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REVIEW

Low-intensity extracorporeal shock wave therapy for erectile dysfunction after radical prostatectomy: a review of preclinical studies

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Abstract
Low-intensity extracorporeal shock wave therapy (LI-ESWT) is a novel treatment for erectile dysfunction (ED). Its ability to improve erectile function has been shown in patients with vasculogenic ED by many randomized-controlled trials against sham procedures. However, the role of LI-ESWT in ED caused by radical prostatectomy (RP) is still questionable because this type of ED was excluded from nearly all clinical studies; it has been investigated in only a few small single-arm trials. This review summarizes preclinical studies on mechanisms of action of LI-ESWT for ED and neurological diseases to explore the potential of this treatment for nerve-impaired ED after RP.

Introduction

Erectile dysfunction (ED) caused by radical prostatectomy (RP) is a challenging problem. Although minimally invasive surgical techniques have been used (such as nerve-sparing techniques), 12- and 24-month potency rates reportedly ranged from 54 to 90% and from 63 to 94%, respectively [1]. Even more unfortunately, less than 50% of patients returned to baseline erectile function (EF), even if they were taking phosphodiesterase type-5 inhibitors (PDE5Is) [2].

Low-intensity extracorporeal shock wave therapy (LI-ESWT) is an emerging approach for ED with a promising therapeutic effect. An up-to-date meta-analysis of seven randomized-controlled trials (RCTs) revealed that it significantly ameliorated EF, as shown by increased International Index of Erectile Function (IIEF) scores (mean difference: 2.00; 95% confidence interval (CI), 0.99–3.00; $P < 0.0001$) and erection hardness scores (risk difference: 0.16; 95% CI, 0.04–0.29; $P = 0.01$) [3]. Apart from few small single-arm trials, current RCTs mainly addressed vasculogenic ED, while excluding patients suffering from post-radical prostatectomy (post-RP) ED. Therefore, the applicability of LI-ESWT in post-RP ED is questionable at this point. However, preclinical studies on the effects of LI-ESWT on neurological diseases and ED can help explore its clinical potential for nerve-impaired ED.

Pathology of post-RP ED

Post-RP ED is predominantly attributed to injured neurovascular bundles (NVBs) that lie alongside the prostate and are responsible for initiating and maintaining the erectile state. Older RP procedures damaged the NVBs completely and permanently, whereas neuropraxia is the common cause of ED after bilateral nerve-sparing RP, as a result of such surgical manipulations as coagulation, traction, and compression [4]. The temporary cavernous nerve injury induces nervous Wallerian degeneration, and thus results in the denervation of the corpora cavernosa and consequent loss of nocturnal erection. Subsequently, long-term penile hypoxia causes penile structural remodeling with smooth muscle apoptosis, fibrosis, and veno-occlusive dysfunction [5]. Therefore, acceleration of nerve recovery could prevent corpora cavernosa from remodeling. In general, human

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peripheral nervous regeneration and reinnervation of target organs after Wallerian degeneration progress slowly(~1 mm/day) [6]; partial EF recovery occurs by 3 months after surgery and most usually occurs by about 18 months [7].

The present clinical status of LI-ESWT for post-RP ED

Vasculogenic disorders are the main study object of clinical LI-ESWT for ED; post-RP ED is rarely referred to in the literature. Current evidence that robustly supports the application of LI-ESWT for ED secondary to RP is therefore lacking.

In a pilot study by Frey et al. [8] that included 16 patients, each with at least 1 year's history of bilateral nerve-sparing RP (NSRP)-associated ED, subjects received two LI-ESWT sessions every other week for 6 weeks. Each session included 1000 shock waves with energy densities of 20, 15, and 12 mJ/mm^2, applied to the root of the penis, to the shaft, and at a few millimeters proximal to the glans, respectively, for a total of 3000 shock waves and frequency of 5 Hz. This study concluded that LI-ESWT might ameliorate EF, with the median improvement to five-item IIEF scores of 3.5 (range: −1 to 8; $P = 0.0049$) and 1 (range: −3 to 14; $P = 0.046$), at 1 month and 1 year after treatment, respectively. The use of erectogenic aids was not prohibited in the study and the combination of LI-ESWT and medicated urethral system for erections (MUSE) and PDE5Is appeared somewhat beneficial for recovery of EF. To our knowledge, it was the only published study to focus specifically on LI-ESWT for post-RP ED.

