Precision Assessment of Platelet Rich Plasma for Joint Preservation

NCT03460236

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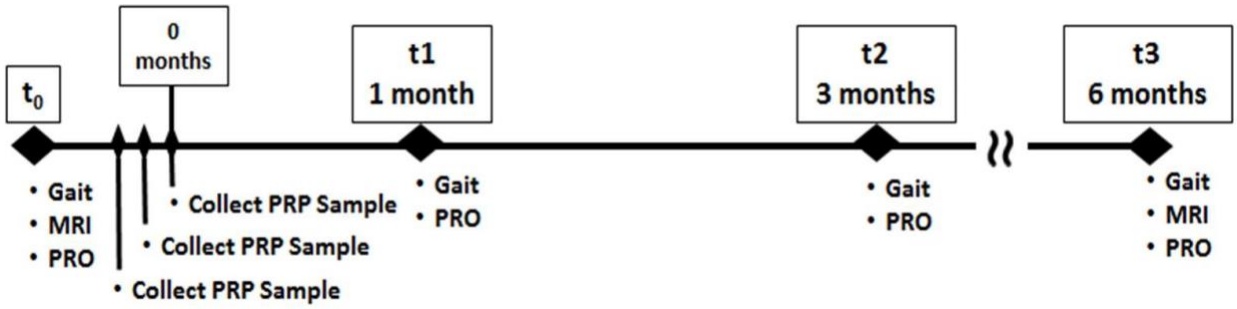
Protocol

We will recruit 130 participants who are undergoing PRP injections for clinical treatment of symptomatic early knee OA into this comprehensive multidisciplinary, prospective, clinical study. Patients who meet the eligibility criteria described below and who provide informed consent will be enrolled. Human subjects will undergo research assessments at baseline, and at 3 clinically relevant time points of 1 month (4 weeks), 3 months and 6 months after completion of PRP injections. For those responding to corticosteroid injections, clinicians typically provide the injections no more frequently than every 3 months due to concerns for adverse effects to the articular cartilage. Over twenty years of clinical use, a 6-month duration of effect from a 3 injection HA series has generally been considered as an adequate response sufficient to justify repeat treatment by this method. We have therefore selected 1, 3 and 6 months for our post-treatment assessment time points.



Baseline: Subjects will be recruited from patients already indicated for and receiving PRP treatment as part of clinical care in the PI's new PRP injection clinic at the VA Palo Alto, or in the practices of the PI and her associates at the affiliated academic center where additional women will be recruited. At the baseline test (t_0), human subjects enrolled in the study will complete self-administered pain/function questionnaires, perform a gait test to determine walking mechanics across the knee prior to PRP injection, and undergo a baseline MRI scan inclusive of T2 map sequences. In addition, medication usage will be recorded.

PRP injection: Subjects will receive a series of three injections of autologous PRP, each approximately one week apart. Twice as much blood as needed for the clinical injection will be drawn and the resulting excess PRP from the actual PRP prepared for clinical treatment and injected into the knee will be saved and taken to the laboratory for analysis. Participants will complete the 3-injection course within a one-month time period.

1-month (4 weeks) and 3-months follow-ups: At the 1-month (t_1) and 3-month (t_2) post-injection visit, gait analysis will be performed and patients will complete self-administered pain/function questionnaires

6-months follow-up: At the 6-month (t_3) post-injection visit, gait analysis will be performed and patients will complete self-administered pain/function questionnaires. Patients will also undergo an MRI scan inclusive of T2 map sequences.

This project will recruit males and females undergoing PRP injection for treatment of symptomatic early tibiofemoral knee OA. Inclusion Criteria: (1) ages 30-70 years, (2) symptomatic early knee OA defined as having knee pain as well as (Kellgren-Lawrence (KL) radiographic grade 1-2 (osteophytes and/or <50% joint space narrowing), or KL grade 0 (normal radiographs) with MRI and/or arthroscopic evidence of cartilage degeneration or loss, (3) full weight-bearing status, and (4) have elected to receive PRP treatment. Exclusion Criteria: (1)

inflammatory arthritis, gout or recurrent pseudogout (2) symptomatic OA of other lower extremity joints, (3) BMI >35 kg/m_2, (4) use of walking, orthopedic, or prosthetic assistive device, (5) severe systemic disease defined as American Society of Anesthesiologists (ASA) 3 or above[56], (6) inability to have MRI, (7) pregnant or intending to become pregnant during the study, (8) predominantly patellofemoral disease.

