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ARTICLE

Low-intensity shockwave therapy (LiST) for erectile dysfunction: a randomized clinical trial assessing the impact of energy flux density (EFD) and frequency of sessions

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Abstract

The impact of energy flux density (EFD) used on low-intensity shockwave therapy (LiST) for erectile dysfunction (ED) has not been explored. Our aim was to compare EFD 0.05 versus 0.10 mJ/mm^2 regarding efficacy and safety of 12-treatment sessions when applied two or three times per week. Ninety-seven patients with vasculogenic ED, PDE5 inhibitors users were randomized into four groups, to receive 12 LiST sessions. Group A ($n = 24$) : two sessions per week, EFD 0.05 mJ/mm^2; Group B ($n = 24$): three sessions per week, EFD 0.05 mJ/mm^2; Group C ($n = 24$): two sessions per week, EFD 0.10 mJ/mm^2; Group D ($n = 25$): three sessions per week, EFD 0.10 mJ/mm^2. International Index for Erectile Function—Erectile Function domain (IIEF-EF), Minimally clinical important differences (MCID), sexual encounter profile, and triplex ultrasonography parameters were used to asses erectile function. Eighty-nine patients completed the 6-month follow-up (FU). All four groups improved in mean IIEF-EF score, average SEP3 "Yes" response rates at 6-month FU visit compared with baseline ($p < 0.001$). MCID at 6-month FU visit was achieved in 82.6%, 77.3%, 87%, and 81% in Groups A, B, C, and D, respectively. Mean PSV (cm/s) at baseline versus 3-month FU visit were 30.32 versus 34.67 for Group A, 30.02 versus 35.02 for Group B, 30.2 versus 36.02, for Group C, 29.43 versus 34.3 for Group D ($p < 0.01$). There were no statistical significant differences in the change of all outcome measures assessing erectile function between different sessions frequency. A tendency for better efficacy using EFD 0.10 mJ/mm^2 was noticed, although it did not reach statistical significance. No treatment-related side-effects were reported. This study lacks a sham-controlled arm. However, all patients were randomized to the four groups, and baseline characteristics were similar between the groups. Moreover, arterial insufficiency was confirmed among all patients by penile triplex ultrasonography. Conclusively, patients may benefit equally when sessions are applied either two or three per week. An EFD of 0.10 mJ/mm^2 could result in better outcomes, but further studies are needed to validate this observation.

Introduction

Efficacy and safety of low-intensity shockwave therapy (LiST) for erectile dysfunction (ED) has been reported previously [1–4]. Published studies have used a wide range of LiST protocols: energy flux density (EFD) ranged from 0.09 to 0.25 mJ/mm^2; session frequency once or twice per week; total number of sessions from 4 to 12, with 12-session protocols typically having a 3-week break between sixth and seventh session. Studies that systematically investigate LiST treatment parameters are lacking [5].

Thus, a series of studies were designed, in an effort to define the optimal LiST protocol for men with vasculogenic ED. Throughout the studies we used consistent inclusion/exclusion criteria, study machine, treatment technique, and experimental design [6]. This enabled an unbiased evaluation of changing parameters, such as shockwave energy levels, number of therapy sessions, and frequency of sessions. Our recent publication showed a dose-dependent effect of LiST: (1) 12 sessions result in greater efficacy,

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compared with 6 and (2) it is meaningful to repeat treatment if the patient requests for more sessions [6]. In that publication, the EFD used was 0.05 mJ/mm^2, and 12 session results were comparable with other 12 session protocols using 0.09 mJ/mm^2.

In clinical practice, we encounter patients who request for a more intensive LiST protocol, in hope of achieving faster and greater improvements of their erectile function. However, there is no clinical study investigating the safety and efficacy of applying more than two sessions of LiST per week, nor is there a study comparing the effect of different EFDs.

The current study explored the following research question: the efficacy and safety of 12 sessions of LiST applied two or three times per week with EFD 0.10 versus 0.05 mJ/mm^2.

Materials and methods

Study design

The study is a prospective, randomized, four parallel-arm, open-label study and was performed at the Andrology outpatient clinic of an academic hospital. The study was conducted according to Good Clinical Practices and the Declaration of Helsinki. It was reviewed and approved by the institutional ethics board and registered in clinicaltrials.gov (NCT03089294). A written informed consent was given by all participants before being enrolled in the study. Patients were recruited from May 2016, and final results were obtained in July 2018.

The trial enrolled patients that clearly stated being in a stable heterosexual relationship, while their clinical background indicated vasculogenic ED, under treatment with PDE5 inhibitors (PDE5i) for at least 3 months, and presence of ED for at least 6 months. During the screening visit, all patients provided information on their sexual and medical history, and underwent laboratory tests and physical examination, so that diagnosis of vasculogenic ED could be corroborated. Patients were given Sexual Encounter Profile (SEP) diaries and were asked to complete them during a 4-week PDE5i washout period and then return for baseline visit. During the baseline visit, all patients filled in the International Index of Erectile Function-Erectile Function Domain (IIEF-EF) and underwent penile triplex ultrasonography by the same experienced investigator (DK).

