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ERECTILE FUNCTION

Effect of Low-Energy Linear Shockwave Therapy on Erectile Dysfunction—A Double-Blinded, Sham-Controlled, Randomized Clinical Trial

Grzegorz L. Fojecki, MD,¹ Stefan Tiessen, MD,² and Palle J. S. Osther, MD, PhD³

ABSTRACT

Introduction: Previous studies have shown that focal low-energy extracorporeal shockwave therapy (Li-ESWT) can have a positive effect in men with erectile dysfunction (ED). Linear Li-ESWT (LLi-ESWT) for ED has not been previously assessed in a randomized trial.

Aim: To evaluate the treatment outcome of LLi-ESWT for ED.

Methods: Men with ED ($n = 126$) and a score lower than 25 points on the International Index of Erectile Function erectile function domain (IIEF-EF) were included. Subjects were allocated to receive LLi-ESWT once a week for 5 weeks or sham treatment once a week for 5 weeks. After a 4-week break, the two groups received active treatment once a week for 5 weeks. Subjects completed the IIEF, Erection Hardness Scale (EHS), Sexual Quality of Life—Men, and the Erectile Dysfunction Inventory of Treatment Satisfaction at baseline, after 9 weeks, and after 18 weeks.

Main Outcome Measures: The primary outcome measurement was an increase of at least five points on the IIEF-EF score. The secondary outcome measurement was an increased EHS score to at least 3 in men with a score no higher than 2 at baseline. Data were analyzed by linear and logistic regression.

Results: Mean IIEF-EF scores were 11.5 at baseline (95% CI = 9.8–13.2), 13.0 after five sessions (95% CI = 11.0–15.0), and 12.6 after 10 sessions (95% CI = 11.0–14.2) in the sham group and correspondingly 10.9 (95% CI = 9.1–12.7), 13.1 (95% CI = 9.3–13.4), and 11.8 (95% CI = 10.1–13.4) in the ESWT group. Success rates based on IIEF-EF score were 38.3% in the sham group and 37.9% in the ESWT group (odds ratio = 0.95, 95% CI = 0.45–2.02, $P = .902$). Success rates based on EHS score were 6.7% in the sham group and 3.5% in the ESWT group (odds ratio = 0.44, 95% CI = 0.08–2.61, $P = .369$). A limitation of this study is that device settings (number of shockwaves and penetration depth) were estimated based on an existing trial on focused ESWT.

Conclusion: No clinically relevant effect of LLi-ESWT on ED was found.

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Key Words: Erectile Dysfunction; Extracorporeal Shockwave Therapy

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INTRODUCTION

Low-energy extracorporeal shockwave therapy (Li-ESWT) is a promising treatment modality in regenerative medicine.^{1,2} However, the mechanism of action of Li-ESWT is unknown. The theory of mechano-transduction seems to be a plausible explanation for its effect, in which the mechanical stimulation of tissue changes the activity of cell membrane channels and affects gene expression.^{3,4} Animal trials have indicated revascularization after heart attack and stimulation of wound healing.^{5–7} Studies on erectile dysfunction (ED) have shown that ESWT might improve blood circulation in the penis,^{8,9} resulting in

spontaneous erection in contrast to existing on-demand treatment.⁸ The effect of ESWT on ED has been evaluated in five randomized trials using the focused delivery of shockwaves.^{8–12} Those results showed a positive effect on ED in a short-term analysis. The use of linear ESWT has not been assessed in a controlled trial.¹³ In medicine, shockwaves are generated by applying one of three physical principles: electrohydraulic, electromagnetic, or piezoelectric. Most available therapy sources deliver pulses focused on a spheroid area. Recently developed linear devices are based on the same principles, but, thanks to a modified configuration of the transducer, they offer a larger therapy zone that has an elliptical cylindrical form.

AIM

The objective of the present trial was to assess the efficacy and safety profile of linear Li-EWST (LLi-ESWT) for ED.

