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Comparing the efficacy of PRP vs hyaluronic acid vs placebo injections in the management of supraspinatus tendinopathy; randomized controlled trial

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***Abstract*---**Objective: To compare the effect of local injection of platelet-rich plasma (PRP), Hyaluronic acid, or Placebo for management of Supraspinatus tendinopathy (SST) and their outcomes regarding functional scores and MRI changes. Design: Double-blind randomized controlled trial with 1-year follow-up. Methods: 60 Participants recruited from an outpatient Orthopaedic clinic had clinically and radiologically (MRI)–demonstrated SST refractory to physical therapy. They received a local injection of either 3.5 mL of PRP, Hyaluronic acid (2 doses a week apart), or 3.0 mL of 1% xylocaine at the lesion and surrounding tendon (20 participants each). Patients aged from 21 to 65 years with symptoms of SST for 3 months or more do not improve after at least 4 weeks of formal physical therapy with magnetic resonance imaging (MRI) changes indicating tendinopathy without RC tears or labral lesions, or significant glenohumeral arthrosis. Exclusion criteria included joint instability, patients on anticoagulation therapy, history of shoulder surgery, full-thickness Supraspinatus tear, Type 3 or 4 acromions, and corticosteroid injection within 3 months. Primary outcome: 0-10 visual analog scale (VAS) and functional shoulder tests assessing

rotator cuff strength and endurance (at baseline and 8 and 12 weeks). Secondary outcomes: UCLA Shoulder rating scale (at baseline and 8 and 12 weeks) and MRI severity (1-5) points [at baseline 12 weeks]). Results: The results showed improvement in pain intensity for PRP cases and HA cases but, showed no significant improvement in pain intensity for Placebo cases. The results showed improvement in shoulder function (Functional outcome measures and UCLA score) in PRP cases and HA cases. However, no significant improvement in Placebo cases with a p-value <.001. No considerable difference between the effects of PRP and HA injection on the function of the shoulder. For MRI follow-up, there is some improvement in the degree of tendinopathy in the PRP group (25% complete improvement and 50 % partial improvement) and HA group (25% complete improvement and 40 % partial improvement). That means, there is a limited correlation between (the degree of shoulder pain and level of function) and the degree of integrity or tendinopathy in MRI. Conclusions: Sub-acromial injection of PRP or HA resulted in safe, significant, sustained improvement of pain, function, and MRI outcomes in participants with refractory SST with significant difference compared to our control group that was injected with local anesthetics only (Placebo). Nevertheless, the lack of long-term follow-up stands to be one of the main limitations of this study.

***Keywords*---**sub-acromial, platelet-rich plasma, supraspinatus tendinopathy, hyaluronic acid.

Introduction

Supraspinatus tendinopathy (SST) is a common problem affecting adults with excessive over-head activities, athletes, and the elderly. It is common in people with. Supraspinatus tendinosis, histologically noninflammatory degenerative tendinopathy, leads to a lack of humeral head control and often subsequent symptoms and signs of subacromial impingement. No treatment is universally successful in managing this condition, which causes considerable time lost at work and recreation.[1]

Treatment options for Supraspinatus tendinopathy include NSAIDS; exercise-based physical therapy; physical therapy modalities including iontophoresis, phonophoresis, ultrasound, transverse friction massage, and low-level laser therapy; corticosteroid injections; glyceryl trinitrate patches; shock wave therapy; sclerotherapy; surgery; growth factor treatment; and stem cell treatment.[1] The tendon healing process is complexly orchestrated by a variety of secreted molecules such as interleukin (IL)-6 and IL-1β, which are produced by the invading inflammatory cells. Later, tissue repair is facilitated by several growth factors, which are released by cells located at the injury site. bFGF (basic fibroblast growth factor), BMPs (bone morphogenetic proteins)-12, -13, and -14, TGFβ (transforming growth factor-beta), IGF-1 (insulin-like growth factor-1), PDGF (platelet-derived growth factor) and VEGF (vascular endothelial growth factor) are involved in different phases of the healing process with diverse

molecular effects. During the repair process, tendon cells are activated and both synthesize and degrade ECM components, thereby participating in the slow, continuous process of tendon remodeling.[2,3,4,5]

