Original Paper

Urologia Internationalis

Urol Int
DOI: 10.1159/000504788

Received: September 3, 2019
Accepted after revision: November 13, 2019
Published online: December 11, 2019

Erectile Dysfunction Treatment Using Focused Linear Low-Intensity Extracorporeal Shockwaves: Single-Blind, Sham-Controlled, Randomized Clinical Trial

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Keywords
Erectile dysfunction · Cardiovascular disease · Low-intensity extracorporeal shockwave · Phosphodiesterase-5 inhibitors

Abstract
Introduction: Low-intensity extracorporeal shock wave therapy (Li-ESWT) is a new treatment modality for erectile dysfunction (ED). Our aim was to evaluate the treatment outcome of Li-ESWT for ED in single-blind, placebo controlled, randomized clinical trial. ***Methods:*** Sixty patients were randomized into 2 age-matched groups: Group A – treatment and Group B – placebo. Treatment consisted of 4 sessions on the PiezoWave2 unit (R. Wolf and ELvation Medical). Effectiveness was assessed according to the International Index of Erectile Function 5 (IIEF-5), Erectile Hardness Score (EHS), questions 2 and 3 of the Sexual Encounter Profile (SEP 2, SEP 3), and Global Assessment Question (GAQ) scores at baseline and 4 and 12 weeks after treatment. We evaluated patient's and partner's subjective satisfaction. ***Results:*** A statistically significant difference between the groups was found at 4 and 12 weeks after treatment with regard to the quality of erection as measured by the IIEF-5 ($p = 0.049$ and $p < 0.001$, respectively), the EHS after week 12 ($p < 0.001$), an increase in the EHS after 4 and 12 weeks ($p = 0.030$ and $p < 0.001$, respectively), after 12 weeks in GAQ ($p < 0.001$), SEP 2 ($p = 0.05$), SEP 3 ($p < 0.001$), and patient's satisfaction ($p < 0.001$) and partner's satisfaction ($p < 0.001$). ***Conclusions:*** The randomized single-blind study confirms that Li-ESWT significantly improves erectile function.

Introduction

Sexual dysfunction can have a major impact on quality of life and psychosocial and emotional well-being [1]. An erection is a complex event that causes changes in the muscles, nerves, and blood vessels of the penis [2]. There are a significant number of men under 40 who experience erectile dysfunction (ED). Many cases of ED are or-

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ganic in origin, including vascular, neurogenic, hormonal, or due to medication side effect. It is the significant prevalence of vascular etiology of ED in young men [3]. Vasculogenic ED is the most common risk factor for ED, with a high prevalence (40%) in men with a high cardiovascular risk [4]. According to the European Association of Urology guidelines for the management and treatment of ED, phosphodiesterase-5 inhibitor (PDE5i) constitutes the first line of therapy [5]. PDE5i has been extensively studied in a wide population with different etiology of ED, including men with renal failure, coronary artery diseases, or men after spinal cord injury (SCI). Results of 6 studies involving 963 patients after SCI confirmed that PDE5i is effective in the treatment of ED secondary to SCI [6]. Successful treatment of ED is important for the quality of life of these handicapped patients. For the past 20 years, the preferred treatment for ED has been oral treatment with PDE5i or intracavernosal injection therapy [5]. But although PDE5i is generally effective, it is associated with treatment failure in up to half the patients [7]. A good alternative treatment or adjunctive treatment for ED may be the hyperbaric oxygen therapy [8]. Diabetics suffer from refractory ED, especially vascular etiology, and there are difficult-to-treat patients and the efficacy of PDE5i is limited. A better therapeutic effect is achieved by intracavernous treatment by prostaglandin E1. The first human study with proven tolerability, safety, and efficacy of intracavernous autologous bone marrow derived mesenchymal stem cell injections was evaluated in diabetic patients [9]. Shockwave therapy also appears to be a good alternative treatment for the prevention of ED in diabetic men. Extracorporeal shockwave therapy (ESWT) has been used in different medical fields for many years (e.g., extracorporeal shockwave lithotripsy, treatment of Peyronie's disease) [10]. Animal studies have demonstrated neoangiogenesis in myocardial tissue following ESWT [11]. Vardi et al. [12] published the first randomized, double-blind, sham-controlled study on the use of low-intensity ESWT (Li-ESWT) to treat ED. Li-ESWT was recently administered in a clinical setting as a novel therapeutic method to treat ED. The studies suggest that Li-ESWT could significantly improve erectile function (EF) in patients with ED. The new treatment modality of Li-ESWT can have a rehabilitative and/or curative effect on ED [13]. Li-ESWT has the potential to improve and permanently restore EF by reinstating penile blood flow [14]. Our goal was to determine the effectiveness and safety of focused Li-ESWT versus placebo in single-blind, placebo controlled, randomized clinical trial.

