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ORIGINAL RESEARCH

INTERVENTIONS

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;15:334–345.**

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

visit. Patients with an IIEF-EF score lower than 26 and cavernosal artery PSV lower than 35 cm/s at the baseline visit were randomized to group A or B. LiST sessions were performed once a week for group A (treatment interval = 7 ± 2 days) or twice a week for group B (treatment interval = 3 ± 1 days). Patients were assessed by the IIEF-EF and SEP at baseline and 4, 12, and 24 weeks after their final LiST session. All questionnaires (IIEF-EF and SEP) were completed by the patients at separate clinical interviews at the aforementioned time points. Triplex Doppler ultrasonography was performed at baseline and at 12-week follow-up.

After completing the 6-month follow-up of phase 1 (6m-FU-1), patients were immediately recruited for phase 2. It should be emphasized that the study protocol and outcome measures were identical between phases 1 and 2. Patients who consented to participate in phase 2 returned for a baseline visit (baseline 2) at which the IIEF and SEP were administered. The absence of any ED aid for all participants was maintained between phases 1 and 2. The baseline 2 visit occurred 0 to 28 days after completion of phase 1 (6m-FU-1), and treatment sessions began at baseline 2. In phase 2, all patients received 6 LiST sessions: patients who received treatment once per week (6 sessions) in phase 1 (group A) received LiST twice a week in phase 2 (treatment interval = 3 ± 1 days). Patients who received treatment twice per week (12 sessions) in phase 1 (group B) received LiST once a week in phase 2 (treatment interval = 7 ± 2 days). Triplex Doppler ultrasonography was performed as in phase 1 at the 12-week follow-up visit (3m-FU-2); it should be noted that based on the protocol of phase 1, triplex ultrasonographic results were available before any LiS treatment (baseline 1) and at the 3-month follow-up of phase 1 (3m-FU-1).

Randomization

At the baseline visit all eligible patients were randomized to group A or B with an equal allocation ratio (1:1). The randomization sequence was generated by computer by the study coordinating team. Treatment allocation was communicated by the coordinating center to the investigators through a web-based registration system to ensure allocation concealment and minimize bias.

Blinding

3 trained investigators applied the treatment protocol in phases 1 and 2. These 3 investigators and the participants could not be blinded because of the different treatment protocol followed by the 2 groups in phases 1 and 2. However, all triplex ultrasonographic measurements were performed while blinded to group randomization by the same experienced clinician (D.K.). Moreover, the clinician responsible for the data collection and the data analyst were blinded to which treatment protocol referred to group A or B.

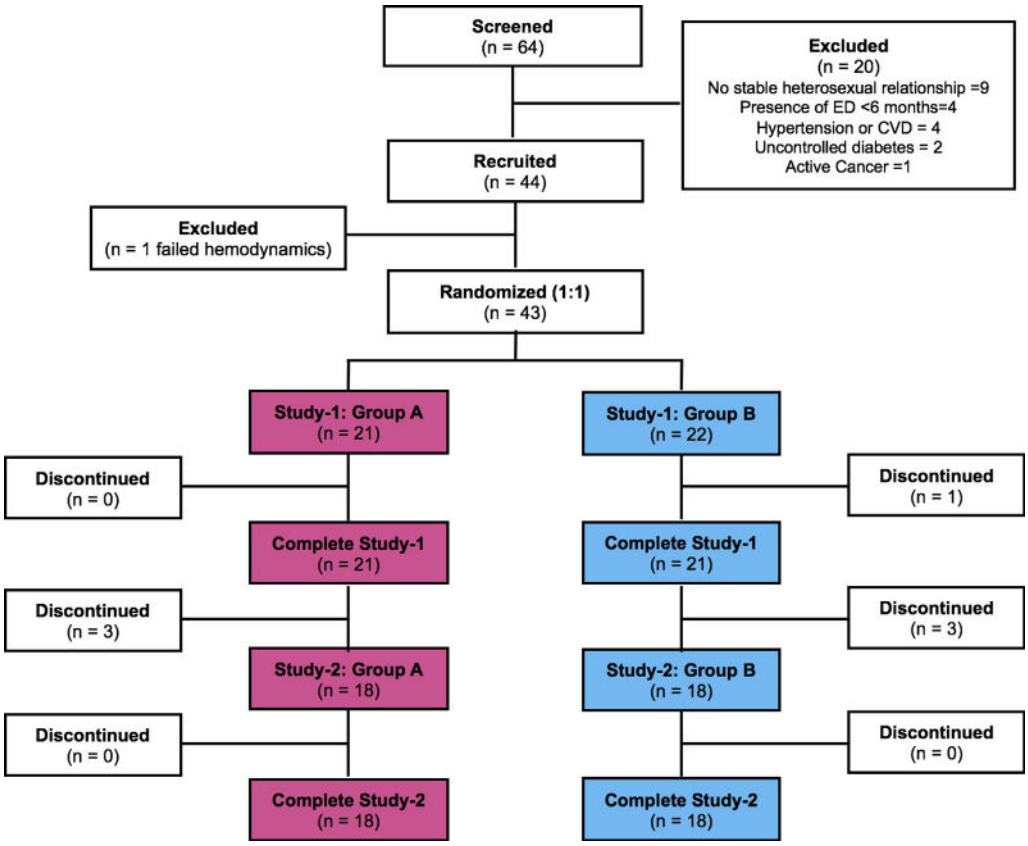

Figure 1. Study flowchart. CVD = cardiovascular disease; ED = erectile dysfunction. Figure 1 is available in color at www.jsm.jsexmed.org.