Platelet-rich plasma (PRP) is an autologous biologic derivative consisting of supra-physiologic levels of platelets that undergo degranulation to release growth factors (GFs) with healing properties.[6] Platelets contain several proteins, cytokines, and other bioactive factors that initiate and regulate basic aspects of wound healing. Platelet-rich plasma, with a platelet concentration of at least 1000000 platelets/μL in 5 mL of plasma, is associated with the enhancement of healing.[7] Multiple types of research have shown that the activity of hyaluronidase is increased in granulation tissue during the healing of equine superficial digital flexor tendon injuries, suggesting that HA plays a relevant role in controlling the healing process in equine tendonitis.[8] Hyaluronic acid (HA) is a long unbranched polysaccharide with repeating disaccharide units of N-acetyl glucosamine and glucuronic acid.[8-10] Thus, studies have reported that HA affected adhesions, gliding resistance, and tendon healing which reduces the formation of scars and granulation tissue and prevents adhesions after tendon repair.[9-10]

Methods

The study protocol has been revised and approved by the Ethical Committee of our institution and all participants were informed and consented before enrolment in the research. From April 2015 to July 2017, Active Adults aged between 21 & 65 years, were recruited from outpatient sports injuries. Candidates with symptoms of SST for 3 months or more after a trial of conservative treatment of at least 4 weeks of physical therapy (including rotator cuff strengthening and scapular and proprioceptive stabilization) were considered for enrollment. Plain x-ray and magnetic resonance imaging (MRI) studies showing signs of SST are mandatory. Exclusion criteria include significant glenohumeral arthrosis, joint instability defined by positive apprehension and evident labral tear on MRI, pregnancy, immune system compromise, significant upper extremity comorbidity, anticoagulation therapy, history of shoulder surgery, full-thickness Supraspinatus tear, Type 3 or 4 acromions, and corticosteroid injection within 3 months. Patients could have both shoulders injected if both shoulders met the criteria. 60 candidates meeting the inclusion and exclusion criteria are included.

Patients are treated with subacromial and peritendinuous injection of either PRP (Group I) or Hyaluronic acid (Group II) or a placebo solution (Group III). Patients were randomly allocated to one of the three groups of the study via Block randomization to ensure an equal number of patients in each group. Participants are considered in blocks. A random number sequence is used to select a particular block, which determines the allocation order for the first four subjects. Each group included 20 candidates with homogenous age and gender distribution. The visual analog scale (VAS) is used as a primary outcome measure assessing current rest pain at baseline and 2, 8, 12, and 52 weeks. Also, functional shoulder tests (Figure 1) are used to assess baseline SST status and response to therapy.[11] Secondary outcomes included UCLA score and MRI

changes. UCLA scores are recorded at baseline and 2, 8, 12 weeks, and 52 weeks along with Visual Analogue Scale Pain and Functional Outcome Measures.

MRI was performed at baseline and 12 weeks. MRIs were scored on a 0-5 severity scale using a rubric modified from Lewis et al[13]: 0, no tendinopathy; 1, mild tendinopathy; 2, moderate tendinopathy; 3, moderate tendinopathy + partial thickness tear present; 4, severe tendinopathy ± Partial-thickness tear present; 5, severe tendinopathy + full-thickness tear present. Patient satisfaction was assessed at 52 weeks using a three-item scale (unsatisfied, partially satisfied, or completely satisfied).

Functional Outcome Measures Were Performed at Baseline and at 8 and 12 Weeks

Functional Exercise Test	Description	Main Parameter Assessed
Empty can exercise with dumbbell resistance	Arm held in position of scaptation (30 degrees of horizontal adduction with shoulder abducted to 90 degrees) with weighted resistance, measured as number of seconds to fatigue (unable to maintain arm at 90 degrees)	Supraspinatus muscle strength and stamina
Drop arm exercise with dumbbell resistance	Arm held in position of 90 degrees of shoulder abduction with weighted resistance, measured as number of seconds to fatigue (unable to maintain arm at 90 degrees)	Supraspinatus muscle strength and stamina
Side-lying external rotation with dumbbell resistance	Side-lying on opposite side, with weight held in hand with elbow flexed to 90 degrees adducted to the side, participant externally rotates through full range of motion at the shoulder. The number of repetitions during a 30-second period are recorded.	Infraspinatus strength and stamina
Full can exercise with dumbbell resistance	Participant parallel to wall with the hand held in a fist and shoulder forward flexed parallel to the floor. A measuring stick is used to measure forward-reach distance. The patient is instructed to reach forward along the yardstick. The patient repeatedly reaches to a maximal distance. The number of repetitions during a 60-second period are recorded.	Rotator cuff strength and stamina, ability to forward flex the shoulder
External rotation at 0 and 90 degrees with Thera-Band resistance	Test 1: Performed at 0 degrees of shoulder abduction. Test 2: Performed at 90 degrees of abduction and external rotation of the shoulder. (Thera-Band resistance was selected according to the patient's ability to perform 20 repetitions with good eccentric control.) The patient is instructed to perform rapid oscillations in a 30-degree arc of external rotation motion until fatigue. The examiner records the number of seconds to fatigue.	Rotator cuff strength and stamina, ability to externally rotate and abduct the shoulder

