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Can Low-Intensity Extracorporeal Shockwave Therapy Improve Erectile Function? A 6-Month Follow-up Pilot Study in Patients with Organic Erectile Dysfunction

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Abstract

Background: Low-intensity extracorporeal shockwave therapy (LI-ESWT) is currently under investigation regarding its ability to promote neovascularization in different organs.
Objective: To evaluate the effect of LI-ESWT on men with erectile dysfunction (ED) who have previously responded to oral phosphodiesterase type 5 inhibitors (PDE5-I).
Design, setting, and participants: We screened 20 men with vasculogenic ED who had International Index of Erectile Function ED (IIEF-ED) domain scores between 5–19 (average: 13.5) and abnormal nocturnal penile tumescence (NPT) parameters. Shockwave therapy comprised two treatment sessions per week for 3 wk, which were repeated after a 3-wk no-treatment interval.
Intervention: LI-ESWT was applied to the penile shaft and crura at five different sites.
Measurements: Assessment of erectile function was performed at screening and at 1 mo after the end of the two treatment sessions using validated sexual function questionnaires, NPT parameters, and penile and systemic endothelial function testing. The IIEF-ED questionnaire was answered at the 3- and 6-mo follow-up examinations.
Results and limitations: We treated 20 middle-aged men (average age: 56.1 yr) with vasculogenic ED (mean duration: 34.7 mo). Eighteen had cardiovascular risk factors. At 1 mo follow-up, significant increases in IIEF-ED domain scores were recorded in all men (20.9 ± 5.8 vs 13.5 ± 4.1, $p < 0.001$); these remained unchanged at 6 mo. Moreover, significant increases in the duration of erection and penile rigidity, and significant improvement in penile endothelial function were demonstrated. Ten men did not require any PDE5-I therapy after 6-mo follow-up. No pain was reported from the treatment and no adverse events were noted during follow-up.
Conclusions: This is the first study that assessed the efficacy of LI-ESWT for ED. This approach was tolerable and effective, suggesting a physiologic impact on corporeal hemodynamics. Its main advantages are the potential to improve erectile function and to contribute to penile rehabilitation without pharmacotherapy. The short-term results are promising, yet demand further evaluation with larger sham-control cohorts and longer follow-up.

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1. Introduction

In the past decade, phosphodiesterase 5 inhibitors (PDE5-Is) have become available for the treatment of erectile dysfunction (ED). However, their effect is still limited to the sexual act and probably do not improve spontaneous erections. These limitations are probably due to their inability to improve penile blood flow for a time period that is sufficient to allow optimal oxygenation and recovery of cavernosal vasculature. Recently, the effect of long-term daily use of PDE5-Is on endothelial function (EnF) has been shown to induce a short-term improvement in erectile function (EF) but probably not a longstanding one [1–3].

In the search for a new treatment modality that would provide a rehabilitative or curative effect for ED, we looked into technologies that could potentially affect endothelial function and improve penile hemodynamics. We came across some related preliminary publications, particularly from the cardiovascular literature, showing that in vitro as well as in vivo (porcine model) low-intensity extracorporeal shockwave therapy (LI-ESWT) could enhance the expression of vascular endothelial growth factor (VEGF) and its receptor Flt-1 [4,5], and induces neovascularization and improves myocardial ischemia [6]. Newer studies further demonstrated this hemodynamic effect in humans [7,11,12]. Moreover, LI-ESWT was found to be effective not only in the myocardium, but also in other organs with impaired vascularity. Recently, this treatment modality using LI-ESWT was found effective in the treatment of chronic diabetic foot ulcers as compared with hyperbaric oxygen therapy, showing better clinical results and local perfusion [8]. In a prospective randomized trial, LI-ESWT was also effective in improving wound healing after vein harvesting for coronary artery bypass graft surgery [9].

The mechanism of action of LI-ESWT is still unclear. It has been shown that this low intensity energy induces non-enzymatic production of physiologic amounts of nitric oxide [10] and activates a cascade of intracellular signaling pathways that lead to the release of angiogenic factors. These encouraging experimental and clinical outcomes provided the theoretic basis for applying this treatment modality to cavernosal tissue in order to improve penile vascular supply and EnF in men with longstanding vasculogenic ED.

2. Patients and methods

The study protocol was reviewed and approved by the local institutional review board and each participant gave his written informed consent.

The methodology used was based on the clinical trials performed in patients with cardiovascular disease using LI-ESWT [11,12]. We adapted the treatment protocol and the probe that was used in these studies for the penis in order to account for the superficial location of the corpora cavernosa and the need to cover the entire corporal surface as well as the crura. Our treatment protocol consisted of two treatment sessions per week for 3 wk, which were repeated after a 3-wk no-treatment interval (Fig. 1).

Shockwaves were delivered by a special probe that was attached to a compact electrohydraulic unit with a focused shockwave source (Omnispec ED1000, Medispec Ltd, Germantown, MD, USA). We applied a standard commercial gel normally used for sonography without any local anesthetic effect on the penis and perineum. The penis was manually stretched; the shockwaves were delivered to the distal, mid, and proximal penile shaft, and the left and right crura. The duration of each LI-ESWT session was about 20 min, and each session comprised 300 shocks per treatment point (1500 per session) at an energy density of 0.09 mJ/mm^2 and a frequency of 120/min. The volume of penile tissue that was exposed to shockwaves at each site was cylindrical (diameter: 18 mm; height: 100 mm). During the treatment period, no psychologic intervention or support was provided and patients were required to maintain their normal sexual habits.

2.1. Inclusion/exclusion criteria

We recruited men with a history of ED for at least 6 mo from our outpatient clinic. Each study patient had abnormal 2-night nocturnal penile tumescence (NPT) parameters at screening, had responded positively to PDE5-I therapy (were able to penetrate during sexual intercourse while on on-demand PDE5-I treatment), and had an International Index of Erectile Function ED (IIEF-ED) domain score between 5–19. Each patient agreed to discontinue PDE5-I therapy until the first 1-mo follow-up examination. The exclusion criteria were psychogenic ED (normal NPT parameters), any neurologic pathology, prior radical prostatectomy, and recovery from any cancer within the past 5 yr.

