Review Article

Effectiveness and relevant factors of platelet-rich plasma treatment in managing plantar fasciitis: A systematic review

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Background: Plantar fasciitis (PF) is a common foot complaint, affects both active sportsmen and physically inactive middle age group. It is believed that PF results from degenerative changes rather than inflammation. Platelet-rich plasma (PRP) therapy has been introduced as an alternative therapy for PF. This study is aimed to systematically review to the effectiveness and relevant factors of PRP treatment in managing PF. **Materials and Methods:** A search was conducted in electronic databases, including PubMed, Scopus, and Google Scholar using different keywords. Publications in English-language from 2010 to 2015 were included. Two reviewers extracted data from selected articles after the quality assessment was done. **Results:** A total of 1126 articles were retrieved, but only 12 articles met inclusion and exclusion criteria. With a total of 455 patients, a number of potentially influencing factors on the effectiveness of PRP for PF was identified. In all these studies, PRP had been injected directly into the plantar fascia, with or without ultrasound guidance. Steps from preparation to injection were found equally crucial. Amount of collected blood, types of blood anti-coagulant, methods in preparing PRP, speed, and numbers of time the blood samples were centrifuged, activating agent added to the PRP and techniques of injection, were varied between different studies. Regardless of these variations, superiority of PRP treatment compared to steroid was reported in all studies. **Conclusion:** In conclusion, PRP therapy might provide an effective alternative to conservative management of PF with no obvious side effect or complication. The onset of action after PRP injection also greatly depended on the degree of degeneration.

Key words: Plantar fasciitis, platelet-rich plasma, treatment

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INTRODUCTION

Plantar fascia is a connective tissue on the bottom of the foot which connects heel bone to toes. It functions to maintain the medial arch of the foot and help in absorbing shocks, in addition, to keep tract with the windlass mechanism during walking.[1,2] Heel pain is commonly due to a condition known as plantar fasciitis (PF) which involves plantar fascia. PF affects not only sport participants, but also those middle-aged individuals who are physically inactive, however, age, obesity, excessive weight bearing, and tight Achilles tendon are the common predisposing factors.[3,4] The peak incidence occurs between 40 and 60-year-old in both gender.[5] Diagnosis of PF is usually made based on history and clinical finding. Generally, patients with PF tend to have worsening of pain when they first step on the floor in the early morning. However, the pain gradually improves with subsequent physical activity. The pain deteriorates when one dorsiflex the toes, as this action pulls the plantar fascia together.[6-8] It was previously assumed that PF occurs as a result of inflammation. Until recent decade, it is accepted that the underlying pathology is actually a degenerative process.[9-11] This degenerative condition takes

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place near the origin of the plantar fascia at the medial tuberosity of the calcaneus.[11,12]

The main-stay of treatments is conservative therapies, such as nonsteroidal anti-inflammatory drugs, physiotherapy which include the plantar fascia stretching exercises, activities modification, use of shoe insoles, corticosteroids injection, and[11] extracorporeal shock wave therapy.[13-16] One of the known effective, but short-term treatment modality is a direct injection of steroid into the plantar fascia.[17-22]

New treatment regimens that stimulate a healing response instead of suppressing the inflammatory process should be regarded as a more effective treatment options. This has prompted to the use of platelet-rich plasma (PRP) which is well-known to induce cell growth and subsequently tissue healing. The rationale for using PRP is to increase tendon regenerative abilities with a high content of cytokines and cells, in hyperphysiologic doses, which should promote cellular chemotaxis, matrix synthesis, and proliferation. Centrifugation functions to mechanically concentrate the level of platelets to levels 7–25 times more than the baseline of whole blood. These have prompt the use of PRP as a vector to deliver growth factors to local muscle and tendon injury and repair zones to induce and accelerate healing.[23-31]

The objective of this study is to systematically review available evidence from published articles to assess the effectiveness and relevant factors of PRP treatment in managing PF. The assessment also would encompass safety, side effect, and complications of this mode of treatment.

MATERIALS AND METHODS

Selection of literature

The searches were performed in the PubMed (2000–2015), Google Scholar (2000–2015), and Scopus (2000–2015) using a series of keywords, terms, and subject headings made from Pub-Med's medical subject headings (MeSH). The search of MeSH included: PF, plantar fasciopathy, heel pain, PRP, and PRP.

