Penile Low Intensity Shock Wave Treatment is Able to Shift PDE5i Nonresponders to Responders: A Double-Blind, Sham Controlled Study

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Abbreviation and Acronyms

CGIC = Clinical Global Impression of Change

ED = erectile dysfunction

EF = erectile function

FMD = flow mediated dilatation

LIST = low intensity shock wave treatment

MCID = minimal clinically important difference

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Purpose: We performed sham controlled evaluation of penile low intensity shock wave treatment effect in patients unable to achieve sexual intercourse using PDE5i (phosphodiesterase type 5 inhibitor).

Materials and Methods: This prospective, randomized, double-blind, sham controlled study was done in patients with vasculogenic erectile dysfunction who stopped using PDE5i due to no efficacy. All patients had an erection hardness score of 2 or less with PDE5i. A total of 58 patients were randomized, including 37 treated with low intensity shock waves (12 sessions of 1,500 pulses of 0.09 mJ/mm^2 at 120 shock waves per minute) and 18 treated with a sham probe. In the sham group 16 patients underwent low intensity shock wave treatment 1 month after sham treatment. All patients were evaluated at baseline and 1 month after the end of treatment using validated erectile dysfunction questionnaires and the flow mediated dilatation technique for penile endothelial function. Erectile function was evaluated while patients were receiving PDE5i.

Results: In the low intensity shock wave treatment group and the sham group 54.1% and 0% of patients, respectively, achieved erection hard enough for vaginal penetration, that is an EHS (Erection Hardness Score) of 3 ($p < 0.0001$). According to changes in the IIEF-EF (International Index of Erectile Function-Erectile Function) score treatment was effective in 40.5% of men who received low intensity shock wave treatment but in none in the sham group ($p = 0.001$). Of patients treated with shock waves after sham treatment 56.3% achieved erection hard enough for penetration ($p < 0.005$).

Conclusions: Low intensity shock wave treatment is effective even in patients with severe erectile dysfunction who are PDE5i nonresponders. After treatment about half of them were able to achieve erection hard enough for penetration with PDE5i. Longer followup is needed to establish the place of low intensity shock wave treatment in these challenging cases.

Key Words: testis, erectile dysfunction, high energy shock waves, phosphodiesterase 5 inhibitors, questionnaires

Extracorporeal LIST of the penis is a novel therapeutic modality for vasculogenic ED.[1] Extracorporeal shock wave therapy has been clinically examined and applied for various indications.[2] The exact mechanism of LIST is not yet clear, although basic and clinical research have been performed to understand its effect. The acoustic energy of LIST generates

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micromechanical forces and microtrauma. It triggers a chain of events that releases angiogenic factors,[3] induces neovascularization and enhances blood flow to the treated area.[4–7] Recruitment of stem and progenitor cells in the repair process is probably a crucial element.[8,9] The angiogenetic properties of LIST were investigated in the management of chronic wounds, peripheral neuropathy and cardiac ischemic disease.[2,4,8]

Following preliminary studies in humans the effect of LIST on EF was examined in an animal model. Shock wave energy improved nerve stimulated erection in diabetic rats, increased the endothelial content of penile tissue, improved the smooth muscle-to-collagen ratio and up-regulated the expression of growth factors.[10–12] Surprisingly this pro-erectile effect is probably not mediated by the nitric oxide/cyclic guanosine monophosphate pathway.[12]

In the last several years penile LIST has been shown to have a significant effect on EF, penile hemodynamics and endothelial function in multiple clinical trials. In 2010 the pioneering study demonstrated the favorable effect of LIST in middle-aged men with moderate-severe ED who responded well to PDE5i.[1] This effect was established in similar patients in the first prospective, randomized, double-blind, sham controlled study.[13] Promising results were recently reported by others who used the same device and protocol[14–16] as well as other devices with different protocols.[17–20]

LIST was also studied in patients with severe ED who responded poorly to PDE5i therapy.[21] In this pilot study about 70% of patients who were unable to achieve sexual intercourse with PDE5i at baseline achieved erection hard enough for vaginal penetration with oral PDE5i after shock wave treatment. The improvement in EF was clearly evident in subjective reports and in objective measurements of penile hemodynamics and endothelial function.

In the current study we investigated the effect of LIST on PDE5i nonresponders in a sham controlled manner.