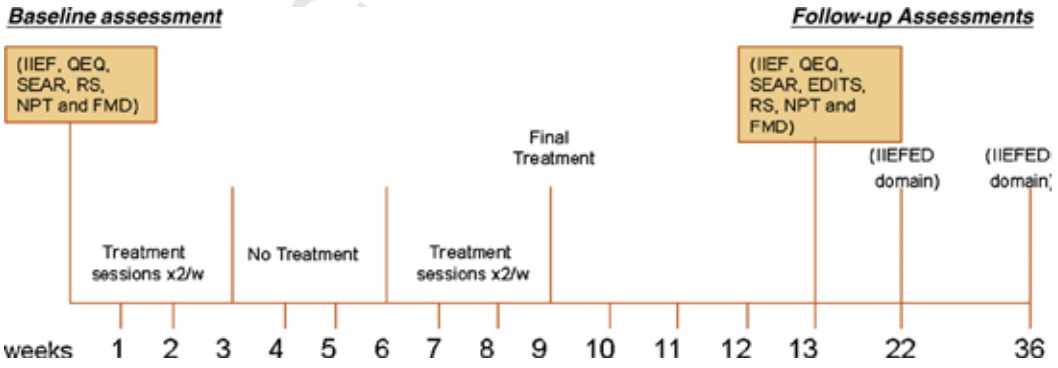

Fig. 1 – Study flow chart.
IIEF = International Index of Erectile Function; QEQ = Quality of Erection Questionnaire; SEAR = Self-Esteem and Relationship Questionnaire; RS = rigidity score; NPT = nocturnal penile tumescence; FMD = flow-mediated dilatation; ED = erectile dysfunction; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction.

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2.2. Study protocol

Upon inclusion (visit 1), after a 4-wk PDE5-I washout period, each participant completed several validated sexual function questionnaires: IIEF, rigidity score (RS), Quality of Erection Questionnaire (QEQ), and the Self-Esteem and Relationship Questionnaire (SEAR). Additionally, penile and forearm EnF testing was done in the last 14 enrolled men using our already-described flow-mediated dilatation (FMD) technique [13,14]. This method uses veno-occlusive strain gauge plethysmography to measure penile and forearm blood flow after a 5-min ischemic period. We used this technique to establish changes in penile EnF by measuring specific indices of endothelial parameters: basal blood flow (P-base), and the maximal postischemic flow. Efficacy was evaluated at 1 mo after end of treatment by completing sexual function questionnaires, determining NPT parameters, EnF testing, and completing an Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire. For long-term evaluation, we used the IIEF-ED domain score at the 3- and 6-mo follow-up examinations. A change in the IIEF-ED domain score of >5 points was used as the main measure of treatment success.

2.3. Statistical analysis

Paired student *t* tests and nonparametric Wilcoxon sign-rank tests were used to examine differences within subjects. Pearson correlation that took into account the changes in systemic EnF was used to examine the relationship between the change in the IIEF-ED scores and the changes in penile EnF at the 1-mo follow-up examination. To this end, we first constructed indices of FMD change using forearm EnF as the reference value before calculating the correlation. The indices were calculated from the difference between the values of the 1-mo and the baseline penile FMD indices, divided by the difference between the 1-mo and the baseline forearm FMD indices. Pearson correlation was also used to examine the degree to which other study parameters or derived indices were related. Lines of best fit were determined and plotted for all correlation analyses. The level of significance for all analyses was set at 5%.

3. Results

This protocol was applied to 20 middle-aged men (mean: 56.1 ± 10.7 yr, range: 33–73 yr) with vasculogenic ED for a mean of 34.7 mo. Eighteen men had one or more cardiovascular risk factors.

Table 1 summarizes the pre- and post-therapy scores of all sexual function questionnaires in all study participants. The characteristics of each study participant and the effect

Table 1 – Results of sexual function questionnaires before and 1 month after low-intensity extracorporeal shock-wave therapy

Test score	Baseline score ± SD	Score 1 mo after treatment ± SD	% change	*p* value
IIEF ED domain	13.5 ± 4.1	20.9 ± 5.8	55	<0.001
Total IIEF	39.3 ± 8.7	54.7 ± 11.7	39	<0.001
QEQ	32.9 ± 18.2	61.4 ± 25.8	83	<0.001
RS	1.45 ± 1.0	2.7 ± 1.1	86	<0.001
SEAR	36.0 ± 10.4	46.5 ± 11.3	32	<0.001

IIEF = International Index of Erectile Dysfunction; ED = erectile dysfunction; QEQ = Quality of Erection Questionnaire; RS = rigidity score; SEAR = Self-Esteem and Relationship Questionnaire.

Table 2 – Patient characteristics and the effect of low-intensity extracorporeal shockwave therapy on the International Index of Erectile Function score for each subject from baseline to 6 months after end of treatment

Patient number	Age	ED duration (mo)	ED risk factors*	IIEF-ED baseline	Δ IIEF-ED at 1 mo	Δ IIEF-ED at 3 mo	Δ IIEF-ED at 6 mo	IIEF-ED 6 mo
1	47	6	3	18	3	6	5	23**
2	47	24	1	16	7	9	12	28**
3	62	36	3 + 4 + 5	11	12	10	13	24**
4	68	60	3	13	8	8	7	21**
5	54	18	3 + 4 + 5	19	−6	−2	−2	17
6	59	24	3	7	3	6	6	13
7	61	60	3 + 4 + 5	16	11	9	9	25**
8	58	24	2	13	2	2	4	17
9	33	144	1	17	6	6	7	24**
10	54	12	2 + 3	16	1	1	0	16
11	65	24	3	5	22	19	18	23
12	62	12	3 + 4	13	14	16	16	29**
13	59	36	3	13	13	10	10	23
14	46	24	3	5	6	6	6	11
15	33	100	2	11	6	6	10	21
16	73	20	3 + 4	11	−3	−3	−3	8
17	68	24	3 + 5	17	11	11	11	28**
18	63	8	3 + 5	16	9	2	2	18
19	58	15	2 + 3	15	12	9	9	24**
20	53	24	2	17	6	7	7	24**

ED = erectile dysfunction; IIEF-ED = International Index of Erectile Function – Erectile Dysfunction;
* 1 = no risk factors; 2 = miscellaneous risk factors (eg, smoking, medications, surgical procedures); 3 = cardiovascular risk factors (eg, hypertension, hypercholesterolemia, hypertriglyceridemia); 4 = coronary disease; 5 = diabetes mellitus.
** Patients with spontaneous erections who did not require phosphodiesterase type 5 inhibitor therapy.

