

TITLE:

**The Effects of Platelet-Rich Plasma vs Prolotherapy Injection on
Functional and Pain Scores in Supraspinatus Tendinopathy: A
Randomized Controlled Trial.**

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The Effects of Platelet-Rich Plasma vs Prolotherapy Injection on Functional and Pain Scores in Supraspinatus Tendinopathy: A Randomized Controlled Trial.

A) Background

Shoulder pain and dysfunction are frequently encountered in the clinical setting. It is a complex problem and affects the person's ability to carry out daily activities and work. The point prevalence of shoulder pain varies from 14% to 21% in the general population^{1,2}. A 14-years follow up study showed the prevalence of shoulder pain increased by 8.5% from the 1990s to 2004³. In primary care, the common causes of shoulder pain and disability are rotator cuff disorders, glenohumeral disorders and acromioclavicular joint disease⁴. Rotator cuff tendinopathy is defined as “pain and weakness, most commonly experienced with movements of shoulder external rotation and elevation, as a consequence of excessive load on the rotator cuff tissues”⁵. The pathology of rotator cuff tendon injury is in a continuum from underloaded/overloaded tendon to reactive tendinopathy, tendon disrepair and finally degenerated tendon⁶. Understanding of the pathological and repair process will enhance the management of a patient with such pathology.

Treatment options ranges from conservative, which consist of non-invasive such as rehabilitation to more invasive injection procedure and finally, surgical treatment. A systematic review showed limited evidence that surgery is more effective in treating rotator cuff tear than conservative treatment alone⁷. At an early stage, the use of anti-inflammatory, exercise and electrotherapeutic modalities are to control the inflammatory phase of tendon disease. However, despite the treatment above, recalcitrant tendinopathy may manifest because, once damaged, the biological and biomechanical properties of tendon tissue never completely restored. Healing times in chronic tendinopathies are prolonged as tendons are relatively less vascular and local blood flow is less than verged delivered to the muscles. Thus, in recent years, the use of platelet rich plasma and prolotherapy has been emerging as a treatment option for rotator cuff tendinopathy⁸. Platelet rich plasma with its supraphysiologic platelet concentration has the potential to release biologically active proteins that promote cellular recruitment, growth and morphogenesis. Tendon healing is thought to be stimulated via enhanced fibroblast migration and proliferation, increased the tissue vascularization and collagen deposition⁹.

Prolotherapy is an injection of small volumes of an irritant such as dextrose into the insertion sites of the damaged tendon, which promotes the growth of normal tissue. Studies hypothesize that the injected substance mimics the natural healing processes by facilitating a

local inflammatory cascade, which triggers the release of growth factors and collagen deposition¹⁰. Both interventions showed a good outcome for the treatment of rotator cuff tendinopathy.

Hypothesis:

1. Participants treated with prolotherapy injection showed a significantly higher clinical and functional scores compared to control group
2. Participants treated with platelet-rich plasma injection showed a significantly higher clinical and function scores compared to control group

Problem statements:

Platelet rich plasma and prolotherapy have been the option treatment for tendinopathy, particularly in lateral epicondylitis and Achilles tendinosis. However, the study on the rotator cuff is still limited. No study compares the effect of PRP to prolotherapy is available. Furthermore, the reviews on the factors that may influence the outcome were minimal.

Literature Review

Traditionally, the first-line management of rotator cuff tendinopathy included anti-inflammatory approach by using NSAIDs or corticosteroid. However, several studies demonstrate little or no inflammation is present in tendinopathy. Histopathologic changes associated with tendinopathy include degeneration and disorganization of collagen fibers, increased cellularity, and minimal inflammation. Macroscopic changes include tendon thickening, loss of mechanical properties, and pain. PRP and prolotherapy are believed to kick start the inflammatory process and promote tendon healing¹¹.

The study on the role of PRP for rotator cuff healing is limited. Most of the study assess the clinical effect of PRP injection after arthroscopic rotator cuff repair^{14,15}. Besides that, majority systematic reviews on the use of PRP not only limited to rotator cuff problem but included other tendinopathies including lateral epicondylitis and Achilles tendinopathies. Moreover studies, vary in PRP preparation methods and PRP class (leukocyte poor vs leukocyte rich PRP) as well as the volume of PRP injected into the tendons (ranges from 1 ml to 5 ml). Studies also differs in the use of platelet activation, and the use of lignocaine before injection^{12,16,17}. In general, the PRP was more efficient than control in reducing tendinopathy pain, with an effect size of 0.47 (95% CI 0.22 to 0.72, $p < 0.001$), signifying a moderate treatment effect⁹.

