Original Article

Enhancement of the Effectiveness of Extracorporeal Shock Wave Therapy with Topical Corticosteroid in Treatment of Chronic Plantar Fasciitis: A Randomized Control Clinical Trial

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Abstract

Background: Chronic recalcitrant plantar fasciitis is a disabling condition. We presumed if shock wave could increase the permeability of skin and facilitate penetration of topical corticosteroid through the skin; the combinational therapeutic effect would be stronger than using shock wave alone. The study purpose was to utilize the synergistic effect of shock wave and topical corticosteroid in treatment of plantar fasciitis. **Materials and Methods:** Patients in both groups (n = 40) received four sessions of shock wave with the same protocol at weekly intervals. At 30 min before each session, we used an occlusive dressing of topical clobetasol for the intervention group and Vaseline oil for the control group. Pain severity was assessed with visual analog scale (VAS) and modified Roles and Maudsley score (RMS) at baseline and 1 month and 3 months after intervention. Plantar fascia (PF) thickness was measured with ultrasonography at baseline and 3 months after intervention. **Results:** One month after intervention, VAS morning showed significant improvement in intervention group (P = 0.006) and RMS showed better improvement in intervention group (P = 0.026). There was no significant difference between the two groups after 3 months in RMS or VAS score. PF thickness was decreased significantly in both groups, but it was not significant between the two groups (P = 0.292). **Conclusions:** This combinational therapy yielded earlier pain reduction and functional improvement than using shock wave alone; topical corticosteroid could enhance the effectiveness of shockwave in short-term in the treatment of recalcitrant plantar fasciitis.

Keywords: *Extracorporeal shock wave, plantar fasciitis, transdermal drug delivery*

Introduction

Plantar fasciitis is a common cause of heel pain affecting 10% of the general population.[1] Its etiology is unclear and likely to be multifactorial. It is believed to be the result of an acute or chronic injury, too much tension of the fascia, biomechanical abnormalities of the foot or inflammation of the plantar fascia (PF). The clinical symptoms are pain and tenderness in the medial calcaneal tuberosity on weight bearing. The pain may be severe, resulting in the alteration of daily activities. Heel spur may be present at the origin of the PF.[2]

The typical patient describes symptoms during the first steps after rising in the morning. In most patients, these symptoms vary in intensity and may resolve after a variable period from a few steps to a few hours. In most cases, symptoms then increase as the day progresses.[3]

Chronic recalcitrant plantar fasciitis is a disabling condition and could have a negative impact on patients' quality of life.[1]

Standard treatment for plantar fasciitis is a conservative treatments, such as anti-inflammatory drugs, corticosteroid injections, splints, orthotics, casts, and physical therapy.[4] Corticosteroid injection is a commonly used modality in the management of plantar fasciitis.[5,6] It can provide short term relief,[7] but it has complications, such as plantar fascial rupture, plantar fat pad atrophy, lateral plantar nerve injury secondary to injection, and calcaneal osteomyelitis.[8,9] Fascial rupture and fat pad atrophy are especially serious complications that can lead to intractable complications.

Ninety percent of patients respond to conservative therapy,[10] but about

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10% fail to respond. After unsuccessful conservative treatment, surgery is eventually recommended.[4] Recently, extracorporeal shock wave therapy (ESWT) has been approved by the FDA and recommended for treatment of chronic plantar fasciitis in patients unresponsive to conservative treatment.[11-14] ESWT is a new non-invasive therapeutic modality with good efficacy and safety in the treatment of chronic plantar fasciitis. The complication rates are low and negligible.[15-18]

ESWT induces a cascade of biological responses and molecular changes, including the ingrowth of neovascularization and up-regulation of angiogenic growth factors leading to the improvement in blood supply and tissue regeneration. There is a close relationship between the decrease of substance P release and pain reduction in the treatment of tendon insertion diseases.[19]

Recently, many drug delivery techniques have been introduced using a different form of energy to facilitate absorption of drugs through the skin. Shock wave is thought to act on cells mechanically with three main consequences: cell destruction, cell detachment, and cell permeabilization. The mechanisms which are responsible for the permeabilization of cells are not yet fully understood. However, they are probably based on direct interactions between the pressure wave and the cell or on the generation of cavitation bubbles.[20,21]

Among various options for treatment of chronic plantar fasciitis, ESWT and corticosteroid injection are the most effective ones; therefore, we aimed to utilize the synergistic effect of the shock wave and topical corticosteroid, considering potentiality of the shock wave in the field of drug delivery. Relying on previous studies, we presumed if shock wave could increase the permeability of skin and facilitate penetration of topical corticosteroid through deep layers, the combinational therapeutic effect would be stronger than using ESWT alone.

