

Low-Intensity Extracorporeal Shock Wave Therapy—A Novel Effective Treatment for Erectile Dysfunction in Severe ED Patients Who Respond Poorly to PDE5 Inhibitor Therapy

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ABSTRACT

Introduction. Low-intensity shock wave therapy (LI-ESWT) has been reported as an effective treatment in men with mild and moderate erectile dysfunction (ED).

Aim. The aim of this study is to determine the efficacy of LI-ESWT in severe ED patients who were poor responders to phosphodiesterase type 5 inhibitor (PDE5i) therapy.

Methods. This was an open-label single-arm prospective study on ED patients with an erection hardness score (EHS) ≤ 2 at baseline. The protocol comprised two treatment sessions per week for 3 weeks, which were repeated after a 3-week no-treatment interval. Patients were followed at 1 month (FU1), and only then an active PDE5i medication was provided for an additional month until final follow-up visit (FU2).

At each treatment session, LI-ESWT was applied on the penile shaft and crus at five different anatomical sites (300 shocks, 0.09 mJ/mm² intensity at 120 shocks/min).

Each subject underwent a full baseline assessment of erectile function using validated questionnaires and objective penile hemodynamic testing before and after LI-ESWT.

Main Outcome Measures. Outcome measures used are changes in the International Index of Erectile Function-erectile function domain (IIEF-ED) scores, the EHS measurement, and the three parameters of penile hemodynamics and endothelial function.

Results. Twenty-nine men (mean age of 61.3) completed the study. Their mean IIEF-ED scores increased from 8.8 ± 1 (baseline) to 12.3 ± 1 at FU1 ($P = 0.035$). At FU2 (on active PDE5i treatment), their IIEF-ED further increased to 18.8 ± 1 ($P < 0.0001$), and 72.4% ($P < 0.0001$) reached an EHS of ≥ 3 (allowing full sexual intercourse). A significant improvement ($P = 0.0001$) in penile hemodynamics was detected after treatment and this improvement significantly correlated with increases in the IIEF-ED ($P < 0.05$). No noteworthy adverse events were reported.

Conclusions. Penile LI-ESWT is a new modality that has the potential to treat a subgroup of severe ED patients. These preliminary data need to be reconfirmed by multicenter sham control studies in a larger group of ED patients.

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Key Words. Low Intensity Extracorporeal Shock Wave Therapy; Erectile Dysfunction; Penis

Introduction

Erectile dysfunction (ED) is one of the most common disorders of middle-aged men that profoundly affect their quality of life [1]. Although tremendous advances for treating this disorder have been made in the past decade, most currently

available treatment modalities still rely on an “on demand” regime, of which up to 35% are unsuccessful [2–4]. From our experience, ED patients who were treated with a phosphodiesterase type 5 inhibitor (PDE5i) tend to search for an alternative treatment modality that would ameliorate their ED. Hence, there is a need for an effective new

treatment concept that would have a durable effect on the spontaneous improvement of erectile function.

We recently reported on the efficacy of a novel therapy, namely, applying low-intensity extracorporeal shock wave therapy (LI-ESWT) to the penis of patients with vasculogenic ED [5]. Results from in vitro and in vivo studies have shown that LI-ESWT induces neovascularization [6–8], and this finding was the theoretical basis for initiating studies on using LI-ESWT for treating ED. The results of our first preliminary research on ED patients who were responsive to PDE5i therapy showed that this treatment modality enhances penile perfusion and substantially improves erectile function [5].

A number of studies have been published on improving efficacy of PDE5i in men who do not respond or respond poorly to PDE5i therapy [9,10], suggesting potential ways to increase the efficacy of PDE5i therapy but not proposing any innovative treatments. Today, patients unsatisfied with response to oral therapy are candidates for either intracavernosal injections or penile implants. As most responders to PDE5i are usually managed by general practitioners in the primary health care setting, poor responders or severe ED patients are mainly referred to urologists and are managed in ED clinics. If LI-ESWT would be proved to be effective in these more severe ED patients, such a unique modality could expand our urological treatment armamentarium in the management of ED. It is against this background that we undertook the current study in which we evaluated the efficacy of

LI-ESWT in severe ED men who were poor responders to PDE5i therapy.

