Original Article

Low-intensity extracorporeal shock wave therapy for patients with severe erectile dysfunction due to radical prostatectomy

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Background: Phosphodiesterase type 5 inhibitor (PDE5I) was proved to be effective for normal treatment, but the response rate of PDE5I is significantly low in patients with erectile dysfunction (ED) due to radical prostatectomy (RP). Low-intensity extracorporeal shockwave therapy (LI-ESWT) was proved to be useful as a safe modality to treat ED. My objective is to determine the efficacy of LI-ESWT for patients with severe ED due to RP.

Methods: This study was an open-label prospective pilot study. Between September 2012 and May 2014, 12 patients with severe ED due to RP were enrolled into this protocol. LI-ESWT comprised two treatment sessions per week for three weeks, which were repeated after a three-week no-treatment interval. LI-ESWT was applied to the penile shaft and crura at five different sites. Assessment of erectile and sexual function during LI-ESWT was determined using the international index of erectile function-erectile function domain (IIEF-EF) score, erection hardness score (EHS), nocturnal penile tumescence (NPT), flow-mediated vasodilation (FMD), and adverse events. We used FMD with the plethysmography technique for objective evaluation of the participant's penile hemodynamics and endothelial function (EnF).

Results: At the one-month follow up examination, the IIEF-EF scores did not change after LI-ESWT. However, the erectile function parameters significantly improved from 0.50±0.19 to 1.13±0.30 for EHS (P=0.0078) and from 0.36±0.14 to 1.06±0.36 for NPT (P=0.0156). Also, the FMD parameters significantly improved from 13.8±1.3 to 24.0±2.5 (P=0.0032). None of the patients reported adverse events.

Conclusions: This is the first study that assessed the efficacy of LI-ESWT for patients with severe ED due to RP. Based on our results, LI-ESWT appeared to have the potential to be an effective treatment option for severe ED patients.

Keywords: Low intensity extracorporeal shock wave therapy; erectile function; plethysmography; penis

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Introduction

Erectile dysfunction (ED) is one of the most common disorders of middle-aged men that considerably affect their quality of life (1). The current mainstream non-surgical treatment for ED is the use of the oral phosphodiesterase type 5 inhibitor (PDE5I). PDE5I was proved to be effective for normal treatment (2), but it is not yet a curative treatment modality for ED. The current study was carried out as an effort to shift the field of ED treatments away from on-demand palliative management. Many studies have

been published on improving the efficacy of PDE5I for patients who do not respond or respond poorly to PDE5I therapy (3,4). They have suggested some potential ways to improve the efficacy of PDE5I therapy but have not proposed any novel treatments.

The ideal goal for treating patients with ED should be rehabilitation or even recovery from pathological changes in the corpus cavernosum, enabling patients to regain spontaneous sexual activity with few adverse events (5). Low-intensity extracorporeal shockwave therapy (LI-ESWT) was proved to be a useful and safe modality for various medical disorders, such as neovascularization in myocardial ischemia and chronic diabetic foot ulcers (6,7). Recently, Vardi *et al*. have investigated the impact of LI-ESWT in the treatment of ED and found positive short-term clinical efficacy on men who responded to PDE5I (8), and clinical studies have shown that LI-ESWT has the potential to affect PDE5I non-responders with ED with few adverse events.

Currently, patients with localized prostate cancer are more likely to have long life expectancies after surgery. Erectile function was drastically decreased three months after radical prostatectomy (RP) but had slightly increased one year after RP (9). Erectile function may take up to four years to return even in younger patients with normal preoperative potency who have performed bilateral nerve sparing (NS)-RP (10-12); however, 20–80% of these patients may never return to normal erectile function (13). The advent of innovative PDE5I ED treatment has led to an average success rate of 60–70% in the general ED population (14). Nevertheless, these rates are significantly low in ED patients due to RP (13).

If LI-ESWT could be proved to be effective for these more severe ED cases following RP, such a unique modality could expand our urological treatment equipment in the management of severe ED. Against this background, we performed this study to evaluate the efficacy of LI-ESWT for patients with severe ED due to RP.

Methods

This study was an open-label prospective pilot study approved by the Hiroshima University Hospital institutional review board. Each participant gave his written informed consent before entering this study. Between September 2012 and May 2014, 12 patients with severe ED due to RP were enrolled into this protocol. We excluded men with (I) an unstable medical or psychiatric condition; (II) a previous history of neurological pathology; and (III) a previous history of PDE5I administration.

