Accepted Manuscript

Comparison of Autologous Conditioned Plasma Injection, Extracorporeal Shockwave Therapy, and Conventional Treatment for Plantar Fasciitis: A Randomized Trial

Kelvin Tai Loon Chew, MBBCH, MSpMed Darren Leong, MBBS Cindy Y. Lin, MD Kay Kiat Lim, MBBS, MMed Benedict Tan, MBBS, MSpMed

PII: S1934-1482(13)01014-9

DOI: 10.1016/j.pmrj.2013.08.590

Reference: PMRJ 1103

To appear in: *PM&R*

Received Date: 9 December 2012

Revised Date: 11 July 2013

Accepted Date: 5 August 2013

Please cite this article as: Loon Chew KT, Leong D, Lin CY, Lim KK, Tan B, Comparison of Autologous Conditioned Plasma Injection, Extracorporeal Shockwave Therapy, and Conventional Treatment for Plantar Fasciitis: A Randomized Trial, *PM&R* (2013), doi: 10.1016/j.pmrj.2013.08.590.

Title: Comparison of Autologous Conditioned Plasma Injection, Extracorporeal Shockwave Therapy, and Conventional Treatment for Plantar Fasciitis: A Randomized Trial

Authors: Kelvin Tai Loon Chew, MBBCH, MSpMed[1], Darren Leong, MBBS[1], Cindy Y. Lin, MD[1,2], Kay Kiat Lim, MBBS, MMed[3,4], and Benedict Tan, MBBS, MSpMed[1]

Institutional Affiliations:

[1]Changi Sports Medicine Centre, Changi General Hospital, Singapore

[2]Spine & Sports Rehabilitation Center, Rehabilitation Institute of Chicago, Chicago, Illinois (affiliation of C.L. when study performed)

[3]Department of Orthopedic Surgery, Changi General Hospital (affiliation of K.L. when study performed), Singapore

[4] Synergy Orthopedic Group, Singapore

Name & Address for Correspondence: Cindy Y. Lin, MD email: cindy.lin@post.harvard.edu Telephone number: 1-650-308-8684

The material was not presented at an AAPM&R Annual Assembly.

Funding Source: Study funded by the Singapore National Medical Research Committee grant. No funding was received by Dornier MedTech or Arthrex, Inc.

1 Title: Comparison of Autologous Conditioned Plasma Injection, Extracorporeal Shockwave Therapy, and

2 Conventional Treatment for Plantar Fasciitis: A Randomized Trial

Abstract

Objective: To evaluate the efficacy of autologous conditioned plasma (ACP) compared to extracorporeal shockwave (ESWT) and conventional treatments for plantar fasciitis.

Design: Randomized trial

Setting: Sports medicine center in a tertiary care hospital.

Patients: 54 subjects (29-71 years) with unilateral chronic plantar fasciitis with greater than 4 months of symptoms.

Methods: Subjects randomized to three groups: 19 to ACP and conventional treatment (ACP group), 19 to ESWT and conventional treatment (ESWT group), and 16 to conventional treatment alone. Conventional treatment included stretching exercises and orthotics if indicated.

Main Outcome Measurements: Outcomes were pain Visual Analog Scale (VAS), American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale, and ultrasound plantar fascia thickness assessed at baseline pre-treatment and at 1 month, 3 months and 6 months post-treatment.

Results: VAS, AOFAS, and plantar fascia thickness improved in all groups. Significant VAS pain score improvements in the ACP group compared with conventional treatments at the 1st month (P=0.037) and for the ESWT group compared to conventional treatments at the 1st, 3rd and 6th months (P=0.017, P=0.022, P=0.042). AOFAS score improved in the ACP group at the 3rd and 6th months (P=0.004 and P=0.013) and for the ESWT group at the 1st and 3rd months (P=0.011, P=0.003) compared to conventional treatments. Significant improvements in plantar fascia thickness were seen in the ACP group at the 1st and 3rd month compared with conventional treatments (P=0.015, P=0.014) and at the 3rd and 6th months compared to the ESWT group (P=0.019, P=0.027). No adverse events reported.

Conclusions: Treatment of plantar fasciitis with ACP or ESWT plus conventional treatments resulted in improved pain and functional outcomes compared with conventional treatments alone. There was no significant difference between ACP and ESWT in terms of VAS and AOFAS improvements, although the ACP group demonstrated greater reductions in plantar fascia thickness.