Inclusion criteria at baseline involved an IIEF-EF score of <26 [7] without use of oral PDE5i or other erectogenic aids (4-week-washout period) and a cavernosal artery peak systolic velocity (PSV) of <35 cm/s [8]. In order to ensure unbiased conclusions for the study results, patients were asked to consent to reserving themselves from all ED therapy throughout the study period. Their consent was updated and affirmed at each study visit.

Eligibility criteria excluded all patients with psychogenic or neurogenic ED, untreated endocrinologic disease (including normal testosterone levels), penile anatomical abnormalities, penile or any major surgery at the pelvis, untreated or uncontrolled diabetes (defined as fasting blood glucose levels >140 mg/dL under diabetic treatment), active cancer, hemophilia, high risk of thrombosis, and psychiatric condition.

The study flowchart is presented in Fig. 1.

Study protocol

The study protocol is illustrated in Fig. 2. After a primary screening, all patients entered into a 4-week-washout period that excluded administration of PDE5is or any other erectogenic aids such as natural herbs, intraurethral alprostadil, intracavernosal injections, and/or vacuum pump devices. Upon completion of the washout period, all patients underwent a baseline visit. Patients, identified with IIEF-EF <26 and cavernosal artery PSV < 35 cm/s during their baseline visit, were randomized into Groups A, B, C, and D. LiST sessions were performed as follows: Groups A and C had sessions twice a week (treatment interval of 7 ± 2 days), while Groups B and D underwent sessions three times per week (treatment interval of 3 ± 1 days). Patients were evaluated using IIEF-EF and SEP scores at baseline, 1, 3, and 6 months after their final LiST session. During these visits, patients were invited to provide their replies for the IIEF-EF and SEP questionnaires in separate clinical visits. Penile triplex ultrasonography was performed during the baseline and the 3-month follow-up (FU) visits. It should be emphasized that the study protocol and its outcome measures are identical with previously published studies, which aimed to study the number (6 vs. 12) and frequency of sessions (once or twice per week) [4, 6].

Randomization–allocation concealment

All eligible patients were randomized to one of the four groups with an equal allocation ratio (1:1:1:1) during their baseline visit. The randomization sequence was computer-generated (using GraphPad^{TM} software) by the study coordinating team. To further minimize bias and in order to ensure concealment, treatment allocation was communicated to the investigators by the coordinating centre via a web-based registration system.

Blinding

The present protocol of the study was executed by three well-trained investigators [3]. Nevertheless, neither the