Materials and Methods

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the local Ethics Committee of Brno University Hospital, Czech Republic, registration number VP/0866/2017. The study was carried out at the Department of Sexology, Brno University Hospital, and ran from September 2017 to March 2018. Patients with mild to severe vasculogenic ED lasting for at least 6 months who provided written consent, had a stable partner, and regular sexual activity at least twice a week were included in the study. Patients with psychogenic and neurogenic ED (neurologic disease, pelvic surgery) were excluded. All patients were at least partial responders to PDE5i. Existing treatment of ED was discontinued. Wash-out period was 4-week. Patients were asked not to take PDE5i or intracavernous injections during the trial. All patients expressed an interest in receiving shockwave treatment. We did not calculate the dropout because all patients were highly motivated patients who were registered and visited our sexology department regularly. All patients were heterosexual and white European. All were patients of the Department of Sexology of Brno University Hospital. Median patient age was 54 years (range 40–70). A total of 60 patients were included in the study.

Randomization: The power analysis was based on the following prerequisites: required power 0.8 and level of statistical significance 0.05. Study endpoint was defined as the proportion of patients with an optimal treatment response. Study endpoint occurrence in the control group was considered to be 20%. The required clinically significant difference in endpoint occurrence between the control group and the treatment group was 35%. The required sample size for the identification of this difference in endpoint occurrence (control group 20%; treatment group 55%) as statistically significant was 30 patients in each study group (total sample size was 60 patients). The analysis was computed using Power Analysis and Sample Size Software 13 (2014; NCSS, LLC, Kaysville, UT, USA). Patients were randomized using the software from Sealed Envelope Ltd. (www.sealedenvelope.com/simple-randomiser/v1/lists) into 2 age-matched groups (Group A: treatment; Group B: placebo) with 30 patients in each group.

Study protocol: Patients underwent a sexological and andrological examination. Blood samples were taken between 8 and 10 a.m. and all treatment sessions were scheduled between 8 and 11 a.m. Variables such as age, duration of ED, body mass index, obesity (≥30 body mass index), waist circumference (obesity ≥102 cm), thyroid-stimulating hormone, prolactin, and comorbidities as hypertension, diabetes mellitus, dyslipidemia, late-onset hypogonadism (total testosterone, tT, cut-off: 12.1 nmol/L based on the guidelines of the European Urological Association) were recorded and monitored. After a 4-week wash-out period, the severity of their ED was determined. We used the International Index of EF 5 (IIEF-5), the Erection Hardness Score (EHS), and Sexual Encounter Profile (SEP) Q 2 and 3 (SEP 2 – Were you able to insert your penis into your partner's vagina? and SEP 3 – Did your erection last long enough for you to have successful intercourse?) to assess EF before the start of treatment. ED severity was classified into 4 categories based on IIEF-5 scores: ≤6, severe; 8–16, moderate; 17–21, mild; and 22–25, none [15]. The EHS is based on self-estimated rigidity, categorized using a scale of 1–4: (1) the penis is larger but not hard, (2) the penis is hard but not hard enough for penetration, (3) the penis is hard enough for

