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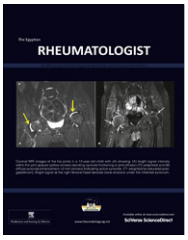

ORIGINAL ARTICLE

Local injection of autologous platelet rich plasma and corticosteroid in treatment of lateral epicondylitis and plantar fasciitis: Randomized clinical trial

Aziza Sayed Omar [a,*], Maha Emad Ibrahim [a], Amal Sayed Ahmed [b], Mahmoud Said [a]

[a] *Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Suez Canal University, Ismailia, Egypt*
[b] *Clinical Pathology Department, Faculty of Medicine, Suez Canal University, Ismailia, Egypt*

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Foot health status questionnaire (FHSQ)

Abstract *Aim of the work:* This randomized controlled study was designed to compare the effectiveness of local injection of autologous platelet rich plasma (PRP) and local steroid in reducing pain and improving function in a cohort of patients with tennis elbow (TE) and plantar fasciitis (PF).

Patients and methods: The study population comprised two groups; Group 1 patients with TE ($n = 30$) and Group 2 patients with PF ($n = 30$). In each group patients were allocated randomly to receive either a steroid or PRP injections. All patients filled in visual analog scale (VAS), disability of arm, shoulder and hand (DASH) score for TE and foot health status questionnaire (FHSQ) for PF at base line and after 6 weeks.

Results: Relative to TE group of patients significant differences were observed between VAS and DASH scores at base line and 6 weeks after treatment in both groups ($p < 0.001$). While no significant differences were observed relative to VAS and DASH score changes between both groups ($p > 0.05$). In PF patients comparison of VAS and FHSQ at base line and 6 weeks after treatment between control group and PRP group showed significant differences for VAS ($p = 0.005$ and

* Corresponding author.
E-mail address: dr.aziza2011@hotmail.com (A.S. Omar).

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$p < 0.001$, respectively), and for FHSQ ($p = 0.03$ and $p < 0.001$, respectively). While highly significant difference were observed between both groups regarding VAS and FHSQ changes ($p = 0.001$).

Conclusion: Local injection of autologous PRP proved to be a promising form of therapy for TE and PF. It is both safe and effective in relieving pain and improving function and superior to local steroids in PF.

1. Introduction

The most common overuse syndrome is related to excessive wrist extension and commonly referred to as tennis elbow (TE), although more common in non-tennis players. Typically, TE affects individuals greater than age 40 years with a history of repetitive activity aggravating the extensor tendons of the forearm. It is also commonly referred to as "lateral epicondylitis", but this is usually a misnomer because, in general, microscopic evaluation of the tendons does not show signs of inflammation, but rather angiofibroblastic degeneration and collagen disarray. On histological level light microscopy reveals both an excess of fibroblasts and blood vessels that are consistent with neovessels or angiogenesis [1]. The tendons are relatively hypovascular proximal to the tendon insertion. This hypovascularity may predispose the tendon to hypoxic tendon degeneration and has been implicated in the etiology of tendinopathies [2].

On the other hand, chronic plantar fasciitis (PF) is the most common cause of foot complaints and, making up 11–15% of the foot symptoms requiring professional care among adults [3]. The incidence of PF peaks in people between the ages of 40–60 years with no bias towards either sex [4]. The underlying condition that causes PF is a degenerative tissue condition that occurs near the site of origin of the plantar fascia at the medial tuberosity of the calcaneous [5]. Steroid injections are a popular method of treating the condition but only seem to be useful in the short term and only to a small degree [6].

The introduction of platelet rich plasma (PRP) as a possible adjunct to conservative and operative treatment has motivated significant research in the topic [7]. PRP is promoted as an ideal autologous biological blood-derived product, which can be exogenously applied to various tissues where it releases high concentrations of platelet derived growth factors that enhance wound, bone and also tendon healing [8].

In an animal model the addition of growth factors to the ruptured tendon has been shown to increase tendon healing [9,10]. In humans it offers encouraging results of an alternative minimally invasive treatment that addresses the pathophysiology of TE that has failed traditional nonsurgical modalities [8]. It was also demonstrated that a single injection of PRP improves pain and function more than corticosteroid injection and these improvements were sustained over time with no reported complications [11].

Relative to PF the injection of PRP into the affected tissue addresses the healing stages necessary to reverse the degenerative process which are going on in the base of the plantar fascia. Moreover the treatment of tendinosis with an injection of PRP may be a nonoperative alternative. This treatment concept directly addresses the existing condition and should prove to be a superior alternative to current conservative treatments for chronic PF [12].

