Article

AMERICAN ORTHOPAEDIC FOOT & ANKLE SOCIETY

Foot & Ankle International®
1–7

DOI: 10.1177/1071100720939066
journals.sagepub.com/home/fai

Prospective Randomized Evaluation of Local Injection of Allogeneic Growth Factors in Plantar Fasciitis

Mahmoud Ibrahim Kandil, MD[1], Eslam Abdelshafi Tabl, MD[1], and Adel Samy Elhammady, MD[1]

Abstract

Background: The aim of this study was to evaluate the efficacy and safety of injection of allogeneic growth factors in patients with plantar fasciitis.

Methods: This study included 150 patients who were randomly divided into 2 equal groups; the patients were locally injected with allogeneic growth factors (GFs) (treatment group) or with saline 0.9% (control group). The patients were assessed using visual analog scale (VAS) and Foot Function Index–Revised short form (FFI-Rs) scores preinjection and 1, 3, 6, and 12 months postinjection. The patients were questioned about their satisfaction. Any adverse effects were recorded.

Results: At baseline, there was no significant difference between both groups regarding the mean VAS and FFI-Rs scores. At 3-month follow-up, the reduction in mean VAS score was 87% in the treatment group and 55% in the control group ($P < .001$), and the reduction in mean FFI-Rs score was 62% in the treatment group and 40% in the control group ($P < .001$). Treatment group and study visit were significant factors affecting both VAS and FFI-Rs scores. Overall, 92% were satisfied in the treatment group, and 78.2% in the control group. Postinjection pain occurred in 5 patients in the treatment group.

Conclusion: This study provides Level I evidence regarding the efficacy and safety of allogeneic GF injection in patients with plantar fasciitis. However, additional studies are needed to evaluate their adverse effects, immunogenicity, and microbiological safety.

Level of Evidence: Level I, prospective randomized controlled case series.

Keywords: plantar fasciitis, allogeneic growth factors, lyophilized human platelet growth factors (L-GFs)

Introduction

Plantar fasciitis is the most common cause of chronic heel pain, affecting up to 15% of adult foot complaints.[25,29,33] It is usually a self-limiting disease as it usually resolves within 8-12 months in approximately 80% to 90% of patients.[14,27] However, it can be a challenging condition as several months to even years may be required before subsidence of symptoms with conservative treatment.[7,8,15,31] There are various methods of conservative treatment including weight reduction, local application of ice, stretching exercises, night splints, nonsteroidal anti-inflammatory drugs, local corticosteroid injection, extracorporeal shock wave therapy, and platelet-rich plasma injection (PRP).[7,17,18,35]

PRP contains a higher concentration of platelets than the whole blood. It enhances wound, bone, and tendon healing by delivering high concentrations of alpha-granules containing biologically active growth factors.[12,16,21,29] The 4 basic growth factors include platelet-derived growth factor, which attracts monocytes and stimulates fibroblasts; transforming growth factor-β, which stimulates all major cell types involved with healing; vascular endothelial growth factor, which stimulates new blood vessel formation; and fibroblast growth factor, which promotes the growth of extracellular matrix.[1,34] It was hypothesized that human platelet growth factors may provide a beneficial effect in treatment of tendinopathies, with the potential to reverse the degenerative process and enhance the regeneration of healthy tendon.[2,6] PRP can eliminate immunologic reactions and disease transmission but cannot be

[1]Orthopedic Surgery, Department of Orthopaedics and Traumatology, Faculty of Medicine, Benha University, Benha, Qalyubia, Egypt

Corresponding Author:
Mahmoud Ibrahim Kandil, MD, Orthopedic Surgery, Department of Orthopaedics and Traumatology, Faculty of Medicine, Benha University, El-Shaheed Farid Nada Street, Benha, Qalyubia 0012, Egypt.
Email: dr_mahmoud_ibrahim@yahoo.com

performed in patients with a deficiency or abnormality of platelet function.[1]

The regenerative properties of PRP preparation depend on the amount of growth factors released after platelet activation. Using a large volume of blood for obtaining allogenic PRP can provide higher concentrations of growth factors. However, this PRP preparation is stable for only 8 hours. Freeze drying (lyophilization) can be used to stabilize the biologic materials for prolonged storage without causing their damage.[22] The allogeneic growth factors are not a true PRP preparation but they are lyophilized human platelets growth factors (L-GFs) that are derived from other individuals within the same species.[24]

