SEXUAL MEDICINE REVIEWS REVIEW

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;XX:XXX–XXX.**

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