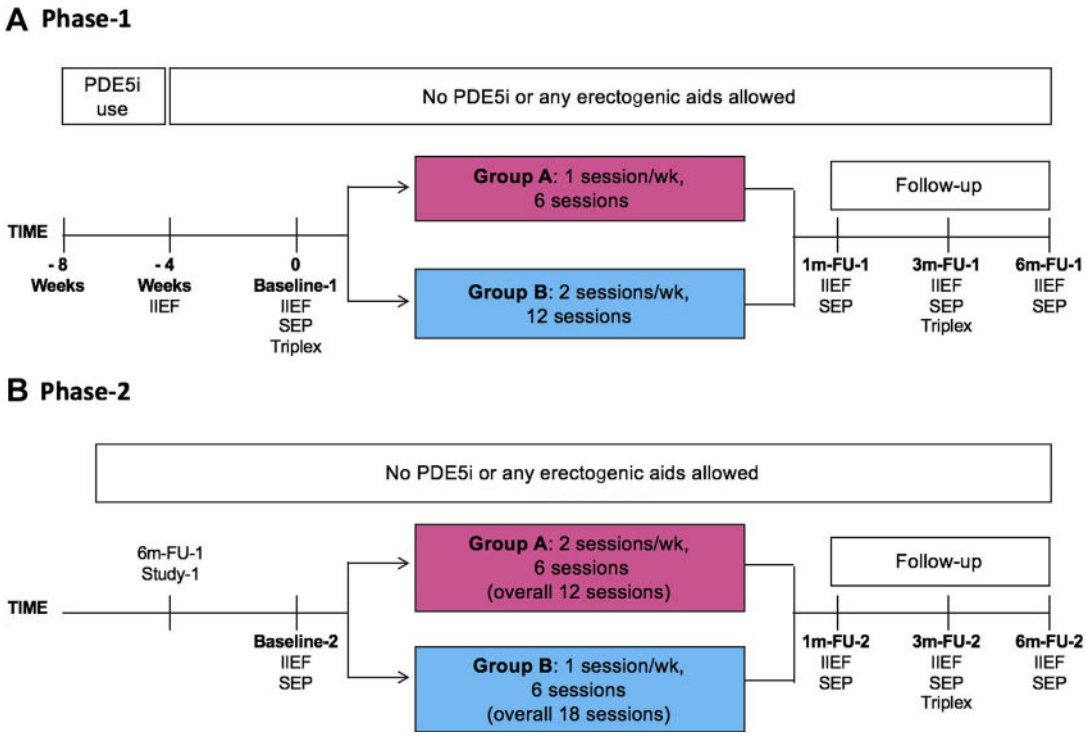

Figure 2. Study protocol. 1m-FU-1 = 1-month follow-up of phase 1; 1m-FU-2 = 1-month follow-up of phase 2; 3m-FU-1 = 3-month follow-up of phase 1; 3m-FU-2 = 3-month follow-up of phase 2; 6m-FU-1 = 6-month follow-up of phase 1; 6m-FU-2 = 6-month follow-up of phase 2; IIEF = International Index of Erectile Function; PDE5i = phosphodiesterase type 5 inhibitor; SEP = Sexual Encounter Profile. Figure 2 is available in color at www.jsm.jsexmed.org.

Penile Triplex Ultrasonography

To assess potential treatment-associated structural changes, penile ultrasonography was performed 3 times—at baseline, 3m-FU-1, and 3m-FU-2—by the same experienced investigator (D.K.). Triplex ultrasonography was performed under pharmaco-stimulation with an intracavernosal tri-mix solution 0.5 mL (papaverine 300 mg, phentolamine 10 mg, alprostadil 100 μg). Re-dosing was performed when needed to achieve complete smooth muscle relaxation. PSV, end-diastolic velocity (EDV), and resistance index (RI) measurements were recorded using a previously described standardized protocol.[4,11] The highest values were recorded. All triplex ultrasonographic measurements were performed blinded to group randomization by the same experienced clinician (D.K.).

Shockwave Therapy application

Patients were treated with a low-energy shockwave generator (ARIES 2 and Smart Focus probe; Dornier MedTech GmbH, Wessling, Germany). Shockwaves were delivered at an energy flux density of 0.05 mJ/mm^2, effective energy (E_{12mm}) of 3.4 mJ, and frequency of 8 Hz (level 4 of the ARIES 2 device). Application was performed by slowly moving the shockwave probe back and forth from the glans penis to the pubis at the left and right sides of the penis to reach the corpora and avoid the urethra. This technique allowed equal application of the energy along the 2 corpora cavernosa.

5,000 shockwaves were applied during each treatment session: 1,000 shockwaves each to the left and right shaft, 1,000 shockwaves each to the 2 crura, and 500 shockwaves each to the left and right penile hilum. A standard commercial gel normally used for sonography was applied to the subject's penis and to the membrane of the shockwave applicator. Each treatment session lasted approximately 20 minutes without local or systemic analgesia. 3 trained investigators applied the treatment protocol in phases 1 and 2 of the study.

Outcome Measures

Identical outcome measures were used in phases 1 and 2. Treatment success was defined as the achievement of a minimally clinical important difference (MCID) in improvement in IIEF-EF score; MCID was defined as a change in IIEF-EF score equal to or greater than 2, 5, and 7 points for mild, moderate, and severe ED, respectively.[12] Sexual performance was assessed by SEP diaries, specifically question 3 (SEP3). PSV, EDV, and RI were used to objectively assess penile hemodynamics.

Statistics

Data analysis was generated using Excel 2013 (Microsoft, Redmond, WA, USA) and Real Statistics Resource Pack 4.11 (copyright 2013–2015 by Charles Zaiontz; www.real-statistics.com). Paired t-test was used to assess changes within a group from baseline to follow-up. 2-tailed Fisher exact test was used to assess significance for discrete variables (eg, difference in

proportion of MCID success rates between groups). 2-tailed t-test for independent samples was used to assess the difference in all other outcome measures between groups. The level of significance for all analyses was set at 5% ($P < 0.05$).