The use of prolotherapy is based on the hypothesis that hypertonic dextrose solutions in the extracellular matrix provide local tissue irritation that initiates an acute inflammatory response and improves fibroblast proliferation and subsequent collagen synthesis, which provides healing and tissue renewal¹⁸. Previous studies differs in the types of prolotherapy used for rotator cuff tendinopathy. Various substances were used by previous studies which include dextrose, phenol-glycerine-glucose (P2G), and sodium morrhuate. Results of the studies were inconsistent, ranging from no effect¹⁹ to some functional improvement²⁰ and pain reduction¹³.

A recent systematic review comparing the effectiveness of injection therapies in rotator cuff pathology concludes: “corticosteroid was more effective only in the short-term in both pain reduction and functional improvement. Network meta-analysis indicated that prolotherapy significantly reduced pain compared with placebo in the long-term [over 24 weeks, SMD: 2.63, 95% confidence interval (CI): 1.88-3.38]; meanwhile PRP significantly improved shoulder

function compared with placebo in the long-term (over 24 weeks, SMD: 0.44, 95% CI: 0.05-0.84)”.²¹

B) Research Objective:

1. To investigate the effects of platelet rich plasma injection on clinical and functional outcome for the treatment of rotator cuff tendinopathy.
2. To investigate the effects of prolotherapy injection on clinical and functional outcome for the treatment of rotator cuff tendinopathy.
3. To compare the effect of platelet rich plasma vs prolotherapy injections for the treatment of rotator cuff tendinopathy
4. To analyses the factors that may result in the different outcome between PRP and prolotherapy intervention.

C) Methodology

Research Plan

This study will implement a three-armed double-blind, randomized control trial design. The study will run for 2 years. Recruitment will be for 12 months with a final follow-up at 6 months post treatment.

Recruitment centers and participant

Participants will be recruited at the University Malaya Medical Centre from Sports Medicine clinic, Orthopedic clinic, Rheumatology clinic and Primary Care clinic. Interested participants will undergo an eligibility assessment before recruitment.

Inclusion criteria are:

- 1) Individual age 18 and above
- 2) Shoulder pain more than 6 weeks3 months
- 3) Diagnosis of painful rotator cuff tendinopathy by Sports Physician/ Orthopaedic Sports Surgeon: by clinical test and ultrasound

Exclusion criteria are:

- 1) Patients with the following medical conditions: autoimmune rheumatology disease, immunocompromised, blood disorder (thrombocytopenia and anemia).
- 2) Patients with the following shoulder conditions: referred pain from cervical, recent shoulder surgery, shoulder instability and dislocation, complete rotator cuff tear, Adhesive capsulitis, grade III acromion (Biligani classification) based on the radiological finding.
- 3) Patient with the following medications: anti-coagulant treatment, steroid injection in less than 2 months
- 4) Patient with the following laboratory findings: Haemoglobin level less than 10 g/L and/or platelet count less than 100,000/ μ L
- 5) Unable to follow study protocol

Sample size calculation and estimation

The sample size was estimated based on the primary outcome of functional score. Improvement was defined by a decrease in the mean Shoulder Pain and Disability Index (SPADI) of 17.7 ± 3.7 in the platelet-rich plasma group¹¹ and 16.12 ± 12.82 ¹¹ for prolotherapy. For this study, the sample size was calculated after taking into account the desired statistical significance level set at 5%, and the power of the study set at 80%, with type I error rate of less than 0.05 is permitted and a false-negative rate of less than 0.20. The sample size is calculated using the G*Power version 3.1.9.2 software¹¹. With the assumption of 30% drop out, hence, to detect a difference in the functional outcome, a minimum of 30 patients in each group is required.

Procedures

Informed consent will be obtained from the patients before intervention. All participants are required to complete the functional questionnaire (name of the functional questionnaire = SPADI??). Participants will be assessed by Sports Physician for eligibility. Subsequently, ultrasound assessment will be performed by one musculoskeletal (MSK) radiologist or a Sports Physician with more than 10 years' experience in performing MSK ultrasound. Blood will be sent for full blood count test to assess the hemoglobin and platelet levels. A plain shoulder radiography (indicate views that will be ordered) will also be

performed to exclude Type III acromion. Electromyogram and strength testing will be done at the first visit for all patients.

Patients who fulfilled the study criteria will be randomly assigned using computer-generated block randomization to receive either PRP, prolotherapy or normal saline injections. On the procedure day, blood will be withdrawn from all the patients to ensure blinding of participants. A covered syringe contains the solutions will be prepared by the investigator to ensure its content is not visible. The procedure will be performed under ultrasound guidance with the patient sitting on a chair, in a modified crass position. All shoulder injection will be performed by a co-investigator who are not involved in outcome measure assessment of patient's progress. Post injection, the patients will be advised to rest, and avoid vigorous shoulder activities. The patients are allowed to take paracetamol if the pain is intolerable (up to 1000mg every 6 hourly. Patient are required to record the amount of paracetamol that they take.