Materials and Methods

This was an open-label single-arm prospective pilot study approved by the local ethics committee. The study had a screening phase, a 12-week LI-ESWT phase, applied to the patient’s genital area, and a 2-month evaluation phase (Figure 1). Only men over 40 in a stable relationship (>3 months), who were previously diagnosed with ED at our outpatient clinic and were registered as poor responders to PDE5i therapy, were eligible for screening. In order to ensure that these men were poor responders, they were thoroughly questioned in regard to the dosage of the PDE5i, the timing of its intake, and the concomitant sexual stimulation. Men who could not provide definite answers were given four tablets of PDE5i and then asked to return for follow-up after they had completed their treatment. At this follow-up examination, the severe ED and poor responders were identified and then recruited for the study. Our key inclusion criterion was a low erection hardness score (EHS) of zero to two during PDE5i therapy. We excluded men (i) with an unstable medical or psychiatric condition, (ii) with a previous history of a neurological pathology, and (iii) after radical pelvic surgery, irradiations, or hormonal therapy.

At screening, written informed consent and demographic data were obtained from each participant. Assessment of erectile and sexual function during PDE5i treatment was determined using the International Index of Erectile Function-erectile

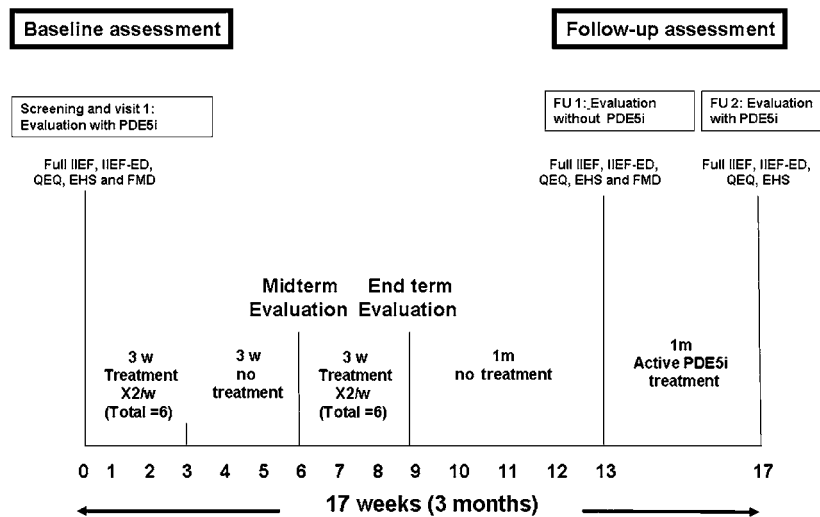


Figure 1 Study flow chart. EHS, erection hardness score; FMD, flow mediated dilatation; FU, follow-up; IIEF-ED, International Index of Erectile Function-erectile function domain; PDE5i, phosphodiesterase type 5 inhibitor; QEQ, Quality of Erection Questionnaire.

function domain (IIEF-ED) score, the Quality of Erection Questionnaire (QEQ), and determination of the EHS. We used the flow mediated dilatation (FMD) technique for objective evaluation of the participant's penile hemodynamics and endothelial function [11,12]. After completion of the assessments, the first of the 12 LI-ESWTs was then administered. In the treatment phase, we used the identical treatment protocol that we used in our first study [5]. The treatment protocol consisted of two treatment sessions per week for 3 weeks, which were repeated after a 3-week no-treatment interval. At each treatment session, LI-ESWT was applied on the penile shaft and crus for 3 minutes at five different penile anatomical sites. Each LI-ESWT comprised 300 shocks per treatment point at an energy density of 0.09 mJ/mm² and a frequency of 120/min. One month after the end of treatment (FU1), the results of LI-ESWT without PDE5i therapy were evaluated using the identical methods that were used at screening. As the main aim of this study was to assess the effect and benefit of LI-ESWT on this specific population of poor responders, we then provided an active PDE5i medication regime to each study participant, which comprised four tablets of a PDE5i that each man selected according to his best personal experience. One month later (FU2), we reassessed erectile function using the identical methods that were used at screening. The main outcome measures for success were changes in the IIEF-ED, the EHS measurement, and the three parameters of penile hemodynamics and endothelial function.