Introduction

Plantar fasciitis is a common cause of heel pain associated with mild to severe activity limitations in athletes and the general population. In the United States, there were an estimated one million outpatient visits per year for plantar fasciitis between 1995-2000.[1] The condition is an enthesopathy at the plantar fascia attachment to the medial plantar tuberosity of the calcaneus. Risk factors for plantar fasciitis include obesity, excessive foot pronation, running, decreased ankle dorsiflexion range, and prolonged standing.[2,3] Current treatment approaches are based on addressing identified anatomic and biomechanical abnormalities and providing pain relief. Conventional non-invasive treatment options include plantar fascia, gastrocnemius, and soleus stretching, customized orthotics, night splints, extracorporeal shock wave therapy (ESWT), and pain medications.[4,5] Generally, plantar fasciitis is a self-limited condition. However, approximately 10 percent of patients with plantar fasciitis do not respond to conventional treatments.[6] Invasive strategies such as corticosteroid injections, and percutaneous, endoscopic, or open fasciotomy have been used in refractory cases with varying results.[7,8,9,10]

The efficacy of blood derived growth factors including autologous conditioned plasma (ACP), autologous conditioned serum (ACS), and platelet rich plasma (PRP), in healing ligaments, tendons, muscles, and cartilage injuries have been investigated in several studies.[11,12,13,14,15] PRP, ACP, or ACS are platelet rich preparations that are derived by drawing peripheral venous blood from the patient and centrifuging it to separate the red blood cells and platelets. The platelet concentrate is then aspirated from the platelet-rich layer of the centrifuged plasma and used for injection.[11] For cases of plantar fasciitis refractory to conventional treatments, these autologous preparations have been suggested as an alternative management strategy.[7,9,16] Few studies have examined the efficacy of ACP for the treatment of plantar fasciitis. A case series of PRP for plantar fasciitis, found that at one year, 7 of the 9 patients had complete pain resolution. All 9 patients had ultrasound evidence of improvement including reduced thickness of the medial plantar fascial band and increased signal intensity of the fascial bands.[16] Another study compared the efficacy of PRP to corticosteroid injection for plantar fasciitis and found no significant difference in outcomes between the groups at 3 weeks and at 6 months follow up.[7]

The aim of this randomized trial was to investigate the efficacy of ACP for treatment of plantar fasciitis compared to that of ESWT and conventional treatments including physiotherapy, stretching exercises, and orthotics if indicated. The primary outcome measures were pain, function as measured by the American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot scale, and changes in plantar fascia thickness seen on ultrasound. This is the first published study to compare ESWT to ACP injection and conventional treatments for plantar fasciitis. Our hypothesis was that ACP would be more effective than ESWT and conventional treatments in relieving pain, improving function, and reducing plantar fascia thickness on ultrasound in chronic plantar fasciitis over 6 months of follow up.

Methods

The study design was a randomized trial evaluating the efficacy of 3 different treatment groups. 54 patients with unilateral plantar fasciitis were recruited at a single sports medicine center in a public tertiary care hospital. Inclusion criteria were clinically diagnosed unilateral chronic plantar fasciitis defined as: at least 4 months of plantar heel pain, point of maximal tenderness on clinical exam over the medial tubercle of the calcaneus, and sonographic features of plantar fasciitis. Increased thickness of the plantar fascia and hypoechoic fascia are recognized as the sonographic findings of plantar fasciitis.[17] As in prior studies, a plantar fascia thickness of greater than 4mm at baseline was taken as abnormal.[18,19] All subjects had an X ray of the symptomatic foot prior to inclusion in the study. Subjects with arthritis, fractures, or tumors of the foot or ankle, rheumatoid arthritis, generalized polyarthritis, seronegative arthropathy, diabetes mellitus, neurological impairments, lower extremity nerve entrapment, vascular abnormalities, prior operative treatment of the foot, or current pregnancy were excluded. Subjects were also excluded if they had received corticosteroid or other injections for plantar fasciitis during the 4 months prior to referral. Subjects were not excluded if they had tried stretching exercises, physiotherapy, or orthoses prior to study enrollment. The study was institutional review board approved and all subjects gave written informed consent. Subjects were randomized to the three groups at time of enrollment by drawing a folded sealed paper with a corresponding group number from a sealed box.

The three groups were: 1) ACP injection and conventional treatment (ACP group), 2) ESWT and

conventional treatment (ESWT group), and 3) conventional treatment alone. All subjects in all three treatment groups received conventional treatments which included 1-2 physical therapy sessions to learn an independent daily home exercise program including: 1) standing lunge stretch of the gastrocnemius and soleus performed with the knee bent and knee straight and the palms of the hands pressed against a wall, and 2) seated plantar fascia stretch by pulling the toes back with their fingers while seated and with the affected leg crossed.[5,6,20] Subjects received 1-2 physical therapy sessions only as the goal was to become independent in the stretching exercises. Subjects were instructed to perform the stretches three times a day, three times for each stretch, and to hold each stretch for 30 seconds at a time. Additionally, all subjects in all treatment groups identified by the physician as having biomechanical foot abnormalities contributing to their symptoms were also referred to podiatry for orthotics evaluation. All subjects in all 3 treatment groups were advised that they could continue any previously prescribed analgesic pain medications on an as needed basis only. No new pain medications were prescribed on study entry.

