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ARTICLE

Low intensity shockwave therapy in combination with phosphodiesterase-5 inhibitors is an effective and safe treatment option in patients with vasculogenic ED who are PDE5i non-responders: a multicenter single-arm clinical trial

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Abstract

Low-intensity shockwave therapy (Li-ESWT) has been shown to be an effective and safe treatment for vasculogenic erectile dysfunction (ED). We aim to evaluate the effectiveness and safety of LiESWT in treating patients affected from vasculogenic ED who did not respond to oral treatment with Phosphodiesterase 5 inhibitors (PDE5-i). It is a multicentric open-label prospective study, in a cohort of patients non-responders to PDE-5i. Li-ESWT was performed in an outpatient setting by using the following schedule: 3000 shockwaves with an energy of 0.25 mJ/mm^2 and a frequency of 4–6 Hz, twice a week for 3 weeks. International Index of Erectile Function, Erection Hardness Score and Sexual Quality of Life-Male questionnaires, and penile doppler ultrasound (PDU) are the outcome measurements. The Student *t*-test or Wilcoxon signed-rank test were applied to compare variables, with results considered statistically significant at $p < 0.05$. 106 (97.2%) completed treatment and performed follow-up visit after 4 weeks. At follow up visit, the mean IIEF-EF increased by 8.6 points (13.47 ± 4.61 vs 22.07 ± 5.27; $p < 0.0001$). A clinically significant improvement of IIEF-EF was achieved in 75 patients (70.7%). An EHS score ≥ 3, sufficient for a full intercourse, was reported by 72 patients (67.9%) at follow-up visit. 37 (34.9%) patients reported a full rigid penis (EHS = 4) after treatment. Li-ESWT treatment was also able to improve quality of life (SQOL-M: 45.56 ± 8.00 vs 55.31 ± 9.56; $p < 0.0001$). Li-ESWT significantly increased mean PSV (27.79 ± 5.50 vs 41.66 ± 8.59; $p < 0.0001$) and decreased mean EDV (5.66 ± 2.03 vs 1.93 ± 2.11; $p < 0.0001$) in PDU. Combination of Li-ESWT and PDE5-i represents an effective and safe treatment for patients affected from ED who do not respond to first line oral therapy.

Introduction

Erectile Dysfunction (ED) is one of the most common disorders in middle-aged men and it may affect the quality of life (QoL) of both patients and their partners (QoL) [1]. ED is a multifactorial phenomenon that involves hormonal,

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neurological, and vascular mechanisms and can represent a sentinel marker of cardiovascular disease [2, 3]. Aim of ED treatment should be to give back erection to patients, restore spontaneity of sexual intercourse, and improve quality of life. Phosphodiesterase 5 (PDE5) inhibitors are considered the first pharmacological therapeutic line in treating ED, regardless of aetiology [4]. Effectiveness of PDE5 inhibitors is estimated to be about 70%, although it can be significantly lower in difficult-to-treat populations [5]. Some different strategies have been proposed to improve PDE5-inhibitors efficacy without changing therapeutic plan [6, 7] and patients who do still not respond to oral drugs can be treated with intracavernosal injections, vacuum device or penile prosthesis [8]. Low-intensity shockwave therapy (Li-ESWT) has been shown to be an effective and safe treatment for vasculogenic ED [9–11]. This is confirmed by a metanalysis of randomized controlled trials, although included studies significantly differed from each other for treatment regimen and subject selection [12]. The theoretical basis of Li-ESWT functioning in improving ED can be summarized by the following mechanisms: activation of neoangiogenesis processes and improvement of microcirculation, recruitment and activation of progenitor cells, regulation of immunity, reduction of fibrosis, and nerve repair [13]. Those mechanisms result in improvement of circulation, remodeling of erectile tissue, increasing cell survival and tissue repair, re-innervation, and reducing inflammatory and cellular stress responses [13–15]. Data have demonstrated that Li-ESWT could convert PDE5-inhibitors non-responders into responders, significantly and persistently improving erection quality [16–18]. Patel et al. in a clinical consultation guide published in 2019 concluded that, according to present scientific literature, Li-ESWT seems to have the best effectiveness in patients suffering from mild ED that respond at least partially to PDE-5i and therefore it should be offered to non-responders only in an investigational setting [19]. Here, we aim to evaluate the effectiveness and safety of Li-ESWT in treating patients affected from vasculogenic erectile dysfunction who did not respond to oral treatment with PDE5 inhibitors. Moreover, we aim to evaluate the improvement of penile blood flow at penile Doppler ultrasound and quality of life after Li-ESWT treatment.