METHODS

The study was conducted as a randomized, double-blinded, sham-controlled study in the Region of Southern Denmark. Men were recruited after an article promoting the trial was published in a local newspaper.¹⁴ Men applying to participate in the study sent an email directly to the investigator or requested their general practitioner for a referral to our clinic. Patients complaining of ED during a consultation at our outpatient clinic for other indications also were offered participation in the trial. Included were men at least 40 years old in stable relationships who had the complaint of ED for at least 6 months. During the first visit, subjects were screened according to the eligibility criteria and filled out the erectile function domain of the International Index of Erectile Function (IIEF-EF) questionnaire. We obtained the subjects' medical history and performed a physical examination. Subjects received a written information form and were offered consideration time. Serum glucose, lipid profile, and total testosterone level were assessed. When subjects met the inclusion criteria and returned a signed consent form, they could enter the trial. All subjects consented not to use other therapies for ED during the study period. Participants previously treated for ED ceased therapy 4 weeks before entering the study. Detailed inclusion and exclusion criteria are listed in Table 1. A patient flow diagram is presented in Figure 1.

Participants gave written informed consent before the study. The regional ethics committee (project ID-20120028), the Danish Ministry of Health (DHMA 2013073909; CIV-13-07-011546), and the regional data protection agency approved the study. An independent good clinical practice unit at the University of Southern Denmark monitored the research process. The trial is registered at www.Clinicaltrials.gov (NCT02063061).

The study was carried out in the Department of Urology at the Hospital of Southern Jutland in Sønderborg, Denmark. This unit

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age > 40 y	Surgery or radiotherapy of pelvic region
Complaining of ED > 6 mo	Treatment with anticoagulants (except acetylsalicylic acid 75 mg)
In stable relationship (>3 mo)	Treatment with antiandrogens
	Anatomic penile deformation or penile prosthesis
	Total testosterone level < 8 nmol/dl
	Serious heart or lung disease
	Psychiatric or neurologic disorder
	Pregnant partner
	IIEF-EF score \geq 25

ED = erectile dysfunction; IIEF-EF = International Index for Erectile Function erectile function domain.

is responsible for the primary urologic care of more than 250,000 inhabitants in southern Denmark within a range of 100 km.

Screening of participants was performed from February 2014 through April 2014. Follow-up was carried out from June 2014 through August 2014.