Subjects randomized to the ACP group had 10mls of peripheral blood drawn and centrifuged at 1500 rpm for 5 minutes using the Arthrex ACP™ Double Syringe System. No buffer or preservative was added per manufacturer's protocol. Using sterile technique, three mls of ACP were extracted and subsequently injected with a 23-gauge 1.5 inch needle at a single perifascial target at the site of plantar fascia thickening and tenderness at the medial calcaneal tubercle. The injection was performed under continuous ultrasound guidance by a single sports medicine physician for all cases. This physician did not perform any of the follow up outcome measure assessments. No tenotomy or fasciotomy was performed. No local anaesthetic was administered. Patients were instructed that they could resume their usual daily activities as tolerated after the procedure.

Subjects in the ESWT group received two sessions of ESWT one week apart using the Dornier EPOS Ultra ESWT Machine delivered under ultrasound guidance to the painful and thickened region of the plantar fascia at the medial calcaneal tubercle. All patients were positioned prone on the exam table with their feet hanging comfortably over the end of the table. The ESWT technique was as follows: ultrasound gel was placed on a water cushion and the ultrasound transducer. The water cushion and ultrasound transducer were placed over the heel and positioned so that the plantar fascia origin at the

calcaneum was visible. The cross hair, which indicates the position of the shock wave focus, was positioned in the thickened and painful region of the plantar fascia.[21] Ultrasound guidance was used to ensure accurate placement of the shock wave focus in the symptomatic region of the plantar fascia and to prevent the shock wave from contacting bone. Each treatment involved 2000 shockwaves with energy levels progressing gradually from 0.02mJ/mm^3 to 0.42mJ/mm^3. Total treatment duration was 10 minutes. No local anaesthetic was administered. Patients were instructed that they could resume their usual daily activities as tolerated after the procedure.

Subjects were assessed at baseline (pre-treatment), 1 month, 3 months and 6 months post-treatment. For the ACP group, the 1st, 3rd, and 6th month time points were assessed post injection. For the ESWT group, the 1st, 3rd, and 6th month time points were assessed after completion of the 2nd ESWT treatment. The Visual Analogue Scale (VAS) of 0 to 10 points was utilized as a self-report of pain at each assessment time point. The American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot scale was used to objectively evaluate functional outcomes.[22] The AOFAS is graded as excellent (100 to 91 points), good (90 to 81 points), fair (80 to 71 points), and poor (<70 points).[23] The AOFAS was selected as a measure because it evaluates pain, function, and alignment and it has been used in multiple prior clinical outcomes studies of plantar fasciitis treatments.[4,24] Ultrasonography of the symptomatic plantar fascia was performed to manually measure the point of maximal proximal thickness at the medial calcaneal tubercle insertion site.[17] Comparison of pre and post intervention changes in plantar fascia thickness on ultrasound has been validated as an objective measure to assess treatment efficacy for plantar fasciitis.[25] Two sports medicine physicians each with greater than 5 years of experience with musculoskeletal ultrasound, assessed the patients for the three outcome measures. They were also blinded to each subject's treatment group at initial and follow up assessments. For each subject, the same assessor performed both the initial and follow up exam assessments. To ensure blinding, these assessors were not the same physicians who performed the ACP injection or ESWT treatment.

Statistical Analysis

The analysis endpoints were changes in VAS pain score, AOFAS score, and plantar fascia thickness at 1 month, 3 month and 6 months follow up. SPSS software was used for statistical analysis. Non-parametric statistical tests were used to compare the difference among the three treatment arms in terms of each analysis endpoint: Kruskal-Wallis test for the global test of no difference between three groups and Mann-Whitney U test for pairwise comparison. To guard against inflated type I error rate due to multiple group comparison, pairwise comparison was interpreted only if the global test of no difference between three groups was rejected. Drop-out rate at the 6 month final visit was compared between groups. Differences in the distribution of binary variables were tested by the Mehta-Patel extension of the Fisher's exact test.[26] *P* value< 0.05 was taken as statistical significance.

Results

Out of the approximately 100 subjects asked to participate in the study, 54 subjects gave informed consent to be included in the study. Nineteen were randomized to the ACP group, 19 to the ESWT group, and 16 to the conventional treatment group. Nine subjects were unable to complete timely follow-up by 6 months, at which point, the number of subjects assessed was 15 in the ACP group, 17 in the ESWT group and 13 in the conventional treatment group. A Fisher's exact test showed that there were no significant differences in the drop-out rates in the three groups at 6 months (*P*=0.506). Table 1 shows the demographic characteristics of the 54 subjects. The three groups were comparable in age, gender, pain duration prior to study enrolment, and left and right side distribution of plantar fasciitis. The conventional treatment group had a better AOFAS score at initial evaluation prior to treatment (*P*=0.03). At baseline, the VAS pain score was lower in the conventional treatment group and the ultrasound plantar fascia thickness was higher in the ACP group, although not reaching statistical significance (*P*=0.606). The ESWT group has slightly higher median BMI and pain duration prior to study participation than the ACP and conventional treatment groups, however, neither demographic characteristic demonstrated a statistically significant difference between the three groups (*P*=0.606, *P*=0.213, respectively).

