SEXUAL MEDICINE ORIGINAL RESEARCH

ERECTILE DYSFUNCTION

Effect of Linear Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction—12-Month Follow-Up of a Randomized, Double-Blinded, Sham-Controlled Study

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ABSTRACT

Introduction: Short-term data on the effect of low-intensity extracorporeal shockwave therapy (Li-ESWT) on erectile dysfunction (ED) have been inconsistent. The suggested mechanisms of action of Li-ESWT on ED include stimulation of cell proliferation, tissue regeneration, and angiogenesis, which can be processes with a long generation time. Therefore, long-term data on the effect of Li-ESWT on ED are strongly warranted.

Aim: To assess the outcome at 6 and 12 months of linear Li-ESWT on ED from a previously published randomized, double-blinded, sham-controlled trial.

Methods: Subjects with ED (N = 126) who scored lower than 25 points in the erectile function domain of the International Index of Erectile Function (IIEF-EF) were eligible for the study. They were allocated to 1 of 2 groups: 5 weekly sessions of sham treatment (group A) or linear Li-ESWT (group B). After a 4-week break, the 2 groups received active treatment once a week for 5 weeks. At baseline and 6 and 12 months, subjects were evaluated by the IIEF-EF, the Erectile Hardness Scale (EHS), and the Sexual Quality of Life in Men.

Main Outcome Measures: The primary outcome measure was an increase of at least 5 points in the IIEF-EF (ΔIIEF-EF score). The secondary outcome measure was an increase in the EHS score to at least 3 in men with a score no higher than 2 at baseline. Data were analyzed by linear and logistic regressions.

Results: Linear regression of the ΔIIEF-EF score from baseline to 12 months included 95 patients (dropout rate = 25%). Adjusted for the IIEF-EF score at baseline, the difference between groups B and A was −1.30 (95% CI = −4.37 to 1.77, $P = .4$). The success rate based on the main outcome parameter (ΔIIEF-EF score ≥ 5) was 54% in group A vs 47% in group B (odds ratio = 0.67, $P = .28$). Improvement based on changes in the EHS score in groups A and B was 34% and 24%, respectively (odds ratio = 0.47, $P = .82$).

Conclusion: Exposure to 2 cycles of linear Li-ESWT for ED is not superior to 1 cycle at 6- and 12-month follow-ups. **Fojecki GL, Tiessen S, Osther PJS. Effect of Linear Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction—12-Month Follow-Up of a Randomized, Double-Blinded, Sham-Controlled Study. Sex Med 2017;X:XXX−XXX.**

Key Words: Erectile Dysfunction; Linear Low-Intensity Extracorporeal Shockwave Therapy

INTRODUCTION

Restoration of natural erection is the ultimate goal of erectile dysfunction (ED) therapy.[1] The introduction of phosphodiesterase type 5 inhibitors (PDE5is) in the late 1990s completely changed the treatment scenario of ED; however, this treatment modality does not represent a cure. Furthermore, most oral medications require planning of sexual intercourse and are associated with, for example, headache, dizziness, or decrease in blood pressure, which can have serious consequences, especially in combination with nitrate preparations.[2,3]

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Penile low-intensity extracorporeal shockwave therapy (Li-ESWT) was previously reported to be capable of curing ED.[4,5] The underlying mechanisms of action remain elusive. Potential beneficial effects related to ED include stimulation of cell proliferation, tissue regeneration, and angiogenesis.[5] In a diabetic rat model, Li-ESWT was shown to promote regeneration of neuronal nitric oxide synthase–positive nerves, endothelium, and smooth muscle cells.[6] The effect seemed to be mediated by the recruitment of endogenous mesenchymal stem cells.[6] In addition, Li-ESWT showed potential in promoting angiogenesis in a pelvic neurovascular injury rat model.[7]

