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Linear Low-Intensity Extracorporeal Shockwave Therapy as a Method for Penile Rehabilitation in Erectile Dysfunction Patients after Radical Prostatectomy: A Randomized, Single-Blinded, Sham-Controlled Clinical Trial

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Keywords
Shockwave therapy · Penile rehabilitation · Erectile dysfunction · Radical prostatectomy

Abstract
Introduction: The objective of this study was to investigate the effect and feasibility of linear low-intensity extracorporeal shockwave therapy (LI-LiESWT) as a penile rehabilitation method for erectile dysfunction (ED) after bilateral nerve-sparing (NS) radical prostatectomy (RP). ***Methods:*** Patients who had undergone bilateral NS RP (either radical retropubic prostatectomy or robot-assisted laparoscopic RP), 3 or more months prior to the study, and who had no ED preoperatively and were suffering from mild to severe postoperative ED were included in the study. Four treatments were given over a 4-week period, using the PiezoWave2 device with a linear shockwave applicator and the linear shockwave tissue coverage (LSTC-ED®) technique. If the improvement in erectile function was still considered insufficient (less than an IIEF-5 score of 22–25) at 2 months after the start of LI-LiESWT, penile rehabilitation was supplemented by pharmacological penile rehabilitation. The final effect of treatment was evaluated after 12 months. The main outcome measure was changes in the five-item International Index of Erectile Function (IIEF-5) score. ***Results:*** Between September 2019 and September 2020, a total of 40 patients were included in the study and randomly divided into 2 groups: treatment group and sham group. Eight patients were excluded from the study and were not evaluated due to other conditions which required additional treatment (COVID-19 disease, postoperative incontinence, urethral stricture, and ischemic stroke). Thirty-two patients were included in the final analysis: 16 in the control group and 16 in the intervention group. At 6 months from the end of treatment, patients in both the treatment and the sham group achieved physiological IIEF-5

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values, and the beneficial effect persisted for 12 months after the end of treatment. ***Conclusions:*** LI-LiESWT using the LSTC-ED® technique is a suitable and safe method for penile rehabilitation in patients with ED after bilateral NS RP, not only because of the vasculogenic effect of LI-LiESWT but also because of its neuroprotective and/or regenerative effects.

Introduction

A number of randomized controlled trials have shown that low-intensity extracorporeal shockwave therapy (LiESWT) can improve erectile function. Nevertheless, the efficacy of LiESWT in patients who develop erectile dysfunction (ED) after radical prostatectomy (RP) remains unclear due to the exclusion of these patients from almost all clinical trials. To date, only a few clinical trials have been carried out which investigate the effect of treatment with LiESWT after radical pelvic surgery. Frey's study stated that LiESWT may improve erectile function after bilateral nerve-sparing (NS) RP, and Zewin's study which included 152 patients after bilateral NS-RCP comes to a conclusion that 16% more patients in the LiESWT group had recovery of potency as compared to the control group [1–3]. Based on the conclusions of these studies, further clinical trials in patients with ED after NS RP are recommended. The standard primary research target in clinical trials of LiESWT focuses on the vasculogenic effect. It has been suggested that, in addition to its vasculogenic effect, LiESWT may also have neuroprotective and/or regenerative effects related to the expression of neuropathic factors and the reduction of free radicals. Both of these factors could be beneficial for patients who have had radical pelvic surgery with varying levels of injury to neurovascular bundles (NVBs), which can occur even with NS surgery [4, 5]. Currently, the widespread use of prostate-specific antigen checks has led to younger men being diagnosed with prostate cancer at an earlier stage. These patients are more likely to have longer life expectancies after RP and may suffer more from the loss of their sexual function. Although some of these patients may improve, 20–80% will never recover their preoperative sexual function status. The aim of this study was to investigate the effect of linear low-intensity extracorporeal shockwave therapy (LI-LiESWT) as a method for penile rehabilitation and to evaluate the effect of phosphodiesterase-5 inhibitors (PDE5is) or prostaglandin E1 combined with LI-LiESWT as an additional (or supportive) treatment option.

Methods

Between September 2019 and September 2020, 40 patients were enrolled in the study and randomly divided into 2 groups: treatment group and sham group. There was no difference in age, surgical techniques used, Gleason score, frequency of vascular comorbidities, testosterone levels, or incontinence between groups (6.2 ± 1.9 vs. 5.8 ± 1.7, $p = 0.590$). Initial IIEF-5 scores for the two groups were 5.4 ± 2.1 versus 5.9 ± 2.4 ($p = 0.515$), which equates to severe ED. Over the course of the study, 8 patients had to be excluded and were not evaluated due to other conditions requiring additional treatment (COVID-19 disease, postoperative incontinence, urethral stricture, and stroke). Thirty-two patients were included in the final analysis: 16 in the control group and 16 in the intervention group.

