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Adjuvant daily therapy with L-arginine 2,500 mg and tadalafil 5 mg increases efficacy and duration of benefits of low-intensity extracorporeal shock wave therapy for erectile dysfunction: A prospective, randomized, single-blinded study with 1-year follow-up

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Purpose: To investigate a therapeutic protocol for erectile dysfunction (ED) based on the combination of low-intensity extracorporeal shock wave therapy (Li-ESWT), tadalafil, and L-arginine.

Materials and Methods: Recruited patients completed the International Index of Erectile Function erectile function domain (IIEF-EF) and the Erection Hardness Score (EHS) questionnaires at baseline and were randomly assigned in two groups: A (treatment group) and B (control group). Men in both groups received six weekly applications of Li-ESWT. Group A was prescribed adjuvant oral therapy with tadalafil 5 mg and L-arginine 2,500 mg. Follow-up visits were scheduled 1, 6, and 12 months after the last Li-ESWT application. At each follow-up visit, the IIEF-EF and EHS questionnaires were administered again. The main outcome measures were the changes from baseline to every follow-up visit in IIEF-EF and EHS scores.

Results: The mean IIEF-EF score in group A was 16.0±4.0, 24.8±3.4, 23.3±4.6, and 21.6±5.5 at baseline, 1, 6, and 12 months of follow-up, respectively, whereas in group B the mean IIEF-EF score was 16.5±4.1, 22.7±4.2, 21.5±4.5, and 19.5±4.9, respectively. We reported an increase in the mean EHS score in group A from 2.07±0.72 at baseline to 3.39±0.59, 3.17±0.67, and 2.98±0.72 at 1, 6, and 12 months, respectively, and in group B from 2.12±0.80 at baseline to 3.07±0.78 and 2.95±0.76 at 1 and 6 months, respectively.

Conclusions: Adjuvant daily therapy with L-arginine 2,500 mg and tadalafil 5 mg was safe and effective in increasing the efficacy and the duration of benefits of Li-ESWT.

Keywords: Erectile dysfunction; L-Arginine; Low-intensity shock wave therapy; Tadalafil

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INTRODUCTION

Erectile dysfunction (ED) is a male sexual dysfunction consisting of the persistent inability to achieve and maintain the penile rigidity necessary for satisfactory sexual activity. According to epidemiologic studies it is a widespread pathology with a prevalence of 30% to 65% in men aged 40 to 80 years [1]. The first-line therapy for ED consists of phosphodiesterase-5 inhibitors (PDE5is) [2]. The main limitation of these drugs is their transient and palliative effect. Moreover, PDE5is reduce the spontaneity of intercourse and many men stop taking them both because of their cost and above all because of the onset of adverse effects [3]. Low-intensity extracorporeal shock wave therapy (Li-ESWT) has been demonstrated by several meta-analyses to be an effective and safe treatment for ED of various etiologies and has been included as a first-line therapy for this disease in the latest guidelines of the European Association of Urology [2,4,5]. Shock wave therapy exerts its benefits through multiple mechanisms of action [6]. Although the clinical effectiveness of Li-ESWT has now been clearly demonstrated, many unexplored aspects remain to be defined to maximize its results. In particular, most published studies have reported only short-term outcomes, and only a few assessed endpoints at 1 year of follow-up [7-11]. Furthermore, these articles published conflicting results, analyzed different types of ED severity, and used different devices and protocols. The current literature suggests that the effects of Li-ESWT fade over time, forcing patients to undergo other courses of therapy or to opt for more invasive interventions. Some articles have shown a potentially synergistic effect of combining Li-ESWT with PDE5is, and similarly positive results were also seen with the concomitant prescription of PDE5is and L-arginine [12-16].

This two-arm, prospective, randomized, single-blind trial was designed to answer the following questions:

1) What are the long-term results of Li-ESWT?

2) Are there any adjuvant therapies capable of increasing the benefits of Li-ESWT and making the results more lasting?

We aimed to investigate the efficacy and safety of a therapeutic protocol for mild and moderate ED based on the combination of Li-ESWT, tadalafil, and L-arginine with 1 year of follow-up. To our knowledge, this is the first study published in the literature investigating these particular aspects.