RESULTS

Study Sample

64 patients were screened and 44 were eligible according to the inclusion criteria. Of the 44 patients, 1 had normal PSV at triplex ultrasonography and was excluded from the study. Of 43 patients who entered the study, 42 completed phase 1. There was no statistically significant difference in baseline patient demographics and disease severity (Table 1). Most patients reported concomitant medical conditions or risk factors associated with vasculogenic ED, and 47.6% had controlled diabetes (Table 1).

36 of 42 patients (85.7%) who completed phase 1 consented to participate in phase 2; all 36 patients completed phase 2. Although there were no significant differences in baseline ED severity at the beginning of phase 1, at the start of phase 2 there were more patients with mild ED in group B (owing to the previous treatment with LiST), but this did not reach statistical significance (Table 2).

Treatment Efficacy vs Baseline (Combined Analysis of All Patients, Phase 1)

Mean IIEF-EF score of the 42 completers of phase 1 increased from 15.8 ± 3.7 at baseline to 19.9 ± 3.8 at 6m-FU-1 ($P < .001$). In 50% of patients IIEF-EF score increased by at least 5 points, which represents 1 IIEF-EF category improvement. Only 7 of 42 patients (16.6%) showed no improvement in IIEF-EF score (≤1-point increase). Improvement in IIEF-EF score was reported at 1-month follow-up in phase 1 (1m-FU-1) and remained stable to the end the study (6m-FU-1). MCID was achieved by 66.6% of patients (28 of 42). Mean yes responses to SEP3 increased from 38.1% at baseline to 56.3% at 6m-FU ($P = .001$). Mean PSV change was +4.9 ± 2.5 cm/s ($P < .001$), mean EDV change was −0.9 ± 2.9 cm/s ($P = .05$), and mean RI increased from 0.80 at baseline to 0.84 at 6m-FU ($P < .001$).

Comparison of 6 vs 12 Sessions (Phase 1)

Group A received 6 sessions of LiST once per week (6 weeks), and group B received 12 sessions of LiST twice per week (6 weeks). For group A, mean IIEF-EF score was 16.2 at baseline and 19.5, 19.0, and 19.3 at 1-, 3-, and 6-month follow-up, respectively ($P < .001$). For group B, mean IIEF-EF score was 15.4 at baseline and 20.6, 20.6, and 20.5 at 1-, 3-, and 6-month follow-up ($P < .001$; Table 2 and Figure 3A). At 3m-FU-1, MCID in IIEF-EF score was achieved by 10 of 21 patients (48%) in group A and by 16 of 21 patients (76%) in group B ($P = .11$ for group A vs B). Group A continued to show improvement; at 6m-FU-1, 13 of 21 patients (62%) in group A and 15 of 21 (71%) in group B achieved the MCID ($P = .74$). Therefore, there was a trend toward improved MCID results in patients receiving 12 sessions, but this did not reach statistical significance (Table 3). Interestingly, patients with moderate and severe ED appeared

Table 1. Patient demographics and baseline disease severity

	Group A	Group B	*P* value*
Sample size in phase 1	21	21	
Age (y), mean ± SD	57.5 ± 10.0	55.6 ± 9.0	.52
BMI (kg/m^2), mean ± SD	28.3 ± 3.9	27.3 ± 3.1	.37
Concomitant condition, n (%)			
Diabetes mellitus	10 (47.6)	7 (33.3)	.53
Cardiovascular risk factors†	20 (95.2)	18 (85.7)	.49
Diagnosed with cardiovascular disease	2 (9.5)	0 (0.0)	.61
Baseline IIEF-EF score, mean ± SD	16.2 ± 3.8	15.4 ± 3.7	.48
Baseline ED severity, n (%)			
Mild ED (IIEF-EF score = 17–25)	12 (57.1)	9 (42.9)	.54
Moderate ED (IIEF-EF score = 11–16)	7 (33.3)	9 (42.9)	.75
Severe ED (IIEF-EF score = 0–10)	2 (9.5)	3 (14.3)	1.00
Sample size in phase 2	18	18	
Baseline 2 IIEF-EF score, mean ± SD	19.9 ± 3.8	20.7 ± 3.2	.51
Baseline 2 ED severity, n (%)			
Mild ED (IIEF-EF score = 17–25)	14 (77.8)	17 (94.4)	.34
Moderate ED (IIEF-EF score = 11–16)	4 (22.2)	1 (5.6)	.34
Severe ED (IIEF-EF score = 0–10)	0 (0.0)	0 (0.0)	1.00

BMI = body mass index; ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function erectile function domain.
*Group A vs B by 2-tailed independent-samples t-test (continuous variables) or 2-tailed Fisher exact test (discrete variables).
†Includes at least 1 of the following: hypertension, hyperlipidemia, obesity, and smoking (current or former).

