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Original Article

Extracorporeal shockwave therapy in the treatment of erectile dysfunction: A prospective, randomized, double-blinded, placebo controlled study

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Abbreviations & Acronyms
ED = erectile dysfunction
EHS = Erection Hardness Score
IIEF-ED = International Index of Erectile Function-ED
Li-ESWT = low-intensity extracorporeal shockwave therapy
PDE5I = phosphodiesterase type 5 inhibitors
SHIM = Sexual Health Inventory for Men

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Objectives: To investigate the role of low-intensity extracorporeal shockwave therapy in the treatment of erectile dysfunction.

Methods: This was a double-blinded, single-center, prospective, randomized, placebo-controlled trial. After a 2-week phosphodiesterase type 5 inhibitor washout period, patients were assessed with Sexual Health Inventory for Men, International Index of Erectile Function-ED domain scores and Erection Hardness Score. Randomization into either the low-intensity extracorporeal shockwave therapy group or the sham group took place. After the 9-week treatment period, patients were followed up 4 weeks later. Follow-up assessment was in the form of International Index of Erectile Function-ED domain score and Erection Hardness Score.

Results: A total of 70 patients were recruited into the study, 58 patients completed the study. A total of 28 patients were randomized into the sham therapy arm, and 30 patients were randomized into the low-intensity extracorporeal shockwave therapy arm. There was no significant difference between these two groups in baseline International Index of Erectile Function-ED domain score and Erection Hardness Score. The mean International Index of Erectile Function-ED domain score of the low-intensity extracorporeal shockwave therapy arm and sham arm in week 13 were 17.8 ± 4.8 and 15.8 ± 6.1, respectively ($P = 0.156$). The mean Erection Hardness Scores in week 13 were 2.7 ± 0.5 and 2.4 ± 0.9, respectively ($P = 0.163$). When patients were stratified into different baseline Sexual Health Inventory for Men subgroups, the pre-intervention and post-intervention difference in low-intensity extracorporeal shockwave therapy was found to be significant in the subgroup with severe erectile dysfunction (low-intensity extracorporeal shockwave therapy International Index of Erectile Function-ED domain improvement: 10.1 ± 4.1 *vs* sham therapy International Index of Erectile Function-ED domain improvement: 3.2 ± 3.3; $P = 0.003$).

Conclusion: The present trial shows the tolerability and clinical efficacy of low-intensity extracorporeal shockwave therapy in a subgroup of patients with erectile dysfunction.

Key words: andrology, erectile dysfunction, randomized controlled trial, shockwave therapy.

Introduction

The current mainstream non-surgical treatment for ED is the use of oral PDE5I and intracavernosal injections of vasodilating agents.[1] These were proved to be effective and safe treatments;[2] however, they all share the inability to modify the underlying pathophysiology of the erectile mechanism. Alternative treatment modalities have undergone development to address these issues. For example, various lipid-lowering agents (statins and niacin) have been used to counteract the atherosclerotic process.[3,4]

Li-ESWT was proved to be useful in various other medical conditions; for example, neovascularization in myocardial ischemia.[5] Recently, Vardi *et al*. have investigated the impact of Li-ESWT in the treatment of ED, and found a positive short-term clinical effect on men who responded to PDE5I.[6] However, at the moment, evidence on this area is still scarce in the literature.

We carried out a prospective, randomized, placebo-controlled trial to study the role of Li-ESWT in the treatment of ED.

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Table 1 Inclusion and exclusion criteria

Inclusion criteria
≥18 years-of-age
≥6-month history of ED
In a heterosexual relationship for ≥6 months
SHIM score ≤21
Exclusion criteria
ED due to known endocrine disease (e.g. hypogonadism)
ED due to drug treatment (e.g. androgen deprivation therapy)
ED due to neurological disease (e.g. spinal cord injury)
ED due to penile structural abnormality
History of radical prostatectomy or other pelvic surgery
History of pelvic irradiation
With penile implant

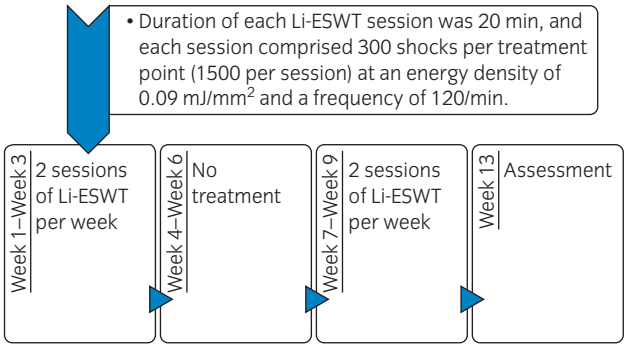

Fig. 1 Li-ESWT treatment protocol.