We performed the LI-ESWT protocol that was similar to the protocol reported by Vardi *et al*. (15). During each session, a special probe delivered LI-ESWT, and it was attached to a compact electrohydraulic unit with a focused shockwave instrument (Omnispec ED1000; Medispec, Germantown, MD, USA). At first, we stretched the penis manually, and shockwaves were delivered to five sites: the distal, mid, and proximal penile shaft and the bilateral crura. The duration of each LI-ESWT session was approximately 20 minutes, and each session consisted 300 shocks per treatment point (1,500 per session) at a frequency of 120/min and an energy density of 0.09 mJ/mm^2. We complete this procedure without local or systemic analgesia in all cases.

The study had a screening phase: 9-week LI-ESWT applied to the patient's genital area and a 4-week evaluation. At screening, demographic data were obtained from each participant. The assessment of erectile and sexual function during LI-ESWT was determined using the international index of erectile function-erectile function domain (IIEF-EF) score, erection hardness score (EHS), nocturnal penile tumescence (NPT), flow-mediated vasodilation (FMD), and adverse events.

We used FMD with the plethysmography technique for objective evaluation of the participant's penile hemodynamics and endothelial function (EnF). The penis was stabilized throughout the entire study using an ad hoc device developed especially for this purpose. A special sphygmomanometer cuff (DP 2.5 disposable penile cuff, D. E. Hokanson, Inc.) located at the penile base was inflated to a pressure of 50 mmHg for 7 seconds to induce venous filling. A mercury-filled Silastic strain gauge (D. E. Hokanson, Inc.) was specially ordered in various circumferences (from 6.5 to 8.5 cm to fit the average penis) and was placed at least 1 to 2 cm above the distal edge of the penile cuff. Deflation was then allowed for 8 seconds. Postischemic penile blood flow was then recorded immediately after deflation until a return to baseline flow was observed.

The primary outcome measurement was the 13-week change from baseline for IIEF-EF after one course of LI-ESWT. The secondary outcome measures included the interval change of NPT, EHS, and FMD as well as any adverse events from LI-ESWT.

Results

Table 1 summarizes the details of baseline patient

Table 1 Baseline patient characteristics

Characteristics	n, $\bar{x}$	%
Total, n	12	
Age, yr, mean (range)	62.1	53–72
BMI, kg/m^2, mean (range)	23.9	19.3–29.0
Postoperative month, mean (range)	10.8	3–48
Radical prostatectomy, n (%)		
RALP	8	66.7
LRP	3	25.0
RPP	1	8.3
Nerve sparing, n (%)		
Yes	5	41.7
No	7	58.3
Risk factors, n (%)		
Hyperlipidemia	3	25.0
Hypertension	2	16.7
Diabetes mellitus	1	8.3

BMI, body mass index; RALP, robot-assisted laparoscopic radical prostatectomy; LRP, laparoscopic radical prostatectomy; RPP, radical perineal prostatectomy.

characteristics. At pre-treatment, IIEF-EF is not more than 10, EHS is not more than 2, and NPT is not more than 2 in all patients, that is, this cohort consists of the patients with very severe ED. *Table 2* shows baseline patient characteristics classified by NS; there was no significant difference between NS and non-NS groups.

At the one-month follow up examination, the IIEF-EF scores did not change after LI-ESWT. However, the erectile function parameters significantly improved from 0.50±0.19 to 1.13±0.30 in EHS (P=0.0078) and from 0.36±0.14 to 1.06±0.36 in NPT (P=0.0156). Also, the pre- and post-treatment FMD parameters significantly improved from 13.8±1.3 to 24.0±2.5 (P=0.0032) (*Figure 1*). This result showed that the EnF was improved by the LI-ESWT; nevertheless the cavernous nerve was damaged severely by RP.

We evaluated the difference in erectile function between the NS and non-NS groups. At the one-month follow up examination, the IIEF-EF scores in the NS group slightly increased by 1.40 points while the scores in the non-NS group slightly increased by 0.57 points, so there was no significant difference between both groups (P=0.6772). However, EHS and NPT increased by 0.90 and 1.22 in the NS group while these scores increased by 0.42 and 0.33 in the non-NS group. These scores were much improved in the NS group compared to those of the non-NS group, but

Table 2 Baseline patient characteristics classified by nerve sparing

Characteristics	Nerve sparing	Non-nerve sparing	P value
Total, n	5	7	
Age, yr, mean [range]	61.8 [53–72]	62.3 [58–68]	0.8764
BMI, kg/m^2, mean (range)	23.1 (19.3–29.0)	24.5 (20.8–28.1)	0.4947
Postoperative month, mean [range]	4.2 [3–6]	15.6 [3–48]	0.1266
Radical prostatectomy, n			
RALP	5	3	
LRP	0	3	
RPP	0	1	
Nerve sparing, n			
Bilateral	2		
Unilateral	3		

BMI, body mass index; RALP, robot-assisted laparoscopic radical prostatectomy; LRP, laparoscopic radical prostatectomy; RPP, radical perineal prostatectomy.