Inclusion criteria

Selected articles were limited to human studies, publications in English-language and all kind of studies, including clinical trial, case series, and case report. This study did not proceed with meta-analysis thus no specific statistical test was done. Inclusion criteria for target population comprised subjects that were diagnosed to have suffered from PF and received PRP treatment. Studies should have clear details of clinical assessments which might be any of the following methods, i.e., evaluation of pain using visual analog scale (VAS), evaluation of function using Roles–Maudsley (RM) scores, evaluation with American Orthopaedic Foot and Ankle Society (AOFAS) scale and ultrasonography evaluation.

Exclusion criteria

Studies were excluded if the patients in the study received local steroid injection within 6 months, have previous surgery of the foot, previous fracture to calcaneus or having other associated diseases of lower limb (vascular insufficiency, Diabetic, neuropathy, and ankle joint disorder). Furthermore, studies with insufficient follow-up during the study were excluded.

Data extraction

Titles and abstracts of all the studies were reviewed by two reviewers to identify relevant studies. Any disagreement for inclusion or exclusion if an article was fixed by discussion with the third reviewer. Two reviewers extracted the data from eligible studies independently. These data were included author, year of publication, study design, sample size, and details of intervention in study and control group, finding of studies, mean age of patients, assessment method, duration of follow-up, any reported complication, duration of symptoms in patient at the beginning of the study, amount of blood collected for PRP, method of PRP preparation, details of PRP injection, method of confirmation/diagnosis for PF before recruiting participants and usage of ultrasound guidance for injection.

Quality assessment

JADAD score was used for the quality assessment of randomized controlled trials (RCTs) and Newcastle–Ottawa Scale (NOS) was used for nonrandomized studies. Studies achieving, at least, JADAD score of three or NOS of seven were considered to bequalify (good) to be included in this systematic review.

RESULTS

A total of 1126 articles were retrieved using different keywords (Google Scholar: 1012, PubMed: 21, Scopus: 93). By reviewing the titles and abstracts, only 102 articles were eligible to be reviewed based on their relevance to the aim of this systematic review. Finally, 12 articles were met all inclusion and exclusion criteria to be reviewed in this study.[32-43] These were four RCTs, seven prospective cohort and one retrospective cohort studies. The rest of articles were excluded in view of non-English language, letter to editor, review articles, incomplete RCT, and protocol [Figure 1]. Tables 1-3 show details of the selected articles.

Descriptive characteristics of twelve studies

Both male and female patients were recruited in these 12 studies. Sample size of the twelve studies ranged from 14

to 60 with a total of 455 patients. The majority of patients have unilateral PF. However, a total of 22 patients from three studies have had bilateral PF. The duration of symptoms (PF) in patients at the beginning of interventions was from 3 to 24 months. Different assessments, including AOFAS, RM scores, visual analog scores (VAS), postinjection foot and ankle outcome scores, foot function index, and 12-item short form health survey (SF-12) were used to measure the outcome of treatments. Only three out of nine studies have used ultrasound guidance for injection of PRP. Seven studies have had a single injection of PRP while the other two studies have done more than one-time injection.

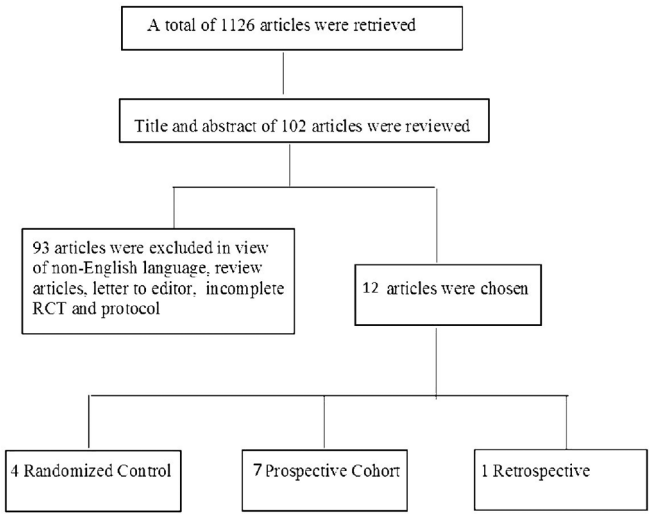

Figure 1: Flowchart of study selection

Blood collected for PRP preparation was ranged from 10 ml to 52 ml. Three studies used double spin centrifugation for PRP preparation and the rest of studies used single spin. Eight out of 12 studies used different commercial systems for the PRP preparation and the other four studies have used normal centrifuge. The injected volume of PRP was between 2 ml and 5 ml. Follow-up for monitoring the improvement or any complications of PRP or steroid was done from 2 weeks up to 24 months.