Table 2. Phase 1 results: IIEF-EF, SEP diaries, and hemodynamic parameters

	Baseline 1	1m-FU-1	3m-FU-1	6m-FU-1
IIEF-EF score, mean ± SD				
Group A (n = 21)	16.2 ± 3.8	19.5 ± 4.2	19.0 ± 4.3	19.3 ± 4.0
Group B (n = 21)	15.4 ± 3.7	20.6 ± 4.2	20.6 ± 3.9	20.5 ± 3.5
P value* (A vs B)	.48	.43	.20	.31
SEP2 (% yes), mean ± SD				
Group A	82.9 ± 23.6	85.7 ± 21.8	88.9 ± 15.4	85.5 ± 20.7
Group B	80.2 ± 27.6	94.5 ± 12.8	93.5 ± 17.7	91.0 ± 14.5
P value (A vs B)	.73	.12	.37	.32
SEP3 (% yes), mean ± SD				
Group A	36.5 ± 29.0	53.2 ± 35.2	37.6 ± 27.8	47.4 ± 23.5
Group B	39.7 ± 26.2	71.0 ± 26.2	67.9 ± 20.2	65.2 ± 25.0
P value* (A vs B)	.71	.07	< .001	.02
PSV (cm/s), mean ± SD				
Group A	29.5 ± 2.2		33.4 ± 3.4	
Group B	29.6 ± 2.0		35.4 ± 3.3	
P value* (A vs B)	.92		.06	
EDV (cm/s), mean ± SD				
Group A	6.5 ± 1.5		5.6 ± 2.5	
Group B	6.4 ± 1.3		5.5 ± 2.5	
P value* (A vs B)	.76		.98	
RI, mean ± SD				
Group A	0.79 ± 0.06		0.84 ± 0.07	
Group B	0.80 ± 0.05		0.85 ± 0.07	
P value* (A vs B)	.31		.87	

1m-FU-1 = 1-month follow-up of phase 1; 3m-FU-1 = 3-month follow-up of phase 1; 6m-FU-1 = 6-month follow-up of phase 1; EDV = end-diastolic velocity; IIEF-EF = International Index of Erectile Function erectile function domain; PSV = peak systolic velocity; RI = resistance index; SEP2 = Sexual Encounter Profile question 2; SEP3 = Sexual Encounter Profile question 3.
*By 2-tailed independent-samples t-test.

to benefit from the more intensive protocol. At 6m-FU-1, only 3 of 7 patients (43%) with moderate ED from group A had achieved the MCID compared with 6 of 9 patients (67%) with moderate ED from group B (Table 3).

The SEP3 showed a clear and statistically significant difference in outcomes between groups A and B (Table 2 and Figure 3B). At 6m-FU-1, the average percentage of yes responses to SEP3 ("Did your erection last long enough for successful intercourse?") was 47% in group A and 65% in group B ($P = .02$).

It should be emphasized that the clinical success rates obtained in group B (12 sessions) were achieved without the 3-week break between the 6th and 7th sessions proposed in previous shockwave studies.[13]

Average cavernosal artery PSV was similar between groups at baseline (group A = 29.5 cm/s; group B = 29.6 cm/s). PSV significantly increased in the 2 groups after treatment ($P < .001$). At 3m-FU-1, average PSV in group B (35.4 cm/s) was higher than in group A (33.4 cm/s), but this was not sufficient for statistical significance ($P = .06$). Similarly, mean EDV and RI, although improved in the 2 groups, showed no statistically significant difference between groups (Table 2). Changes in penile hemodynamics were comparable to our previously reported study, performed by the same experienced investigator, but using a different shockwave machine.[4]

High Responders vs Non-Responders to LiST (Study 1)

Regardless of baseline disease severity and treatment protocol, we noticed that 50% of patients were high responders to LiST (≥5-point increase), whereas a small proportion (7 of 42) were non-responders with almost no response (≤1-point increase). We compared baseline characteristics of these high responders with those of non-responders to investigate possible prognostic factors. Of all factors considered, including age, body mass index, baseline 1 IIEF-EF score, mean PSV, change or decrease in IIEF-EF score after PDE5i washout, and mean baseline 1 percentage of yes responses to SEP question 2 and SEP3, only age and change or decrease in IIEF-EF score after PDE5i washout were statistically significant (Figure 4). High responders were likely to be younger (average age = 55.9 vs 66.1 years) and more responsive to PDE5i (average IIEF-EF change = −9.0 vs −6.1).

Retreatment Efficacy (Phase 2)

Retreatment with 6 additional sessions of LiST demonstrated further improvements in erectile function. Mean

