Low-Intensity Shockwave Therapy for Erectile Dysfunction

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ABSTRACT

Background: Vasculogenic erectile dysfunction (ED) is one of the leading causes of male sexual dysfunction. In the past decade, multiple studies have examined the use of low-intensity extracorporeal shockwave therapy (Li-ESWT) for the treatment of ED.

Aim: Investigate the efficacy of Li-ESWT for the treatment of ED.

Methods: We reviewed the published literature, including randomized controlled trials (RCTs), meta-analyses, and select single-arm studies on the use of Li-ESWT for the treatment of ED.

Outcomes: Changes in International Index of Erectile Function scores were evaluated in patients undergoing Li-ESWT.

Results: There is no consensus from RCTs on the efficacy of Li-ESWT for the treatment of ED. Published meta-analyses have shown significant improvement in International Index of Erectile Function—erectile function domain scores in men undergoing Li-ESWT, especially when compared to men receiving sham treatment. However, differences in treatment protocols limit the generalizability of these findings. Li-ESWT may be more beneficial in cases of mild ED or when combined with phosphodiesterase type 5 inhibitors in men with moderate to severe ED. The role of Li-ESWT in the treatment of non-vasculogenic ED remains poorly defined.

Conclusions: Li-ESWT could be beneficial in specific sub-sets of men with vasculogenic ED. However, future RCTs should attempt to optimize treatment protocols and have more stringent inclusion criteria to confirm these findings. **Rizk PJ, Krieger JR, Kohn TP, et al. Low-Intensity Shockwave Therapy for Erectile Dysfunction. Sex Med Rev 2018;6:624–630.**

Key Words: Erectile Dysfunction; Shockwave; Low-Intensity Shockwave Therapy; Vascular

INTRODUCTION

Erectile dysfunction (ED) is the leading cause of sexual dysfunction in men, with 1 in 5 U.S. men affected.[1] ED is defined as the inability to achieve or maintain a penile erection satisfactory for sexual intercourse. The causes of ED are multifaceted, and include psychogenic, neurogenic, endocrine, vasculogenic, and drug-induced etiologies among others.[2] Vasculogenic ED is the most common type of ED, and there is a high prevalence of ED in men with cardiovascular disease—the Massachusetts Male Aging Study found that close to 40% of men with heart disease have severe ED.[3,4]

First-line therapy for ED includes phosphodiesterase type 5 inhibitors (PDE5i), which since their introduction in 1998 have revolutionized ED therapy. For men who do not respond to these oral agents, vacuum erection devices, urethral suppositories, intracavernosal injections, and penile prostheses can provide satisfactory alternatives.[2] However, such treatment options can be invasive and can be associated with adverse events or reduction in sexual spontaneity.

In 2010, low-intensity extracorporeal shockwave therapy (Li-ESWT) was first used as a novel and minimally invasive treatment approach for ED.[5] Shockwave therapy has been used therapeutically in other fields of medicine, including in the treatment of cardiac or limb ischemia, diabetic foot ulcers, and wound healing.[6–9] Though its mechanism of action was not clear at the time of its introduction, in vitro studies on cardiac tissue have since demonstrated that shockwave therapy induces neovascularization, as well as an increase in the expression of vascular endothelial growth factor (VEGF) and its receptor Flt-1.[6] Because ED is often associated with vascular conditions, Vardi et al[5] proposed that Li-ESWT may increase blood flow to the penis and thus reverse the effects of ED by fundamentally reversing its pathogenesis. The initial results of the Vardi et al[5]

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study were promising: 20 men (average age 56.1 years) who received two 3-week treatment courses of Li-ESWT showed improvements in erection at 1 month, which were maintained at 6-month follow-up (International Index of Erectile Function [IIEF]—erectile function domain [EF] score of 20.9 ± 5.8 vs 13.5 ± 4.1 at baseline, $P < .001$).

Since the Vardi et al[5] study, multiple other studies and clinical trials have endorsed the therapeutic potential of Li-ESWT for the treatment of ED. Manufacturers and urology clinics in multiple countries are currently advertising this therapy to the general public as a treatment for ED. The European Urological Association has listed Li-ESWT as a treatment for ED, yet remains vague in regard to which patients may benefit most from this therapy.[10] In the United States, Li-ESWT for the treatment of ED is under review by the Food and Drug Administration (FDA).