Inclusion criteria for the study were

- Three to eighteen months post-NS RP (median 7 months)
- Rigidity score ≤2 during PDE5i therapy
- In a stable heterosexual relationship for more than 6 months
- Patients were informed that the study protocol does not permit any PDE5i treatment until week 12 and consented to this
- No evidence of hypogonadism or other endocrinological diseases such as hyperprolactinemia or hypothyroidism

Exclusion criteria were

- Previous surgery or radiotherapy of the pelvic region
- Penile anatomical abnormalities
- Clinically significant chronic hematological disease
- Anti-androgens, oral or injectable androgens
- Cardiovascular conditions that prevent sexual activity

This was our first experience of administering LI-LiESWT treatment to patients with oncological pelvic disease (prostate cancer). We therefore took the decision to use lower doses (4,000 shocks in one session) when treating patients. In healthy individuals, we usually apply an average of 8,000 shocks during one session. LI-LiESWT was performed using a PiezoWave2 device (RichardWolf/ELvation GmbH). The penis is placed in a dedicated penile holder, stretched, and shockwaves are administered with a linear therapy source (applicator) using the linear shockwave tissue coverage (LSTC-ED®) technique which makes it possible to administer shockwaves homogenously to all of the erectile tissue. We applied 2,000 shocks with an energy flux density of 0.16 mJ/mm^2 and a focal shockwave depth of 10 mm at a frequency of 8 Hz to the penile shaft and 2,000 shocks with the same parameters over the crura of the penis. In the placebo group, a special therapy source 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. Four treatments were given over a 4-week period. Two months after the end of the treatment, selected patients were additionally allowed to take the PDE5i tadalafil 5 mg daily, and after 6 months, they were permitted topical or intracavernous prostaglandin E1. The final treatment outcomes were evaluated after 12 months. The main outcome measure was changes in the five-item International Index of Erectile Function (IIEF-5) scores. Any increase in the IIEF-5 score has been classified as a success as we consider the treatment of severe ED in patients after RP very difficult.

Table 1. Basic characteristics and comparison of both groups

	Treatment group (*N* = 16)	Sham group (*N* = 16)	*p* value
Age	58.3 (±4.9)	60 (±5)	0.515
Surgical technique, *n* (%)			
RRP	6 (37.5)	6 (37.5)	0.999
RALP	10 (62.5)	10 (62.5)	
Gleason score, *n* (%)			
3+3	3 (18.8)	3 (18.8)	
3+4	11 (68.8)	10 (62.5)	0.999
4+3	2 (12.5)	3 (18.8)	
TST	19.3 (±5.3)	17.1 (±5.2)	0.102
Comorbidity, *n* (%)			
Hypertension	9 (56.3)	10 (62.5)	0.999
HLP	8 (50.0)	5 (31.3)	0.473
DM	2 (12.5)	0 (0.0)	0.484
Obesity	3 (18.8)	4 (25.0)	0.999
CHD	2 (12.5)	0 (0.0)	0.484
Incontinence, *n* (%)			
Ano	5 (31.3)	9 (56.3)	0.285
Additional treatment, *n* (%)			
ICI	8 (50.0)	10 (62.5)	
PDE	5 (31.3)	3 (18.8)	0.887
Vitaros	3 (18.8)	3 (18.8)	

Categorical variables are described by absolute and relative frequencies; for continuous variables, the mean and standard deviation are given. The *p* value of Fisher's exact test (for categorical variables) and the *p* value of the Mann-Whitney test (for continuous variables) are given. A *p* value <0.05 indicates a statistically significant result.

