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ORIGINAL RESEARCH

ERECTILE FUNCTION

Low-Intensity Shockwave Therapy Improves Hemodynamic Parameters in Patients With Vasculogenic Erectile Dysfunction: A Triplex Ultrasonography-Based Sham-Controlled Trial

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ABSTRACT

Background: Although several reports have documented the subjective improvement of erectile function after low-intensity extracorporeal shockwave therapy (LI-ESWT) in patients with vasculogenic erectile dysfunction (ED), objective assessment data of penile hemodynamics are lacking.

Aim: To assess penile hemodynamics before and 3 months after LI-ESWT in a group of patients with documented vasculogenic ED.

Methods: This was a double-blinded, randomized, sham-controlled trial. Forty-six patients with ED were randomized; 30 underwent LI-ESWT and 16 had a sham procedure in double-blinded fashion. All patients underwent penile triplex ultrasonography by the same investigator immediately before and 3 months after treatment. Patient demographics, International Index of Erectile Function erectile function domain (IIEF-ED) score, and minimal clinically important difference were assessed at baseline and 1, 3, 6, 9, and 12 months after treatment.

Outcomes: Changes in peak systolic velocity and resistance index as measured by triplex ultrasonography at baseline and 3 months after treatment were the main outcomes of the study. Secondary outcomes were changes in the IIEF-EF score from baseline to 1, 3, 6, 9, and 12 months after treatment and the percentage of patients reaching a minimal clinically important difference during the same period for the two groups.

Results: IIEF-EF minimal clinically important differences for the active vs sham group were observed for 56.7% vs 12.5% ($P = .005$) at 1 month, 56.7% vs 12.5% ($P = .003$) at 3 months, 63.3% vs 18.8% ($P = .006$) at 6 months, 66.7% vs 31.3% ($P = .022$) at 9 months, and 75% vs 25% ($P = .008$) at 12 months. Mean peak systolic velocity increased by 4.5 and 0.6 cm/s in the LI-ESWT and sham groups, respectively ($P < .001$).

Clinical Implications: Such results offer objective and subjective documentation of the value of this novel treatment modality for men with vasculogenic ED.

Strengths and Limitations: Strengths include the prospective, randomized, sham-controlled type of study and the assessment of penile hemodynamics. Limitations include the small sample and strict inclusion criteria that do not reflect everyday clinical practice.

Conclusion: The present study confirms the beneficial effect of LI-ESWT on penile hemodynamics and the beneficial effect of this treatment up to 12 months. **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;14:891−897.**

Key Words: Low-Intensity Shockwave Therapy; Erectile Dysfunction; Peak Systolic Velocity; Penile Doppler

INTRODUCTION

Several treatment effective options are available for vasculogenic erectile dysfunction (ED); phosphodiesterase type 5 (PDE5) inhibitors and intracavernosal injections are effective and safe vasodilating agents.[1] The main disadvantage of currently available pharmacotherapy is the inability to alter the underlying predominant pathology in patients with vasculogenic ED (eg, cavernosal artery insufficiency). Furthermore, PDE5 inhibitors might be contraindicated or should be used with caution in some patients.[2]

Low-intensity extracorporeal shockwave therapy (LI-ESWT) has shown encouraging results for patients with ischemic heart

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disease,[3] chronic diabetic foot ulcers, or wound healing.[4,5] Basic research has shown that low-intensity shockwaves act by provoking microtrauma in the endothelium of the helicine arteries, leading to the release of angiogenic factors, such as nitric oxide synthase and vascular endothelial growth factor, and endothelial cell proliferation factors, such as proliferating cell nuclear antigen.[6,7]

Recent sham-controlled clinical trials have reported subjective improvement in erectile function and systemic endothelial function measured by nocturnal penile tumescence and flow-mediated dilatation, respectively.[8–10] However, most of the published studies did not assess penile hemodynamics. The purpose of the study was to assess penile hemodynamics before and after LI-ESWT and subjective long-term improvement of erectile function.