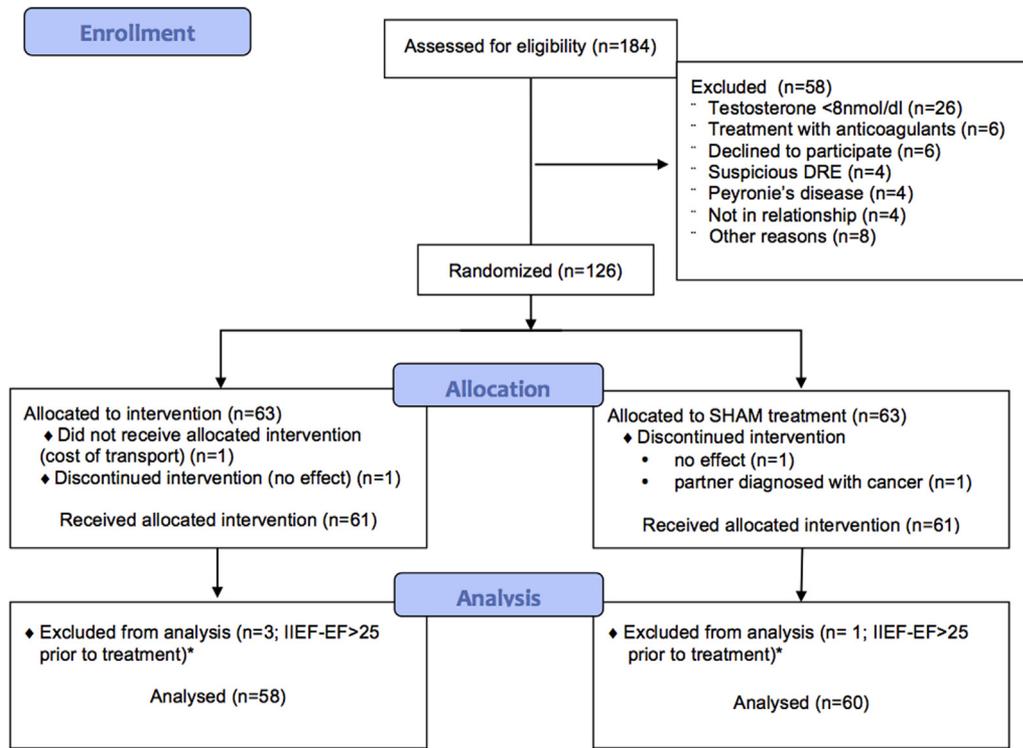
Randomization

A random list of numbers was generated (<http://www.randomization.com>). When the participants met inclusion criteria, they were allocated at a 1:1 ratio into two groups: one group received LLi-ESWT and the other group initially received sham treatment.

Study Protocol

Each participant received two rounds of five weekly treatment sessions with a 4-week interval. At baseline they completed the IIEF, Erection Hardness Scale (EHS), and Sexual Quality of Life—Men (SQoL-M) questionnaires. When subjects met for the second round at week 9, they completed the IIEF and EHS. The two groups received active LLi-ESWT at the second round without knowledge of the change. Subjects were informed that they were assigned to an active or simulated treatment and that all subjects would be offered active therapy if the results were positive. To achieve good compliance, subjects received a short text message on their mobile phone a day before each visit.

The follow-up visit was scheduled 4 weeks after the last session, and participants completed the IIEF, EHS, SQoL-M, and Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaires (Figure 2). Subjects completed the questionnaires using tablets in a separate room and were not disturbed by other participants or investigators. A research nurse was available to any subject who requested help. Subjects were required to answer all questions to complete the survey. Completed surveys were sent to a server that generated a table with all responses (<http://www.surveyexact.dk>).



DRE = Digital Rectal Examination; IIEF-EF = International Index for Erectile Function-Erectile Function Domain; *see text.

Figure 1. Extracorporeal shockwave therapy for erectile dysfunction—Consolidated Standards of Reporting Trials (CONSORT) flowchart.

During each session, 600 shockwaves (energy flux density = 0.09 mJ/mm², frequency = 5 Hz) were applied to the corpora cavernosa using a piezoelectric linear therapy source (FBL10, Richard-Wolf GmbH, Knitlingen, Germany). In total, 6,000 shockwaves were delivered during a period of 10 weeks in the active group. The device is equipped with several gel pads, which allow adjusting the depth of shockwave penetration. This study used gel pad type 0, which covers an area 5 cm wide and 1 cm deep. The dose was calculated based on an existing trial reporting

a positive outcome of ESWT using a focused transducer.⁸ Men included in the study of Vardi et al⁸ received 1,500 pulses per session (energy flux density = 0.09 mJ/mm²). Treatment was administered twice a week for 3 weeks and repeated after a 3-week break. After adjusting for the fact that the linear transducer delivers shockwaves to a larger area of the penis, we calculated the equivalent number of shockwaves that was delivered per square centimeter. With the subject standing up, 300 pulses were delivered to the penis shaft. The physician stretched the penis by pulling the glans with the left hand and moving the probe around the dorsal site of the penis at 3 to 9 o'clock with the right hand. Subsequently, 150 pulses were delivered to each crus in the lithotomy position. For coupling, a standard ultrasound gel was applied.