MATERIALS AND METHODS

All patients affected by ED who visited our two centers specializing in male sexual dysfunction were considered for recruitment. The diagnosis of ED at the first consultation was based on the patient's sexual and medical history and the results of a physical examination and standard laboratory analysis. For all recruited patients, age, marital status, cigarette smoking history, full medical history, and current therapy were recorded. During the screening phase, all patients completed two questionnaires: the International Index of Erectile Function erectile function domain (IIEF-EF) and the Erection Hardness Score (EHS) [17,18]. Inclusion criteria were as follows: age ≥18 years; having mild (IIEF-EF score 18–25) or moderate (IIEF-EF score 11–17) ED for at least 3 months without the use of erectogenic aids after 1 month of washout; and being in a stable relationship and desiring an active heterosexual life. Exclusion criteria were as follows: severe ED (IIEF-EF score 0–10), kidney disease of any type or severity, macroalbuminuria, severe retinopathy, liver failure, coronary artery disease, peripheral or cerebrovascular disease, diabetic or nondiabetic neuropathy, endocrine diseases, pelvic surgery, drug or alcohol abuse, testes hypotrophy, Peyronie disease, and major psychiatric disorders. The following medications were contraindicated during the trial: nitrates, estrogens, antiandrogens, anxiolytic drugs, LH-RH analogues, and tricyclic antidepressants. The use of other drugs that may have affected erectile disorders and may have been prescribed once a patient entered the trial was restricted. All patients were asked to sign an informed consent in conformity with the Declaration of Helsinki. All procedures performed in this study were in accordance with the ethical standards of Gallo Uro-Andrology Centre ethics committees (approval number: 2017005).

All eligible patients were randomly assigned to two groups with an equal allocation ratio (1:1). The randomization sequence was generated by writing the treatment options on papers, which were sealed in individual envelopes and opened after the patient signed the informed consent. Recruited patients in both groups received six weekly applications of Li-ESWT by use of the focused shock wave electromagnetic generator Duolith SD1 T-TOP (Storz Medical AG, Tägerwilen, Switzerland). Each session was performed by the same operator (L.G.) who was fully trained in the procedure and consisted of 3,000 shock waves delivered at an energy density of 0.25 mJ/mm^2 and an emission frequency of 4 Hz. Meticulous attention was paid to distribute the impulses homogeneously throughout the penis. For this purpose, the penis was divided into six areas: 1) right base shaft,

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2) left base shaft, 3) right distal shaft, 4) left distal shaft, 5) right crura, and 6) left crura. Each area received an average of 500 shock waves. The treatment on the shaft (base and distal portion) was carried out by the operator manually stretching the penis and the patient lying in a supine position. To deliver the impulses to the crura, patients were asked to flex the knees, spread the legs apart, and raise the scrotum as much as possible to fully expose the perineum. Each session lasted approximately 15 minutes and was performed in an outpatient setting without local or systemic analgesia. Individuals included in group A (treatment group) received concomitantly with the first application of Li-ESWT the prescription of adjuvant oral therapy with daily tadalafil 5 mg for 3 months and daily L-arginine 2,500 mg for 6 months. Men in group B (control group) received only Li-ESWT without oral therapy and were informed that the use of PDE-5 inhibitors was prohibited during the study.

Follow-up visits were scheduled, respectively, 1, 6, and 12 months after the last Li-ESWT application. At each follow-up visit, the IIEF-EF and EHS questionnaires were administered again.

To reduce bias, all follow-up visits were executed by a second investigator (S.P.) who was blinded to group allocation. The study Consort diagram is presented in Fig. 1.

The main outcome measures were the changes from baseline to every follow-up visit in IIEF-EF and EHS scores. Moreover, we evaluated the percentage of patients who reached a minimal clinically important difference (MCID) in IIEF-EF. MCID was defined as an increase in IIEF-EF score of 2 points for patients with baseline mild ED (IIEF-EF scores of 18–25) and of 5 points for patients with baseline moderate ED (IIEF-EF scores of 11–17) [19].

Appropriate statistical tests were carried out for the comparison of two means (z-test) and for the comparison of two proportions (t-test). These tests were initially executed at baseline to verify the homogeneity of the two groups for all the evaluated features. Subsequently, after having previously verified the hypothesis of homogeneity of the variances, to verify the effectiveness of the treatment, variations in the IIEF-EF score, EHS, and MCID were evaluated at every follow-up visit with respect to baseline in both groups. This analysis concerned both the overall samples and the subgroups that were constructed considering age (less or more than 50 years) and the severity of ED (mild or moderate). To test the possible superiority of one group over the other, the improvements obtained through the two treatments were compared, in both the whole sample and in subgroups. The software used was IBM SPSS Statistics ver. 22 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p<0.05$.