Materials and Methods

This clinical trial was designed as a randomized, controlled, triple-blind with two parallel groups and randomization with a 1:1 allocation.

Participants

This clinical trial was conducted on patients with clinical diagnosis of plantar fasciitis referred to the physical medicine and rehabilitation clinic of the Alzahra hospital from December 2015 to October 2016.

Diagnosis of plantar fasciitis was made based on the patient's history and physical findings of point tenderness at or near the medial calcaneal insertion of the PF.

Criteria for inclusion were patients older than 18 years with chronic recalcitrant plantar fasciitis (lasting at least 6 months and refractory to conservative treatment). Only patients with Roles and Maudsley score (RMS) of 4 and PF thickness of >4 mm were enrolled in this study. Plantar fasciitis was considered present when the PF thickness was >4 mm with reduced echogenicity.[22-24]

Criteria for exclusion were patients who suffered from diabetes, peripheral neuropathy, coagulopathies, vasculitis, or vascular problems. Patients with any foot and ankle pathology including tarsal tunnel syndrome, instability, arthritis or evidence of malignancy, acute infection, and dermatological problems were excluded from the study. Patients with open growth plate or pregnant ones were not enrolled into this study. Other reasons for exclusion were a history of surgical interventions or recent trauma to the foot and ankle or plantar fasciitis corticosteroid injection in the preceding 6 weeks.

Informed consent was obtained from all patients and the process of treatment and probable side effects were explained completely. The patients were informed that it is possible to quit the study at any time. The protocol of this study was approved by Ethics Committee of Isfahan University of Medical Sciences with the reference number of IR.MUI.REC.1394.3.764.

All patients received plantar fasciitis adjuvant therapy:
- Calf muscle and PF stretching
- Passive dorsiflexion of the toes
- Intrinsic foot muscle strengthening
- Shoes modification like soft medial longitudinal arch support or silicon heel pad (as needed).

The patients were asked to limit physical activity and avoid using nonsteroidal anti-inflammatory drug tablets during the intervention period.

Patients in both groups received four sessions of low energy ESWT with the same protocol at weekly intervals by Storz Medical Duolith SD1 machine (FDA approved this device at January 2016 for chronic plantar fasciitis).
- Focus-SW Shock: 2000 Energy: 0.2–0.3 mJ/mm^2 Frequency: 4 Hz Fixed
- Radial-SW Shock: 3000 Energy: 1.8–3 mJ/mm^2 Frequency: 15H movable.

The point of maximal tenderness was palpated and marked with a skin marker as the target area for shock wave. The procedure was performed in the clinic without anesthesia.

30 min before each shock wave session, we applied topical clobetasol ointment (three fingertip unit) with an occlusive dressing for the intervention group and Vaseline oil with occlusive dressing for the control group.

For adequate saturation of stratum corneum which is an important barrier to transcutaneous drug absorption, we used occlusive dressing to maintain moisture and enhanced absorption capacity of the skin.[25] Furthermore, the skin denuded of the stratum corneum has a greater potential for

allowing drug diffusion,[26] we asked patients to scrub the plantar skin with pumice for safe removal of dead skin and calluses areas before each session. After occlusive dressing, patients hung their feet from examination table for better blood circulation in extremities and increasing absorption of the topical drug.[26] After 30 min of dressing, we cleaned the feet with wet wipe and used coupling gel on the point of tenderness to utilize the shock wave potential for increasing the permeability of the skin.

Pain severity was assessed using visual analog scale (VAS) at baseline and 1 and 3 months after intervention (0 = no pain, 10 = the worst imaginable pain).