Results

None of the patients complained of pain or any adverse effects following treatment with LI-LiESWT. Thirty-two patients completed the study protocol. There were no significant differences with regard to age, surgical techniques used, Gleason score, frequency of vascular comorbidities, testosterone levels, and time from surgery between the two groups (6.2 ± 1.9 vs. 5.8 ± 1.7, $p = 0.590$). The IIEF-5 baseline scores for both groups indicated severe ED (see Table 1). Categorical variables are given in absolute and relative frequencies; mean and standard deviation are given for continuous variables. The *p* values for categorical variables were calculated with Fisher's exact test, and the *p* values for continuous variables were calculated using the Mann-Whitney U test. A *p* value <0.05 indicates a statistically significant result. We started by evaluating the effect of LI-LiESWT treatment 2 months after the end of the treatment when, according to a previous randomized control trial, the early effect of LI-LiESWT could become apparent. The difference between the groups was statistically significant (IIEF-5 scores: 10.1 ± 3.4 vs. 7.6 ± 1.9, $p = 0.005$). However, the clinical improvement was not significant. Tadalafil 5 mg daily was therefore additionally given to both groups to potentiate the effect of penile rehabilitation. A statistically significant difference persisted between the two groups after 3 months of treatment (IIEF-5 scores: 15.6 ± 3.7 vs. 10.9 ± 3.3, $p = 0.001$). After 3 months, both groups received standard treatment for ED according to the EAU Guidelines, with PDE5i administered on demand or topical/intracavernous prostaglandin E1. By 6 months from the end of

Table 2. Development of IIEF-5 test values over time

IIEF-5 score	Treatment group (*N* = 16)	Sham group (*N* = 16)	*p* value
Basis score	5.4 (±2.1)	5.9 (±2.4)	0.515
2 months	10.1 (±3.4)	7.6 (±1.9)	0.005
3 months	15.6 (±3.7)	10.9 (±3.3)	0.001
6 months	21.3 (±2.3)	22.4 (±1.4)	0.138
12 months	22.5 (±1.2)	23.1 (±1.3)	0.184

The mean and standard deviation and the *p* value of the Mann-Whitney test are given.

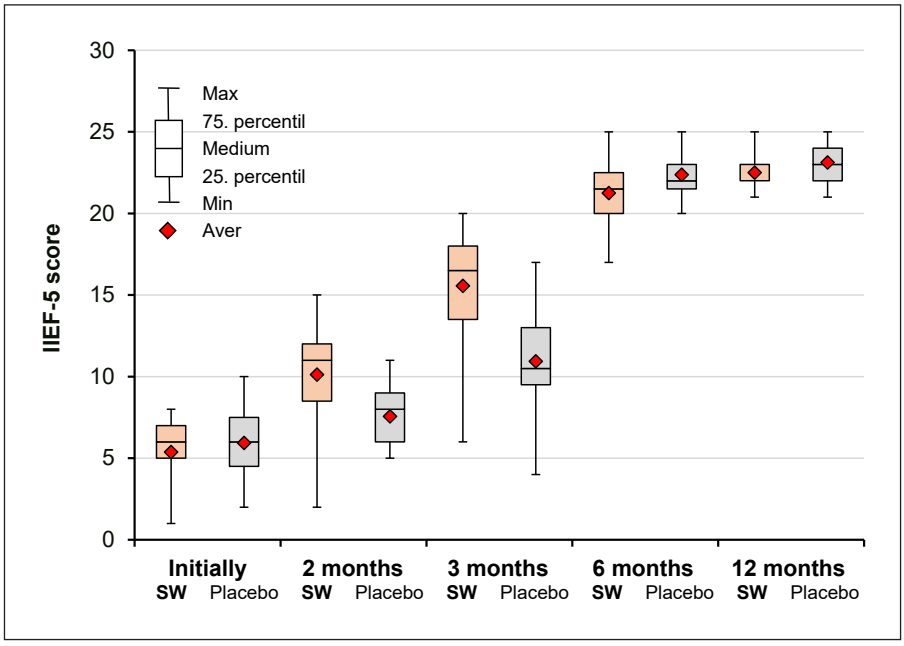

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Fig. 1. Graph: development of IIEF-5 test values over time.

LI-LiESWT treatment, patients in both the treatment and the sham group had achieved physiological IIEF-5 scores, and the beneficial effect of combination therapy persisted for 12 months after the end of treatment (see Table 2; Fig. 1).