An L-GF vial is a preparation consisting of lyophilized human platelets growth factors. It is based on the use of allogeneic pathogen-free platelets instead of autologous platelets as a source of growth factors. Platelet concentrates are then subjected to in vitro activation, with the subsequent release of growth factors from their site of storage in the alpha granules. The released growth factors suspended in plasma are then separated from the fibrin clot and cellular debris, and are dispensed into vials prior to lyophilization. The volume dispensed in each L-GF vial is adjusted to maintain a concentration of growth factors equivalent to that obtained from a PRP preparation coming from 20 mL of whole blood with a platelet count of $10^6/\mu L$. Lyophilized growth factors have a much longer shelf life than the autologous PRP (12-18 months vs 8 hours). L-GFs are suitable for intralesional injection as it is a water-soluble product with no gel formation.[11]

The aim of this prospective, single-blinded, randomized controlled study was to evaluate the efficacy and safety of local injection of allogeneic growth factors compared with placebo injection in patients with plantar fasciitis.

Methods

This prospective study was conducted between May 2017 and November 2019 on 150 patients with plantar fasciitis at the orthopedic department of our University Hospital after approval of the ethical standards of the University. Any patient older than 20 years with plantar fasciitis was included in this study. Any patient with systemic disorders (eg, coagulation disorders, diabetes mellitus, hepatitis, or disorders associated with enthesopathy such as gout, Reiter syndrome, or rheumatoid arthritis), local conditions of the ankle region (arthritis, previous local corticosteroid or PRP injections, previous ankle surgery or trauma, nerve entrapment, infection, or local malignancy), pregnancy, or psychiatric disorder was excluded from the study. All the patients included in the study had previous failed conservative treatment for at least 6 weeks (ranged from 6 to 20 weeks with an average of 12) in the form of NSAIDs, soft heel cups, stretching exercises, and ice packs. None of them received any form of local injection or had been operated on before for such condition.

Complete physical examination was done to all patients and revealed that all the patients included in the study had the typical pain of plantar fasciitis that was more severe in the early morning and gradually declined in severity after the first few steps. Point tenderness at the inferior and medial part of the heel was noted in all patients. Laboratory investigations (complete blood count, glucose level, erythrocyte sedimentation rate, C-reactive protein, bleeding profile, Rheumatoid factor) and imaging studies (plain radiographs of the ankle and foot anteroposterior, oblique, and lateral views) were done in all patients.

The patients were randomly divided into 2 groups: a treatment group (n=75) in which each patient received a single local injection of allogeneic GFs, and a control group (n=75) in which each patient received a single local injection of normal saline 0.9% as a placebo. The process of randomization was done via sealed opaque envelopes in which the allocation group was stated inside each envelope. The patients were blinded to their treatment assignment and unaware if they were receiving allogeneic GFs or placebo injection.

The baseline patients' criteria are outlined in Table 1. One hundred fifty patients with unilateral plantar fasciitis were included, including 87 women (58%) and 63 men (42%). The mean age was 40.1 years. Overall, 130 were heavily to moderately active (86.6%), and 55 were considered obese, with body mass index (BMI) greater than 30 (36.7%). There was no statistically significant difference between the treatment and control groups regarding their age, gender, BMI, or the level of activity.

The pre-prepared vial of allogeneic GFs was obtained from the Cairo Medical Centre Blood Bank (CMCBB). The L-GF vial was prepared from platelets derived from individual whole blood donations. Each unit of platelets was tested for hepatitis B surface antigen, HIV I and II antibodies, HIV p-24 antigen, hepatitis C virus antibodies, and antibodies to *Treponema pallidum*, by licensed assay methods. Seronegative plasma was further examined by nuclear acid testing. Furthermore, viral inactivation by ultraviolet radiation and riboflavin was performed by the Mirasol system (pathogen reduction technology system; Terumo BCT, Inc.). The platelets in the buffy coat layer were then activated to release the growth factors. Excess water, cellular elements, and fibrinogen were removed, and the remaining growth factors were ultraconcentrated. Lyophilization of the obtained growth factors was then performed. The L-GF vial was supplied as powder in a sealed container. Before use, the vial was allowed to reach ambient temperature as it was stored between 2 and 8 °C. The L-GF vial content was then mixed with 3 mL sterile water. The vial was gently swirled for 3 minutes and allowed to stand at ambient temperature for 5 minutes, to ensure complete protein rehydration.