We recorded VAS score as follows:

- Heel pain while taking the first steps in the morning (VAS morning)
- Heel pain while doing a daily activity (VAS daily).

Activity limitation due to pain was assessed with the modified RMS 1 and 3 months after intervention. The modified Roles and the Maudsley score is a four-point scale to evaluate the patients' pain in relation to normal daily activities.

1. RMS 1: Excellent quality of life (no symptoms; unlimited walking ability without pain; patient satisfied with the treatment outcome [when assessed after intervention])
2. RMS 2: Good quality of life (ability to walk more than 1 h without pain; symptoms substantially decreased after treatment; patient satisfied with the treatment outcome)
3. RMS 3: Acceptable quality of life (inability to walk more than 1 h without pain; symptoms somewhat better and pain more tolerable than before treatment; patient slightly satisfied with the treatment outcome)
4. RMS 4: Poor quality of life (inability to walk without severe pain; symptoms not better or even worse after treatment; patient not satisfied with the treatment outcome).

We used ultrasonography for diagnosis of plantar fasciitis and measuring PF thickness. It is an effective diagnostic tool by documenting inflammatory findings and fascia thickness. It is non-invasive, cost-effective, and free of radiation.[27] PF thickness is postulated as an objective outcome measure for the assessment of treatment response.[28]

Sonographic examinations were performed bilaterally at baseline and 3 months after intervention with a commercially available scanner (Affinity 70; Philips) and a 5.0–12.0 MHz linear transducer [Figure 1]. All ultrasound examinations were performed by the same radiologist, who was unaware of the patient's group. The patients lay prone with their feet hanging free over the end of the examination table (knee in full extension and ankles in 90° of dorsiflexion). Sagittal imaging was performed with a perpendicular approach, and PF thickness was measured at a standard reference point where the PF crosses the anterior aspect of the inferior border of the calcaneus. PF thickness was measured twice, and the average was recorded to avoid error due to transducer obliquity.

Response to treatment was defined as following by primary outcomes (changes in pain score measured by VAS and RMS) and secondary outcome (changes in PF thickness).

- Changing the modified Roles and Maudsley score to 1 or 2 in follow-up studies[29]
- Score ≤4 on the 11 point scale (VAS) or improvement of more than 50% over baseline in follow-up studies[30]
- Reduced PF thickness; we considered a true reduction in PF thickness to be more than 0.7 mm to eliminate the measurement error.[31]

All patients were followed for any possible side effect or complications such as:

- Possible transient moderate increase in pain
- Redness and swelling
- Hematoma and petechial hemorrhage
- Short-term hypesthesia.

Considering type I error (alpha) of 0.05 and study power of 90%, the sample size was calculated as at least forty patients in each group of intervention and control.

We used for randomization the GraphPad software (GraphPad software, Inc., California, USA) to generate random numbers with a 1:1 allocation. For concealment, the project assistant defined groups as A and B (Intervention: A and Control: B); no one except the assistant was aware of this coding.

This study is a triple-blind clinical trial. To reduce the bias, the project assistant packed clobetasol and Vaseline oil in new similar containers with coding A (clobetasol) and B (Vaseline oil). Neither patients nor the people who involved in this project (PM and R resident, radiologist and analyzer) were aware of the coding. Only after data analyses, decoding was done.

Data were analyzed using the SPSS Statistics 20 for windows (SPSS Inc., Chicago, IL, USA).

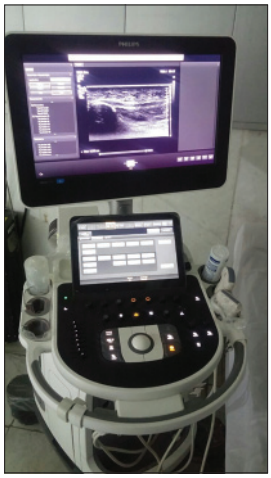

Figure 1: Ultrasound examination of plantar fasciitis

Descriptive analyses are presented as mean ± standard deviation or number (%).

We used Chi-squared and independent *t*-test for sex, BMI and age.

We used Fisher's exact test and Chi-squared test to compare the treatment success regarding RMS, VAS, and fascia thickness between the two groups.