Patients and methods

Study schedule

It is a multicentric open-label prospective study carried out in eight Italian centers under the coordination of the Italian Society of Andrology (SIA). Patients were recruited on an outpatient basis. The study consisted of a screening phase, a run-in phase of four weeks and a treatment phase of 6 weeks with a 4-week period of follow-up (Fig. 1).

Inclusion and exclusion criteria

Patients included in the study were sexually active men ≥18 years old, with at least one vascular risk factors (diabetes, hypertension, coronary artery disease, and/or dyslipidemia) affected from ED that were non-responders to PDE-5 inhibitors. A patient was considered unresponsive to PDE5-is when presented an IIEF-EF score lower than 26 even if all measures for the correct use for on demand or chronic drugs were applied [6, 7]. All patients with an history of hypogonadism, previous pelvic surgery, pelvic radiotherapy, penile abnormalities (hypospadias, epispadias, micropenis or buried penis, peyronie's disease, previous penile fracture), psychiatric comorbidities, or suspected neurogenic ED have been excluded from the study.

Patient's clinical and instrumental examination

During the screening phase, medical and sexual history were taken and physical examination was performed. During the run-in phase patients had sexual intercourses with the maximum dose of a PDE5-is of their choice. Before

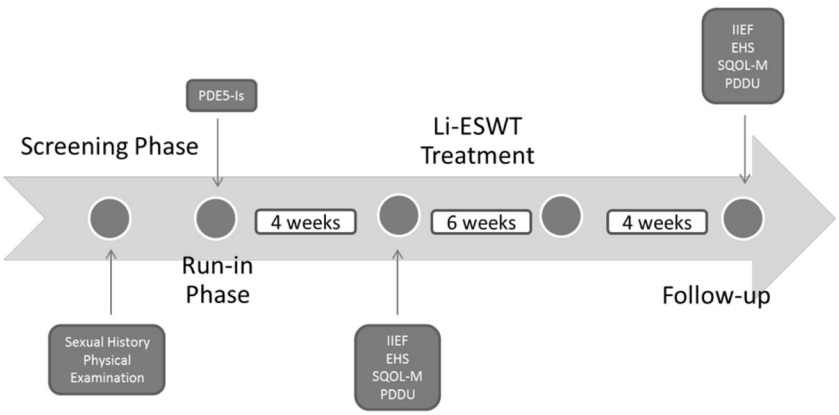

Fig. 1 Study Schedule. The figure shows the study schedule. Li-ESWT: Low-intensity shockwave therapy.

starting treatment, patients filled out the International Index of Erectile Function (IIEF) questionnaire [20, 21], the Erection Hardness Score (EHS) [22], and the Sexual Quality of Life Questionnaire-Male (SQoL-M) [23] and underwent Penile Dynamic Duplex Ultrasound with 10 µg of intacavernous alprostadil. Penile Doppler Ultrasound was performed in all patients using a penile color Doppler ultrasound device equipped with an 7.5-MHz imaging frequency and a pulsed Doppler unit. Transverse (cross-sectional) and longitudinal (sagittal) ultrasonographic images of the cavernosal arteries were obtained at flaccid state. Following 10 µg of intracavernous alprosatdil, ultrasonographic B-mode image of either left or right cavernosal artery had been achieved. By shifting to Doppler mode, systolic/end-diastolic velocities (cm/s) were determined and Resistance Index (RI) was automatically calculated. Flow measurements were performed at 5, 10, 15, 20, and 30 min. A peak systolic blood flow (PSV) > 30 cm/s and/or an end-diastolic velocity (EDV) < 3 cm/s and a RI > 0.80 were considered normal [24].

Treatment schedule

Li-ESWT was performed using Duolith SD1 T-TOP (Storz Medical AG, Tägerwilen, Switzerland—focused shockwaves produced by an electromagnetic generator with a cylindrical coil) in an outpatient setting, without local or general anesthesia. All patients received a total six treatment sessions, twice a week for 3 weeks, with 1-week interval. Each session consists of 3000 shockwaves delivered to the tip of penis shaft, just below the glans (1000 shockwaves), the base of penis shaft (1000 shockwaves), and the crura (500 shockwaves for each side). An energy density of 0.25 mJ/mm^2 and emission frequency of 4–6 Hz were set according to the manufacturer's recommendation and according to previous studies [25]. Shockwave therapy was offered free of charge to enrolled patients. All operators were fully trained during a preparation course held by Italian Society of Andrology. During treatment, patients continued the prescribed therapy with PDE5-is.