In a conference abstract, Inoue et al. suggested that ED secondary to non-nerve-sparing (non-NS) laparoscopic RP probably did not benefit from LI-ESWT [9]. Chung et al. briefly mentioned in their paper that current data only supported the use of LI-ESWT in vasculogenic ED [10], and that use of LI-ESWT led to greater improvement in EF from vasculogenic-caused ED than from post-RP ED ($P < 0.05$). However, neither of the two papers gave more detail on this subject.

To further investigate whether LI-ESWT is indicated for post-RP ED, we searched ClinicalTrials.gov and identified three relevant registered clinical trials (Identifier: NCT02746094, NCT01317680, and NCT02422277), but none of them had completed. Before adopting LI-ESWT into routine clinical management of post-RP ED, the results of these rigorously designed randomized trials are needed urgently.

Mechanisms of LI-ESWT for rehabilitation of nerve injury in neurological diseases

The capacity of LI-ESWT to improve functional outcome after nerve injury has been observed in neurological diseases. Its neuroprotective and/or regenerative effects are considered to be related to local angiogenesis, modulated inflammation, continuous expression of neurotrophic factors, and reduction of free radicals. However, the exact mechanisms are still under investigation.

Lobenwein et al. found that LI-ESWT improved limb strength, motor forelimb impairment, motor coordination and balance deficits, and motor activity and movements in a mouse after ischemic spinal cord injury [11]. The intervention was shown to protect against neuronal degeneration by macrophage-modulated inflammation via Toll-like receptor (TLR)-3 stimulation and subsequent TLR4 downregulation; it also induced angiogenesis, which facilitated axonal regeneration after spinal cord injury (SCI) to provide nerve fiber regeneration, synaptic reconstruction, tissue repair, and functional recovery with nutrients by blood vessels [12].

Vascular endothelial growth factor (VEGF) is an angiogenic and neurogenic factor, and might have an important role in neural recovery by stimulating endothelial cells to promote neovascularization and neural cells to induce neuroprotective effects [13]. Yahata et al. demonstrated that LI-ESWT suppressed cell death and axonal damage by inducing VEGF protein expression in various neural cells (neurons, astrocytes, and oligodendrocytes) and enhancing angiogenesis in impaired neural tissue; it consequently improved locomotor and sensory functions after SCI in rat model [14].

In a study using the leptin-deficient (ob/ob) mouse model of peripheral neuropathy in type 2 diabetes mellitus (DM), Chen et al. found LI-ESWT effectively prevented diabetic neuropathy through suppression of inflammation and oxidative stress, and endothelium-enhancing effect [15]. Moreover, the continued expression of neurotrophic factors, such as neurotrophin-3, stimulated by shock wave treatment, likely aid regeneration and redistribution of neurons after crushed sciatic nerve injury [16].

A study by Hausner et al. that investigated the effect of the early application of LI-ESWT on nerve regeneration found nerve conduction velocity and amplitude increased more, and faster, in the group that received LI-ESWT immediately after sciatic nerve injury than in the control group without the treatment [17]. Therefore, in the initial injury phase, the positive effects of the therapy on regeneration and redistribution of neurons after peripheral nerve impairment could be enhanced via exogenous support stimulation.