METHODS

We recruited men who a history of vasculogenic ED for at least 6 months. Diagnosis was based on sexual and medical history, clinical examination, and laboratory test results. Eligible subjects were at least 18 years old, had ED for at least 6 months, and were at least partial responders to PDE5 inhibitors (able to penetrate at least half the time while taking a PDE5 inhibitor). For inclusion in the study, after a 4-week washout period, the baseline International Index of Erectile Function erectile function domain (IIEF-EF) score had to be at least 6 (mild to moderate ED) to 21 (moderate and severe ED). Patients with no ED or with mild ED were excluded. All subjects had been in a stable heterosexual relationship with the same partner for more than 3 months. The exclusion criteria were radical prostatectomy; psychogenic ED; penile anatomic abnormalities; neurogenic ED; hormonal abnormalities; antiandrogen therapy; history of heart attack, stroke, or life-threatening arrhythmia within 6 months before enrollment in the study; and recovery from any cancer within the past 5 years. All patients accepted and signed the informed consent form for the study, which was approved by the institutional review board.

Study Sample

Sample size calculation was based on a difference of at least 3.5 in changes from baseline to month 12 in IIEF-EF score between the study groups, with 80% power and 5% statistical significance. The calculation assumes a common SD of the change of 3.5 and a ratio of 2:1 between the groups. A two-group t-test with a 0.05 two-sided significance level would have 80% power to detect the difference of at least 3.5 in IIEF-EF score between groups when the sample sizes were 15 for the sham group and 30 for the active treatment group.

Study Protocol

The study consisted of the following phases. The screening phase included a 4-week run-in phase of using PDE5 inhibitors to identify at least partial response to PDE5 inhibitors. Subjects who met the inclusion criteria underwent a 4-week PDE5 inhibitor washout period and completed the IIEF questionnaire, and data were selected by a research assistant. At the end of the washout phase, eligible patients underwent triplex ultrasonography of the cavernosal arteries by the same investigator to assess penile hemodynamics.[11] All patients were blindly randomized to one of two active treatment groups or to a sham control group. The groups were marked as A, B, and C, two of which indicated active treatment groups and one of which indicated a sham control group. The treatment protocol was applied by two investigators in double-blinded fashion and included biweekly treatment sessions at the first, second, third, seventh, eighth, and ninth weeks after the washout period, for a total of 12 treatments (sessions). All patients underwent penile triplex ultrasonography by the same investigator at baseline and 3 months after treatment. Side effect profile was assessed at every visit during the treatment period, and the IIEF score was assessed before and at 1, 3, 6, 9, and 12 months after treatment (Figure 1).

Blinding and Randomization

Study procedures were identical for the active treatment and sham control groups, but the sham treatment was conducted using a distinctively designed shockwave applicator. The sham shockwave applicator contained an element that blocked delivery of shockwaves. The two types of shockwave applicator (active and sham) looked identical. All patients were blindly randomized using specific computer software into one of two active treatment groups or into a sham control group in a 2:1 ratio, respectively.

LI-ESWT Methodology

We applied a standard commercial gel normally used for sonography on the subject's penis and on the membrane of the shockwave applicator. The treatment included a standard protocol of 300 shocks to each treatment location (three locations on the penile shaft and two locations on the penile crura for a total of 1,500 shocks) using a specialized focused shockwave probe (Omnispec ED1000, Medispec Ltd, Yehud, Israel) as described in previous studies.[9,10] The treatment was performed at an energy intensity of 0.09 mJ/mm^2; the energy level was automatically predetermined by the device. The treatment was performed at an energy intensity of 0.09 mJ/mm^2 and frequency of 160 pulses/min. Each treatment session lasted approximately 20 minutes without local or systemic analgesia.

Penile Triplex Ultrasonography Protocol

Penile triplex ultrasonography was performed (BK Flex Focus 400, BK Ultrasound, Peabody, MA, USA) to assess penile hemodynamics at baseline and 3 months after the final LI-ESWT treatment. The test was performed as follows: 0.5 mL of vasoactive agent (tri-mix solution) was injected into the corpus cavernosum and the time of injection was recorded. Then, the ultrasound B-mode probe was placed on the left and right