Statistical Analysis

A repeated-measures analysis of variance (ANOVA) was used to investigate the overall effects of treatment by comparing the effect of LI-ESWT on the study parameters at visit 1 to those from FU1 (net effect without PDE5i therapy) and at visit 1 to those from FU2 (under PDE5i treatment). The Tukey test was used to investigate the specific pairwise differences in the IIEF-ED, the QEQ scores, and the maximum FMD values. ANOVA results are reported as least squares mean \pm the pooled standard error of the least squares mean (sem).

The binomial test was used to determine the proportion of treatment successes after treatment at FU1 and FU2 and the significance of the difference between the two proportions.

The changes in the EHS values for each study participant were compared by Bowker's test. For

this purpose, the study group was divided into two subgroups: those who achieved a score of three to four on each follow-up visit and those who did not, and then comparing their scores with those that were determined at baseline, where none had scored three or four.

Spearman rank correlation was used to establish the relationship between the changes in the penile hemodynamics and endothelial function and the changes in the IIEF-ED from visit 1 to FU1.

All data were statistically analyzed using JMP Discovery Software (SAS Institute, NC, USA); statistical significance was at 5%.

Results

Thirty-three men entered the study after screening. Four men discontinued due to study non-compliance [2] and protocol violation [2]. The remaining 29 men who met the inclusion-exclusion had a mean IIEF-ED of 8.8 and a median ED duration of 60 months. Other detailed baseline characteristics are displayed in Table 1. The men were middle-aged with coronary heart disease, diabetes mellitus, or cardiovascular risk factors, had severe ED for more than a year, and were incapable of full sexual intercourse.

At FU1, subjects reported improved erectile function, as measured by significantly increased ($P = 0.035$) IIEF-ED (Figure 2), and 10 (34.5%) also reported increased penile rigidity (Figure 3).

Two months after end of the treatment (FU2), while on PDE5i therapy, the mean IIEF-ED increased by 10 points (18.8 ± 1 [standard deviation], $P < 0.0001$) (graph 1). In fact, eight men (27.6%) were normalized according to the IIEF-ED (≥ 25), and the IIEF-ED domain scores improved in 22 men (75.9%) by at least five points. Twenty-one men (72.4%) reported an EHS value ≥ 3 ($P < 0.0001$; see Figure 3). On average, the men noted some improvement in their erectile function, 3 weeks after the start of LI-ESWT, which was usually between the sixth and eighth treatment sessions.

Table 1 Baseline patient characteristics

| | | |
|-----------------------------|-------|---------|
| Mean age (years) | 61.3 | |
| Age range (years) | 41–79 | |
| Cardiovascular risk factors | N | Percent |
| Hypertension | 24 | 83.7% |
| Hypercholesterolemia | 27 | 93.1% |
| Heavy smoker | 12 | 41.4% |
| Obesity | 8 | 27.5% |
| Coronary artery disease | 16 | 55.1% |
| Diabetes mellitus | 21 | 72.4% |

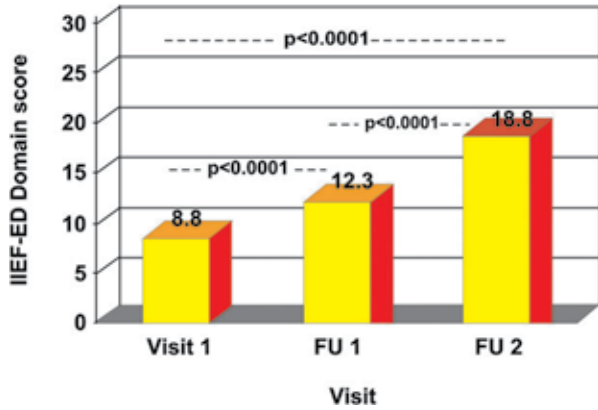


Figure 2 Mean IIEF-ED scores before and after LI-ESWT. FU, follow-up; IIEF-ED, International Index of Erectile Function-erectile function domain; LI-ESWT, low-intensity extracorporeal shock wave therapy.