Mechanisms of LI-ESWT for diabetic ED

Mechanisms for the effects of LI-ESWT on ED were mainly studied in diabetic rats, and a ED rat model of type I DM

Table 1 Mechanisms of LI-ESWT for improving EF in rat model of streptozotocin-induced diabetes mellitus

Penile change at the level of tissue and cell after LI-ESWT	Relative detected markers			
Angiogenesis [18–21]	vWF ↑ [18, 20]	RECA-1 ↑ [18, 19]	VEGF ↑ [18, 20]	CD31 ↑ [21]
Nerve regeneration [18–20]	$nNOS^+$ ↑ [18–20]	–	–	–
Progenitor cell recruitment [19, 21, 25]	The number of EdU^+ cells ↑ [19, 25]	SDF-1 ↑ [21]	Circulating CD31/CD34-positive EPC numbers ↑ [21]	Local transplanted CM-DiO-labeled BMSC ↑ [21]
Endothelial functional improvement [18, 21]	eNOS ↑ [18, 21]	–	–	–
Alleviation of fibrosis [18, 20]	Collagen I/collagen III ratio examined by picrosirius red staining ↑ [18]	Hart elastin ↑ [18, 20]	TGF-β1 ↓ [18]	CTGF ↓ [18]
Restoration of smooth muscle [18–21]	αSMA ↑ [18, 20, 21]	Smooth muscle/collagen ratio examined by Masson ↑ [18, 20, 21]	SM was stained by Alexa-488-conjugated phalloidin ↑ [19]	–
Improvement of microenviroment [20]	RAGE↓ [20]	–	–	–

BMSC bone marrow mesenchymal stem cells, *CD31* platelet endothelial cell adhesion molecule-1, *CTGF* connective tissue growth factor, *DAPI* 40,6-diamidino-2-phenylindole (dye for nuclei), *EdU* 5-ethynyl-20-deoxyuridine, *eNOS* endothelial nitric oxide synthase, *nNOS* neuronal nitric oxide synthase, *RAGE* receptor for advanced glycation end products, *RECA-1* rat endothelial cell antigen-1, *SDF-1* chemokine stromal-derived factor 1, *SM* smooth muscle, *αSMA* α-smooth muscle actin, *TGF-β1* transforming growth factor-β1, *vWF* von Willebrand factor, *VEGF* vascular endothelial growth factor, ↑ upregulation, ↓ downregulation

(T1DM) induced by streptozotocin was used most frequently in the available studies. LI-ESWT reversed penile fibrosis [18], protected neuronal nitric oxide synthase (nNOS)-positive nerves and endothelial and smooth muscle contents, and also promoted angiogenesis, thus improving EF in the T1DM models [18–21]. Functional and histological changes were considered to be related to recruitment of mesenchymal stem cells (MSCs) [19]. Additionally, expression of endothelial nitric oxide synthase (eNOS) was also elevated after LI-ESWT [18, 21]. These details are summarized in Table 1.

Recently, a standardized preclinical LI-ESWT procedure for ED was developed to simulate the treatment performed in ED patients with a device suitable for rat size and anatomy, to thus deliver the exact desired energy. A study of Goto-Kakizaki rats, a validated model of type II DM, using the standardized procedure, showed through functional analysis that a NO/cGMP signaling pathway was not associated with LI-ESWT-caused EF improvement [22]. Assaly-Kaddoum suggested that increased penile blood flow after LI-ESWT might be associated with pro-angiogenesis effect through a cNO/cGMP-independent mechanism [22].

Mechanisms of LI-ESWT for post-RP ED

In preclinical experiments, post-RP ED rat models have been characterized by bilateral cavernous nerve crush injury. Recently, Li et al. developed a new ED rat model of pelvic neurovascular injury by damaging bilateral cavernous nerve and internal pudendal bundle, which closely mimics human surgical and traumatic pelvic injury and a long duration of ED [23]. No matter which model is used, LI-ESWT was observed to improve nerve-impaired EF significantly compared with sham procedures. In the two rat models treated with LI-ESWT, angiogenesis in dorsal neurovascular region, endothelium regeneration in penile sinusoid [23], recruitment of progenitor cells or cells with stem properties in the cavernosal tissues [23], and attenuation of cellular apoptosis and maintenance of penile smooth muscle [24] were shown. These therapeutic tissue changes were similar to those in the diabetic ED rat model treated with LI-ESWT (Fig. 1 and Table 2). However, results reported in the current literature about LI-ESWT for promoting cavernous nerve recovery remain controversial.