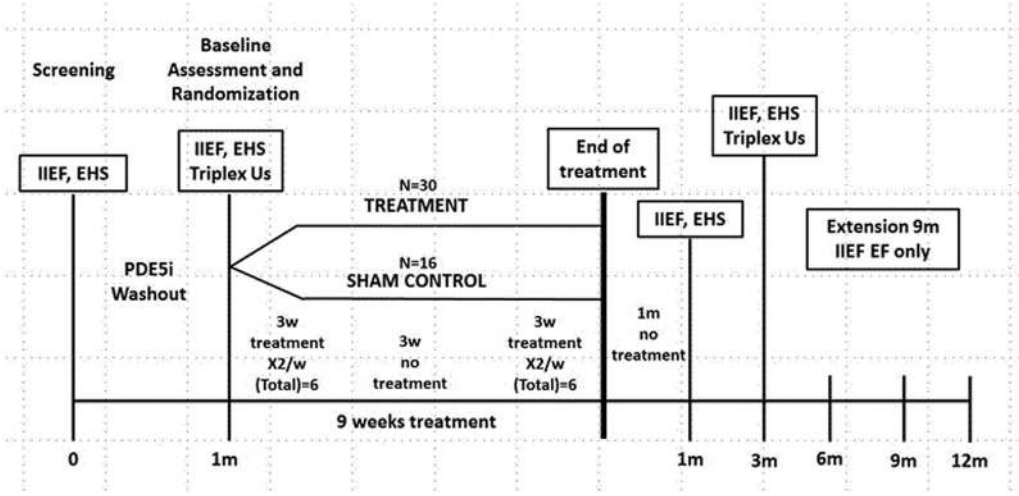

Figure 1. Study flowchart. EHS = Erection Hardness Scale; IIEF = International Index of Erectile Function; IIEF-EF = International Index of Erectile Function erectile function domain; m = months; PDE5i = phosphodiesterase type 5 inhibitor; Us = ultrasonography.

cavernous arteries. By shifting to Doppler mode, focusing the cursor, and adapting a right angle at 60°, the systolic and end-diastolic velocities (centimeters per second) were determined. Doppler angle was not changed during the evaluation. An evaluation of peak systolic velocity (PSV) to end-diastolic velocity blood flow with automatic calculation of the resistance index (RI) at various time points was followed for up to 30 minutes. Flow measurements were performed at 5, 10, 15, and 20 minutes, reserving a measurement at 30 minutes for patients who did not achieve adequate penile hardness or a purely erectile response; in such cases, re-dosing with 0.5 mL of tri-mix solution was followed and all measurements were repeated. The highest values achieved were reported.

Main Outcome Measures

Changes in PSV and RI as measured by triplex ultrasonography at baseline and 3 month after treatment were the main outcomes of the study. The IIEF-EF score was used to evaluate erectile function. Improvement in IIEF-EF score from baseline to 12-month follow-up; the minimal clinically important difference in IIEF-EF score; and a change in IIEF-EF score equal to or greater than 2, 5, and 7 points for mild, moderate, and severe ED, respectively, were measured.[12]

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 20.0 (IBM Corp, Armonk, NY, USA). Normality of measurements for PSV, RI, and IIEF-EF score was tested using the Shapiro-Wilk test to establish that normality was not violated in most cases. Parametric tests and models were used for analyses of the data. Study parameters were summarized in tables by treatment and presented as mean ± SD, median ± range, or frequency (percentage) according to the distribution of the parameter. Comparative analysis of baseline characteristics was applied using the two-sample t-test or median test for quantitative parameters and the χ^2 test for categorical parameters. The repeated measures general linear model was applied for analyzing the difference in IIEF-EF scores and changes from baseline between treatments. Changes from baseline in PSV and RI were analyzed within each treatment using paired-samples t-test. The level of significance for all analyses was set at 5%.

RESULTS

Fifty-nine patients were screened; 46 who met the inclusion criteria were randomized into groups. All 46 patients completed the study; the sham control group and the active treatment group consisted of 16 and 30 randomly assigned patients, respectively. Table 1 presents the baseline characteristics of the two study groups.

IIEF-EF Score Changes

At baseline and 1, 3, 6, 9, and 12 months after the last treatment, the IIEF-EF scores in the active treated group were 13.8 ± 3.6, 18.46 ± 3.6, 18.46 ± 3.5, 19.0 ± 3.3, 18.63 ± 3.0 and 19.1 ± 2.8, respectively. The IIEF-EF scores in the sham group were 14.6 ± 3.4, 16.43 ± 3.5, 15.93 ± 3.6, 16.12 ± 2.6, 16.00 ± 3.0, and 16.00 ± 2.8 (Figure 2). One patient achieved an IIEF-EF score of 26 (no ED). We tested whether there were significant differences among the six repeated measurements of IIEF-EF score over time. The model showed no difference for the pretreatment measurement between the two groups ($P = .475$). In addition, the difference in the mean IIEF-EF score the first month after treatment showed a tendency toward significance ($P = .072$) but became significant between the two groups after month 3 ($P = .02$), whereas after months 6, 9, and 12 months the differences were highly statistically significant ($P < .01$ for all comparisons).