During the follow up, the Sports Physician and or radiologist who assess the patient at baseline will repeat the assessment. The involved physician will not be informed of the intervention received by the participants. (Refer to Figure 1: Flowchart of the study).

Intervention

Platelet rich plasma: We will use a commercially available kit (YCELLBIO Kit). The autologous PRP will be prepared in accordance with the manufacturer's guideline. Fifteen (15) ml blood will be collected, according to a standard PRP kit; this volume can produce approximately 3 mL of PRP. Two milliliters of the PRP will be delivered to the injured area under ultrasound guidance.

Prolotherapy: We will dilute dextrose 50% in bacteriostatic water to get 16.5 % solution. One to two ml of the dextrose solution will be injected into the area of painful tendinosis under ultrasound guidance.

All participants will receive single injection. The injection will be under ultrasound guided intralesional.

Outcome measures

Study assessments will include the following assessment at baseline, 3 weeks, 3 months and 6 months.

- Clinical outcome: Range of movement and special test for rotator cuff
- Functional outcome: Shoulder Pain and Disability Index (SPADI) questionnaire
- Pain: Visual analogue score (VAS)
- Ultrasound assessment characteristics: tendon thickening, changes in the normal contour and echotexture lost in the fibrillar pattern, hypoechoic changes, swelling, neovascularization, and partial tear.
- Biomechanics analysis: dynamometer for strength and electromyogram of periscapular muscle

Statistical Analysis

The primary outcome of the study which consist of the mean difference in pain and shoulder function will be analyzed with independent T-test. For secondary outcome, range of movement, strength, ultrasound findings and electromyogram result independent T-test will be used for continuous data and Fisher exact test for categorical data.

D) Expected Results/Benefit

i. Novel theories/New findings/Knowledge

Platelet rich plasma and prolotherapy is a treatment of choice for recalcitrant supraspinatus tendinopathy. However, the effect may be influenced by several factors such as clinical examination at presentation and ultrasound findings.

ii. Specific or Potential Applications:

PRP and prolotherapy can result in improvement of shoulder function in patients with chronic shoulder pain. The costs are cheaper compared to surgery.

Appendix 1: Flowchart of the study:

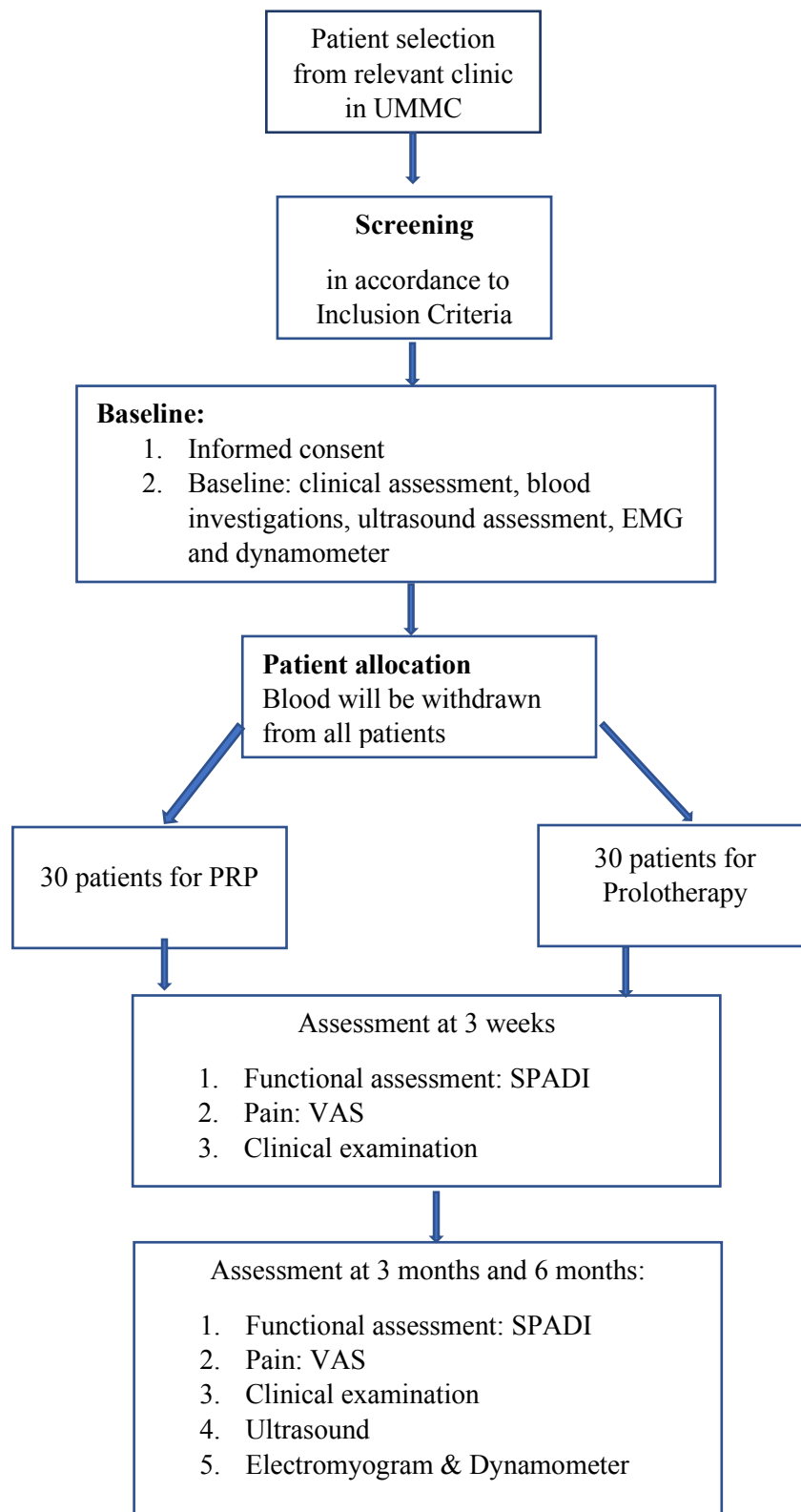


Figure 1: Flowchart of research activity

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Appendix 1

SHOULDER PAIN AND DISABILITY INDEX (SPADI)

Please place a mark on the line that best represents your experience during the last week attributable to your shoulder problem.

Pain scale

How severe is your pain?

Circle the number that best describes your pain where: 0 = no pain and 10 = the worst pain imaginable.

At its worst?	0	1	2	3	4	5	6	7	8	9	10
When lying on the involved side?	0	1	2	3	4	5	6	7	8	9	10
Reaching for something on a high shelf?	0	1	2	3	4	5	6	7	8	9	10
Touching the back of your neck?	0	1	2	3	4	5	6	7	8	9	10
Pushing with the involved arm?	0	1	2	3	4	5	6	7	8	9	10

Disability scale

How much difficulty do you have?

Circle the number that best describes your experience where: 0 = no difficulty and 10 = so difficult it requires help.

Washing your hair?	0	1	2	3	4	5	6	7	8	9	10
Washing your back?	0	1	2	3	4	5	6	7	8	9	10
Putting on an undershirt or jumper?	0	1	2	3	4	5	6	7	8	9	10
Putting on a shirt that buttons down the front?	0	1	2	3	4	5	6	7	8	9	10
Putting on your pants?	0	1	2	3	4	5	6	7	8	9	10
Placing an object on a high shelf?	0	1	2	3	4	5	6	7	8	9	10
Carrying a heavy object of 10 pounds (4.5 kilograms)	0	1	2	3	4	5	6	7	8	9	10
Removing something from your back pocket?	0	1	2	3	4	5	6	7	8	9	10

Appendix 2

PATIENT'S FORM

Patients' History

Name:

RN:

Age:

Gender: Male/ Female

Ethnics: Malay/ Chinese/ Indian/ Others _____

Occupation:

Job description:

Smoker: No / Yes

Medical Illness: No/ Yes

Medication:

Clinical Examination

Height:

Weight:

BMI:

Dominant Hand: Right/ Left

Involved Side: Right/ Left/ Bilateral

Range of movement (goniometer):

ROM	Degrees	ROM	Degrees
Forward flexion		Internal Rotation (hand at side)	
Extension		Internal rotation (90)	
Abduction		External rotation (hand at side)	
Adduction		External Rotation (90)	

Painful site (most tender area)

Non-specific anterior		Supraspinatus fossa	
Non-specific posterior		AC joint	
Greater tuberosity		Others:	
Bicipital groove			

Special Test:

		Description
Empty can (Jobe's test)	+ / - / NA	
Full can test		
Resisted external		
Gerber's lift off test		
Hawkin's Kennedy		
Neer's Sign		
Drop arm test		
Other test with positive findings:		

Handheld (Commander dynamometer test)

	T1	T2	T3	Avg		T1	T2	T3	Avg
Forward flexion					Internal Rotation (hand at side)				
Abduction					Internal rotation (90°)				
Abduction 30°					External rotation (hand at side)				
Adduction					External Rotation (90°)				

*T- Trial

Avg- Average