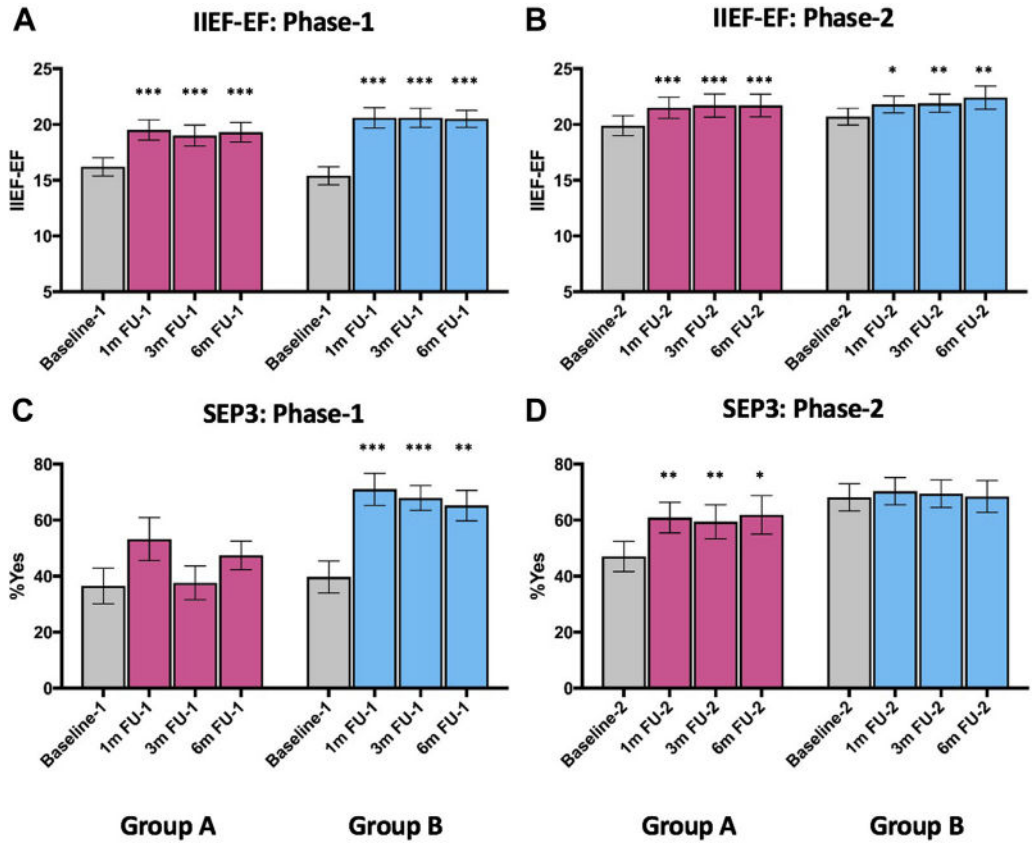

Figure 3. Erectile function assessment at phases 1 and 2 of the study. Panels A and B show mean ± standard error of the mean for IIEF-EF scores at different time points. Panels C and D show mean ± standard error of the mean for SEP3 at different time points. *P* values in panels A and C indicate the change from baseline 1 to the follow-up time point within each group (n = 21 per group) by paired t-test. *P* values in panels B and D indicate the change from baseline 2 to the follow-up time point within each group (n = 18 per group) by paired t-test. **P* < .05; ***P* < .01; ****P* < .001. 1m-FU-1 = 1-month follow-up of phase 1; 1m-FU-2 = 1-month follow-up of phase 2; 3m-FU-1 = 3-month follow-up of phase 1; 3m-FU-2 = 3-month follow-up of phase 2; 6m-FU-1 = 6-month follow-up of phase 1; 6m-FU-2 = 6-month follow-up of phase 2; IIEF-EF = International Index of Erectile Function erectile function domain; SEP3 = Sexual Encounter Profile question 3. Figure 3 is available in color at www.jsm.jsexmed.org.

IIEF-EF score of the 36 completers increased from 20.3 ± 3.5 at baseline to 22.1 ± 4.3 at 6m-FU-2 ($P < .001$). In 50% of patients (18 of 36), little or no improvement in IIEF-EF score was noted (≤1-point increase). Improvement in IIEF-EF score was reported at 1m-FU-2 (average change in IIEF-EF score = 1.4 ± 1.5) and continued to increase slightly to the end of the study (average change in IIEF-EF score at 6m-FU-2 = 1.8 ± 1.8). At 6m-FU-2, MCID from baseline 2 was achieved by 44% of patients (16 of 36). Mean yes responses to SEP3 increased from 57.6% at baseline 2 to 65.2% at 6m-FU-2 ($P = .057$). At 3m-FU-2, mean PSV change from the phase 1 end point (3m-FU-1) was +1.1 cm/s ($P = .055$), mean EDV change was −0.88 cm/s ($P = .74$), and mean RI remained unchanged at 0.85.

Table 3. Minimally clinical important difference by severity of erectile dysfunction (6-month follow-up)

	Mild (%)	Moderate (%)	Severe (%)	Total (%)	*P* value*, A vs B
Phase 1: baseline to 6m-FU-1					
Group A (6)	10/12 (83)	3/7 (43)	0/2 (0)	13/21 (62)	.744
Group B (12)	8/9 (89)	6/9 (67)	1/3 (33)	15/21 (71)	
Phase 2: baseline to 6m-FU-2					
Group A (6 + 6)	7/14 (50)	0/4 (0)	—	7/18 (39)	.738
Group B (12 + 6)	9/17 (53)	0/1 (0)	—	9/18 (50)	

6m-FU-1 = 6-month follow-up of phase 1; 6m-FU-2 = 6-month follow-up of phase 2.
*Group A vs B by 2-tailed Fisher exact test.

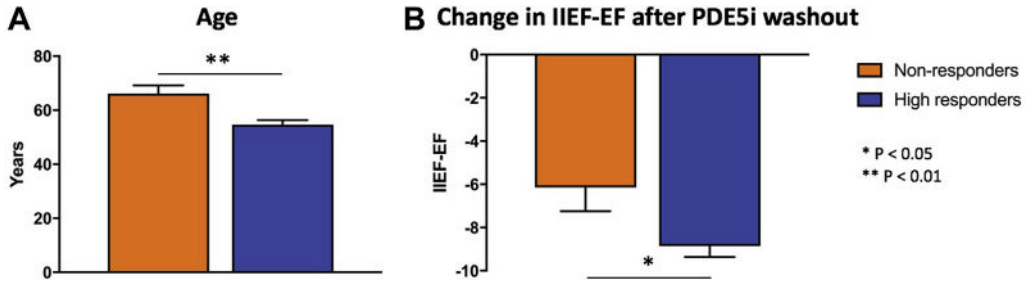

Figure 4. Factors associated with treatment response. Panels A and B show mean ± standard error of the mean for patient age and change in IIEF-EF score after PDE5i washout, respectively, between shockwave therapy non-responders (n = 7) and high responders (n = 21). High responders to low-intensity shockwave therapy were defined as having an increase of at least 5 points in IIEF-EF score, whereas non-responders had an increase no higher than 1 point. *P* values represent the comparison of non-responders with high responders by 2-tailed independent-samples t-test. IIEF-EF = International Index of Erectile Function erectile function domain; PDE5i = phosphodiesterase type 5 inhibitor. Figure 4 is available in color at www.jsm.jsexmed.org.

