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A Pilot Study on the Effectiveness of a Novel Herbal Patch for the Treatment of Plantar Fasciitis

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Abstract: The study was to evaluate the safety and anti-inflammatory effects of a herbal patch. The formula of the herbal patch included three herbs *Flos Carthami* (紅), *Radix Dipsaci* (續斷), *Rhizoma Rhei* (大黃) and *Borneolum Syntheticum* (冰片). 10 subjects suffering from chronic heel pain were recruited. The herbal patch was applied to the heel for 6 weeks. The Pain score Visual Analogue Scale (VAS) and Foot Function Index (FFI) questionnaires were conducted to measure pain and disability. Blood was taken to measure the inflammatory cytokines (IL-8 and hs-CRP). All the assessments were processed on before and after the treatment intervention. After treatment, the pain score and foot function index were remarkably improved. Inflammation Cytokine IL-8 was decreased. The novel herbal patch used in this pilot study had laboratory evidences of anti-inflammation and pro-angiogenesis. The primary results indicated that the study herbal patch is safe and can be an alternative to treatment in plantar fasciitis. With its mildly penetrative property, it could be a suitable additional tool for patients' self-care.

Keywords: Plantar Fasciitis, Herbal Patch, Anti-inflammatory Effects

1. Introduction

The plantar fascia is a thick triangular aponeurosis spreading from its origin at the calcaneous, outwards along the metatarsal rays to the digital areas of the toes. Inflammation is very common and the inflamed sites are the origin and insertions of the fascia. Plantar fasciitis is the most common cause of heel pain and accounts for 15% of foot disorders [1]. In US it is estimated that 2 million people suffer from plantar fasciitis and require treatment [2]. Treatment of this common condition includes the use of systemic anti-inflammatory agents or local injection of steroidal compounds.

Plantar fasciitis usually starts as an acute inflammation at the proximal attachment of the plantar fascia. The inflammation turns chronic and subsides into "fiber fragmentation" in association with myxoid degeneration [3]. Predisposing causes include foot arch abnormalities causing increasing tension on the plantar fascia, over-weight, work related prolonged standing and degenerative changes [4]. Our previous experimental studies demonstrated that the herbal patch was effective in the promotion of fracture healing, pain relief and anti-inflammation. Clinically heel pain with exacerbation on standing is the major presentation. Ultrasonic investigation might indicate thickening of the plantar fascia at its calcaneal attachment [5]. Radiological detection of a calcaneal bone spur might not be a proof of the pathology.

Management for plantar fasciitis is simple and straight forward: including anti-inflammatory drug administration, physiotherapy with mechanical stretching, shock wave, or local steroidal injections. However, recurrences are common, and many cases may turn chronic [6]. Orthosis and night splints might help, but again, relief tends to be partial. Local topical application of drugs is usually considered useless and futile.

The purpose of this pilot study is to observe the safety and efficacy of the herbal patch regarding its anti-inflammatory in terms of pain control and tenderness of the plantar fasciitis and the change of fascia thickness.

2. Methods

2.1. Investigational Agent

Chinese herbs have been commonly used as topical agents in musculo-skeletal injuries by traditional bone setters. Our early studies, using 4 herbs with well-known anti-inflammatory and proangiogenic activities, viz. *Flos Carthami* (紅花), *Radix Dipsaci* (續斷), *Rhizoma Rhei* (大黃) and *Borneolum Syntheticum* (冰片), have shown and proven their pharmacological effects in *in-vitro* and *in-vivo* experiments [7]. We selected *Rhizoma Rhei* (大黃), and *Radix Dipsaci* (續斷) because their bioactive compounds were found capable of penetrating through the skin into the deeper tissues to exert their therapeutic effects. Our previous study also demonstrated that *Flos Carthami* (紅花) could strongly promote anti-inflammation effects. *Syntheticum Borneolum* (冰片) is one of the common enhancers to facilitate the transdermal transport of topical herbal agents. It was therefore used as a 2.0% supplement in the formula as an enhancer. There is sufficient evidence that the topical application would send chemical molecules across the skin barrier to reach deeper tissues and general circulation as was indicated in the analysis of the standard chemical markers unique for the herbs [8].

The herbal patch was manufactured from the three herbal extracts and *Borneolum Syntheticum* (冰片), and laid onto a self-adherent fabric carrier to produce a herbal medicinal patch for the topical treatment of Plantar fasciitis.