MATERIALS AND METHODS

We performed a prospective, randomized, double-blind, sham controlled study of 86 men who underwent initial screening, including medical history and physical examination. Because 28 patients did not meet study inclusion criteria, 58 were randomized on a 2:1 ratio to LIST (40) or sham treatment (18). A total of 37 patients completed the study after active LIST with 3 dropouts as well as 18 in the sham group with no dropouts. Patients in the sham group were offered the choice of starting post-sham active treatment with an identical protocol and 16 of them completed the post-sham protocol (fig. 1). The study protocol was reviewed and approved by the institutional ethics review board. The study is listed in ClinicalTrials.gov (NCT01262157).

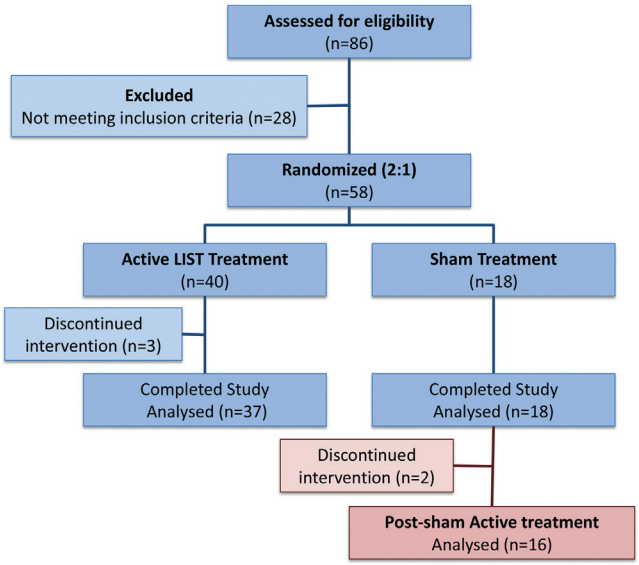

Figure 1.

Inclusion and Exclusion Criteria

All patients included in study were previous PDE5i responders, that is they had been able to achieve satisfactory intercourse with PDE5i according to self-report. They had stopped using PDE5i due to lack of efficacy less than 12 months before screening. At baseline all patients could not achieve erection hard enough for vaginal penetration after electing to receive the dose of PDE5i (EHS 2 or less). Men were excluded from study if they had any penile anatomical abnormality, an unstable medical condition, or neurological or hormonal abnormalities, or they were being treated for prostate cancer.

Study Protocol

After primary screening all participants had a 4-week run-in period. During this time they had sexual intercourse at least once per week after receiving the maximum dose of a PDE5i (sildenafil, tadalafil or vardenafil according to patient preference). At the first visit patients answered validated ED questionnaires as described. Patients who met study inclusion criteria were assigned in a 2:1 ratio to 1 of 2 groups, including the active LIST group and the sham group. In addition to subjective evaluation of ED penile hemodynamics were also evaluated at the first visit using our previously described FMD technique in which penile blood flow is measured at rest and after a 5-minute ischemic period using veno-occlusive strain gauge plethysmography.[22,23]

Each subject then began the 9-week treatment protocol, which was similar to that in our previous studies.[1,13,21] The protocol included 2 sessions per week for 3 weeks, which were repeated after a 3-week interval. A month after the last treatment session EF and penile hemodynamics were reassessed with maximal doses of the same PDE5i that was used in the run-in period (fig. 2).

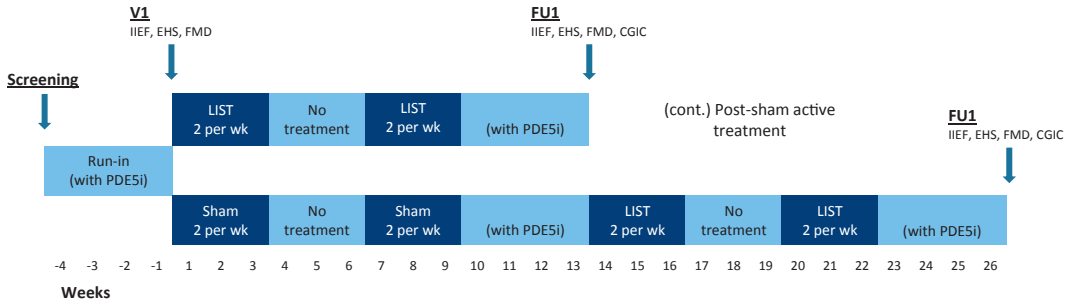

Figure 2. *V*, visit. *FU*, followup.