The purpose of this review is to present and discuss the current literature examining the efficacy of Li-ESWT in the treatment of ED, as well as the barriers this technology faces moving forward.

LI-ESWT TREATMENT PROTOCOLS

The low-intensity shockwaves used in most Li-ESWT treatment protocols published to date emit an energy density of 0.09 mJ/mm^2. For reference, the energy densities used for renal stone lithotripsy range from 0.2−1.1 mJ/mm^2. Though no standardized Li-ESWT treatment protocol has been established, study protocols often give 1−2 sessions per week over the course of 5−10 weeks. Approximately 1,500 shocks are delivered focally to multiple areas of the penis, notably the 2 corpora cavernosa and the 2 crura, with each treatment session lasting ∼15 minutes. Shocks are delivered by either a hand-held probe or a fixed emitter, and manufacturers include Medispec (Israel), Storz (Switzerland), Richard-Wolf GmbH (Germany), and Direx (Argentina). Treatment is offered in an outpatient setting with no analgesia needed. Most protocols described in the literature are derived from the original protocol of Vardi et al,[5] which itself is based on a protocol used to improve cardiac blood flow.[11,12] While no published literature exists as to the cost of shockwave therapy, several clinic websites currently offering the treatment in the United States or Europe cite costs of around US$400 per treatment or US$4,000 for a total regimen, though some charge as much as US$1,000 per treatment.[13−15]

MECHANISMS OF ACTION OF LI-ESWT

Multiple theories have been proposed for how Li-ESWT restores erectile function. The first consists of micro-trauma caused by shockwaves leading to the release of vascular growth factors including VEGF.[6] Given that the most common causes of ED are vasculogenic, promotion in blood vessel growth could logically lead to improved erections. Another theory posits that shockwaves could directly increase nitrous oxide (NO) synthesis in penile tissues, as in vitro studies have shown that shockwaves can non-enzymatically generate NO in solution containing hydrogen peroxide and L-arginine.[16] NO plays a key role in promoting erection, facilitating corporal smooth muscle relaxation, and thus increased penile blood flow.[17]

A novel theory for Li-ESWT action recently proposed by Lin et al[18] suggests that shockwave−based stimulation of stem cell expansion within the corpora could occur either independently or in conjunction with the micro-trauma mechanism. In this study, male rats were injected with the radioactive nucleotide 5-ethyl-2′-deoxyuridine (EdU), a marker that is taken up by new cells, and their penises treated with Li-ESWT. Control rats were injected with EdU but did not undergo shockwave treatment. At 48 hours and then 1 week after treatment, shockwave−treated rats had significant increases in EdU positivity at both time points, supporting greater cell proliferation, likely from progenitor cells ($P < .01$). The majority of new cells were localized within sub-tunical spaces. The increased uptake of EdU by these shockwave−treated cells seems to suggest stem cell activation after exposure to shockwaves. Furthermore, when compared to older rats, younger rats undergoing therapy had increased cell activation, which suggests animal age might predict the efficacy of therapy.

Interestingly, in this same study by Lin et al,[18] Li-ESWT stimulated cell proliferation by increased phosphorylation of Erk1/2, which is within the same pathway that stimulates VEGF production, suggesting that both neovascularization as well as stem cell proliferation may be instrumental in the penile response to Li-ESWT.

STUDIES EXAMINING EFFICACY OF LI-ESWT IN THE TREATMENT OF ED

Most clinical studies have used the validated IIEF questionnaire to objectively determine erectile function.[19] The IIEF is comprised of 15 questions across 5 domains (EF, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) to assess sexual function. The IIEF-EF consists of 6 questions to which participants provide a score ranging from 1 (very low) to 5 (very high), with the sum of the scores representing the severity of the patient's ED. No ED is represented by a score of 26−30, mild ED is 22−25, mild to moderate ED is 17−21, moderate ED is 11−16, and severe ED is 6−10.[20] The IIEF-5, or Sexual Health Inventory for Men, is a validated, 5-question version of the questionnaire, with slightly different cutoffs, and rated on a scale that goes up to 25.[21] No ED is a score ≥22, mild ED is 17−21, moderate ED is 8−16, and severe ED is ≤7. As a reference, in a 2006 meta-analysis, Berner et al[22] showed an IIEF-EF score improvement of 9.2 points (95% CI 8.50−10.79) with daily 100-mg sildenafil during a period of 4−12 weeks.