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Table 3 – Changes in nocturnal penile tumescence parameters before and 1 month after low-intensity extracorporeal shockwave therapy ($n = 18$)

Parameter	Baseline (mean ± SD)	1 mo after treatment (mean ± SD)
Total number of erection	3.9 ± 2.2	4.6 ± 2.3
Total erection time, h	1.3 ± 1.3	1.4 ± 0.9
Average tip rigidity	37.2 ± 18.9	42.1 ± 22.8
Average base rigidity	47.5 ± 18.1	52.5 ± 22.0
Max rigidity best event, tip	52.6 ± 20.7	61.0 ± 29.6
Max rigidity best event, base	66.9 ± 16.5	68.6 ± 26.6

of LI-ESWT on their IIEF-ED during the study period are presented in Table 2.

At the 1-mo follow-up examination, the IIEF-ED domain scores significantly increased from 13.5 ± 4.1 to 20.9 ± 5.8 ($p < 0.001$). The scores of 14 men increased by >5 points and of 7 men by >10 points. The treatment satisfaction scores were also high at the 1-mo follow-up examination (mean score: 23.2). At the 3- and 6-mo follow-up examinations, the improved IIEF-ED domain scores were maintained, and the average increase at the 6-mo follow-up was 7.1 ($p = 0.001$). A significant improvement in EF was recorded in six men with severe ED at baseline (IIEF-ED domain scores <12); their average IIEF-ED domain score rose from 8.3 to 16.6 at the 6-mo follow-up examination.

Pre- and post-treatment NPT parameters were collected from 18 men (2 patients refused to perform the second NPT). All NPT parameters improved at the 1-mo examination, especially the rigidity parameters (Table 3).

Penile EnF improved significantly after LI-ESWT (Table 4): basal flow (7.3 ml/min per deciliter vs 17.8 ml/min per deciliter; $p < 0.001$) and post-ischemic maximal flow (12.0 ml/min per deciliter vs 28.9 ml/min per deciliter, $p < 0.001$). No significant changes were measured in forearm EnF (Table 4). A strong correlation was found between the changes in the IIEF-ED scores and the changes in EnF parameters at the 1-mo follow-up examination (Fig. 2).

At the 3- and 6-mo follow-up examinations, 10 men reported that they had spontaneous erections that were sufficient for penetration and did not require PDE5-I support before sexual intercourse.

None of the study participants reported any pain during the treatment and follow-up periods, and no adverse effects were recorded.

4. Discussion

All currently available treatments for ED enhance sexual function by improving the quality of erections, yet none are curative. The search for an ED cure is the next step, and should be the goal of this coming decade. Examples of the different therapeutic targets and strategies for curing ED include the Rho/Rho-kinase signaling pathway [15], gene therapy [16], and stem cell regeneration [17]. Advanced treatment protocols for rehabilitating or preserving EnF in men with ED using chronic PDE5-Is have been proposed and are currently undergoing evaluation [1,2,18]. To date, data on the therapeutic benefits of these treatment protocols to restore spontaneous EF are still scarce.

High-intensity ESWT (lithotripsy) is a well-established treatment for kidney stones. The results of attempts to destroy the fibrotic plaques of Peyronie's disease using this high energy have been published with debatable success, except for pain relief [19,20]. Beneficial therapeutic effects of moderate intensity also have been reported in certain orthopedic conditions, such as plantar fasciitis, Achilles tendonitis, and tennis elbow, probably due to the attenuating action on inflammatory processes [21–24]. More

Table 4 – Changes in flow-mediated dilatation parameters in both penile and forearm blood flow before and 1 month after treatment

Location		Baseline	1 mo	% change	p value
Forearm	Baseline flow (ml/min/dl)	4.0 ± 2.2	4.8 ± 3.3	19	0.258
	Maximal flow (ml/min/dl)	12.0 ± 9.0	10.6 ± 7.4	−12	0.544
Penis	Baseline flow (ml/min/dl)	7.3 ± 4.7	17.8 ± 11.0	145	0.004
	Maximal flow (ml/min/dl)	12.0 ± 8.3	28.9 ± 15.2	140	<0.001

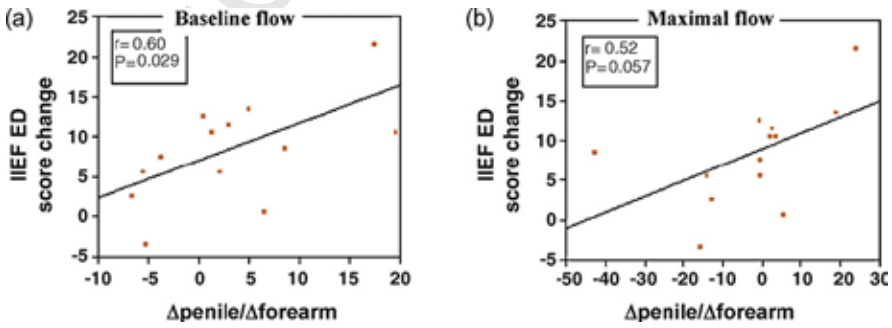

Fig. 2 – Correlation between the adjusted flow-mediated dilatation indices for (a) baseline and (b) maximal flow and the changes in the International Index of Erectile Function erectile dysfunction score 1 mo after treatment.
IIEF ED = International Index of Erectile Function—Erectile Dysfunction domain.

