

NYULMC IRB PROTOCOL

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TITLE:

Clinical Outcomes of Platelet Rich Plasma Injection versus Corticosteroid Injection for Baker's Cyst

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1. BRIEF SUMMARY

Baker's cyst is a common entity in adults who have knee pathologies, having different ways to approach it with different recurrence rates. We will attempt to report the outcome of treating Baker's cysts with ultrasound-guided Platelets-Rich-Plasma injection into the cyst versus ultrasound guided Corticosteroid injection into the cyst with at least 6 months follow-up. We plan on evaluating recurrence rates and persistence of symptoms.

2. PURPOSE OF STUDY AND BACKGROUND:

I. Purpose:

To evaluate the long term clinical outcome of Ultrasound-guided Platelets-Rich-Plasma injection versus Ultrasound guided Corticosteroid Injection in Baker's cysts.

II. Background:

The treatment of Baker's Cysts are based on its presentation, asymptomatic cysts are currently managed conservatively, symptomatic cysts are treated with joint aspiration and Corticosteroid injection, which have shown according to literature a decrease of the cyst size in approximately two-thirds of patients within 2-7 days but only complete disappearance in approximately 7 %. Ultrasound guided cyst aspiration and Corticosteroid injection are also used with reduction of cyst's size with recurrence in 6 months of 19%. Surgical options to remove the cyst include, Open Resection with a recurrence of 50%, 25% of patients have motion limitation recurrence, 37% have wound healing problems or tense swelling of the calf and 75% of patients have joint pain lasting more than 2 days⁴. Arthroscopic resection, with no recurrence in ultrasound performed 6 and 12 months after procedure, pain lasting more than 3 days in 28% of patients, mild hematoma in 7% of patients and 7% where converted into an open procedure⁴

There is no study using ultrasound guided aspiration of cysts with platelet-rich-plasma injection (PRP). The rationale for the use of PRP is the belief that the additional platelets will exponentially increase the concentration and release of multiple growth and differentiation factors at the injury site to augment the natural healing process⁹. PRP does not have any described negative side effect due to the fact that is being prepared from subject's own blood, with no risk of allergy or cross infection, relatively easy for a practiced clinician, and reproducible⁷. Studies have shown no negative side effects from the use of PRP injections since its source is the own patient's blood⁶, there is only one study describing local inflammation after a patellar injection of PRP in a patient with Diabetes type I, probably due to the injection and not the PRP itself, hence we are excluding patients having diabetes or any immunologic deficiency as risk factor¹¹. . PRP is FDA approved, due to no side effects caused by PRP directly, assuring its safety for clinical use. Steinert et al⁹. shows all the latest studies using PRP in sports medicine, showing effectiveness in the use PRP and no side effects, hence, PRP injections are safe to use in clinical subjects. ,

III. Study Design:

Prospective study with Randomized patients into Ultrasound-guided Platelets-Rich-Plasma injection and Ultrasound guided Corticosteroid Injection and at least 6 months follow up at our institution.

IV. Aims:

- 1) To evaluate the outcome of baker's cysts with the use of Platelets-Rich-Plasma versus Corticosteroid
- 2) To evaluate the recurrence of baker's cysts treated on each group
- 3) To evaluate complications
- 4) To evaluate side effects

3. CHARACTERISTICS OF RESEARCH POPULATION

I. *Sample Size Justification:*

Assuming normality of the data, we calculated the statistical power assuming effect size 0.3 that is the difference in proportions of people who change their score in their follow-up. We also assume a standardized normal (Z) distribution for one sided test, we aim to achieve 80 % of the power fixing the type one error (alpha) level at 0.05 and we repeated the calculation under different assumption of score changing proportions at each group.

<i>P1</i>	<i>P2</i>	α (Type I error)	$1 - \beta$ (power)	Each Group	Total
0.1	0.4	0.05	0.80	25	50
0.05	0.35	0.05	0.80	21	42
0.01	0.30	0.05	0.80	19	38

From the table, we expect that our study will have an enough power to detect the true difference with at least 80% of probability with 25 samples for each arm even allowing less conservative score change proportions. The sample size determined also accounts for screen failures. The total number of subjects to participate in the study is 50.