For most of the studies examining efficacy of Li-ESWT in men responsive to PDE5is, men with a history of ED of at least 6 months' duration and with a previous positive response to

Table 1. Summary of select randomized controlled trials on low-intensity extracorporeal shock wave therapy in erectile dysfunction responsive to phosphodiesterase type 5 inhibitors

Study	Year published	Duration of treatment, wk	Duration of follow-up, wk	Treatments/wk	Shocks/ treatment, n	Machine, manufacturer	Baseline IIEF score		Change in IIEF score		Men in each study arm, n		Age, y		Diabetes, %	
							Treated	Sham	Treated	Sham	Treated	Sham	Treated	Sham	Treated	Sham
Vardi et al[24]	2012	6	13	2	1,500	Omnispec ED1000, Medispec	12.6 ± 0.75	11.5 ± 0.86	6.7 ± 0.9	3.0 ± 1.4	40	20	58	57	30	30
Yee et al[25]	2014	6	13	2	1,500	Omnispec ED1000, Medispec	10.2 ± 3.8	10.2 ± 3.2	5.3 ± 5.5	3.8 ± 3.6	30	28	58.9	63.3	37	29
Srini et al[26]	2015	6	13	2	1,500	Omnispec ED1000, Medispec	9.5 ± 2.4	9.2 ± 2.0	12.5 ± 3.3	1.4 ± 2.6	95	40	40.1	31.8	n/a	n/a
Olsen et al[27]	2015	5	5	1	3,000	Duolith SD1, Storz	n/a	n/a	n/a	n/a	51	54	59	60	9	7
Fojecki et al[28]	2017	10	18	1	600	FBL10, Richard-Wolf GmbH	10.9 ± 1.8	11.5 ± 1.7	0.9 ± 0.7	1.1 ± 1.0	63	63	65.4	63.3	6	9

IIEF = International Index of Erectile Function; n/a = not applicable this particular study.

PDE5is were included. Most studies excluded men with a penile deformity or those who had previously undergone prostatectomy. Many older studies on Li-ESWT for ED are retrospective, while most new studies are prospective.[23] In this review, we will focus on randomized controlled trials (RCTs) and discuss a few of these studies here. Specifics on these trials are included in Table 1. For the purpose of further sub-dividing these studies, we have elected to discuss the effectiveness of shockwave therapy separately for the following groups: men with ED responsive to PDE5is, men with ED resistant to PDE5is, and men with post-prostatectomy ED.

LI-ESWT IN ED RESPONSIVE TO PDE5IS

In 2012, Vardi et al[24] conducted the first randomized, double-blind, sham-controlled study using Li-ESWT for ED. The study included 67 men with ED of greater than 6 months' duration and with IIEF-EF scores of ≥19 while on PDE5i, as well as in a heterosexual relationship for more than 3 months. The men underwent a 1-month PDE5i washout period, followed by a 9-week treatment period during which they received 2 treatment sessions a week for 3 weeks, followed by no treatment for 3 weeks, followed by another 3-week treatment period. The authors found greater improvement in IIEF-EF scores in the treatment vs the sham group (6.7 ± 0.9 vs 3.0 ± 1.4, $P = .03$) 1 month after the final treatment session. The Vardi et al[24] study also examined penile blood flow using veno-occlusive plethysmography penile hemodynamics and found improved blood flow in the treatment vs sham group (8.2 vs 0.1 mL/min/dL, $P < .01$). No adverse effects were observed in this study, including pain, bruising, or hematuria.

Yee et al[25] conducted a similar RCT in 2014, excluding men with any history of pelvic radiation, hypogonadism, pelvic surgery, or penile implant (number of patients: 30 treated/28 sham, protocol: 2 treatments per week of 1,500 shocks each, given over 6 weeks, follow-up: 13 weeks). The difference in IIEF-EF scores for both sham and treatment groups at 13 weeks post-treatment did not reach statistical significance (ΔIIEF-EF: 5.3 ± 5.5 treatment vs 3.8 ± 3.6 sham, $P = .24$), possibly due to a small sample size.

In 2015, Srini et al[26] performed a RCT examining men who had previously responded to PDE5i and underwent a 1-month PDE5i washout period before starting Li-ESWT, thereby only including men with vasculogenic ED (number of patients: 95 treated/40 sham, protocol: 2 treatments per week of 1,500 shocks each, given over 6 weeks, follow-up: 13 weeks). They found that 71% of men in the treatment group vs 0% in the sham group were able to achieve an erection satisfactory for intercourse at 12-month follow-up ($P < .01$).

