World Journal of Urology
https://doi.org/10.1007/s00345-020-03373-y

ORIGINAL ARTICLE

Penile low intensity shock wave treatment for PDE5I refractory erectile dysfunction: a randomized double-blind sham-controlled clinical trial

Jose Vinay[1,2,3] · Daniel Moreno[1] · Osvaldo Rajmil[1] · Eduard Ruiz-Castañe[1] · Josvany Sanchez-Curbelo[1]

Received: 12 June 2020 / Accepted: 16 July 2020

Abstract

Purpose Over the last decade, penile low-intensity extracorporeal shockwave therapy (LI-ESWT) has emerged as a promising alternative for the treatment of erectile dysfunction (ED). The aim of this trial is to assess the effect of electromagnetic LI-ESWT on the erectile function of vascular phosphodiesterase type 5 inhibitor (PDE5I) refractory ED patients.

Methods Randomized, double-blind, sham-controlled study. 76 patients with vascular PDE5I-refractory ED completed the study. 40 men were treated with LI-ESWT (1 session/week for 4 weeks, 5000 shocks/session, 0.09 mJ/mm^2 energy density) and 36 were treated with a sham probe. Baseline and post-treatment (1, 3 and 6 months) evaluations were performed using validated erectile function questionnaires (IIEF-EF, EHS, SEP2, SEP3 and GAQ1). The groups were compared using Mann–Whitney–Wilcoxon and chi-squared tests, with results considered statistically significant at $p < 0.05$.

Results At the 3-month follow-up, median change in IIEF-EF score for active and sham groups was 3.5 (IQR 0–10) and −0.5 (IQR −11 to 1), respectively ($p < 0.05$). Six months after treatment, 52.5% of patients (21/40) in the active group and 27.8% of patients (10/36) in the sham group presented an EHS > 2 ($p < 0.05$). At the same evaluation, 40.0% (16/40) and 13.9% (5/36) of patients had positive answers to GAQ-1, in the treated and sham groups, respectively ($p < 0.05$). No adverse events were observed during the study.

Conclusion This study showed that penile electromagnetic shockwave therapy may improve erectile function, to a modest extent, on certain patients that do not respond to PDE5I; making it an alternative for vascular ED patients that reject more invasive therapies.

Keywords Erectile dysfunction · Low intensity extracorporeal shockwave therapy · Neo-angiogenesis · Nerve regeneration

Introduction

Approximately 52% of men over 40 years old experience erectile dysfunction (ED) and the prevalence of ED increases with age [1]. Several treatments are available, including oral phosphodiesterase type 5 inhibitors (PDE5I), vacuum devices, intraurethral and topical alprostadil, intra-cavernous injection therapy and penile implants [2].

✉ Jose Vinay
jose.vinay@gmail.com

1 Andrology Department, Fundació Puigvert/Universidad Autònoma de Barcelona, Carrer de Cartagena, 340-350, 08025 Barcelona, Spain

2 Urology Department, University of Chile Clinical Hospital, Santiago, Chile

3 Andrology Unit, Shady Grove Fertility, Santiago, Chile

There is a large number of disorders known to contribute to the development of ED, including diabetes, hypogonadism, metabolic syndrome, hypertension, ischemic heart disease, smoking, pelvic nerve injury, and local penile abnormalities [3]. The most prevalent ED causes can be attributed to vascular disorders, sharing multiple risk factors with cardiovascular disease (CVD). Endothelial dysfunction has been defined as one of the main components of both ED and CVD pathophysiology [4].

Traditional treatments carry risks of adverse events and complications, and most available treatments take the spontaneity out of sex [1]. Furthermore, these modalities are solely providing symptom relief and do not provide a permanent improvement by targeting underlying pathophysiological events [3].

Over the last decade, penile low-intensity extracorporeal shockwave therapy (LI-ESWT) has emerged as a promising option for the treatment of ED [5]. Originally used to

Published online: 21 July 2020

treat other conditions like bone fractures, musculoskeletal disorders, CVD and chronic wounds; LI-ESWT already has been used in ED protocols all over the world [6]. The exact mechanism of action of LI-ESWT is still not completely elucidated, but energy from the acoustic waves is hypothesized to activate cellular pathways that increase the expression of local growth factors, improving endothelial function, angiogenesis and potentially regenerating nerve fibers [1, 7].