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recently, the potential efficacy of LI-ESWT has been investigated in other clinical conditions [6,8,9]. It has been demonstrated that this form of energy triggers the activation of various intracellular signaling pathways and causes upregulation of numerous angiogenic factors to promote neovascularization [4]. In a porcine model of myocardial ischemia, Nishida et al demonstrated that cardiac LI-ESWT induces angiogenesis and markedly ameliorates myocardial ischemia without any adverse effects [5]. In another series of studies, Wang et al. [25,26] demonstrated similar processes in other animal models. The above scientific research led to the assumption that LI-ESWT also might be beneficial in enhancing blood flow in the corpora cavernosa of vasculogenic ED patients.

We structured our treatment protocol on what has been previously used in cardiology for achieving neovascularization. The rationale for including a no-treatment interval in our protocol is based on the finding that biologic responses to LI-ESWT appear to be time-dependent as the peak expression of the neovascularization response occurs 4 wk after treatment [27].

We initially started this investigation as a pilot study in patients with vasculogenic ED. After analyzing the results of the first six men, we were surprised by the positive responses. We decided to increase the number of participants and to include measurements of EnF into our protocol. Another reason for adding EnF was to overcome the problems of comparing pre- and post-therapy NPT parameters and to gain some insight into the underlying hemodynamic mechanism induced by this treatment.

For this purpose, we decided to use our FMD methodology, and not Doppler sonography; we wanted to obtain objective, measurable, and comparable hemodynamic results that did not require a pharmacologically-induced vasoactive intervention and to eliminate any operator-dependent bias. Our results show impressive objective data that confirm the beneficial effect of LI-ESWT on penile hemodynamics and its correlation with an improved clinical response, as demonstrated by an increase in the IIEF-ED scores 1 mo after LI-ESWT.

Although a considerable placebo effect can be expected with our treatment protocol, our high response rate (>70%) is substantially higher than that of any previously published placebo-controlled trial in men with ED. Moreover, the fact that this effect was maintained without any additional active intervention 6 mo after treatment provides additional evidence that LI-ESWT exerts a genuine physiologic effect on cavernosal tissue.

Although our positive results were obtained using validated scientific instruments, we would like to emphasize that the most striking clinical observation was that almost every participant gave a highly positive feedback, sometimes as early as the second treatment session, with the efficacy still present 6 mo later.

This is a proof-of-concept study that was performed to demonstrate the clinical efficacy of LI-ESWT in a small number of highly selected patients with a relatively short follow-up using an adapted empirical protocol. For LI-ESWT to become a recognized curative treatment in patients with ED, large multicenter, long-term, randomized and sham-controlled studies should now be performed. Moreover, other LI-ESWT protocols need to be evaluated, and there is a need to better define those patients who respond to this type of treatment and evaluate the duration of its effect. More data also are needed with regard to the possible long-term impact of shockwaves on penile tissue.

5. Conclusions

The results of this pilot study emphasize the efficacy and tolerability of penile LI-ESWT in ED. Our short-term results are extremely encouraging, but demand further evaluation. In the future, this could be one of the few nonpharmacologic treatment modalities that are able to improve EF without any adverse effects. Based on our results, LI-ESWT appears to have the potential to be a rapid and curative therapy for ED. Even if the therapeutic effect will be short-lasting, it can be easily repeated. The promising results of this pilot study will hopefully encourage basic research to explore and understand the mechanism of action of this energy on biologic systems, as well as assist in finding further applications of this novel therapeutic modality in other fields of medicine.

Author contributions: Yoram Vardi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gruenwald, Vardi.
Acquisition of data: Gruenwald, Vardi, Appel, Massarwi.
Analysis and interpretation of data: Gruenwald, Vardi, Appel, Jacob.
Drafting of the manuscript: Gruenwald, Vardi.
Critical revision of the manuscript for important intellectual content: Gruenwald, Vardi.
Statistical analysis: Gruenwald, Vardi.
Obtaining funding: Vardi.
Administrative, technical, or material support: Gruenwald, Vardi, Appel.
Supervision: Gruenwald, Vardi.
Other (specify): None.

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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

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Purpose: We investigated the clinical and physiological effect of low intensity extracorporeal shock wave therapy on men with organic erectile dysfunction who are phosphodiesterase type 5 inhibitor responders.

Materials and Methods: After a 1-month phosphodiesterase type 5 inhibitor washout period, 67 men were randomized in a 2:1 ratio to receive 12 sessions of low intensity extracorporeal shock wave therapy or sham therapy. Erectile function and penile hemodynamics were assessed before the first treatment (visit 1) and 1 month after the final treatment (followup 1) using validated sexual function questionnaires and venoocclusive strain gauge plethysmography.

Results: Clinically we found a significantly greater increase in the International Index of Erectile Function-Erectile Function domain score from visit 1 to followup 1 in the treated group than in the sham treated group (mean ± SEM 6.7 ± 0.9 vs 3.0 ± 1.4, p = 0.0322). There were 19 men in the treated group who were initially unable to achieve erections hard enough for penetration (Erection Hardness Score 2 or less) who were able to achieve erections sufficiently firm for penetration (Erection Hardness Score 3 or greater) after low intensity extracorporeal shock wave therapy, compared to none in the sham group. Physiologically penile hemodynamics significantly improved in the treated group but not in the sham group (maximal post-ischemic penile blood flow 8.2 vs 0.1 ml per minute per dl, p <0.0001). None of the men experienced discomfort or reported any adverse effects from the treatment.

Conclusions: This is the first randomized, double-blind, sham controlled study to our knowledge that shows that low intensity extracorporeal shock wave therapy has a positive short-term clinical and physiological effect on the erectile function of men who respond to oral phosphodiesterase type 5 inhibitor therapy. The feasibility and tolerability of this treatment, coupled with its potential rehabilitative characteristics, make it an attractive new therapeutic option for men with erectile dysfunction.

