ORIGINAL RESEARCH

A study to evaluate the efficacy of PRP treatment for tendinopathy

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ABSTRACT
Aim: The aim of the present study was to evaluate the efficacy of PRP treatment for tendinopathy. M**ethods:** The present study was conducted in the Department of Orthopedics and the study used the data for specific methodological purposes, inclusion and exclusion criteria, clinical and ultrasound evaluation, PRP preparation procedure and treatment schedules and 100 patients were included in the study. **Results:** 100 patients suffering from mid-portion tendonitis submitted to PRP therapy were included in the study. There were 52 male and 48 females in the study. 85% patients had no habit of smoking and 25% had metabolic disorders. The individual basal values of VISA-A scores were widely scattered, so showing that subjects with different degrees of impairment were included in the trial. At 3 and 6 months post-treatment, mean VISA-A score increased significantly (63.7 ± 13.8 at 3 months (p = 0.00001) and 67.2 ± 14.1 at 6 months (p = 0.00001)). A positive relationship between Likert score and VISA-A score at 6 months was present (r = 0.55). Different degrees of patient satisfaction were observed for similar increases of the score. **Conclusion:** Tendinopathy is a highly prevalent tendon disorder and plagues a range of individuals from the common person to elite athletes. It may cause extreme pain and affect tendon function, which can impair normal life activities. Because the mechanisms of tendinopathy are not completely understood, the current treatment options for this tendon disease remain largely palliative. PRP is a popular cell-free therapy that is used worldwide to treat tendinopathy.
Key words: PRP, tendinopathy, outcome

INTRODUCTION

Tendons are dense connective tissues that link muscles to bones. Thus, they transmit muscular forces to bones and enable joint movements. As a consequence, tendons are subject to large mechanical loads that may cause injuries and affect tendon function. In orthopaedic clinics, tendon and ligament injuries are one of the most prevalent health problems with about 16.4 million individuals seeking medical intervention every year.[1,2] Among the tendons, Achilles, patellar, rotator cuff, and forearm extensor tendons are the easiest to injure due to overuse.[3] Typically, tendons are hypovascular. However, histopathological observations of chronic tendon injury or tendinopathy have revealed hypervascularity and disorganization in vessel distribution, which may affect the mechanical properties of tendons and induce pain. Tendinopathic tendons also feature interstitial gaps (microtears), discontinuous collagen fibers, and a number of degenerative changes including lipid deposition, proteoglycan accumulation, and calcification.[2] They also have decreased total collagen content, increased collagen type III/collagen type I ratio, increased expression of matrix metalloproteinases (MMPs), MMP-1, MMP-3, and MMP-9, and decreased expression of the MMP inhibitors.[4,5] Apart from changes in tendon metabolism, high inflammation has been also reported at the microinjury sites that damage the tendon tissue if left untreated.[6-8]

Tendinopathy is the most common musculo- skeletal complaint in patients seeking medical care.[9] The most common sites of presentation include the elbow, rotator cuff, Achilles tendon and patellar tendon. With early diagnosis and timely application of traditional non-surgical treatments such as activity modification, gentle static stretching, anti-inflammatory medications and/or eccentric loading, the prognosis is favourable in the acute stage. However, symptoms may persist in some patients despite exhausting these treatment options. Recalcitrant tendinopathy may manifest because, once damaged, the biological and biomechanical properties of connective tissue are never completely restored. Healing times in chronic tendinopathies are prolonged as tendons are relatively hypovascular and local blood flow is only about one-third of that delivered to the muscles.[10]

With the development of relevant research, scholars have discovered that growth factors play a crucial role in tendon repair and have considered using platelet-rich plasma (PRP) to treat these tendon disorders. High platelet counts and supraphysiological concentrations of platelet-derived growth factors, chemokines, and cytokines are necessary for the tissue healing and regenerative characteristics of platelet concentrate, such as PRP, platelet-rich fibrin (PRF), and concentrated growth factor (CGF).[11,12] Preparing PRP is simple and rapid, and the quality of PRP products may be evaluated by determining the percentages of platelets, leukocytes, and growth factors present.

The aim of the present study was to evaluate the efficacy of PRP treatment for tendinopathy.

MATERIALS AND METHODS

The present study was conducted in the Department of Orthopedics and the study used the data for specific methodological purposes, inclusion and exclusion criteria, clinical and ultrasound evaluation, PRP preparation procedure and treatment schedules and 100 patients were included in the study.

Patients suffering from mid-portion tendonitis for more than 3 months, refractory to previous treatments were enrolled, excluding those with tendon tears or history of surgery, and treatment within the previous three months with steroids and/or physical therapies. Demographic and clinical data were collected. Ultrasound evaluation was performed using a high-resolution, multi-frequency (6-15 MHz) linear array transducer. PRP was obtained from 8 mL of autologous blood using the Regen Kit®A-PRP device (RegenLab- Switzerland), which provides (as mean) a3× native platelet concentration, > 80% platelet recovery, no leukocytes, red blood cell remnant < 0.3%. Small PRP depots were left at the site of most damaged areas for a total amount of 4–5 mL. Three injections of PRP were per-formed once a week. After the second injection, a rehabilitation program, based on eccentric training and stretching, was recommended twice daily at least for 3 months.