No major adverse events including haematoma, deep vein thrombosis, nerve injury, or infection were reported in any of the subjects during the treatment and follow-up period for ESWT and ACP. All

patients tolerated the procedures well with no complications.

VAS Pain Score

Reductions in VAS pain scores were seen in all treatment groups from baseline to six months follow up. Table 2 shows the median and range values of the VAS pain scores at all assessment timepoints. Table 3 and Figure 1 show the VAS pain score median change from baseline to all follow up assessment time points. At one month follow up, all three groups demonstrated significant improvement in VAS pain score compared to baseline (P=0.036). The median change in VAS pain score in the ACP and ESWT groups was greater than one point reduction at all assessment time points compared with the conventional treatment group. The ESWT group demonstrated significant improvements in VAS pain scores at all assessment time points compared to the conventional treatment group. The ACP group demonstrated significant improvements at only the 1st month evaluation compared to the conventional treatment group (P=0.037). There was no statistically significant difference in VAS pain score improvements between the ACP and ESWT groups at the 1st, 3rd, and 6th months (P=0.575, P=0.947, P=0.791, respectively).

AOFAS Score

Improvements in AOFAS scores were seen in all treatment groups from baseline to 6 months follow up. Table 2 shows the median and range values of the AOFAS scores at all assessment timepoints. Table 4 and Figure 2 show the AOFAS score median changes from baseline to all follow up assessment time points. All three groups demonstrated significant improvements in AOFAS scores from the baseline to 1st (P=0.045) and 3rd (P=0.004) month follow up. The baseline median AOFAS scores in the conventional treatment group were significantly higher than that of the ESWT and ACP groups (P=0.024). The ACP group demonstrated a median improvement of 36 points in AOFAS score, 28 points in the ESWT group and 15.5 points in the conventional treatment group overall at 6 months. At all follow up assessment time points, the conventional treatment group had the lowest median change in AOFAS scores. The ACP group demonstrated significant improvements at the 3rd and 6th month evaluation

(*P*=0.004, *P*=0.013) compared to the conventional treatment group, whereas the ESWT group showed greater improvements at the 1st and 3rd month evaluation (*P*=0.011, *P*=0.003) compared with the conventional treatment group. There was no significant difference in median AOFAS score improvements between ACP and ESWT groups at all follow up assessment time points.

Plantar Fascia Thickness

All groups demonstrated improvements in plantar fascia thickness from baseline to the end of the evaluation period. Table 2 shows the median and range of the plantar fascia thickness at all assessment timepoints. Table 5 and Figure 3 show the median changes in ultrasound plantar fascia thickness at all follow up assessment time points. All three groups demonstrated significant decrease in plantar fascia thickness at 1st (*P*=0.042) and 3rd (*P*=0.02) month follow up compared to baseline. The median ultrasound plantar fascia thickness improvement in ACP group at 6th months follow up was 1.3mm compared with the ESWT and conventional treatment groups which both showed improvements of 0.6mm at 6 months. At the 1st and 3rd month, there were statistically significant differences in reduction in plantar fascia thickness in all groups (*P*=0.042 and *P*=0.020 respectively). Significant improvements were seen in the ACP group at the 1st and 3rd month compared with the conventional treatment group (*P*=0.015, *P*=0.014, respectively). There was no significant difference in the median plantar fascia thickness change at 6 months follow up compared to baseline between all three groups. There was also no significant difference between the absolute plantar fascia thickness measurements at 6 months follow up between all three groups.

The ACP group demonstrated significant improvements in plantar fascia thickness at the 3rd and 6th month compared with the ESWT group (*P*=0.019, *P*=0.027). No significant difference was seen between the ESWT and conventional treatment groups at all follow up assessment time points for median change in plantar fascia thickness (*P*=0.908, *P*=0.575, *P*=0.934, respectively).

Discussion

Previous studies of biological treatments for the plantar fascia have involved injections of

autologous whole blood and of PRP.[7,8,9] This is the first study evaluating the effectiveness of a single injection of ACP for treating chronic plantar fasciitis compared to ESWT and conventional treatments. The reason for the comparison to ESWT in this study was to compare ACP's effectiveness in pain relief as ESWT has been reported to provide good pain relief for chronic plantar fasciitis.[27,87] The mechanism of pain relief with ESWT is thought to be due to release of enzymes affecting nociceptors.[24] ESWT can be considered as a treatment option after conventional treatments have failed.