The secondary outcome measures that were used to assess the effect of LI-ESWT on erectile function were the total IIEF and the QEQ scores. Both scores increased significantly from baseline to FU2 (IIEF 30.6 vs. 48.9; QEQ scores: 12.2 vs. 45.5, $P < 0.0001$ for both).

Penile endothelial function improved significantly ($P = 0.0001$) after LI-ESWT, as assessed by the three parameters of penile hemodynamics and endothelial function, namely, maximal postischemic blood flow (Figure 4), basal blood flow, and the area under the flow-time curve (AUC).

We noted a strong correlation between the changes in the IIEF-ED and the changes in those three parameters at baseline and FU1, namely, maximal postischemic blood flow ($P = 0.0087$; Figure 5), basal blood flow ($P = 0.0448$), and AUC ($P = 0.0109$).

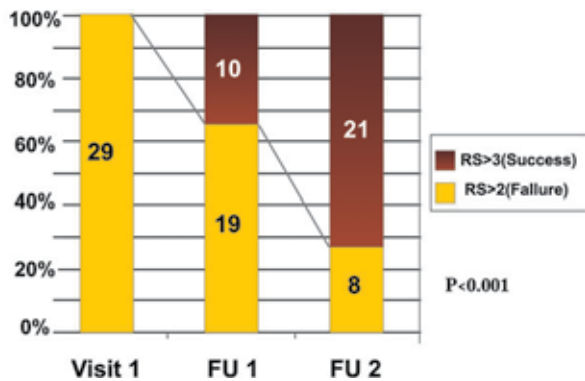


Figure 3 Changes in rigidity scales according to visit. RS, rigidity scale.

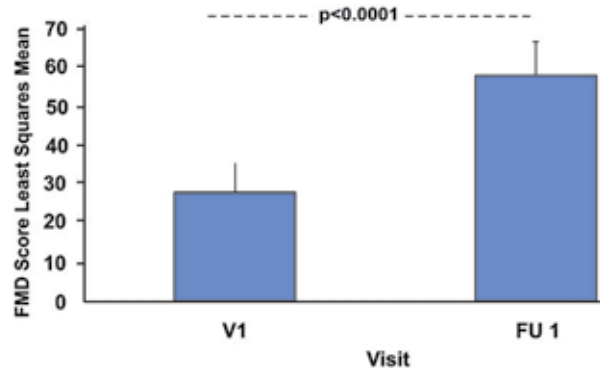


Figure 4 Maximal postischemic blood flow measured at the penis level per visit. FU, follow-up.

None of the men reported pain or any adverse events due to or after the treatment. In fact, the only adverse event was a mild transient allergic reaction to the gel in one man when it was applied at treatment session 2.

Discussion

This is our second report on the effect of LI-ESWT in ED patients. The results of our first

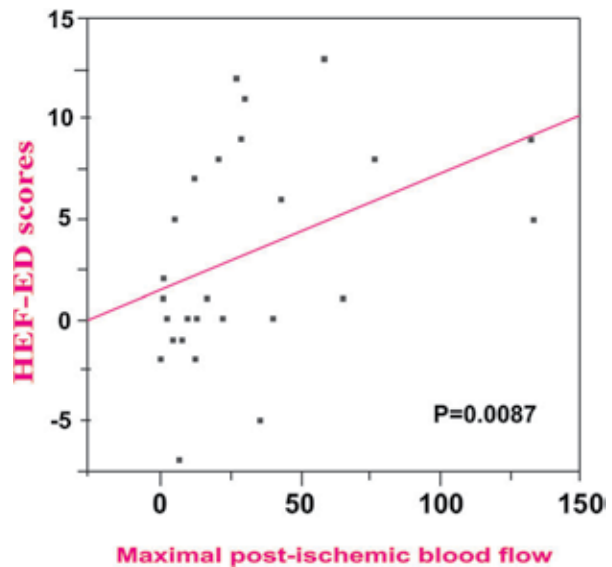


Figure 5 Spearman rank correlation between the changes in the maximal postischemic blood flow parameter and changes in IIEF-ED scores. Graph 4: Spearman rank correlation between the changes in the maximal postischemic blood flow parameter and changes in IIEF-ED score. IIEF-ED, International Index of Erectile Function-erectile function domain.