Comparison Between Groups A and B After Retreatment (Phase 2)

For group A (6 + 6 sessions), mean IIEF-EF score was 19.9 at baseline and 21.5, 21.7, and 21.7 at 1-, 3-, and 6-month follow-up, respectively ($P < .001$). For group B (12 + 6 sessions), mean IIEF-EF score was 20.7 at baseline and 21.8, 21.9, and 22.4 at 1-, 3-, and 6-month follow-up ($P = .003$; Table 4 and Figure 3). MCID at 6-month follow-up from baseline 2 was achieved by 7 of 18 patients (38.9%) from group A and 9 of 18 (50%) from group B ($P = .74$; Table 3). This suggests that 38.9% of patients who received 6 sessions and 50% of patients who received 12 sessions could have derived a clinically significant benefit from an additional 6 sessions of shockwaves.

Groups A and B achieved a statistically significant increase in IIEF-EF score from baseline 2 to 6m-FU-2 ($P < .001$ for group A; $P = .003$ for group B). However, the average increase in IIEF-EF score was the same for the 2 groups (+1.8 points in groups A and B; Table 3). In contrast, group A showed a greater increase in yes responses to SEP3 (group A = +14.9; group B = +0.3; $P = .055$; Figure 3D) and a greater increase in cavernosal artery PSV (group A = +1.96 cm/s; group B = +0.13 cm/s; $P = .082$; Figure 5), but the differences were not statistically significant. Therefore, when considering SEP3 and PSV, our data indicate that an additional 6 sessions of shockwave therapy might be more beneficial to patients who previously received only 6 sessions (group A), whereas patients who had received 12 sessions might be approaching dose saturation (Figures 3 and 5).

Efficacy of 12 Sessions of LiST With and Without an Interval (Phases 1 and 2)

Using the results of phase 1, we explored the effect of 12 sessions of LiST in patients who received 12 sessions within 6 weeks (group B in phase 1; n = 21) vs patients who initially received 6 sessions and, after a 6-month break, received an additional 6 sessions (6 + 6 sessions; patients in group A who completed phases 1 and 2; n = 18). Interestingly, the average increases in IIEF-EF score, SEP3 score, and PSV were almost identical for those receiving 12 sessions in 2 courses (6 + 6 sessions) and those receiving 12 sessions in 1 course (Figure 6).

Table 4. Phase 2: IIEF-EF domain and SEP2 and SEP3 changes

	Baseline 2	1m-FU-2	3m-FU-2	6m-FU-2
IIEF-EF score, mean ± SD				
Group A (n = 18)	19.9 ± 3.8	21.5 ± 4.1	21.7 ± 4.4	21.7 ± 4.3
Group B (n = 18)	20.7 ± 3.2	21.8 ± 4.0	21.9 ± 3.4	22.4 ± 4.4
P value* (A vs B)	.51	.81	.90	.59
SEP2 (% yes), mean ± SD				
Group A	86.9 ± 16.4	89.9 ± 15.2	86.1 ± 21.4	88.2 ± 21.2
Group B	90.0 ± 15.0	91.9 ± 14.2	89.2 ± 12.5	87.0 ± 16.0
P value* (A vs B)	.45	.69	.60	.85
SEP3 (% yes), mean ± SD				
Group A	47.0 ± 22.8	60.9 ± 23.3	59.4 ± 25.8	61.9 ± 29.2
Group B	68.1 ± 20.7	70.3 ± 20.7	69.4 ± 20.9	68.4 ± 24.3
P value* (A vs B)	.006	.21	.21	.48

1m-FU-2 = 1-month follow-up of phase 2; 3m-FU-2 = 3-month follow-up of phase 2; 6m-FU-2 = 6-month follow-up of phase 2; IIEF-EF = International Index of Erectile Function erectile function domain; SEP2 = Sexual Encounter Profile question 2; SEP3 = Sexual Encounter Profile question 3.
*Group A vs B by 2-tailed independent-samples t-test.

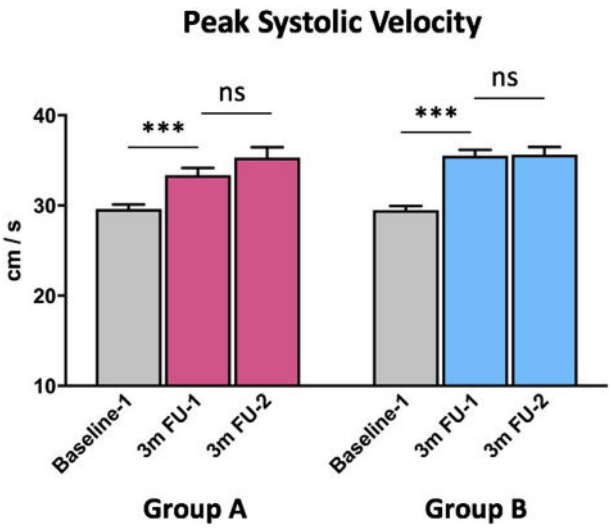

Figure 5. Peak systolic velocity changes (mean ± standard error of the mean) at phases 1 and 2. Triplex ultrasonography was performed at baseline and at 3m-FU-1 and 3m-FU-2. ***$P < 0.001$ by paired t-test (n = 18 per group). 3m-FU-1 = 3-month follow-up of phase 1; 3m-FU-2 = 3-month follow-up of phase 2; ns = not significant ($P > .05$). Figure 5 is available in color at www.jsm.jsexmed.org.

Effect of 6 vs 12 vs 18 Sessions (Phases 1 and 2)

Because the outcomes are similar between 6 + 6 and 12 sessions and the identical methodology was used for the initial study and the present study, we combined the results of these 2 studies to investigate the impact of 6 vs 12 vs 18 sessions of shockwave therapy. Changes in outcome measures were compared with the initial baseline (before any treatment session, ie, baseline 1).