There has been an increasingly prevalent use of autologous blood derived growth factor rich preparations in musculoskeletal disorders.[7,12,13,15] Growth factors such as insulin-like growth factor-1, basic fibroblast growth factor, platelet-derived growth factor, epidermal growth factor, vascular endothelial growth factor, and transforming growth factor-B1 are a diverse group of polypeptides that regulate growth and tissue development.[29,31,35] It is believed that these cellular and humeral mediators provide conditions favourable for tissue healing.[11,29,30] Animal models have demonstrated up-regulation in temporal expression of growth factors and their receptors during the healing process in tendons,[32,33] while healing has also been shown to take place in response to local injection of growth factors.[34,35]

Our study found that ACP and ESWT were comparable in terms of pain relief. ACP and ESWT resulted in greater median improvements in functional AOFAS scores than the conventional treatment group. Our study demonstrated a greater than one point median reduction in VAS pain scores in the ACP and ESWT groups compared to conventional treatments, which was both statistically and clinically significant. Prior studies have indicated that the minimally important clinical improvement in VAS scores for foot pain is 9mm on a 100mm VAS scale, which corresponds to a 0.9 point improvement on the 10 point VAS scale.[36] ACP treatment resulted in greater decreases in ultrasound plantar fascia thickness than ESWT but not when ACP was compared to the conventional treatment group at 6 months follow up. The ACP treatment group displayed better objective improvements with an overall median decrease of ultrasound plantar fascia thickness by 1.3mm at 6 months follow up. Changes in plantar fascia thickness greater than 0.6 mm are considered changes in thickness not due to measurement error.[37] Changes in plantar fascia thickness are a valid objective measurement of assessing the effectiveness of plantar fascia treatments.[38]

No adverse events such as fever, infection, haematoma, deep vein thrombosis were reported among study subjects. The risks associated with ACP injections are low as the preparations are derived from the patient's own blood, thus there is negligible risk of exogenous bloodborne infections.[29,39] The harvesting procedure is simple and fast, allowing for treatment to be administered easily in an outpatient clinic setting.

Limitations

The study's small sample size, which was limited by timeframe and funding, may have resulted in positive or negative effects being under detected. Future larger trials evaluating ACP for treatment of the plantar fasciitis are needed. At baseline, the median AOFAS scores were higher in the conventional treatment group. This may partly explain why this score did not improve as much for the conventional treatment group as they started out at a higher baseline.

Subjects were unblinded to the treatments they received, which may have biased their response. The subjects who received ACP or ESWT may have perceived their treatment as more high tech and a more effective treatment modality than conventional treatments since ACP involved an injection and ESWT was performed using a machine. Future studies including the use of placebo controlled injections compared to ACP are warranted to isolate treatment effect of the injectate alone for plantar fasciitis. Subjects did not keep a compliance log for their stretching exercises or orthotic use, thus it is unknown if compliance was comparable between the groups. If the conventional treatment group did not perform the stretching exercises, it is possible that this group represents the natural history of plantar fasciitis. Subjects also did not keep a pain medication use or an activity log.

The single assessor who performed ultrasound measurements of plantar fascia thickness manually measured the plantar fascia thickness once at each assessment time point. The interobserver reliability of the ultrasound measurement could have been increased if multiple measurements were averaged.[38]

Future studies comparing the relative efficacies of different preparations of ACP, PRP, and whole blood injections are needed to better understand the optimal concentration of platelets and appropriate relative concentration of platelets to leukocytes. The ACP from Arthex ACP™ overall has concentrated

platelets (1.99×) and diminished leukocytes (0.13×) compared with venous blood. ACP also has less catabolic cytokines than the Biomet GPS III Mini Platelet Concentrate System for PRP.[40] Platelets increase anabolic signaling whereas leukocytes increase catabolic or inflammatory signaling molecules that may degrade normal tissue matrix.[40] The ACP from the Arthrex ACP™ system has been reported to have a mean platelet concentration of 361,000/uL, whereas in venous blood, the mean platelet concentration is 183,000/*u*L.[40]

As our study investigated the use of a single injection only, future trials investigating the optimal number of ACP injections are needed. Longer term follow up outcome studies to one year and beyond that examine outcomes are also needed to determine the duration of treatment effect. There is substantial variability in the injection techniques for platelet rich preparations in the published studies. For plantar fasciitis, no single injection technique whether peri-fascial, intrafascial, peppering, layering, or percutaneous tenotomy and with or without ultrasound guidance has been identified as the most effective.[7,16,41] In our study, a peri-fascial approach under ultrasound guidance was selected so we could best isolate the treatment effect of ACP alone. We did not perform tenotomy or peppering, as was performed in the Ragab and Othman and Barrett and Erredge studies, [16,42] as the microtrauma to the fascia from the needling technique itself has been postulated to mediate healing. [42] We also did not perform a posterior tibial and sural nerve anesthetic block prior to the injection, as was performed in the Barrett and Erredge study to increase patient tolerance of an intrafascial injection.[16] Further studies comparing different injection technique for platelet rich injections to the plantar fascia are needed to determine whether there is an optimal technique.

Conclusion

Treatment of plantar fasciitis with either ACP or ESWT resulted in modestly improved pain and functional score improvements compared with conventional treatments alone over a 6 months follow up period. Though there were no significant differences between ACP and ESWT in terms of VAS pain scores and AOFAS functional score improvements, ACP demonstrated greater objective improvements in terms of plantar fascia thickness reduction. ACP and ESWT are treatments that may be considered in

300 patients with plantar fasciitis who have not responded to conventional treatments.

