

Focused shock wave therapy in chronic plantar heel pain a randomized Placebo controlled trial,.

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## INTRODUCTION

Plantar fasciitis is the most common cause of heel pain and accounts for approximately 11 to 15 percent of all foot symptoms requiring professional care in the adult <sup>1-3</sup>. The course of disease is typically self-limiting, and about 90 percent of patients are successfully treated with conservative measures <sup>1,2,4</sup>. The self-limiting character of the disease also explains the relatively high success rates observed in the placebo arm of double-blind, randomized controlled trials <sup>1-7</sup>. Nevertheless, the remaining patients enter a state of recalcitrant painful

heel syndrome, often requiring operative intervention <sup>1,2,4,5</sup>. Thereby, operative treatments like fasciotomy have shown promising results but are often associated with long recovery times, and especially athletes seek for alternative treatment modalities allowing continued training <sup>1,2,4,5</sup>.

Extracorporeal shock wave therapy (ESWT) has been introduced for the treatment of recalcitrant painful heel syndrome as an alternative to surgery, allowing fast recovery times without the necessity of reduced weight-bearing or immobilization <sup>8-12</sup>. However, randomized controlled trials assessing ESWT in chronic painful heel syndrome have revealed contradictory results, and the clinical effectiveness has been discussed controversially <sup>2,9,13-19</sup>. By reviewing the published trials it becomes obvious that the different treatment parameters of ESWT are of utmost importance for the outcome of treatment <sup>8-10,14,17</sup>. In this respect, especially the application of local anesthesia has been shown to reduce efficacy <sup>20,21</sup>. Furthermore, higher energies have been associated with greater pain reduction <sup>9,11,22</sup>. It becomes apparent that pooling data of different treatment protocols in meta-analyses or systematic reviews is critical <sup>7,8,10</sup>. Therefore, in assessing the effectiveness of ESWT in plantar fasciitis, only specific treatment protocols should be evaluated and results could not be generalized.

ESWT has been introduced into medicine as a cost-effective and easy to apply shock wave technology <sup>23,24</sup>. It's an alternative to invasive interventions. Shock waves are generated by transforming kinetic energy into acoustic energetic shock waves <sup>23,24</sup>. Compared to radial shock waves, the focused shock waves show deeper tissue penetration with significantly higher energies concentrated to the ROI <sup>3,23-26</sup>. This article reports on a randomized controlled and double-blinded FDA study evaluating the efficacy and safety of focused ESWT in patients with chronic painful heel syndrome.

## **METHODS**

### **Study design and follow-up**

This double-blind, randomized, placebo-controlled trial with parallel group design was conducted internationally at 5 study centers in the United States. A total of 250 patients were randomly assigned to receive either ESWT or placebo treatment with concealed allocation in permuted blocks of four to eight, stratified by treatment center, with the use of a computer-generated random list. Both patients and assessing physicians were blinded to randomization as well as the blinded evaluating physician. The trial was conducted as a FDA approval study. In designing the study we adhered to the standardized guidelines of good clinical practice (GCP) from the International Conference on Harmonization ICH <sup>27,28</sup>.

After applying shock wave or placebo treatment, patients were followed until the end of the follow up 1 period (12 weeks after the last shock wave treatment). At this visit, the participants' response to treatment was rated and patients who showed sufficient response on a clinically relevant level continued entered the follow up 2 phase which ended 12 months after the last ESWT.

### **Subjects**

Patients were recruited from the participating study sites and from community-based referring physicians (primary care physicians, podiatrists, orthopedic surgeons). The study was approved by the FDA and the responsible independent institutional review boards. Written informed consent was obtained from all participants. A total of 495 patients with plantar heel pain were screened, 250 patients fulfill the inclusion criteria and were enrolled in the study.

**Inclusion criteria**

See table below.

**Study procedures**

ESWT or identical placebo were administered in three sessions, each 1 week ( $\pm$  4 days) apart. 2000 shock waves of the assigned treatment were delivered per treatment session with the Storz Duolith shock wave device (Storz medical Systems, Switzerland). Before treatment, the point of maximum tenderness was clinically located by the treating physician and the hand-piece was coupled to the identified area by using specific ultrasound coupling gel.