There has been a low number of sham-controlled randomized trials, and only one of them has presented data regarding ED patients that do not respond to PDE5I therapy [3]. The current study aimed to assess the effect of LI-ESWT on vascular PDE5I-refractory ED patients in a sham-controlled manner.

Materials and methods

This is a prospective, randomized, double-blind, sham controlled study of 80 men with PDE5I-refractory ED. They were randomized on a 1:1 ratio to LI-ESWT ($n=40$) or sham treatment ($n=40$). All patients completed the study protocol in the active LI-ESWT group. There were 4 dropouts in the sham group. This study was reviewed and approved by the Institutional Ethics Review Board. Participants provided written informed consent before enrolling in the study.

Inclusion and exclusion criteria

All participants included in this study were recruited from the Andrology Clinic of a University Hospital. They presented a history of ED of more than 6 months not responding to PDE5I drugs. PDE5I non-responders were defined as patients with an inadequate erectile response after at least four attempts using the highest tolerated drug [8]. All patients were correctly treated with on-demand use of at least two of the following drugs: sildenafil 100 mg, tadalafil 20 mg or vardenafil 20 mg.

At baseline all patients had an International Index of Erectile Function–Erectile Function domain (IIEF-EF) score < 26. Men were excluded from the study if they had any penile anatomical abnormality, an unstable medical condition, neurological/hormonal abnormalities, history of pelvic surgery/radiotherapy, current use of psychotropic drugs or a diagnosis of a specific ED etiology different to vascular ED.

Study protocol

At the first visit, patients were evaluated with IIEF-EF and Erection Hardness Score (EHS) questionnaires as well as the Questions 2 and 3 of the Sexual Encounter Profile (SEP2 and SEP3). Patients who met study inclusion criteria were assigned in a 1:1 ratio (using a randomization software) to the active LI-ESWT group and the sham group. Each subject then began the 4-week treatment protocol. The protocol included 1 session per week for 4 weeks. The safety of the LI-ESWT was monitored throughout the study and adverse events were evaluated in each visit. Response to therapy was measured 1, 3 and 6 months after the last session using IIEF-EF, EHS, SEP2, SEP3 and the Global Assessment Question (GAQ1). All patients stopped using ED drugs during study protocol and follow-up, with a wash-out period of 2 months. In each of the four LI-EWST sessions and three post-treatment evaluations, patients were questioned about the use of ED drugs.

LI-EWST specifications

Patients were treated with the RENOVA® electromagnetic device (Direx Group, Wiesbaden, Germany) which produces linear low intensity shock waves (0.09 mJ/mm^2 with a frequency of 120 shock waves per minute). Each session comprised 5000 pulses using a specialized probe divided in 4 foci: 900 shocks to each corpora cavernosa and 1600 shocks to each crus. No analgesia was needed. When treating the control group, the device probe was replaced with one that had the same shape, weight and sound, but did not generate shockwaves. Both patient and probe operator were blind to the procedure.

Outcome measures

The primary outcome measurement was the median change of IIEF-EF score from baseline. Secondary outcome measurements consisted of percentage of patients with an EHS > 2 (which indicates the penis is hard enough for penetration) and with positive answers to SEP2, SEP3 and GAQ1 questions. All of the erectile function (EF) questionnaires were applied at baseline and during the three post-treatment evaluations (1, 3 and 6 months after final session).

Statistical analysis

Quantitative parameters were presented as medians with interquartile range (IQR) and compared between the groups using Mann–Whitney–Wilcoxon test. The change of IIEF-EF scores has been used by several authors to compare LI-ESWT effects between active and sham treated patients [9, 10]. Linear regression analysis was performed on IIEF-EF results. Qualitative parameters were shown as absolutes numbers and percentages. The groups were compared using the Chi-square test. Sample size was calculated to detect a change in IIEF-EF score of 4 points at 80% power. All results with $p < 0.5$ considered statistically significant.

SPSS® software (IBM Statistics, Armonk, New York, USA) was used for analysis.

Results

In the active LI-ESWT and sham groups 40 and 36 patients, respectively, completed the study. Table 1 shows the baseline parameters for both groups, with no statistically significant differences between them. Subjects were, predominantly, middle-aged men with a high prevalence of multiple cardiovascular risk factors. Both active and sham groups were consisting of patients with largely moderate ED, with median IIEF-EF scores of 12 (IQR 8–17) and 13 (IQR 8–17), respectively.