References

1. Riddle DL, Schappert SM. Volume of ambulatory care visits and patterns of care for patients diagnosed with plantar fasciitis: a national study of medical doctors. *Foot Ankle Int*. 2004 May;25(5):303-310.

2. Irving DB, Cook JL, Young MA, Menz HB. Obesity and pronated foot type may increase the risk of chronic plantar heel pain: a matched case-control study. *BMC Musculoskelet Disord*. 2007 May 17;8:41.

3. Riddle DL, Pulisic M, Pidcoe P, Johnson RE. Risk factors for plantar fasciitis: a matched case-control study. *J Bone Joint Surg Am*. 2003 May;85-A(5):872-877.

4. Chuckpaiwong B, Berkson EM, Theodore GH. Extracorporeal shock wave for chronic proximal plantar fasciitis: 225 patients with results and outcome predictors. *J Foot Ankle Surg*. 2009 Mar-Apr;48(2):148-155.

5. Crawford F, Thomson C. Interventions for treating plantar heel pain. *Cochrane Database Syst Rev*. 2003;(3):CD000416.

6. Davis PF, Severud E, Baxter DE. Painful heel syndrome: results of nonoperative treatment. *Foot Ankle Int*. 1994 Oct;15(10):531-535.

7. Aksahin E, Dogruyol D, Yuksel HY, Hapa O, Dogan O, Celebi L, Bicimoglu A. The comparison of the effect of corticosteroids and platelet-rich plasma (PRP) for the treatment of plantar fasciitis. *Arch Orthop Trauma Surg*. Epub 2012 Mar 8. PMID: 22399039.

8. Kalaci A, Cakici H, Hapa O, Yanat AN, Dogramaci Y, Sevinç TT. Treatment of plantar fasciitis using four different local injection modalities: a randomized prospective clinical trial. *J Am Podiatr Med Assoc*. 2009;99(2):108-113.

9. Lee TG, Ahmad TS. Intralesional autologous blood injection compared to corticosteroid injection for treatment of chronic plantar fasciitis. A prospective, randomized, controlled trial. *Foot Ankle Int*. 2007

Sep;28(9):984-990.

10. Urovitz EP, Birk-Urovitz A, Birk-Urovitz E. Endoscopic plantar fasciotomy in the treatment of chronic heel pain. *Can J Surg*. 2008 Aug;51(4):281-283.

11. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med* 2009;37:2259-2272.

12. Hammond JW, Hinton RY, Curl LA, Muriel JM, Lovering RM. Use of autologous platelet-rich plasma to treat muscle strain injuries. *Am J Sports Med*. 2009;37:1135-1142.

13. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med*. 2006;34:1774-1778.

14. Murray MM, Spindler KP, Ballard P, Welch TP, Zurakowski D, Nanney LB. Enhanced histologic repair in a central wound in the ACL with a collagen-platelet-rich plasma scaffold. *J Orthop Res*. 2007;25:1007-1017.

15. Sanchez M, Anitua E, Azofra J, et al. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. *Am J Sports Med*. 2007;35:245-251.

16. Barrett S, Erredge S. Growth factors for chronic plantar fasciitis. *Podiatry Today*. 2004;17:37-42.

17. Cardinal E, Chhem RK, Beauregard CG, Aubin B, Pelletier M. Plantar fasciitis: Sonographic evaluation. *Radiology.* 1996;201:257-259.

18. McMillan AM, Landorf KB, Barrett JT, Menz HB, Bird AR. Diagnostic imaging for chronic plantar heel pain: a systematic review and meta-analysis. J Foot Ankle Res. 2009 Nov 13;2:32.

19. Sabir N, Demirlenk S, Yagci B, Karabulut N, Cubukcu S. Clinical utility of sonography in diagnosing plantar fasciitis. J Ultrasound Med. 2005 Aug;24(8):1041-8.

20. DiGiovanni BF, Nawoczenski DA, Lintal ME, Moore EA, Murray JC, Wilding GE, Baumhauer JF. Tissue-specific plantar fascia-stretching exercise enhances outcomes in patients with chronic heel pain. A prospective, randomized study. J Bone Joint Surg Am. 2003 Jul;85-A(7):1270-7.

21. Buchbinder R, Ptasznik R, Gordon J, Buchanan J, Prabaharan V, Forbes A. Ultrasound-guided extracorporeal shock wave therapy for plantar fasciitis: a randomized controlled trial. JAMA. 2002 Sep 18;288(11):1364-72.

22. Kitaoka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, Sanders M. Clinical rating systems for the ankle-hindfoot, midfoot, hallux and lesser toes. *Foot Ankle Int*. 1994;15:349-353.

23. Becker HP, Ebner S, Ebner D, et al. 12-year outcome after modified Watson-Jones tenodesis for ankle instability. *Clin Orthop*. 1999;358:194-204.