LIST Specifications

Patients were treated with the Omnispec ED1000 electrohydraulic device (Medispec, Yehud, Israel), which produces low intensity shock waves (0.09 mJ/mm^2 and frequency 120 shock waves per minute). Each 20-minute session comprised 1,500 pulses to 5 foci along the penile shaft and crura using a specialized probe. No analgesia was needed. The sham probe looked identical to the active probe with the same noise and vibration but without delivering any shock wave energy. The operator and the patient were blinded to treatment type.

Outcome Measures

The 2 main outcome measures to evaluate EF were EHS and the IIEF-EF domain questionnaire. Treatment success was defined as EHS 3 or greater (erection hard enough for vaginal penetration) and improvement on IIEF-EF according to MCID criteria.[24] The latter was defined as a change in IIEF-EF greater than 7 points for severe ED and 5 points for moderate ED. Secondary outcome measures were FMD penile time-flow AUC as an indicator of penile endothelial function and the CGIC questionnaire. For CGIC the patient was asked to describe his current condition compared to baseline on a 7-point scale of −3 (much worse) to 3 (much better).

Statistical Analysis

Distributions of quantitative data were examined for normality. Summary data are expressed as the median and IQR as all data, including demographics, were not normally distributed. Quantitative parameters were compared between the groups using the Wilcoxon signed rank test. Qualitative parameters are shown as the count and percent. The groups were compared using the Fisher exact or chi-square test with results considered statistically significant at $p < 0.05$. JMP® was used for analysis.

RESULTS

In the active LIST and sham groups 37 and 18 patients, respectively, completed the study. Table 1 lists patient baseline parameters. Participants were mostly middle-aged men with significant comorbidities and long-lasting severe ED. At the 1-month followup examination the median IIEF-EF domain score increased from 7 (IQR 6–10) at baseline to 13 (9–18) in the LIST group and from 8 (IQR 6–10) to 8.5 (IQR 6–10) in the sham group. The median change in IIEF-EF domain score in the LIST group was 5 (IQR 0–9.5) and 0 (IQR −1–1.25) in the sham group ($p = 0.0006$, table 2). In the LIST group 20 patients (54.1%) vs no patient in the sham group achieved erection hard enough for vaginal penetration (EHS = 3) ($p < 0.0001$, fig. 3). According to the changes in the IIEF-EF domain score by MCID treatment was effective in 15 LIST patients (40.5%) but in no patients in the sham group ($p = 0.001$).

The change in penile hemodynamic parameters was also statistically significant. The median change in penile post-ischemic time-flow AUC was 152 ml per minute per dl tissue per second (IQR 22.5–376.5) in the LIST group vs −8 (IQR −52.2–15.8) in the sham group ($p < 0.0001$). As in our previously published studies[1,13,21] there was no significant change in FMD hemodynamic parameters of the forearm, which were measured concomitantly as a reference. According to CGIC 21 patients (56.8%) in the LIST group reported clinical improvement (CGIC = +1/+2) vs only 5 (27.8%) in

Table 1. *Baseline characteristics of study population at randomization*

	Active Treatment	Sham Treatment
No. pts	37	18
Median age (range)	60 (28–78)	64 (29–81)
Median mos ED (range)	60 (11–240)	72 (8–180)
No. concomitant condition (%):		
Cardiovascular risk factor*	31 (83.8)	16 (88.9)
Cardiovascular disease	18 (48.6)	7 (38.9)
Diabetes mellitus	21 (56.8)	13 (72.2)
Median IIEF-EF score (range)	7 (6–12)	8 (6–12)
No. ED severity (%):		
Severe	32 (86.5)	15 (83.3)
Moderate	5	3
No. EHS:		
0	5	6
1	18	3
2	14	9

No significant differences between treatment groups for any parameter.
*Cigarette smoking, hypercholesterolemia, hypertension and/or obesity.