There were not significant differences in EF questionnaire scores between groups at the 1-month follow up evaluation (Table 2). The median change in IIEF-EF domain score was 1 (IQR −1 to 6) in the active group and 0 (IQR −8 to 4) in the sham group ($p=0.066$). No significant differences were observed between groups regarding the percentage of men with an EHS > 2 or the number of positive answers to SEP2, SEP3 and GAQ1 during the first month evaluation.

At the 3-month follow-up, there was a median change in IIEF-EF score of 3.5 (IQR 0–10) and −0.5 (IQR −11 to 1) in the active and sham groups, respectively ($p=0.004$). Differences between patients with EHS > 2 or positive answers to SEP2, SEP3 and GAQ1 were not significant at this specific time-point.

Table 1 Baseline characteristics of study population at randomization

	Active	Sham	*p*-value
Number of patients	40	36	
Median age [years] (IQR)	60 (54–66)	60 (53–65)	0.826
Median ED duration [years] (IQR)	3 (2–6)	4.5 (3–6)	0.099
Median BMI [kg/m^2] (IQR)	27 (25–30)	28 (26–29.8)	0.313
Cardiovascular risk factors (%)			
Diabetes mellitus	12 (30.0%)	11 (30.6%)	1.000
Ischemic heart disease	1 (12.5%)	4 (11.1%)	0.184
Hypertension	23 (57.5%)	27 (75.0%)	0.491
Dyslipedemia	14 (35.0%)	19 (52.8%)	0.165
Median IIEF-EF score (IQR)	12 (8–17)	13 (8–17)	0.352
Median EHS (IQR)	2 (1–3)	2 (1–3)	0.478
Patients with positive SEP-2 (%)	17 (42.5%)	19 (52.8%)	0.491
Patients with positive SEP-3 (%)	6 (15.0%)	8 (22.2%)	0.556

ED Erectile dysfunction, *BMI* Body mass index, *IIEF-EF* International Index of Erectile function–erectile function domain, *EHS* Erection hardness score, *SEP-2* Question 2 of the sexual encounter profile, *SEP-3* Question 3 of the sexual encounter profile

Table 2 Post-treatment erection function parameters

	Active	Sham	*p*-value
Median IIEF-EF score (IQR)			
Baseline	12 (8–17)	13 (8–17)	0.352
1 month	11 (8–20)	10 (6–19)	
Change	1 (−1–6)	0 (−8–4)	0.066
3 months	15 (9–23)	9 (5–21)	
Change	3.5 (0–10)	−0.5 (−11–1)	0.004*
6 months	15 (7–22)	8 (6–17)	
Change	1 (−1–7)	0 (−4–2)	0.246
Patients with EHS >2			
Baseline	13 (32.5%)	14 (38.9%)	0.561
1 month	18 (45.0%)	12 (33.3%)	0.378
3 months	18 (45.0%)	15 (41.7%)	0.807
6 months	21 (52.5%)	10 (27.8%)	0.028*
Patients with positive SEP-2 (%)			
Baseline	17 (42.5%)	19 (52.8%)	0.491
1 month	23 (57.5%)	21 (58.3%)	0.884
3 months	18 (45.0%)	22 (61.1%)	0.258
6 months	21 (52.5%)	20 (55.6%)	0.821
Patients with positive SEP-3 (%)			
Baseline	6 (15.0%)	8 (22.2%)	0.556
1 month	9 (22.5%)	8 (22.2%)	0.762
3 months	12 (30.0%)	11 (30.6%)	0.864
6 months	11 (27.5%)	5 (13.9%)	0.146
Patients with positive GAQ-1 (%)			
1 month	15 (37.5%)	14 (38.9%)	0.878
3 months	18 (45.0%)	11 (30.6%)	0.342
6 months	16 (40.0%)	5 (13.9%)	0.011*

IIEF-EF International Index of Erectile Function–Erectile Function domain, *EHS* Erection hardness score, *SEP-2* Question 2 of the Sexual Encounter Profile, *SEP-3* Question 3 of the Sexual Encounter Profile

*$p<0.05$

The percentage of subjects in the active group that described an EHS > 2 showed an increasing trend through the study (Fig. 1).