2.2. Study Design

A self-control pilot study was designed to observe the effectiveness of the topical treatment for plantar fasciitis using the herbal patch. Patients suffering from unilateral or bilateral heel pain diagnosed as plantar fasciitis and treated at the orthopaedic clinic and podiatrist clinic of the Prince of Wales Hospital were recruited on a voluntary basis. All volunteers had heel pain for more than 30 days. Proper consent declarations were signed. Patients with foot ulcerations and known to be allergic to herbs were excluded. The participant received ultrasonography to measure the thickness of fascia which further confirmed the pathology of plantar fasciitis.. The Foot Function index questionnaires were conducted to measure pain and disability. 8 ml blood was taken to measure the inflammation cytokines. All the assessments were processed before and after the treatment intervention. During the treatment period, a self-administrated diary was used to record the pain in visual analog scale and compliance.

Assessment criteria included Foot Functional Index for foot pain and disability [9, 10], ultrasonography for the swelling at the plantar fascia and serum inflammation cytokines. The pilot study was designed for a total of 10 patients. Two patients who suffered from chronic heel pain diagnosed as plantar fasciitis (case 1 for 4 weeks and case 2 for 156 weeks) did not receive any pharmaceutical treatment at the time of recruitment were chosen for this report because they represented the shortest and longest clinical duration in this cohort.

2.3. Recruitment

The patients were required to keep the self-adherent medicinal patch in contact with the heel for more than 6 hours per days, and the patch should be renewed every day. The two patients followed completely the requirements for 6 weeks. Follow up visits and checkups were given every two weeks, when pain score and foot functional index were taken.

Patients suffering from unilateral or bilateral plantar fasciitis diagnosed and treated at the orthopaedic clinic and podiatrist clinic were recruited on a voluntary basis. Proper consent declarations were signed. Inclusion criteria included:

a) Unilateral or bilateral plantar fasciitis
b) Male and female volunteers
c) Ages of 18 to 65 years old
d) Had plantar fasciitis of one or both feet for more than 4 weeks
e) Signed informed consent

Patients with foot ulcerations and known to be allergic to herbs were excluded.

a) Patients with ulcerations
b) Allergic to herbs and bandage
c) Taking any investigational drugs in the past 30 days
d) Pregnancy or breast feeding

Patients were free to withdraw from the study at any time without giving a reason. The investigator could also withdraw patients from the trial if they deemed it appropriate for safety or ethical reasons or if it was considered to be to be detrimental to the well-being of the patient. Patients who withdrew or were withdrawn underwent a final evaluation.

2.4. Study Procedures

The participant performed ultrasonography to measure the thickness of fascia. The Foot Function index questionnaires were conducted to measure pain and disability. 8 ml blood was taken to measure the inflammation cytokines. All the assessments were processed on before and after the treatment intervention.

2.5. Efficacy and Safety Variables

The efficacy outcomes were pain and foot function index (FFI) as measured by Visual Analogue Scale (VAS) (0-10 point scale) and the Foot Function Index (FFI) questionnaire (0-9 point scale), and plantar fascia thickness, measured by ultrasound at baseline and the 6th weeks.

Visit 1 (Day 1)	Consent signing Confirmation of inclusion US imaging Pain scales Visual Analogue Scale (VAS) Foot Function Index (FFI), Mapping site of pain & tenderness, Patch on foot heel

	(onto the calcaneal insertion of the plantar fascia) Blood taking for TNF-α test and Inflammation cytokine
Visit 2 (Day 22)	Assessment (Research staff)
Visit 3 (Day 43)	Mapping site of pain & tenderness US imaging, Blood test (TNF-α and Inflammation cytokine) Foot Function Index (FFI) Visual Analogue Scale (VAS)

2.5.1. Ultrasound Measurement

All patients were evaluated through high resolution Ultrasound imaging, to measure the thickness of plantar fascia in the affected and the sound sides. The thickness of the plantar fascia was measured at the thickest portion from the base of the medial calcaneal tubercle where a bright echogenic linewas easily visible.(Figure 1)

Plantar fascia thickness was measured by diagnostic ultrasonography at a standard location where the fascia crosses the anterior aspect of the inferior calcaneal border (Figure 2).