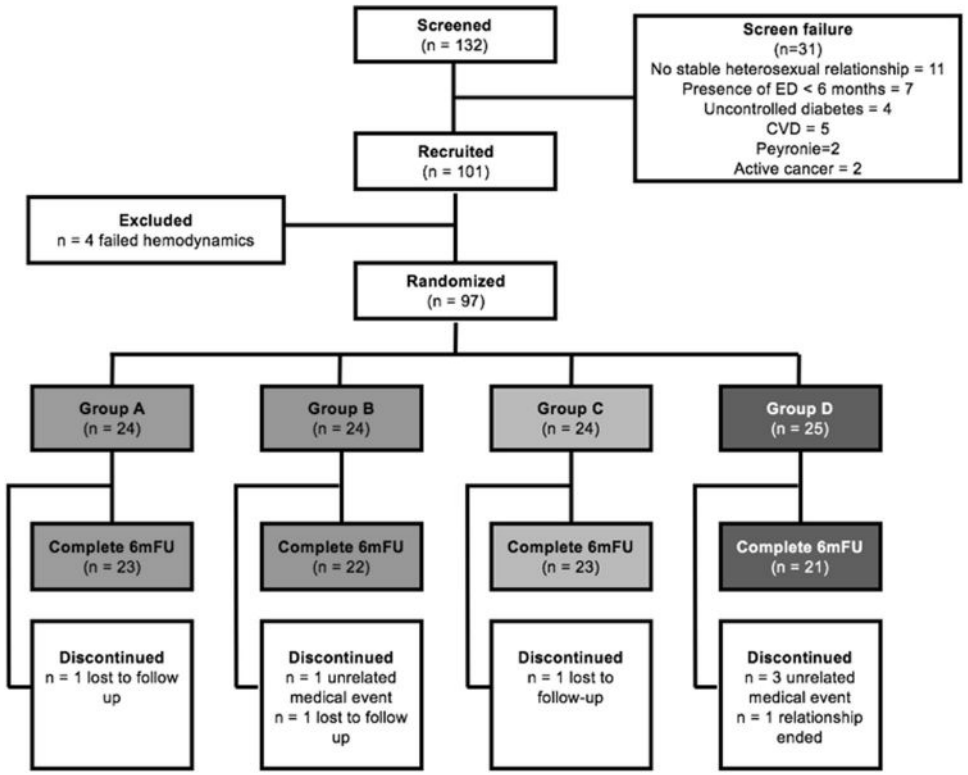

Fig. 1 Study flowchart

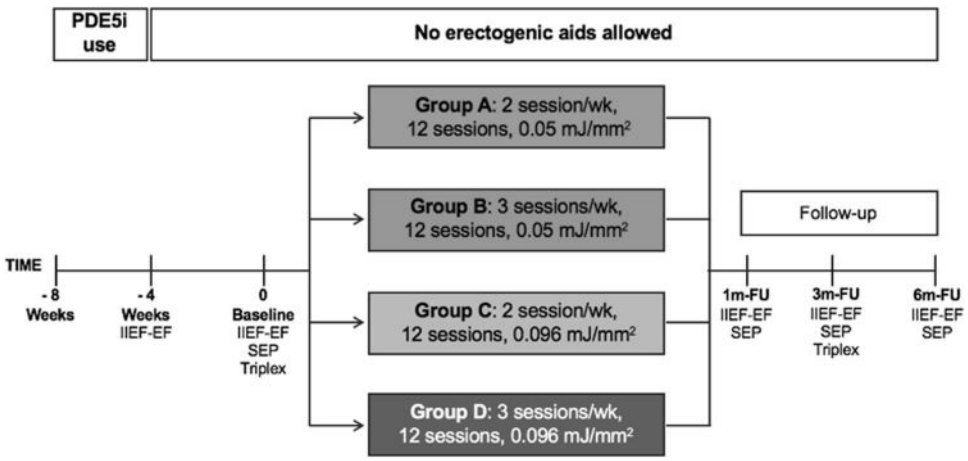

Fig. 2 Study protocol

participants nor the study investigators could be blinded because of the different treatment protocols applied to each group. Yet, all triplex ultrasonography measurements were performed blind to the group randomization, by the same experienced clinician (DK). In addition, the data collection clinician as well as data analyst were both blinded as to which treatment protocol refers to Groups A–D.

Penile triplex ultrasonography

For assessment of potential treatment-related structural changes, we performed penile ultrasonography twice: at baseline and at 3-month FU visit, both times using the same experienced investigator (DK) and a previously published protocol. Performance of Triplex Ultrasonography was drug-induced with an intracavernosal trimix solution 0.5 ml (papaverine 300 mg—phentolamine 10 mg—alprostadil 100 µg). Redosing was administered on demand aiming for complete smooth muscle relaxation. Quantification of the PSV, EDV, and RI was performed according to the standardized protocol [4]. We only recorded the highest values achieved. The same experienced clinician (DK) performed all triplex ultrasonography measurements, who was not involved in any other aspect of the trial.

Shockwave therapy application

Three trained investigators applied the following treatment protocol in 20-min sessions using a standard commercial gel normally used for sonography on the subject's penis and on the membrane of the shockwave applicator. No local or systemic analgesia was administered. Patients were subjected to treatment with a low energy shockwave generator ARIES 2 and the Smart focus probe (Dornier MedTech GmbH, Wessling, Germany). Shockwaves were delivered at EFD 0.05 mJ/mm^2 for Groups A and B and 0.10 mJ/mm^2 for Groups C and D. Effective energy ($E_{12\,mm}$) was 3.4 mJ and frequency at 8 Hz for Groups A and B (level 4, ARIES 2 device), while effective energy ($E_{12\,mm}$) was 6.6 mJ and frequency at 5 Hz for Groups C and D (level 7, ARIES 2 device). As previously published [4, 6], in order to reach both corpora and avoid the urethra at the same time, special attention was paid to the shockwave application, which was performed by slowly advancing the shockwave probe back and forth from the glans penis to the pubis. This method of treatment application enables evenly distributed energy along both corpora cavernosa.

Each treatment session involved the application of 5000 shockwaves with the penis manually stretched: 1000 shockwaves each to the left and right mid and distal penile shaft, 1000 shockwaves to each of the two crura and finally 500 shockwaves each to the left and right proximal penile shaft.

Outcome measures

The outcome measures were identical with our previously published study [4, 6]. The IIEF-EF score was used as to evaluate treatment success, which was defined as achievement of the minimal clinical important difference (MCID); MCID has been defined as an IIEF-EF score increase equal to or >2, 5, and 7 points for mild, moderate, and severe ED, respectively [9]. Sexual performance was assessed via the SEP diaries, emphasizing in question 3 (SEP3): "Did your erection last long enough for you to have successful intercourse?". Moreover, for the objective assessment of penile hemodynamics, the standard parameters PSV, EDV, and RI were used.

Sample size

When the study was planned, there were no previous studies comparing different LiST energies to use for reference and sample size calculation. We estimated that 20 patients per group would be sufficient to establish some preliminary data for future work. Hence, we recruited 97 patients in total (24–25 per group, four groups).

Statistics

Data analysis was generated using Microsoft Excel^{TM} (2013) and Graphpad Prism 7^{TM}. Baseline variables were analyzed by one-way ANOVA (continuous variables) or Chi-square test (discrete variables). Paired *t*-test was used to assess changes within a group from baseline to follow-up. Two-tailed Fisher's exact test was used to assess significance for discrete variables (e.g., the difference in proportion of MCID success rates between the groups). Two-tailed *t*-test for independent samples was used to assess the difference in all other outcome measures between the groups. The level of significance for all analyses was set at 5% (p-value < 0.05).