A minimal clinically important difference of the IIEF-EF score for the active treatment vs sham group was 56.7% vs 12.5%

Table 1. Baseline characteristics of study population at randomization (no phosphodiesterase type 5 inhibitor use)

	Sham	Treatment	*P* value
Men, n	16	30	
Age (y), median (range)	55.1 (38–72)	53.0 (31–72)	.52†
ED (y), median (range)	5.5 (1–15)	5.5 (1–20)	.99†
Concomitant condition, %			
Cardiovascular risk factors*	56.3	50	.69§
Diabetes mellitus	37.5	26.7	.45§
IIEF-EF domain score, mean ± SD	14.6 ± 3.4	13.8 ± 3.6	.47‡
EHSG score, mean ± SD	2.75 ± 0.45	2.95 ± 0.41	.70‡
PSV (cm/s), mean ± SD	30.7 ± 3.55	31.1 ± 3.23	.70‡
EDV (cm/s), mean ± SD	5.95 ± 1.87	5.86 ± 1.65	.86‡
RI, mean ± SD	0.81 ± 0.07	0.80 ± 0.05	.53‡

ED = erectile dysfunction; EDV = end-diastolic velocity; EHSG = Erection Hardness Grading Scale; IIEF-EF = International Index of Erectile Function erectile function domain; PSV = peak systolic velocity; RI = resistance index.
*Including at least one of the following: hypertension, metabolic syndrome, obesity, smoking, and hypercholesterolemia.
†By median test.
‡By Student t-test.
§By χ^2 test

(P = .005) at 1 month, 56.7% vs 12.5% (P = .003) at 3 months, 63.3% vs 18.8% (P = .006) at 6 months, 66.7% vs 31.3% (P = .022) at 9 months, and 75% vs 25% (P = .008) at 12 months (Figure 3).

Penile Hemodynamics Changes

Penile triplex ultrasonographic measurements were used as an objective method to assess penile hemodynamics before and 3 months after treatment. The mean change of PSV was 4.5 and 0.6 for the treatment and sham-control groups, respectively, from baseline to 3 months after the last treatment (Table 2). The mean change of the RI was 0.04 and −0.01 for the treatment and placebo groups, respectively, from baseline to 3 months after treatment. We tested whether there was a significant difference between baseline and post-treatment PSV and RI. P values were greater than .05 for the sham control group and less than 0.001 for the active group. Individual plots describing maximal PSV at baseline and at 3-month follow-up clearly showed an