Table 1. Baseline Patients' Criteria.

	Treatment group (n = 75)	Control group (n = 75)	*P* value
Age, y, mean ± SD (range)	37.1±7.1 (25-58)	43.0±6.6 (27-63)	.92
Gender, n (%)			
Male	35 (47)	28 (37)	.32
Female	40 (53)	47 (63)	
Level of activity, n (%)			
Heavy	23 (30.7)	30 (40)	.45
Moderate	41 (54.7)	36 (48)	
Mild	11 (14.7)	9 (12)	
BMI, mean ± SD (range)	29.3±4.3 (19-35)	29.7±4.5 (18-37)	.875
VAS (preinjection), mean ± SD (range)	8.1±1.2 (7-9)	7.8±1.2 (6-9)	.45
FFI-Rs (preinjection), mean ± SD	58.3±2.3	55.6±4.2	.79

Abbreviations: BMI, body mass index; FFI-Rs, Foot Function Index–Revised short form; VAS, visual analog scale.

Technique of Injection

The technique of local injection was the same in both groups. The area of maximum tenderness was determined by palpating the heel. The patients were supine with mild knee flexion, externally rotated limb, and neutral ankle position. The procedure was done under aseptic condition with single skin entry and multiple pricks to the plantar fascia (peppering technique)[19] and the contents of syringe were slowly injected using an 18-guage needle. Patients were injected with 3 mL of allogeneic growth factors in the treatment group and 3 mL of normal saline 0.9% in the control group.

Postinjection Protocol

The site of the injection was covered by a sterile dressing. All the patients were advised to rest in supine position without moving for 15-30 minutes. Paracetamol 500-mg tablets were given to the patients with cold applied at the site of the local injection. All the patients were advised to avoid the use of NSAIDs 2 weeks before and after the procedure as those drugs may inhibit the inflammatory response of the growth factors.

After 2 weeks, a standardized stretching protocol of the plantar fascia and Achilles tendon was initiated (toe extension, standing calf stretch, and towel stretch) that was repeated 4 to 6 times per day. One month after the procedure, the patients were allowed to proceed with recreational activities (ie, walking slowly, slow dancing) as tolerated. The patients were strictly advised not to participate in heavy activities (such as running, jumping rope) for 3 months. The patients were instructed to wear standard insoles with soft heel cups for 1 year.

Assessment

All the patients were assessed for pain using visual analog scale (VAS) and functional improvement using the Foot Function Index–Revised short form (FFI-Rs) preinjection and at 1, 3, 6, and 12 months postinjection. The FFI-R is a self-reporting measure that assessed multiple dimensions of foot function depending on patient-centered values.[4,5] It has 4 subscales, pain, disability, activity limitation, and psychosocial activities and quality of life related to foot health.[4] The FFI-R items were developed from the original 23 FFI items, and more items were added. The results were the FFI-R long form (FFI-R L; 68 items) and the FFI-R short form (FFI-Rs; 34 items).[4] The total FFI-Rs score is between 0% and 100%. Lower score correlates with better foot function.[10]

Finally, the patients were queried about their satisfaction and classified into completely satisfied, some reservations, important reservations, and dissatisfied. Any adverse effect or complication related to the procedure was also recorded.

Statistical Analysis

Statistical analysis was done in this study using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY, USA). Significant correlation was considered when $P < .05$.

Results

The primary efficacy endpoint was change in the VAS score between preinjection and at 3-month follow-up (Table 2). At baseline, there was no statistically significant difference between the 2 groups regarding the mean VAS score ($P = .45$). At 3-month follow-up, the reduction in the mean VAS score was 87% in the treatment group (from 8.6 to 1.2) and 55% in the control group (from 7.8 to 3.5) ($P < .001$). At the 6- and 12-month follow-ups, the mean VAS score was 1.3 and 1.4 in the treatment group and 3.8 and 3.6 in the control group, respectively.