Li et al. [23] found that LI-ESWT could stimulate recovery of the dorsal nerve examined with immunofluorescence (IF) staining of neurofilament, and regeneration of $nNOS^+$ nerves (containing cavernous nerve and dorsal penile nerve) from the major pelvic ganglion to the penis examined with IF staining of nNOS. Conversely, Jeon et al. [24] suggested that low-energy shock wave treatment

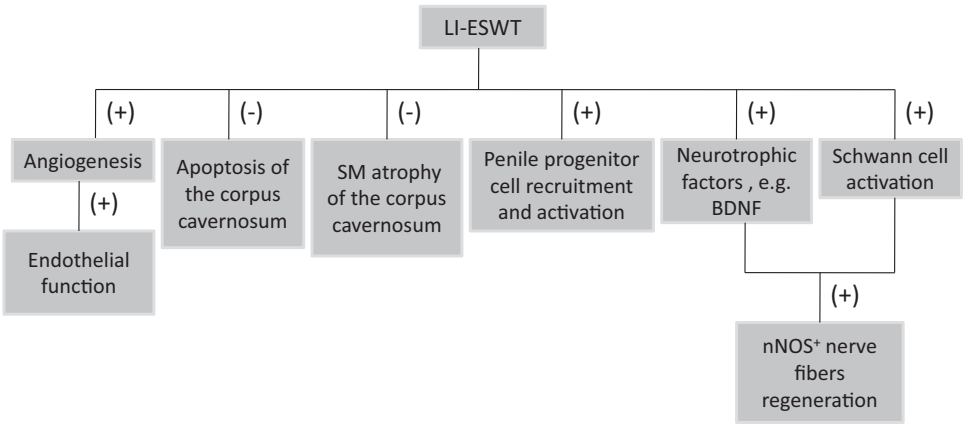

Fig. 1 The effects of LI-ESWT on penile tissue after radical prostatectomy in rat model of erectile dysfunction. BDNF brain-derived neurotrophic factor, nNOS neuronal nitric oxide synthase, SM smooth muscle, (+) improvement effect, (−) attenuation effect

applied to the penis could not promote cavernous nerve recovery, and showed no change of neuron-specific β-III tubulin expression, although nNOS content was elevated in the dorsal penile nerve. Although the neurogenic effect of LI-ESWT on the cavernous nerve is controversial; the elevated expression of nNOS has been demonstrated consistently in these experiments. In Goto-Kakizaki rats, the NO/cGMP pathway was proved not to be associated with LI-ESWT for improving EF [22]; however, the role of the elevated nNOS in nerve-impaired ED must be further explored in the post-RP ED rat model. Even so, some beneficial factors of neuronal recovery induced by the therapy were observed in penile tissue.

Schwann cell activation plays an important role in peripheral nerve regeneration after injury. Compared with the sham group, more mature Schwann cells were seen in damaged dorsal nerves in the LI-ESWT group [23]. However, the mechanism of promoting Schwann cell proliferation is still unclear. LI-ESWT could induce activation of ERK/MAPK and p75 to induce Schwann cells dedifferentiation and proliferation in the damaged nerves [23]. Erk1/2 phosphorylation as an activation signaling pathway mediator plays a key role in cell proliferation induction and LI-ESWT increased the level of p-Erk1/2 significantly [23, 25].

Neurotrophic factors enhance nerve regeneration processes and functional recovery in animal models. LI-ESWT could release a range of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which plays a central role in neuronal development, maturation, and survival after injury. LI-ESWT may stimulate the expression of BDNF in penile tissue through activation of PERK/ATF4 signaling pathway [26]. Schwann cell BDNF expression was also increased after LI-ESWT [26].

Pluripotent cells, such as stem cells and progenitor cells, have differentiation and/or paracrine-expressing capabilities; and stem cell-based treatments for post-RP ED are under investigation [27], In addition to preventing apoptosis of the cavernosal smooth muscle and endothelial cells, human adipose-derived stem cells injected around the injured cavernous nerve improved injured cavernous nerve recovery [24]. Recently, an animal study demonstrated that LI-ESWT could activate penile stem or progenitor cells, most of which were located within subtunical spaces, with the remainder in the para-sinusoid area and penile nerve and blood vessels [25], possibly induced by high expression of a chemoattractant, stromal-derived factor 1 [23]. LI-ESWT has been suggested to promote nerve recovery though the recruitment of penile stem or progenitor cells in nerve-impaired ED.