At the 6-month follow-up, the proportion of patients with EHS > 2 was 52.5% (21/40) in the LI-ESWT group and 27.8% (10/36) in the sham group ($p=0.028$). Patients with positive answers to GAQ-1 were 16/40 (40.0%) and 5/36 (13.9%) in the active and sham groups, respectively ($p=0.011$). SEP2 and SEP3 positive answers did not present significant differences between groups in any of the follow-up evaluations (Table 2).

Linear regression analyses adjusted for baseline parameters was performed on IIEF-EF changes. It showed that being in the active treatment group is predictive of a higher

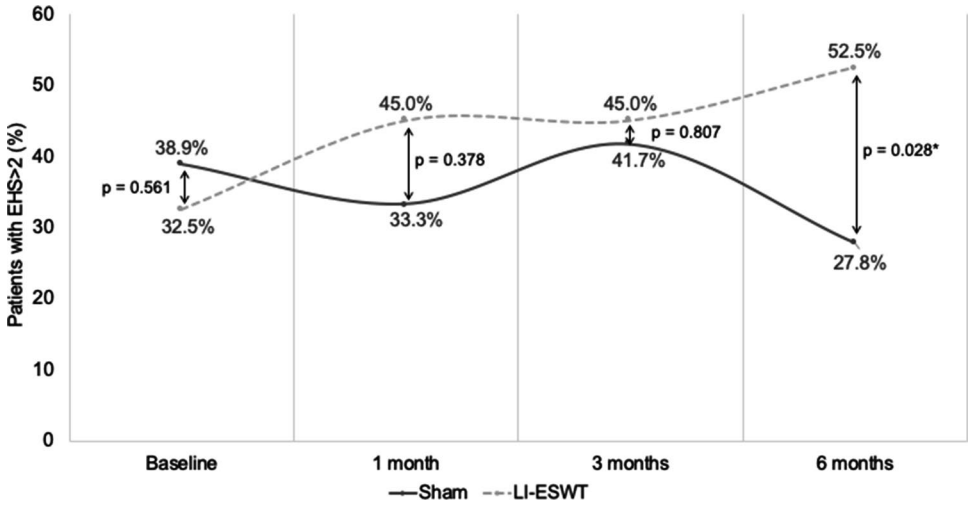

Fig. 1 Percentage of patients with EHS > 2. *EHS* erection hardness score, *LI-ESWT* low-intensity extracorporeal shockwave therapy. *$p < 0.05$

magnitude of IIEF-EF increase with a β coefficient of 3.44 [95% Confidence interval 0.23–6.57] ($p = 0.028$).

There were not any adverse events described by the participants, in neither group, during the 4-week treatment or the 6-month follow up period.

Discussion

Although LI-ESWT has been studied for more than a decade in ED patients, this is still a controversial therapy with different degrees of recommendation depending on the specific clinical guideline of scientific societies [11]. For example, position statements and clinical guidelines from the American Urological Association, the European Society of Sexual Medicine and the Sexual Medicine Society of North America recommend that LI-ESWT should be considered an experimental therapy and be used under research protocols [11–13]. On the other hand, for the first time the European Association of Urology in their 2020 Guidelines recommend the use of LI-ESWT as a first-line therapy for mild vasculogenic ED [14] clearly acknowledging the recent evidence supporting the use of shockwave therapy in this specific ED etiology.

In the last 10 years, several in vitro and animal trials have shown that LI-ESWT may improve EF through neoangiogenesis, recruitment of progenitor cells, modulation of vasodilation and nerve regeneration [1, 15–18]. It seems that LI-EWST induces synthesis of pro-angiogenic factors and chemokines [19]. Other studies have exhibited the effects of LI-ESWT on restoring normal penile histology after pelvic neurovascular damage [20].

The current study shows a modest improvement in EF parameters after 3 and 6 months following penile shockwave therapy. Median change in IIEF-EF scores are significantly higher in the active group after 3 months of LI-ESWT. The decrease of control group scores could be explained because subjects do not experience any improvements and become gradually frustrated without being able to use PDE5I. At 6 months of follow-up, the proportion of patients with EHS > 2 and the number of patients that feel that LI-ESWT improved their EF (positive answer to GAQ-1) is significantly higher in the active group (Table 2). The significant difference in penile rigidity between the two groups (Fig. 1) is relevant, as other authors have considered the EHS one of the most robust parameters to evaluate EF [11].