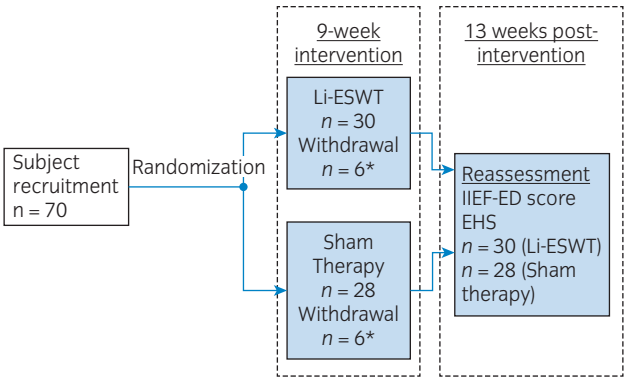

Fig. 2 Study flowchart. *All withdrawals were because of the inconvenience associated with intervention.

Methods

The study protocol was approved by The Chinese University of Hong Kong, Hong Kong, China, ethics committee. Written informed consent was given by all participants before entering the study.

It was a double-blind, single-center, prospective, randomized, placebo-controlled trial. We recruited patients with more than a 6-month history of ED, who scored ≤21 in the SHIM. Previous use of PDE5I would require a 2-week washout period during the trial. Details of the inclusion/exclusion criteria are listed in Table 1.

The study procedure and follow up was carried out on an outpatient basis. Patients were assessed with IIEF-ED scores and EHS. They were assigned into either the treatment group (with Li-ESWT) or the sham group (sham therapy) in a 1:1 ratio using a computer-generated table of random numbers. The randomization process was in a block-size of two and four, without stratification. All investigators and research assistants involved in the assessment of the participants were blind to group assignment. For patients with a history of PDE5I use, they underwent a 2-week washout period before the randomization process.

The Li-ESWT protocol was similar to the protocol suggested by Vardi *et al*.,[6] as shown in Figure 1. During each session, Li-ESWT was delivered by a special probe that was attached to a compact electrohydraulic unit with a focused shockwave source (Omnispec ED1000; Medispec, Germantown, MD, USA). The penis was manually stretched, and shockwaves were delivered to the distal, mid and proximal penile shaft, and both the left and right crura. The duration of each Li-ESWT session was approximately 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 exposed to shockwaves at each site was cylindrical (diameter: 18 mm; height: 100 mm). No local or systemic analgesia was necessary during the procedure.

For the sham therapy, same probe as in the Li-ESWT therapy was used, except the energy setting was 0 during each treatment, and a similar noise was produced during the procedure. The intervention course takes 9 weeks, which consists of two 3-week therapy segments separated by a 3-week rest segment in between (Fig. 1). At week 13; that is, 4 weeks after completion of treatment, patients were evaluated by IIEF-ED score, EHS and any adverse events.

The primary outcome measurement was the 13-week change from baseline for IIEF-ED score after one course of Li-ESWT. Secondary outcome measures included the interval change of EHS, as well as any adverse events from Li-ESWT therapy.

Sample size calculation was based on the results from our previous study.[4] To achieve 80% power, assuming 5.2-point difference to detect a two-sided 5% significance and a 20% dropout rate, a total of 70 participants were required for the study.

All randomized participants who had completed at least one outcome measurement were included in the final analysis. The χ^2-test was used to look for relationships of categorical measures. The between-group relationships of baseline and 13-week data were evaluated by using the Student's *t*-test or Mann–Whitney *U*-test where appropriate. Two-way ANOVA was used to assess the change in pre-intervention and post-intervention between different baseline SHIM severity group. Multiple linear regression was carried out to test the variables associated with treatment outcome. *P*-values <0.05 were considered statistically significant.

