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HOSPITAL ITALIANO
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Comparison between Platelet Rich Plasma and Corticosteroids for the Treatment of Rotator Cuff Tendinopathy

Randomized Controlled Double Blind Clinical Trial

IRB number: 5269

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Introduction

Rotator cuff tendinopathy represents the most common pathology of the shoulder, and is the main reason for outpatient consultation for pathologies related to the shoulder girdle.[1,2] First-line treatment for rotator cuff tendinopathy usually consists of activity modification, stretching and strengthening exercises, oral anti-inflammatory medications.[3-6] When these initial measures are not effective, a second line of treatment consists of local infiltrations with corticosteroids.[3-6] Corticosteroid injections are often used as an inexpensive and effective treatment to reduce pain and improve movement. However, most of the studies evaluating the effectiveness of corticosteroids in patients with rotator cuff tendinopathy show that the clinical results are usually short-lived.[6-7] In addition, corticosteroids do not have any biological effect that helps to regenerate or reverse the structural changes that occur in the rotator cuff tendons as a consequence of chronic inflammation. [6-7]

In this sense, platelet-rich plasma (PRP) emerges as a promising alternative due to its ability to release pro-regenerative growth factors (FsC) and cytokines at the lesion site (cite).[8-9] Platelet Rich Plasma is considered a minimal handling product. It is commonly used in the United States, Europe and all of America. According to the FDA it falls within the scope of section 361 (Public Health Service Law, Code 21 of Federal Regulation 1271) of minimally manipulated therapies and according to ANMAT under law 16463 and decree 9763/64. In addition, the centrifuge that will be used in the following study at the Hospital Italiano de Buenos Aires is approved by the ANMAT in (RegenLab disposition 13735). Specifically, at the Hospital Italiano de Buenos Aires (HIBA), platelet-rich plasma has been used for more than 10 years for different musculoskeletal conditions, both on an outpatient basis or as an adjuvant to

different surgical procedures. Its use is framed within Rule 789; code 5851121. The main indications for which PRP is used in the HIBA orthopedic service and for which favorable results have been published are: muscle tears, diabetic foot ulcers, knee and hip osteoarthritis, osteochondral knee lesions, partial lesions of the anterior cruciate ligament, glenohumeral osteoarthritis and rotator cuff pathology.[8-12]

FsCs released by platelets have been shown to perform pro-regenerative functions in vitro, including promoting stem and progenitor cell proliferation and recruitment, as well as modulating inflammatory responses and stimulating angiogenesis.[13-15] Furthermore, FsCs released by platelets have been shown not only to increase the proliferation of rotator cuff-derived tenocytes but also to promote the production of key extracellular matrix proteins, including collagen types I, II, and X; decorin; aggrecan; and biglycan.[14] In addition, PRP is also known to offer protection against oxidative stress, which prevents cell apoptosis after injury, and also inhibits the inflammatory effects of interleukin-1b (IL1b), which can lead to cuff tendon degeneration. rotator.[15]

Several small cohort studies and randomized controlled trials have examined the clinical benefit of PRP for treating patients with rotator cuff tendinopathy, however their results have been confounded by small patient samples, lack of a control group, variable or insufficient data from the PRP preparations and short-term follow-up.[16] clinical trials using

Different autologous PRP formulations to treat patients with rotator cuff tendinopathy have yielded controversial results.[16] Recently, Hurley et al.[16] performed a systematic review of randomized controlled trials on the use of PRP for the non-surgical

treatment of rotator cuff disease. Five randomized controlled trials met the inclusion criteria, with 108 patients treated with PRP and 106 treated with a control. Two studies found that PRP produced better outcomes, mainly pain scores, compared to a control. One study showed no difference in clinical outcomes and two other studies reported that PRP alone produced inferior results to control groups.[16]. Controlled trials were needed to further investigate the benefits of PRP in early rotator cuff disease.[16]