These results are similar to the ones presented in other clinical trials. However, studies differ in ED etiology, type of device used (source of energy, focal vs linear), shockwave protocol (duration, energy intensity, number and frequency of shocks) and patient-reported outcomes evaluated [3, 11]. Moreover, several studies have important limitations, drop-out rates and biases, making it difficult to draw conclusions or recommendations from those results [11, 21].

The optimal patient and treatment protocol are yet to be determined. It appears that more shocks and stronger shocks typically lead to greater improvements in EF [22]. Linear distribution of shockwaves may provide a better coverage of the corpora cavernosa than focal devices thus improving treatment outcomes [3].

To this date, there is only 13 randomized placebo controlled clinical trials investigating LI-ESWT as a treatment for ED [9, 10, 21, 23–31]. Additionally, there has been five meta-analyses published regarding LI-ESWT studies [32–36]. Some of them have not excluded studies at high risk of bias or have included studies with equivocal data. Since the studies most burdened with a high risk of bias also have the largest reported effects size, the inclusion of these trials distorts the results of meta-analyses towards positive results for LI-ESWT compared to placebo [3]. Taking the five recent meta-analyses into account, and in spite of methodological flaws, most of these analyses report a modest

statistically significant benefit for active treatment vs placebo group. IIEF-EF improvements of 2.00, 2.54 and 4.57 are presented in the Lu et al., Angulo et al. and Clavijo et al. meta-analyses, respectively [1, 32, 34, 35].

This study has been designed because PDE5I non-responders are seldomly considered in shockwave studies [35]. There is only one sham-controlled randomized clinical trial that has included the same PDEI-refractory population as in the current study. In 2016 Kitrey et al. conducted a randomized study on a small sample of 55 refractory ED patients (active group = 37, sham group = 18) with only 1 month of follow-up. The median change from baseline in the IIEF-EF score was 5 points in the treatment group and 0 points in the sham treatment group ($P = 0.0006$), while the percentage of EHS = 3 patients was 54% in the active group vs 0% in the sham group ($P < 0.0001$) [9, 11]. In this study, LI-ESWT effect was evaluated only during obligatory PDE5I treatment. They aimed to convert PDE5I non-responders into responders. The current study aims to show the changes in several EF parameters without using any ED drugs. This pivotal difference makes the comparison of both studies difficult.

Several clinical guidelines still consider shockwaves as an experimental therapy [11, 13]. This could be explained by the high level of heterogeneity and risk of biases of published clinical trials. Meta-analyses currently available show important methodological flaws, by including unpublished data, studies at high risk of bias, studies with ED as a secondary end point, non-randomized trials [1] and incorrect citation of IIEF data (confusion of IIEF with IIEF-EF) [37].

The current clinical trial shows that this specific linear electromagnetic shockwave protocol may improve EF, to a modest extent, on certain patients that do not respond to oral therapy. Hence, it could be an alternative for vascular ED patients that do not respond to traditional first line PDE5I and reject more invasive therapies.

The study has several limitations. There was a limited sample size; however, this is common among LI-ESWT clinical trials. Penile hemodynamics were not measured to diagnose vasculogenic ED or to confirm the improvement of cavernous blood inflow or penile rigidity. Penile doppler ultrasound could be considered to measure arterial inflow and venous outflow. Although 6 months of follow-up is higher than the duration of several other trials, > 1 year of follow-up would be better to correctly assess the long-term effects of this therapy.

Conclusion

This randomized double-blind sham-controlled trial showed moderate improvement in different EF parameters at 3 and 6 months of follow-up. It is of the utmost importance to elaborate randomized sham-controlled studies with long follow ups, that compare different ED etiologies and protocol characteristics, to elucidate the real role of LI-EWST in the treatment of ED.

Author contributions JV: project development, data collection, data analysis, manuscript writing. DM: data collection. OR: project development. ER-C: project development. JS-C: project development, data collection, manuscript writing

Compliance with ethical standards

Conflicts of interest The researchers received materials for the LI-EWST device from the manufacturer (Direx Group, Wiesbaden, Germany) to carry out the clinical trial. No special funding was received.

Research involving human participants and/or animals This study was reviewed and approved by Fundació Puigvert Ethics Review Board: (FP-ANDRO-2016/01).

Informed consent Participants provided written informed consent before enrolling in the study.