penetration but not completely hard, and (4) the penis is completely hard and fully rigid for coitus [16]. Patients received 4 sessions (2 per week). The exact number of shockwaves in each session has been calculated by the algorithm for tailored treatment which is the first of its kind and it suggests an optimal number of shocks (and thereby an energy dose) to be applied. It takes into account major factors that could influence the treatment results such as initial IEF-5 score and patient's comorbidities. Currently we are still working on its refinement. However, in our study average 6,000 shocks per session were applied, half of which were delivered to the crura and half to the shaft. This means that patients received an average of 24,000 pulses over the course of treatment. Shockwaves were administered with the PiezoWave2 unit (Richard Wolf GmbH and ELvation Medical GmbH) and the FBL10 × 5G2 linear focusing shockwave applicator, using the Linear Shockwave Tissue Coverage – ED technique which applies shockwaves to all erectile tissue. The linear piezo shockwave therapy source is applied at right angles to the corpora cavernosa and then moved lengthwise along the penis (corpora cavernosa) and the perineum (crura penis). Logical assumption is that this concept of "complete coverage" might improve therapy outcomes. The energy flow density was 0.160 mJ/mm^2 (level 20) and focus penetration depth was 15 mm. This means that the SW field depth was from 0 to 30 mm.

Effectiveness was assessed using IIEF-5, EHS, Global Assessment Question (GAQ; improvement of erection after treatment), SEP 2 (Were you able to insert your penis into your partner's vagina?), and SEP 3 (Did your erection last long enough for you to have successful intercourse?) scores at 4 and 12 weeks after treatment [17]. We evaluated the patient's and their partner's subjective satisfaction. We correlated the effect of treatment with observed variables such as patient age, duration and severity of ED, and comorbidities such as coronary artery disease, hypertension, dyslipidemia, diabetes, obesity, smoking, and late-onset hypogonadism.

Blinding: In the placebo group, a special applicator probe was used with a gel head that blocked shockwaves. The device produced shockwaves and their accompanying noises, thus patients could not know whether their treatment was a placebo.

Statistics: Standard descriptive statistics were used for the analysis. Categorical variables were described using absolute and relative frequencies, quantitative variables were described using mean supplemented with standard deviation or 95% CI and median with a min-max range. The statistical significance of differences between groups was analyzed using maximum likelihood chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Relations between continuous variables were described using Spearman's correlation coefficient and their statistical significance. Analyses were done with SPSS 25.0.0.1 (IBM Corporation, 2018). Due to the low sample size for multivariate analysis, only univariate statistical analysis of the relations between treatment groups and patients' characteristics/outcomes was performed.

The primary outcome measures was the proportion of patients with an optimal treatment response (IIEF-5 ≥22); other endpoints were mean change of IIEF-5, EHS the SEP Q2 and 3, the GAQ scores at baseline and at 4 and 12 weeks after treatment, and the evaluation of the patient's and their partner's subjective satisfaction. The safety of the focused linear Li-ESWT was monitored throughout the study.

Results

We managed to collect data for all 60 patients. All the patients were highly motivated and none of the patients discontinued treatment prematurely. There were no significant differences between Groups A and B and no statistically significant differences were found for baseline characteristics (Table 1).

A statistically significant difference between the Groups A and B was found at 4 and 12 weeks after treatment with regard to the quality of erection. After 12 weeks, the difference between Groups A and B had increased as measured by an increase in the IIEF-5 score and the Significant differences between Groups A and B were found after 12 weeks in GAQ, SEP 2, SEP 3, patient's satisfaction and partner's satisfaction, which is given in Table 2.

We found no statistical significance for other variables correlated with the outcome of treatment; however, the relationship with age (the success rate decreases with age) was close to significance, which is given in Table 3. Only 3 (5%) patients in Group A experienced mild side effects of treatment based on a subjectively perceived tingling sensation at the application site, the intensity of which decreased with the number of sessions completed. These difficulties did not lead either to discontinuation of treatment or to a change in the protocol.