All theses new lines of evidences inspired us to evaluate the effectiveness of local injection of autologous PRP in reducing pain and improving function in patients with TE and PF compared with local injection of corticosteroid.

2. Patients and methods

This randomized clinical study was carried out in the Rheumatology and Rehabilitation outpatient clinic in Suez Canal University Hospital from October 2009–May 2010. A total of 60 patients were recruited for the study, with 30 cases had TE (Group I) and another 30 cases had PF (Group II). In each group, patients were allocated randomly to receive either a steroid injection ($n = 15$) (control group) or PRP injection ($n = 15$) (PRP group).

2.1. Clinical assessment

Thirty patients diagnosed as having TE and 30 with PF of both genders, aged above 18 years (for TE: having pain and tenderness over the lateral aspect of the elbow, which is related to activity level, with a positive wrist extension test, for PF: having inferior heel pain that is usually worse with their first steps in the morning or after a period of inactivity, with maximal tenderness over the anteromedial aspect of the inferior heel). None of our patients received local steroid injections, nonsteroidal anti-inflammatory at least 4 weeks prior to the study.

Patients with history of anemia (hemoglobin < 7.0 g/dl), thrombocytopenia (platelets $< 150 \times 10^3$ μL) or bleeding dyscrasias, significant cardiovascular, renal or hepatic disease, (local) malignancy were excluded. In PF group of patients further exclusion criteria were; previous surgery for PF, vascular insufficiency or neuropathy related to heel pain, hypothyroidism and diabetics.

All included patients on the 1st visit were evaluated by a full medical history and physical examination then marked the level of pain on the visual analog scale (VAS) (0–10). The score records the patient's reported pain using a scale of 0–10, where 0 is pain-free and 10 is the worst pain imaginable. The score will be marked at the point on the line that corresponds with the patient's response.

2.2. Radiographic assessment

All affected patients in both groups were screened with standard X-ray projections. The aim is to exclude calcific tendinitis or other pathology in case of TE and to exclude bony abnormalities of the calcaneus in case of PF.

Functional assessment was done for TE patients by using the disability of Arm, Shoulder and Hand (DASH) score [13]. The DASH questionnaire is a standardized regional outcome measure that captures upper extremity disability from the perspective of the patient and is used to study clinical outcome in musculoskeletal disorders. The DASH has been shown to be a reliable, valid and responsive tool for evaluating both proximal and distal disorders, confirming its usefulness across the whole extremity. While functional assessment for PF patients was assessed by the foot health status questionnaire (FHSQ) [14].

After the procedure all patients were instructed to rest the elbow and wrist (in cases of TE) and to avoid weight bearing (in cases of PF) for 48 h with a subsequent increase in ambulation over the next days. Patients instructed to receive acetaminophen for pain while the use of any non-steroidal anti-inflammatory medication is strictly prohibited. PF patients were allowed to return to a comfortable shoe after two days. Six weeks later, all patients were re-evaluated and refilled VAS and DASH score for TE patients and FHSQ for PF patients.

2.3. Preparation of PRP

A closed system was used throughout the process to avoid contamination, at least 24 h before injection. Into quadruple pediatric blood bag system containing 63 ml citrate phosphate dextrose (CPD) as an anticoagulant [JMS Singapore Ltd.], 150 ml bloods withdrawn from TE and PF patients after adjusting CPD volume in the original pack to 21 ml, passing excess anticoagulant to the distal satellite pack (JMS hemoscale was used for shacking and adjusting the donated volume). From donated blood in one satellite pack, PRP separated by two-step centrifugation at ambient temperature [for 15 min at 320*g* (soft spin) then at 2000*g* for 15 min (hard spine)] and kept at +200 °C with continuous shaking on a horizontal shaker (Forma Scientific, Marietta, oH). The platelet count was done using Cell Dyne 1700 (ABBOT Diagnostics, USA) before and after preparation. Accepted PRP contained at least two times increase in platelet concentration [15].

All patients gave an informed written consent, which was approved by local ethical committee in our university.

Statistical analysis: Quantitative variables were described using mean ± standard deviation (SD) and categorical data by frequency and percentage. Student's *t*-test was used to compare quantitative variables between groups of patients. Levene's test for equality of variances and *t*-test for equality of means were used to examine the changes of VAS, DASH score and FHSQ at base line and at follow-up after treatment. In all tests, p value <0.05 was considered to be statistically significant.