References

1. Fode M, Hatzichristodoulou G, Serefoglu EC et al (2017) Low-intensity shockwave therapy for erectile dysfunction: Is the evidence strong enough? Nat Rev Urol 14:593–606. https://doi.org/10.1038/nrurol.2017.119
2. Hatzimouratidis K, Amar E, Eardley I et al (2010) Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol 57:804–814. https://doi.org/10.1016/j.eururo.2010.02.020
3. Schoofs E, Fode M, Capogrosso P, Albersen M (2019) Current guideline recommendations and analysis of evidence quality on low-intensity shockwave therapy for erectile dysfunction. Int J Impot Res 31:209–217. https://doi.org/10.1038/s41443-019-0132-0
4. Besiroglu H, Otunctemur A, Ozbek E (2015) The relationship between metabolic syndrome, its components, and erectile dysfunction: a systematic review and a meta-analysis of observational studies. J Sex Med 12:1309–1318. https://doi.org/10.1111/jsm.12885
5. Vardi Y, Appel B, Jacob G et al (2010) Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol 58:243–248. https://doi.org/10.1016/j.eururo.2010.04.004
6. Gruenwald I, Kitrey ND, Appel B, Vardi Y (2013) Low-intensity extracorporeal shock wave therapy in vascular disease and erectile dysfunction: theory and outcomes. Sex Med Rev 1:83–90. https://doi.org/10.1002/smrj.9
7. Gruenwald I, Appel B, Vardi Y (2012) Low-intensity extracorporeal shock wave therapy-a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. J Sex Med 9:259–264. https://doi.org/10.1111/j.1743-6109.2011.02498.x
8. Carson C, Giuliano F, Goldstein I et al (2004) The "effectiveness" scale—Therapeutic outcome of pharmacologic therapies