Figure 1: Shoulder functional tests [11]

Scale for shoulder classification - UCLA modified

Pain	
Continuously present, unbearable, frequent use of strong medication	*1*
Continuously present, bearable, occasionaly strong medication	*2*
No pain or less pain during rest or light activity frequent use of salycilates	*4*
Pain during hard activities isolated, occasional use of salycilates	*6*
Ocasional or not significant	*8*
No pain	*10*
Function	
Incapacity to use the arm	*1*
Possible only for light activities	*2*
Capable of performing light tasks or the majority of daily activities	*4*
The majority of home tasks, drive, comb dress or undress	*6*
Only few restrictions. Can perform work above the level of shoulder	*8*
Normal activities	*10*
Anterior flexion activities	
Bigger than 150°	*5*
120° to 150°	*4*
90° to 120°	*3*
45° to 90°	*2*
30° to 45°	*1*
Less than 30°	*0*
Resistance to anterior flexion (hand muscular test)	
Grade 5 – Normal	*5*
Grade 4 – Good	*4*
Grade 3 – Moderate	*3*
Grade 2 – Bad	*2*
Grade 1 – Muscular contraction	*1*
Grade 0 – None	*0*
Patient satisfaction	
Satisfied or better	*5*
Not satisfied or worse	*0*

Figure 2: UCLA score[12]

Intervention

Group I: 20 patients received a single injection of PRP. prepared in the OPD. 21 cc of blood sample was harvested from each patient.1 cc was used for complete blood cell count while the rest of the sample were divided into 2 tubes, mixed with 1.5 cc adenosine-citrate-dextrose-acid (ACD-A) solution. Platelet count in the blood sample is measured and recorded. Tubes were centrifuged for 15 minutes at 4,000 RPM, then the buffy coat layer and some of the serum layers were harvested together using a 10 cc syringe equipped with a spinal needle. The upper portion of that volume that contains mostly PPP (platelet-poor plasma) is removed. Pellets are homogenized in the lower 1/3rd (5 ml of plasma) to create the PRP (Platelet-Rich Plasma) (figure 3). A single injection of PRP will be given in the sub-acromial space. The lesion was marked and the area sterilely prepped. The needle is inserted at the proximal aspect of the lesion and slowly removed while infiltrating 3.5 mL of PRP without activation with CaCl/thrombin at the lesion and surrounding tendon. Post-treatment pain control (500 mg) was used.

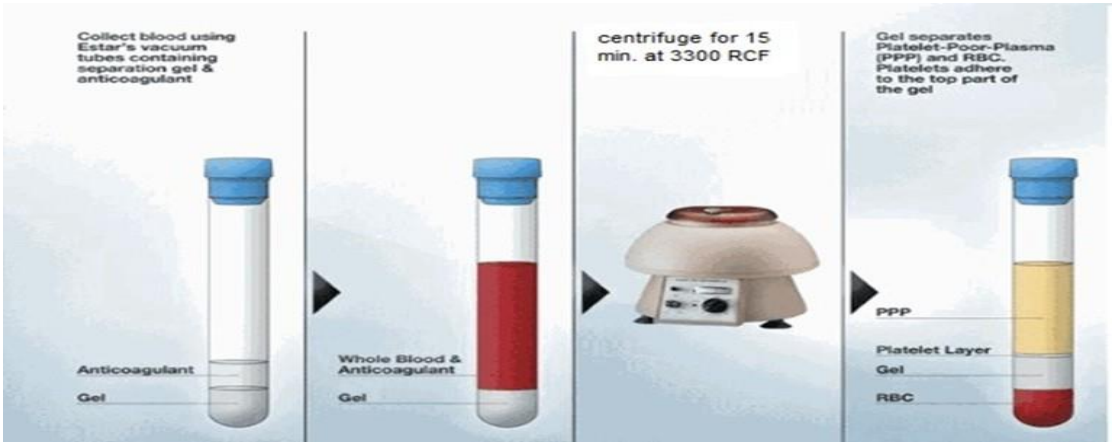

Figure 3: Platelet-Rich Plasma preparation[7]