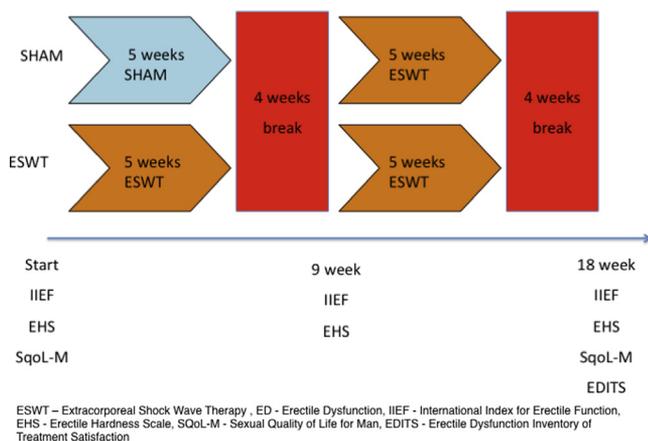


Figure 2. Extracorporeal shockwave therapy for erectile dysfunction—study design. Figure 2 is available in color at www.jsm.jssexmed.org.

Blinding

The subjects and the physician were blinded throughout the trial. The manufacturer provided three identical-looking gel pads to achieve double blinding. Sham treatment was delivered with a gel pad that prevented the passage of energy. All gel pads were tested at the manufacturer's laboratory before the study and properly marked. We used identical-looking gel pads in the active and sham groups during the first treatment round. During the second round, we applied another active gel pad, which was essential to maintain the concealed group allocation for the investigator. The treatment device was set to the desired settings.

The fact that ESWT treatment is painless further ensured that the subjects and the physician were unaware of the group allocation. Subjects in the two groups reported a slight pricking or vibrating sensation in the penis while treatment was administered. This phenomenon reported by the sham group was probably due to the noise and vibrations of the probe because no energy was transmitted through the sham pad. The investigator wore a pair of cotton gloves under latex gloves to prevent energy from passing through the tissue. Subjects were unblinded after the final follow-up visit.

The safety of the LLI-ESWT was monitored throughout the study. At the beginning of each session, subjects were asked about potential side effects that occurred between visits. Furthermore, they reported any discomfort or sensations right after each treatment. Subjects received a mobile phone number, which was available 24 hours per day for 7 days per week, allowing them to contact an investigator for any complication. All adverse events were reported to the regional ethics committee and the Danish Ministry of Health.

The primary investigator was responsible for screening the subjects and performing the intervention and follow-up.

MAIN OUTCOME MEASURES

The primary outcome measurement was the mean change of IIEF-EF score. An increase of at least five points was considered a significant clinical effect.

Secondary outcome measurements consisted of changes in the EHS score to at least 3, which indicates the penis is hard enough for vaginal penetration. This was applied to men whose initial score was no higher than 2 ($n = 83$). Changes over time (0, 5, and 10 treatments) of the IIEF-EF and EHS scores were assessed. In addition, changes in subjects' scores on sexual quality of life (SQoL-M)¹⁵ and treatment satisfaction (EDITS)¹⁶ were measured. The safety of the LLI-ESWT was monitored throughout the trial.

Statistics

The trial was powered for the primary end point assuming a comparison of mean IIEF-EF values. The type I error was 5% and the power was 80%. We expected a dropout rate of 10%. Based on a comparison of independent means assuming a common SD of 9.3, we calculated that 56 subjects in each group were needed to show a difference of at least five points in the primary end point. To account for dropouts, we aimed at including 63 subjects in each group. We used linear regression adjustment for baseline values to compare the means of the primary outcome between treatment groups and logistic regression to assess the secondary end point of success related to the improvement in IIEF-EF and EHS scores at any time. Change over time was assessed and compared between groups using mixed-effects linear regression, modeling the interaction with time, and assuming random effects from subjects. All analyses