Olsen et al,[27] in their 2015 RCT did not distinguish between men on or off a PDE5i at the start of treatment, and included men who were unable to achieve intercourse (number of patients: 51 treated/54 sham, protocol: 1 treatment per week of

1,500 shocks, given over 5 weeks, follow-up: 5 weeks). Similar to the Srini et al[26] study, Olsen et al[27] observed that 57% of men in the treatment group vs 9% in the sham group were able to have sexual intercourse without medication 5 weeks after treatment ($P < .01$). Interestingly, 23% of men in the sham group who underwent Li-ESWT after sham therapy responded. It is important to note that no significant differences in IIEF scores were observed for any of the groups.

Most recently, Fojecki et al[28] looked at men with IIEF-EF scores <25 (number of patients: 63 treated/63 sham, protocol: 1 treatment per week of 600 shocks each, given over 10 weeks, follow-up: 18 weeks). This study first provided either Li-ESWT or sham therapy for 4 weeks to 2 different treatment groups. Then after a 4-week hiatus, both groups received true Li-ESWT. The authors observed no clinically relevant difference between the 2 groups in IIEF-EF scores ($P = .9$). Importantly, however, no distinction was made between PDE5i responders and non-responders.

The conclusions from the above studies are conflicting and limited due to differences in treatments protocols, number of treatments, and time at follow-up. 2 Meta-analyses have been published recently to attempt to draw a more definite conclusion as to the efficacy of Li-EWST for ED.[10,23] The 2017 meta-analysis by Lu et al[23] examined 14 studies, including RCTs and cohort studies, for a total of 833 patients from 2005−2015, and found that IIEF-EF score could be significantly improved (mean difference between the change in IIEF-EF for treatment group and control group: 2.00; 95% CI 0.99−3.00; $P < .01$) in patients treated with Li-ESWT. The authors found a more significant positive response in men with mild vs more severe ED. However, across studies, there were significant differences in treatment protocols that limited generalization of the results, and while changes in IIEF scores were statistically significant, they may not have been clinically significant, highlighting the importance of determining a minimally clinically important difference (MCID) for IIEF score. Examining data from 17 RCTs, Rosen et al[29] had previously determined that these values varied according to ED severity, with an MCID of 2, 5, or 7 for mild, moderate, and severe ED, respectively. Furthermore, while most studies use an energy density of 0.09 mJ/mm^2, no studies have explicitly compared energy densities. Longer and more frequent treatment courses, however, were not associated with improved IIEF scores. Lu et al[23] underscored the importance of detailed descriptions of blinding and treatment protocols for future RCTs, as many current studies did not provide significant details.

In 2017, Clavijo et al[10] published a meta-analysis specifically examining RCTs using IIEF-EF score as outcome. 7 RCTs were included in their analysis, including 2 studies published only as abstracts; trials performed between 2010 and 2016 were included, for a total of 602 participants and an average follow-up of about 5 months. The authors found that the IIEF-EF score improved by 4.17 points for the Li-ESWT treatment group over the control group ($P < .01$), which is likely to be clinically significant. Due to the heterogeneity between the trials, the authors also provided a list of recommendations for future trials that would facilitate more accurate comparisons. These included ensuring randomization of future studies, follow-up periods of longer than 3 months, PDE5i washout periods, and detailed treatment protocols, including trials of various length and strength to ensure optimum efficiency. They also suggested initial screening by penile ultrasound to ensure that only men with vasculogenic ED are included. Common across both meta-analyses was a need to accurately document co-morbidities such as diabetes or depression at the start of treatment to rule out other causes of ED.

A more recent meta-analysis by Man and Li[30] also corroborates the therapeutic benefit of shockwave therapy for ED, with a mean difference in IIEF of 2.54 ($P < .05$) between treatment and sham groups across studies. The authors found that shorter treatment courses were associated with improved erectile outcome, with a mean difference of 3.73 points in IIEF scores for subjects receiving therapy for less than 6 weeks, in comparison with those receiving therapy for longer ($P < .05$). Interestingly, the authors also found that shockwave probes by different manufacturers had varying effects on IIEF scores (Medispec, mean difference 4.14, $P < .01$ vs Storz, mean difference 2.7, $P < .01$).