Table 2. *Treatment success of LIST vs sham treatment vs post-sham LIST*

	LIST	Sham	p Value	Post-Sham LIST	p Value
No. pts	37	18	—	16	—
Median IIEF-EF (IQR):					
Baseline	7 (6—10)	8 (6—10)	—	9 (6.5—10)	—
After treatment	13 (9—18)	8.5 (6—10)	—	10.5 (10—15)	—
Change	5 (0—9.5)	0 (−1—1.25)	<0.005	4 (0—6.75)	<0.05
No. success (%):					
IIEF-EF (MCID)	15 (40.5)	0	<0.005	4 (25)	<0.05
EHS = 3	20 (54.1)	0	<0.005	9 (56.3)	<0.005
Median post-ischemic AUC penile FMD change (IQR)	152 (22.5—376.5)	−8 (−52.2—15.7)	<0.005	58 (−5.2—306)	<0.05
No. pos CGIC (%)	21 (56.8)	5 (27.8)	Not significant	8 (50)	—

the sham group. Statistical analysis approached but did not achieve significance ($p = 0.051$).

In the sham group 16 patients were treated with LIST after they completed the sham protocol. After active treatment median IIEF-EF improved by 4 points (IQR 0—6.75, $p < 0.05$, fig. 4). Nine patients (56.3%) achieved erection hard enough for penetration (EHS = 3) ($p < 0.005$). In 4 patients (25%) treatment was effective according to the IIEF-EF MCID ($p < 0.05$).

No study participants reported any pain or other adverse event during treatment or followup.

DISCUSSION

The treatment of patients with ED who do not respond to oral medications is a challenging task. These patients are usually referred by the primary care physician to a sexual medicine clinic. Unfortunately the ability to salvage PDE5i nonresponders is limited. Nonresponders may be treated with counseling and education,[25] improved control of risk factors, testosterone supplementation and a change to another type of PDE5i. Evidence to support these maneuvers is not conclusive.[26] One of the common strategies is switching to daily treatment with PDE5i (ie tadalafil once daily), which is appealing but not effective enough in a large subset of patients. Moreover it probably does not change the basic ED mechanism or its progressive deterioration. Even after completing 1 year of daily treatment EF returns to baseline.[27]

Patients who are disappointed and no longer use PDE5i are usually candidates for intracavernous injections, a vacuum device or penile prosthesis surgery. Although intracavernous injections are

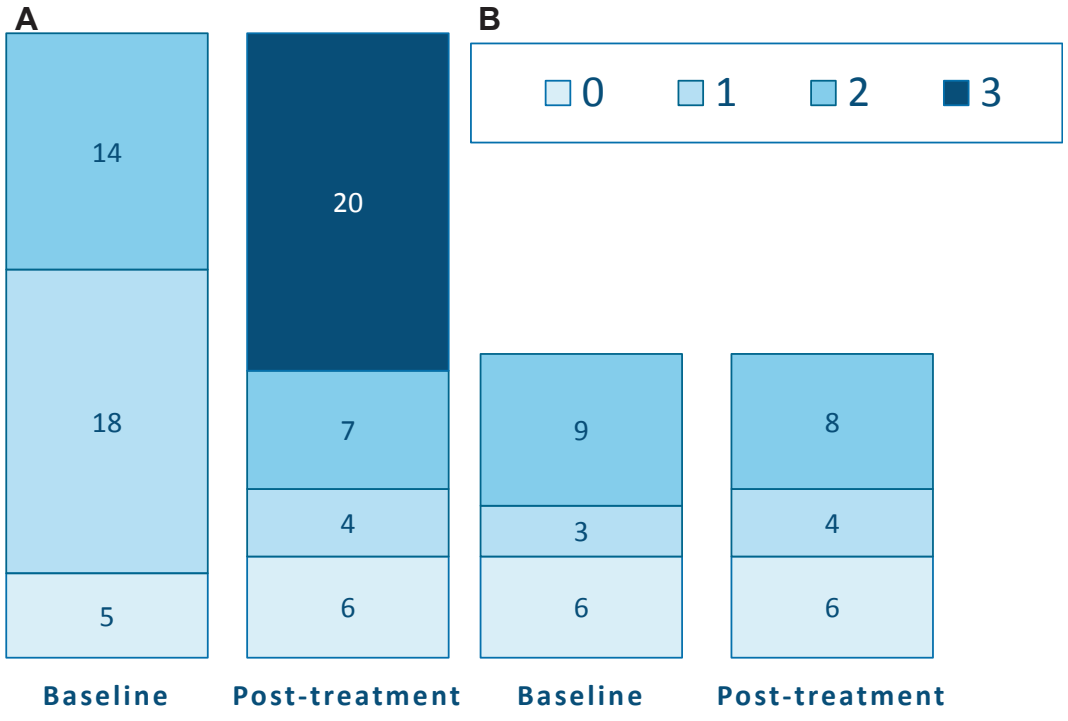

Figure 3. Baseline and posttreatment EHS. *A*, active LIST. *B*, sham treatment.