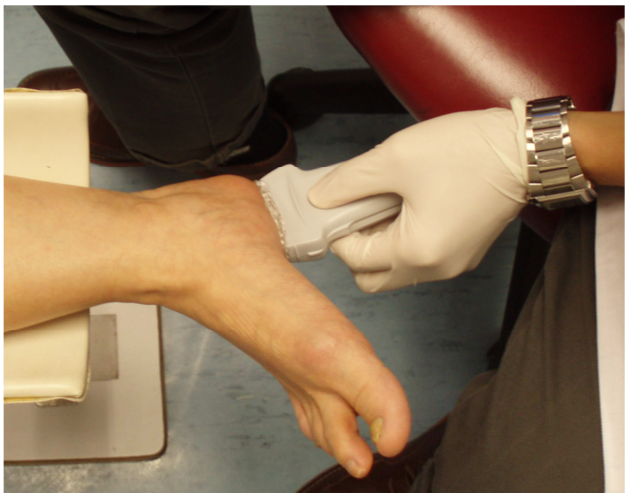

Figure 1. *Ultrasound measurement.*

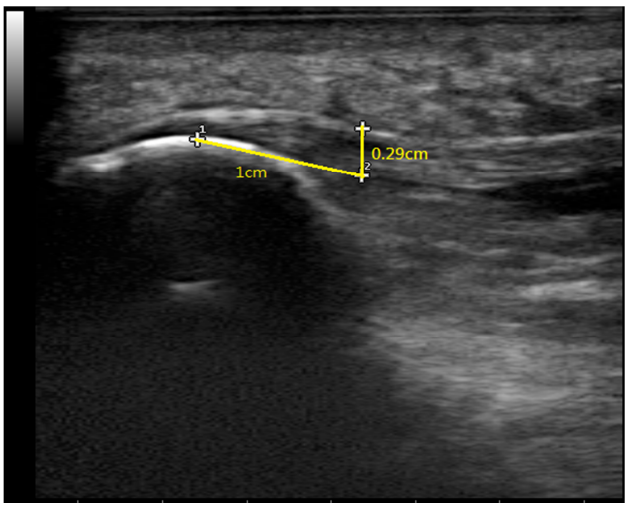

Figure 2. *Thickness of the plantar fascia was measured 1cm from the base of the medial calcaneal tubercle.*

2.5.2. Visual Analog Scale (VAS) and Foot Function Index (FFI) Evaluation

Patients were requested to assess pain every day before (i.e., at baseline) as well as Day 1, 22 and 43 after treatment. The Visual Analogue Scale score and Foot Function Index (FFI) were used.

The Visual Analogue Scale (VAS) was a horizontal, 10 cm-long line with the phrase “no pain” on the left side (score: 0) and the phrase “pain as bad as it could be” on the right side of the line (score: 9). Patients were asked to place a hatch mark on the line that corresponds to their current level of pain. The distance between the phrase “no pain” and the hatch mark was used as linear measure of the VAS score. All patients scored substantial pain of at least 5 or greater on the Visual Analogue Scale at baseline.

The FFI was a questionnaire designed specifically for ankle and foot symptoms. It included 23 items that were divided into three subscales: activity limitation (5 items), disability (9 items), and pain (9 items). Every question was answered on a visual analogue scale for conversion to scores ranging from 0 to 9. The higher the score, the more severe the pain or restriction. [3, 4, 5]

2.5.3. Treatment Procedure

Eligible patients were treated with a paste containing extracts of the herbs under study (消炎贴) in the form of a standard patch on the heel (to the calcaneal insertion of plantar fascia) for maximum 6 weeks or until pain disappears, 8 hours per day. The herbal patch was changed daily.

Table 1. showed the schedule of examinations and procedures.

Table 1. *Schedule of examinations and procedures.*

Visit	1	2	3
Day	1	22	43
Confirmation of inclusion	X		
Informed Consent	X		
Pain & tenderness measurement	X		X
Foot Function Index (FFI)	X		X
Image assessment*	US		US
TNF-α	X		X
Inflammation cytokine	X		X
Clinical Photo	X		X
Questionnaire	X		X
Adverse Events		X	X
Dispense study drug	X	X	

*US: Ultrasound.

2.6. Data Analysis

Paired Student t-test was used to analyse the changes in pain score and Image changes of the plantar fascia after treatment and inflammation if distribution of the data is normal, otherwise Wilcoxon signed-ranks test was used instead.

Differences of post-treatment and baseline with an error probability of less than 5% ($p<0.05$) for two-sided were considered statistically significant.

The statistical analyses were made with SPSS for Windows 18.0.

3. Results

3.1. Study Population

All individuals with recalcitrant PF visiting our Orthopaedics & Traumatology specialist outpatient clinic from October 2013 to January 2014 were evaluated. 10 subjects aged 18 to 65 and suffering from Plantar Fasciitis were recruited from Orthopaedics & Traumatology specialist outpatient clinic at Prince of Wales Hospital. Baseline characteristics of patients were shown in Table 2. The study procedures, potential risks and benefits of the treatment were explained to eligible subjects and after fully understood the nature of the study, written informed consent was obtained.