24. Kudo P, Dainty K, Clarfield M, Coughlin L, Lavoie P, Lebrun C. Randomized, placebo-controlled, double-blind clinical trial evaluating the treatment of plantar fasciitis with an extracoporeal shockwave therapy (ESWT) device: a North American confirmatory study. *J Orthop Res*. 2006 Feb;24(2):115-123.

25. Mahowald S, Legge BS, Grady JF. The correlation between plantar fascia thickness and symptoms of plantar fasciitis. *J Am Podiatr Med Assoc*. 2011 Sep;101(5):385-389.

26. Mehta CR, Patel NR. A network algorithm for performing fisher's exact test in r × c contingency tables. *J Amer Statistical Assoc*. 1983;78(382):427-434.

27. Lowell SW, Thomas SR, Borrelli AH. Extracorporeal shock wave therapy for treatment of chronic plantar fasciitis: indications, protocol, intermediate results, and a comparison of results to fasciotomy. *J Foot Ankle Surg*. 2002;41(3):166–172

28. Malay DS, Pressman MM, Assili A, Kline JT, York S, Buren B, Heyman ER, Borowsky P, LeMay C.

Extracorporeal shockwave therapy versus placebo for the treatment of chronic proximal plantar fasciitis: results of a randomized, placebo-controlled, double-blinded, multicenter intervention trial. *J Foot Ankle Surg*. 2006 Jul-Aug;45(4):196-210.

29. Creaney L, Hamilton B. Growth factor delivery methods in the management of sports injuries: the state of play. *Br J Sports Med*. 2008 May;42(5):314-320.

30. Marx RE. Platelet-rich plasma: evidence to support its use. *J Oral Maxillofac Surg*. 2004;62:489-496.

31. Woodall J Jr, Tucci M, Mishra A, Asfour A, Benghuzzi H. Cellular Effects of Platelet Rich Plasma: Interleukin-1 release from PRP treated macrophage cells. *Biomed Sci Instrum*. 2008;44:489–494.

32. Boyer MI, Watson J, Lou J, Manske PR, Gelberman RH, Cai SR. Quantitative variation in vascular endothelial growth factor mRNA expression during early flexor tendon healing: an investigation in a canine model. *J Orthop Res*. 2001;19:869-872

33. Dahlgren LA, Mohammed HO, Nixon AJ. Temporal expression of GF and matrix molecules in healing tendon lesions. *J Orthop Res*. 2005;23:84-92.

34. Chan BP, Fu S, Qin L, Lee K, Rolf CG, Chan K. Effects of bFGF on early stages of tendon healing: a rat patellar tendon model. *Acta Orthop Scand*. 2000;71:513-518.

35. Molloy T, Wang Y, Murrell GAC. The roles of growth factors in tendon and ligament healing. *Sports Med*. 2003;33:381-394.

36. Landorf KB, Radford JA, Hudson S. Minimal Important Difference (MID) of two commonly used outcome measures for foot problems. J Foot Ankle Res. 2010 May 14;3:7.

37. Skovdal Rathleff M, Moelgaard C, Lykkegaard Olesen J. Intra- and interobserver reliability of

quantitative ultrasound measurement of the plantar fascia. J Clin Ultrasound. 2011 Mar-Apr;39(3):128-34.

38. Mahowald S, Legge BS, Grady JF. The correlation between plantar fascia thickness and symptoms of plantar fasciitis. *J Am Podiatr Med Assoc.* 2011 Sep-Oct;101(5):385-9.

39. Woodall JR, Tucci M, Mishra A, Asfour A, Benghuzzi H. Cellular effects of platelet rich plasma: a study on HL-60 macrophage-like cells. *Biomed Sci Instrum*. 2007;43:266–71.

40. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med*. 2011 August;39(10):2135-2140.

41. Ragab EM, Othman AM. Platelets rich plasma for treatment of chronic plantar fasciitis. Arch Orthop Trauma Surg. 2012 Aug;132(8):1065-70.

42. Finnoff JT, Fowler SP, Lai JK, Santrach PJ, Willis EA, Sayeed YA, Smith J. Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. PM R. 2011 Oct;3(10):900-11.

406

407 Table 1. Patient Demographic Characteristics at Enrollment

Characteristics	ACP (n=19)	ESWT (n=19)	Conventional Treatment (n=16)	*P*-value
Age (years)	46 (38, 51)	45 (37, 53)	47.5 (41, 53)	0.833
Gender (Male:Female)	10 : 9	11 : 8	8 : 8	0.891
Side (Left:Right)	8 : 11	8 : 11	10 : 6	0.391
Pain duration (months)	12 (7, 24)	18 (7, 24)	10.5 (6, 16)	0.213
BMI (kg/m^2)	23.4 (21.9, 27.7)	25.3 (23.1, 27.2)	24.7 (22.6, 27.4)	0.606
AOFAS	65 (49, 72)	62 (52, 69)	72 (71, 75)	*0.030*
VAS Pain Score	7 (5, 8)	7 (6, 8)	6 (5, 8)	0.606
Plantar Fascia thickness (mm)	6.4 (5, 7)	5.4 (5, 6)	5.55 (5, 7)	0.126

408 For a binary endpoint, the count and the proportion is reported. For a continuous endpoint, the median and interquartile range is
409 reported.

