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ORIGINAL ARTICLE

Erectile Dysfunction

Impact of low-intensity extracorporeal shockwave therapy on vascular parameters and sexual function in patients with arteriogenic erectile dysfunction

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Previous published studies have shown an improvement of penile hemodynamic parameters after low-intensity extracorporeal shockwave therapy (Li-ESWT). However, the clinical significance of these findings remains unclear, and definitive selection criteria for Li-ESWT based on preexisting comorbidities have yet to be established. This was an observational study of 113 patients with ED, evaluated between January 2019 and December 2021 in Andrology Unit at the Department of Urology and Renal Transplantation, University of Foggia (Foggia, Italy). Penile dynamic Doppler was performed to evaluate vascular parameters and 5-item version of the International Index of Erectile Dysfunction (IIEF-5) questionnaire was administered to assess the severity of ED. This was repeated 1 month after treatment. Patients with a peak systolic velocity (PSV) <30 cm s^{-1} were considered eligible for Li-ESWT. Our protocol consisted of 8 weekly sessions with 1500 strokes distributed in 5 different locations along the penis. After treatment, a significant mean (±standard deviation [s.d.]) PSV increase of 5.0 (±3.4) cm s^{-1} was recorded and 52/113 (46.0%) patients reached a PSV >30 cm s^{-1} at posttherapeutic penile dynamic Doppler. A clinically significant IIEF-5 score improvement was observed in 7 patients, 21 patients, and 2 patients with mild-to-moderate, moderate, and severe pretreatment ED, respectively. No different outcomes were assessed based on smoking habits, previous pelvic surgery, or use of oral phosphodiesterase-5 inhibitor (PDE5i). On the other side, only 1 (6.7%) in 15 patients with diabetes mellitus showed an IIEF-5 score improvement after Li-ESWT. Shockwave treatment determined a significant increase in PSV and correlated IIEF-5 improvement in ED patients. This advantage seemed particularly evident for moderate ED and was not affected by smoking habits, previous pelvic surgery, and use of PDE5i. Conversely, diabetic patients did not benefit from the treatment.

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INTRODUCTION

Erectile dysfunction (ED) is the consistent or recurrent inability to attain or maintain a penile erection that is sufficient for sexual satisfaction, including satisfactory sexual performance.[1] The prevalence of ED in the general population ranges from 30% to 65% in men aged 40–80 years.[2] The treatment is based on phosphodiesterase type 5 inhibitors (PDE5i) for most of the patients.[3]

PDE5i efficacy is limited to the management of the symptoms without any curative implication, not impacting on genesis and progression of vasculogenic ED. Furthermore, some patients might not response to the therapy or may be deemed ineligible for it due to contraindications. Similarly, the efficacy might decrease over a long-term period of use.[4]

In the last few years, much attention has been given to the study of new regenerative therapies, with the aim to find a cure that might at least slow down those mechanisms responsible for vascular damage underlying vasculogenic ED. Among these, low-intensity extracorporeal shockwave therapy (Li-ESWT) has shown encouraging results for ED patients with arterial hypo-inflow.

A shockwave is a wave of abrupt pressure (vibration movement) produced by an object that travels faster than the speed of sound (<10 ns) producing external pressure differences and increased temperature.[5] Based on previous experiences in other medical field,[6] the application of shockwave therapy to the penis seems to increase blood flow and improve endothelial function through the stimulation of angiogenesis in the corpus cavernosum. Although the mechanism of action is still not completely elucidated, the mechanic stress and microtrauma produced by shockwaves seem responsible for a biological cascade that favors the release of angiogenic factors leading to neovascularization and blood supply increase.[6–9] Recent clinical trials have reported subjective improvement in the 5-item version of the International Index of Erectile Dysfunction (IIEF-5)

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after Li-ESWT, although this improvement was modest and limited to mild dysfunction.[10–12]

Although previous studies have evaluated the efficacy of this treatment through penile hemodynamic parameters assessment,[13,14] a comprehensive analysis of its effect with respect to preexisting comorbidities remains outstanding. The primary objective of this study was to examine the effect of Li-ESWT on penile hemodynamic parameters of patients with ED and its subsequent clinical impact on sexual activity. Furthermore, we aimed to investigate how specific preexisting comorbidities, including smoking habit, presence of diabetes mellitus, and prior pelvic surgery, might affect the efficacy of Li-ESWT.