LI-ESWT IN MEN WITH ED UNRESPONSIVE TO PDE5I TREATMENT

Few studies have looked specifically at the effect of Li-ESWT on ED that is unresponsive to PDE5is. The RCT of Kitrey et al[31] examined men with ED that had become unresponsive to PDE5is in the 12 months preceding Li-ESWT, but that had been responsive to PDE5i in the past by self-report (number of patients: 37 treated/16 sham, protocol: 2 treatments per week of 1,500 shocks each, given over 6 weeks, follow-up: 13 weeks). Unique to this study, men with severe vasculogenic ED were enrolled, and during the trial, all patients were re-started on a PDE5i. The authors evaluated treatment success as an IIEF-EF MCID of greater than 7 points for severe ED and 5 points for moderate ED. They found that 40.5% of men in the Li-ESWT group and 0% in the sham group responded to therapy ($P < .01$) after 9 weeks. Of the men in the sham group, 16 underwent Li-ESWT treatment and 25% of these post-sham patients saw clinically significant improvements in IIEF score ($P < .01$).

Gruenwald et al[32] and Bechara et al[33] both published cohort studies looking at men with ED that was unresponsive or minimally responsive to PDE5i therapy, following up 29 and 50 men, respectively. In Gruenwald et al,[32] after two 3-week treatment blocks separated by 3 weeks of no treatment and followed by 1 month of recovery, an increase in mean IIEF-EF score from 8.8−12.3 points ($P = .04$) was observed. Subjects did not take PDE5is up until that point in the study. After

re-starting a PDE5i, on follow-up 4 weeks later, the IIEF-EF score further increased to 18.8 points ($P < .01$). Bechara et al[33] found that in their intent-to-treat group, assuming patients who did not follow through to the end of follow-up at 12 months were unsatisfied with their results, the response rate would be 48% ($P < .05$), a rate similar to that observed by Kitrey et al.[31]

These studies suggest that Li-ESWT could play a beneficial role in improving erectile function when combined with PDE5i in men with moderate to severe ED.

LI-ESWT IN MEN WITH POST-PROSTATECTOMY ED

In 2016, Frey et al[34] studied 16 men with no prior ED who underwent robotic nerve-sparing prostatectomy that resulted in post-operative ED. At the start of the study, median IIEF-5 score was 9.5 and median time since surgery was 24 months. Subjects underwent 2 Li-ESWT treatments per week, every other week, for a total of 6 weeks, with a total of 3,000 shocks delivered per treatment session. At 1 month, median change in IIEF-5 score was +3.5 points ($P < .01$) and at 1 year, this score was +1.0 points ($P < .05$). A lack of treatment control group and a lack of control for PDE5i use limit the generalizability of these results and most men in this study, even with the improvements in IIEF score, were unable to maintain erections sufficient for intercourse despite Li-ESWT. The fact that IIEF increased and then decreased following Li-ESWT is also an interesting finding, suggesting either a natural progression of the ED or a reversible effect of Li-ESWT on ED.

SAFETY OF LI-ESWT

None of the studies included in this review reported adverse effects for Li-ESWT, except for 1 patient who reported an allergic reaction to the gel used during treatment.[32] Notably, no bruising or hematomas were reported. It therefore appears that in the short term at least, Li-ESWT is safe. Without further, longer-term study and outcomes, the safety profile of Li-ESWT remains unclear. Assuming that micro-trauma is induced during Li-ESWT, no current data are available examining whether men undergoing Li-ESWT have an increased predisposition to Peyronie's disease or any other long-term complication. Long-term follow-up as part of RCTs is needed to fully assess risks of therapy.

CLINICAL ATTITUDES

In a study published on clinical attitudes toward the use of shockwaves for ED at the European Society for Sexual Medicine conference, 83% of 144 respondents in attendance who had heard of the therapy considered it safe, and 72% considered it effective.[35] Li-ESWT has already been adopted as therapy for ED by many urologists worldwide, though no consensus currently exists on its value in the United States, as the therapy has only recently acquired more widespread recognition and is still pending approval from the FDA.

CONCLUSIONS AND FUTURE DIRECTIONS

Most data from RCTs support a benefit of Li-ESWT in the treatment of at least mild ED, with some data supporting efficacy in moderate to severe ED, particularly when used with PDE5i. However, heterogeneity in study design and outcomes limits interpretation and generalizability of these data. Future, rigorous RCTs will better inform whether Li-ESWT is truly effective, and in what groups of patients.

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