Group II: Another 20 patients received Hyaluronic acid injection around the affected tendon once a week for a total of 2 injections using the same technique and precautions used with PRP. The form used is a re-filled syringe with 2 ml of low molecular weight Na hyaluronan (20 mg) and molecular weight of 0.5-0.73 mill D.(HYALGAN® - Fidia Pharma USA Inc.)
Group III: Another 20 patients received a 3 ml of 1% xylocaine that is injected once as a placebo using the same techniques described for groups I & II.
In-person assessment occurred at 2, 8, and 12 weeks and by phone at 52 weeks. Patients were discouraged from using nonsteroidal anti-inflammatory medications and starting new therapies for SST. Participants were advised to rest including 2 days off work, then slowly advance to activities of daily living for 2 weeks and gradual return to activity.

Analysis

Data were analyzed using SPSS© Statistics version 21 (IBM© Corp., Armonk, NY, USA). Categorical variables were presented as ratio or numbers and percentages

and between-group differences were compared using Fisher's exact test (for nominal data) or the chi-squared test for trend (for ordinal data). The normality of numerical data distribution was examined using the Shapiro-Wilk test. Normally distributed numerical variables were presented as mean ± SD and inter-group differences were compared using one-way analysis of variance (ANOVA) with the application of the Student- Newman-Keuls post hoc test for multiple pairwise comparisons if there was a statistically significant difference among the groups. Serial measurements analysis was used for the analysis of the main outcome measures-time curves. The area under the curve (AUC) and the time-weighted average (TWA) were estimated as summary measures and were compared using one-way ANOVA with the application of the Student-Newman-Keuls test for pairwise comparisons if needed. P-values < .05 are considered statistically significant.

Results

VAS score: The results showed improvement in pain intensity for Group I; PRP (Baseline Mean; 7.2 ± 0.6 — 52 weeks Post-injection Mean; 1.8 ± 1.2) and Group II; HA (Baseline Mean; ± 0.8 — 52 weeks Post-injection Mean; 2.0 ± 1.3). While group III; Placebo showed no significant improvement in pain intensity (Baseline Mean; 7.1 ± 0.3 — 52 weeks Post injection

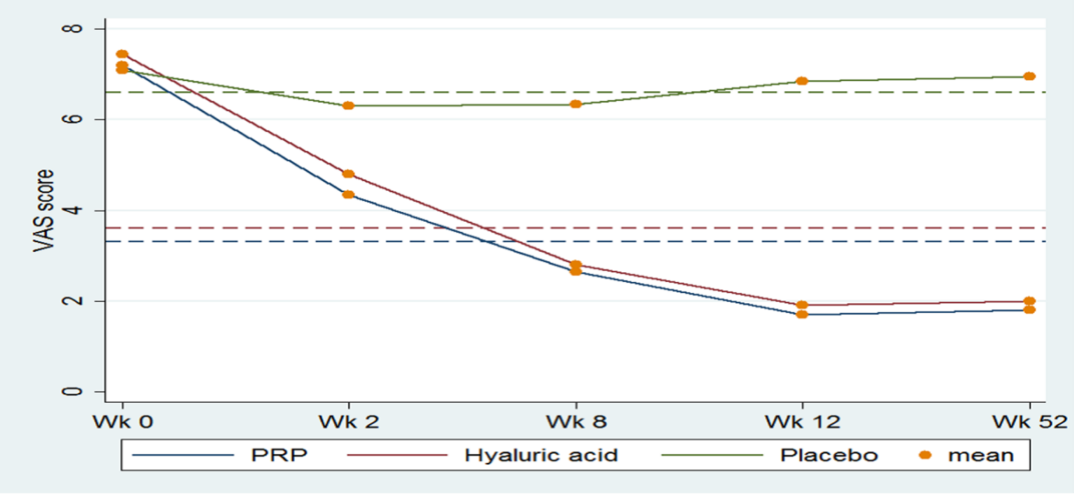

Figure 4: The area under the VAS score-time curve in the three study groups. Solid lines represent the area under the curve (AUC) and dashed lines represent the time-weighted average (TWA).