PATIENTS AND METHODS

Patients

This was a longitudinal and observational study conducted in Andrology Unit at the Department of Urology and Renal Transplantation, University of Foggia (Foggia, Italy) between January 2019 and December 2021. Patients were evaluated for ED with physical examination, medical history, and IIEF-5 questionnaire administration. Patients who exhibited an IIEF-5 score ≤25 underwent penile dynamic color-coded Doppler ultrasonography (PCDU).

PCDU was performed to evaluate vascular parameters including peak systolic velocity (PSV) and resistant index (RI). PSV and RI were assessed before and after self-manual genital and pharmacological stimulation with 20–40 mg of prostaglandin E1 injection (Pfizer Inc., New York, NY, USA) in penile corpus cavernosum. Erection hardness score and sympathetic tone were evaluated by the physician during PCDU. The main inclusion criterion for Li-ESWT was arteriogenic ED documented by a PSV <30 cm s^{-1} (normal value >30 cm s^{-1}). Patients with concomitant Peyronie's disease, penile deformations, hormonal defects, testosterone abnormalities, or previous radiotherapy were excluded from the study.

The study was conducted according to the Good Clinical Practices and the Declaration of Helsinki. Approval by the local research Ethics Committee at University of Foggia (Approval No. Li-ESWT-2019-01) was obtained and all patients signed an informed consent form before being enrolled in the study.

Device and treatment description

The protocol used included eight sessions of Li-ESWT, 1 per week, of about 15 min each and with 1500 strokes equally distributed in 5 different penile locations (ventral surface, dorsal surface, lateral surface, and at the level of the crura). The treated areas were standardized at each session. All sessions were performed without anesthesia in an outpatient setting. This trial was performed using Ortho Gold 100 (MTS Medical, Konstanz, Germany), a modern extracorporeal electro-hydraulic Li-ESWT device. This equipment exploits the high voltage applied between two electrodes placed in the focus F1 at a distance of 1 mm and inside an ellipsoid filled with water. The voltaic arc generated causes the evaporation of the surrounding water and the consequent formation of a spherical pressure wave induced by the rapid growth of the vapor bubble (focus F1). The primary wave (which already has the characteristics of a shockwave) thus formed is focused by the ellipsoid and is concentrated uniformly in the focal volume around the focus F2 and thus can apply shockwaves with greater precision at the penile crura and corpus cavernosum.[14]

Outcome measures

One month after the end of treatment, all patients repeated PCDU and IIEF-5 questionnaire to evaluate any improvement in vascular parameters and sexual function.

Primary endpoint was to evaluate the impact of Li-ESWT on PSV and IIEF-5 score, defined as the difference on measurement before and after treatment (D-PSV and D-IIEF-5). Severity of ED was classified into five categories (IIEF-5 score range: 6–30 points): no ED (score: 26–30 points), mild (score: 22–25 points), mild to moderate (score: 17–21 points), moderate (score: 11–16 points), and severe (score: 6–10 points).

PSV and IR measurements were assessed at the penoscrotal angle bilaterally; subsequently, a mean between the two measurements was assessed for each patient. Overall, pre- and posttherapeutic median PSV and IR were assessed among the entire cohort. A clinically significant IIEF-5 improvement was defined as an increase of at least 7 points, 5 points, and 2 points for severe, moderate, and mild ED, respectively.[16] Of note, clinical improvement for mild-to-moderate ED was defined using moderate cut-off.

Therefore, we evaluated the relationship between the increase of PSV and consequent IIEF-5 score improvement, as well as the different impact of Li-ESWT based on preexisting comorbidities recorded through medical history.

Statistical analyses

Clinicopathological characteristics of our population were studied using descriptive statistics. Median and interquartile range (IQR) were reported for continuous variables such as age, while vascular parameters were reported as mean and respective standard deviation (s.d.).

Wilcoxon sign-rank test was used to compare difference in measurements among patients, previous and after Li-ESWT, given that the normality assumption was observed to be violated in the distribution of our data. The Loess curve depicted the relationship between PSV kinetics and IIEF-5 score eventual improvement after treatment. The Chi-square test was used to compare the proportion of ED severity before and after treatment. All tests were two-sided and statistical significance was defined as $P < 0.05$. All analyses were performed using RStudio© (2023.6.1.524; Rstudio Team, Posit PBC, Vienna, Austria).

RESULTS

Clinicopathological characteristics of our cohort are described in **Table 1**. Of the 1145 patients who underwent ED screening, 113 (9.9%) were eligible for Li-ESWT after exclusion criteria were applied. The median age was 50 (IQR: 40–60) years. Twenty-seven (23.9%) of the 113 patients were active smokers, 19 of whom smoked at least 1 pack of cigarettes per day. Thirty (26.5%) were former smokers, while the remaining 56 (49.6%) were nonsmokers.