Paired samples *t*-test was used to assess the PF thickness before and after intervention. Independent *t*-test was used for detecting any significant differences in PF thickness between the two groups.

A $P \leq 0.05$ was considered statistically significant in all analyses.

Results

Patients' baseline characteristics are summarized in Table 1. There was no significant difference between the two groups ($P > 0.05$).

The total number of 80 patients were randomized into intervention and control groups.

Patients' flow diagram from enrollment to analyses is on Figure 2.

Treatment success was calculated as follows:

The number of patients who recover regarding our improvement criteria divided by the total initial number of patients in each group; 1 and 3 months after intervention.

One month after the intervention, RMS score showed better improvement in the intervention group compared to control group (65% vs. 40%, $P = 0.026$), but there was no significant difference in RMS improvement between the two groups after 3 months ($P = 0.351$).

One month after intervention, VAS morning score showed significant improvement in intervention group compared to control group (75% vs. 45%, $P = 0.006$), but there was no significant difference between the two groups after 3 months ($P = 0.135$).

There was no significant difference between the two groups regarding the VAS daily score 1 month ($P = 0.653$) and 3 months after intervention ($P = 0.351$).

Table 1: Patients' baseline characteristic

Characteristic	Intervention (*n*=40)	Control (*n*=40)	*P*
Sex (%)			
Females	34 (85)	32 (80)	0.558
Age (year)	51.4±6.9	48.1±8.9	0.067
BMI (kg/m²)	28.5±3.4	29.7±3.3	0.113
PF thickness (mm)	5.17±0.73	5.24±0.5	0.618

Data are presented as mean±SD or *n* (%). SD: Standard deviation, BMI: Body mass index, PF: Plantar fascia

Three months after intervention, PF thickness decreased (>7 mm) in 55% of the intervention group and 60% of control group, the difference was not significant ($P = 0.653$).

Comparison of treatment success in both groups regarding VAS (morning and daily), RMS and PF thickness are shown in Table 2.

There was no significant difference in compression of PF thickness between the two groups at baseline ($P = 0.618$) and 3 months after intervention ($P = 0.292$) but PF thickness was decreased significantly ($P = 0.001$) in both groups after intervention compared with baseline [Table 3].

One month after intervention, patients with RMS 4 (refractory, since our inclusion criteria were RMS 4) or the ones who get worst were excluded from the study to receive another therapeutic option. The percent of refractory patients was not statistically significant between the two groups ($P = 0.501$).

Three months after intervention, RMS improvement (defined as RMS 1, 2) was 70% in intervention group and 60% in control group, the difference was not significant ($P = 0.351$).

Recurrence was defined as regression of RMS to 3 or 4 after primary improvement in RMS.

The recurrence rate was not statistically significant between the two groups ($P = 0.398$).

The patients' RMS distribution is summarized in Table 4.

Side effects

In follow-ups for evaluating side effects or complications, some people reported of transiently increased pain after shock wave therapy. We did not have any report of hematoma, swelling or any serious complications.

Discussion

Among various options for treatment of chronic plantar fasciitis, ESWT, and corticosteroid injection are the most effective ones.

To the best of our knowledge, this study would be the first one which evaluates the combinational effect of ESWT and a topical corticosteroid, considering potentiality of the shock wave in the field of drug delivery. Shock wave was performed on painful heels to take advantage of its therapeutic effect on plantar fasciitis and also to penetrate topical clobetasol through the deep layers with mentioned below possible mechanisms; cavitation and disruption of stratum corneum.

As previously stated, many drug delivery techniques have been introduced that using a different form of