Discussion

Li-ESWT is a new, non-pharmacological method to treat ED. According to the European Association of Urology guidelines, Li-ESWT the first line of ED treatment. The efficacy of Li-ESWT for ED has received hard criticism. Sokolakis and Hatzichristodoulou [18] published the systematic review and meta-analysis of randomized sham-controlled trials (RCT) including 10 studies in 873 patients published from January 2010 to September 2018. The primary outcomes using IIEF-EF were included. Pooling data of these studies showed that Li-ESWT could significantly improve EF in men with ED regarding both patient-subjective outcome (IIEF-EF, $p < 0.0001$) and patients-objective outcome (peak systolic velocity, $p < 0.00001$). The authors concluded that the present meta-analysis provide results showing that Li-ESWT significantly improves EF in patients with vasculogenic ED [18]. Our aim was to increase the number of randomized clinical trials, introduce a short therapeutic protocol for patient compliance, and monitor the safety, efficacy of

Table 1. Baseline characteristics (n = 60)

	Study group, n (%)		p value
	control (n = 30)	intervention (n = 30)	
SEP 2	11 (36.7)	17 (56.7)	0.195
SEP 3	0 (0.0)	0 (0.0)	1.000
Cardiovascular diseases			
hypertension	24 (80.0)	17 (56.7)	0.095
Dyslipidemia	22 (73.3)	21 (70.0)	1.000
Diabetes	13 (43.3)	8 (26.7)	0.279
CAD	6 (20.0)	3 (10.0)	0.472
Obesity (BMI ≥30)	13 (43.3)	12 (40.0)	1.000
Late onset hypogonadism	4 (13.3)	3 (10.0)	1.000
Smoking	4 (13.3)	5 (16.7)	1.000
Previous treatment	20 (66.7)	20 (66.7)	1.000
(a) PDE5i	16 (53.3)	19 (63.3)	0.601
(b) Alprostadil	4 (13.3)	1 (3.3)	0.353
Age at the time of examination, years	54.7 (9.2)	53.9 (9.3)	0.767
ED duration	45.0 (6.0–204.0)	42.0 (6.0–204.0)	0.929
BMI	29.6 (4.2)	29.6 (4.8)	0.885
Testosterone, nmol/L	18.1 (5.8)	18.8 (5.7)	0.487
IIEF-5	13.1 (3.6)	12.8 (3.9)	0.864
EHS	2.1 (0.5)	2.1 (0.5)	0.619

Absolute and relative frequencies for categorical variables; mean supplemented with SD for continuous variables; EF duration described by median (min–max) due to asymmetric distribution.

Categorical variables tested using maximum likelihood chi-square test; Mann-Whitney U test for continuous variables.

SEP 2, Sexual Encounter Profile Q 2; SEP 3, Sexual Encounter Profile Q 3; CAD, coronary artery disease; BMI, body mass index; PDE5i, phosphodiesterase-5 inhibitors; ED, erectile dysfunction; IIEF-5, International Index of Erectile Function 5; EHS, Erection Hardness Score.