Statistical Analysis Plan

The primary outcome consists of the counts (and percentages) of PRP recipients whose self-reported KOOS Pain and WOMAC Functional improvements between pre-treatment and 6-month post-treatment assessments exceeded the minimal important change (MIC) thresholds for those scales: +12.4 points, -17 points, respectively (Silva et al , 2023).

Silva MDC, Perriman DM, Fearon AM, Couldrick JM, Scarvell JM. Minimal important change and difference for knee osteoarthritis outcome measurement tools after non-surgical interventions: a systematic review. BMJ open 2023; 13(5): e063026.

Are you participating in any other research studies? _____ yes _____no

PURPOSE OF RESEARCH

You are invited to participate in a research study about the effect of platelet enriched plasma (PRP). We hope to learn the clinical effect of platelet enriched plasma (PRP) treatment in knee osteoarthritis (OA). You were selected as a possible subject in this study because you have medial compartment knee OA.

This study is being done together by researchers at VA Palo Alto and Stanford University.

This research study is looking for 130 people with medial compartment knee OA. The VA Palo Alto expects to enroll 100 research study subjects.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 10 years. Your active participation in this study will last up to 60 months, with active in-person testing (in laboratory) of approximately 15 hours total.

PROCEDURES

If you choose to participate, Dr. Chu, or a designated representative of her research staff, will describe the study procedures to you.

Screening Procedures:

Dr. Constance Chu and her research study staff will tell you about the study and give you a copy of the consent form. After you have read the consent form and have all your questions answered, both you and the research staff will sign and date the document. You will be given a copy. We will ask questions regarding your health and all the eligibility records, including pertinent past medical records, will be reviewed. In order to

help us determine the amount of arthritis you have, there may be up to four x-ray view taken of your legs. We will not allow anyone who is pregnant participate in this trial because it may have an effect on the fetus, and we may do a pregnancy test.

Experimental Procedures:
At a baseline test, we will ask you to complete questionnaires, have a motion analysis test, blood draw (up to 3 tablespoon), and have an MRI scan.

Dr. Chu and her research study staff will have you answer survey questions about your knee, your pain, your activities, and your overall quality of life. It should take about 20 minutes to answer the survey questions. You have the right to refuse to answer particular questions.

You will be scheduled for a motion pattern analysis in the gait analysis lab where you will wear reflective markers so that we can view and assess your motion. Motion analysis will take approximately 1.5 to 2 hours of your time. The motion analysis study involves going to the laboratory where a study team member will have you change into a pair of shorts. The investigators in the gait laboratory will identify various landmarks on your upper body, pelvis, legs, and feet and will attach special adhesive reflectors onto these various locations. We will ask you to perform a number of activities of daily living while we record your actions with special video cameras that are designed to track only the movement of the reflective markers. You may experience mild discomfort when the small adhesive reflective markers are removed from your skin. This discomfort is similar to that experienced when removing a Band-Aid.

If you do not have a suitable clinical MRI, you will be scheduled for an MRI scan of your knees to determine disease severity. The MRI scans will take approximately 2 hours. The MRI may be obtained at the VA or Stanford University.

At the time of your clinical treatment(s), we will save a sample of the joint injection for this research.

We will be also be obtaining about 4 tablespoons of blood for this research study at each of your clinical injections. You will be asked to donate additional tube(s) of blood specifically for this research study. If you are scheduled to have a blood draw, this will be done at the same time to avoid the use of an additional needle stick.

If synovial fluid will be removed as part of your clinical care, we would like to save a sample of the fluid (which is normally discarded) for this research.