Table 2. Changes in the Mean VAS Score During the Follow-up Period.

	Mean VAS score	
	Treatment group	Control group
Preinjection	8.6±1.2	7.8±1.2
At 1 mo	3.1±3.3	7.7±5.3
At 3 mo	1.2±1.4	3.5±3.8
At 6 mo	1.3±1.3	3.8±3.5
At 12 mo	1.4±1.7	3.6±2.3
Paired difference[a]	7.4±3.6	4.3±2.5
P value[b]	<.001	

Abbreviation: VAS, visual analog scale.
[a]Difference in mean VAS score between preinjection and at 3-month follow up.
[b]*P* value on paired differences.

Table 3. Changes in the Mean FFI-Rs Score During the Follow-up Period.

	Mean FFI-Rs Score	
	Treatment Group	Control Group
Preinjection	58.3±2.3	55.6±4.2
At 1 mo	35.3±3.6	44.7±4.5
At 3 mo	22.2±2.5	33.2±3.5
At 6 mo	21.4±1.9	33.5±3.8
At 12 mo	21.7±2.1	32.6±2.6
Paired difference[a]	36.1±2.7	22.4±2.9
P value[b]	<.001	

Abbreviation: FFI-Rs, Foot Function Index–Revised short form.
[a]Difference in mean FFI-Rs score between preinjection and at 3-month follow up.
[b]*P* value on paired differences.

The secondary efficacy endpoint was change in the FFI-Rs score between preinjection and at the 3-month follow-up (Table 3). At baseline, there was no statistically significant difference between the 2 groups regarding the mean FFI-Rs score ($P = .79$). At 3-month follow-up, the reduction in mean FFI-Rs score was 62% in the treatment group (from 85.3 to 22.2) and 40% in the control group (from 55.6 to 33.2) ($P < .001$). At the 6- and 12-month follow-ups, the mean FFI-Rs score was 21.4 and 21.7 in the treatment group and 33.5 and 32.6 in the control group, respectively.

Correlation between variables (age, gender, BMI, level of activity, treatment given, and visits) and the outcomes (VAS and FFI-Rs scores) was analyzed (Table 4). When controlling all other variables, treatment group and study visit were significant factors affecting both VAS and FFI-Rs scores ($P < .001$). Both BMI and activity level had a significant correlation in FFI-Rs score when controlling for other variables ($P = .023$ and .043, respectively). FFI-Rs score was lower with decreased BMI and low level of activity. Age and gender had no correlation with either score.

Table 4. Analysis for Variables Affecting the Outcomes.

Variable	VAS score, *P* value	FFI-Rs score, *P* value
Age	.45	.38
Gender	.27	.87
BMI	.56	.023
Level of activity	.37	.043
Injection (L-GFs, placebo)	<.001	<.001
Study visit[a]	<.001	<.001

Abbreviations: BMI, body mass index; FFI-Rs, Foot Function Index–Revised short form; L-GFs, lyophilized growth factors; VAS, visual analog scale.
[a]Study visit preinjection and at 1-, 3-, 6-, and 12-month follow-up visits.

Table 5. Patient Satisfaction at the Final Follow-up.

	Completely satisfied	Some reservations	Important reservations	Dissatisfied
Treatment group, n (%)	60 (80)	6 (8)	3 (4)	6 (8)
Control group, n (%)	18 (24)	14 (18.7)	27 (36)	16 (22.3)
Total, n (%)	78 (52)	20 (13.3)	30 (20)	22 (14.7)

Regarding the patients' satisfaction; 92% were satisfied (either completely or with reservations) in the treatment group, and 78.2% in the control group (Table 5). Five patients in the treatment group experienced mild postinjection pain, which resolved within 2 to 4 days. Apart from this, no other adverse effects related to the procedure (such as infection, hypersensitivity reaction, etc) were reported until the final follow-up.

Discussion

Plantar fasciitis is a common problem.[10] Although most patients with plantar fasciitis respond well to conservative treatment, most of the treatment modalities lack high-quality evidence of efficacy.[6,9,18,20] A desirable treatment for plantar fasciitis is the one that can interrupt the process of inflammation and degeneration before long-term damage.[6] The aim of this prospective, blinded, randomized controlled study was to evaluate the efficacy and safety of local injection of allogeneic growth factors compared to placebo injection in patients with plantar fasciitis.