Results

Study sample

A total of 132 patients were screened and 97 were eligible according to the inclusion criteria. Of the 97 patients enrolled to the study, 89 of them completed the 6-month FU visit (Fig. 1). There was no statistically significant difference in baseline patient demographics and disease severity between the groups (Table 1). No significant differences in baseline IIEF-EF were found. Group D had more patients with severe ED, but this did not reach statistical significance (Table 1).

Treatment efficacy (6-month FU vs. baseline)

A statistically significant improvement in mean IIEF-EF score and SEP3 "Yes" responses rate was observed at 1-month FU visit compared with baseline values and remained durable till the 6-month FU visit for all groups. ($p < 0.001$) (Fig. 3a, b, Table 2). In 67.5% of the patients (60/89) IIEF-EF increased by at least five points, which represents one IIEF-EF category improvement. Only in 9% (8/89) of the patients, no IIEF-EF improvement was noted (≤1 point increase). MCID was achieved in 82% (73/89) of all patients (Table 3). Moreover, mean PSV (cm/s) at baseline versus 3-month FU visit revealed a statistically significant improvement for all groups ($p < 0.001$) (Fig. 3c).

Comparison of two versus three sessions per week

Both Group A and B received 12 sessions of LiST with EFD 0.05 mJ/mm^2 but Group A with a frequency of two sessions per week (6-week-treatment period), while Group B with a frequency of three sessions per week (4-week-treatment period). No statistically significant difference between the two groups was reported regarding change of

Table 1 Patients demographics and baseline disease severity

	Group A		Group B		Group C		Group D		*p*-value
Sample size (completers)	23		22		23		21		
Age (year), mean ± SD	58.7 ± 9.5		57.2 ± 9.3		56.5 ± 7.6		57.6 ± 6.9		0.84
BMI, mean ± SD	29.0 ± 3.7		28.3 ± 4.6		30.1 ± 4.0		28.0 ± 3.0		0.28
Concomitant condition, number (%)									
Diabetes mellitus	6	(26.1)	7	(31.8)	7	(30.4)	6	(28.6)	0.98
Cardiovascular risk factors[a]	21	(91.3)	20	(90.9)	21	(91.3)	20	(95.2)	0.95
Hypertension	9	(39.1)	9	(40.9)	8	(34.7)	10	(47.6)	
Hyperlipidemia	9	(39.1)	10	(45.4)	9	(39.1)	11	(52.3)	
Obesity	11	(47.8)	10	(45.4)	12	(52.1)	12	(57.1)	
Smoking (current or former)	16	(69.5)	17	(77.2)	17	(73.9)	16	(76.1)	
Diagnosed cardiovascular disease	6	(26.1)	4	(18.2)	1	(4.3)	7	(33.3)	0.09
Baseline IIEF-EF score, mean ± SD	18.3 ± 4.2		17.0 ± 3.4		17.5 ± 4.5		16.1 ± 4.9		0.39
Baseline ED severity, number (%)									
Mild ED (IIEF-EF 17–25)	14	(60.9)	15	(68.2)	12	(52.2)	10	(47.6)	0.52
Moderate ED (IIEF-EF 11–16)	7	(30.4)	6	(27.3)	11	(47.8)	7	(30.4)	0.48
Severe ED (IIEF-EF 0–10)	2	(8.7)	1	(4.5)	0	(0.0)	4	(19.0)	0.11

P-values describe the comparison between all four groups, obtained by one-way ANOVA (continuous variables), or Chi-square test (discrete variables)

[a]Including at least one of the following: hypertension, hyperlipidemia, obesity, and smoking (current or former)