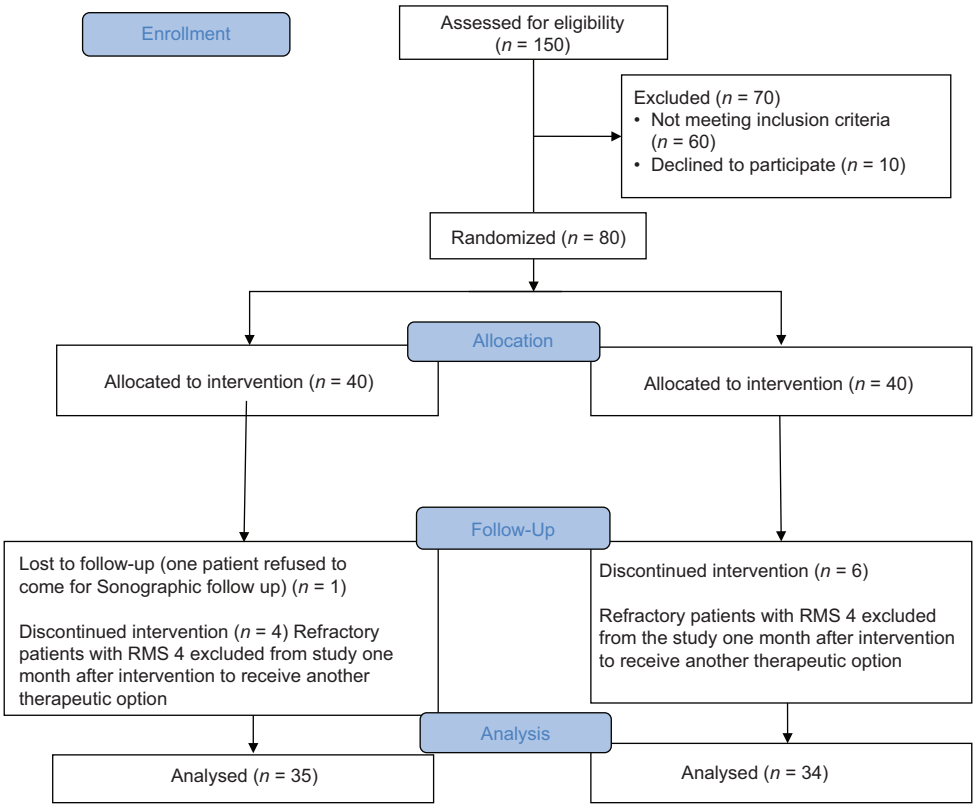

Figure 2: Patients' flow diagram

Table 2: Comparison of treatment success in both groups regarding visual analogue scale score, modified Roles and Maudsley score and plantar fascia thickness

Treatment success	1 month after treatment (*n*=40)		*P*	3 months after treatment (*n*=40)		*P*
	Intervention, *n* (%)	Control, *n* (%)		Intervention, *n* (%)	Control, *n* (%)	
RMS[a]	26 (65)	16 (40)	0.026	28 (70)	24 (60)	0.351
VAS morning[b]	30 (75)	18 (45)	0.006	32 (80)	26 (65)	0.135
VAS daily[c]	24 (60)	22 (55)	0.653	28 (70)	24 (60)	0.351
PF thickness[d]				22 (55)	24 (60)	0.653

Data are presented as *n* (%). [a]Changing the RMS to 1 or 2 in follow up studies. [b,c]If score was ≤4 on the 11 point scale (VAS) or improvement of >50% over baseline in follow up studies. [d]PF thickness reduction >0.7 mm. RMS: Roles and Maudsley score, VAS: Visual analogue scale, PF: Plantar fascia

Table 3: Comparison of the plantar fascia thickness between the two groups and before and after intervention in each group

PF thickness	Baseline	After 3 months	*P*[a]
Intervention	5.17±0.73	4.51±0.98	0.001
Control	5.24±0.50	4.31±0.68	0.001
P[b]	0.618	0.292	

Data are presented as mean±SD. [a]*P* value before and after intervention in each group. [b]*P* value between the two groups. SD: Standard deviation. PF: Plantar fascia

energy to facilitate absorption of drugs through the skin. Iontophoresis and phonophoresis are emerging technologies capable of enhancing drug penetration through the stratum corneum that is the principal barrier to percutaneous absorption.[32-34]

A pressure wave or shock wave can facilitate the delivery of macromolecules in the epidermis and deep into the dermis through disruption of the hydrophilic domains of the stratum corneum.[20] Shock waves have been shown to cause a transient increase in the permeability of the cell membrane *in vitro* and *in vivo*. The mechanism of permeabilization is probably based on the generation of cavitation bubbles.[20,21] In addition, recent studies have demonstrated ultrasound cavitational effect leading to reduced skin barrier efficiency.[35,36] Cavitation does not lead to cell death and enables the transfer of large molecules into the cells. Some of the energy from cavitation is transformed into other forms of energy such as heat, shock waves, or hydrodynamic shear fields, which can disrupt biological tissues and facilitate diffusion.[37,38]