study showed that this treatment exerts a beneficial effect on 20 ED men who were responders to PDE5is. Here, we report that LI-ESWT is also beneficial when given to 29 poor responders with severe ED and significant cardiovascular risk factors. These results also confirm that this modality exerts a genuine physiological effect on the erectile mechanism when applied directly to the cavernosal tissue.

For this study, we used the identical protocol from our first trial of which the obtained good results did not justify any modification at this time. This does not mean that this treatment protocol is optimal. Hence, additional studies using different protocols need to be done in order to reach the desired clinical outcome.

We recruited men that were already on routine follow-up at our outpatient ED clinic.

Seven were on injection therapy and two were candidates for a penile implant. The others were relatively new patients who were poor or nonresponders to PDE5is and had been referred to our clinic for further treatment. At screening, we interviewed each man using a detailed intake sheet, documented their sexual difficulties in real-life situations, and compared the data with their IIEF-ED. This way, we assured that the study population consisted of true poor or nonresponders and allowed us to simplify the protocol and to assure patient compliance.

Our primary end points were the change in IIEF-ED and in the EHS value. We selected the IIEF-ED as it is the “gold standard” and the most commonly used instrument for evaluating ED. The EHS value was selected as it can precisely make a distinction between those who are able to penetrate and achieve full sexual intercourse from those who are unable to do so. We believe that the EHS value is a reliable measure of the functional capability of our study participants, and because of its simplicity, it should be used more frequently in other ED trials.

The results of the current study showed that the EHS value was three or more in 72.4% of the men after LI-ESWT. This result is remarkable as LI-ESWT significantly improved their response to PDE5i therapy and enabled these nonsexually functioning men to now achieve vaginal penetration and full sexual intercourse. This achievement is also noteworthy because it enabled 34% of these men to function sexually without using any medication. These results are supported by the corresponding improvement in their penile hemodynamics. Both the subjective and objective

measurements of erectile function coincide, emphasizing that LI-ESWT exerts a genuine effect on the erectile mechanism by improving penile blood flow.

We noticed that most men feel some initial improvement between the sixth and eighth treatment sessions and sometimes a later effect is reported even after the end of treatment.

Limitations of this study are the lack of a sham-controlled arm and the relatively low number of participants. Despite these weaknesses, the substantial changes in the IIEF-ED and the EHS values, as well as the clinically significant effect that was achieved in this group of severe ED patients, cannot be undervalued.

Our finding that this emerging new and exciting treatment modality exerts a beneficial effect in men with severe ED suggests that LI-ESWT could be used as an alternative treatment or as an addition to PDE5i therapy. Noteworthy is our finding that the 21 diabetic patients in our study responded to this energy. As such men are considered a difficult to treat population for ED, this finding raises the question whether LI-ESWT is specifically effective in diabetic ED. Evaluation of the efficacy of LI-ESWT in such men using randomized, double-blind, sham-controlled studies is now needed, and we are in the midst of performing such a study. There is also a need for studies whose aim is to define the optimal treatment protocol in order to be able to offer the best results when using LI-ESWT in ED patients.

Conclusions

These preliminary results of the effect of LI-ESWT in a group of men with severe ED who were nonresponders to PDE5is suggest that LI-ESWT probably has a physiologic effect on the erectile mechanism, a fact that still needs to be reconfirmed in a placebo-controlled manner.

The fact that the magnitude of response is impressive and the objective hemodynamic data showed significant changes posttreatment drives us to believe that there is more than just a placebo effect, especially due to the severity of this study group.

We are aware of the skepticism that this new therapeutic approach may arouse but hope that the data provided in this preliminary study will persuade the reader to at least remain open-minded to this optional treatment strategy. This will probably happen only after better understanding of the

basic physiological effect that this energy has on the cavernosal tissue and the availability of multi-center clinical data.

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