Basically the extracorporeal shock wave therapy was performed without local anesthesia. Due to a possible pain sensation caused by the shock wave treatment, the working pressure was increased smoothly from lowest energy level  $0.01 \text{ mJ/mm}^2$ ) up to a level of  $0.25 \text{ mJ/mm}^2$  within the first 500 impulses. In the treatment group, 2000 impulses of shock waves with an energy flux density of  $0.25 \text{ mJ/mm}^2$  with an impulse rate of 4 Hz were applied at each treatment session. Patients in the control group received identical placebo therapy with a placebo hand-piece that prevented transmission of shock waves. The placebo hand-piece was designed in the same design, shape and weight to assure that there is no way to identify the placebo hand-piece. The treatment in the placebo group was the same compared to the active one. Thereby, set up and sound created by the shock wave device was identical in both groups; however, no energy was administered in the placebo group. The treatment was performed by locating the tip of the applicator to the most tender

point at the medial calcaneal tubercle, controlling proper placement by patient-controlled feedback and adjusted during treatment if necessary.

### **Outcome measures**

The primary outcome measure was overall heel pain reduction measured by the percentage change of the VAS composite score 12 weeks after treatment compared to baseline

The further primary efficacy criteria were the single success rates and the overall success rate with regard to heel pain defined as percentage decrease of heel pain larger than 60% from baseline at 12 weeks after treatment for at least two of the three heel pain (VAS) measurements.

The primary endpoint for comparison of groups was 12 weeks after the last treatment.

Secondary outcome measures were: changes in Roles and Maudsley and SF-36 score.

### **Safety criteria**

All patients who have had at least one treatment session were analyzed for safety. Patients were followed throughout the study and all local tissue effects and adverse events were recorded. Additionally, the investigator's global judgment of tolerability was assessed on a

7-point rating scale 12 weeks after the last treatment. To assess local adverse event Tendon rupture observation, Semmes-Weinstein 5.07 (10g) Monofilament Assessment, Toe Clawing Observation and Ankle-Brachial Assessment of the lower extremity were performed at each visit.

### **Statistical analysis**

The study had a statistical power of 90 percent to detect a reduction by 60 percentage points in the primary outcome measure, reduction of VAS composite score from baseline to 12 weeks after completion of shock wave treatment. A drop out rate of 10 percent was calculated as well prior the study started.

## **RESULTS**

3 month after ESWT success was observed in all criteria. The rate difference in all items after ESWT were statistically significant better in favor of the ESWT treatment. Regarding the change of pain score after ESWT the VAS composite score decrease from 8.3 at baseline down to 2.7 after ESWT, compared to 5.31 after identical placebo. The percent change was '69% after ESWT and '34% after placebo. The a priori ordered hypotheses of the final statistical analysis plan was statistically significant ( $P < 0.025$  one-sided) in all criteria.

### **Secondary outcome measures**

The efficacy results demonstrated superiority of the ESWT group not only in the confirmatory analyses, but also in the supportive sensitivity analyses and in the analysis of the secondary outcome measures. All tested secondary efficacy criteria including the SF-36 score and the Roles and Maudsley Score showed better outcome at the primary endpoint in favor to the ESWT group, and all test results were statistically significant ( $P < 0.025$  one-sided), see table below.

### **Adverse events and Safety criteria**

Only minor side effects as petechial bleeding, swelling and discomfort during treatment were detected. No adverse or severe adverse event occurred regarding tendon rupture observation, Semmes-Weinstein 5.07 (10g) Monofilament Assessment, Toe Clawing Observation and Ankle-Brachial Assessment.

### **DISCUSSION**

ESWT demonstrated safety and effectiveness with a protocol of three consecutive treatments (3x2000 impulses, 0.25 mJ/mm<sup>2</sup>), applied without anesthesia to the spot of greatest tenderness. ESWT can be strongly recommended for patients with therapy resistant plantar painful heel syndrome. Especially in the cases of failed conservative treatment, ESWT represents an excellent option to surgery, since anesthesia is not required and long recovery times can be avoided. Furthermore, ESWT represents a cost-effective treatment modality that can be administered on an outpatient basis.