Table 2. Subjects' basic characteristics

	ESWT ($n = 63$)	Sham ($n = 63$)
Age (y), mean (SD)	65.4 (7.9)	63.3 (9.5)
BMI (kg/m^2), mean (SD)	27.3 (3.8)	27.5 (3.4)
Total testosterone (nmol/dL), mean (SD)	14.4 (4.7)	13.5 (4.1)
Smoking status, n (%)	7 (11.1)	15 (23.8)
Myocardial infarction, n (%)	8 (12.6)	7 (11.1)
Hypercholesterolemia, n (%)	44/26* (69.8)	49/28* (77.8)
Peripheral artery disease, n (%)	8 (12.6)	3 (4.7)
Hypertension, n (%)	28 (44.4)	26 (41.2)
Diabetes, n (%)	6 (9.4)	9 (14.3)
Effect of previous treatment with PDE-5i, n (%)		
Responders	28 (44.4)	25 (39.7)
Non-responders	19 (30.2)	9 (14.3)
Never used	16 (25.4)	29 (46)

BMI = body mass index; ESWT = extracorporeal shockwave therapy; PDE-5i = phosphodiesterase type 5 inhibitor.

*Diagnosed during inclusion assessment.

were repeated explanatorily in the subgroup of responders to phosphodiesterase type 5 inhibitor (PDE-5i). Outcomes are presented with 95% CI and a P value less than .05 was considered significant. Analysis was performed using STATA 14 (STATA Corp, College Station, TX, USA).

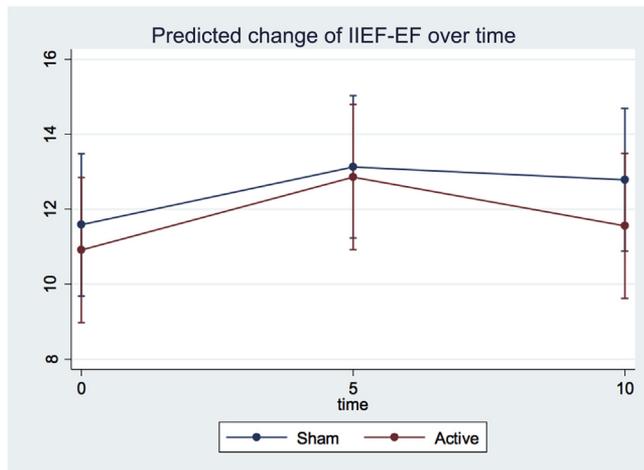
RESULTS

We screened 184 men from February through May 2014. Of these, 126 participants were recruited for the study. Follow-up was completed in September 2014. Baseline characteristics are listed in Table 2.

Sixty of 63 men in the sham group and 58 of 63 men in the active group were assessed in a modified intention-to-treat analysis. Subjects who were found ineligible after randomization ($n = 4$ men who met all inclusion criteria but with a baseline IIEF-EF score > 25) and those with missing primary outcome data ($n = 4$) were excluded (Figure 1).

Primary Analysis

Mean IIEF-EF scores in the sham group were 11.5 at baseline (95% CI = 9.8–13.2) and 13 after five sham sessions (95% CI = 11–15). After an additional five active treatment sessions in the second stage, the mean score was 12.6 (95% CI = 10.6–14.6). Mean scores in the active group were correspondingly 10.9 (95% CI = 9.1–12.7), 13.1 (95% CI = 9.3–13.4), and 11.8 (95% CI = 9.3–13.4; Figure 3). Success rates based on the IIEF-EF score were 38.3% in the sham group and 37.9% in the active group (odds ratio [OR] = 0.95, 95% CI = 0.45–2.02, $P = .902$). Success rates based on the EHS score were 6.7% in the sham group and 3.5% in the active group



IIEF-EF = International Index for Erectile Function – erectile function domain

Figure 3. Change of International Index of Erectile Function erectile function domain score. Figure 3 is available in color at www.jsm.jsexmed.org.