410

411
412 Table 2. Median and range of VAS pain scores, AOFAS scores, and plantar fascia thickness (mm) at all

413 assessment time points

VAS Pain Scores			
Time Point	ACP	ESWT	Conventional Treatment
Pre-Intervention	7	7	6
	(4, 10)	(5, 8.5)	(3, 8)
1 month	4	5	5
	(1, 10)	(0, 7)	(3, 8)
3 months	4	4	4
	(0, 8)	(0, 7)	(1, 9)
6 months	2	3	3
	(0, 6)	(0, 8)	(0, 7)
AOFAS Scores			
Time Point	ACP	ESWT	Conventional Treatment
Pre-Intervention	65	62	72
	(38, 77)	(44, 79)	(51, 77)
1 month	75	73	75
	(35, 84)	(52, 92)	(55, 82)
3 months	86	85	80
	(67, 100)	(72, 100)	(53, 90)
6 months	90	90	87
	(77, 100)	(72, 100)	(73, 100)
Plantar Fascia Thickness (mm)			
Time Point	ACP	ESWT	Conventional Treatment
Pre-Intervention	6.4	5.4	5.6
	(4.6, 7.9)	(4.4, 8.1)	(4.8, 8.0)
1 month	5.4	5.4	5.6
	(4.0, 6.9)	(3.8, 7.9)	(5.1, 7.6)
3 months	5.3	5.1	5.4
	(3.4, 6.9)	(3.2, 6.8)	(4.4, 6.6)
6 months	4.8	4.9	4.8
	(3.5, 6.0)	(3.6, 7.0)	(3.3, 6.7)

414

Table 3. Median change and interquartile range in VAS pain scores at all assessment time points

Change from baseline *	ACP	ESWT	Conventional Treatment	*P*-value			
				Global	ACP vs Conventional Treatment	ESWT vs Conventional Treatment	ACP vs ESWT
1 month	-2.0 (-3.0, -1.0)	-2.0 (-3.8, -1.0)	-0.75 (-2.0, 1.0)	*0.036*	*0.037*	*0.017*	0.575
3 months	-3.0 (-5.0, -1.5)	-3.25 (-4.5, -2.0)	-1.0 (-3.0, 0.5)	0.053	0.053	*0.022*	0.947
6 months	-5.0 (-6.5, -3.0)	-5.5 (-6.5, -4.0)	-3.0 (-4.0, -2.0)	0.090	0.080	*0.042*	0.791

*Scores at 1, 3 and 6 months minus score at baseline

Table 4. Median change and interquartile range in AOFAS scores at all assessment time points

Change from baseline *	ACP	ESWT	Conventional Treatment	*P*-value			
				Global	ACP vs Conventional Treatment	ESWT vs Conventional Treatment	ACP vs ESWT
1 month	10.0 (0.0, 26.0)	14.5 (4.0, 23.0)	0.5 (0.0, 7.5)	*0.045*	0.062	*0.011*	0.749
3 months	15.0 (12.0, 36.0)	21.0 (13.0, 30.0)	5.0 (3.0, 13.0)	*0.004*	*0.004*	*0.003*	0.986
6 months	36.0 (18.0, 40.0)	28.0 (10.0, 41.0)	15.5 (8.5, 23.0)	0.061	*0.013*	0.187	0.419

*Scores at 1, 3 and 6 months minus score at baseline

Table 5. Median change and interquartile range of plantar fascia thickness (mm) at all assessment time points

Change from baseline *	ACP	ESWT	Conventional Treatment	*P*-value			
				Global	ACP vs Conventional Treatment	ESWT vs Conventional Treatment	ACP vs ESWT
1 month	-0.9 (-1.2, -0.1)	0.2 (-1.0, 0.7)	0.0 (-0.5, 0.2)	*0.042*	*0.015*	0.908	0.056
3 months	-1.2 (-1.6, -0.9)	-0.3 (-1.1, 0.0)	-0.7 (-1.0, -0.1)	*0.020*	*0.014*	0.575	*0.019*
6 months	-1.3 (-1.8, -1.1)	-0.6 (-1.2, -0.1)	-0.6 (-1.3, -1.0)	0.068	0.080	0.934	*0.027*

* Scores at 1, 3 and 6 months minus score at baseline

FIGURE LEGENDS

Figure 1. Median and range of VAS Pain scores in ACP, ESWT and conventional treatment groups at all assessment time points

Figure 2. Median and range of AOFAS score in ACP, ESWT and conventional treatment groups at all assessment time points

Figure 3. Median and range of plantar fascia thickness (mm) in ACP, ESWT and conventional treatment groups at all assessment time points