3. Results

The mean age of the control group in TE patients was 37.5 ± 17.5 years, and in PRP patients were 40.5 ± 15.5 years. The control group includes 5 males and 10 females, while the PRP group includes 6 males and 9 females. The mean age of the control group in PF patients was 44.5 ± 15.5 years, and among PRP group were 42.5 ± 17.5 years. All patients in with PF were females. In the control group, 7 patients had right heel affection, and 8 had affection of the left heel. In the PRP group, 11 patients had right heel affection and 4 had affection of the left heel.

Table 1 compares the mean VAS and DASH scales during 1st and 2nd visit among patients with TE. Highly significant differences were observed between both groups relative to VAS and DASH scores before (1st visit) and 6 weeks after treatment (2nd visit), ($p < 0.001$) (Fig. 1a–d). While comparisons of VAS and DASH scores changes among control and PRP groups of patients showed insignificant differences relative to the outcome measures evaluated ($p > 0.05$).

Table 2 compares the mean VAS and FHSQ score scores during 1st and 2nd visit in PF group of patients. Significant differences were observed between both groups relative to VAS assessment (1st visit versus 2nd visit) in both control group ($p = 0.005$) and PRP group of patients ($p = 0.03$). Relative to FHSQ score highly significant differences were observed between control group and PRP group of patients ($p < 0.001$), (Fig. 2a–d).

While comparisons of VAS and FHSQ score changes among control and PRP groups of patients with PF showed no significant difference between both groups regarding base line VAS ($p = 0.152$) and baseline FHSQ ($p = 0.761$). While highly significant difference were observed between both groups regarding VAS 2nd visit ($p < 0.001$) and FHSQ 2nd visit ($p = 0.001$) and another highly significant difference between both groups regarding VAS and FHSQ changes ($p = 0.001$). However PRP treated group of patients showed much significant improvement compared to control group reflecting better efficacy.

4. Discussion

The current study revealed that local injection of PRP, which is a novel form of treatment, provides significant relief of pain and improvement in function that is comparable to the steroid injection in treatment of TE and more superior in treatment of PF compared to local steroid injection. Moreover, it provides a safer option for patients who have contraindications to steroid therapy (e.g. diabetics), and an option for patients who are considered for surgical intervention.

Although refractory chronic tendinopathy may be responsive to PRP injection, yet the data available to date are limited by quality and size of study, as well as length of follow-up, and are currently insufficient to recommend this modality for routine clinical use [16]. However autologous PRP was proved to improve the early neotendon properties [17] and improve tissue healing by enhancing cellular chemotaxis, proliferation and differentiation, removal of tissue debris, angiogenesis, and the laying down of extracellular matrix [18].

Relative to TE our results confirm the suggested positive effect in vivo as described by Mishra and Pavelko [19]. In their report a significant improvement of symptoms after 8 weeks in 60% of the patients treated with PRP. At 6 months, PRP treated patients, noted 81% improvement in their visual analog pain scores ($p = .0001$). In another study Edwards and Calandruccio [8] reported that 22 patients (79%) with TE in whom nonsurgical modalities had failed were relieved completely of pain even during strenuous activity. Their study

Table 1 Comparison of TE patients regarding VAS and DASH scores in both control and PRP treated groups.

Parameter	TE (control group) mean ± SD		*p* value	TE (PRP group) mean ± SD		*p* value
	1st visit	2nd visit		1st visit	2nd visit	
VAS (0–10)	8.6 ± 1.6	4.3 ± 2.1	< 0.001**	8.0 ± 1.4	3.8 ± 1.9	< 0.001**
DASH score	57.3 ± 10.3	20.2 ± 14.0	< 0.001**	58.9 ± 10.5	19.9 ± 12.9	< 0.001**

VAS, visual analog score; TE, tennis elbow; PRP, platelet rich plasma; DASH, disability of arm, shoulder and hand score.
** Highly significant ($p < 0.001$).