(OR = 0.44, 95% CI = 0.08–2.61, $P = .369$). The predicted change over time in the IIEF-EF score showed no statistically significant difference between treatment groups. Baseline values for the SQoL-M score were 41.7 (95% CI = 36.2–47.3) in the sham group and 43.2 (95% CI = 36.2–50.2) in the active group, and the predicted values after 10 treatments were 43.3 (95% CI = 36.7–49.9) and 45.4 (95% CI = 37.6–53.2, $P = .911$), respectively. In the subgroup of responders to PDE-5i, the mean IIEF-EF scores in the sham group were 12.7 at baseline (95% CI = 9.7–15.7), 10.9 after five sessions (95% CI = 7.7–14.1), and 10.9 after 10 sessions (95% CI = 7.8–14). Correspondingly, scores in the active group were 12.2 (95% CI = 9.4–15), 13.5 (95% CI = 10.6–14.1), and 12 (95% CI = 8.8–15.2). Similarly, no indications of significant results were seen for any of the other end points in the explorative analyses. Furthermore, we noted similar low overall treatment satisfaction EDITS scores of 50% in the sham group and 51% in the active group, which reflected the negative outcome.

We did not record any serious adverse events of LLI-ESWT. Other than local irritation, no adverse effects were encountered.

DISCUSSION

Treatment with focused Li-ESWT has been suggested to improve erectile function in men with ED of vascular etiology. Li-ESWT can stimulate the growth of new blood vessels, potentially enabling penile tissue to regain the ability for spontaneous erection, and indeed previously published randomized trials evaluating outcomes of ESWT on ED using focused transducers have shown some effect on erectile function.^{8–12} Three trials found a significant positive effect in the IIEF-EF score,^{8,9,12} whereas two other trials found no significant difference in the overall population for this outcome measurement.^{10,11} However, a subgroup analysis of one of the latter

studies showed a positive effect in the group of men with severe ED.¹⁰ Furthermore, in three trials including PDE-5i responders only,^{8,11,12} a significant positive effect was noted in the EHS score, indicating that ESWT might be used to recover a natural erection in this subgroup. A summary of cited studies is presented in Table 3.

We applied standardized subjective outcome measurements (IIEF-EF, EHS, and SQoL-M scores), because patients are mainly interested in resolving their ED symptoms. Changes in penile hemodynamics as assessed by Vardi et al⁸ and Kitrey et al⁹ showed a significant increase in penile blood flow after ESWT. Applying hemodynamic measurements in the present series might have added to the explanation of the data. None of the previous published randomized trials included data on sexual quality of life, which in our trial mirrored the outcome data. In addition, treatment satisfaction (EDITS score) of ESWT on ED has not been evaluated previously.

This study showed no improvement in erectile function in the overall population. Furthermore, an analysis of PDE-5i responders did not show any difference between the sham and active groups. However, it should be noted that our trial was not specifically powered for this purpose. This study included PDE-5i responders and non-responders and men naive to the treatment. Performing a study with more selective inclusion criteria might have produced different results.

Overall the treatment was safe and well tolerated, and, as in all existing trials, no serious adverse events were reported.^{8–12,17,18} Therefore, future trials on LLI-ESWT could safely explore the effect of increasing the number of shockwaves and changing the penetration depth. In general, anticoagulants should be discontinued when applying ESWT.¹⁹ In our study, 10% of patients received low-dose acetylsalicylic acid therapy (75 mg/d), and no adverse effects were seen. Therefore, we consider the administration of this medication safe during Li-ESWT.

Strengths

The dropout rate was very low (3%) compared with previous controlled trials (5% in Olsen et al,¹¹ 15% in Vardi et al⁸ and Yee et al,¹⁰ and 40% in Srini et al¹²). Our design, which promised all participants active treatment, could have helped achieve the low dropout rate. In previously published controlled studies, sequence generation was reported adequately in only three of five trials,^{8,9,11} whereas the process of randomization was unclear in the other trials.^{10,12} The randomization process of the present study can be considered very robust in securely masking allocation until the necessary number of subjects was achieved and until data analysis was finalized. Furthermore, all phases of the study, including data entry and management, were monitored by an independent good clinical practice unit.