for ED: an international consensus panel report. Int J Impot Res 16:207–213. https://doi.org/10.1038/sj.ijir.3901227
9. Kitrey ND, Gruenwald I, Appel B et al (2016) Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. J Urol 195:1550–1555. https://doi.org/10.1016/j.juro.2015.12.049
10. Fojecki GL, Tiessen S, Osther PJS (2018) 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 6:1–7. https://doi.org/10.1016/j.esxm.2017.09.002
11. Capogrosso P, Frey A, Jensen CFS et al (2019) Low-intensity shock wave therapy in sexual medicine—clinical recommendations from the European Society of Sexual Medicine (ESSM). J Sex Med 16:1490–1505. https://doi.org/10.1016/j.jsxm.2019.07.016
12. Patel P, Huang C, Molina M, Ramasamy R (2019) Clinical trial update on shockwave therapy and future of erectile function restoration. Int J Impot Res 31:206–208. https://doi.org/10.1038/s41443-019-0115-1
13. Burnett AL, Nehra A, Breau RH et al (2018) Erectile dysfunction: AUA guideline. J Urol 200:633–641. https://doi.org/10.1016/j.juro.2018.05.004
14. Salonia A, Bettocchi C, Carvalho J CG, Jones TH, Kadioglu A M-SJ, Minhas S, Serefoglu EC (2020) VP EAU guidelines on sexual and reproductive health. Eur Assoc Urol
15. Qiu X, Lin G, Xin Z et al (2013) Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. J Sex Med 10:738–746. https://doi.org/10.1111/jsm.12024
16. Ciampa AR, De Prati AC, Amelio E et al (2005) Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves. FEBS Lett 579:6839–6845. https://doi.org/10.1016/j.febslet.2005.11.023
17. Hausner T, Pajer K, Halat G et al (2012) Improved rate of peripheral nerve regeneration induced by extracorporeal shock wave treatment in the rat. Exp Neurol 236:363–370. https://doi.org/10.1016/j.expneurol.2012.04.019
18. Schuh C, Hausner T, Redl H (2016) A therapeutic shock propels Schwann cells to proliferate in peripheral nerve injury. Brain Circ 2:138. https://doi.org/10.4103/2394-8108.192520
19. Tepeköylü C, Wang FS, Kozaryn R et al (2013) Shock wave treatment induces angiogenesis and mobilizes endogenous CD31/CD34-positive endothelial cells in a hindlimb ischemia model: implications for angiogenesis and vasculogenesis. J Thorac Cardiovasc Surg 146:971–978. https://doi.org/10.1016/j.jtcvs.2013.01.017
20. Lei H, Xin H, Guan R et al (2015) Low-intensity Pulsed ultrasound improves erectile function in streptozotocin-induced type i diabetic rats. Urology 86:1241.e11–1241.e18. https://doi.org/10.1016/j.urology.2015.07.026
21. Srini VS, Reddy RK, Shultz T, Denes B (2015) Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. Can J Urol 22:7614–7622
22. Yang H, Seftel AD (2019) Controversies in low intensity extracorporeal shockwave therapy for erectile dysfunction. Int J Impot Res 31:239–242
23. Vardi Y, Appel B, Kilchevsky A, Gruenwald I (2012) Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. J Urol 187:1769–1775. https://doi.org/10.1016/j.juro.2011.12.117
24. Fojecki GL, Tiessen S, Osther PJS (2017) Effect of Low-energy linear shockwave therapy on erectile dysfunction—a double-blinded, sham-controlled, randomized clinical trial. J Sex Med 14:106–112. https://doi.org/10.1016/j.jsxm.2016.11.307
25. Yee CH, Chan ESY, Hou SSM, Ng CF (2014) Extracorporeal shockwave therapy in the treatment of erectile dysfunction: a prospective, randomized, double-blinded, placebo controlled study. Int J Urol 21:1041–1045. https://doi.org/10.1111/iju.12506
26. Olsen AB, Persiani M, Boie S et al (2015) Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study. Scand J Urol 49:329–333. https://doi.org/10.3109/21681805.2014.984326
27. Motil I, Kubis I, Sramkova T (2016) Treatment of vasculogenic erectile dysfunction with piezowave2 device. application of low intensity shockwaves using novel linear shockwave tissue coverage (LSTC-ED®) technique. A prospective, multicentric placebo-controlled study. Adv Sex Med 06:15–18. https://doi.org/10.4236/asm.2016.62002
28. Yamaçake KGR, Carneiro F, Cury J et al (2019) Low-intensity shockwave therapy for erectile dysfunction in kidney transplant recipients. A prospective, randomized, double blinded, sham-controlled study with evaluation by penile Doppler ultrasonography. Int J Impot Res 31:195–203. https://doi.org/10.1038/s41443-018-0062-2
29. Kalyvianakis D, Hatzichristou D (2017) Low-intensity shockwave therapy improves hemodynamic parameters in patients with vasculogenic erectile dysfunction: a triplex ultrasonography-based sham-controlled trial. J Sex Med 14:891–897. https://doi.org/10.1016/j.jsxm.2017.05.012
30. Baccaglini W, Pazeto CL, Corrêa Barros EA et al (2020) The role of the low-intensity extracorporeal shockwave therapy on penile rehabilitation after radical prostatectomy: a randomized clinical trial. J Sex Med 17:688–694. https://doi.org/10.1016/j.jsxm.2019.12.024
31. Sramkova T, Motil I, Jarkovsky J, Sramkova K (2019) Erectile dysfunction treatment using focused linear low-intensity extracorporeal shockwaves: single-blind, sham-controlled, randomized clinical trial. Urol Int. https://doi.org/10.1159/000504788
32. Lu Z, Lin G, Reed-Maldonado A et al (2017) Low-intensity extracorporeal shock wave treatment improves erectile function: a systematic review and meta-analysis. Eur Urol 71:223–233
33. Man L, Li G (2018) Low-intensity extracorporeal shock wave therapy for erectile dysfunction: a systematic review and meta-analysis. Urology 119:97–103. https://doi.org/10.1016/j.urology.2017.09.011
34. Clavijo RI, Kohn TP, Kohn JR, Ramasamy R (2017) Effects of Low-intensity extracorporeal shockwave therapy on erectile dysfunction: a systematic review and meta-analysis. J Sex Med 14:27–35
35. Angulo JC, Arance I, de Heras MM et al (2017) Efficacy of low-intensity shock wave therapy for erectile dysfunction: a systematic review and meta-analysis. Actas Urol Esp 41:479–490. https://doi.org/10.1016/j.acuroe.2017.07.001
36. Zou ZJ, Tang LY, Liu ZH et al (2017) Short-term efficacy and safety of low-intensity extracorporeal shock wave therapy in erectile dysfunction: a systematic review and meta-analysis. Int Braz J Urol 43:805–821
37. Poulakis V, Skriapas K, de Vries R et al (2006) Extracorporeal shockwave therapy for Peyronie's disease: an alternative treatment? Asian J Androl 8:361–366. https://doi.org/10.1111/j.1745-7262.2006.00138.x