3.2. Participant Flow

Ten subjects were screened and all of them were eligible for the pilot study. No subject withdrew during study period. (Fig. 3)

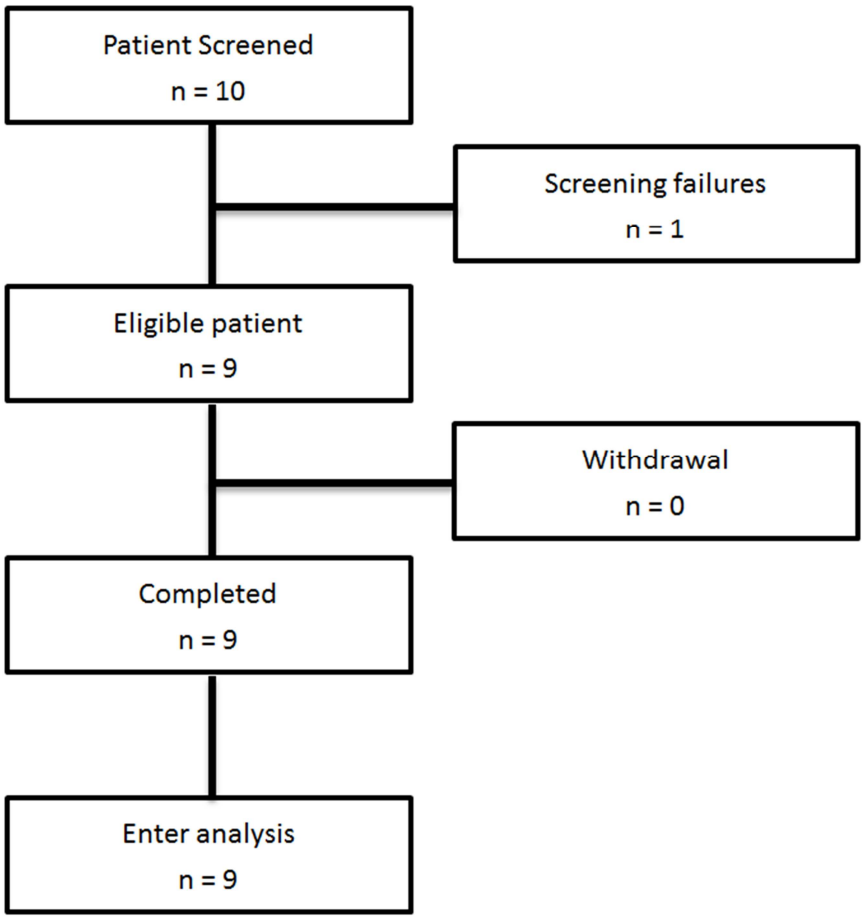

Figure 3. *Flow Chart of Plantar fasciitis.*

Table 2. *Patient baseline characteristics.*

	Subject N=9
Sex	
M	2
F	7
Age (Range)	57.3 (51-65)
BMI	24.94 (21.6-29.35)
Pain Duration (week)	46.5 (4-156)
Plantar Fasciitis	
Unilateral	7
Bilateral	2
Continual Standing or Walking Work	3
Analgesic Drug for PRN usage	5

3.3. Visual Analogue Scale (VAS) Heel Pain Scoring

The primary end point was the success rate defined by a minimum of 50% reduction in visual analogue scale (VAS) compared with baseline. Success was determined independently for pain at first steps in the morning.

Table 3. *Visual Analog Scale Heel Pain Scoring in the Morning-Individual Scoring.*

Subject No	Baseline	D1	D7	D14	D21	D28	D35	D42
PF001	**2**	**Missing**	**Missing**	**Missing**	**Missing**	**Missing**	**Missing**	**Missing**
PF002	10	2	0	0	0	0	0	0
PF003	5	8	5	5	5	5	3	2
PF004	1	2	2	2	2	1	1	1
PF006	7	6	5	5	4	4	4	4
PF007	3	3	3	3	2	0	0	0
PF008	7	6	5	2	2	2	2	2
PF009	4	2	3	1	1	1	1	1
PF010	6	5	5	4	7	6	4	3
Mean±SD	5.4±2.8	4.3±2.3	3.5±1.9	2.8±1.8	2.9±2.3	2.4±2.3	1.9±1.6	1.6±1.4
P value*	--	0.351	0.167	0.074	0.098	0.040	0.013	0.008

*compared with baseline.