Key Words: erectile dysfunction, high-energy shock waves, penis, hemodynamics

Abbreviations and Acronyms

ED = erectile dysfunction

EHS = Erection Hardness Score

FMD = flow mediated dilatation

FU1 = followup 1

FU2 = followup 2

IIEF = International Index of Erectile Function

IIEF-EF = International Index of Erectile Function-Erectile Function domain score

LI-ESWT = low intensity extracorporeal shock wave therapy

PDE5i = phosphodiesterase type 5 inhibitors

V1 = visit 1

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Study received institutional ethics review board approval.

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NUMEROUS therapeutic strategies exist for improving erectile function. While these therapies have been proven to be safe and effective, they are limited for use before the sexual act and do not modify the physiological mechanism of penile erection.[1] Gene and stem cell therapies are current examples of treatment strategies whose therapeutic goals are to restore erectile function as part of the present trend to shift the field of ED treat-

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ments away from on demand palliative treatments.[2,3]

Adopting this new treatment strategy we began exploring the use of LI-ESWT to achieve this goal.[4,5] Using LI-ESWT as a treatment modality is not new. In 1990 Young and Dyson discovered that therapeutic ultrasound encourages angiogenesis by enhancing the expression of vascular endothelial growth factor.[6–8] This finding led clinicians to begin using shock wave therapy in the treatment of coronary artery disease,[9] bone fractures,[10] calcifying tendonitis[11] and diabetic foot ulcers.[12]

The results of our pioneer pilot study demonstrated that LI-ESWT improved erectile function and penile hemodynamics in men with ED who respond to pharmacotherapy.[4] We also reported that LI-ESWT effectively converted PDE5i nonresponders to responders.[5] While these results were encouraging, our studies were limited by the small sample size and lack of an appropriate control group. To validate our previously published results and to demonstrate whether LI-ESWT has a true physiological effect on the erectile mechanism, we conducted a larger, randomized, double-blind, sham controlled study in men with ED and cardiovascular risk factors who responded to PDE5i.

MATERIALS AND METHODS

The study protocol was reviewed and approved by our institution's Ethics Review Board. All participants gave written informed consent before entering the study.

Screening, Inclusion and Exclusion Criteria

We recruited men with a history of ED for at least 6 months who were already responding to PDE5i from our outpatient ED clinic between July 2009 and October 2010. A total of 77 men underwent an initial screening, including a complete medical history and physical examination (fig. 1). For study inclusion each man had to have an IIEF-EF of 19 or greater while on PDE5i and had to be in a stable heterosexual relationship for more than 3 months. Each man also had to agree to discontinue PDE5i during the entire study period. Men were excluded from analysis if they had undergone radical prostatectomy, received pelvic radiotherapy or hormonal therapy, were receiving ongoing treatment for a psychiatric condition, or had any anatomical, neurological or hormonal abnormalities. Ultimately 10 men met the exclusion criteria.

Study Protocol

The 67 participants who met the inclusion criteria underwent a 4-week PDE5i washout period. At V1 the men were assigned into 2 groups of those who received LI-ESWT (treated group) and those who were given sham therapy (sham group) in a 2:1 ratio using a computer generated table of random numbers. At the same visit each man completed a full IIEF and EHS questionnaire while not on PDE5i. The penile hemodynamics of each man was also evaluated at V1 using our previously described FMD technique in which penile blood flow is measured at rest and after a 5-minute ischemic period using venoocclusive strain gauge plethysmography.[13,14] Each subject then began the 9-week treatment period, which was comprised of 2 treatment sessions per week for 3 weeks that were repeated after a 3-week no treatment interval. A month after the final treatment session (FU1) erectile function and penile hemodynamics were reassessed while the men were still not taking PDE5i (fig. 2).

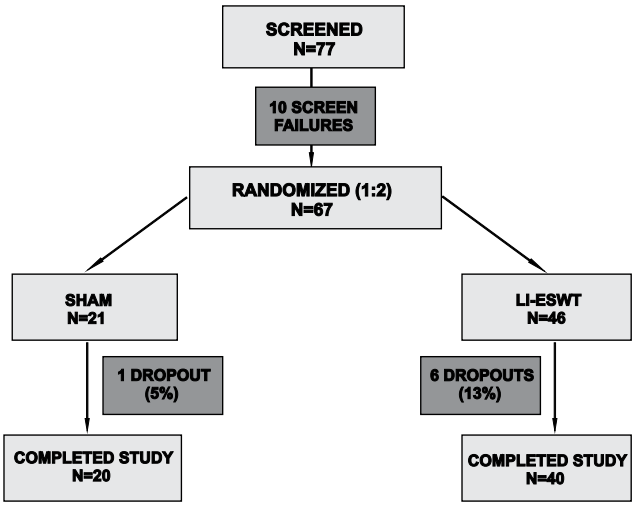

Figure 1. Patient screening and randomization flowchart

Specifics of LI-ESWT

We applied a standard commercial gel normally used for sonography to the penis. The shock waves were delivered to the distal, mid and proximal penile shaft, and the left and right crura using a specialized focused shock wave probe (Omnispec ED1000, Medispec Ltd., Yehud, Israel) as described in our previous studies (fig. 3).[4,5] Since the depth of the shock waves reached both corpora, treatment was delivered on 1 side of the penile shaft only. The 300 shocks at an energy density of 0.09 mJ/mm^2 and a frequency of 120 shocks per minute were delivered at each of the 5 treatment points. Each treatment session was 15 minutes. Due to the low energy density, no local or systemic analgesia was needed.

Followup

To improve the recruitment and compliance rates, all men were eligible to receive an additional treatment course if they were unsatisfied with the initial outcome and had an IIEF-EF of less than 25 at FU1 without PDE5i, regardless of the group to which they were originally assigned. The IIEF of the men who did not undergo additional treatment was reevaluated after 3 months (FU2).