Finally, regarding the safety of platelet-rich plasma, it has been shown to be a safe product in multiple clinical trials. A recent Chocrane meta-analysis evaluated the adverse effects and complications of PRP in 19 clinical trials (1088 patients).[17] This study included patients who had undergone surgery for multiple orthopedic conditions including rotator cuff tears, anterior cruciate ligament tears, Achilles and patellar tendinopathy, and epicondylitis. The percentage of complications associated with treatment was 1.1% (12/1088 patients). In 15 of the 19 clinical trials there were no adverse effects or complications related to PRP. Reported complications were generally mild, including injection site hyperesthesia, local edema, and superficial injection site infections. No severe complications associated with the procedure were reported in any of the 1088 patients.[17]

The purpose of this study is to perform a double-blind randomized controlled trial, comparing PRP with corticosteroids to provide pain relief and improve function in patients with rotator cuff tendinopathy. The hypothesis of this study is that PRP would provide improved pain relief and function in patients with rotator cuff tendinopathy compared to standard treatment of CS injections.

Hypothesis

In patients with rotator cuff tendinopathy, PRP subacromial injections produce significantly greater improvement in shoulder pain and function than standard treatment with corticosteroid subacromial injection.

Goals

primary objective

To evaluate in patients with rotator cuff tendinopathy whether a subacromial infiltration with PRP produces a significant improvement in pain (measured through the visual analogue scale (VAS) for pain) compared to a control group treated with standard corticosteroid therapy.

secondary objective

2. To assess whether the use of PRP applied as a subacromial infiltration in patients with rotator cuff tendinopathy improves the functional **results** (measured using the American Shoulder and Elbow Surgeons (ASES) score) [18] and Constant's score,[19] compared to a control group that underwent subacromial infiltration with corticosteroids.

3. To assess whether the use of PRP applied as a subacromial infiltration in patients with rotator cuff tendinopathy improves the sleep **disorders** (measured using the Pittsburgh score) [20] compared to a control group that underwent subacromial infiltration with corticosteroids.

4. Confirm that platelet-rich plasma is a procedure**safe** through the systematic recording of adverse effects and complications associated with its use.

Materials and methods

Design

Randomized controlled clinical trial, with intervention group and control group, usual treatment, blind for the treatment received by the patient and for clinical and radiological evaluation.

Scope

The entire study will be carried out at the Hospital Italiano de Buenos Aires headquarters.

Schedule - masking - intervention

Stage 1: All patients with rotator cuff tendinopathy, clinically diagnosed and confirmed by MRI, will be invited to participate in this study.

After confirming that the patient meets the inclusion criteria, the study will be explained in detail through the informed consent process (See Consent Annex 1).

Stage 2: Once the patient agrees to participate and has signed the informed consent, they will be randomized (see randomization).

To the patients of group **1**: (control) a subacromial infiltration with corticosteroids (betamethasone 2 mg) will be performed under ultrasound control.

To the patients of group **2**: (Intervention) a subacromial infiltration with PRP will be performed under ultrasound control.

The week prior to the infiltration, all patients will undergo a prior ultrasound to confirm rotator cuff tendinopathy and rule out associated supraspinatus ruptures.

Masking of patients:

At the time of blood collection, patients will be placed in a hemotherapy extraction chair with a screen that will prevent the patient from seeing their arm at the time of blood collection. All patients will have a local anesthetic (cutaneous lidocaine) placed in the crease of the elbow at the extraction site. The patients in the intervention group will be injected with the extraction needle and 20 ml of blood will be obtained for the preparation of the PRP.

On the other hand, the patients in the control group (corticosteroid) will be given anesthetic and a dermal micro-puncture will be performed with the vacutainer simulating blood extraction. After this, they will wait 1 minute, simulating the time it takes for the extraction bag to fill with 20 ml.

In this way, we will ensure the masking of the treatment received, an essential condition in this type of study since the scores used and validated for the clinical evaluation of this pathology have a subjective component that could be altered or biased if the patient knows which treatment received. On the other hand, the control group, although it has active masking, only consists of a skin micropuncture with a previous local anesthetic, which does not present complications or adverse effects and may not be perceived by the patient due to the local anesthesia.

Both procedures will be carried out under antiseptic conditions by a Hemotherapy technician in the procedure room of the Hemotherapy Service.