II. **Gender of Subjects:**

Both men and women will be selected for the study without gender preference

III. **Age of Subjects:**

There will be no upper age restriction in this study. No participants under age 18 will be selected.

IV. **Racial and Ethnic Origin:**

There is no ethnic preference or restriction for this study

V. **Inclusion criteria**

- Patients at least 18 years old.
- Patients with baker's cyst who also present with at least one of the following: swelling, local pain or discomfort, limited range of motion or any other symptom directly caused by the baker's cyst.

VI. **Exclusion criteria**

- Patients younger than 18 years old
- Local or Systemic active infection

- Active cancer treatment
- Immunodeficiency
- Diabetes
- Hypersensitivity or allergy to Corticosteroid or Lidocaine

VII. Vulnerable Subjects:

We do not anticipate inclusion of vulnerable populations within our study group

4. METHODS AND PROCEDURES

I. Methods and procedures

Patients who meet the inclusion criteria and do not meet any of the exclusion criteria will be identified during office hours by the PI and co-investigators. Our research staff will explain the purpose of the study to the patient, and will go over the consent form, to fully inform and answer any questions the subject may have.

After patients accept to participate in the study and are formally enrolled in the study, the same day, patients will be asked the Visual Analogue Score (VAS), demographic information will be collected, along with any associated medical history with special interest in knee pathologies and previous treatments. They will be also classified according to their symptoms by the Rauschning and Lindgren criteria which are used to clinically evaluate the presence of the popliteal cysts, pain, posterior sense of tension in the popliteal fossa and its clinical importance for range of motion reduction. They will also complete the Knee Injury and Osteoarthritis Outcome Score (KOOS) to assess short and long term outcome of knee related conditions.

Rauschning and Lindgren criteria:

Grade 0: absence of swelling and pain, no limitation of range of motion

Grade 1: light swelling or a sense of posterior tension after intense activity, minimal limitation of ROM

Grade 2: swelling and pain after normal activity, ROM limitation less than 20 degrees

Grade 3: swelling and pain even when resting, ROM limitation more than 20 degrees

The Knee Injury and Osteoarthritis Outcome Score (KOOS)¹⁰:

- Pain
- Other Symptoms
- Function in daily living (ADL)
- Function in sport and recreation
- Knee-related quality of life (QOL)

We will blindly set 25 envelopes sealed for each group, and randomly assign one of them to each patient. Patients will then be part of either the Platelets-Rich-Plasma group or the Corticosteroid group.

Platelets-Rich-Plasma group: Patients will be asked to stop taking any type of anti-inflammatory medication from 7 days before the procedure to 2 weeks after. At the moment of the procedure, at CMC, the radiology team will draw 30cc of venous blood from the patient and the blood will be processed with the PRP kit and centrifuged in the SmartPrep PRP machine.. The patient is then scanned prone using a linear 14 or 9 MHz transducer. A 20 Gauge spinal needle is usually employed for purposes of aspiration. We can use sterile saline to confirm needle placement in the cyst in lieu of lidocaine and then inject the PRP by the radiologist.

The procedure will be done without using any local anesthetic to avoid pharmacological interaction with the injected substance. A compression bandage will be placed locally for 7 days. Investigators will monitor any side effect from the injection and treat the patients per standard care, this can include

prescription of analgesics. No remaining biomaterial or any blood sample will be collected or stored for future studies.

It must be noted that the radiology team (technicians and radiologist) in charge of the PRP processing and handling, are well trained in this matter, since they have been using PRP and Harvestech SmartPrep PRP machine in a weekly and sometimes daily basis, as part of patient's treatment or as part of previous clinical trials. Dr Adler, who is one of the Co-investigators, will be the radiologist supervising the study in the radiology department, to minimize any potential risk, and assuring appropriate preparation of the product and execution of the procedure.