Table 4: Patients' modified Roles and Maudsley score distribution at the end of study

RMS distribution	Refractory[a] (%)	Recurrence[b] (%)	RMS 3[d] (%)	Improvement[c] (%)
Intervention (*n*=40)	4 (10)	4 (10)	4 (10)	28 (70)
Control (*n*=40)	6 (15)	2 (5)	8 (20)	24 (60)
P	0.501	0.398	0.213	0.351

Data are presented as *n* (%).[a]1 month after intervention, patients with RMS 4 or the ones who get worst (refractor) were excluded from the study to receive another therapeutic option. [b]Recurrence was defined as regression of RMS to 3 or 4 in follow up studies after primary improvement in RMS. [c]Changing the RMS to 1 or 2 in follow up studies. [d]Not met our improvement criteria. RMS: Roles and Maudsley score

Permeabilization of tumor cells using shock waves provides a useful tool for introducing molecules into cells which might be of interest for drug targeting in tumor therapy *in vivo*.[21] Enhancement of chemotherapeutic effects with focused shock waves seems to be as a result of increased intracellular concentration of the agent.[37] Furthermore, needle-less vaccine delivery using micro-shock waves seems promising.[39]

One month after the intervention, VAS morning and RMS decreased significantly in the intervention group due to the synergistic effect of shock wave therapy and topical corticosteroid, but 3 months after intervention, the results were not significantly different between the two groups.

The expected mechanism for better improvement in short-term is that shock wave had facilitated delivery of topical clobetasol from saturated stratum corneum through deep layers. Further research with a larger sample size is needed for clarifying this issue; reproducible results are valuable. In a study about corticosteroid iontophoresis, Gudeman *et al*. found that dexamethasone iontophoresis is effective in improving pain immediately after treatment, but not more than placebo in the longer term.[40]

VAS morning decreased more significantly than VAS daily in intervention group. This is probably on account of VAS morning is less correlated with patients' physical activity and environment factors.

We found comparable long-term results between the two groups evident by both subjective and objective measures. This could be the result of long-term biological effects of shock wave or patients spontaneous recovery.

Maier *et al*. showed that the initial burst of pain came from an increase of release of substance P. However this initial release is followed by a subsequent decrease in levels of substance P within 24 h. This reduction in substance P release lasts for over 6 weeks and may go on as long as 2 years.[41] This study suggests that shock wave effects could be started within a few hours and continue for a long time. Obliviously, this time frame varies from patient to patient.

Chronic recalcitrant plantar fasciitis is a disabling condition and has a negative impact on patients' quality of life. This combinational therapy is effective in reducing pain expeditiously in short-term and it is worthwhile for these patients.

This study has shortcomings to its novelty. We cannot compare our results to previous investigations since this study was conducted for the first time.

We did not use medication gel because its impact as a changed conductive medium on shock wave penetration was not clear. The aim was to take advantage of shock wave effects both therapeutic and drug delivery potential rather than just transferring medication like phonophoresis, that is why we used the occlusive dressing for saturating the stratum corneum instead of medication gel. The effect of medication gel on shock wave should be addressed in future studies. We used both radial and focus probes. Comprehensive studies are needed to perform with different shock wave protocols to define the most appropriate shocks, sessions, and intervals as they are still not defined precisely.

Conclusions

The study shows that combination of ESWT with topical corticosteroid yielded earlier pain reduction and functional improvement than using shock wave alone; topical corticosteroid could enhance the effectiveness of shock wave in short-term in the treatment of recalcitrant plantar fasciitis.

Using topical corticosteroid does not require extra equipment or cost and easily applied. In addition, it is without serious side effects of corticosteroid injection such as PF rupture or heel pad atrophy.

The combination of ESWT with topical corticosteroid is a novel idea and further comparative studies are required.

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Conflicts of interest

There are no conflicts of interest.

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