Randomization and Sham Treatment

At randomization each man received a numeric identifier code that was paired to a treatment or sham probe supplied by the manufacturer. The sham probe looked identical to and made the same noise as the treatment probe, but contained a metal plate that prevented the shock wave energy from being applied to the penis. Since the noise and vibration of the probes used in both groups were

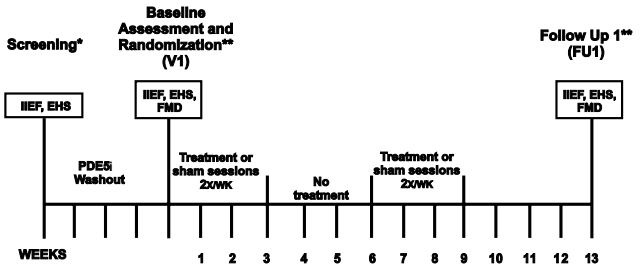

Figure 2. Study flowchart. Single asterisk indicates with PDE5i. Double asterisk indicates without PDE5i.

similar, and the treatment was painless, the operator and subject were blind to the treatment type.

Main Outcome Measures

We used the IIEF-EF to evaluate erectile function. Treatment success was defined as a 5-point or greater improvement in the IIEF-EF between V1 and FU1 because this value indicates an improvement of erectile function by at least 1 severity category. The secondary outcome measures were defined as significant increases in the IIEF subcategories, an increase in EHS from 2 or less at V1 to 3 or more at FU1, and an improvement in penile blood flow.

Statistical Analysis

The data were analyzed using statistical software (JMP®, SAS), and the data are expressed as median and range or mean ± SEM. The values of the study parameters from the 2 study groups were compared by Student's t test with pooled variances or the Wilcoxon signed rank test as appropriate. The linear relationship between changes in the IIEF-EF and changes in penile blood flow at FU1 was assessed by Spearman's rank order correlation. A chi-square contingency analysis was used to examine the relationship between the IIEF-EF and penile hemodynamics, with statistical significance set at 5%.

RESULTS

The baseline characteristics of the 2 study groups were similar (table 1). Six (13%) men in the treated group and 1 (5%) man in the sham group did not complete the study protocol (fig. 1). Of these men 3 took PDE5i, 2 could not meet the necessary time commitments, 1 separated from his wife and 1 had a prolonged hospitalization.

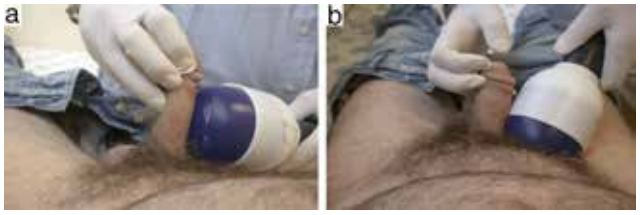

Figure 3. Application of shock wave probe to penile shaft (*a*) and crura (*b*).

Table 1. *Baseline characteristics of the study population at randomization while off PDE5i therapy*

	Sham	Treatment
No. men	20	40
Median age (range)	57 (35–77)	58 (27–72)
Median mos ED (range)	60 (6–240)	42 (6–240)
Concomitant condition (% of men):		
Cardiovascular risk factors*	60	75
Coronary artery disease	10	20
Diabetes mellitus	30	30
Mean ± SEM IIEF-EF domain scores	11.5 ± 0.86	12.6 ± 0.75
Median IIEF-EF domain scores (range)	12.5 (6–17)	13.5 (6–19)
Disease stratification (% of men):†		
Severe dysfunction (IIEF-EF 0–6)	20	12.5
Moderate dysfunction (IIEF-EF 7–12)	30	32.5
Mild to moderate dysfunction (IIEF-EF 13–18)	50	42.5
Mild dysfunction (IIEF-EF 19–24)	0	12.5

All values not significant ($p > 0.05$).

* Including at least 1 of cigarette smoking, hypercholesterolemia, hypertension or obesity.

† Statistical assessment of possible treatment group differences in disease severity distributions of patients could not be performed due to the small numbers in some subgroups.

Efficacy

At FU1 the mean IIEF-EF in the treated group increased by 6.7 points while the score in the sham group increased by 3.0 points ($p = 0.0322$, fig. 4). There were 26 (65%) men in the treated group and 4 (20%) in the sham group who had a 5-point or greater increase in IIEF-EF ($p = 0.0001$). The treated men had significantly improved mean scores in the IIEF subcategories of Sexual Desire ($p = 0.0348$) and Overall Satisfaction ($p = 0.0054$, fig. 4). Of 28 men in the treated group who had an EHS of 2 or less at V1, 19 reported an increase in EHS to 3 or greater at FU1 vs no men in the sham group (fig. 5).

Penile hemodynamics were assessed in 59 of the 60 men who presented at FU1 (1 man in the treated group refused this assessment after treatment). Penile hemodynamics improved significantly in the treated group (table 2, $p < 0.0001$). Furthermore, we noted a strong positive correlation between changes in the IIEF-EF and changes in the resting and maximal post-ischemic penile blood flow at FU1 ($p < 0.0001$). The IIEF-EF and the post-ischemic maximal blood flow improved ($p < 0.001$) in 22 (56%) men in the treated group and 1 (5%) man in the sham group.

Adverse Events

Unlike painful higher intensity shock wave energy used to treat nephrolithiasis and Peyronie disease (0.2 to 1.1 mJ/mm^2), the low intensity shock wave energy (0.09 mJ/mm^2) used in this study was not associated with any pain or side effects such as ecchymoses or hematuria.

Post-Study Followup

A total of 23 men including 16 (80%) from the sham group opted to receive a second series of treatments