Discussion

Although all urological surgeons use NS surgical techniques, the reported rate of ED at 12 months postoperatively still ranges from 54% to 90% [6]. Post-RP ED is mainly caused by temporary or permanent injury to NVBs as a result of intraoperative manipulations such as traction, compression, and coagulation [7]. Long-term lasting nerve degeneration and penile hypoxia lead to structural remodeling of cavernous tissues with smooth muscle apoptosis, fibrosis, and sinusoidal obstruction [8]. Thus, early intervention to improve cavernous oxygenation and promote tissue regeneration is very important. The main methods for penile rehabilitation include daily oral administration of PDE5i and topical administration or intracavernosal injection of prostaglandin E1 [9]. Early use of LI-LiESWT to promote penile rehabilitation could accelerate neural recovery and improve tissue regeneration, blood flow, and cavernosal oxygenation, preventing cavernous tissue remodeling. Regarding the neuroregenerative effect of the NVBs damaged during RP surgery – this hypothesis has been investigated by Yahata's et al. study [10] which confirmed that the ESWT-based VEGF expression stimulates not only endothelial cells to promote angiogenesis but also neural cells to induce neuroprotective effects. Low-energy ESWT also significantly promoted CD31 and α-SMA expressions in the injured spinal cords and also significantly reduces the TUNEL-positive cells in the injured spinal cords.

Conduction of our study, data collection, and statistical evaluation were negatively affected and delayed by the ongoing COVID-19 pandemic. However, we were finally able to collect and process all acquired data. In patients who received LI-LiESWT treatment, we found a significant increase in IIEF-5 scores compared to the control group at 2 months after the end of the treatment. The addition of tadalafil 5 mg daily emphasized the significant difference between groups, demonstrating the beneficial effect of LI-LiESWT for vascular penile rehabilitation in patients after RP. We did not expect LI-LiESWT monotherapy in patients with severe ED after RP to lead to complete restoration of erectile function. Using standard treatment methods according to the EAU Guidelines (oral treatment with PDE5i, topical and intracavernous application of PGE1) to augment the effect of our treatment, we achieved restoration of erectile function and therefore sexual life for all patients in both examined groups. Interestingly, 6 months after treatment, both groups achieved physiological IIEF-5 scores. It is unclear

to what extent this long-term positive effect can be attributed to LI-LiESWT or the addition of the standard treatment according to the EAU Guidelines. By applying an overall similar number of shockwaves, Oginski et al. [11] reported improved erectile function lasting more than 6 months in only 7% of patients. However, we assume our approach might have been too cautious and believe if more shocks are applied and more energy is delivered to the tissues, results might be better and of longer duration. Our goal, in addition to evaluate the effect of SW in penile rehabilitation, was to achieve ED recovery in all oncological patients after RP. The results show that during penile rehabilitation with the help of SW, better and faster protection of the cavernous tissues has been achieved in the group with effective treatment. However the study has some limitations. LiESWT treatment should probably be initiated much sooner after pelvic surgery as it has been reported that treatment initiated between 48 and 72 h after nerve injury is associated with positive results [12, 13]. The energy doses delivered to the target tissues in our study were lower than those we usually apply, and the number of patients treated in our study was not large. It is clear that the use of LiESWT to treat post-RP ED deserves further validation, and we believe that further clinical studies on the use of LiESWT for vascular penile rehabilitation in patients after RP will support our optimistic conclusions summarized below.

Conclusions

Despite some limitations of the study, we conclude that LI-LiESWT is a safe treatment option for penile rehabilitation, offering satisfactory results with no side effects. Based on our collected data, we can state that LiESWT using the LSTC-ED® technique can be used for penile rehabilitation in patients with ED after bilateral NS RP, not only because of its vasculogenic effect but also because of its neuroprotective and/or regenerative effects. We are also of the opinion that combining LiESWT with PDE5i or prostaglandin E1 can have a synergistic effect on cavernous tissue regeneration. Based on our results, further randomized controlled trials with higher energy doses, larger groups, and longer follow-up periods are justified. The effect of LI-LiESWT by itself versus its potential synergistic effect when combined with PDE5i or prostaglandin E1 also needs to be evaluated more precisely.

Statement of Ethics

The principles of the Helsinki Declaration (as revised in 2013) were followed during the study, and patient data confidentiality was ensured. The study was approved by the Ethics Committee of University Hospital Brno, Czech Republic, in accordance with legal regulations (23-120619/Ek). A written informed consent has been obtained from all participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Igor Motil developed the concept and design, drafted the manuscript, and also contributed to the acquisition of patients. Daniel Macik contributed to the acquisition of patients. Katerina Sramkova helped with data analysis and contributed to the acquisition of patients. Jiri Jarkovsky carried out randomization and statistical analysis and interpreted data, tables, and figures; helped to draft the manuscript; and revised it for intellectual content. Tatjana Sramkova carried out the concept and design of the study; acquired, analyzed, and interpreted data; helped to draft the manuscript; and revised it for intellectual content.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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