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Low-Intensity Shockwave Therapy for Erectile Dysfunction: A Randomized Clinical Trial Comparing 2 Treatment Protocols and the Impact of Repeating Treatment

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ABSTRACT

Background: There is lack of evidence-based optimization of the protocol for low-intensity shockwave therapy for erectile dysfunction. Furthermore, the safety and efficacy of repeating shockwave therapy have not been explored.

Aim: To compare the efficacy and safety of 6 and 12 treatment sessions within a 6-week treatment period and investigate the effect of repeat treatment after a 6-month period in a 2-phase study.

Methods: Patients with vasculogenic erectile dysfunction that responded to phosphodiesterase type 5 inhibitors were randomized into 2 groups: low-intensity shockwave therapy sessions once (group A, n = 21) or twice (group B, n = 21) per week for 6 consecutive weeks (phase 1). Patients who completed 6-month follow-up were offered 6 additional sessions (phase 2); group A received 2 sessions per week and group B received 1 session per week. Patients were followed for 6 months.

Outcomes: International Index for Erectile Function erectile function domain (IIEF-EF) score, minimally clinical important differences (MCIDs), Sexual Encounter Profile question 3 (SEP3) score, and triplex ultrasonographic parameters.

Results: In phase 1, groups A and B showed improvement in IIEF-EF score, MCID, SEP3 score, and mean peak systolic velocity compared with baseline. MCIDs were achieved in 62% of group A and 71% of group B, and the percentage of yes responses to SEP3 was 47% in group A and 65% in group B ($P = .02$). Mean peak systolic velocity at baseline and at 3-month follow-up were 29.5 and 33.4 cm/s for group A and 29.6 and 35.4 cm/s for group B ($P = .06$). In phase 2, group A showed a greater increase in the percentage of yes responses to SEP3 (group A = +14.9; group B = +0.3). When the impact of the total number of sessions received was examined, MCIDs in IIEF-EF score from baseline were achieved in 62%, 74%, and 83% of patients after 6, 12, and 18 sessions, respectively. No treatment-related side effects were reported.

Clinical Implications: The total number of low-intensity shockwave therapy sessions affects the efficacy of erectile dysfunction treatment. Retreating patients after 6 months could further improve erectile function without side effects. 12 sessions can be delivered within 6 weeks without a 3-week break period.

Strengths and Limitations: This study lacked a sham-controlled arm. However, all patients were randomized to different groups, and baseline characteristics were similar between groups. Also, all patients were confirmed by triplex ultrasonography to have arterial insufficiency.

Conclusion: Patients can benefit more in sexual performance from 12 sessions twice per week compared with 6 sessions once a week. Shockwave therapy can be repeated up to a total of 18 sessions. **Kalyvianakis D, Memmos E, Mykoniatis I, et al. Low-Intensity Shockwave Therapy for Erectile Dysfunction: A Randomized Clinical Trial Comparing 2 Treatment Protocols and the Impact of Repeating Treatment. J Sex Med 2018;XX:XXX–XXX.**

Key Words: Erectile Dysfunction; Shockwave; Treatment; Low-Intensity Shockwave Therapy (LiST); Extracorporeal Shockwave Therapy (ESWT)

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INTRODUCTION

Low-intensity shockwave therapy (LiST) has been shown to be an efficacious and safe treatment for erectile dysfunction (ED).[1–4] Published clinical studies have used different machines and different treatment protocols without rigorous clinical justification for choosing a particular protocol.[5] Actually, all available published studies used protocols derived from other organ or disease applications (eg, cardiology) or animal studies.[6,7] In most published studies, the energy flux density ranged from 0.09 to 0.25 mJ/mm^2 and the number of shockwave pulses per treatment ranged from 1,500 to 5,000. The duration of LiST directed at multiple sites on the penis during each session in most studies was not longer than 6 weeks.[5] Because each study used different machines, delivered shockwaves to different anatomic sites, and used different measures of erectile function, it is impossible to draw reliable conclusions about the effect of the each variable. The only clear conclusion is that all protocols tested are safe.