Freeze-dried PRP is of potential value for various clinical applications. However, L-GFs have not been well studied.[22] Elgohary et al[11] have investigated the effectiveness of intra-articular injection of allogeneic L-GFs in Egyptian patients with symptomatic knee OA. They concluded that allogeneic L-GFs showed encouraging results and were well tolerated. To the authors' knowledge, this is the first study that evaluates

the allogeneic GFs in treatment of plantar fasciitis and compares their outcome with placebo. This study revealed that the patients receiving allogeneic GF injections had a significantly greater reduction in the VAS score for pain and significantly greater improvement in function than those receiving placebo injections at 3-, 6-, and 12-month follow-up without any recorded adverse effects.

The normal blood solid components are composed of red blood cells (93%), platelets (6%), and white blood cells (1%), whereas that of PRP preparation is platelets and plasma (94%), red blood cells (5%), and full component of clotting factors and secretory proteins (1%).[26] However, there is a large variability of the composition of autologous PRP preparation due to variations in the volume of the blood sample taken from the patient, the speed of the centrifuge, efficacy of the platelet recovery, the final volume of plasma in which the platelets are suspended, presence and/or absence of red blood cells and white blood cells in the preparation, and the presence or absence of anticoagulant in the sample.[30]

The allogeneic GFs are not a true PRP preparation as they contain multiple highly concentrated growth factors with long-term, sustained release. In contrary to autologous PRP, they are available in larger quantities, not affected by patients' hemoglobin levels or platelet count, their activity is maintained for more than 1 year, and they are regulated for the temperature and speed of the centrifugation, techniques of separation, and processing.[28] Moreover, there is no need for adding platelet-activating agents such as thrombin (which may produce coagulopathies) or calcium chloride (which causes more pain during the injection and may last for a few days after the injection).[23,36]

Regarding microbiologic safety, there are no issues of disease transmission with allogeneic GFs, as the seronegative pheresis platelets from normal blood bank donors were subjected to a step of pathogen reduction. Each individual unit of pheresis platelets used for L-GFs production was tested for hepatitis B surface antigen, hepatitis C virus antibodies, HIV I&II antibodies, HIV p-24 antigen, and antibodies to *T pallidum* by licensed assay methods. Seronegative plasma of such units was further examined by nuclear acid testing. It was then subjected to viral inactivation by ultraviolet C radiation and riboflavin; thus, all risks of any potential microbiological contamination were eliminated.

Prior to lyophilization, the platelets were stimulated in vitro with subsequent platelet activation and release of growth factors and cytokines from alpha granules. Plasma rich in supraphysiological doses of platelet growth factors was then lyophilized and sterile filtered. Zhang et al[36] demonstrated that the promising use of allogeneic PRP had negligible immunogenicity, great healing power, and no adverse effects. Analyzing the effects of allogeneic freeze-dried PRP on immunologic response in rabbits, Rachmawati et al[24] concluded that allogeneic freeze-dried PRP did not cause an inflammatory response and that the levels of IgM had not increased.

Although patients in the treatment group experienced significantly greater improvement, patients in the control group reported pain reduction and improved function over time as well. The improvement in the control group could be explained by placebo effect of the injection itself due to patient blinding or natural resolution of the symptoms as plantar fasciitis is a self-limiting disease. Moreover, the injection itself (irrespective of the injected material) may have beneficial effects in treating such a condition that resulted from the bleeding caused by forcing fluid through tissue planes.[3,19]

As GF injection is considered as a new treatment modality in plantar fasciitis, it is important to evaluate the cost of this modality in relation to other modalities. The cost of a single injection of L-GF vial was approximately $300. And the cost of PRP preparation varies depending on the equipment and the technique used. Extracorporeal shock wave therapy costs up to $3000 as it may require several treatment sessions.[1] The cost of the operative intervention for plantar fasciitis (including the physician and inpatient charges) ranges up to $10000.[32]