Results

Between October 2011 and October 2012, 70 patients were enrolled into the study (Fig. 2). During this period, 12 patients withdrew from the trial before completing the intervention.

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Table 2 Participants' demographics and characteristics

	Overall	Sham therapy	Li-ESWT	*P*-value
Participants (*n*)	58	28	30	
Mean age (years)	61.0 ± 7.3	63.3 ± 6.4	58.9 ± 7.6	0.020
Mean no. ED risk factors†	1.4 ± 1.1	1.5 ± 1.2	1.4 ± 1.0	0.420
Incidence of ED risk factors (*n*)				
Diabetes	19	8	11	
Hypertension	37	20	17	
Dyslipidemia	31	14	17	
Ischemic heart disease	1	1	0	
Smoker	13	7	6	
Mean baseline IIEF-ED score	10.2 ± 3.8	10.2 ± 3.8	10.2 ± 3.8	0.526
Baseline SHIM group‡				
Mild/mild to moderate	21 (36.2%)	9 (32.1%)	12 (40.0%)	0.728
Moderate	19 (32.8%)	9 (32.1%)	10 (33.3%)	
Severe	18 (31.0%)	10 (35.7%)	8 (26.7%)	
Baseline EHS	1.4 ± 0.6	1.4 ± 0.6	1.5 ± 0.6	0.331
Duration of ED (years)	7.0 ± 3.6	7.4 ± 4.3	6.5 ± 2.8	0.331

†ED risk factors taken into account are: diabetes, hypertension, dyslipidemia, ischemic heart disease, smoking. ‡SHIM score mild: 17–21; mild to moderate: 12–16; moderate: 8–11; severe: 5–7. *P*-value signifies the difference between the sham therapy arm and Li-ESWT arm.

Each arm accounted for six patients. They withdrew themselves from the study mostly because of the inconvenience associated with intervention; for example, long distance from home to ESWT center and work not allowing them to repeatedly take leave for ESWT intervention. In the end, a total of 58 patients managed to finish the study. A total of 28 patients were randomized into the sham therapy arm, and 30 patients were randomized into the Li-ESWT arm. The Li-ESWT group had a younger mean age when compared with the sham therapy group (58.9 ± 7.6 *vs* 63.3 ± 6.4, $P = 0.020$). Risk factors for ED were explored, including diabetes mellitus, hypertension, ischemic heart disease, dyslipidemia and smoking. Both the Li-ESWT and sham groups had a similar number of risk factors present in the participants (Li-ESWT: 1.4 ± 1.0 *vs* sham: 1.5 ± 1.2, $P = 0.420$). There was no significant difference between these two groups in terms of baseline IIEF-ED score, baseline EHS and the time since their diagnosis of ED (Table 2). After breaking down baseline SHIM score into mild/mild to moderate, moderate and severe groups (mild: 17–21; mild to moderate: 12–16; moderate: 8–11; severe: 5–7), both the Li-ESWT arm and the sham therapy arm had a similar composition ($P = 0.728$). All patients who had completed the intervention protocol were assessed in week 13 of the study.

When comparing between the mean IIEF-ED score of the two arms in week 13, the Li-ESWT group achieved a score of 17.8 ± 4.8 and the sham therapy group achieved a score of 15.8 ± 6.1 (Table 3). However, such difference did not reach statistical significance ($P = 0.156$). A higher mean EHS for the Li-ESWT group was also noted in week 13 (2.7 ± 0.5 *vs* 2.4 ± 0.9), but it was not statistically significant ($P = 0.163$).