Table 1: Descriptive characteristics of twelve studies on effectiveness of PRP

Author/year	Study design and quality	Number of patients	Intervention	Control	Results
Ragheb and Othman 2012[33]	Prospective cohort (good)	25	5 ml PRP injection	None	Injection of PRP is safe, reduce post injection pain and doesn't affect the biomechanical function of the foot
Martinelli *et al*. 2013[34]	Prospective cohort (good)	14	PRP injection (volume not mentioned)	None	PRP is safe and has significantly reduced pain and improved function
Kumar *et al*. 2013[35]	Prospective cohort (good)	44 (50 heels)	2.5-3.5 ml PRP injection	None	PRP produce an efficacy rate, approaching 2 out of every 3. The procedure was safe
O' Malley *et al*. 2013[36]	Retrospective cohort (good)	23	2-3 ml PRP injection	None	Pain, symptoms and quality of life improved significantly with PRP injection, with safety assured
Kim and Lee 2013[37]	RCT (good)	21 (10 in PRP group, 11 in Dextrose group)	2 ml PRP injection	2cc Dextrose/ lidocaine injection	Both group showed improvement, even though PRP showed better initial improvement, there is no statistical significance between these group
Aksahin *et al*. 2012[38]	RCT (good)	60 (30 in each group)	3 ml PRP injection	Steroid injection (40 mg methyprednisolone)	Both group showed significantly lowered pain score but no significant different between these groups. PRP was safer than steroid with same effectiveness
Monto 2014[39]	RCT (good)	40 (Cortisone: 20+ PRP: 20)	3 ml PRP injection	40 mg DepoMedrol Cortisone injection	Significant difference between 2 groups. PRP was more effective and durable than cortisone
Jain *et al*. 2015[40]	Prospective cohort (good)	46 Patients (60 heels)	2.5 ml PRP injection	Triamcinolone 40 mg and Chirocaine injection (no volume is mentioned)	At 3 months, all scores had significantly improved in both groups. At 6 months, there was no statistically significant difference between the two groups. At 12 months, PRP is significantly more effective than Steroid
Sherpy *et al*. 2015[41]	RCT (good)	50 Patients (25 in each group)	3 ml PRP injection	2 ml triamcinolone acetonide (40 mg/ml)	At 1.5 months post-injection, there was more improvement in the PRP than in the steroid group. There was no significant difference between both groups at 3 months
Shetty *et al*. 2014[42]	Prospective cohort (good)	60 Patients (30 in each group)	8 ml PRP	40 mg of triamcinolone acetonide and 3 ml of 2% lignocaine	There was significant clinical improvement in PRP group at three months after the injection
Wilson *et al*. 2014[43]	Prospective cohort (case series) (good)	22 Patients (24 heels)	5 ml PRP injection	None	Treatment with PRP injection resulted in clinically and statistically significant improvements in self-reported pain and functioning compared with preinjection baseline measurements
Say *et al*. 2014[44]	Prospective cohort (good)	50 Patients (25 in each group)	2.5 ml PRP injection	40 mg/1 ml of methylprednisolone and 1 ml of prilocaine	The PRP group had significantly higher mean AFAS and VAS scores at follow-up than the steroid group (P<0.001)