Functional outcome measures

The shoulder function of Group I improved from a baseline Mean score of 205.7 ± 10.4 to a 52 weeks post-injection Mean score of 312.1 ± 48.1. Also, the results showed an improvement in shoulder function of Group II from a Mean score of 206.7 ± 14.8 to a Mean score of 320.0 ± 47.5 at week 52 post-injection. Group III results did not show any significant improvement at week 52 of Placebo cases as the mean score at baseline was (Baseline; 214.6 ± 8.2 and W 52 post-injection;

223.0 ± 18.6 with p-value < .001. Comparing Groups, I and II, there is no significant difference between groups' effects of PRP and HA injection on the function of the shoulder.

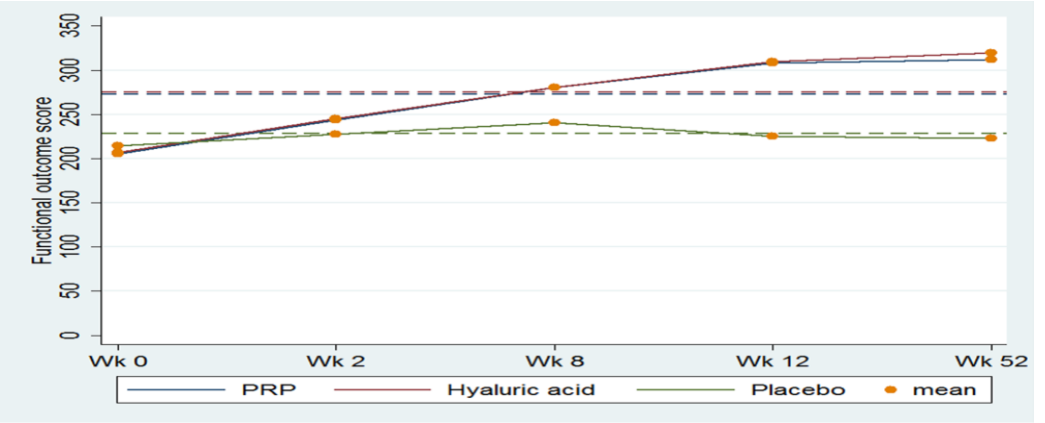

Figure 5: The area under the functional outcome score-time curve in the three study groups. Solid lines represent the area under the curve (AUC) and dashed lines represent the time-weighted average (TWA).

UCLA score: The results showed an improvement of the UCLA score for PRP cases whose mean score at baseline was 17.4 ± 1.8 and increased to 28.5 ± 5.1 at 52 weeks post-injection. Also, the results showed an improvement in the score for HA cases whose mean score at baseline was 17.7 ± 1.9 and increased to 28.4 ± 5.2 at 52 weeks post-injection. However, Placebo cases didn't show significant improvement in the UCLA score as the mean score at baseline was 18.0 ± 1.7 which increased to 18.4 ± 2.1 at 52 weeks post-injection.