Mean change in IIEF-EF score at 6-month follow-up was +3.1, +5.2, and +7.2 points after 6, 12, and 18 sessions, respectively (6 vs 12 sessions, $P = .003$; 12 vs 18 sessions, $P = .01$). Clinical success as defined by MCID in IIEF-EF score was 62%, 74%, and 83% after 6, 12, and 18 sessions (Table 5). Mean change in yes responses to SEP3 at 6-month follow-up was +10.9%, +26.5%, and +30.4% after 6, 12, and 18 sessions (6 vs 12 sessions, $P = .09$; 12 vs 18 sessions, $P = .68$). Mean PSV change at 3-month follow-up was +3.9, +5.8, and +6.2 cm/s after 6, 12, and 18 sessions (6 vs 12, $P = .02$; 12 vs 18, $P = .65$). These results indicated a dose-dependent effect, with 18 sessions producing the greatest efficacy.

Safety

Even at the highest energy "dose" of 18 sessions, all patients tolerated the treatment without reporting side effects. Patients reported no pain. Penile palpation was normal. To assess potential structural changes, penile ultrasonography was performed 3 times—at baseline, 3m-FU-1, and 3m-FU-2—and did not show any structural changes. Up to 18 sessions of LiST with the Dornier ARIES 2 machine at energy 0.05 mJ/mm^2 (level 4 in the ARIES 2 machine) did not appear to pose any safety concerns.

DISCUSSION

LiST is the 1st therapy proposed to modify the underlying pathophysiology in patients with ED.[14,15] Despite the enthusiasm of the scientific community for this novel treatment modality, many basic science and clinical questions remain unanswered. In the clinical setting, there is an emerging need to empirically determine the optimal treatment protocol for each machine and patient population.[16]

Our study offers several answers to questions raised in systemic reviews and meta-analysis regarding the appropriate use of this novel method: number of sessions, frequency of sessions per week, breaks between treatment sessions, and safety of multiple sessions.[4,14,16–18]

Phase 1 compared 2 different shockwave protocols to answer 3 main research questions: (i) Are 6 and 12 treatment sessions efficacious and safe when treatment is applied once or twice per week? (ii) Is there a need for a break after the initial 6 sessions when 12 sessions are applied? (iii) Is there any benefit in treating patients with 12 vs 6 sessions?

Results of phase 1 clearly demonstrated that (i) 6 or 12 sessions are efficacious and safe, with durable effects up to 6-month follow-up; (ii) 12 sessions can be safely applied without a break between the 6th and 7th sessions; and (iii) 12 sessions yielded greater improvements in erectile function and penile hemodynamics.

Phase 2 examined the effects of repeat treatment to answer 3 additional research questions: (iv) Is it safe and effective to repeat shockwave therapy up to 18 sessions? (v) Is there a difference between delivering 12 sessions in 1 treatment course and 6 sessions in 2 courses? (vi) Is efficacy dependent on the number of sessions per week?

Phase 2 results indicated that (iv) it is safe and meaningful to repeat shockwave therapy. There appears to be a dose-dependent effect, with greatest efficacy (83% MCID) after 18 sessions. There could be treatment saturation at 18 sessions, but this needs to be studied further. (v) Similar gains in erectile function and penile hemodynamics can be obtained after 12 sessions, whether delivered within 1 treatment course or divided into 2 courses. (vi) Our study design and data do not allow us to directly compare the effects of changing session frequency. However, our data suggest that session frequency can be once or twice per week without major effects on the efficacy rate.

In the 1st trials of shockwave therapy for ED,[13] the 3-week interval after the first 6 sessions was designed as a safety measure, but this interval was arbitrarily selected and not based on any evidence of benefit in safety and efficacy. In our study, elimination of the 3-week break period did not result in any