PDE5i medications were recorded in 111/113 (98.2%) patients, 41 (36.9%) of whom with daily intake of 5 mg tadalafil plus sildenafil maximum 3 times a week on demand. The remaining 70 patients (63.1%) used PDE5i only on demand.

Table 1: Demographic characteristics (*n*=113)

Characteristic	*Value*
Age (year), median (IQR)	50 (40–60)
Previous pelvic surgery, *n* (%)	41 (36.3)
Smoking habit, *n* (%)	
None	50 (44.2)
Former smokers	36 (31.9)
Active smokers	27 (23.9)
Cardiopathy, *n* (%)	19 (16.8)
Obesity, *n* (%)	11 (9.7)
Hypertension, *n* (%)	41 (36.3)
Diabetes, *n* (%)	15 (13.3)

IQR: interquartile range

At screening, 12 (11.0%) patients exhibited mild ED, 47 (41.0%) mild to moderate, 12 (10.6%) moderate, and 42 (37.2%) severe dysfunction (**Table 2**). The median IIEF-5 was 12 (IQR: 4–14) points. The mean (±s.d.) PSV and IR were 25.5 (±4.6) cm s^{-1} and 0.86 (±0.09), respectively. After treatment, a significant mean PSV and IIEF-5 increase of 5.0 (s.d.: ±3.4) cm s^{-1} and 2 points were recorded, respectively (both $P < 0.001$; **Table 1**). A nonstatistically significant increase of 0.09 IR variation was assessed ($P > 0.05$). After treatment, 52/113 (46.0%) patients showed a PSV>30 cm s^{-1} at posttherapeutic penile dynamic Doppler. A normal IIEF-5 score of 22 or more points was recorded in 8 (7.1%) patients, while 33 (29.2%) of them exhibited mild ED. A clinically significant IIEF-5 score improvement was observed in 7 patients, 21 patients, and 2 patients with mild-to-moderate, moderate, and severe pretreatment ED, respectively. The proportion of ED assessment within the cohort before and after treatment is displayed in **Figure 1** (all $P < 0.001$).

No significant difference in both PSV and IIEF-5 improvement was observed based on smoking habits, previous pelvic surgery (only radical prostatectomy), and PDE5i intake (daily *vs* only on demand). On the other side, patients with diabetes exhibited almost half of the increase in PSV after treatment, when compared with nondiabetic patients (7.0 cm s^{-1} *vs* 3.2 cm s^{-1}, $P < 0.001$). Results for each subgroup are shown in **Table 3**. Moreover, only 1 (6.7%) among 15 diabetic patients exhibited enhancement in their IIEF-5 score, reflecting a shift in ED severity from moderate to mild to moderate.

The Loess curve depicted the relationship between D-PSV and respective IIEF-5 increase (**Figure 2**).

Table 2: Pre- and posttreatment parameters

Parameter	*Pretreatment*	*Posttreatment*
IIEF-5 score (ED category), *n* (%)		
26–30 (no ED)	0 (0)	8 (7.1)
22–25 (mild)	12 (10.6)	33 (29.2)
17–21 (mild to moderate)	47 (41.6)	19 (16.8)
11–16 (moderate)	12 (10.6)	11 (9.7)
6–10 (severe)	42 (37.2)	42 (37.2)
PSV (cm s^{-1}), mean (±s.d.)	25.5 (±4.6)	30.7 (±6.5)
RI, mean (±s.d.)	0.86 (±0.09)	0.95 (±0.11)

IIEF-5: 5-item version of the International Index of Erectile Function; ED: erectile dysfunction; PSV: peak systolic velocity; RI: resistance index; s.d.: standard deviation

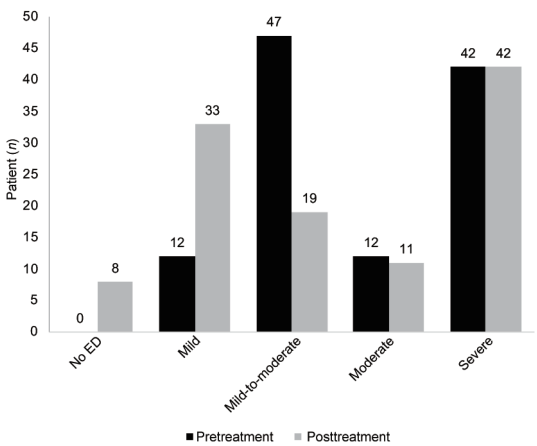

Figure 1: Erectile dysfunction assessment before and after treatments with Li-ESWT ($P < 0.001$). ED: erectile dysfunction; Li-ESWT: low-intensity extracorporeal shockwave therapy.