Outcome measures and follow up evaluations

Patients were considered responders to treatment when reported a clinically significant improvement of IIEF-EF. Minimal clinically important differences (MCIDs) in the EF domain according to baseline ED severity were considered two points for mild ED, five points for moderate ED and seven points for severe ED [26]. Follow-up visit was performed after 4 weeks from the end of LiESWT sessions. Patients filled out again IIEF, EHS, and SQOL-M questionnaires. All adverse events during the treatment were recorded.

Ethical and statistical considerations

Statistical analysis was performed with SPSS v.22.0 (IBM Corp., Armonk, NY, USA) computer software. Values of the study variables have been compared using the Student's *t*-test or Wilcoxon signed-rank test, as appropriate, with results considered statistically significant at $p < 0.05$. The study was conducted following the Good Clinical Practices and the Declaration of Helsinki and all patients signed an informed consent form before receiving treatment.

Results

One hundred and nine patients were enrolled and 106 (97,2%) completed treatment and performed follow-up visit after 4 weeks. Three patients did not complete the treatment, one for no improvement after the fourth application, the other two for personal reasons. Mean age was 57.9 ± 10.7 (range 21–78) years and duration of ED was 33.3 ± 28.2 (range 3–103) months. Mean pre-treatment IIEF-EF was 13.47 ± 4.61. 2 patients (1.8%) presented mild ED, 29 (27.3%) mild to moderate ED, 38 (35.9%) moderate ED, and 37 (35%) severe ED. Seventy-sevn patients (72.6%) presented a lower PSV and/or a higher EDV compared with reference values. In Table 1, vascular risk factors are listed. At follow up visit, the mean IIEF-EF increased by 8.6 points (13.47 ± 4.61 vs 22.07 ± 5.27; $p < 0.0001$). A clinically significant improvement of IIEF-EF according to MCIDs criteria was achieved in 75 patients (70.7%). Thirty patients (28.3%) reached a normal erectile function (IIEF-EF ≥ 26) under active PDE5-is treatment. All others domains of IIEF questionnaire improved after treatment with Li-ESWT (Table 2). No patients experienced a worsening of IIEF. An EHS score ≥ 3, sufficient for a full intercourse, was reported by 72 patients (67.9%) at follow-up visit. Thirty-seven (34.9%) patients reported a full rigid penis (EHS = 4) after treatment. Mean EHS improved significantly after shockwave administration (2.19 ± 0.52 vs 3.4 ± 0.60; $p < 0.0001$). Regarding penile doppler ultrasound, Li-ESWT significantly increased mean PSV (27.79 ± 5.50 vs 41.66 ± 8.59; $p < 0.0001$) and decreased mean EDV (5.66 ± 2.03 vs 1.93 ± 2.11; $p < 0.0001$). 55

Table 1 Vascular risk factors.

Risk factor	Yes *N* (%)	No *N* (%)	Total *N* (%)
Diabetes	36 (34%)	70 (66%)	106 (100%)
Hypertension	61 (57.5%)	45 (42.5%)	106 (100%)
CVD	9 (8.5%)	97 (91.5%)	106 (100%)
Dyslipidemia	63 (59.4%)	43 (40.6%)	106 (100%)
Smoking	36 (34%)	70 (66%)	106 (100%)

Table 2 Outcomes of Li-ESWT treatment.

	Basal	FU visit	*p*
Mean PSV (cm/s)	27.79 ± 5.50	41.66 ± 8.59	<0.0001
Mean EDV (cm/s)	5.66 ± 2.07	1.93 ± 2.11	<0.0001
IR	0.75 ± 0.07	0.90 ± 0.07	<0.0001
IIEF_EF	13.47 ± 4.61	22.07 ± 5.27	<0.0001
IIEF_OF	5.46 ± 2.08	7.73 ± 1.58	<0.0001
IIEF_SD	5.30 ± 1.55	7.60 ± 1.24	<0.0001
IIEF_IS	7.66 ± 2.27	10.94 ± 2.49	<0.0001
IIEF_OS	4.91 ± 1.51	8.01 ± 1.61	<0.0001
EHS	2.19 ± 0.52	3.40 ± 0.60	<0.0001
SQOL-M	45.56 ± 8.00	55.31 ± 9.56	<0.0001