Following your clinical treatment, we will ask you to return for follow-up visits at 1, 3, and 6 months after the end of your treatment(s). At 1 month and 3 month follow-up visits, we will ask you to have a motion analysis test and complete questionnaires. At the 6 month follow-up visit, we will ask you to complete a motion analysis test, complete questionnaires, and have a second MRI scan. We may also ask you to complete up 10 questionnaires in the course of the study.

MRI (Magnetic Resonance Imaging)

MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body interior. The scanning procedure is very much like an X-ray or CT scan. You will be asked to lie on a long narrow couch for a certain amount of time (approximately 2 hours) while the machine gathers data. During this time you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance (MR) scanner. We will provide earplugs or headphones that you will be required to wear. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling.

Risks:

Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, or if you could be pregnant, you should notify the operator/investigator. You should also notify the operator/investigator if you have any tattoos on your body, including eyeliner and other permanent makeup. Tattoos could become warm and irritated during the scan and remain so for several days. If you would prefer not to participate in the MR scan due to the presence of tattoos on your body, please inform a research team member.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. However, you may have the scan stopped at any time if this occurs.

Some of the radio frequency imaging coils, imaging software and devices being used in your scan are not approved by the FDA but are similar to counterparts that have been approved by the FDA. There is a small risk of heating from the cables associated with these devices. Please report any heating sensation immediately.

Dizziness or nausea may occur if you move your head rapidly within the magnet.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

The scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. The investigators for this project may not be trained to perform medical diagnosis. The investigators are not responsible for failure to find existing abnormalities with these MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. If this occurs, a doctor will be asked to look at the images to see if any medical follow-up is needed. If so, the investigator will contact you and recommend you inform your doctor about the findings. Because the images are taken using research settings they will not be made available for clinical purposes.

<u>Women of Childbearing Potential</u>

If you are pregnant, you may not participate in this study. You understand that if you are pregnant, you or your child may be exposed to an unknown risk. You agree to notify the investigator as soon as possible if you become pregnant, which may result in your being withdrawn from the study.

<u>Tissue Banking for Future Research</u>

As part of this research we would like to save any leftover samples for future research. Your samples will be stored at the Palo Alto VA or Stanford University and will be used for future research on knee osteoarthritis and related diseases. Your samples will used for research until the sample is all used up. Your sample and information about you will be labeled with a code that does not contain your name, initials, SSN, date of birth, or other ways that identify who you are. The research we conduct with your samples is being done for research purposes only and we will not tell you or your doctor about the results of the research.

Future Use of Private Information and/or Specimens

Research using private information and/or specimens is an important way to try to understand human disease. You are being given this information because the investigators want to save private information and/or specimens for future research.

Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

You may withdraw your permission for us to use your samples for future research at any time. Contact Dr. Constance Chu or the study staff at 650-493-5000 x62388 to withdraw your permission. If you take back your permission, the research team can continue to use information about you collected before you decided to take back your permission, but they will not collect any information about you going forward and any remaining samples will be destroyed.

The research we conduct using your samples may result in inventions or discoveries that could be used to make new products or diagnostic or therapeutic agents. These inventions and discoveries may become financially valuable. You will not receive any money or other benefits from any commercial or other products that are made using your specimens.

We may share data and de-identified samples with Dr. Chu's Stanford Collaborators.

Future Studies

_____ Yes, I would like to be contacted about future studies.

_____ No, I would not like to be contacted about future studies.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the investigators and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the investigators or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the investigators or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the investigators or research staff if you believe you might be pregnant
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the investigators or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled and your decision will not affect your ability to receive medical care for your condition.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by calling Dr. Constance Chu or her research staff at 650-493-5000 x62388.

The investigators may also withdraw you from the study for one or more of the following reasons:

- Failure to follow the instructions of the investigators and/or study staff.
- The investigators decide that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

This study involves the following risks, discomforts, and possible inconveniences:

There is a discomfort of travel, time and effort involved with study participation.

