spinal needle will be advanced from distal to proximal under ultrasound guidance towards the head-neck junction of the hip joint. Approximately 10 ml of 1% Lidocaine will be used for anesthesia of the skin and subcutaneous tissue. Once the hip joint has been reached, the injectate will consist of the final PRP product (approximately 6-8 ml).

Patient and Investigator Blinding

In order to keep the subject blinded towards the type of procedure all patients will have a blood draw. Study investigators and personnel, with the exception of Ms. Enselman and Ms. Gauthier, will be blinded. Ms. Enselman will use the randomization code above and allocate consecutive patients to the intervention. When patients present for treatment, she will prepare the appropriate syringe (PRP or corticosteroid) and then place an opaque sleeve over it so as to conceal which intervention is being given. Each syringe will be marked with the patient's name, ID number, and will be labeled 'Investigational Use Only", and the intervention assigned to this patient will be recorded by Ms. Enselman. This will ensure blinding of the patient, the treating physician (Dr. Awan), and the investigators.

Post-Procedure Care:

Patients will remain in the clinic 30 minutes after injection to monitor for any adverse reactions.

All study patients will be advised to take Acetaminophen for up to 7 days post procedure, 650 mg every 6 hours as needed. Patients will also be provided with a standard FAI rehabilitation program[27].

Patients will be called 3-5 days after the procedure to collect information on any potential adverse events or reactions to the injection

Follow-up Visits:
Subjects will return to the clinic at 6 weeks, 3 months, 6 months and 12 months.
At each visit, the following will be performed:

- Physical exam;
- 7 point visual analog pain scale;
- the WOMAC, the HOOS, and the PROMIS Global Health scale;
- Hip Radiographs including standing AP pelvis, lateral Dunn views, and false profile view (initial encounter and at 12 months only);
- serum biomarkers (IFN-g, IL-6, MCP-1, MIP-1b, IL-1b, TNF-alpha, highly sensitive CRP, COMP) at all time points; and
- any adverse events, regardless of severity

Billing:
Neither patients nor their insurance companies will be billed for the costs of injection of steroid or PRP, blood draws or radiographs used in the study.

Risks:
Standard risks involved with intra-articular hip injection including bleeding, infection, nerve damage, increased pain, reaction to anesthetic.
For Kenalog, complications are infrequent, though some mild local complications may occur, as listed in the FDA approved label dated June 2011. Some of these are atrophy of the skin at the injection site, facial flush, and post-injection flare (soreness and inflammation following the injection) . Systemic side effects such as infection, increased blood glucose, hypercortisolism, and others are rarely seen. There is a rare risk of anaphylaxis, including death

Confidentiality:
Standard clinical protocol regarding patient confidentiality. All data will be maintained by the primary investigator in a locked office and password-protected computer.

Data Collection:
Data collection will be collected and entered by orthopedic surgery research team member assigned to the study and stored into a REDCap database via Ipad. This includes clinical data, radiographic data and analysis of serum biomarkers.

Subjects' hip pain levels will be assessed via standardized orthopedic survey tools (7 point pain VAS, Western Ontario and McMaster Universities Arthritis Index (WOMAC), Hip Disability and Osteoarthritis Outcome Score (HOOS), Patient Reported Outcome Measurement Information System (PROMIS) Global Health Scale) at baseline,
6 weeks, 3 month, 6 months, and 12 months.

Hip radiographs will be performed at baseline and at 12 months, and graded Stage 1-4 via Kellgren-Lawrence classification in a blinded fashion by Dr. Morag as described[26].

Biomarkers analysis will be performed in Dr. Mendias' lab as described[23,24]. Serum will be aliquoted and stored at -80ºC in a de-identified fashion in secured freezers in Dr. Mendias' lab.

Samples will be analyzed in duplicate at each time point, and interassay coefficients of variation will be calculated. For hsCRP (Calbiotech) and COMP (R&D Systems), ELISAs will be performed following manufacturer's instructions. For IFN-g, IL-6, MCP-1, MIP-1b, IL-1b and TNF-alpha, a multiplex Luminex-based assay (Millipore) will be performed following manufacturer's instructions.

Data and Patient Safety Monitoring Plan

All data will be maintained by the primary investigator in a locked office and password-protected computer.

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately. All clearly related signs, symptoms and abnormal diagnostics should be recorded.

Recording of Adverse Events:

All adverse events occurring during the study period will be recorded. Adverse event data collection will begin the moment informed consent is signed. The clinical course of each event will be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause.

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the necessary paperwork and/or log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

Survey Assessments:

- 7 point VAS for pain
- Hip Disability and Osteoarthritis Outcome Score (HOOS)
    - Western Ontario and McMaster Universities Arthritis Index (WOMAC), calculated as a subscore from HOOS
- Patient Reported Outcome Measurement Information System (PROMIS) Global Health Scale

Compensation:

Patients will be compensated 25 dollars at the initial visit, and 10 dollars at each follow-up visit. This will be provided in the form of a Visa gift card mailed to the patient's home address.