As shown in Table 3 there were highly significant differences after 4 weeks (Day 28) of treatment for outcome measures (VAS), with much better improvement in the pain scoring as compared to the baseline (Fig. 4).

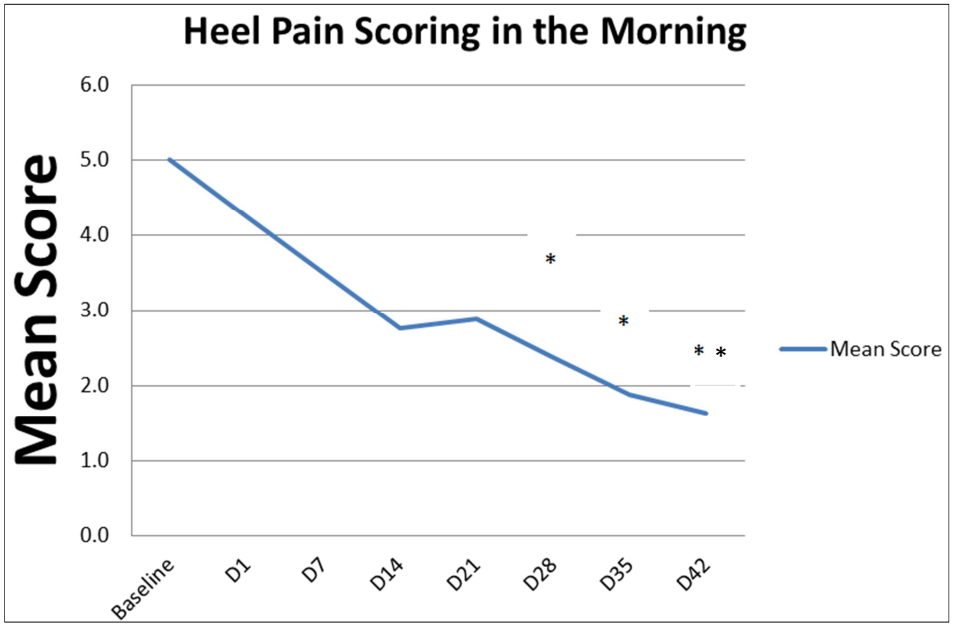

Figure 4. *Change from baseline to 6 weeks after treatment in VAS pain mean scores (*p<0.05;**p<0.01).*

3.4. Ultrasound Measurement and Foot Function Index (FFI)

Table 4 presented the results for the outcome of plantar fascia thickness (measured by ultrasound). Reduction in plantar fascia thickness was remarkable (10% reduction) after 6 weeks herbal patch treatment although it did not attain the statistical significance (p=0.076).

Table 4. *Ultrasound and foot function index Measurement.*

	Pre (n= 9)	Post (n=9)	p-value
Ultrasound swollen thickness (cm)	0.401 (0.032)	0.359 (0.042) (-10%)	0.076
Foot Function Index			
Pain	53.22 (21.554)	29.77 (15.163)	0.001
Difficulty	45.47 (17.056)	20.68 (16.877)	0.001
Activity Restriction	28.81 (19.492)	13.99 (15.358)	0.018
Total Score	42.49 (16.933)	21.48 (11.902)	0.001

Foot Function Index (FFI) including pain, difficulty, activity restriction and total score was significantly decreased after six-week treatment when compared with baseline (p<0.01). (Table 4)

3.5. Blood Assessment

Table 5. *Cytokine IL-8 and hs-CRP test results.*

Subject No	IL-8 (pg/mL)		hs-CRP	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
PF001	4.5	4.6	6.39	4.29
PF002	4.9	<=3.6	3.18	2.15
PF003	5.0	<=3.6	1.61	4.54
PF004	3.7	<=3.6	63	62
PF006	<=3.6*	<=3.6	1.01	2.23
PF007	4.2	<=3.6	1.16	2.14
PF008	4.5	<=3.6	63	1.10
PF009	5.5	<=3.6	1.02	85
PF010	5.7	<=3.6	31	32
Mean	4.7 ± 0.6	--	1.63±1.87	1.86±1.54

*undetectable.