Subsequently, the patients will be accompanied to the procedure room where the assigned treatment will be applied under ultrasound control by the principal investigator. For patients in the CS group, 1 vial of 2 ml of Betamethasone will be

applied. The injection will be performed through a posterolateral approach. The CS will infiltrate the subacromial bursa. For patients in the PRP group, a volume of 5 ml will also be injected through a posterolateral approach. Patients will be informed about possible adverse reactions to both injections. Patients will be allowed to continue activity as tolerated after the injection and each patient will receive a specific exercise program to do at home. Patients will not know what treatment they received, meaning they will be blinded to the intervention. For this, at the time of injection, the syringe will be covered with black insulating tape so that the patient cannot see the contents of the syringe.

stage 3: Once the intervention is finished, all the patients will be rehabilitated by the shoulder team of the rehabilitation center of the Italian Hospital of Buenos Aires. The rehabilitation protocol will be the one recommended by the American Shoulder and Elbow Society (ASES).[21] which is commonly used in the hospital.

***Stage 4*:** During the development of the rehabilitation protocol, the evolution of the patient will be objectively evaluated with the analogous visual scale, the ASES score, the Constant score and the Pittsburgh score.*(Annex 3 -4 and 5)* one month, 3 and 6 months post-infiltration. The physician in charge of the objective evaluation and documentation of the patient's scores will be the shoulder improvement fellow who will be blind to the intervention received by the patient.

Population

1. Adults between 18 and 50 years with rotator cuff tendinopathy.

Selection criteria

Inclusion criteria

1. Adults between 18 and 50 years old with rotator cuff tendinopathy defined as clinically compatible and confirmed by ultrasound.
2. At least 3 months of failed conservative treatment (decreased activity, anti-inflammatories, kinesiology for at least 3 months before diagnosis).

Exclusion criteria

1. Refusal to participate or informed consent,
2. previous shoulder surgery,
3. Partial or total tears of the rotator cuff,
4. Patients with shoulder osteoarthritis > 2 according to the Samilson and Prieto classification
5. Advanced fatty infiltration of the rotator cuff muscles (STAGE 3 or 4 according to Goutallier)[32]
6. Systemic or rheumatoid arthritis,
7. uncontrolled diabetes,
8. Acute or chronic infections of the shoulder to be operated on
9. Ongoing cancer chemotherapy therapies
10. Sepsis, septic arthritis, osteomyelitis or other ongoing infectious processes;
11. Patients with autoimmune diseases;
12. pregnant,

Eligible patients will be enrolled in the study by giving their informed consent.

Preparation of platelet-rich plasma

For the PRP group, a leukocyte-poor preparation from a prepackaged kit (RegenLab, Lausanne, Switzerland) will be used. According to the manufacturer's manual, 10 ml of venous blood will be drawn into a blood collection tube containing a sodium citrate anticoagulant and a proprietary separating gel (thixotropic gel) to isolate the red and white blood cells from the PRP. Samples will be centrifuged at 1500g for 5 minutes to produce approximately 7 mL of 80% platelets at 1.6x concentration. The manufacturer reports a filtration of 99.7%, 87 to 89%, 70 to 75%, and 96.5% of red blood cells, white blood cells, mononuclear cells, and granulocytes, respectively. The supernatant is then resuspended by inverting the tube several times and withdrawn into a separate 5 mL syringe for subacromial injection.

This procedure will be performed 2 times in each patient. The product from the first kit will be injected into the patient. Instead, the product from the second kit will be used to evaluate the final composition of the PRP. These specific measurements will include: the final average of platelets, leukocytes and erythrocytes, and the specific formula of leukocytes and growth factors. This will allow us to establish a correlation between the specific composition of the PRP and the functional results of the patient.

Variables to be measured and data documentation

All the variables to be measured will be recorded in a RedCap database specially designed for this clinical trial.

A) Demographic and related to the injury.

They will be recorded by the principal investigator 24-48 hours prior to the infiltration.