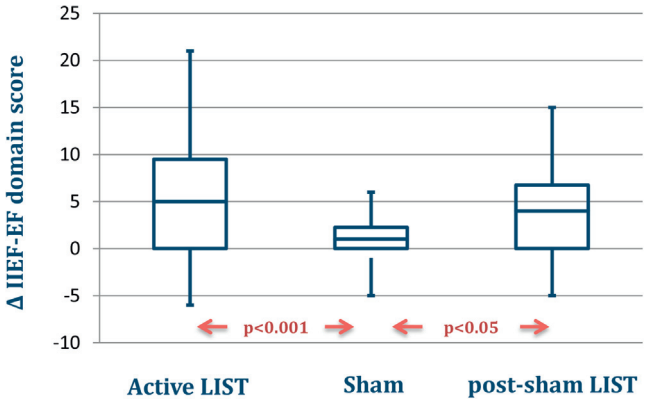

Figure 4.

usually effective, they have significant drawbacks and most patients withdraw from treatment.[28] Newer treatment modalities are unquestionably necessary. The future might include tissue engineering, nanoparticles or innovative endovascular treatment but research is still preliminary.[29]

The effect of low intensity shock waves on cavernous tissue and EF was established in a series of animal and clinical studies. Nevertheless several questions remain to be answered. The current study addresses 2 main questions, that is 1) who are the patients who will benefit from LIST and 2) to whom should we offer it. The current results clearly show that LIST is effective in patients with severe ED who have recently stopped using PDE5i because it was ineffective. About half of the patients who were treated with penile LIST were able to achieve erection hard enough for vaginal penetration using PDE5i. LIST was able to convert true PDE5i nonresponders to responders. A positive effect, although less impressive, was also noted in patients who received active LIST after sham treatment. The lower response rate might be explained by small patient number and by the frustration felt by these patients after about 6 months of treatment.

All patients enrolled in this study had used PDE5i successfully less than 12 months before screening. This time limit is arbitrary but we believe that a longer time with irreversible penile histopathological changes decreases the chance that LIST will be effective. PDE5i treatment was obligatory during the run-in period and posttreatment evaluation but it was not allowed during active treatments in this study in an attempt to isolate the LIST effect. Patients used the same PDE5i before and after LIST.

There are several limitations of the current series. Because to our knowledge this is the first double-blind, sham controlled study in this group of patients, the number of patients is relatively small and followup is limited. The LIST effect was evaluated only during obligatory PDE5i treatment and therefore the proportion of patients who can achieve satisfactory erection without PDE5i is unclear and the net effect is unknown. Moreover the effect of LIST on EF was evaluated 1 month after the end of the treatment protocol. The clinical impact will be genuinely significant only if this effect lasts so that longer followup is important. In a previous study of patients who were mainly PDE5i responders a longer followup of 2 years revealed that the beneficial effect of LIST lasted in about half of the patients.[30] Notably none of the patients treated with LIST achieved full erection (EHS = 4). They achieved "good enough" erections but erection was not normalized. This fact emphasizes the need for a more efficient shock wave protocol or for combination therapy, which should be explained to patients.

The future of LIST research should focus on 2 directions, including basic science and clinical studies. Extensive basic research is mandatory to understand the mechanism of action of LIST. Recently important progress has been made[12] but still there are more questions than answers. Today various devices are available in the market based on electrohydraulic, electromagnetic and piezoelectric generators. Each device has a distinct treatment protocol. Additional studies are required to compare the different devices and protocols. Multicenter, well performed clinical trials are urgently needed to optimize shock wave ED treatment. Future research may be able to define the modifications needed in the treatment plan to improve its efficacy and durability.

CONCLUSIONS

LIST is effective in the short term even in men with severe ED who are no longer able to achieve satisfactory sexual intercourse with PDE5i medications. Physicians who treat these patients now have evidence regarding the success rate and can advise patients accordingly. After penile LIST about half of the patients are able to achieve erection hard enough for vaginal penetration using PDE5i. Longer followup is needed to establish the place of LIST in this subset of patients.

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