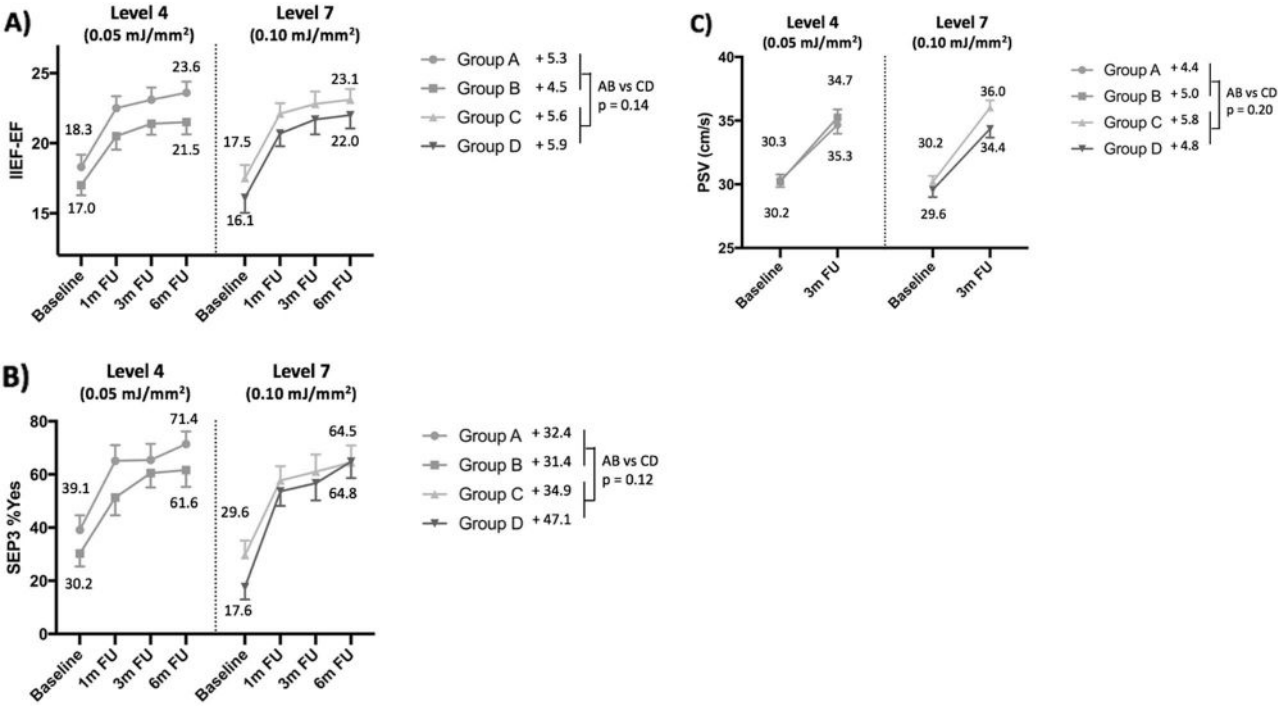

Fig. 3 Erectile function assessment tools. Mean ± SEM of **a** IIEF-EF scores, **b** SEP3, and **c** PSV at different time points. $N = 21$–23 per group. *p*-values describe the comparison of combined results of Groups A and B (energy level 4) versus combined results of Groups C and D (energy level 7), obtained by two-tailed *t*-test of independent samples

mean IIEF-EF score ($p = 0.36$), and average SEP3 "Yes" responses rate ($p = 0.90$) from baseline to 6-month FU visit. A statistically significant difference was not reached neither at 1-month nor at 3-month FU visit compared with baseline (Table 4). Moreover, the increase of mean PSV from baseline to 3-month FU did not revealed statistically

Table 2 Average IIEF-EF score and SEP-Q3 (% Yes) rates

		Screening (+PDE5i)	Baseline (washout)	1-month FU	3-month FU	6-month FU	6-month FU baseline
Average IIEF-EF	A ($n = 23$)	25.4	18.3	22.5	23.1	23.6	+5.3
	B ($n = 22$)	23.5	17.0	20.5	21.4	21.5	+4.5
	C ($n = 23$)	25.5	17.5	22.1	22.8	23.1	+5.6
	D ($n = 21$)	25.3	16.1	20.7	21.7	22.0	+5.9
Average SEP-Q3 (% Yes)	A ($n = 23$)	–	39.1%	65.1%	65.4%	71.4%	+32.4
	B ($n = 22$)	–	30.2%	51.3%	60.5%	61.6%	+31.4
	C ($n = 23$)	–	29.6%	57.7%	61.0%	64.5%	+34.9
	D ($n = 21$)	–	17.6%	53.6%	56.7%	64.8%	+47.1

Table 3 Clinical success rates by ED severity, at 6-month follow-up

	Mild (%)				Moderate (%)		Severe (%)		Total (%)
Group A	12/14	(85.7)	6/7	(85.7)	1/2	(50.0)	19/23	(82.6)	
Group B	12/15	(80.0)	5/6	(83.3)	0/1	(0.0)	17/22	(77.3)	
Group C	10/12	(83.3)	10/11	(90.9)	0/0	–	20/23	(87.0)	
Group D	9/10	(90.0)	5/7	(71.4)	3/4	(75.0)	17/21	(81.0)	
AB vs. CD *p*-value	1.00		1.00		0.49		0.78		

Clinical success is based on attainment of the minimal clinical important difference in IIEF-EF score. *p*-values describe the comparison of the combined results of Groups A and B versus combined results of Groups C and D, obtained by two-tailed Fisher's exact test

significant difference between Group A and B outcomes ($p = 0.32$) (Table 4).

Similar results were reported for Group C (12 sessions of LiST, EFD 0.10 mJ/mm^2, two sessions per week) versus Group D (12 sessions of LiST, EFD 0.10 mJ/mm^2, three sessions per week) as there was no statistically significant difference regarding the change of all erectile function assessment tools (mean IIEF-EF score, average SEP3 "Yes" responses rate and mean PSV) values from baseline to 1, 3, and 6-month FU visit (Table 4).

Hence, 12 LiST sessions for ED seems to have similar efficacy when applied with a frequency protocol of two or three times per week.