Human clinical trials of Li-ESWT have produced inconsistent results.[8–16] A recent systematic review and meta-analysis concluded that Li-ESWT might be especially suitable for men with mild ED[5]; yet 1 of the included trials only implicated a potential value for severe ED.[11] In addition, in several of the trials, an inconsistency was reported of ED outcome measures after Li-ESWT—International Index of Erectile Function (IIEF) vs Erectile Hardness Scale (EHS)—which are difficult to explain.[17] One reason for the conflicting results might be that the potential of the Li-ESWT–induced tissue regeneration and angiogenesis, which are inherently slow biological processes, might not have reached its maximum at time of analysis. Thus, the effect of nerve regeneration and angiogenesis on ED might have considerable interindividual variance, and therefore long-term data on the effect of Li-ESWT on ED could better elucidate statistical intervariance.[4,5,17]

In this article, we report on outcomes at 6- and 12-month follow-up from a previously published randomized, sham-controlled clinical trial on linear Li-ESWT (LLi-ESWT) for ED.[15]

The objective of the study was to evaluate the effects of LLi-ESWT on ED assessed by the IIEF-EF, EHS, and Sexual Quality of Life in Men (SQoL-M) questionnaires.

The hypothesis of the study was that LLi-ESWT would improve erectile function at 6 and 12 months, possibly through regenerative processes and angiogenesis.

METHODS

Details of the trial (NCT02063061), in which short-term data were reported, were previously published.[15] Participants underwent a standard assessment that included medical history, physical examination, and blood testing. Subjects with vasculogenic ED were selected based on inclusion and exclusion criteria (Table 1). Use of any erectogenic therapy was restricted during treatment and short-term follow-up. Furthermore, in subjects previously treated for ED, a 4-week washout period was implemented.

The study was carried out from February through August 2014 at the Department of Urology at the Hospital of Southern Jutland (Sønderborg, Denmark). This department offers primary urologic care to almost 250,000 inhabitants within a 100-km range.

Table 1. Inclusion and exclusion criteria

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

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

The research secretary generated a random list (www.randomisation.org) with a 1:1 ratio. 126 subjects were allocated to group A or B. The manufacturer of the ESWT device (Richard Wolf GmbH, Knittlingen, Germany) provided 3 identically looking gel pads that were specially designed for this study. In the 1st phase of treatment, a non-penetrable active gel pad was used. Pads were marked A or B, which corresponded to the sham or active group. In the 2nd phase of the trial, all patients received LLi-ESWT using another active gel pad. It had an outer design identical to those used during the 1st phase, allowing for concealed group allocation during the entire study period for investigator and patients. Participants received 5 weekly treatment sessions of LLi-ESWT or sham. After a 4-week break, the 2 groups received LLi-ESWT. We imitated the crossover design from pharmacologic studies. We chose to treat all subjects in the 2nd phase because we expected that treatment would have a prolonged effect. A summary of the study is presented in Figure 1.

The primary outcome measure was the change in IIEF-EF score from baseline to after 6 or 12 months (ΔIIEF-EF). To enable comparison of our findings with results of other trials,[11,12,16] changes in IIEF-EF score of at least 5 points were considered clinically relevant. Secondarily, we looked for changes in the EHS score in which an increase to at least 3 indicated improvement. Changes in SQoL-M score from baseline to final follow-up assessment also were recorded. Use of additional pharmacologic treatment for ED was controlled using a national prescription database, which is an online platform that enables

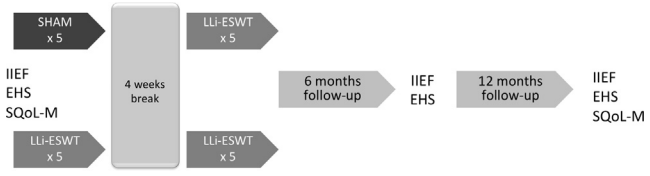

Figure 1. Study design. EHS = Erectile Hardness Scale; IIEF = International Index for Erectile Function; LLi-ESWT = linear low-energy extracorporeal shockwave therapy; SQoL-M = Sexual Quality of Life for Man.