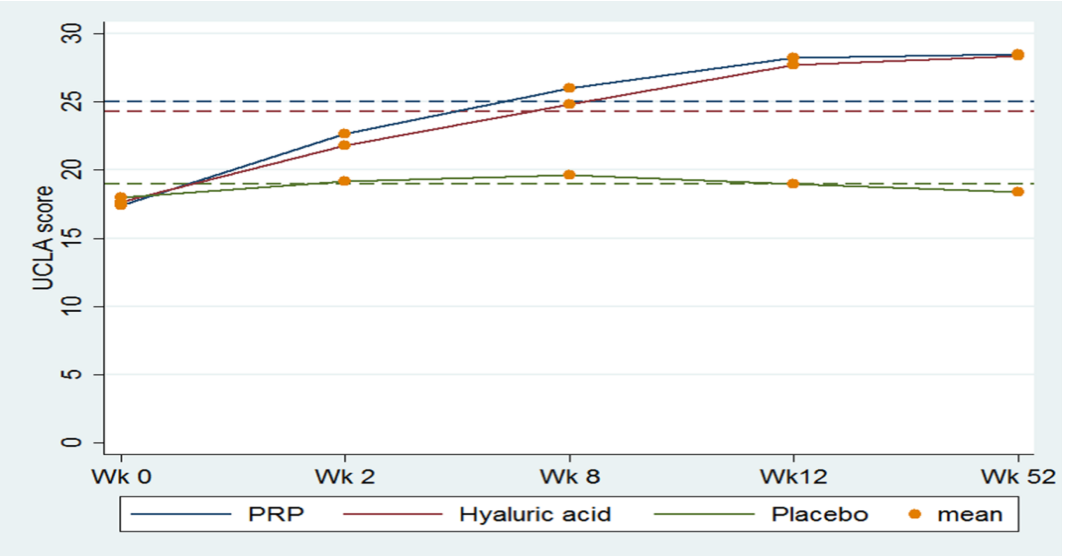

Figure 6:The area under the UCLA score-time curve in the three study groups. Solid lines represent the area under the curve (AUC) and dashed lines represent the time-weighted average (TWA)

Satisfaction: For the PRP group, five participants reported that they were “completely satisfied” with care, ten were “satisfied,” and three responded that they were “unsatisfied.” For the HA group, five participants reported that they were “completely satisfied” with care, eight were “satisfied,” and Four responded that they were “unsatisfied.” For the Placebo group, ten patients showed very mild improvement within 2 weeks post-injection only as of the placebo effect.

MRI changes: No detectable MRI changes have been noted for Group III (Placebo) at week 12 when compared to the baseline MRI did to assess SS tendinopathy at the start of the study. However, positive changes could be detected in the degree of tendinopathy in Groups I & II. 70 % of cases in Group 1 showed signs of moderate to severe degrees of tendinopathy (with or without partial tears) at the baseline MRI study while only 20 % maintained this degree of tendinopathy at week 12. Also, 60 % of cases of group III showed moderate to severe MRI changes at baseline while only 35 % continued to show the same levels at week 12. Significant improvements have been reported in Groups I & II with a statistically significant difference when comparing groups, I & II to Group II (placebo) at week 12 (P-value .011).

Discussion

Various injections can and have been used to aid in the diagnosis or treatment of RC tendinopathy. Physical therapy is often the first line of management for symptomatic SST with active exercises protocols while surgery is reserved only for completely torn SS tendons and or acromion Type 3 or 4).[14] This study is conducted as a Double-blinded randomized controlled trial (Quantitative, comparative, controlled experiments). where participants have been allocated randomly into a three-armed study. Participants either received PRP, Hyaluronic acid, or placebo injection and the efficacy and outcomes of each are compared to the baseline and against each other.

Our results report a strong clinical effect of local injection of either PRP or HA proximal to a lesion at a tendinopathic area or tear and surrounding it. Improved pain scores were accompanied by improved functional and UCLA scores, suggesting that healing occurred at the tissue level. MRI changes are noted to justify the improvement in these scores which suggest relative tendon healing and subsidence of the degree of chronic inflammation.

The use of either PRP or Sodium hyaluronate to treat inflammatory conditions is documented in the literature with several studies supporting their efficacy in the management of tendinopathies. There is growing evidence that they both contribute to healing on the tissue level and improvement in functional scores with pain reduction in rotator cuff disease. The mechanisms are still unclear and further studies are encouraged to help with that. the combination of both drugs is even being studied recently but the influence of PRP on the rheological and biological properties of HA-based viscosupplements is still mostly unknown. To our knowledge, this is the first study comparing three preparations one of them is a placebo. Many RCTs already compared either one PRP or HA with placebo or Corticosteroids but their results are mixed. Rha et al.[15] showed a statistically significant improvement in both the shoulder pain and disability index and range

of motion with PRP when compared with dry needling over 6 months.[15] Several in vivo studies have reported that PRP-treated tendons healed at an earlier time point and were of superior quality to control tendons, with better organization of fibroblasts and collagen bundles.[16] Scarpone M. et al.[17] evaluated PRP for refractory RCT in a pilot-level prospective open-label study to test the hypothesis that a single ultrasound-guided PRP injection improves clinical, functional, and radiological outcome measures compared to baseline status. Improvements in pain and function outcomes are consistent with those reported in other studies of PRP for chronic musculoskeletal pain. They concluded that a single intralesional injection of PRP under ultrasound guidance resulted in a safe, significant, sustained improvement in pain, function, and MRI outcomes for participants with refractory RCT. This suggests that PRP has the potential to heal the muscle-tendon unit of the rotator cuff at the level of degenerative tissue and may be a primary nonsurgical treatment for refractory RCT. [17-19]