Comparison between two different EFD levels

When combined efficacy results of Groups A and B (Level 4, EFD = 0.05 mJ/mm^2) versus combined results of Groups C and D (Level 7, EFD = 0.10 mJ/mm^2) were calculated, most outcome measures (IIEF-EF, SEP3, and PSV) showed a trend toward greater efficacy in Groups C and D compared with Groups A and B. However, this did not reach statistical significance (Table 4). For example, there was a trend toward a higher increase in mean IIEF-EF score from baseline to 3-month FU visit when EFD of 0.10 mJ/mm^2 was applied ($p = 0.09$). This trend persisted at 6-month FU visit ($p = 0.14$) (Table 4).

Nevertheless, when percent of men who achieved MCID at 6-month FU visit was calculated, energy Level 4 (EFD = 0.05 mJ/mm^2) proved to have similar efficacy results compared with energy Level 7 (EFD = 0.096 mJ/mm^2) in all ED severity subgroup (mild–moderate–severe) of patients ($p = 0.78$) (Table 3).

High responders versus nonresponders to LiST

In order to explore predicting factors for LiST responders, we arbitrarily defined as high responders those patients with ≥5-point increase in IIEF-EF score, while patients with ≤1-point increase in IIEF-EF score were classified as nonresponders. Regardless of baseline disease severity and treatment protocol, we noticed that 67% (60/89) of patients were high responders to LiST, whereas a small proportion (9/89) were nonresponders with almost no response. Baseline characteristics of these high responders were compared versus those of nonresponders to investigate possible prognostic factors. Of all factors considered, including age, baseline IIEF-EF score, body mass index, mean PSV, change or decrease in IIEF-EF score after PDE5i washout, and mean baseline percentage of Yes responses to SEP3, only average decrease of IIEF-EF score after PDE5i washout reached statistically significant difference between LiST high responders and LiST nonresponders group (−8.4 vs. −4.9). We found that patients with higher response to PDE5i were also high responders to LiST ($p < 0.01$). This observation has been published previously [4, 6]. On the contrary, younger age did not correlate with LiST efficacy in the present study, as average age did not differ significantly between LiST high responders (57.5 years old) and LiST nonresponders (60.0 years old) ($p = 0.39$).

Safety

Safety of the method was assessed by performing personal interview before and after each LiST session and at the FU

Table 4 Change in outcome measures from baseline to 1-month FU, 3-month FU, and 6-month FU

		Group A	Group B	A vs. B *p*-value	Group C	Group D	C vs. D *p*-value	AB vs. CD *p*-value
IIEF-EF	1-month FU	4.2 ± 1.6	3.5 ± 3.0	0.35	4.6 ± 2.7	4.6 ± 2.9	0.99	0.19
	3-month FU	4.7 ± 2.2	4.4 ± 1.8	0.53	5.3 ± 2.9	5.6 ± 2.8	0.76	0.09
	6-month FU	5.3 ± 2.8	4.5 ± 2.8	0.36	5.6 ± 2.5	5.9 ± 2.3	0.69	0.14
SEP3 (% Yes)	1-month FU	26.0 ± 20.2	21.1 ± 22.5	0.44	28.1 ± 24.2	35.9 ± 22.6	0.27	0.09
	3-month FU	26.3 ± 26.8	30.3 ± 21.1	0.58	31.4 ± 25.9	39.0 ± 30.2	0.37	0.22
	6-month FU	32.4 ± 20.8	31.4 ± 29.1	0.90	34.9 ± 27.3	47.1 ± 29.1	0.16	0.12
PSV (cm/s)	3-month FU	4.35 ± 2.23	5.04 ± 2.33	0.32	5.82 ± 2.44	4.79 ± 2.22	0.15	0.20
EDV (cm/s)	3-month FU	−0.59 ± 2.36	−0.07 ± 2.70	0.49	−0.25 ± 2.40	−1.11 ± 2.36	0.24	0.53
RI	3-month FU	0.04 ± 0.08	0.04 ± 0.09	0.81	0.04 ± 0.08	0.06 ± 0.07	0.38	0.77

Results are described as mean ± standard deviation

p-values describe the comparison of combined results of Groups A and B versus combined results of Groups C and D, obtained by two-tailed *t*-test of independent sample

visits. Patients were asked to report any side effect they might have experienced during the session or at the time interval between sessions or FU visits. Open ended questions were used such as: "Did you experience any side effect during the session?" or "Do you want to report something you believe is relevant to LiST treatment you received?". Also, clinical examination was performed, including penile and scrotal review and palpation, before and after each LiST session and at the FU visits. Moreover, penile ultrasound was performed at baseline and at 3-month FU visit in order to exclude subclinical structure changes or subclinical penile hematomas. Even at the highest EFD (0.10 mJ/mm^2) and frequency of sessions three times per week (12 sessions in 4 weeks), all patients tolerated LiST without any side effects being reported. No abnormal findings were seen during clinical examination and penile ultrasound. Thus, up to 12 sessions, three times per week of LiST with the Dornier Aries 2 machine at energy 0.10 mJ/mm^2 (Level 7) does not appear to pose any safety concerns.