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**Appendix A: Inclusion criteria**

1. Age greater than 18 years
2. Ability to give written informed consent after being told of the potential benefits and risks of participating in the study
3. Signed informed consent
4. Diagnosis of painful heel proven by clinical examination
5. 6 months of unsuccessful conservative treatment i.e., must have undergone at least 2 unsuccessful non-pharmacological treatments and at least 2 unsuccessful pharmacological treatments (see examples below). The prior conservative treatments may have been completed as single, combined or consecutive treatments.

Non-pharmacological treatments

- Physical therapy e.g., ice, heat, ultrasound, iontophoresis and electromyostimulation
- Physiotherapy e.g., massage and stretching
- OTC-devices like orthosis, taping and heel pads
- Prescribed orthosis
- Shoe modification like higher heels
- Cast/immobilization
- Night splints

Pharmacological treatments

- External (topical) application of analgesic and/or anti-inflammatory gels
  - Therapy with prescription analgesics and/or NSAIDs
  - Local anesthetic injections
  - Local corticosteroid injections
6. Time gap of at least:
    - 6 weeks since the last corticosteroid injection
    - 4 weeks since the last anesthetic injection; iontophoresis, ultrasound and electromyostimulation
    - 1 week since the last NSAIDs and
    - 2 days since the last prescription or non-prescription analgesics, heat, ice, massage, stretching, modification of night splinting and orthosis
  7. Scores of  $\geq 5$  on all three VAS pain scales
  8. Roles and Maudsley Score of “fair” or “poor”
  9. Willingness to refrain from the following painful heel related, concomitant therapy: iontophoresis; electromyostimulation; ultrasound; NSAIDs; steroid injections or surgery – until end of follow up 1
  10. Willingness to keep a Subject Heel Pain, Medication and Other Heel Pain Therapy Diary until 12 months after the last treatment
  11. Females of childbearing potential may be entered if they provide a negative urine pregnancy test immediately before the first ESWT treatment

12. Willingness of females of childbearing potential to use contraceptive measures for 2 months after enrollment into the study

**Appendix B:** Exclusion criteria

1. Subjects suffering from tendon rupture, neurological or vascular insufficiencies of the painful heel
2. Subjects suffering from inflammation of the lower and upper ankle
3. History of rheumatic diseases, collagenosis or metabolic disorders
4. Subjects with a history of hyperthyroidism
5. Malignant disease with or without metastases
6. Subjects suffering from Paget disease or calcaneal fat pad atrophy
7. Subjects suffering from osteomyelitis (acute, sub acute, chronic)
8. Subjects with a history of fracture of the calcaneus
9. Subjects with an immunosuppressive therapy
10. Subjects with a long-term treatment with corticosteroids
11. Subjects suffering from diabetes mellitus, severe cardiac or respiratory disease
12. Subjects suffering from coagulation disturbance and/or therapy with Phenprocoumon, Acetylsalicylic acid or Warfarin
13. Bilateral painful heel, i.e., if both feet need medical treatment

14. Subjects who, at entry, are known to have treatment planned within the next 8 weeks, which may abruptly alter the degree or nature of pain experienced on the painful heel and the shock wave therapy will no longer be necessary (e.g., surgery)
15. Time gap of less than:
  - 6 weeks since the last corticosteroid injection;
  - 4 weeks since the last anesthetic injection; iontophoresis, ultrasound and electromyostimulation;
  - 1 week since the last NSAIDs and
  - 2 days since the last prescription or non-prescription analgesics, heat, ice, massage, stretching, modification of night splinting and orthosis
16. Previous surgery of the painful heel
17. Previous unsuccessful treatment of the painful heel with a similar shock wave device
18. History of allergy or hypersensitivity to bupivacaine or local anesthetic sprays
19. Subjects with significant abnormalities in hepatic function
20. Subjects in a poor physical condition
21. Pregnant female
22. Infection in the treatment area recently or in medical history
23. History or documented evidence of peripheral neuropathy such as nerve entrapment, tarsal tunnel syndrome, etc.

24. History or documented evidence of systemic inflammatory disease such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, aseptic bone necrosis, Reiter's syndrome, and etc.
25. History or documented evidence of worker's compensation or litigation
26. Participation in a clinical study within 30 days prior to selection or current inclusion in any other clinical study or research project
27. Subjects who, in the opinion of the investigator, are inappropriate for inclusion into this clinical study or will not comply with the study requirements