To define the optimal LiST protocol for vasculogenic ED, a series of studies was designed using consistent inclusion and exclusion criteria, study machine, treatment technique, and experimental design. This was done to enable the evaluation of changing parameters such as the number of therapy sessions, frequency of sessions, and shockwave energy levels.

This 1st study sought to answer 2 fundamental clinical questions about LiST for vasculogenic ED: (i) Does delivering more sessions result in greater efficacy? (ii) Is it meaningful to repeat treatment if the patient requests more sessions? We hypothesized that the efficacy of LiST for ED would be dose dependent and that increasing the number of treatment sessions could increase efficacy up to a threshold level.

To answer these questions, a 2-phase study was conducted to examine, for the 1st time, (i) the safety and efficacy of 6 vs 12 sessions of LiST and (ii) the safety and efficacy of a second round of shockwave therapy.

METHODS

The trial was conducted in 2 phases. Phase 1 compared 6 with 12 treatment sessions, and phase 2 investigated the safety and efficacy of a second round of shockwave therapy.

Study Design

The study was a prospective, randomized, 2-parallel-arm, open-label study performed at the andrology outpatient clinic of an academic hospital. Study protocols were reviewed and approved by the institutional ethics board and registered at clinicaltrials.gov (phase 1: NCT03089307; phase 2: NCT03089372). All participants gave written informed consent before being enrolled in each phase of the study. Patients were recruited for phase 1 from August through December 2015 and the final results of phase 2 were obtained in March 2017.

Patients with a clinical history indicating vasculogenic ED, under treatment with phosphodiesterase type 5 inhibitors (PDE5is) for at least 3 months, in a stable heterosexual relationship, and with ED for at least 6 months were recruited for the trial. Diagnosis of ED at screening was based on sexual and medical history, laboratory tests, and physical examination (including positive intracavernosal injection test result). Sexual Encounter Profile (SEP) diaries were issued at the screening to be completed during a 4-week PDE5i washout period, and patients returned for the baseline visit. During the baseline visit, all patients completed the International Index of Erectile Function (IIEF) and underwent triplex ultrasonography by the same experienced investigator.

Inclusion criteria at baseline were an IIEF erectile function domain (IIEF-EF) score lower than 26[8] without use of oral PDE5i or other erectogenic aids (4-week washout period) and a cavernosal artery peak systolic velocity (PSV) lower than 35 cm/s.[9] All participants agreed to withhold all ED therapy for the duration of the study, an agreement that was confirmed at each study visit to maintain the unbiased interpretation of the study results.

Patients with psychogenic ED, neurogenic ED, penile anatomic abnormalities or surgery, untreated endocrinologic disease (including normal testosterone levels), untreated or uncontrolled diabetes (defined as fasting blood glucose levels $>$ 140 mg/dL under diabetic treatment), hypertension or cardiovascular disease, hemophilia, high risk of thrombosis, active cancer, a psychiatric condition, or any major pelvic surgery were excluded.

Patients who completed phase 1 were offered participation in phase 2. The study flowchart is presented in Figure 1. The protocol for phase 2 was reviewed and approved by the institutional ethics board and registered at clinicaltrials.gov (NCT03089372). All participants gave written informed consent before being enrolled in the study.

Sample Size Calculation

Data from our group using a different shockwave machine showed an IIEF-EF score increase of 5.2 points after 12 sessions of LiST.[4] However data using the study device suggested an IIEF-EF score increase of 7.7 points after only 5 sessions.[10]

We powered our study by assuming an increase in IIEF-EF score of 6 points after 12 sessions and an increase of 3 points after 6 sessions (SD = 3 points). For 90% power and 2-sided significance of 0.05, the sample size required was 21 per group. Therefore, for this study, 43 patients were randomized to the 2 study groups.

Study Protocol

The protocols for phases 1 and 2 are presented in Figure 2. After a primary screening, all patients had a 4-week washout period without PDE5is or other erectogenic aids, including natural herbs, intracavernosal injections, intraurethral alprostadil, and vacuum pump devices. Then, patients returned for a baseline