PRP = Platelet-rich plasma

Table 2: Characterizations of patients and study design

Author	Mean age of patients	Assessment method	Follow Up	Complication	Symptoms duration
Ragheb and Othman[33]	Mean age of 44 years	VAS Score	10.3 months (range 9-13 months	No complications from PRP injection	At least 6 months
Martinelli *et al*.[34]	Mean age 49.2±8.8 years	RM score and VAS for pain	12 months	No systemic or local complications but Posttreatment pain resolved about two hours after infiltration	9.9±2.6 months
Kumar *et al*.[35]	Mean age of 51 years (ranged 25-79)	RM score, VAS score, AOFAS score	3 and 6 months	No complications were reported	At least 12 months
O' Malley *et al*.[36]	average age of 47 (ranged, 25-63 years)	FAOS, 12-item short form health survey (SF-12), and VAS scores	6.7 months (range, 6 to 10 months)	No complications were reported	9 months (range, 6 to 12 months)
Kim and Lee[37]	36.2 (20 to 57)	Foot Function Index (FFI)	2 weeks (before the second injections), at 10 and 28 weeks (after the second injections)	Local pain or discomfort that started on the day of injection and subsided gradually	Mean of 2.8 (ranged from 1-6) years
Aksahin *et al*.[38]	46.36±8.49 (ranged 22-68 years)	VAS heel pain scores	3 weeks and at 6 months	No complications	9.02±5.28 months
Monto[39]	PRP group: 51 years (ranged, 21 to 67). Cortisone group: 59 (range, 24 to 74)	AOFAS, hindfoot scoring	3, 6, 12, and 24 months	Has not been reported	Mean 5.7 (ranged, 4 to 26) months in PRP group and mean 5.4 (range, 4 to 24) months for Cortisone group
Jain *et al*.[40]	55.6 years (ranged 31-79 years)	RM score, VAS for pain and AOFAS score	3, 6 and 12 months	No complication in either group	At least 12 months
Sherpy *et al*.[41]	PRP group: 37.48±8.75 years, steroid group: 38.52±6.2 years	VAS and ultrasonography	3 months	No complication in either group	PRP group: 7.25±1.12 months Steroid group: 7.58±1.02 months
Shetty *et al*.[42]	PRP group: 34.0±9.15, steroid group: 39.2±9.35)	VAS, FADI and AOFAS	3 months	No complication in either group	At least 3 months
Wilson *et al*.[43]	Mean of 44±11.64 years (ranged 21-60 years)	FAAM scores Foot-SANE scores, SF-12v2	4, 8, 12, 16, 32, and 52 weeks postinjection	The most common side effects were temporary pain and swelling following the injection	Mean duration of 30.67 months (ranged 3.25-96 months)
Say *et al*[44]	PRP group: mean age 47 years, steroid group: mean age 48.6	AOFAS and VAS scores	6th week and 6th month	No local or systemic complications were seen	At least 3 months

AOFAS = American Orthopedic Foot and Ankle Society; RM = Roles-Maudsley score; VAS = Visual analogue scale; FAOS= Post injection foot and ankle outcome scores; FFI = Foot function index; FADI = Foot and ankle disability index; SF-12v2 = Short form-12 health survey version 2; FAAM = Foot and ankle ability measure; Foot-SANE = Foot-single Assessment numeric evaluation

DISCUSSION

PRP has shown promise in the treatment of various musculoskeletal conditions including chronic lateral epicondylitis, osteoarthritis, muscle strain, ligament sprain, cartilage damage, fractures, and tendon injury and has been approved by the International Olympic Committee in the treatment of soft tissue injuries and tendon disorders.[26,27,44-47] Furthermore, PRP might be considered as an alternative treatment for plantar fascia. The steps from preparation to injection are equally crucial when we are assessing the effectiveness of PRP in the treatment of PF. In all the selected studies, PRP injection has been done directly into the plantar fascia. However four of these studies have used ultrasound guidance during injection.[35,36,38,42] It is arguable that ultrasound guidance may promise a more accurate placement of PRP and injection without ultrasound guidance may be considered as a shortcoming of a study. Nevertheless, no advantage of ultrasound guidance over direct palpation guidance was reported by Kane *et al*.[1] during steroid injection for PF.

The technique of injection may also indirectly affect the outcome of this study, for example, peppering or direct single injection. In peppering technique, the needle was placed into the target tissue and withdrawn slowly while maintaining the tip of the needle within the tissue. The needle was then