- Sex: male - female
- Age: Age in years on the day of infiltration
- Smoking: yes-no

B) Cynic variables

Pre-infiltration evaluation: It will be in charge of the principal investigator and it will be carried out 24-48 hours before the infiltration in the orthopedics office.

In it will be evaluated:

clinical variables: Mobility - Pain - Functional Scores (ASES - Constant) - Sleep disorders (Pittburgh Score)

Imaging variables: Chronic tendinopathy will be defined as the presence of a hyperintense signal in the supraspinatus on magnetic resonance imaging (carried out a maximum of 6 months prior to clinical diagnosis), with the absence of partial or total ruptures of the tendon or as the presence of a hyperechoic signal in the supraspinatus. supraspinatus with increased intratendon Doppler flow. The presence of the tendinopathy will be confirmed by ultrasound the week prior to the infiltration to rule out the progression of the tendinopathy to a partial rupture of the tendon and to evaluate the presence of flow within the supraspinatus as a sign of tendinopathy with echodoppler.

Post-infiltration evaluation:

In it will be evaluated:

clinical variables: Mobility - Pain - Functional Scores (ASES - Constant) - (Pittburgh Score) at one month, 3 months and 6 months postinfiltration. It will be in charge of the Shoulder Fellow who will not know to which branch of treatment the patient was assigned. That is to say it will be***blinded to intervention***.

Imaging variables: The presence of vascular flow within the tendon will be measured in the musculoskeletal ultrasound 6 months after the infiltration in the usual way. It will be in charge of a doctor specialized in musculoskeletal ultrasound who does not

will know to which treatment arm the patient was assigned. That is to say it will be***blinded to intervention***.

The variables that will be evaluated are described below:

- *Mobility:The 4 mobility parameters will be measured in degrees with a goniometer*

  -Anterior flexion

  -Abduction

  -External Rotation with the arm at $90^0$of abduction

  -Internal Rotation with the arm at $90^0$of abduction

- Pain: The visual analogue scale (VAS) will be used to assess the level of pain during activities of daily living. 0 will be considered as "absence of pain" and 10 as "the worst pain of your life".
- General function of the shoulder:The ASES (American Shoulder and Elbow Surgeons) score will be used.[15] ***(Annex 2)*** and Constant's score[16] ***(Annex 3)*** Both scores evaluate the general functionality of the shoulder in different activities of daily living, the global mobility of the shoulder, and pain with usual tasks. They are scores ranging from 0 to 100. Both scores are validated and are the reference scores for clinical research on rotator cuff pathology.[15,16]
- Sleep disorders: The Pittsburgh score will be used.[20] ***(Annex 4)***

c) Imaging variables

- Magnetic resonance imaging (MRI) of the affected shoulder:

The preinfiltration MRI will measure the presence of pathological hyperintensity in the supraspinatus, in the absence of partial or total tears of the rotator cuff.

The resonance must have been performed a maximum of 6 months prior to the clinical diagnosis of the tendinopathy. Otherwise it will be repeated.

Ultrasound 1 week before infiltration and 6 months after infiltration:

The shoulder musculoskeletal ultrasound that will be performed on all patients 1 week before infiltration will confirm the diagnosis of cuff tendinopathy and the absence of partial or total cuff tears. In addition, an echodoppler will be performed to determine the presence of intratendinous flow as a manifestation of tendinopathy. In the post-infiltration control musculoskeletal ultrasound 3 months after the infiltration, tendon healing will be evaluated, which will be defined as the absence of intratendinous vascular flow. Both MRI and ultrasound are part of the study and routine follow-up of patients treated for rotator cuff tendinopathy.

d) Variables related to security

Adverse effects and immediate post-infiltration complications, one month, 3 months and 6 months post-infiltration will be recorded.

In the event that the patient presents a complication, they will have the contact number of the principal investigator to be attended by him or by a surgeon from the team in the orthopedic clinics or on duty at the Italian Hospital of Buenos Aires. Likewise, the doctors on duty will be informed about the development of the following protocol in order to notify the principal investigator or a member of the team in the event that a patient presents any post-infiltration complication.