A questionnaire was used to assess the clinical stage of the tendinopathy.[13] It contains eight questions that cover the three domains of pain, function, and activity. Questions one to seven were scored out of 10 whereas the question 8 (which concerns the sport activities) carries a maximum of 30. Therefore, a subject who is able to perform without pain a sport activity which involves an over loadfor the Achilles tendon would score a maximum of 100 points. The post-treatment patient's satisfaction was assessed by means of the Likert Scale (0 = no at all satisfied; 1 = slightly satisfied;2 = somewhat satisfied; 3 = very satisfied; 4 = extremely satisfied).[14] All the measures were performed at baseline, and after 3- and 6-months follow-up.

STATISTICAL ANALYSIS

The mean of VISA-A score was calculated; therefore, for each subject the difference of VISA-A values between baseline and post-treatment was computed. Cut-off levels were fixed to define the outcome clinically no detectable, detectable and evident (0 to 9 points change, 10 to 19, and ≥ 20, respectively). The significance level was determined at $p < 0.05$. Finally, the Pearson correlation was used to evaluate the relation-ships between VISA-A values and Likert patient's satisfaction score.

RESULTS

Table 1: Demographic and clinical data at baseline

Variables	**N=100**
Age	42.8 ±13.7
M:F	52:48
Symptoms duration (months)	12.7±4.3
VISA-A	50.1±9.1
Body Part of Injection	
Achilles	28 (28)
Elbow	22 (22)
Shoulder	20 (20)
Knee	20 (20)
Others	10 (10)
Smoking N (%)	
Yes	15 (15)
No	85 (85)
Metabolic disorders N (%)	
Present	25 (25)
Absent	75 (75)

Sport activities	70 (70)
Previous treatments	
Steroids	5 (5)
Hyaluronic acid	10 (10)
Laser therapy	60 (60)
Ultrasound	45 (45)
Thermotherapy	75 (75)
Physiotherapy	90 (90)
VISA A Score	
At 3 months	63.7 ± 13.8
At 6 months	67.2 ± 14.1

100 patients suffering from mid-portion tendonitis submitted to PRP therapy were included in the study. There were 52 male and 48 females in the study. 85% patients had no habit of smoking and 25% had metabolic disorders. The individual basal values of VISA-A scores were widely scattered, so showing that subjects with different degrees of impairment were included in the trial. At 3 and 6 months post-treatment, mean VISA-A score increased significantly (63.7 ± 13.8 at 3 months (p = 0.00001) and 67.2 ± 14.1 at 6 months (p = 0.00001)). The most commonly injected body parts were the Achilles tendon (28%), elbow (22%), patella tendon (20%) and shoulder (20%).

Table 2: Satisfaction in relation to different classes of VISA-A score improvement at 3- and 6-months follow-up

	Likert scale					
Changes in VISA-A score	**N**	**0**	**1**	**2**	**3**	**4**
3 months						
0-9	20	20	0	0	0	0
10-19	50	10	25	8	4	3
20-29	25	1	6	7	6	5
>30	5	0	0	0	3	2
6 months						
0-9	22	22	0	0	0	0
10-19	40	5	20	8	4	3
20-29	20	2	7	7	3	3
>30	18	0	0	0	9	9

A positive relationship between Likert score and VISA-A score at 6 months was present (r = 0.55). Different degrees of patient satisfaction were observed for similar increases of the score.

Table 3: MANOVA Analysis of the study Assessing Change Scores Between Pre-Injection and 6-month Post-Injection

	VAS Pain	**VAS Function**	**VAS Sports Activities**
Gender			
Male	1.8 (2.5)	1.4 (2.5)	2.7 (2.7)
Female	2.8 (2.4)	2.5 (2.5)	2.7 (2.6)
P Value	0.03	0.01	0.990
Body Part			
Achilles	2.3 (2.7)	2.4 (2.9)	2.7 (2.6)
Elbow	2.3 (2.2)	2.0 (2.3)	2.6 (3.0)
Shoulder	2.6 (2.9)	1.9 (2.7)	2.4 (3.0)
Knee	1.8 (2.7)	1.1 (2.5)	2.6 (2.5)
Others	2.2 (2.2)	1.8 (2.2)	3.3 (2.4)
P Value	0.20	0.92	0.48

MANOVA analysis evaluating differences across covariates found that pain intensity VAS and daily activity ability VAS were significantly different between genders ($p<0.05$). Females improved more on both pain (2.8 vs. 1.8) and function (2.5 vs. 1.4) compared to males. No other variables showed statistically significant differences among/between other classifications.