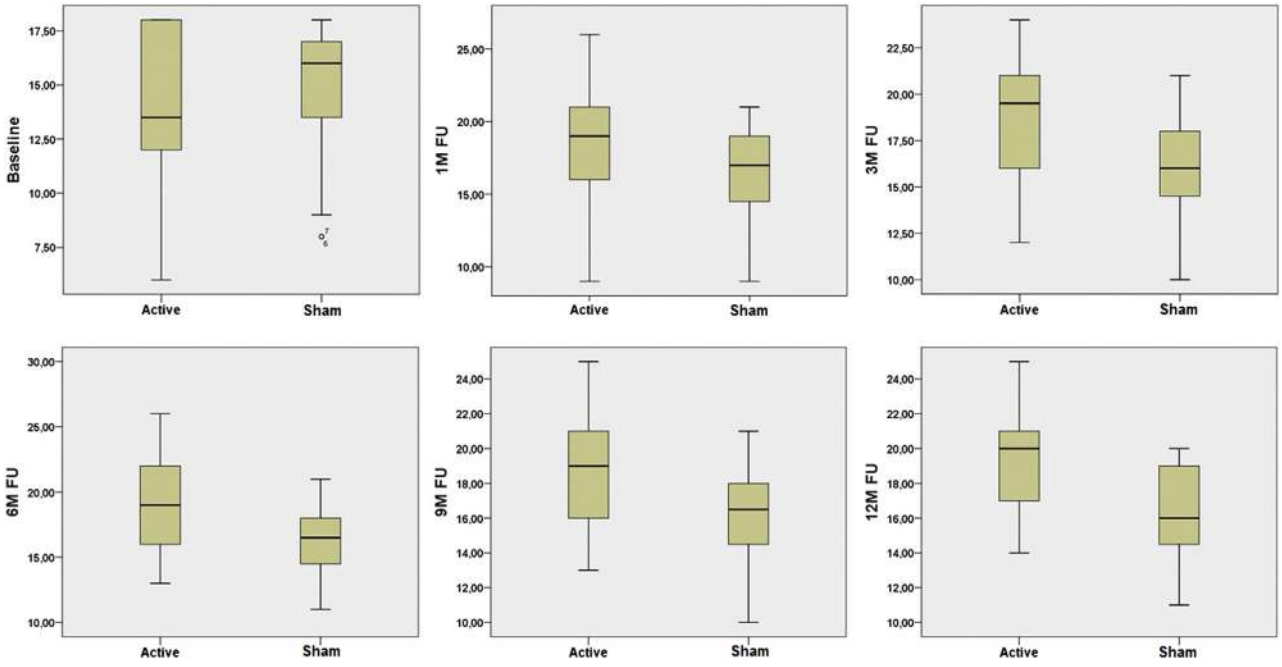

Figure 2. Twelve-month FU of International Index of Erectile Function erectile function score. All analyses were done using Student t-test. FU = follow-up; M = month. Figure 2 is available online at www.jsm.jsexmed.org.

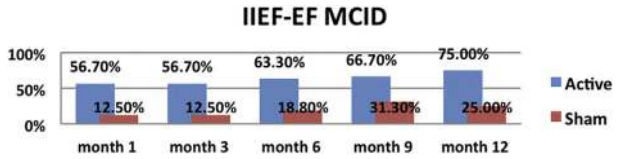

Figure 3. IIEF-EF score MCID in active and sham groups at 1-, 3-, 6-, 9-, and 12-month follow-up visits ($P < .02$ by χ^2 test). IIEF-EF = International Index of Erectile Function erectile function domain; MCID = minimal clinically important difference. Figure 3 is available online at www.jsm.jsexmed.org.

improvement in arterial inflow in all but one patient in the active treatment group (Figure 4). No pain or any other side effect was observed in any patient.

DISCUSSION

During the past decade, the use of LI-ESWT has been added as novel therapy to the treatment algorithm of ED. The increased reports and clinical studies of this therapy have emphasized LI-ESWT as a therapeutic method for ED with great acceptance by the research community and patients. The positive treatment effect of LI-ESWT in patients with ED has been confirmed recently by the first meta-analyses on this method.[13,14] Nevertheless, in all studies included in these meta-analyses, the treatment benefit of LI-ESWT was evaluated mainly by improvement in IIEF score, a patient-reported assessment that is purely subjective.

The present study clearly demonstrated the beneficial effects of LI-ESWT on penile hemodynamics as measured by the most commonly performed diagnostic test for the diagnosis of vasculogenic ED. Our finding that PSV increased in all but one patient in the active group strengthens the clinical evidence that LI-ESWT improves penile hemodynamics. The main disadvantages of penile duplex ultrasonography include operator dependence and inadequate smooth muscle relaxation; all hemodynamic assessments were performed by the same experienced investigator using a standardized protocol[11] and adapting the re-dosing principle to achieve maximum smooth muscle relaxation. The scheme of the shockwave therapy was the same as that used in cardiology[15] and that used in all published randomized control trials for the treatment of ED. Such methodology allows comparison of the present data with previously published data. The present results were consistent with those of previous studies for changes in IIEF-EF score.[11] An important finding of our study is that IIEF score and PSV increased significantly at 3 months in a linear fashion. Patients with no improvement in IIEF score had no improvement in PSV. The increase in IIEF-ED score remained statistically significant even at 12-month follow-up in the active treatment group, clearly showing the long-term benefit of LI-ESWT.

The concept of improving endothelial function and neovascularization using low-intensity shockwave energy is not new.[16] Well-established therapeutic protocols have been established in cardiology and diabetology to exploit this application.[15,17,18] In sexual medicine, the application of LI-SWT is a novelty and emerged by the unmet need for a non-pharmaceutical therapy that could be used to supplement existing modalities.[10] Unfortunately, existing treatments for ED offer only temporary symptomatic relief and none are curative. Targeting the etiology of ED is an extremely demanding clinical feat that appears to be served satisfactorily by LI-ESWT. In particular, clinical researchers have shown an overall improvement in IIEF score and a very high rate of conversion of non-responders to PDE5 inhibitors after application of LI-ESWT.[8,10] Although the exact mode of action of LI-ESWT is not known, it appears to be mediated by a local induction of neoangiogenesis and endothelial repair[19,20] by stimulating the expression of angiogenesis-related growth factors (nitric oxide synthase and vascular endothelial growth factor) and endothelial cell proliferation factors(proliferating cell nuclear antigen).[21,22] Further basic research is urgently needed to gain insight into the mechanism of action of LI-ESWT on cavernosal structures.