An IIEF-5 score improvement was shown when patients exhibited a respective increase of PSV at least of 5 cm s^{-1}. A steady significant IIEF-5 improvement (>5 points) was observed when PSV increased at least of ≥12.5 cm s^{-1}. The minimum PSV increase to determine a clinically significant improvement in IIEF-5 score was 7.5 cm s^{-1}, 17.5 cm s^{-1}, and 10 cm s^{-1} for mild-to-moderate, moderate, and severe ED, respectively. None of the patients discontinued or stopped treatment due to side effects, which were all self-limited (ecchymosis, edema, and penile discomfort/mild pain) with ice application and/or anti-inflammatory on demand intake.

DISCUSSION

Our study evaluated longitudinally 113 patients affected by ED undergoing Li-ESWT treatment, also assessing penile hemodynamics. After eight scheduled sessions, significant and parallel improvements both in D-PSV of 5 cm s^{-1} and IIEF-5 score >5 points (46.0% and 30.1%, respectively) were observed. This advantage seemed particularly evident for moderate ED and was not affected by smoking habits, previous pelvic surgery, and use of PDE5i. Conversely, diabetic patients did not benefit from the treatment. Our population was diverse with multiple common comorbidities, providing a real-world picture. The effectiveness of this treatment in patients affected by diabetes resulted to be reduced in our series, in contrast with patients with smoking habit. These results may represent a first step to better selecting patients who may really benefit from the use of Li-ESWT.

Several studies have demonstrated the efficacy of Li-ESWT treatment in patients with arteriogenic ED to improve significantly the blood flow to the penis, although the underlying mechanism has not yet been fully clarified.[6,8,9,17] As demonstrated in the meta-analysis of Sokolakis and Hatzichristodoulou,[17] the three main biological processes involved are cellular proliferation, tissue regeneration, and neoangiogenesis. The latter seems to be the basis on the improvement of penile hemodynamics and consequently of the effectiveness of shockwave therapy in clinical practice for ED.

Vardi *et al*.[12] suggested Li-ESWT as a potential treatment for ED in the first place, showing an IIEF-ED domain improvement with no need of pharmacological treatment in 10 out of 20 men included. Thus, the efficacy of this approach is likely due to upregulation of angiogenic factors involved into neovascularization.[12] Thereby, Li-ESWT has been arousing attention as a new option in the management of ED, also according to the most recent European Association of Urology (EAU) Guidelines.

Encouraging results are reported in literature about this innovative topic. Among different randomized clinical trials, data suggested that

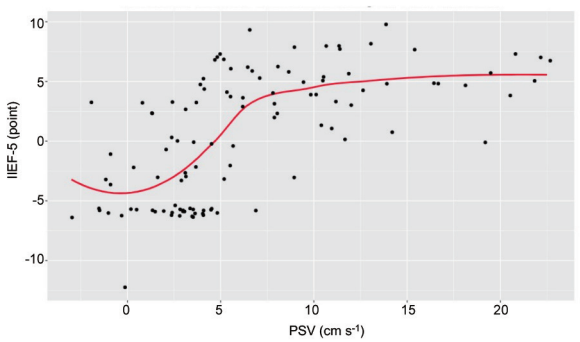

Figure 2: Loess curve evaluating the IIEF-5 improvement with increasing of respective PSV, after Li-ESWT treatment. Li-ESWT: low-intensity extracorporeal shockwave therapy; IIEF-5: 5-item version of the International Index of Erectile Function; PSV: peak systolic velocity.