treatment, and the patient's and partner's satisfaction. Li-ESWT was studied in 20 men after kidney transplantation in double-blind, prospective, sham RCT. Penile Doppler was performed before and after treatment. The mean change in IIEF score after 12 months was 4.8 in Li-ESWT group. Author concluded that Li-ESWT is a treatment with clinical efficacy. But penile Doppler parameters were similar between groups and did not present improvements [19]. Clavijo et al. [20] published a systematic review and meta-analysis and were able to demonstrate a statistically significant improvement in IIEF-EF scores compared with men who received sham therapy. The authors concluded that more stringent RCTs were warranted prior to widespread acceptance of this treatment [20]. In our randomized single-blind study of 60 patients, we were able to demonstrate a significant improvement of EF in patients with mild to severe vasculogenic ED. We noted a high level satisfaction among patients as well as their partners. Patients appreciated the non-pharmacological treatment, its non-invasiveness, safety, and efficacy. In their meta-analysis, Man and Guizhong [21] showed that Li-ESWT could significantly improve IIEF-5 and EHS. The therapeutic efficacy persisted for at least 3 months. Lower energy densities (0.09 mJ/mm^2), higher numbers of pulses (3,000 pulses per treatment), and a shorter course of treatment (<6 weeks) resulted in better therapeutic efficacy. We believe that our study brings the novel information. We introduced a complete tissue coverage technique (Linear Shockwave Tissue Coverage) which is unique, we shortened the treatment protocol from usually used 6 or 4–2 weeks and we also introduced, for the first time, an original treatment algorithm for tailored treatment (which is naturally still subject to further refinement and testing with the growing number of patients and experiences). Moreover, we pointed out that the low energy settings without complete and sufficient tissue coverage clearly results in an ineffective treatment.

Olsen et al. [22] presented the results of a prospective, randomized, placebo-controlled study of 112 patients with ED of organic origin who responded to PDE5i. The

Table 2. Study endpoints (n = 60)

	Study group, n (%)		p value
	control (n = 30)	intervention (n = 30)	
After 4 weeks of treatment			
Primary endpoint: IIEF5 ≥22	5 (16.7)	12 (40.0%)	0.043
IIEF-5	16.3 (14.6–18.1)	18.7 (16.9–20.4)	0.049
Change of IIEF-5	3.2 (2.0–4.4)	5.6 (3.9–7.4)	0.092
EHS	2.7 (2.4–3.0)	3.1 (2.8–3.5)	0.059
Change of EHS	0.6 (0.3–0.8)	1.1 (0.7–1.4)	0.030
GAQ	12 (40.0)	19 (63.3)	0.120
SEP 2	21 (70.0)	25 (83.3)	0.360
SEP 3	8 (26.7)	16 (53.3)	0.064
Patients/partner satisfaction	13 (43.3)	19 (63.3)	0.195
After 12 weeks of treatment			
Primary endpoint: IIEF5 ≥22	4 (13.3)	20 (66.7)	<0.001
IIIEF-5	15.5 (13.7–17.4)	20.8 (19.3–22.3)	<0.001
Change of IIEF5	2.5 (1.2–3.8)	7.7 (5.9–9.5)	<0.001
EHS	2.4 (2.1–2.7)	3.6 (3.3–3.8)	<0.001
Change of EHS	0.3 (0.0–0.6)	1.5 (1.2–1.8)	<0.001
GAQ	9 (30.0)	23 (76.7)	<0.001
SEP2	18 (60.0)	27 (90.0)	0.005
SEP3	4 (13.3)	22 (73.3)	<0.001
Patients/partner satisfaction	9 (30.0)	25 (83.3)	<0.001

Absolute and relative frequencies for categorical variables; mean supplemented with 95% CI. Categorical variables tested using maximum likelihood chi-square test; Mann-Whitney U test for continuous variables.

IIEF-5, International Index of Erectile Function 5; EHS, Erection Hardness Score; GAQ, Global Assessment Question; SEP 2, Sexual Encounter Profile Q 2; SEP 3, Sexual Encounter Profile Q 3.

Table 3. Correlation of outcome with patients' characteristics based on treated group of patients (n = 30)

	Change of IIEF-5		Change of EHS	
	correlation coefficient*	p value	correlation coefficient*	p value
Age at the time of examination	–0.346	0.061	–0.226	0.231
ED duration	0.073	0.700	0.041	0.830
Number of comorbidities	0.062	0.744	–0.022	0.909
IIEF-5 at baseline	–0.319	0.086	–0.096	0.613
EHS at baseline	–0.246	0.190	–0.242	0.198

* Spearman correlation coefficient.