Data Analysis:

The study sample size is based upon power calculations for change in pain score data from a previous study by our group in patients with FAI[23]. To detect a difference in the change in pain between the first and last visit of 1.7 units, on a 7-point pain scale, using a power of 80% and α=0.05, requires at total N of 32, or 16 per group. To account for 20% of patients who might withdraw, we will recruit 8 additional subjects for a total of 40 patients. We will use a mixed-effects linear regression model to look at the changes in individual parameters at multiple time points over the course of the study, as well as the associations between changes of multiple parameters. Independent variables in the model are treatment assignment and time, dependent

variables are outcomes scores, biomarkers and Kellgren-Lawrence scores. First, we will perform univariate and univariable models to explore the relative importance of each predictor variable followed by a stepwise procedure in which we will include all significant variables in multivariable model followed by dropping the highest non-significant variable (significance will be set at p=0.10) until only significant variables remain. This will be repeated for each dependent variable. The robustness will be tested by performing model fitting and examining residual plots.

Potential Pitfalls and Limitations:

The study team has extensive experience studying FAI in patients in our MedSport clinic at the University of Michigan. All techniques and methodologies are currently in use and have previously been published in top orthopaedic journals. The main limitation we perceive is recruiting a sufficient number of subjects to the study. However, we have a high volume of patients pursuing treatment for FAI and anticipate it would be easy to recruit subjects into the study. While we think that a mixed-effects linear regression model is appropriate and informative for this study, an alternative approach would be a two-way repeat measures ANOVA. Given the statistical expertise of the study team, we do not anticipate any problems in performing analyses.

Future Directions:

We hope this study is the first of several evaluating the use of PRP in the treatment of FAI. If the results from this study are promising, larger multicenter studies and extended time points would be warranted. Identifying specific pro-inflammatory or pro-atrophy cytokines which are elevated could also support the potential use of targeted inhibitors of these factors to reduce inflammation and improve strength.

Study Team Experience:

Tariq M. Awan, D.O. is an Assistant Professor at the University of Michigan in the Department of Orthopaedic Surgery and will serve as the PI on this study. He will be responsible for IRB approvals and regulatory compliance, performing patient interventions, ensure patient safety, coordinate weekly meetings with research personnel, monthly meetings with study Co-Is, guide the translational nature of the project and prepare the manuscript to report the study findings. Dr. Awan completed his residency in Family Medicine at Henry Ford Hospital in Detroit, Michigan, where he served as Chief Resident. Dr. Awan completed his fellowship training in Primary Care Sports medicine at the Mayo Clinic in Jacksonville, Florida. Dr. Awan joined the Department of Orthopaedic Surgery faculty at the University of Michigan in July 2014. He has clinical experience in providing non-operative orthopaedic care ranging from the recreational to the professional athletes. Clinically, Dr. Awan treats multiple musculoskeletal conditions and sports injuries of the extremities and pelvis in adolescents and adults. He has a particular clinical interest in chronic tendon disorders, musculoskeletal ultrasound for interventional procedures, and the use of biologic treatments/platelet rich plasma for the treatment of musculoskeletal problems and acute sports injuries. Dr. Awan has also been active at the national level in teaching musculoskeletal ultrasound. He has been an invited lecturer and has been teaching faculty for multiple courses geared at teaching physicians how to incorporate this technology within an orthopaedic and sports medicine practice. Dr. Awan is board certified by the American Academy of Family Physicians, The American Osteopathic Board of Family Medicine and has a certificate of added qualification in Sports Medicine.

Joel J. Gagnier, PhD, MSc, ND, is a Clinical Epidemiologist and Assistant Professor in the Departments of Orthopedic Surgery and Epidemiology at the University of Michigan. Dr. Gagnier will serve as a Co-Investigator on this study and will provide expertise in clinical trials study design, data interpretation and statistical analyses and will supervise Dr. Robbins. Dr. Gagnier's research program focuses on clinical and methodological research related to musculoskeletal conditions and clinical care.

Christopher Mendias, PhD, ATC is an Assistant Professor of Orthopaedic Surgery and Molecular & Integrative Physiology at the University of Michigan Medical School. Dr. Mendias will serve as a Co-Investigator and perform the biochemical assays and analysis in his lab. Dr. Mendias is a rehabilitation clinician scientist with a basic and clinical research program focused on gaining a greater understanding of the genes and signaling pathways that regulate muscle and tendon structure and function, and in the development of new therapeutic interventions for the treatment of tendon and muscle injuries and diseases.

Asheesh Bedi, MD is the Harold and Helen W. Gehring Early Career Professor of Orthopaedic Surgery and an Associate Professor of Orthopaedic Surgery and Chief of Sports Medicine. Dr. Bedi will serve as a Co-Investigator and will work with study investigators in analyzing and interpreting data. Dr. Bedi's research program is focused on clinical and translational musculoskeletal research. He has a large practice and research program focused on the surgical treatment of FAI and other hip degenerative conditions.

Yoav Morag MD is an Associate Professor of Radiology and a member of the Division of Musculoskeletal Radiology. Dr. Morag will serve as a Co-Investigator and will be responsible for analysis and interpretation of radiographs in this study. Dr. Morag has broad research program and extensive in musculoskeletal radiology.

Elizabeth Sibilsky Enselman, MEd, ATC, CCRP is a clinical research coordinator and athletic trainer and will assist Dr. Awan with preparing and delivering interventions and performing blood draws on subjects.

Christopher Robbins, PhD is a Research Area Specialist Senior II in Dr. Gagnier's lab and will establish and maintain the REDCap database and perform data analyses in this study and assist Dr. Awan in preparing the manuscript for submission.

Jaimee Gauthier, BS, CCRP is the department clinical research coordinator and will generate the randomization scheme, and assist Dr. Awan in maintaining IRB approvals and regulatory compliance.

Bibilography:

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