On the other hand, some studies recommended PRP use and questioned its efficacy in reducing pain and improving function. Kesikburun S. et al[20] concluded that In patients with rotator cuff tendinopathy, the injection of PRP did not improve pain and shoulder function more than the placebo did. The efficacy of subacromial injections of HA alone in patients with chronic RC tendinopathy is also reported in the literature. In an open-label multicenter study.[21] Kim et al.[22], in a prospective randomized single-blind comparative study on 105 patients with subacromial impingement, found that hyaluronate injections produced more significant pain reduction and similar functional improvement compared to corticosteroids at 12 weeks. On the contrary, concerning our results, Penning et al.[23] reported a significant reduction in pain at short- and long-term follow-up with corticosteroid injections compared with hyaluronic acid and the long-term placebo, injections showed the best results.[21-23]

Despite the significant clinical and functional improvement reported in groups I & II compared to the placebo group in our study, stronger and more consistent statistical correlations between pain and functional and MRI outcomes have been expected. We owe this to the high variability in individual baseline and follow-up scores with small sample size. In addition, MRI findings may not correlate well with patient-reported symptoms related to rotator cuff disease in all circumstances. Improvements in pain and function outcomes are consistent with those reported in other studies of PRP or HA for chronic musculoskeletal pain.

The merits of this study include being a three-armed randomized controlled trial comparing PRP and HA to a control placebo group in shoulder tendinopathies and to our knowledge, this is one of the first clinical trials in recent literature. This confirms the positive effects of intraarticular PRP and HA when either is injected to treat Tendinopathies conservatively. Also, block randomization is used to ensure a balance in the number of patients allocated to each of the groups in the trial. This eliminates selection bias and balances known and unknown confounding factors to create a control group that is as similar as possible to the treatment group. Another merit is blinding which has been used to abolish the risks of bias when subjective outcome measures are being used.

Power and sample size calculation (60 patients) has been revised before enrolment which allows detection of any difference between the groups and increases the credibility and strength of the results. Moreover, the ease of the PRP harvesting technique with relatively decreased costs adds to the reproducibility of the technique. Lastly,

A 52-week follow-up period with repeated measurements throughout the study confirms the outcome data and helps to pull strong information out of the results. On the other hand, there is no study without Limitations. First, the primary 0–10-point VAS outcome measure is not validated for RCT; however, VAS scores are an accepted measure of pain and have been used as primary outcomes in studies of chronic pain and injection therapy specifically. Second, Immediate post-treatment pain scores and use of narcotic pain medication were not recorded; therefore, it is unclear how painful PRP therapy was. The study also was limited by the lack of MRI follow-up beyond the 12 weeks. Although MRI imaging during this period (12 weeks) demonstrated structural improvements in the majority of tendons, the long-term tissue-modifying potential of PRP or HA on SST is not known. Also, the ultrasound-guided injection could be more accurate avoiding technical faults and this has not been readily available to be used in all our study cases. Lastly, the platelet count in each injectable solution has not been measured in our current study and is recommended to be able to solidify the effect of PRP injection. This has been lacking in most of the recent studies that study the effects of PRP but we recommend it in future studies.

Conclusion

Subacromial injection of PRP or HA resulted in safe, significant, sustained improvement of pain, function, and MRI outcomes in participants with refractory SST with a significant difference compared to our control group that was injected with local anesthetics only (Placebo). We believe that PRP use in musculoskeletal conditions is yet to be further extended and more thoroughly studied in comparison to other available injectables. This study hypothesizes and provides evidence for the positive potential effects of PRP injections in tendinopathies. functional and radiological outcomes of PRP are positive along with HA when compared directly to placebo (local anesthetic) injections that showed no detectable improvement. Future studies shall use larger sample sizes with a longer follow-up period with definite platelet count figures to further support the use of PRP in such conditions along with HA viscosupplements and may even combine it together with other studies.

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