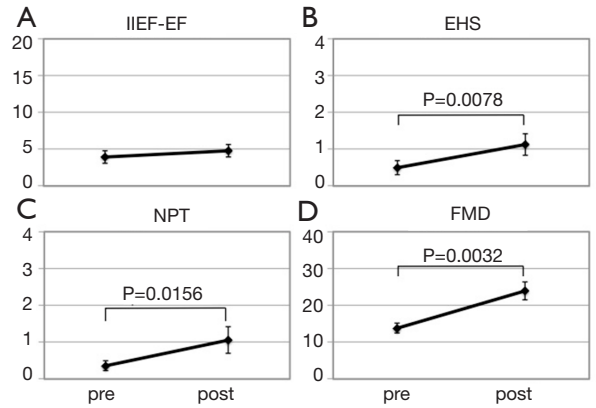

Figure 1 Changes in parameters before and 1 month after low intensity extracorporeal shockwave therapy. (A) IIEF-EF; (B) EHS; (C) NPT; (D) FMD. IIEF-EF, international index of erectile function-erectile function; EHS, erection hardness score; NPT, nocturnal penile tumescence; FMD, flow-mediated vasodilation.

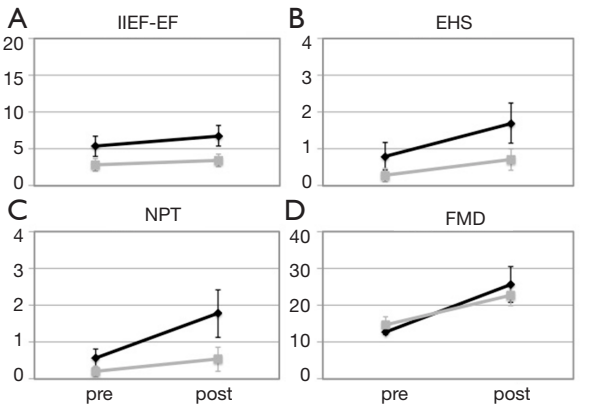

Figure 2 Changes in parameters before and 1 month after low intensity extracorporeal shockwave therapy classified by nerve sparing. Black is nerve sparing; gray is non-nerve sparing group. (A) IIEF-EF; (B) EHS; (C) NPT; (D) FMD. IIEF-EF, international index of erectile function-erectile function; EHS, erection hardness score; NPT, nocturnal penile tumescence; FMD, flow-mediated vasodilation.

there were no significant differences in EHS (P=0.1667) and NPT (P=0.1955) between both groups. FMD improved by 13.0 in the NS group and 8.2 in the non-NS group, so there was no significant difference between both groups (P=0.4424) (*Figure 2*). This result showed that the EnF was improved by the LI-ESWT in the NS group; however, there was no significant difference in the parameters of sexual function between both groups.

None of the patients reported any pain or adverse events such as ecchymoses or hematuria during or after the trial due to the LI-ESWT.

Discussion

The first application of high intensity shockwaves was by Chaussy *et al*. (16) in Germany in 1980. This was called extracorporeal shockwave lithotripsy and was used to treat renal calculi without open surgery. These LI-ESWT applications in the medical field date back to the late 1990s. Shockwaves carry energy; when these waves are targeted and focused, they interact with the targeted deep tissues causing mechanical stress and microtrauma. This was a medical revolution, and this technology was subsequently used to treat pancreatic stones, gall stones, and even bone non-union and pseudarthrosis (17-21).

In vitro and animal experiments have indicated angiogenesis-growth factors were stimulated after LI-ESWT. Nishida *et al*. (6) reported on the effectiveness of LI-ESWT for the treatment of cardiovascular disease because it has been shown to promote neovascularization by upregulating the expression of related molecules, including VEGF. When LI-ESWT is applied to an organ, the relatively weak yet focused shockwaves interact with the targeted deep tissues, and these shockwaves make mechanical stress and microtrauma, also known as shear stress (22). This shear force causes the release of angiogenic factors, inducing neovascularization of the affected tissues and enhancing of the blood flow. These findings have reached to the assumption if LI-ESWT applied to the corpora cavernosa, shockwave therapy could improve blood flow and EnF by stimulating angiogenesis in the penile tissue (5).