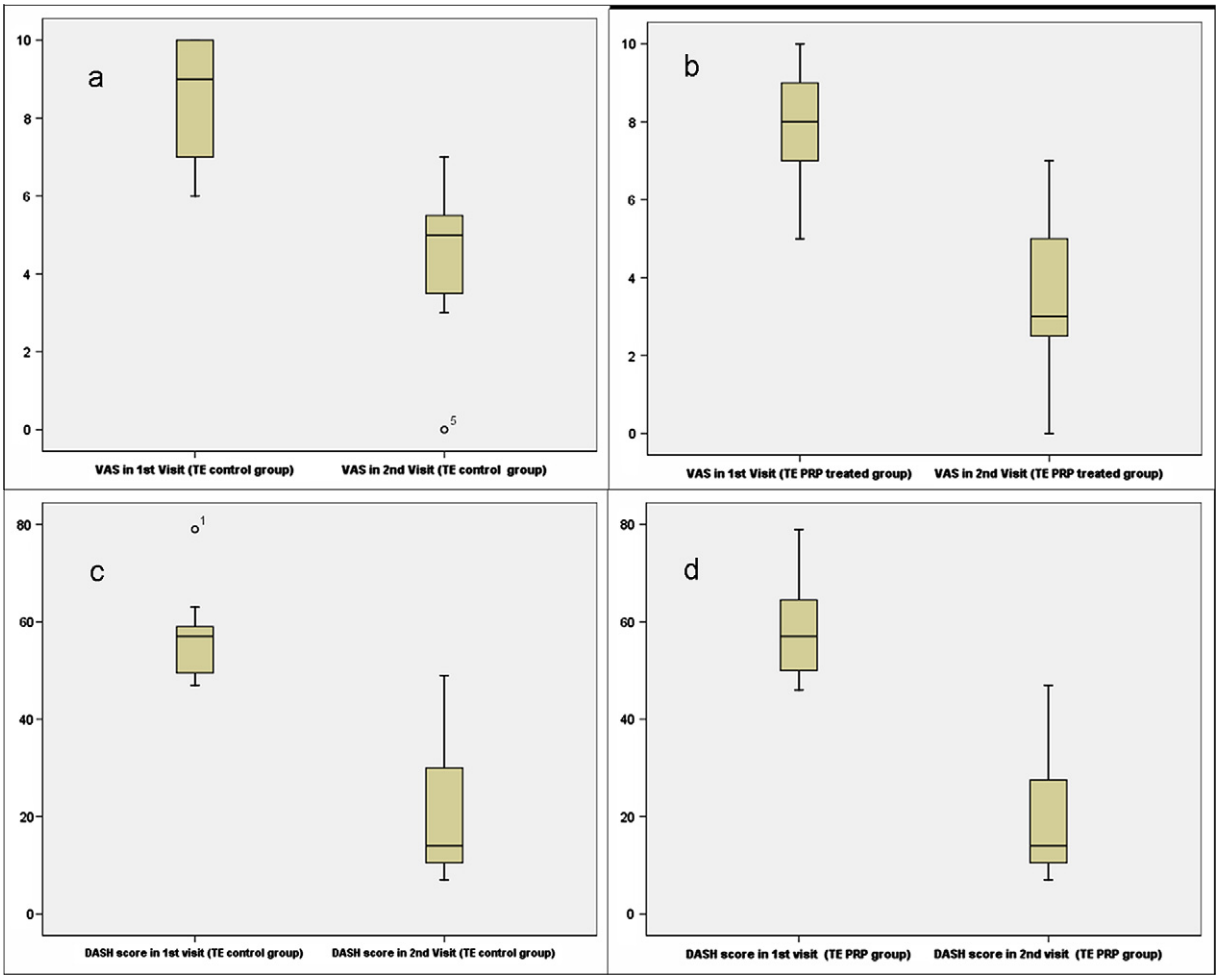

Figure 1 Boxplots showing the significant difference between visual analog scale (VAS) and disability of arm, shoulder and hand (DASH) scores (1st visit) versus (2nd visit) in both control group and PRP group of patients with TE.

Table 2 Comparison of PF patients regarding visual analog score and foot health status questionnaire in control and PRP treated groups.

Parameter	PF (steroid treated group) mean ± SD		*p* value	PF (PRP treated group) mean ± SD		*p* value
	1st visit	2nd visit		1st visit	2nd visit	
VAS (0–10)	8.8 ± 0.9	6.5 ± 2.6	0.005*	8.2 ± 1.3	2.6 ± 2.1	< 0.000**
FHSQ score	57.5 ± 9.4	49.0 ± 19.1	0.030*	58.5 ± 9.6	25.1 ± 12.4	< 0.000**

VAS, visual analog scale; PF, plantar fasciitis; PRP, platelet rich plasma; FHSQ, foot health status questionnaire.
* Significant ($p < 0.05$).
** Highly significant ($p < 0.001$).