Limitations

The results of our trial were obtained in routine clinical settings and showed no positive effect of LLI-ESWT 4 weeks

Table 3. Summary of RCTs on ESWT for erectile dysfunction

Study	Device type	Design	Energy density (mJ/mm ²)	Impulses per session, n	Hz	Treatment protocol (mo)	Follow-up (mo)	Effect of PDE-5i before study	Dropout, n %	Outcome measurements	Mean changes of IIEF score (active vs sham), %	Men with EHS score ≤ 2 at baseline that increased ≥ 3 after treatment, %
Vardi et al ⁸	focused electrohydraulic	RCT	0.09	1,500	2	12 sessions	1	responders	67 10	IIEF, EHS, plethysmography	6.7 vs 3	68
Yee et al ¹⁰	focused electrohydraulic	RCT	0.09	1,500	2	12 sessions	1	responders and non-responders	70 18	IIEF, EHS	7.8 vs 5.8	?
Srini et al ¹²	focused electrohydraulic	RCT	0.09	1,500	2	12 sessions	1, 3, 6, 12	responders	135 43	IIEF, EHS	12.5 vs 1.4	90
Olsen et al ¹¹	focused electromagnetic	RCT	0.15	3,000	5	5 sessions	1, 3, 6	responders	112 8	IIEF, EHS	43 vs 38 (increase ≥ 5 points)	57 vs 9
Kitrey et al ⁹	focused electrohydraulic	RCT	0.09	1,500	2	12 sessions	1	non-responders	58 5	IIEF, EHS, plethysmography	5 vs 0	54 vs 0
Present study	linear piezoelectric	RCT	0.09	600	5	10 sessions	1	responders and non-responders	126 3	IIEF, EHS, SQoL-M, EDITS	2.2 vs 1.5	3.5 vs 6.7

EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; EHS = Erection Hardness Scale; ESWT = extracorporeal shockwave therapy; IIEF = International Index for Erectile Function; PDE-5i = phosphodiesterase type 5 inhibitor; RCT = randomized controlled trial; SQoL-M = Sexual Quality of Life—Men.

after treatment. Comparison of baseline characteristics showed a significantly larger proportion of PDE-5i non-responders in the active group. This difference could undermine the overall results. However, the chosen study design should partly overcome this limitation, because eventually the two groups received LLi-ESWT, and we did not record improvement in the sham group after the second stage of treatment.

Compared with previously published studies, the number of pulses was smaller in the present trial. At the time we designed our study, there was only one randomized controlled trial⁸ available and reports of non-randomized trials showing an encouraging effect of Li-ESWT. Our dose was estimated based on the trial of Vardi et al⁸ and an assumption that the linear configuration of shockwaves, covering a larger area of the penis shaft and crura, would be more efficient than the use of a focused transducer. However, increasing the number of pulses and changing the penetration depth might be more effective. This possibility is supported by the results of an open-label study performed by Bechara et al²⁰ who applied a linear device (14,400 shockwaves during a period of 4 weeks). The energy flux density (0.09 mJ/mm²) applied in our trial was the same as in other randomized controlled trials on ED.^{8–10,12} It is unknown whether other treatment settings, such as the type of device (electrohydraulic, electromagnetic, or piezoelectric), frequency, or penetration depth, might influence the treatment outcome, and further studies on these aspects are warranted. Furthermore, we strongly recommend conducting a dose-finding study to establish a treatment protocol before trials testing ESWT devices for new indications.

CONCLUSION

LLi-ESWT using 600 shockwaves per treatment session for 10 weeks (total = 6,000 shockwaves) with an energy flux density of 0.09 mJ/mm² and a frequency of 5 Hz did not improve erectile function in men with ED. Future studies should evaluate whether a larger number of pulses and changing the shockwave penetration depth might increase efficacy.

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