Corticosteroid group: Patients will be asked to stop taking any kind of anti-inflammatory medication from 7 days before the procedure to 2 weeks after.. The radiology team will draw 30cc of blood from the patient, and this blood will then immediately be discarded out of sight from the patient. The blood does not need to be used for the control group, and none of it will be stored for future use. Blood draw is crucial in this group as it will keep the research activities consistent between the groups and prevent any patient from knowing if they are in the treatment or control group. It is crucial to keep the patient blinded for the study to eliminate any bias in the outcomes.

An ultrasound guided aspiration and triamcinolone (40 mg) diluted with lidocaine without epinephrine and ropivacaine will be used to anesthetize the tissues down to the cyst(including within the cyst for steroid injections). A compression bandage will be placed locally for 7 days. Investigators will monitor any side effect from the injection and treat the patients per standard care, this can include prescription of analgesics.

Both groups will be asked to have a follow up after 3 months and 6 months of the day of the procedure with measurements of the dimensions of the baker's cysts with ultrasound, Visual Analogue Score, and Rauschning and Lindgren criteria and reclassification.

SCHEDULE OF EVENTS - CONTROL GROUP (Corticosteroid)

Description	Visit 1 (Baseline)	Visit 2 (12 Week)	Visit 3 (24 Week)
Study Visit Windows			
Informed Consent	x		
Complete Physical & Medical History	x		
Knee Assessment/Brief Exam	x		
Ultrasound	x	x	x
Aspiration and Steroid Injection	x		
Visual Analogue Score	x	x	x
Knee Injury and Osteoarthritis Outcome Score	x	x	x
Rauschning and Lindgren criteria	x	x	x

SCHEDULE OF EVENTS - TREATMENT GROUP (PRP)

Description	Visit 1 (Baseline)	Visit 2 (12 Week)	Visit 3 (24 Week)
Study Visit Windows		+/-2 days	+/-2 days
Informed Consent	x		

Complete Physical & Medical History	x		
Knee Assessment/Brief Exam	x		
Ultrasound	x	x	x
Aspiration and PRP	x		
Visual Analogue Score	x	x	x
Knee Injury and Osteoarthritis Outcome Score	x	x	x
Rauschning and Lindgren criteria	x	x	x

II. Data Analysis and Monitoring

Descriptive statistics will be provided to compare baseline distribution of two groups, those who are treated by a traditional method and those who are treated by Cortisone for Baker's Cyst. Basically, we are comparing the change of scores in two groups in this study: a matched T-test (for a continuous score) or a chi-squared test (for a discrete score) or using non-parametric tests, Wilcoxon rank test and/or Kruskal-Wallis test. The type of test will be decided after we check the normality of score distributions using Kolmogorov-Smirnov test or Shapiro-Wilks test.

III. Data Safety Monitoring Plan (DSMP)

I. Description of the types of data or events that will be captured

a. SAFETY information to be collected

All disease signs and symptoms experienced by the patient, as defined below as AE, TEAE, SAE, and UADE, will be recorded from questionnaires during each visit and clinic visits. Specific information collected about the adverse event will include the nature, date and time of the event. There will also be a determination of seriousness, frequency, severity, corrective treatment, outcome, and the principal investigator's opinion of the relationship to the Ultrasound guided aspiration and injection of either Corticosteroid or Platelet-Rich-Plasma. Documentation will begin at the time the patient signs the informed consent form to the completion of the final study visit.

- Adverse Event (AE)

An AE is any untoward or unfavorable medical occurrence in a patient involved in a study associated with the use of a medical treatment or procedure regardless of whether it is considered related to the treatment or procedure. AEs therefore include any undesirable physical, psychological or behavioral effect experienced by a subject during their participation in this investigational study, whether or not the effect is considered interrelated.