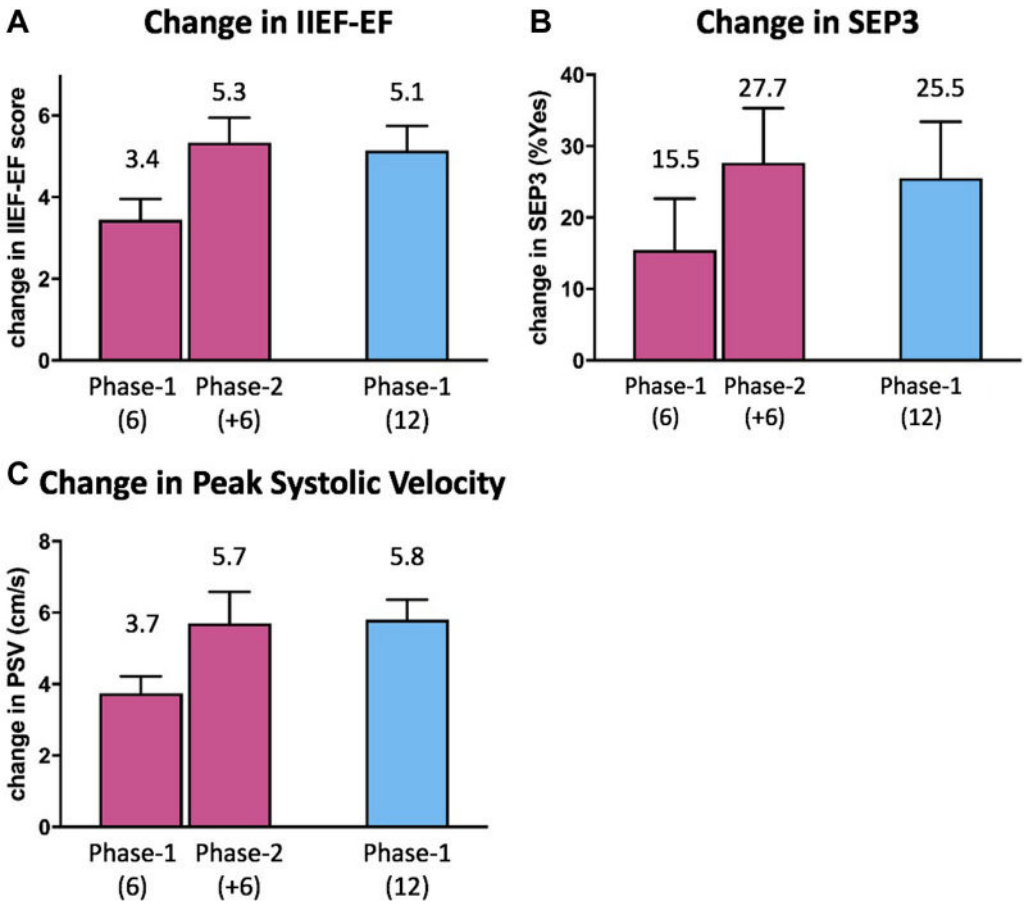

Figure 6. Comparison of delivering 12 sessions in 1 treatment course with 2 courses of 6 sessions per course. Panels A, B, and C show mean change ± standard error of the mean in IIEF-EF score, SEP3, and PSV, respectively, after 6 (n = 18), 6 + 6, (n = 18), or 12 sessions (n = 21) of shockwave therapy at 6-month follow-up. IIEF-EF = International Index of Erectile Function erectile function domain; PSV = peak systolic velocity; SEP3 = Sexual Encounter Profile question 3. Figure 6 is available in color at www.jsm.jsexmed.org.

adverse events. The similar efficacy independent of the frequency of sessions per week and the possibility for a 0- to 6-month interval between courses of 6 sessions allow patients and physicians good logistical and financial flexibility when opting for shockwave therapy.

In our effort to develop a standard treatment protocol, some critical questions remain unanswered.[16] Our study used a relatively low energy flux density of 0.05 mJ/mm^2 and effective energy (E_{12mm}) of 3.4 mJ. Most published studies have used an energy flux density of 0.09 mJ/mm^2,[1–3] but have not reported the effective energy. Effective energy (E_{12mm}) is the energy transmitted by a shockwave pulse over a 12-mm circular area at the focal plane, whereas energy flux density as reported refers only to the energy transmitted at the focal point; therefore, energy flux density and effective energy are crucial parameters to compare clinical trials results using different shockwave machines and probes.

We started with a low energy level for safety purposes, because 12 sessions were offered without interval in phase 1 and an additional 6 sessions were applied in phase 2. Another question arises regarding the frequency of sessions per week; the possibility of offering treatment sessions 3 times per week would allow patients to minimize treatment duration. Based on our results, we are currently investigating the possibility of using LiST 3 times per week and an energy flux density of 0.096 mJ/mm^2.

Organic ED is strongly linked to chronic, progressive mechanisms such as diabetes, cardiovascular disease, and aging.[19–21] It is hypothesized that early intervention might prevent or slow the development of irreversible damage such as cavernosal fibrosis and neuronal degeneration.[19] However, current treatment of ED focuses on temporary symptomatic relief rather than on addressing the cause.[22] Shockwave therapy could play an important role as the only currently available option that focuses on disease modification and restoration of erectile function.

Table 5. Minimally clinical important difference* by number of low-intensity shockwave therapy sessions at 6-month follow-up

Sessions	Mild (%)	Moderate (%)	Severe (%)	Total (%)
6	10/12 (83)	3/7 (43)	0/2 (0)	13/21 (62)
12†	18/20 (90)	10/14 (71)	1/5 (20)	29/39 (74)
18†	8/8 (100)	5/7 (71)	2/3 (67)	15/18 (83)

*Based on attainment with baseline 1 as the reference time point.
†Data are derived from a combination of phase 1 and 2 results; hence, patients received 12 or 18 sessions at different treatment intervals.

Interestingly, our preliminary analysis indicates that high responders to LiST are younger and respond more strongly to PDE5i. A physiologic explanation could be that younger patients and high responders to PDE5i have limited ultrastructural changes within the corporal tissue. Therefore, a more viable penile tissue can generate a more effective biological and clinical response to shockwave therapy. If this hypothesis proves to be true, it will raise intriguing questions of whether shockwave therapy would be most effective as early 1st-line treatment or could considered a preventative strategy against ED in high-risk patients (eg, those with diabetes). The results of phase 2, which showed that repeat treatment with LiST is safe and beneficial, suggest that repeated LiST as a regular maintenance therapy could be feasible. This opens the opportunity to develop new care models for our patients.

Limitations of our study include its small sample and lack of a sham-controlled arm. However, all patients were randomized to different groups, and baseline characteristics were similar between groups at baseline 1 (phase 1). Moreover, the lack of a sham arm is compensated in part with the use of triplex ultrasonography, performed blindly by the same experienced investigator, to include only patients with objectively documented arteriogenic ED. In fact, our penile hemodynamics results mirror the conclusions drawn from patient-reported outcomes (ie, efficacy in the 2 groups), with slightly greater efficacy in the 12-session group. The strong dose-dependent effect, high efficacy rate, and durability of results up to 6 months suggest that our results are not due to a placebo effect.

In conclusion, LiST is an effective and safe treatment option for patients with vasculogenic ED. It can be applied once or twice per week, without any break. Increasing the number of sessions from 6 to 12 further improves the number of successful sexual encounters. 12 sessions can be applied in 2 courses of 6 sessions with an interval up to 6 months. Retreatment with low-intensity shockwaves can further improve erectile function without side effects. The observed improvement in IIEF-EF score by 5 to 7 points after 12 to 18 sessions shifts ED severity by at least 1 category (eg, from moderate to mild ED). We postulate that LiST could be opening the door to an era of practical and accessible disease modification therapy for ED.

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