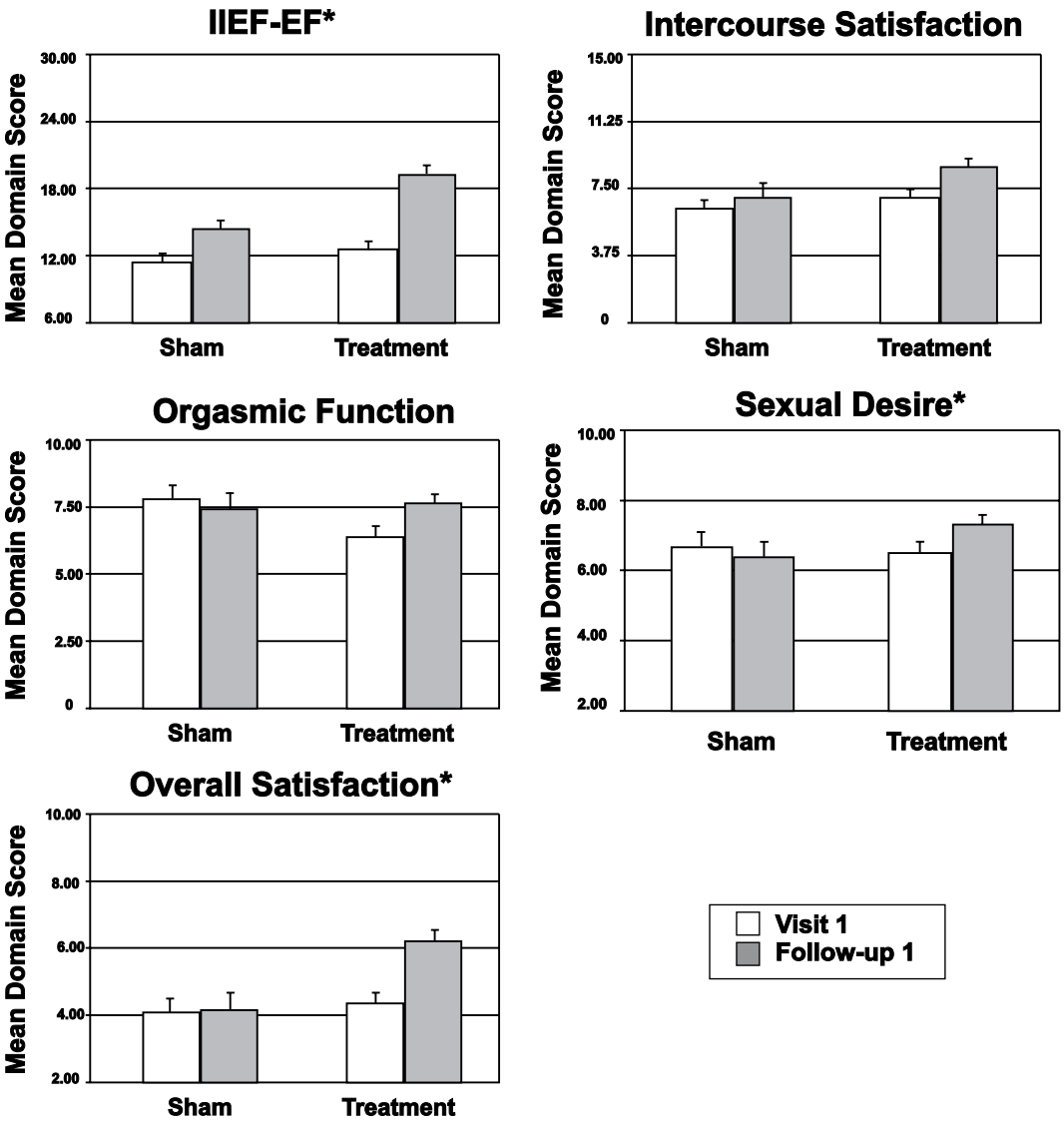

Figure 4. IIEF domain scores (mean ± SEM) for men treated with LI-ESWT or sham therapy at V1 or FU1. Asterisk indicates $p < 0.05$ and represents significance of difference between 2 groups.

without knowing their original group (fig. 6). Mean IIEF-EF of men continuing on to a second round of treatments was 12.2 at FU1, while the remaining 36 men who had followup at 3 months had an additional increase in mean IIEF-EF from 20.7 at FU1 to 22.1 at FU2.

DISCUSSION

Due to the skepticism surrounding this novel treatment, insufficient scientific background and disappointing results of penile shock wave therapy in Peyronie disease, it was crucial to further establish the validity of LI-ESWT by conducting a randomized, double-blind, sham controlled study. We chose to use measurement tools that are validated and widely accepted such as the IIEF and EHS. While validated in men receiving on demand PDE5i, these questionnaires have a high degree of sensitivity and specificity for detecting treatment related changes in the erectile mechanism.[15–17] Since LI-ESWT is a nonpharmacological intervention whose effect is not defined per sexual encounter but during a prolonged period, questionnaires such as the sexual encounter profile were not used.

We postulated that the underlying mechanism of LI-ESWT action is to improve penile hemodynamics. To confirm this hypothesis, objective and quantifiable measures of penile hemodynamics are required. Our experience with nocturnal penile tumescence testing in our first pilot study led us to conclude that nocturnal penile tumescence is not suitable to be used as an investigative tool due to difficulties in interpreting the results in terms of meaningful pa-

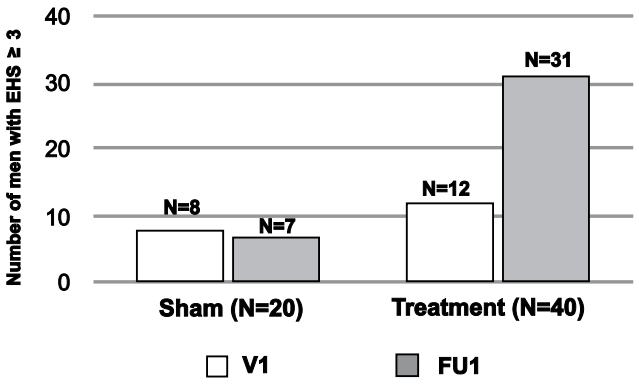

Figure 5. Number of men with EHS 3 or greater at V1 and FU1. For EHS clinical interpretation, grade definitions characterizing penis are grade 1—larger but not hard, grade 2—hard but not hard enough for penetration, grade 3—hard enough for penetration but not completely hard, grade 4—completely hard and fully rigid.