The Principal Investigator will assess relationship between the AE and study treatment according to the following definitions:

- Unrelated: There is no relationship between the AE and the use of the investigational device or any study treatment. This may include but is not limited to the incident being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the patient experienced.
- Remote/unlikely: There is no clear relationship between the AE and the use of the device under investigation or study treatment and it is unlikely that there is some relationship.
- Possible: There is no clear relationship between the AE and the use of the study device or study treatment; however, one cannot definitely conclude that there is no relationship.

- Probable: While a clear relationship to the device under investigation or study treatment cannot be established, the AE is associated with an expected AE or there is no other medical condition or intervention, which could explain the occurrence of such an event.
- Definite: The relationship of the AE and the use of the study device or the execution of the study treatment can definitely established.

- Treatment Emergent Adverse Event (TEAE)

A TEAE is defined as any event not present prior to the initiation of the treatment or any event already present that worsens in either intensity or frequency following exposure to the treatments. The assessment of TEAEs and their relationship to the study treatment will be assessed by the Principal Investigator.

- Serious Adverse Event (SAE)

A SAE is defined as any AE, irrespective of a possible relationship to the study device that results in any of the following outcomes:

- Death
- Life-threatening event
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly
- An important medical event defined as an AE that may jeopardize the subject and may require medical or surgical intervention in order to prevent one of the outcomes listed above

- Unexpected Adverse Device Effect (UADE)

A UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in product labeling, the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with the study device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

b. Clinical Outcomes of Platelet Rich Plasma Injection versus Corticosteroid Injection for Baker's Cyst, information to be collected

- History and physical exam of the patient
- History and physical exam of the study lower extremity
- Concomitant medications
 - Type
 - Dose
 - Frequency
 - Duration
- Patient Outcomes Assessments
 - Visual analog scale (VAS) for rating activity-related pain
 - Rauschnig and Lindgren criteria for rating clinical presence of Baker's cyst
 - Knee Injury and Osteoarthritis Outcome Score (KOOS) for rating outcome of knee related conditions
- Ultrasound of Study Lower extremity
- Reportable and/or adverse events

II. Plan for assuring data accuracy and protocol compliance

Study Monitor

The Principal Investigator for this study will also serve as the Study Monitor. He will conduct interim monitoring of accumulated data from research activities to assure the continuing safety of research participants, relevance of the study hypothesis, appropriateness of the study, and integrity of the accumulating data.

Principal Investigator

On a quarterly basis, the PI will be the Study Monitor and will meet periodically with the Research Co-investigator(s) and research staff to discuss the current findings and analysis. During these meetings, the PI will also be responsible for verifying data accuracy, and compliance with the study protocol.

Research Coordinator

As the coordinator, he will be responsible for providing data management support to the PI by collecting and documenting the required study data. This information will be documented in a secure, excel spreadsheet with appropriate subsections to distinguish the various types of data/events. Each quarter, the Research Coordinator will meet with the PI and Co-Investigator(s) to discuss the current findings/analysis, concerns/issues (unanticipated problems and adverse events), and the overall study in general.

III. Timeframes for reporting adverse events and unanticipated problems to the monitoring entity

All reportable events will be sent to the IRB in accordance with the timeframes specified by NYU School of Medicine guidelines. The Principal Investigator will have the responsibility of completing and submitting a Reportable Events form to the IRB. This form can be found at the following web address:

<http://irb.med.nyu.edu/for-researchers/other-submissions-and-reviews/events-and-information-require-prompt-reporting-irb-re>

IV. Frequency of monitoring entity's assessment of data or events

The study monitor will assess all safety data immediately as they occur. Study data will be assessed on a weekly basis.

V. Specific triggers or stopping rules

In case UADEs or SAEs occur, which are thought to be possibly related to steroid or Platelet-Rich-Plasma injections and are considered to be a potential health risk for participating subjects, the study monitor who is also the PI will report this information immediately to the IRB. At this point, the PI may decide, in consultation with the participating Investigators, to either 1) postpone treatment of newly-enrolled patients and to discontinue the treatment of established study subjects or 2) close out the study. If the study is postponed, the study will not resume until the investigators have thoroughly examined the event(s) and conclude that continuation of the clinical trial is justified. A review of the event, by the IRB, the PI, or both, may necessitate modifications to the protocol to ensure patient safety.