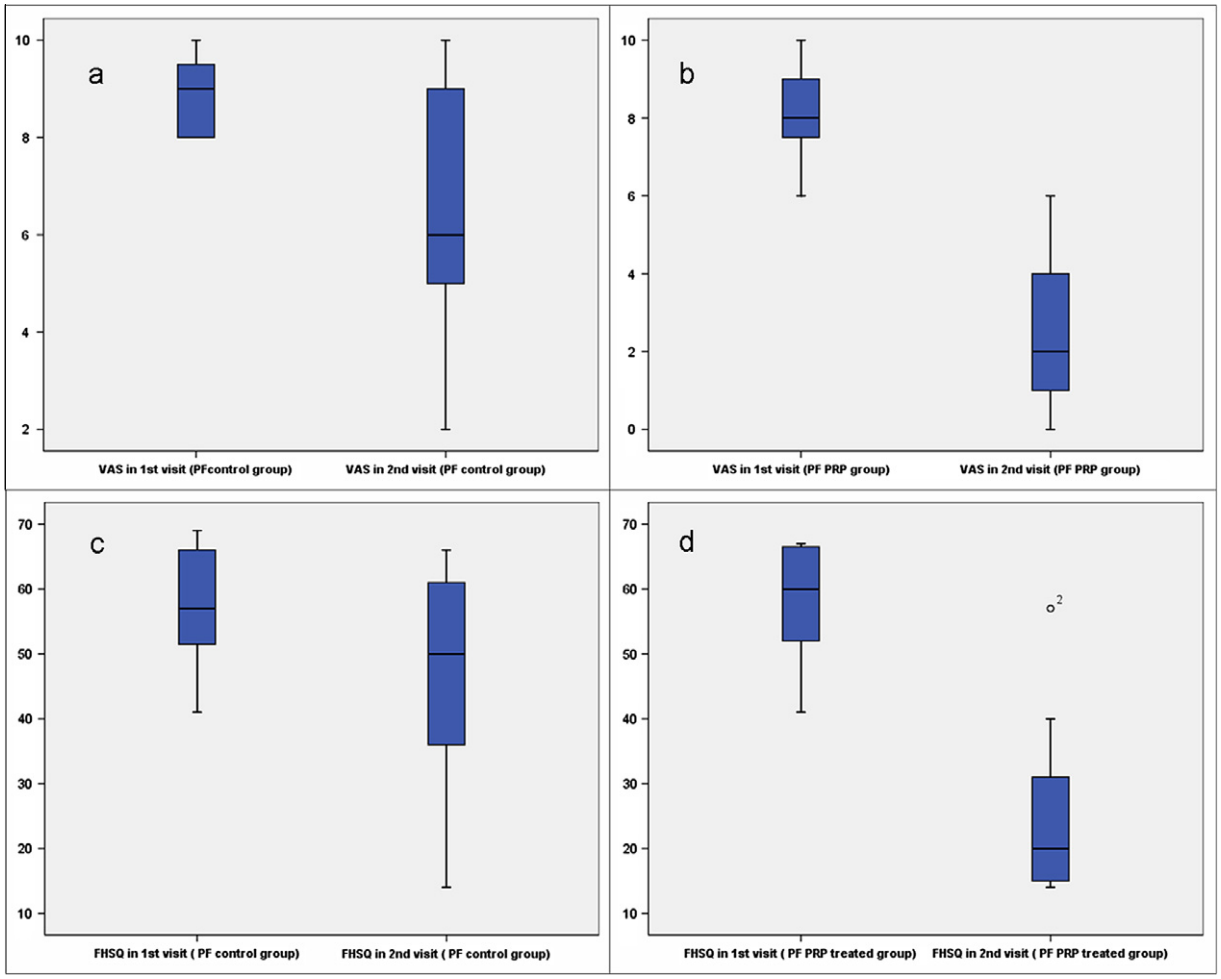

Figure 2 Boxplots showing the significant difference between VAS and foot health status questionnaire (FHSQ) scores (1st visit) versus (2nd visit) in both control group and PRP group of patients with PF.

offers encouraging results of an alternative minimally invasive treatment that addresses the pathophysiology of TE that has failed traditional nonsurgical modalities.