It was reported by Gruenwald *et al*. (23) LI-ESWT had potential of a treatment option for patients with severe ED. After treatment, the mean IIEF-EF scores increased, and a significant improvement in penile hemodynamics was detected. Severe adverse events were not reported during this study. As our data shows, LI-ESWT might be appropriate for a subgroup of patients with ED, particularly those with severe ED. Often the severe ED patients or poor responders to PDE5I were referred to urologists for further management. It was indicated unique modality of LI-ESWT could develop novel treatment options in the management of severe ED patients.

A number of approaches have been used in penile rehabilitation, all of which have drawbacks and are controversial in terms of success in preserving sexual function. The primary methods are (I) regular dosing with PDE5I; (II) intracavernosal injection of PGE1; and (III) vacuum erection devices (24). A recent review of all studies related to penile rehabilitation reached the conclusion that theoretical considerations warrant early implementation of penile rehabilitation. These findings have led clinical evidence the use of our protocols support penile rehabilitation (25). However, there has not been easily administered effective treatment of ED following RP (24). The potential of LI-ESWT to both induce erections and increase blood flow into the penis could make it a useful therapeutic for penile rehabilitation.

IIEF-EF is a good measurement to evaluate sexual function. However, there are very few Japanese patients that can have sexual intercourse after radical prostatectomy; therefore, the IIEF-EF score is necessarily very low, and this score does not reflect erectile function correctly. Also, we need an objective and physiological measurement to precisely evaluate erectile function. FMD is a well-recognized technique for assessing peripheral vascular EnF (26,27).

In this study, for the first time we introduce clinical measurement of penile EnF using strain gauge plethysmography for objective evaluation of LI-ESWT. However, our method provides a total organ flow assessment of dorsal and cavernous arterial flows. Another advantage of our method is it is not operator dependent and the results are obtainable in a flaccid state, allowing us to avoid invasive pharmacological agents or sexual stimulation. This methodology may also be feasible in the erect state, which may provide further information regarding cavernosal EnF during erection. We would like to emphasize that implementing our proposed methodology in the erect state is tempting since all our ED diagnostic tests are performed using invasive pharmacological interventions. During full penile arterial flow, decreases in the erect state and its occlusion would not provide enough shear stress after the ischemic cessation. Nevertheless, the feasibility and information obtained by performing this method in the flaccid and erect states should be tested.

There were some limitations to this study. The small sample size (12 patients) makes it impossible to state any general conclusions. No studies have been performed using LI-ESWT for severe ED patients due to RP. A more extensive randomized comparison between severe ED patients with and without RP using tools designed to detect differences in erectile function so that we can prevent selection bias should be performed. Moreover, we do not have any data about combined PDE5I and LI-ESWT therapy, so we should evaluate combined therapy for patients with severe ED due to RP in the near future. Despite these weaknesses, substantial changes in the EHS, NPT, and FMD values were achieved in this group of patients with severe ED due to RP.

This is the first study in which LI-ESWT has been shown to have a beneficial effect on erectile function in patients with severe ED due to RP. While we do not know the precise mechanism of the LI-ESWT action, we objectively measured EnF using penile strain gauge plethysmography, and this result led us to presume this treatment modality works by improving penile hemodynamics even in the patients with severe ED patients due to RP. Our study suggests LI-ESWT could be used as treatment option for severe ED patients even if the patients' ED was due to RP. There is also a need for studies to define the optimal treatment protocol to be able to offer the best results when using LI-ESWT for severe ED patients.

Conclusions

These preliminary results of LI-ESWT in a group of patients with severe ED due to RP suggest that the intervention of LI-ESWT can consistently improve erectile function. This treatment approach was effective because we evaluated erectile function using penile strain gauge plethysmography and these results indicate EnF was improved by LI-ESWT. The short-term results are promising, but we need further evaluation with large cohorts and a longer follow-up. This is the first study that assessed the efficacy of LI-ESWT for patients with severe ED due to RP. Based on our results, LI-ESWT appeared to have the potential to be an effective treatment option for severe ED patients.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Hiroshima

University Hospital institutional review board (No. 40052) and written informed consent was obtained from all patients.

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