Risks of MRI: The MRI exam involves no exposure to x-rays or radioactivity. However, there is a potential risk of the strong magnetic field of the scanner attracting ferromagnetic (material with a high magnetic permeability) or metallic objects toward the magnet. For this reason you will be carefully screened for metallic objects in your possession before entering the magnet room. All such metallic objects will be collected and placed in a locker outside of the magnet room. You will be screened for MRI safety (no pacemakers, implanted metal, claustrophobia, etc.) upon enrollment to the study.

Risks of Radiographs: This research study may involve exposure to radiation from knee x-rays that is not necessary for medical care and is for research purposes only. The additional amount of radiation is approximately equal to 1 day of radiation exposure from natural sources like the sun, ground and water.

Risk of blood collection: The risks of drawing blood include temporary discomfort from the needle stick, bruising, and rarely infection. A trained individual will draw the blood using sterile, disposable equipment. There is a chance that you will experience pain, bruising, excessive bleeding, feeling faint, or infection at the site of blood withdrawal.

Risk of Gait Analysis: The only possible hazard is the slight risk that a subject will fall or feel fatigue down while performing the exam. All subjects may be at some risk of discomfort when the markers used to observe how their body moves while walking are removed. Removing the markers is similar to taking off a band-aid, but some find this slightly uncomfortable. Subjects may feel some emotional stress while wearing garments provided for walking in the laboratory. Visitors or other observers during data collection are only permitted with participant concurrence which can be revoked at any time during the experiment.

There are procedures in this study may involve other risks, which are currently unforeseeable.

POTENTIAL BENEFITS

We cannot and do not guarantee or promise that you will receive any benefits from this study. However, we may be able to benefit the future population to have a better understanding of joint and soft tissue disease through your outcomes.

ALTERNATIVES

The alternative to this study is not to participate.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

We will keep your name and all the information about you used in this study as confidential as possible. We may publish the results of this study for others to read about, but you will not be identified in any articles about the study by name, social security number, address, telephone number, or any other direct personal identifier. Also, other federal agencies as required, such as the VA Office of Research Oversight and the VA Office of the Inspector General may have access to your information.

Because this study involves an investigational device, the Food and Drug Administration may also have access to information about you collected in this study.

FINANCIAL CONSIDERATIONS

Payment

You will receive up to $100 for completion of each of the following study visits: baseline, 1 month follow-up and 3 month follow-up. You will receive up to $150 for completion of the 6 month follow-up, for a total possible payment amount of $450. No payment will be made for completion of the x-rays, as they are to determine your eligibility in the study, or for questionnaires after 6 month visits.

If you are unable to complete in-person testing, and complete patient-reported outcomes only for any of the baseline, 1, 3, or 6 month visits, you will receive $25 for completion of the questionnaires only.

You may need to provide your social security number to receive payment.

Costs

There will be no costs to you for any of the treatment or testing done as part of this research study. However, medical care and services provided by the VA that are not part of this study (e.g., normal hospital and prescription expenses which are not part of the research study) may require co-payments if your VA-eligibility category requires co-payment for VA services.

Sponsor

The Department of Veterans Affairs is providing financial support for this study.

COMPENSATION for Research Related Injury

If you are injured as a direct result of being in this study, medical treatment will be available. If you are eligible for veteran's benefits, the cost of such treatment will be covered by the VA. If not, the cost of such treatments may still be covered by the VA depending on a number of factors. In most circumstances, the treatment must be provided in a VA medical facility. No other form of compensation for injuries is available. However, by signing this form you have not released the VA from liability for negligence. For further information, you may call the Human Protections Administrator at (650) 493-5000, ext. 67593 or the V.A. Regional Counsel at (415) 750-2288.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the principal investigator, Dr. Constance Chu, at 650-493-5000 x62388. You should also contact her at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-

866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact the research study staff at 650-493-5000 x62388.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____

Signature of Participant Date

_____

Print Name of Participant

_____ _____

Signature of Person Obtaining Consent Date

_____

Print Name of Person Obtaining Consent

HIPAA regulations require the participant to give separate written permission (signature) for the use of their protected health information.

Person Obtaining Consent HIPAA Authorization confirmation:

☐ Confirm the participant signed the VA HIPAA Authorization (VA 10-0493)