VI. Procedures for communicating the outcome of the reviews by the Monitoring Entity to the IRB, the study sponsor, and other appropriate entities

Outcomes of monitoring reviews will be communicated to the IRB through quarterly summaries/reports that will include a narrative on all adverse and reportable events (previously reported or not, serious or not), as well as any proposed changes to the protocol and/or study analysis.

IV. Data Storage and Confidentiality

All research data will be recorded into a password-protected database and stored in the offices of the investigators on a password-protected computer. After initial data collection, all private health information will be removed, and patients will be tracked with an anonymous study number. The collected data will be permanently deleted immediately after the completed study is accepted in full for publication.

5. RISKS AND BENEFITS

I. Risks:

Subjects involved in the study will be at risk of complications associated with the injection such as pain at the site of the injection, infection, bleeding or hematoma formation.

Subjects in the Corticosteroid group: Studies have shown that corticosteroid injection into soft tissues is safe, and no serious unexpected reactions have been reported. In general, corticosteroid injection into the cyst may result in local atrophy and post injection flare but the use of Triamcinolone lowers the frequency of these complications from happening due to its pharmacological characteristics.

Subjects in the PRP group: Although There has been no data about using PRP into a baker's cyst, studies have stated that the side effects of Platelets-Rich-Plasma injections in soft tissues are very limited as the patients are utilizing their own blood. The main risk includes local infection (less than 1%) and flare reaction beginning the day after the injection.

Breach of confidentiality is an unlikely, but possible risk to subjects included in this study.

II. Protection Against Risks:

Medical protection for Corticosteroid group: Studies have reported that the use of triamcinolone acetate and its dilution with lidocaine without epinephrine decrease the risk of local atrophy and post injection flares. Study investigators will monitor any side effect from the injection and treat them per standard practice. This can include prescription of oral anti-inflammatory medications or analgesics, provision of counseling for self-management by the patient and referral for further treatment as necessary.

Medical Protection for PRP group: The study investigators will monitor the patients and any side effect from the injection and treat them as necessary, including the prescription of analgesics, provision of counseling for self-management by the patient and referral of the patient for further treated if needed.

All patients will be deidentified and given a code. Information linking the patient codes to the participants' names and medical record numbers will be stored in a secure location separate from the medical information. Access to the information linking the linkage codes with participant identifiers shall be documented.

Participant medical information will be stored electronically within a password protected spreadsheet available only to the PI, co-investigators, and research staff as necessary for data analysis. The names and medical record numbers of the study participants will be deleted from their stored medical information and replaced with a linkage code. Access to participant medical information contained within the registry will be restricted.

III. Potential Benefits to the Subjects:

The main benefit to patients will be future adjustments to recommend Ultrasound-guided Platelets-Rich-Plasma injection versus Ultrasound guided Corticosteroid Injection for management of symptomatic baker's cyst.

IV. Costs/Reimbursement

All study-related costs associated with the subject being in this study will be paid by the sports division of the orthopedic department. The patient or the insurance of the patient, will be charged or held responsible for the costs of the routine care of the baker's cyst. (The care would be received by the patient if were not participating in the study)

The Patient will not receive any compensation for participating in this study.

6. SUBJECT IDENTIFICATION

Method of Subject Identification and Recruitment:

Subjects will be identified prospectively by investigator and co-investigator during office visit, and patients will be consented right after the office visit by one of our research personnel, the research personnel will be properly trained to describe in detail every item of the written consent form, and answer any question that the subjects may have. After being consented, the subjects will decide whether or not to participate in the study, if they decide to do so, They will sign and receive a copy of the written consent form. In order to minimize the risk of breach of confidentiality, we will maintain the data and informed consent forms on a secure and password protected database accessible only to study staff. After initial data collection, all private health information will be removed, and patients will be tracked with an anonymous study number. The collected data will be permanently deleted immediately after the completed study is accepted in full for publication.

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