Scheme of the evaluation points in time, responsible for the evaluation and the variables that will be recorded

	pre-infiltration (24-48 hours prior)		**1 month post-infiltration**		**3 months post-infiltration**		**6 months post-infiltration**
Evaluator	Principal investigator		Shoulder Fellow		Shoulder Fellow (clinical variables) Sonographer (imaging variables)		Shoulder Fellow (clinical variables)
Variables Clinics	-Demographic -Mobility -Pain -Functional Scores (ASES – Constant - Pittsburgh)		-Mobility -Pain -Functional Scores (ASES – Constant-Pittsburgh) -complications		-Mobility -Pain -Functional Scores (ASES – Constant-Pittsburgh) -complications		-Mobility -Pain -Functional Scores (ASES – Constant-Pittsburgh) -complications
Imaging variables	Magnetic nuclear resonance Ecodoppler musculoesquelético				Ecodoppler musculoesquelético		

Statistical analysis raised

Quantitative variables will be presented as mean and standard deviation or median and interquartile interval according to the observed distribution. Categorical variables will be presented as proportions. The 95% confidence intervals will be calculated for each of the estimators.

The comparison of continuous data between two groups will be analyzed with the t test if the distribution of the variables is normal or with the Mann-Withney-Wilcoxon test if it is not. The analysis of categorical data will be carried out with the chi-square test. Statistical analysis will be performed with STATA MP version 16 (Stata Corporation, College Station, TX). A p value less than 0.05 will be considered statistically significant.

Sample size

To calculate the sample size, the expected values of the variable "pain" represented by the VAS, which is the main outcome variable, are used. The minimal clinically relevant difference (MCID) was previously described in the setting of rotator cuff disease as 1.5 points with a standard deviation of 2.41 points on a 10-point scale for shoulder pain.[22] We will work with a type I error probability of 5% and a power of 90%. Using these parameters in a superiority formula, a sample size of 45 patients per group was calculated. Considering the possibility of a loss to follow-up of 10% of the patients per group, 50 patients per group will be included, with a total final sample of 100 patients. The sample size was calculated using the formula of Fleiss et al.[23]

Randomization

All included patients will be randomized after obtaining informed consent. Each patient will be randomly assigned a treatment arm using the online randomizer (http://protocolos.hospitalitaliano.org.ar) to treatment arms 1 (control) or 2 (intervention)

ethical considerations

Participation in the study will be in all cases voluntary and certified by the informed consent process. The study will be carried out in full accordance with current national and international regulations: Declaration of Helsinki of the World Medical Association, Provision 6677/10 of ANMAT, and the Standards of Good Clinical Practices ICH E6.

The proposed intervention does not frequently present adverse events and there are known contraindications for its application. The procedure will be paid for by the financing of the study, it will not imply any cost to the patient or their health coverage. The costs of monitoring and periodic evaluations will be borne by the study investigators.

All study data will be treated with the utmost confidentiality, with restricted access only to authorized personnel for the purposes of the study in accordance with current legal regulations National Law on Protection of Personal Data 25,326 (Habeas Data Law.

Damage or complications

The coverage for the risk of Institutional Malpractice is attached, of the Clinical Trial that will be contracted to carry out the following study once approved by the Ethics Committee.***(Annex 5)*** In the same Coverage is granted to the claim or claims that occur due to any injury, illness or death of Patients, caused or alleged to have been caused, by: The administration of medicinal products indicated in the Investigation Protocol, By acts of Medical Praxis committed during the execution of the Clinical Trial (negligence, incompetence, imprudence and non-observance of duties). In this multidisciplinary work, 2 Orthopedics and Hemotherapy services will be included. Each service will be responsible for the costs of interventions free of charge and with overtime.

In the case of the preparation of the PRP, they will be carried out free of charge by a Hemotherapy service plant doctor.

The infiltrations will be carried out by ***a*** doctor of the Shoulder Pathology team of the Orthopedics and Traumatology Service of the Italian Hospital of Buenos Aires

The rehabilitation will be carried out with the standard HIBA kinesiology protocol for patients with chronic rotator cuff tendinopathy and will be carried out by the rehabilitation ***team*** of the HIBA Kinesiology service.

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