IIEF-5, International Index of Erectile Function 5; EHS, Erectile Hardness Score; ED, erectile dysfunction.

trial was carried out over a period of 5 weeks and showed that that Li-ESWT had a positive effect in 57% of the men. Our study showed positive effect of Li-ESWT in 66.7% of the patients in the intervention group in week 12 after treatment. Feldman et al. [23] analyzed pooled data from 5 randomized, placebo-controlled studies and 3 single-arm open-label studies. The mean change in IIEF-EF from baseline was 5, 6.8, 6.2, and 7 points at the midterm. In our study, the mean change in IIEF-5 was 7.7 points (95% CI 5.9–9.5). Bechara et al. [24] studied the efficacy of Li-ESWT in patients unresponsive to treatment with PDE5i and found that Li-ESWT was effective in 60% of

treated patients. Efficacy and safety of Li-ESWT, PDE5i, and control group were evaluated in 128 men after radical cystoprostatectomy in penile rehabilitation. Potency recovery rates at 9 months were 76.2, 79.1, and 60.5% in Li-ESWT, PDE5i, and control groups. There was no significant difference between the 3 groups during all follow-up periods. During last follow-up, 16% more patients in Li-ESWT group had recovery of potency as compared to the control group. In conclusion, Li-ESWT is as safe as oral PDE5i in penile rehabilitation post nerve-sparing radical cystoprostatectomy. Although the difference is not statistically significant, it is of clinical importance [25]. Managing patients with ED who failed to respond to PDE5i is a challenging task. Li-ESWT improves ED by enhancing perfusion of the penis. An open-label single-arm prospective study was performed to evaluate whether combined treatment with Li-ESWT and PDE5i can restore EF in patients who failed to respond to PDE5i alone. After Li-ESWT treatment, 35 of the 52 patients (67.3%) could achieve an erection hard enough for intercourse (EHS 3) under PDE5i use at the 1-month follow-up. Thirty-three of the 35 (94.3%) subjects who responded to Li-ESWT could still maintain their EF at the 3-month follow-up. Li-ESWT can serve as a salvage therapy for ED patients who failed to respond to PDE5i. Initial severity of ED was an important predictor of a successful response [26]. Li-ESWT has more recently been shown to improve patient response to oral PDE5i and may allow patients who previously did not respond to these drugs to have erections sufficient for penetration using them following Li-ESWT. After Li-ESWT treatment, about half of the patients (54.1%) were able to achieve erection hard enough for penetration with PDE5i [27]. Fojecki et al. [28] performed a well-designed study regarding linear focused Li-ESWT of ED, but with completely inappropriate settings. We are using the same device; so we calculated the energy used by Fojecki et al. [28] The setting they used delivers 6 mJ energy for every pulse; in the setting we use, every pulse has 15.45 mJ energy. Multiplied with the amount of pulses used (6,000 Pulses × 4 Sessions × 15.45 mJ), this is about 370,000 mJ in total. Multiplied with the pulses used, the Danish group used (6,000 Pulses in total × 6 mJ) about 36,000 mJ in total. Then, we reduced the working energy because of the fact that Fojecki et al. [28] used Pad 0 mm (shockwave focus in 0 mm depth, means the highest energy level, is on the skin surface). Therefore, we end up with an energy delivery total of about 20,000 mJ, which is 4.3% of the energy we are using. In our setting, the shockwave penetration depth is 10 (15) mm (shockwave focus is in the cavernous tissues). The only good conclusion is that this extra low dose of already low-intensity setting is not creating any side effect, and therefore a very positive finding that Fojecki et al. [28] dosage has no effect. So, finally, we decided to perform a similar study with more suitable settings [28]. Our single-blind study confirms that focused linear Li-ESWT significantly improves EF. Ensuring the delivery of a sufficient amount of energy, optimal tissue coverage, and a focal shockwave depth of 15 mm are crucial factors that affect treatment outcomes. We conclude that focused linear Li-ESWT is a safe, effective, non-pharmacological treatment for ED.