DISCUSSION

The outcomes of Platelet Rich Plasma (PRP) treatment in tendinopathy may be measured by means of a number of scales (self-report or objective) which explore specific domains: symptoms and function (pain, muscle power and endurance), activity limitations (twisting, lifting, jumping), work and sport participation, tendon structure (ultra-sound and magnetic resonance imaging), and quality of life.[15] In recent years, a popular option for treating musculoskeletal injuries including tendinopathy is Platelet-Rich Plasma (PRP).[16-18] The key components of PRP are the platelets, which are a nucleate cytoplasmic fragments produced by megakaryocytes in the bone marrow.[19] Platelets have long been recognized to maintain tissue hemostasis. But accumulating evidence indicates that platelets may have a much wider role in tissue healing because they store and release a wide range of bioactive factors including growth factors (e.g., TGF-β and HGF). These factors are secreted by the dense granules, α-granules, and lysosomes in platelets.[20]

Injections of PRP are widely utilised in therapeutic settings to enhance healing and regeneration. Platelet concentration in PRP is two to six times more than in whole blood.[21] Once activated, concentrated platelets can theoretically release greater than physiological levels of autologous growth factors to enhance healing and regeneration, such as in musculoskeletal treatment.[22,23] Verrall *et al.* [24] observed that mobility during AT treatment was equivalent to stopping exercise for 6 weeks. Rest may improve prognosis. Van der Plas *et al*. [25] found that in 46 patients (58 AT), the VISA-A score significantly increased from 49.2 at baseline to 83.6 after 5 years ($p<0.001$) of eccentric exercise. At follow-up, 39.7% reported pain relief, and the sagittal Achilles tendon thickness decreased from 8.05 to 7.50 mm. Eccentric exercise eases chronic tendinitis and accelerates tendon remodelling and tissue recovery.[26]

100 patients suffering from mid-portion tendonitis submitted to PRP therapy were included in the study. There were 52 male and 48 females in the study. 85% patients had no habit of smoking and 25% had metabolic disorders. The individual basal values of VISA-A scores were widely scattered, so showing that subjects with different degrees of impairment were included in the trial. At 3-and 6-months post-treatment, mean VISA-A score increased significantly (63.7 ± 13.8 at 3 months ($p = 0.00001$) and 67.2 ± 14.1 at 6 months ($p = 0.00001$)). A positive relationship between Likert score and VISA-A score at 6 months was present ($r = 0.55$). Different degrees of patient satisfaction were observed for similar increases of the score.

Recent biologics approaches have also combined PRP with other tissue engineering modalities to enhance tendon healing. Particularly, stem cells in conjunction with PRP have shown promising results in the treatment of tendinopathy. PRP + BMSC treatment of tendon wounds in dogs significantly increased the strength and stiffness of healing tendons compared to the groups that used either of them separately.[27] Carvalho *et al*. performed an animal RCT (Randomized Controlled Trial) and found that, after 16weeks, the combination of ADMSCs and platelet concentrate prevented the progression of lesion, induced a greater organization of collagen fibers, and decreased inflammatory infiltrates.[28] Other modalities have also been used along with PRP to treat tendon injuries. Moshiri *et al*. reported that the use of platelet gel embedded within a 3D collagen implant in an Achilles tendon defect in rabbits was effective in healing, modeling, and remodeling the tendon.[29] Besides, Barbosa *et al*. Reported that low-level laser therapy combined with PRP increased the deposition of collagen type I and enhanced regeneration of the tendon tissue.[30]

Foremost, each PRP synthesis procedure provides products with different biological functions; thus, there are no universal standards for producing and using PRP in basic or clinical research. While most studies have used equal frequencies of PRP injections in intervention groups, PRP injection quality and amount may differ, resulting in clinical heterogeneity and ambiguity. The Food and Drug Administration has approved various commercial PRP formulation designs, but worldwide formulation standards and quality evaluation have not yet been established. In the included studies, blood collection volume, centrifugation speed/time, and platelet activation techniques varied, influencing PRP preparation yield, purity, viability, and platelet activation status, as well as quality and quantity. A study by Keene *et al.* [31] detailed the exact amounts of platelets, leukocytes, and representative growth factors in their PRP injections.

CONCLUSION

Tendinopathy is a highly prevalent tendon disorder and plagues a range of individuals from the common person to elite athletes. It may cause extreme pain and affect tendon function, which can impair normal life activities. Because the mechanisms of tendinopathy are not completely understood, the current treatment options for this tendon disease remain largely palliative. PRP is a popular cell-free therapy that is used worldwide to treat tendinopathy. Basic science studies have consistently shown the beneficial effects of PRP on tendons including increased tendon cell proliferation, increased expression of anabolic genes and proteins, and reduced tendon inflammation. However, the efficacy of PRP in clinical trials is not consistent leading to the controversies regarding the PRP treatment efficacy. Among clinical studies, RCTs are considered to be the gold standard in assessing the efficacy of PRP treatments in clinical settings.

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