patients out of 77 with an altered penile hemodynamics (71.4%) backed to normal (PSV > 30 cm/s; EDV < 3 cm/s; RI > 0.80) 4 week after treatment. All patients with a clinically significant increase of the IIEF score after treatment presented a significant improve of hemodynamic parameters at penile doppler. Li-ESWT treatment was able to improve quality of life as testified by the significant increase of SQOL-M score (45.56 ± 8.00 vs 55.31 ± 9.56; $p < 0.0001$). No adverse events were reported during treatment, except for one patient who complained penile dorsal curvature and palpable distal plaque due to a Peyronie's disease.

Discussion

In our population, we demonstrated that Li-ESWT combined to PDE5-Inhibitors represent an effective second line treatment for patients affected from ED who do not respond to oral therapy, improving penile hemodynamics and quality of life. About 30% of patients affected by ED receiving PDE5-Inhibitors are not responders to oral drugs [27]. PD5-i non-responders to date are candidates to a second line therapy (intracavernosal or intraurethral alprostadil, vacuum device), that presents a high drop-out rate [28, 29], or to a penile prosthesis implant. First evidence of effectiveness of Li-ESWT in treating ED was published in 2010 by Vardi et al. [30] They demonstrated that shockwave therapy was able to restore erectile function and to increase endothelial function, evaluated by plethysmography in patients affected from vasculogenic ED responders to PDE5-iS [30]. A successive trial from the same group demonstrated for the first time that LI-ESWT therapy can convert patients who poorly respond to PDE5-IS into responders. They included in the study patients on active PDE5i treatment with an EHS ≤ 2 and after treatment 72.4% of them presented an EHS ≥ 3, sufficient to a satisfactory full sexual intercourse. Also a significant improvement in penile hemodynamics, measured with the veno-occlusive plethysmography, was found with a direct correlation with IIEF improvement [9]. These results were confirmed in a randomized, double-blind study in which 58 patients who did not respond to oral drugs (EHS ≤ 2) were randomized to receive Li-ESWT or a sham treatment. 54.1% of enrolled subjects in treatment group vs no one in sham group reached an EHS score sufficient for a sexual intercourse. Nevertheless, no patient achieved the EHS of 4 after treatment. Again, a significant improvement of penile blood flow was observed during plethysmography after treatment compared with sham treatment. Authors concluded that their results clearly have demonstrated that Li-ESWT is effective in patients with severe ED who did not respond to PDE5-is. The low number of patients and the short follow-up were the main limitations of this study [16]. All the results listed before have been achieved with a single Li-ESWT electrohydraulic device, with a standard treatment protocol (twice a week for 6 week), by the same research group. To date, various devices are available based on different shockwaves generators (electrohydraulic, electromagnetic, and piezoelectric). Each device has its treatment protocol and no comparative studies have been performed. Effectiveness of Li-ESWT in treating PDE5-is non responders has been confirmed in other studies with different devices. Bechara et al. have used a device with an electromagnetic generator that provides linear shockwaves in an open-label, longitudinal, observational study in 50 patients in which PDE5-is were ineffective based on IIEF-EF score. An improvement of IIEF-EF, SEP-2, and -3 and EHS was found in 60% of patients at 3 months after treatment and these parameters were maintained in almost all patients (91.7%) after 12 months of follow-up [16]. In our multicentric study we treated patients with the Duolith SD1 T-TOP, a device that provides focused shockwaves from an electromagnetic generator with a cylindrical coil. The generator guarantees the largest energy penetration depth (up to 65 mm), that it could be useful to better reach the crura of the penis during treatment. This allowed us to perform treatment using a six sessions protocol (twice a week for 3 weeks), according to manufacturer's suggestion. Effectiveness of this device in treating vasculogenic ED in patients who respond to oral drugs has been demonstrated in an open label prospective study and in a prospective randomized study. Chung et al. reported an improvement of the IIEF-5 score and the EDIT index in 60% of patients treated with Li-ESWT [25]. Olsen et al. performed a randomized, double blind, placebo controlled trial demonstrating that 57% of patients treated with Li-ESWT were able to have sexual intercourse without drugs compared with the 9% in the placebo group [11]. Tsai et al. performed the first trial in PDE5-is non-responders using the Duolith SD1 T TOP device with an energy of 0,15 mJ/mm^2. They enrolled 52