Our findings further support the growing evidence for the clinical use of LI-ESWT in patients with vasculogenic ED. The prospective, randomized, sham-controlled study, the assessment of penile hemodynamics, and the report of patients who achieved a minimal clinically important difference are the strengths of this study. Limitations include the small sample and strict inclusion criteria that do not reflect everyday clinical practice; however, such criteria strengthen the results of this triplex-based study. Future randomized clinical trials are important to identify the best treatment protocol for each patient (timeframe and need for maintenance therapy) depending on the severity of ED (patients

Table 2. Change from baseline in PSV and RI at 3-Month FU

	Sham group	*P* value	Active group	*P* value
PSV (cm/s)		0.45		<.001*
Baseline	30.7 ± 3.55		31.1 ± 3.23	
3-mo FU	31.1 ± 3.50		35.5 ± 3.60	
RI		0.75		<.001*
Baseline	0.81 ± 0.07		0.80 ± 0.05	
3-mo FU	0.80 ± 0.05		0.84 ± 0.04	

FU = follow-up; PSV = peak systolic velocity; RI = resistance index.
*By paired-samples t-test.

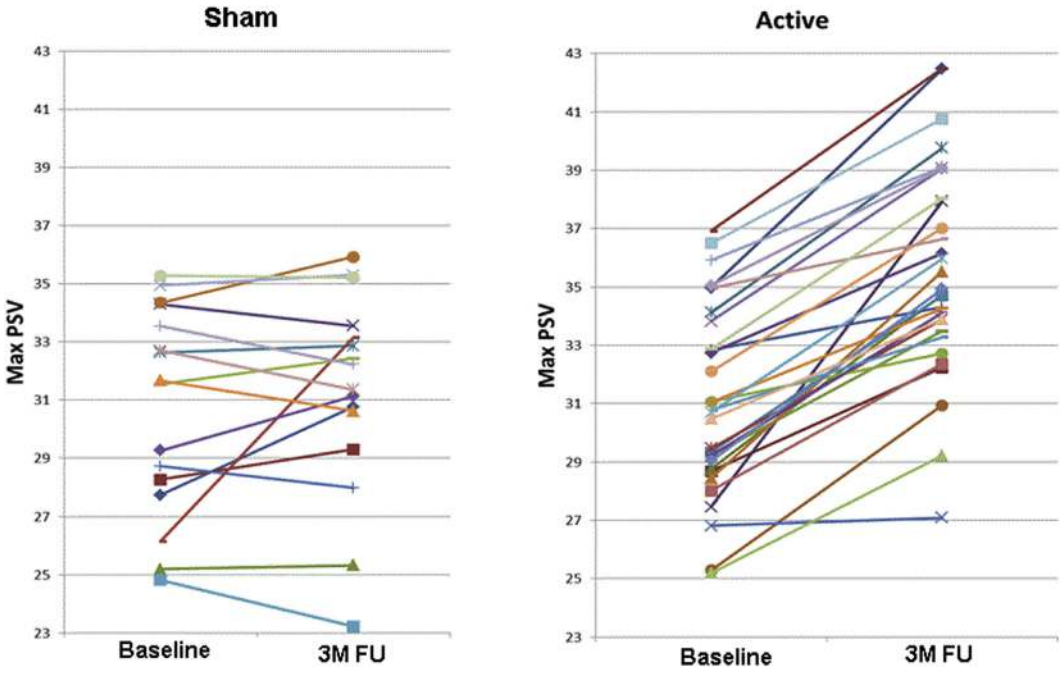

Figure 4. Individual plots of maximum PSV at baseline and at 3 months after low-intensity shockwave therapy. All but one patient showed an increase in PSV in the active group. 3M FU = 3-month follow-up; Max PSV = maximum peak systolic velocity. Figure 4 is available online at www.jsm.jsexmed.org.

with mild or moderate ED might need fewer treatment sessions) and specific subpopulations such as those with diabetes and different age groups. Such research will identify those who could really benefit from this revolutionary therapy and make the indications of this novel treatment modality more accurate.[23,24]

CONCLUSIONS

The present study demonstrated the beneficial effect of LI-ESWT on penile hemodynamics. Also, the study confirmed previous findings that application of LI-ESWT to the penile shaft is safe and effective for the treatment of vasculogenic ED.

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