In our study we observed highly significant differences between both groups relative to VAS and DASH scores before and 6 weeks after treatment ($p < 0.001$) while comparisons of VAS and DASH changes among control and PRP groups of patients showed insignificant differences ($p > 0.05$). Our results are in agreement with that observed by Peerbooms et al. [11] who reported that, 24 of the 49 patients (49%) in the corticosteroid group and 37 of the 51 patients (73%) in the PRP group were successful ($p < 0.001$). Furthermore, in their study according to the DASH scores, 25 of the 49 patients (51%) in the corticosteroid group and 37 of the 51 patients (73%) in the PRP group were successful ($p = 0.005$). Important to note in their study is that the corticosteroid group was better initially and then declined, whereas the PRP group progressively improved. In the most recent work treatment of patients with chronic TE with PRP reduces pain and increases function significantly, exceeding the effect of corticosteroid injection even after a follow-up of 2 years [20]. The later findings explain efficacy and longstanding improvement of this promising therapeutic option. Nevertheless Finnoff et al. [21] observed that PRP injection following ultrasound guided percutaneous needle tenotomy for TE was associated with sonographically apparent improvements in tendon morphology.

In fact, histology of chronic cases with PF has shown no signs of inflammatory cell invasion into the affected area. The tissue instead is characterized histologically by infiltration with macrophages, lymphocytes, and plasma cells; tissue destruction; and repair involving immature vascularization and fibrosis .The normal fascia tissue is replaced by an angiofibroblastic hyperplastic tissue which spreads itself throughout the surrounding tissue creating a self-perpetuating cycle of degeneration [22]. Steroid injections are a popular method of treating the condition but only seem to be useful in the short term and only to a small degree [6]. However treatment with corticosteroids has a high frequency of relapse and recurrence, probably because intra fascial injection may lead to permanent adverse changes within the structure of the fascia and because patients tend to overuse the foot after injection as a result of direct pain relief [23]. Additionally and more seriously is that repeated corticosteroids injections could predispose to rupture of the plantar fascia and consequently surgical intervention. The later complication was critically addressed in the study by Acevedo and Beskin [24]. In their study a total of 765 patients with PF were evaluated. Fifty-one patients were diagnosed with plantar fascia rupture, and 44 of these ruptures

were associated with corticosteroid injection. Most important to conclude from their study is that thirty-nine of these patients were evaluated at an average 27-month follow-up. Thirty patients (68%) reported a sudden onset of tearing at the heel, and 14 (32%) had a gradual onset of symptoms. In most cases the original heel pain was relieved by rupture. However, these patients subsequently developed new problems including longitudinal arch strain, lateral and dorsal midfoot strain, lateral plantar nerve dysfunction, stress fracture, hammertoe deformity, swelling, and/or antalgia.

In our study we observed significant difference between control and PRP group regarding VAS and FHSQ scores (1st visit versus 2nd visit) and highly significant difference regarding VAS ($p = 0.001$) and FHSQ scores changes ($p < 0.001$) between both groups. Importantly the PRP treated group showed much significant improvement compared to control group reflecting better efficacy. However sustained efficacy should be further evaluated in longitudinal follow-up studies.

In previous work Lee et al. [25] conducted prospective, randomized, controlled, observer-blinded study over a period of 6 months. In their study Sixty-four patients were randomly allocated to either the autologous blood or corticosteroid treatment group. The authors reported that the reduction in VAS for both groups was significant over time ($p < 0.0001$). At 6 weeks and 3 months, the corticosteroid group had significantly lower VAS than the PRP group ($p < 0.011$ and $p < 0.005$, respectively), but the difference was not significant at 6 months. The authors concluded that intralesional autologous blood injection is efficacious in lowering pain and tenderness in chronic PF, but corticosteroid is more superior in terms of speed and probably extent of improvement. A forthcoming randomized controlled multi center trial will be performed by Peerbooms et al. [12]. The study population will consists of 120 patients of 18 years and older. Patients with chronic PF will be allocated randomly to have a steroid injection or PRP injections. Data will be collected before the procedure, 4, 8, 12, 26 weeks and 1 year after the procedure. The authors postulate that the concentrated growth factors work in a synergetic manner to initiate a tendon healing response. Their authors suggested that transforming growth factor β1 is shown to significantly increase type I collagen production by tendon sheath fibroblasts. This same mechanism is likely to be active in chronic PF [26].

In conclusion, local injection of autologous PRP proved to be a promising form of therapy for TE and PF. It is both safe and effective in relieving pain and improving function. The current available data support that repeated steroid injections is deleterious and may lead to serious consequences .In our study PRP treated group of patients with PF showed much significant improvement compared to steroid treated group reflecting better efficacy. However sustained efficacy of this promising and safer therapeutic option should be further evaluated in longitudinal follow-up studies that include larger number of patients.

5. Conflict of interest

All the authors responsible for this work declare no conflict of interest.

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