Discussion

Previously available nonsurgical ED treatment options produce only temporary symptomatic relief [10]. LiST is the first treatment modality proposed to modify the underlying pathophysiology in men with organic ED [11]. In the clinical setting, there is an emerging need for an evidence-based protocol in order to standardize the method and inform clinical decisions [12].

Crucial clinical questions raised in previous systemic reviews and meta-analyses regarding the appropriate use of this novel ED treatment method, such as frequency of sessions per week and impact of EFD to the efficacy and safety of the treatment [4, 5, 11–14]. The main point of criticism is the lack of a standardized and evidenced based LiST protocols for ED and the use of various shockwave applicators in different LiST protocols making the comparison impossible [15, 16].

In that direction, the current study compared for the first time four different LiST protocols, all using Dornier Aries 2 device, in order to answer three main research questions of great clinical importance: (1) Is application of 12 treatment sessions within 4 weeks (3 per week) as efficacious and safe as within 6 weeks (2 per week)? (2) Is there any benefit treating the patients with EFD 0.10 mJ/mm^2 versus 0.05 mJ/mm^2? (3) Are there any safety concerns when applying EFD 0.10 mJ/mm^2 three times per week?

Our results demonstrated that (1) 12 sessions of LiST applied either two or three times per week (6- or 4-week-treatment period)—without a break between the sixth and seventh session—are both efficacious and safe with durable effects up to 6-months follow-up; (2) EFD 0.10 mJ/mm^2 may be more efficacious, but this could not be proven given the sample size in this study; and (3) 12 sessions applied either two or three times per week with EFD 0.10 mJ/mm^2 should be considered safe, without any side effects.

There may be a slight energy dose-dependent effect, with a trend for greater efficacy with EFD 0.10 mJ/mm^2 compared with EFD 0.05 mJ/mm^2. In contrast, changing session frequency from two to three times per week does not appear to affect clinical efficacy. At this point we have to highlight that a smart focus energy machine was used in the study and the same results cannot be assimilated for different types of shockwave energy and devices. In our current study, we report both the EFD and effective energy ($E_{12\,mm}$) in which shockwaves were delivered for each group. Most published studies have used an EFD of 0.09 mJ/mm^2 without reporting the effective energy. Effective energy ($E_{12\,mm}$) is the energy transmitted by a shockwave pulse over a 12-mm

circular area at the focal plane, whereas EFD as reported refers only to the energy transmitted at the focal point; Interestingly, two shockwave devices could have the same EFD but differ regarding their effective energy ($E_{12\,mm}$). Therefore, both EFD and effective energy are crucial physical parameters to compare clinical trials results using different shockwave machines and probes. As a recent meta-analysis points out, new comparison indexes should emerge that would include all the crucial parameters of LiST (number of shockwaves, frequency of sessions, EFD, type of energy delivered, device and method of application), calculating the "biologically effective energy" of each protocol and shockwave applicator in order to compare different protocols and devices [5]. Moreover, in this way, it could be investigated more clearly if there is a threshold level of shockwaves number or "energy" which can be applied regarding saturation effect and also safety of repeated treatments.

In the first trials of shockwave therapy for ED [17], the 3-week interval after the first six 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 adverse events, an advantage which, together with the options to offer sessions once, twice or three times per week, allow patients and physicians to have excellent logistical flexibility when opting for shockwave therapy. Our study adds to the effort to develop a standard LiST protocol, as our results suggests the possibility of offering the treatment sessions three times per week, minimizing treatment duration to 4 weeks.

The finding that high responders to PDE5i are also high responders to LiST can be easily explained as efficacy of both therapeutic options depends on the severity of the underlying pathology [18–20]. Moreover, the majority of the potential working mechanisms and cellular signaling pathways of LiST for ED, which have been recently presented are also involved to the PDE5i mechanism of action [21, 22]. The finding that age per se did not predict LiST response may be explained from the fact that health status rather than age determines the quality of the erectile tissue. A theory previously supported in an animal study in which LiST application in naturally aged rats, without any comorbidities, showed a positive effect by partially reversing changes associated with aging in erectile tissue [23]. Based on this observation, it is postulated that early intervention may prevent or slow the development of irreversible damage such as cavernosal fibrosis and neuronal degeneration [18, 24].

Limitations of our study include its small sample size, which eventually resulted in a slightly underpowered comparison between the groups, the nonblinded design and the lack of a sham-controlled arm. However, all patients were randomized to the different groups, and baseline characteristics were similar between the groups at baseline. Moreover, the lack of a sham arm is partly compensated with the use of triplex ultrasonography—performed blindly by the same experienced investigator—in order to include only patients with objectively documented arteriogenic ED. In fact, our penile hemodynamics results mirror the conclusions drawn from the patient reported outcomes. Finally, 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. Nevertheless, it is clear that properly-designed double blind randomized sham-controlled clinical trials with adequate sample sizing and longer follow-up periods are still needed in order to evaluate the efficacy and safety of LiST as novel ED treatment modality.