Additionally, elevated expression of VEGF [24, 28] and local angiogenesis, induced by LI-ESWT, are considered to be conducive to neuronal recovery.

Factors that influence LI-ESWT's effects in post-RP ED

Biological effects of LI-ESWT depend on energy flux density (EFD). In the field of ED treatment, animal experiments indicate that the energy level should be between 0.03 and 0.1 mJ/mm^2, because the limited shock waves induce regenerative effects without destruction to penile tissue. The aforementioned beneficial effects of the therapy are influenced by different EFDs; high energy (0.09 mJ/mm^2) for ED seemed to be more effective than low energy (0.06 mJ/mm^2) [23].

Shock waves are characterized by acoustic waves generating pressure impulses. Various currently available medical devices to deliver shock waves use three main mechanisms to produce shock waves: electrohydraulic, electromagnetic, and piezoelectric mechanism, which depend on a spark-gap source, piezoelectric crystals, and interactions between an electrical coil and a metal plate, respectively. Although devices designed according to these different principles produced shock waves with similar basic shapes, their physical parameters (e.g., peak pressure, EFD, focus size, and total energy) were different [29]. In

Table 2 Mechanisms of LI-ESWT for improving EF in rat model of pelvic nerve injury

Penile change at the level of tissue and cell after LI-ESWT	Relative detected markers				Cell cycle assay
Angiogenesis [23, 24]	Vascular SMA was stained by Alexa- 488-conjugated phalloidin ↑ [23]	vWF↑ [23]	VEGF ↑ [24]	–	–
Nerve regeneration [23, 24]	NF ↑ [23]	$nNOS^+$ ↑ [23, 24]	β-III tubulin → [24]	–	–
Progenitor cell recruitment [23]	The number of EdU^+ cells ↑ [23]	SDF-1↑ [23]	–	–	–
Activation of Schwann cells [23]	Nucleus was stained by DAPI ↑ [23]	S100 ↑ [23]	p75 ↑ [23]	p-Erk 1/2 ↑ [23]	A higher percent of cells entered the S phase and the G2/M [23]
Endothelial functional improvement [24]	eNOS ↑ [24]	cGMP ↑ [24]	–	–	–
Restoration of smooth muscle [24]	α-SMA ↑ [24]	Apoptosis of corpus cavernosum stained by TUNEL ↓ [24]	–	–	–

cGMP cyclic guanosine monophosphate, *DAPI* 40,6-diamidino-2-phenylindole (dye for nuclei), *eNOS* endothelial nitric oxide synthase, *EdU* 5-ethynyl-20-deoxyuridine, *nNOS* neuronal nitric oxide synthase, *NF* neurofilament, *p75* p75 neurotrophin receptor, *p-Erk* phosphorylated extracellular regulated protein kinases, *S100* a maturation gene, *SDF-1* chemokine stromal-derived factor 1, *SMA* smooth muscle actin, *TUNEL* terminal deoxynucleotidyl transferase dUTP nick end labeling assay, *vWF* von Willebrand factor, *VEGF* vascular endothelial growth factor, ↑ upregulation, ↓ downregulation, → no change

preclinical experiments, shock wave devices based on any of the three principles had positive effects on nerve-impaired ED [23, 24, 26] (Table 3). Notably, however, one device type needed a specialized protocol to produce maximal effect; thus, a shared protocol for all devices might not be suitable.

The start time of LI-ESWT for post-RP ED may also affect therapeutic effects. Depending on the pathological state of penile tissues after RP, early use of LI-ESWT should be aimed at promoting neuronal recovery, improving cavernosal oxygenation, and preventing penile remodeling, whereas late use, especially 2 months or more after surgery should be mainly aimed at reversing penile fibrotic remodeling [30]. In all available studies [23, 24, 26], start times were between 48 and 72 h after nerve injury and were supported with positive results. Preclinical outcomes from diabetic ED rat models, which showed the positive effects of LI-ESWT on chronic pathological remodeling of penis, may give us some hints; the effects and mechanisms of late use of LI-ESWT for post-RP ED need further study.