patients who failed to respond to PDE5-is (EHS ≤ 2) and performed a treatment session once weekly for 12 weeks. 67.3% of patients reported a successful response based on EHS and a significative increase of IIEF-5 compared with baseline (9.6 ± 2.9 vs 15.0 ± 5.0) [18]. Our results showed a response rate of 70.7% based on IIEF-EF score and a 67.9% based on EHS and are consistent with previous published study, very close to those provided by Gruenwald et al. [9] even with a lower number of treatment session. This is not surprising as Lu et al. in a recent metanalysis showed that a treatment duration of <6 week reported a significant increase in IIEF and that a longer treatment course did not improve erectile function significantly [31]. In a successive more recent trial, Kalyvianakis et al. stated that 12 session (twice a week) provides better results compared with six session (once a week) [32]. Their findings are consistent with the use of a device with a lower energy (0.05 mJ/mm^2) and a different penetration depth [32]. Nevertheless, we totally agree that the schedule of two treatment for week is the preferable choice for LI-ESWT administration. To date, a standard protocol for ESWT treatment cannot be provided to the differences between the available devices and the effective energy administered to the tissues. In our series, Li-ESWT was able to totally restore erectile function in 28.3% of patients. This finding is similar to the 32.5% reported by Bechara et al., which is the only study besides ours that considers IIEF-EF score as parameter to enroll patients [17]. Improvement of quality of life evaluated by SQOL-M questionnaire (+9.7) is consistent with previous published data, confirming a crucial impact of sexual function on overall man's health [33]. In all published studies no adverse events have been recorded following shockwave treatment. In our series, only one patient reported the development of a Peyronie's Disease (PD). To our knowledge, no physiopathological connection can be found between Li-ESWT treatment and PD onset. We think that probably it was misdiagnosed by the physician before enrolling the patient in the study. Previous publications showed a significant improvement in penile hemodynamics evaluated by veno-occlusive plethysmography after Li-ESWT treatment for both responders and non-responders to oral drugs and this change is positively correlated with IIEF score [9, 16]. Kalyvianakis et al. have demonstrated that after treatment with Li-ESWT in patients at least partial responders to PDE5 inhibitors, there is a mean increase of PSV of 4.5 cm/s vs 0.6 cm/s for the treatment and sham groups, respectively at 3 months of follow-up [34]. We found a mean difference in PSV value from baseline in treated patients of 13.8 cm/s. This could be explained by the fact that most patients presented a pathologic Doppler ultrasound and a lower mean PSV as non-responders and the magnitude of vascular response was higher than in patients with a normal Doppler, as it correlates with the improvement of IIEF and EHS [35, 36]. Also, differences in performing penile Doppler could contribute to this result. In our series all patients who had a clinically significant improvement of erectile function presented an improvement of penile doppler parameters, testifying a strict relationship between penile hemodynamic and erection improvement after shockwaves therapy. The number of included patients is the highest among clinical studies on the topic and this was possible because of the multicentric design of the study. Moreover, no significant differences in response rate has been detected between the centers and this testifies that the treatment is repeatable and not dependent by the operator, as long as he is adequately trained before starting treatments. The absence of a control group with a sham treatment and the short follow-up are the main limitation of our study. Data from long term follow-up of 2 years showed that about a half of patients (46.5%) reported a treatment failure, especially those affected with more severe ED at baseline [37]. Based upon these findings, our results need to be confirmed on a longer follow-up. Moreover, the lack of a control group cannot allow us to exclude a potential placebo effect of LIESWT in treating ED. The improvement of penile hemodynamics in all patients who experienced an increasing of IIEF score brought us to think that there is a correlation between LI-ESWT treatment and the restoration of a clinical response to PDE5-inhibitors, as demonstrated in previous studies performed with a control group [16]. LI-ESWT has a high effectiveness in clinical and empirical practice and present a very good safety profile. It is easy to perform after a short training and the compliance of treated patients is really excellent. A schedule of 3000 shockwaves for six sessions is effective for optimize treatments in patients with ED when vascular risk factors are associated.

Conclusion

Li-ESWT represents an effective and safe second line treatment for patients affected from vasculogenic ED who do not respond to oral therapy with PDE5-Inhibitors. Shockwave treatment in combination with PDE5-inhibitors treatment significantly improve erectile function, penile hemodynamics, and quality of life in non-responders patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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