Table 3: Details of PRP preparation and injection

Author	Amount of blood collected for PRP	Method of PRP preparation	PRP Injection details	Method of confirmation/diagnosis for PF before recruiting participants	Ultrasound guidance for injection
Ragheb and Othman[33]	50 ml	Single spin at 3000 rpm for 15 min, 5 ml PRP injection	Single injection using a peppering technique	Ultrasound measurement of the medial, central and lateral bands of the plantar fascia was done prior to injection of PRP in the aVected foot and for the asymptomatic foot for comparison and to serve as a control	No
Martinelli *et al.*[34]	10 ml	Arthrex ACP Double Syringe System™, Single spin at 1500 rpm for 5 min, PRP injection (volume not mentioned)	3 injections at the plantar fascia once per week	Heel pain felt maximally over the plantar aspect for at least six months continuously and had radiographic evidence of calcaneal spur	No
Kumar *et al.*[35]	27 ml	GPSIIIsystem, Single spin at 3200 rpm for 15 min, 2.5-3.5 ml PRP injection	Single injection for 38 patients and bilateral injection for 6 patients	Not clearly mentioned	No
O' Malley *et al.*[36]	52 ml	Double spins, 7 minute each, rate not mentioned, 2-3 ml PRP injection	18 patients have one injection and 5 patients two injections in the same foot (interval injections 7 weeks). peppering technique	Chronic plantar fasciitis was defined as characteristic symptoms lasting longer than 6 months. The diagnosis was made clinically by the appropriate history as well as pain localized along the plantar fascia at the plantar medial heel	Yes
Kim and Lee[37]	20 ml	Huons HC-1000 System, Single spin at 3200 rpm for 3 min, 2 ml PRP injection	Peppering technique	To confirm the diagnosis, the thickness of the proximal plantar fascia was measured by ultrasound at the inferior calcaneal border, and patients with a plantar fascia thickness ≥4 mm were included	
Aksahin *et al.*[38]	25 ml	Double spin, 1800 rpm for 15 min, followed by 3500 for 10 min, 3 ml PRP injection	Single injection of PRP	Has not been mentioned	
Monto.[39]	27 ml	Accelerate Sport Platelet Concentration System, Single spin, 2400 rpm for 12 min, 3 ml PRP injection	Single injection of PRP	Screened with plain radiographs and MRI to confirm the diagnosis of plantar fasciitis	
Jain *et al.*[40]	27 ml	GPSIIIsystem, Single spin, 3200 rpm for 15 min, 2.5 ml PRP injection	Single injection of PRP, peppering technique	Has not been mentioned.	No
Sherpy *et al.*[41]	10 ml	Double spin, 1800 rpm for 15 min followed by 3500 rpm for 10 min. 3 ml of PRP injection	Single injection	Sonographic examination was performed on both symptomatic and asymptomatic heels. The thickness of the plantar fascia was measured. PF was defined as plantar fascia thickness >4 mm or when there was >1 mm difference in plantar fascia thickness between symptomatic and asymptomatic heels	No
Shetty *et al.*[42]	54 ml	SmartPReP system 8 ml PRP injection	Single injection	Clinical examination	No
Wilson *et al.*[43]	45ml	Magellan Arteriocyte Platelet Concentrator System centrifuge, 3 to 5 ml PRP injection	Single injection	Clinical examination- and imaging-confirmed PF	Yes
Say *et al.*[44]	30 ml	Single spin at 1800 rpm for 8 minutes, 2.5 ml PRP injection	Single injection	Clinical examination. And direct radiographs were examined to rule out other heel pathologies	No

PRP = Platelet-rich plasma, RCT = Randomized controlled trials

angulated and reinserted to make another puncture onto the fascia at different sites. Peppering on the plantar fascia could possibly stimulate the release of endogenous growth factors that help in regeneration. Kalaci *et al.*[18] reported a superior effect in his study when peppering technique was used as compared to single direct injection.

Another potentially influencing factor in this assessment was the amount of collected blood and different methods are used in preparing PRP. After venous blood was drawn from the patients, centrifugation was done to separate the PRP and platelet-poor plasma. These studies reported various method and speed of centrifugation, and the number of time

the blood samples were centrifuged (some single – spin, while others were double – spinning). Furthermore, the different types of anti-coagulant or activating agent added to the PRP may also affect the outcome of the effectiveness of PRP in treating PF.[17,48]

The main purpose of blood centrifugation is to concentrate the growth factors within the platelet. Some investigators believe that the action of growth factors is dose-dependent.[24] This means that only at certain concentration can it generate new cells growth. No data had been published to date to indicate the quantity of growth factors required to stimulate the healing process. However, there were studies which showed clinical efficacy could be expected when there is minimal 4- to 6-fold increase in platelet concentration from the whole blood baseline.[49,50] Thus, platelet concentration appears as an important factor in ensuring cell regeneration. Despite having achieved the desired concentration, the amount or volume of PRP may also play an important role in determining the effectiveness. Kumar *et al*.[34] found that three of his patients who had bilateral plantar fasciitis injections at the same setting failed to improve. The explanation for this can be attributed to the small amount of PRP that was injected into each heel (only 1.5 ml to each heel). During the subsequent injections to these three patients, improvement was noted after injection of 3 ml of PRP into each heel. This strongly suggested that tissue regeneration may take place only with adequate volume of PRP.