In the category of pre-intervention and post-intervention IIEF-ED score difference, crude comparison between the two arms did not yield a statistical significant difference (Table 3). However, with two-way ANOVA calculation, a significant difference between the two arms in "post-intervention IIEF-ED score improvement" was noted if we stratified the results into different baseline SHIM subgroups. Further univariate post-hoc analysis reviewed that such difference was significant in the subgroup with severe ED on baseline SHIM score (Li-ESWT IIEF-ED improvement: 10.1 ± 4.1 *vs* sham therapy IIEF-ED improvement: 3.2 ± 3.3; $P = 0.003$; Fig. 3). In other words, when we examined the subgroup with baseline severe ED, treatment with Li-ESWT resulted in a statistically higher IIEF-ED score improvement when compared with the sham therapy group. Multiple linear regression taking different variables (age, ED duration, baseline SHIM subgroup, treatment group) into account again showed that IIEF-ED improvement was significantly greater in this subgroup of severe ED, with a mean change in IIEF-ED score of 7.1 (95% CI 3.8–10.4, $P < 0.001$) in the Li-ESWT arm.

Table 3 Li-ESWT treatment outcome

	Sham therapy	Li-ESWT	*P*-value
IIEF-ED score at week 13 ± SD	15.8 ± 6.1	17.8 ± 4.8	0.156
EHS score at week 13 ± SD	2.4 ± 0.9	2.7 ± 0.5	0.163
Pre- and post-intervention IIEF-ED score difference	3.8 ± 3.6	5.3 ± 5.5	0.243

Side-effects and complications were observed for throughout the study period; for example, pain, hematoma, hematuria and bruising. No adverse event was reported during Li-ESWT treatment and after the intervention.

Discussion

PDE5I and intracavernosal injections of vasodilating agents are common and yet non-curative treatment modalities for ED. The ultimate objective of ED treatment for men should be an effort that is rehabilitative or even curative. The current study was carried out as an endeavor to shift the field of ED treatments away from on-demand palliative management.

Application of Li-ESWT in the medical field was dated back to the late 1990s.[7] These acoustic waves carry energy, and when

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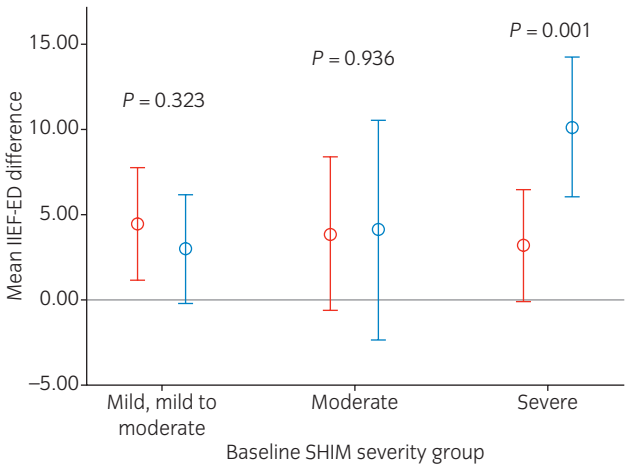

Fig. 3 Subgroup analysis of Li-ESWT treatment outcome. SHIM score mild: 17–21; mild to moderate: 12–16; moderate: 8–11; severe: 5–7. Error bars ±1 SD. ○, Control; ○, Treatment; I, Control; I, Treatment.

targeted and focused, interact with the targeted deep tissues causing mechanical stress and microtrauma. *In vitro* and animal studies have shown that angiogenesis-growth factors were stimulated after Li-ESWT.[8]

To the best of our knowledge, before the present study there was only one randomized-control trial regarding the use of Li-ESWT in ED reported in the literature.[6] The present study has made another attempt to verify the clinical application of Li-ESWT in ED patients. Although statistical significance was yet to be reached, there was a trend that after two courses of Li-ESWT, the intervention arm achieved a higher IIEF-ED score than the sham therapy arm (17.8 ± 4.8 *vs* 15.8 ± 6.1, $P = 0.156$). Although this trend may become statistically significant with a larger number of subjects, in our study such improvement in erectile function with Li-ESWT was more evident and marked in the subgroup of patients belonging to severe ED on baseline SHIM score. In patients having SHIM score 5–7 upon entry of the study, the pre- and post-treatment difference in IIEF-ED score was 10.1 ± 4.1 for the Li-ESWT group and 3.2 ± 3.3 for the sham therapy group ($P = 0.003$).