The strength of the present study lies in being prospective, randomized, single-blinded, and controlled. Also, the follow-up period was long enough to allow evaluating the efficacy and safety of allogeneic GF injection for treatment of plantar fasciitis. However, there are some limitations in this study. First, there was no other comparative group receiving another active therapy. Second, we did not use ultrasonography to guide injections. However, Kane et al[13] showed that there were no advantages of ultrasonographic guidance over direct palpation of the most tender area for guidance for the local injection. Third, the thickness of the plantar fascia was not assessed by using ultrasonography before and after the procedure. Fourth, a single injection was given to the patients. It is unknown if repeated injections are of any benefit, so the efficacy of additional injections has to be evaluated. Finally, all patients were instructed to do stretching exercises of the plantar fascia. Although it is unknown if this could affect the study outcomes in both groups, we assume that this would not bias the outcomes, because the main intervention was L-GF injection and these exercises did not help the studied patients before inclusion in our study.

Conclusion

The results of this randomized controlled, single-blind study provide Level I evidence regarding the positive efficacy and safety of allogeneic GFs injection in patients with plantar fasciitis. However, additional studies are needed to evaluate their adverse effects, immunogenicity, and microbiological safety.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. ICMJE forms for all authors are available online.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Mahmoud Ibrahim Kandil, MD, https://orcid.org/0000-0001-6785-1756
Eslam Abdelshafi Tabl, MD, https://orcid.org/0000-0001-5561-6361

Supplemental Material

Supplementary material is available online with this article.

References

1. Alsousou J, Thompson M, Hulley P, Noble A, Willett K. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: a review of the literature. *J Bone Joint Surg Br*. 2009;91(8):987-996.
2. Andres BM, Murrell GAC. Treatment of tendinopathy: what works, what does not, and what is on the horizon. *Clin Orthop Relat Res*. 2008;466(7):1539-1554.
3. Ansari MAQ, Shah SA, Jidgekar SR. Tennis elbow—efficacy of local corticosteroid injection in its management. *IOSR J Sports Phys Educ (IOSR-JSPE)*. 2016;3(3):12-16.
4. Budiman-Mak E, Conrad KJ, Mazza J, Stuck RM. A review of the Foot Function Index and the Foot Function Index–Revised. *J Foot Ankle Res*. 2013;6:5.
5. Budiman-Mak E, Conrad K, Stuck R, Matters M. Theoretical model and Rasch analysis to develop a revised Foot Function Index. *Foot Ankle Int*. 2006;27(7):519-527.
6. Cazzell S, Stewart J, Agnew PS, et al. Randomized controlled trial of micronized dehydrated human amnion/chorion membrane (dHACM) injection compared to placebo for the treatment of plantar fasciitis. *Foot Ankle Int*. 2018;39(10):1151-1161.
7. Cole C, Seto C, Gazewood J. Plantar fasciitis: evidence-based review of diagnosis and therapy. *Am Fam Physician*. 2005;72(11):2237-2242.
8. Cornwall MW, McPoil TG. Plantar fasciitis: etiology and treatment. *J Orthop Sports Phys Ther*. 1999;29(12):756-760.
9. Crawford F, Thomson C. Interventions for treating plantar heel pain. *Cochrane Database Syst Rev*. 2003;3:CD000416.
10. Egmond JC, Breugem SJM, Driessen M, Bruijn DJ. Platelet-rich-plasma injection seems to be effective in treatment of plantar fasciitis: a case series. *Acta Orthop Belg*. 2015;81(2):315-320.
11. Elgohary R, Diab A, Elgndy H, Fahmy H, Gado K. Evaluating the effectiveness of intra-articular knee injection using allogenic platelet derived lyophilized growth factors in Egyptian patients with symptomatic primary knee osteoarthritis. *Ann Rheum Dis*. 2019;78(suppl 2):1866-1866.
12. Gautam VK, Verma S, Batra S, Bhatnagar N, Arora S. Platelet-rich plasma versus corticosteroid injection for recalcitrant lateral epicondylitis: clinical and ultrasonographic evaluation. *J Orthop Surg (Hong Kong)*. 2015;23(1):1-5.
13. Kane D, Greaney T, Shanahan M, et al. The role of ultrasonography in the diagnosis and management of idiopathic plantar fasciitis. *Rheumatology (Oxford)*. 2001;40:1002-1008.
14. League AC. Current concepts review: plantar fasciitis. *Foot Ankle Int*. 2008;29(3):358-366.
15. Martinelli N, Marinozzi A, Carni S, Trovato U, Bianchi A, Denaro V. Platelet-rich plasma injections for chronic plantar fasciitis. *Int Orthop*. 2013;37(5):839-842.
16. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med*. 2006;34(11):1774-1778.
17. Monto RR. Platelet-rich plasma and plantar fasciitis. *Sports Med Arthrosc Rev*. 2013;21(4):220-224.
18. Neufeld SK, Cerrato R. Plantar fasciitis: evaluation and treatment. *J Am Acad Orthop Surg*. 2008;16:338-346.
19. Okcu G, Erkan S, Senturk M, Ozalp RT, Yercan HS. Evaluation of injection techniques in the treatment of lateral epicondylitis: a prospective randomized clinical trial. *Acta Orthop Traumatol Turc*. 2012;46:26-29.
20. Orchard J. Plantar fasciitis. *BMJ*. 2012;345:e6603.
21. Othman AMA. Treatment of chronic lateral epicondylitis: platelet rich plasma versus extra-corporeal shock wave therapy. *Open J Orthop*. 2014;4:77-83.
22. Pan L, Yong Z, Yuk KS, Hoon KY, Yuedong S, Xu J. Growth factor release from lyophilized porcine platelet-rich plasma: quantitative analysis and implications for clinical applications. *Aesth Plast Surg*. 2016;40:157-163.
23. Pretorius E, Briedenhann S, Marx J, et al. Ultrastructural comparison of the morphology of three different platelet and fibrin fiber preparations. *Anat Rec*. 2007;290:188-198.
24. Rachmawati T, Astuti SP, Purwati. The effect of allogeneic freeze dried platelet-rich plasma in immunological responses of rabbits. *Sch Acad J Biosci*. 2015;3(4):325-327.
25. Rizk AS, Kandel WA, Tabl EA, Kandil MI. Mid-sole release of the plantar fascia combined with percutaneous drilling of the calcaneus for treatment of resistant heel pain. *Foot Ankle Int*. 2017;38(11):1271-1277.
26. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. *Curr Rev Musculoskeletal Med*. 2008;1(3-4):165-174.
27. Shetty VD, Dhillon M, Hegde C, Jagtap P, Shetty S. A study to compare the efficacy of corticosteroid therapy with platelet-rich plasma therapy in recalcitrant plantar fasciitis: a preliminary report. *Foot Ankle Surg*. 2014;20(1):10-13.
28. Sonker A, Dubey A, Bhatnagar A, Chaudhary R. Platelet growth factors from allogeneic platelet-rich plasma for clinical improvement in split-thickness skin graft. *Asian J Transfus Sci*. 2015;9(2):155-158.
29. Sriram Thanigai T, Deviprasad S, Sathik Babu MB, Nithin PS. Effectiveness of platelet-rich plasma in chronic severe plantar fasciitis: a prospective analysis. *Indian J Orthop Surg*. 2015;1(4):282-285.