Treatment site is another factor that should be studied further. Post-RP ED is mainly characterized by pelvic neurovascular injury. Therefore, the pelvis seems to be a logical treatment site. Considering accompanying penile tissue changes, penis also should be a target. In the referred animal studies, shock waves were delivered to the pelvic region, except for the Korean group, who delivered them to the penis [24]. Considering the small size of the rat penis and its nearness to the pelvis, pelvic nerves and penile tissue could still be stimulated at the same time in these studies [23, 24, 26].

Extent of nerve injury is also a key influencer of LI-ESWT's therapeutic effects. The animal model used in the studies was developed by crushing pelvic nerves; mimicking the ED secondary to traditional RP with extensive dissection of neurovascular bundles is difficult, unless bilateral pelvic nerves of model were resected completely. Although we expect that ED secondary to non-NSRP would probably not benefit from LI-ESWT, an experiment is still needed to prove it.

LI-ESWT for post-RP ED in the future

The feasibility of LI-ESWT for post-RP ED needs to be further validated. More large-scale, well-designed RCTs with long follow-up periods are essential before LI-ESWT can be recommended to post-RP ED patients confidently. Many questions require further investigation, such as optimal protocol, energy density, numbers of pulses and sessions, and treatment duration, and even individualized strategies. To get robust basic research evidence, the role of LI-ESWT in post-RP ED should be evaluated using standardized preclinical procedure and animal models. In

Table 3 Post-radical prostatectomy erectile dysfunction-related low-intensity extracorporeal shock wave therapy studies in the field of preclinical study

Authors	Publication year	Animal model	Device	EFD, pulses, frequency	Protocol	Treatment site	Start time after surgery
Wang BH et al. [26]	2017	11-week-old rats BCNI rats	A electromagnetic unit with an unfocused shock wave source (LiteMed, Taipei, Taiwan)	0.06 mJ/mm^2, 500 pulses, 3 Hz	No detail	Pelvic region	48 h
Li HX et al. [23]	2016	12-week-old rats BCNI and IPBI rats	A electrohydraulic unit with a focused shock wave source (DermaGold, MTS Europe GmbH, Konstanz, Germany)	0.06 mJ/mm^2, 300 pulses, 3 Hz vs. 0.09 mJ/mm^2, 1000 pulses, 3 Hz	4 weeks without detail	Pelvic region	48 h
Jeon SH et al. [24]	2015	8-week-old rats BCNI rats	A Piezo Wave2 shock wave applicator (Richard Wolf GmbH, Knittlingen, Germany)	0.1 mJ/mm^2, 300 pulses, 2 Hz	3 times per week for 3 weeks	Penis	72 h

BCNI bilateral cavernous nerve injury, *IPBI* internal pudendal bundle injury

addition, the mechanisms of all factors that may affect LI-ESWT outcomes, such as physical parameters of shock wave, different devices, protocols, start time and region of the therapy, and treatment duration should be explored. Furthermore, mechanism of action should not only focus on protein expression, but also include functional analyses. The study of omics and bioinformatics in the field may provide further insight into the mechanism of action of LI-ESWT on penile tissue.

Conclusion

LI-ESWT can improve EF in post-RP ED rat models. Angiogenesis and prevention of penile tissue apoptosis induced by the therapy contributed to EF recovery to some extent. Although the ability of LI-ESWT to promote cavernous nerve regeneration lacks direct and consistent evidence, some pro-neurogenic changes, such as Schwann cell activation, release of neurotrophic factors, and penile stem or progenitor cell recruitment and activation were observed in penile tissue after LI-ESWT. The results of LI-ESWT for neurological diseases also indirectly support its promotion of nerve regeneration in post-RP ED. In brief, LI-ESWT is a potential treatment of post-RP ED, but many questions should be resolved before its widespread use.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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