In conclusion, LiST is an effective and safe treatment option for patients with vasculogenic ED. A 12 LiST sessions protocol can be applied twice or three times per week, without any break, minimizing the therapy duration. Increasing EFD up to 0.10 mJ/mm^2, may further improve the number of successful sexual encounters, however we could not prove this conclusively in this study. We postulate that LiST may play an important role as an emerging option offering the chance of disease modification and improvement of erectile function.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Gruenwald I, Appel B, Vardi Y. Low-intensity extracorporeal shock wave therapy–a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. J Sex Med. 2012;9:259–64.
2. Kitrey ND, Gruenwald I, Appel B, Shechter A, Massarwa O, Vardi Y. Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. J Urol. 2016;195:1550–5.
3. Vardi Y, Appel B, Kilchevsky A, Gruenwald I. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. J Urol. 2012;187:1769–75.
4. Kalyvianakis D, Hatzichristou D. Low-intensity shockwave therapy improves hemodynamic parameters in patients with vasculogenic erectile dysfunction: a triplex ultrasonography-based sham-controlled trial. J Sex Med. 2017;14:891–7.

5. Sokolakis I, Hatzichristodoulou G. Clinical studies on low intensity extracorporeal shockwave therapy for erectile dysfunction: a systematic review and meta-analysis of randomised controlled trials. Int J Impot Res. 2019;31:177–94.
6. Kalyvianakis D, Memmos E, Mykoniatis I, Kapoteli P, Memmos D, Hatzichristou D. 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;15:334–45.
7. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. Urology. 1999;54:346–51.
8. Benson CB, Aruny JE, Vickers MA Jr. Correlation of duplex sonography with arteriography in patients with erectile dysfunction. AJR Am J Roentgenol. 1993;160:71–3.
9. Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol. 2011; 60:1010–6.
10. Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, et al. Erectile dysfunction. Nat Rev Dis Prim. 2016;2:16003.
11. Young Academic Urologists Men's Health G, Fode M, Hatzichristodoulou G, Serefoglu EC, Verze P, Albersen M. Low-intensity shockwave therapy for erectile dysfunction: is the evidence strong enough? Nat Rev Urol. 2017;14:593–606.
12. Hatzichristou D. Low-intensity extracorporeal shock waves therapy (LI-ESWT) for the treatment of erectile dysfunction: where do we stand? Eur Urol. 2017;71:234–6.
13. Qiu X, Lin G, Xin Z, Ferretti L, Zhang H, Lue TF, et al. Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. J Sex Med. 2013;10:738–46.
14. Clavijo RI, Kohn TP, Kohn JR, Ramasamy R. Effects of low-intensity extracorporeal shockwave therapy on erectile dysfunction: a systematic review and meta-analysis. J Sex Med. 2017;14:27–35.
15. Schoofs E, Fode M, Capogrosso P, Albersen M. For the European association of urology young academic urologists men's health G. Current guideline recommendations and analysis of evidence quality on low-intensity shockwave therapy for erectile dysfunction. Int J Impot Res. 2019;31:209–17.
16. Yang H, Seftel AD. Controversies in low intensity extracorporeal shockwave therapy for erectile dysfunction. Int J Impot Res. 2019;31:239–42.
17. Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol. 2010;58:243–8.
18. Musicki B, Bella AJ, Bivalacqua TJ, Davies KP, DiSanto ME, Gonzalez-Cadavid NF, et al. Basic science evidence for the link between erectile dysfunction and cardiometabolic dysfunction. J Sex Med. 2015;12:2233–55.
19. Cellek S, Cameron NE, Cotter MA, Muneer A. Pathophysiology of diabetic erectile dysfunction: potential contribution of vasa nervorum and advanced glycation endproducts. Int J Impot Res. 2013;25:1–6.
20. Echeverri Tirado LC, Ferrer JE, Herrera AM. Aging and erectile dysfunction. Sex Med Rev. 2016;4:63–73.
21. Sokolakis I, Dimitriadis F, Teo P, Hatzichristodoulou G, Hatzichristou D, Giuliano F. The basic science behind low-intensity extracorporeal shockwave therapy for erectile dysfunction: a systematic scoping review of pre-clinical studies. J Sex Med. 2019;16:168–94.
22. Liu T, Shindel AW, Lin G, Lue TF. Cellular signaling pathways modulated by low-intensity extracorporeal shock wave therapy. international journal of impotence research. Int J Impot Res. 2019;31:170–6.
23. Sokolakis I, Dimitriadis F, Psalla D, Karakiulakis G, Kalyvianakis D, Hatzichristou D. Effects of low-intensity shock wave therapy (LiST) on the erectile tissue of naturally aged rats. Int J Impot Res. 2019;31:162–9.
24. Gruenwald I, Spector A, Shultz T, Lischinsky D, Kimmel E. The beginning of a new era: treatment of erectile dysfunction by use of physical energies as an alternative to pharmaceuticals. Int J Impot Res. 2019;31:155–61.