This finding of a good response to Li-ESWT among severe ED patients was also echoed by an open-label, single-arm, prospective study by Gruenwald *et al*.[9] In their study, they only recruited poor responders to PDE5I, and underwent the same regime of Li-ESWT as in the present study. A total of 29 men (mean age of 61.3 years) eventually completed the study, and at week 13 of the trial, it was reported that their mean IIEF-ED scores increased from 8.8 ± 1 (baseline) to 12.3 ± 1 ($P = 0.035$). The present double-blind, randomized-controlled trial has further strengthened the evidence of benefit regarding Li-ESWT for severe ED patients. Although the present subgroup analysis provided additional information to the previous trial by Vardi *et al*.,[6] it also showed the clinical significance of Li-ESWT in ED management. For ED patients, most satisfactory responders to PDE5I are usually managed by family physicians in the primary healthcare setting. It was often the severe ED patients or poor responders to PDE5I who were referred to urologists for further management. From the present data, it was suggested that such a unique modality of shockwave could expand our urological treatment options in the treatment of ED.

The regime of ESWT treatment in the present trial consisted of two treatment sessions per week for 3 weeks. Assessment was made 4 weeks after the last treatment session. Such arrangement could be interpreted in the light of previous animal studies. Wang *et al*. reported the application of Li-ESWT to the tendon–bone junction of rabbits.[8] Using the expression of vascular endothelial growth factor, endothelial nitric oxide synthase and proliferating cell nuclear antigen to determine the extent of neovascularization, they observed that angiogenic marker levels rose significantly 1 week after Li-ESWT. Furthermore, they showed that neovascularization and cell proliferation were evident 4 weeks after Li-ESWT, and these persisted for more than 12 weeks after application. Similar findings were also seen in a canine study.[10] This temporal relationship between Li-ESWT and the response in cellular level corresponded to our positive result when the patients were assessed 4 weeks after they had finished the whole course of Li-ESWT. However, as a result of the relatively short follow up of the present study, we could not evaluate how lasting the Li-ESWT benefit was in ED patients. Further studies with a longer follow up would give us a better understanding in the physiological changes after Li-ESWT, and thus allow us to generate a more suitable protocol regarding Li-ESWT administration intervals.

Although PDE5I is currently the most commonly used remedy for ED, it was well reported that 10–25% of patients experienced side-effects from this class of medication, ranging from dyspepsia to flushing and headache.[11] On the contrary, during the course of the present, study no adverse effect was reported from our patients. This added an edge to Li-ESWT over other ED treatment options.

SHIM is an abridged five-item version of the 15-item IIEF. It was developed and validated as a brief, easily administered, patient-reported diagnostic tool.[12] This was the assessment tool we used in the present study. From our results, patients belonging to the severe ED group showed the greatest improvement in IIEF-ED score. This was an effort to identify the most optimal target group for Li-ESWT in the management of ED. Although further study might be required to validate the present results, the promising role of this simple tool of SHIM in pre-Li-ESWT assessment would mean that it could be used as a convenient way to estimate the response of such treatment. This could allow both the patients and clinicians to have a more accurate expectation of the treatment outcome.

The present study's findings supported Li-ESWT as a potential treatment modality for men with severe ED. It could be used as an alternative treatment to PDE5I therapy. However, the number of participants recruited into our trial was relatively small, and patients involved in each SHIM subgroup analysis ranged from 18 to 21 in number. Future studies of a larger scale could provide more solid evidence for Li-ESWT. Furthermore, as it is an emerging new technique, more data would be required to better define the best targets for such treatment, and to evaluate the duration of its effect. Basic research to understand the mechanism and physiology together with a large multicenter long-term trial go hand-in-hand in answering these questions.

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In conclusion, the present study was a double-blind, randomized-controlled trial that showed the clinical efficacy of Li-ESWT in a subgroup of patients, and its tolerability with a relatively short follow up. Further validation with respect to such treatment's optimal targets and ideal protocol require more studies to arrive at a conclusion. In the future, this could be one of the few non-pharmacological ED treatment modalities with rehabilitative features. By fully evaluating the efficacy of this new therapy, we would be able to determine if Li-ESWT could become a recognized curative treatment in patients with ED.

Conflict of interest

None declared.

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