Blood analysis was performed and hsCRP, Cytokines (IL-1 beta, IL-8, IL-6, IL-10, IL-12) and TNF-alpha were tested at pre- and post-treatment. Because of the localized inflammatory disease of foot, all the tested inflammatory cytokines in plasma were very low and most of them were undetectable (<=3.6). Only IL-8 and hs-CRP were detectable, however, after treatment, IL-8 was undetectable in most subjects and no difference was observed in hs-CRP when compared with pre-treatment (p=0.601). (Table 5)

3.6. Concomitant Medication

Each subject was required to record the drug name and frequency of use every day. Table 6 was the status of concomitant medication during the study period.

Table 6. *Concomitant medication.*

Subject No	% of drug use day*	Drug name
PF001	10%	Diclofenac
PF002	0%	
PF003	33%	Diclofenac
PF004	0%	
PF005	52%	Celecoxib
PF006	5%	Diclofenac
PF007	90%	Voltaren
PF008	0%	
PF009	0%	
PF010	2%	NSAIDS

*(day of drug use ÷ study period 42 days) × 100%.

Table 6 shown that six of the ten subjects used anti-inflammation drug, most of them were light users (frequency from 2% to 33%), and only two subjects were heavy users of the anti-inflammation medication (52% and 90%). None of the participant increased anti-inflammation drug intake during the study period.

3.7. Safety Evaluation

The study herbal patch was well tolerated by all the patients. None of the patients experienced any side effects or adverse reactions, such as pain increase or skin irritation/sensitization.

4. Discussion and Conclusions

The plantar fascia is a thick fibrous tissue on the bottom of the foot that protects sensitive plantar structures such as nerves, vessels, muscles, and tendons, and in addition, is responsible for maintaining the plantar arch. Plantar fasciitis (PF) is defined as a tensile overload of the plantar fascia at its origin on the medial tubercle of the calcaneus [6].

The symptoms usually start as a dull intermittent pain that most often progresses to a sharp persistent pain. The patient typically suffers pain with the first steps in the morning or after period of prolonged sitting. Standard care at present is conservative treatment, but about 10% of patients fail to respond or heal spontaneously [7]. This extremely painful condition has been reported to effect up to 20% of the general population over their lifetime [8].

PF is considered a self-limiting condition. It may require a resolution time ranging from 6 to 18 months and sometimes even longer which can lead to frustration on both, the physician and the patient [9, 10.]. In this study the subjects before entered the study had suffered from the pain for 41.6 weeks (Table 2). Six weeks after herbal patch the pain had decreased by 64%. The 6-week herbal patch administration could significantly improve the pain score, pain estimation on the visual analogue scale had improved significantly after herbal patch administration. When the difference in pain scores was compared between the baseline and post-treatment at week 4, week 5 and week 6, the improvement was statistically significant (Table 3). The study indicated that the herbal preparation is beneficial for pain control. In addition, the results for plantar fascia thickness reported in the study supporting the anti-inflammation effects, in which plantar fascia thickness was shown to remarkably decrease after 6 weeks treatment (Table 4).

The results of this trial suggest that measuring plantar fascia thickness (with ultrasound) is a useful objective method for monitoring the progress of treatment. Thickening of the plantar fascia (more than 4 mm) is a well-established sonographic criterion for the diagnosis of plantar fasciitis [11]. According to our results, there was a reduction in mean plantar fascia thickness although it did

not attain statistical significance (p=0.076) because of the small sample size.

Blood test results showed that all the tested inflammatory cytokines in plasma were very low and most of them were undetectable (<=3.6). Only IL-8 was detectable before treatment (4.7 pg/mL), however, after treatment, it was undetectable in most subjects (Table 5). IL-8 is known to be associated with inflammation [12, 13]. IL-8 and the related cytokines are produced in several tissues upon infection, inflammation, ischemia, trauma etc., and are thought to be the main cause of local neutrophil accumulation [14]. This preliminary result might indicate the anti-inflammation effects of the study herbal patch.

Our study had several limitations. The first limitation was the small sample size that limited the power of the study. Secondly, the lack of a control group and unblinded study might introduce expectation and assessment bias. And lastly, anti-inflammation medications were not washed out before enrollment. However, we recruited only chronic patients who had failed anti-inflammation treatment prior to participation and none of the participant increased anti-inflammation intake during the trial. Six of the ten subjects used anti-inflammation drug, most of them were light users (frequency from 2% to 33%), and only two subjects were heavy users of the anti-inflammation medication (52% and 90%).

5. Conclusion

We believe that the study herbal patch is safe and can be an alternative to treatment in plantar fasciitis, not responsive to conservative means although it was involved a small number of patients with a short treatment period. The findings of this pilot study can be relevant in clinical practice.

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