30. Steven AP, Oscar C, Yenern Y. On the horizon from the ORS. *J Am Acad Orthop Surg*. 2010;18(7):445-448.
31. Stuber K, Kristmanson K. Conservative therapy for plantar fasciitis: a narrative review of randomized controlled trials. *J Can Chiropr Assoc*. 2006;50(2):118-133.
32. Tong KB, Furia J. Economic burden of plantar fasciitis treatment in the United States. *Am J Orthop*. 2010;39(5):227-231.
33. Venkatesh Gupta SK, Bandari D. Autologous platelet-rich plasma injection in tennis elbow and plantar fasciitis. *Curr Orthop Pract*. 2016;27(4):405-408.
34. Yadav R, Kothari SY, Borah D. Comparison of local injection of platelet rich plasma and corticosteroids in the treatment of lateral epicondylitis of humerus. *J Clin Diagn Res*. 2015;9(7):RC05-RC07.
35. Young CC, Rutherford DS, Niedfeldt MW. Treatment of plantar fasciitis. *Am Fam Physician*. 2001;63:467-474, 477-478.
36. Zhang ZY, Huang AW, Fan JJ, et al. The potential use of allogeneic platelet-rich plasma for large bone defect treatment: immunogenicity and defect healing efficacy. *Cell Transplant*. 2013;22:175-187.