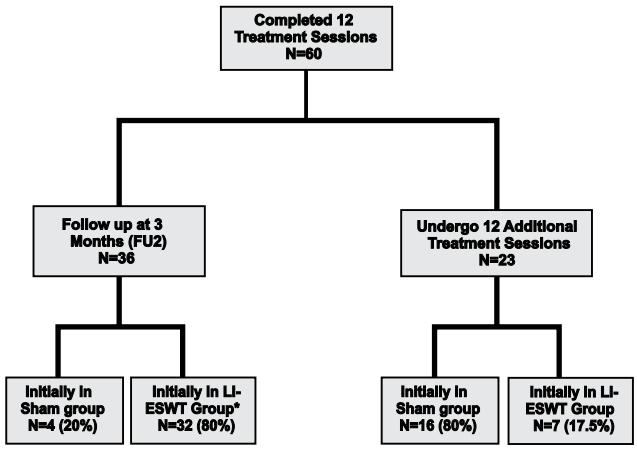

Figure 6. Patient followup after 12 treatment sessions. Asterisk indicates 1 patient (2.5%) was lost to FU2.

rameter changes and changes in penile hemodynamics. We did not use duplex ultrasonography because it mainly measures cavernous artery flow, is operator dependent, and is reliant on the timely response of injected vasoactive agents and patient disposition. Although it is an excellent test to evaluate penile vascular status, duplex ultrasonography may be problematic for the comparison of changes in penile hemodynamics before and after intervention. We used venoocclusive plethysmography to measure penile hemodynamics because it can objectively assess penile perfusion in the flaccid state in a simple and reproducible fashion, it is not operator dependent and it has previously been proven to reflect changes in erectile function after intervention.[13,14] Furthermore, while our group was the first to describe the FMD technique in the penis, it is not principally different from the widely used FMD technique to assess endothelial function in the brachial artery.

The IIEF-EF of the treated men significantly improved at FU1. The increase was not as great as the increases in the IIEF-EF that were reported in studies that introduced the therapeutic effects of PDE5i.[18–20] Admittedly, comparing the efficacies of an on demand treatment to a nonpharmacological rehabilitative intervention that is unrelated to the sexual act is inherently problematic. Unlike the ED naive cases in the first sildenafil studies that had not previously experienced treatment success, those in our study had a different definition of therapeutic success because they already had a positive experience with PDE5i. Furthermore, many of the original PDE5i studies included a mixed ED population, as opposed to our group of men with similar ED risk factors. Our exclusion criteria may also account for the 25% sham effect seen in our study compared to a placebo effect as high as 46% reported in the original PDE5i studies.[21] The results of later studies that excluded patients with psychogenic ED, and examined the effect of PDE5i on men with organic ED and cardiovascular risk factors, are comparable to the results of our study.[22,23] Nevertheless, it is possible that our empirical LI-ESWT protocol is less effective than PDE5i therapy.

Table 2. *Changes in penile blood flow at FU1*

	Resting Blood Flow (ml/min/dl)	Max Blood Flow (ml/min/dl)
Sham:		
Median	0.2	−0.1
Min	−6.7	−9.2
Max	7.6	18.5
Treatment:		
Median	4.6	8.2
Min	−15.5	−17.0
Max	80.2	124.8

All values $p < 0.0001$.

An unexpected finding was the significant improvement in the IIEF Sexual Desire domain scores of the treated men, a finding that has been reported in at least 1 of the previous studies that evaluated pharmacotherapy.[19] While our finding was statistically significant, the clinical importance of a 1-point increase in this score remains unclear.

We did not find statistically significant improvement in the IIEF Sexual Satisfaction domain score. We attribute this lack of improvement to our subjects' previous positive experience with PDE5i. Nevertheless, the IIEF Overall Satisfaction domain score did increase significantly after treatment, indicating a beneficial effect of LI-ESWT.

The EHS data also revealed that more men in the treated group than in the sham group were able to achieve erections sufficiently hard for penetration.

Ease of definition and applicability make the EHS a valuable tool for simple clinical assessment. However, it is statistically ill suited for pre-post and 2-group study designs such as ours.

Physiological evidence that LI-ESWT improves penile hemodynamics comes from the finding that the 2 measures of penile blood flow improved significantly in the treated group and were positively correlated with the increases in IIEF-EF. Moreover, in seeking a success criteria based on clinical and physiological outcomes, we found that of the patients who had a 5-point or greater improvement in the IIEF-EF and improved penile hemodynamics all but 1 came from the treated group. Further supporting our contention that LI-ESWT improves penile hemodynamics is our finding that most of the treated men reported improvement in erectile function between treatment sessions 6 and 8, which is probably the time needed for LI-ESWT to induce the physiological changes.

While the purpose of this study was to evaluate the physiological effects of LI-ESWT on the penis, our finding that the IIEF-EF remained increased 3 months after the final treatment suggests that the positive physiological effect is preserved. This finding is similar to that of our previous study demonstrating that the subjects' IIEF-EF remained high at the 3 and 6-month followup.[4]

The treatment protocol that we used in all our studies to date was based on that described in the cardiology literature.[24,25] This empirical protocol had not been previously tested in animal or human penile tissue and, therefore, will likely change as more protocols are examined.

Although our final study population was comprised of only 60 men, this number of participants was sufficient to achieve our main goal of determining whether our treatment protocol could yield a genuine physiological effect on cavernous tissue.

To date, no deleterious side effects have been reported in the long-term followup of patients undergoing high intensity penile shock wave therapy for the treatment of Peyronie disease,[26,27] despite findings that such shock waves may lead to the collagenization of corporal smooth muscle in the rat.[28] While our subjects did not report any adverse effects to the treatment, the long-term risk of LI-ESWT on penile tissue has yet to be fully elucidated.

CONCLUSIONS

This is the first randomized, double-blind, sham controlled study in which LI-ESWT has been shown to have a beneficial effect on erectile function in men with ED and cardiovascular risk factors. While we do not know the precise mechanism of action of LI-ESWT, our objective measures lead us to presume that this therapy works by improving penile hemodynamics. We also found that this treatment is feasible and tolerable, and is unique in that it has rehabilitative characteristics. Additional studies with long-term followup are now needed to fully evaluate the efficacy of this new therapy and confirm our findings. These studies must be backed by basic science research whose aims are to fully understand the mechanism of action of this energy. With this additional knowledge, our hope is that LI-ESWT will make its way into the armamentarium of treatment options currently being used in the long-term clinical management of ED.

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