It seems that Li-ESWT may have the potential to become the first-choice non-invasive treatment for patients with ED [29]. Li-ESWT may increase blood flow and improve endothelial function through the stimulation of angiogenesis in the corpus cavernosum, which is good option for patients with vasculogenic ED [30].

Hatzichristou has proposed a stepwise research and development approach for Li-ESWT. Suggested steps include a therapeutic protocol (energy density, pulses, sessions), alternative therapeutic protocols (depending on ED severity), investigating the efficacy and safety in a general ED population, investigating the long-term outcomes, studying the efficacy of repeat treatments, and studying the efficacy of Li-ESWT in difficult-to-treat patient cohorts such as men with diabetes or after radical prostatectomy (RP) [31].

Randomized controlled studies investigating the effect of Li-ESWT in men with vasculogenic ED, patients with ED developed after RP, are excluded in nearly all clinical trials. Usta et al. [32] published a critical review examining the potential utility Li-ESWT in men with ED after RP. It's necessary to have more RCT studies with long-term follow-up data and protocol standardization. The authors concluded that Li-ESWT is a potential restorative therapy for post-RP ED, but additional studies are required.

Frey et al. [33] carried out a pilot study in 18 patients who had robot-assisted bilateral nerve-sparing RP. In this study, patients with no history of preoperative ED were treated 2 times per week, every other week a total of 6 weeks. All patients had mild to moderate ED after RP and Li-ESWT was initiated 1-year post RP. Treatment efficacy was evaluated using IIEF score at 1 month and 1 year after the last Li-ESWT session. The median change in IIEF score was +3.5 and +1 at 1-month and 1-year follow-up, respectively. The authors concluded that Li-ESWT may improve EF after nerve-sparing RP, but not to a clinically significant extent [33].

Li-ESWT is a potential restorative therapy for post-RP ED; however, additional preclinical and clinical studies are required before its widespread use [32].

Current nonsurgical treatment options of ED, including PDE5i, provide temporary relief but have failed to provide a permanent improvement of the condition. The use of Li-ESWT has previously been described in other disease contexts, such as ischemic heart disease, bone fractures, and burns, in which it improves neoangiogenesis; similar principles seem to apply in the erectile tissue. The major potential advantage of the treatment, therefore, is the possibility to restore natural EF. Li-ESWT has also been suggested to improve the effect of PDE5i in non-responders, reducing the need for more invasive treatment. The search for the clinical value of Li-ESWT for ED represents a dynamic and continuing field of enquiry [34].

Therapeutic potential of Li-ESWT is in sexual medicine other than ED. In Peyronie's disease, Li-ESWT has been shown to decrease pain but not clinically relevant benefits regarding plaque size or penile curvature have been shown in randomized clinical trials. The application of Li-ESWT to the tissue after stem cell transplantation may increase the erectile response following cavernous nerve injury due to diabetic damage. Li-ESWT has shown promise in pelvic pain. Other studies are needed, before considering this new treatment as the new standard for the treatment of ED [35].

Limitations

The limitations of the study are the relatively small number of patients, short follow-up period and only single-blind study.

Acknowledgments

We would like to thank University Hospital Brno.

Statement of Ethics

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the local Ethics Committee of Brno University Hospital, Czech Republic, registration number VP/0866/2017. All patients signed informed consent, which was approved by the Ethics Committee.

Disclosure Statement

The authors declare no conflicts of interest. This article has no commercial and financial interest.

Funding Sources

University Hospital Brno, Czech Republic.

Author Contributions

T.S. carried out the conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, and revised it for intellectual content. I.M. carried out the conception and design and revised it for intellectual content. J.J. carried out the statistical analysis, interpretation of data and tables, helped to draft the manuscript, and revised it for intellectual content. K.S. carried out the acquisition of data, analysis of data, and helped to draft the manuscript. All authors read and approved the final manuscript.

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