Table 3: Pre- and posttreatment IIEF-5 and Doppler ultrasound parameters

Parameter	*Nondiabetics vs diabetics*			*Nonsmoker vs smoker*			*No previous pelvic surgery vs previous pelvic surgery*		
	Nondiabetics	*Diabetics*	*P*	*Nonsmoker*	*Smoker*	*P*	*No previous pelvic surgery*	*Previous pelvic surgery*	*P*
Pretreatment									
IIEF-5 (point)	11.4 (±4.2)	7.3 (±3.0)	<0.001	10.6 (±4.2)	11.8 (±4.6)	0.2	11.1 (±4.3)	10.4 (±4.4)	0.4
PSV (cm s^{-1})	25.4 (±4.4)	20.6 (±3.9)	<0.001	24.5 (±4.2)	25.8 (±5.8)	0.2	25.2 (±4.9)	24.1 (±4.2)	0.2
RI	0.9 (±0.1)	0.8 (±0.1)	<0.001	0.9 (±0.1)	0.9 (±0.1)	0.5	0.9 (±0.1)	0.9 (±0.1)	0.6
Posttreatment									
IIEF-5 (point)	12.9 (±8.4)	3.2 (±5.8)	<0.001	11.4 (±8.5)	12.1 (±9.5)	0.7	11.5 (±8.6)	11.6 (±9.0)	1.0
PSV (cm s^{-1})	32.5 (±9.1)	23.8 (±5.1)	<0.001	30.8 (±8.7)	32.7 (±10.6)	0.4	31.6 (±9.4)	30.8 (±8.7)	0.7
RI	1.0 (±0.1)	0.8 (±0.1)	<0.001	0.9 (±0.1)	0.9 (±0.1)	1.0	0.9 (±0.1)	0.9 (±0.1)	0.9
Delta PSV	7.0 (±3.0)	3.2 (±2.1)	0.017	6.4 (±3.8)	6.9 (±3.0)	0.7	6.4 (±4.8)	6.7 (±4.1)	0.8

All the values are presented as mean (±s.d.). IIEF-5: 5-item version of the International Index of Erectile Function; PSV: peak systolic velocity; RI: resistance index; s.d.: standard deviation

patients diagnosed with moderate or severe ED could benefit from shockwave treatment alone[17-19] and also improve their response to PDE5i.[20]

Lately, penile hemodynamics along with Li-ESWT treatment has been arousing attention. Kalyvianakis and Hatzichristou[14] evaluated PSV with penile ultrasound at baseline and 3 months after treatment in their double-blinded, randomized, and sham-controlled trial of 46 men with vasculogenic ED. This study showed a significant PSV increment in patients who had undergone shockwave treatment.[14] Another double-blinded, prospective, sham-controlled study performed penile Doppler ultrasound in 20 kidney transplant recipients affected by ED before and after Li-ESWT, showing similar ultrasound parameters without significant improvements compared to the sham group.[21]

In a single-arm study involving 30 patients who had undergone shockwave treatment, Scroppo *et al*.[22] observed a statistically significant increase in the median IIEF-5 post-ESWT. This observation suggests an overall increase in patients' sexual activities following the treatment, accompanied by a significant improvement in the number of observed third-order helicine arteries, PSV, and Penile Brachial Pressure Index (PBPI) after the shockwave therapy. The findings further imply an increase in vascularization within the corpora cavernosa, highlighting the potential benefits of shockwave therapy in enhancing penile function.

A large cohort of 111 patients treated with Li-ESWT with 3 months and 6 months of follow-up was presented by Caretta *et al*.[13] Both IIEF-5 score and hemodynamic parameters resulted significantly improved after shockwave treatment and patients with mild ED and without cavernous disease have benefited most from treatment (93.9%).

Our study demonstrated the effectiveness of shockwave therapy in improving vascular parameters and consequently, the sexual function in patients with arteriogenic ED, with a particular focus on its relationship with patients' comorbidities. Treatment efficacy was objectively assessed through the IIEF-5 questionnaire and objectively with penile Doppler ultrasound. Our study is not devoid of limitations. First, the retrospective nature limits the strength of our findings that must be seen as a hypothesis generating. Moreover, a longer follow-up would have provided better and more reliable results. However, to the best of our knowledge, this is a very large cohort of patients undergoing Li-EWST with the same standardized treatment protocol.

Future studies should focus on the evaluating the best treatment protocol and provide standardized clinical guidance in patients undergoing Li-ESWT. In this perspective, selection of patients who stand to benefit most from this therapy remains an outstanding challenge. Although our results have not assessed conclusive selection criteria, we were among the pioneers to investigate how specific preexisting comorbidities might affect the efficacy of Li-ESWT. In the wait of stronger evidence, we believed that our study could provide a significant insight, when counseling patients with any of the aforementioned preexisting conditions.

CONCLUSIONS

Our experience showed how shockwave treatment determined a significant increase in PSV and correlated IIEF-5 improvement in ED patients. This advantage seemed particularly evident for moderate ED and was not affected by smoking habits, previous pelvic surgery, or use of PDE5i. Conversely, diabetic patients did not benefit from the treatment.

AUTHOR CONTRIBUTIONS

MR, AR, and MF took responsibility for the integrity of the data and accuracy of the data analysis. GMB, PA, and LC developed the review concept and design of the review. MR, VM, UGF, GMB, CB, and GC drafted the manuscript. GMB, CB, GC, and LC supervised the entire project. All authors contributed to acquisition, analysis, and/or interpretation of data and read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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