Diagnosis of PF is commonly made base on clinical examination and observations. It is, therefore, crucial to have a precise and accurate diagnosis. A wrong diagnosis could possibly be an important factor affecting the outcome of the effectiveness of PRP in the management of PF. This is because diseases respond differently according to their underlying pathophysiology. As in the prospective study done by Kumar *et al*.,[34] one patient with tarsal tunnel syndrome only showed improvement after surgical decompression. Therefore in resistant cases, it is important to exclude other conditions which sign and symptoms might resemble PF, such as tarsal tunnel syndrome and stress fractures. Further investigations may be necessary for us to arrive at correct diagnosis, such as magnetic resonance imaging scan or nerve conduction study.

The efficacy of PRP treatment should also take into account the onset of effect and the duration for the patient to remain symptoms free. Most patients would prefer something that offer instant pain relief with no recurrence of symptoms. In most of the studies, the improvement was observed during the first 3 months after injection. Significant improvement was also noted when the patient was followed up till 12 months postinjection. The onset of action after PRP injection also greatly depends on the degree of degeneration as the organ or tissue is in demand for longer recovery time for a complete regeneration. The coupled home therapy after the injection may affect the outcome of the effectiveness of PRP. Those patients who reported relief of pain and other improvement, believed on direct effect of PRP injection, although all patients were also recommended to remain under conventional treatment, including gel heel cups and stretching exercises.

Steroid injection has been a popular mode of treatment when conservative management failed. However, corticosteroid injection is effective only in the short-term and only to a limited degree.[51-53] There is also close association with a higher rate of relapse and recurrence. Moreover direct pain relief after injection results in a tendency to overuse the affected foot.[21,54] Besides, it also carries the risk of tendon rupture as mentioned earlier. There were few studies that compare the results of steroid and PRP injections in other chronic tendon disorder apart from PF.[55-57] Peerbooms *et al*.[56] found a positive effect of PRP injection for lateral epicondylitis. This was the first comparison of PRP with corticosteroid injection in patient with lateral epicondylitis. The results indicated that a single injection of PRP decreased pain and improves function better than a corticosteroid injection.

As direct injection onto a degenerative area of the plantar fascia, should not arise any adverse side effect or complication then theoretically PRP injection also should not have any side effect. As expected, none of the above studies reported any complication from PRP injection. In fact to date, study of PRP injection for musculoskeletal conditions has not revealed any serious adverse[58,59] events. PRP should thus be deemed as a safe procedure in treating PF.

CONCLUSION

PF is a common cause of foot complaints resulting from degeneration of planter fascia. Treatment that stimulates tissue regeneration should be deemed as a better alternative for conservative managements. All the selected and reviewed studies showed significant improvement with no evidence of side effect or complications when PRP was used in treating PF. This suggests that PRP could be an effective mode of treatment for PF with promised safety. It helps in stimulation of new cell growth and thus should be regarded as a suitable modality in treating a degenerative disease. Studies also showed the superiority of PRP when compared with steroid injection.

One of the limitations of these studies include the sample sizes which were frequently small, Absence of placebo, diagnosis of PF, and duration of follow-up might appear to be another limiting factors in the process of assessing the efficacy of PRP. Besides, when selecting a preparation system, many factors must be taken into account, such as

volume of autologous blood drawn, centrifuge rate/time, leukocyte concentration, delivery method, activating agent, final PRP volume and final platelet and growth-factor concentration. Due to differences in PRP characteristics, reported evidence for the clinical effectiveness of PRP cannot be generalized to all of these systems. Furthermore, variation of hematologic parameters between patients may also affect the final PRP preparation. Controversies regarding the optimal quantity of platelets and growth factors required for muscle and tendon healing still persist. PRP's effectiveness is demonstrated with less concentrated preparations.

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Conflicts of interest
There are no conflicts of interest.

AUTHORS' CONTRIBUTION

All authors contributed equally to this work. SKC developed the concept of the work, conducting the literature search, writing the first draft and approval of the final version of the manuscript. FA contributed in the conception of the study, literature search and drafting, revising and approving the manuscript. TSR contributed in, conducting the study, drafting and revising the draft, approval of the final version of the manuscript. All the authors agreed for all aspects of the work.

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