RESULTS

From January 2018 to December 2019, a total of 238 patients with a complaint of ED who visited our two centers

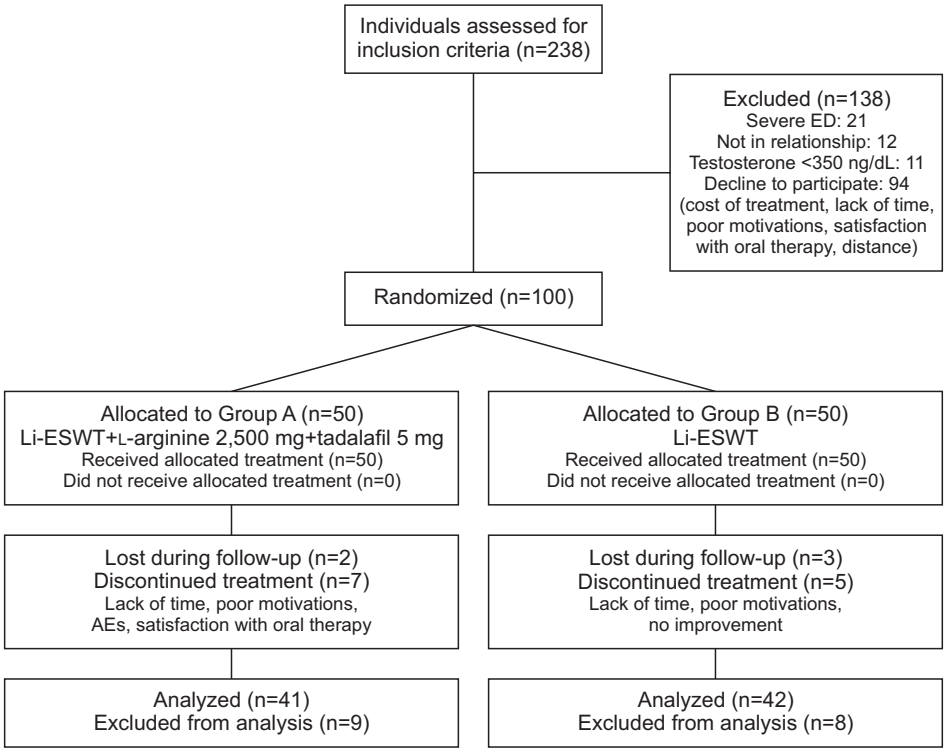

Fig. 1. Consort diagram. ED, erectile dysfunction; Li-ESWT, low-intensity extracorporeal shock wave therapy; AE, adverse event.

were assessed for inclusion. A total of 138 men were excluded during the screening phase: 21 had severe ED, 12 were not in a stable relationship, 11 had a testosterone level lower than 350 ng/dL, and 94 declined to participate for various reasons. A total of 100 individuals were randomly assigned, 50 to each group. All patients received the allocated treatment but 12 did not complete it: 7 in group A and 5 in group B. Among these 12, 9 discontinued the allocated therapy for lack of time and poor motivation in both groups. In group A, one patient did not complete treatment for myalgia and another man because he was satisfied with oral therapy. In group B, one man dropped because did not report improvement after three sessions. Two individuals in group A and three in group B were lost during follow-up (Fig. 1).

Table 1. Patient demographics and baseline disease severity

Variable	Group A	Group B	p-value
Sample size	41	42	
Age (y)	50.5±13.7	49.6±14.0	0.38
Concomitant condition			
Diabetes mellitus	5 (12.2)	4 (9.5)	0.35
Cardiovascular risk factors[a]	31 (75.6)	29 (69.0)	0.25
Baseline ED severity			
Mild ED (IIEF-EF score 18–25)	18 (43.9)	19 (45.2)	
Moderate ED (IIEF-EF score 11–17)	23 (56.1)	23 (54.8)	
Baseline IIEF-EF score	16.0±4.0	16.5±4.1	0.29
Baseline EHS	2.07±0.72	2.12±0.80	0.38

Values are presented as number only, mean±standard deviation, or number (%).
ED, erectile dysfunction; IIEF-EF, International Index of Erectile Function erectile function domain; EHS, Erection Hardness Score.
[a]:Including at least one of the following: hypertension, hyperlipidemia, obesity, and smoking.

At baseline the two groups were homogeneous for all the features evaluated in the present study as reported in Table 1. The mean IIEF-EF scores in group A were 16.0±4.0, 24.8±3.4, 23.3±4.6, and 21.6±5.5 at baseline, 1, 6, and 12 months of follow-up, whereas in group B the mean IIEF-EF scores were 16.5±4.1, 22.7±4.2, 21.5±4.5, and 19.5±4.9, respectively. We reported an increase in mean EHS score in group A from 2.07±0.72 at baseline to 3.39±0.59, 3.17±0.67, and 2.98±0.72 at 1, 6, and 12 months, respectively, and in group B from 2.12±0.80 at baseline to 3.07±0.78 and 2.95±0.76 at 1 and 6 months, respectively. The percentage of men who reached a MCID was 100% and 88.1% at 1 month, 87.8% and 76.2% at 6 months, and 75.6% and 66.7% after 1 year for group A and group B, respectively (Fig. 2).

Our outcomes were further analyzed according to ED severity (mild or moderate) and age (less or more than 50

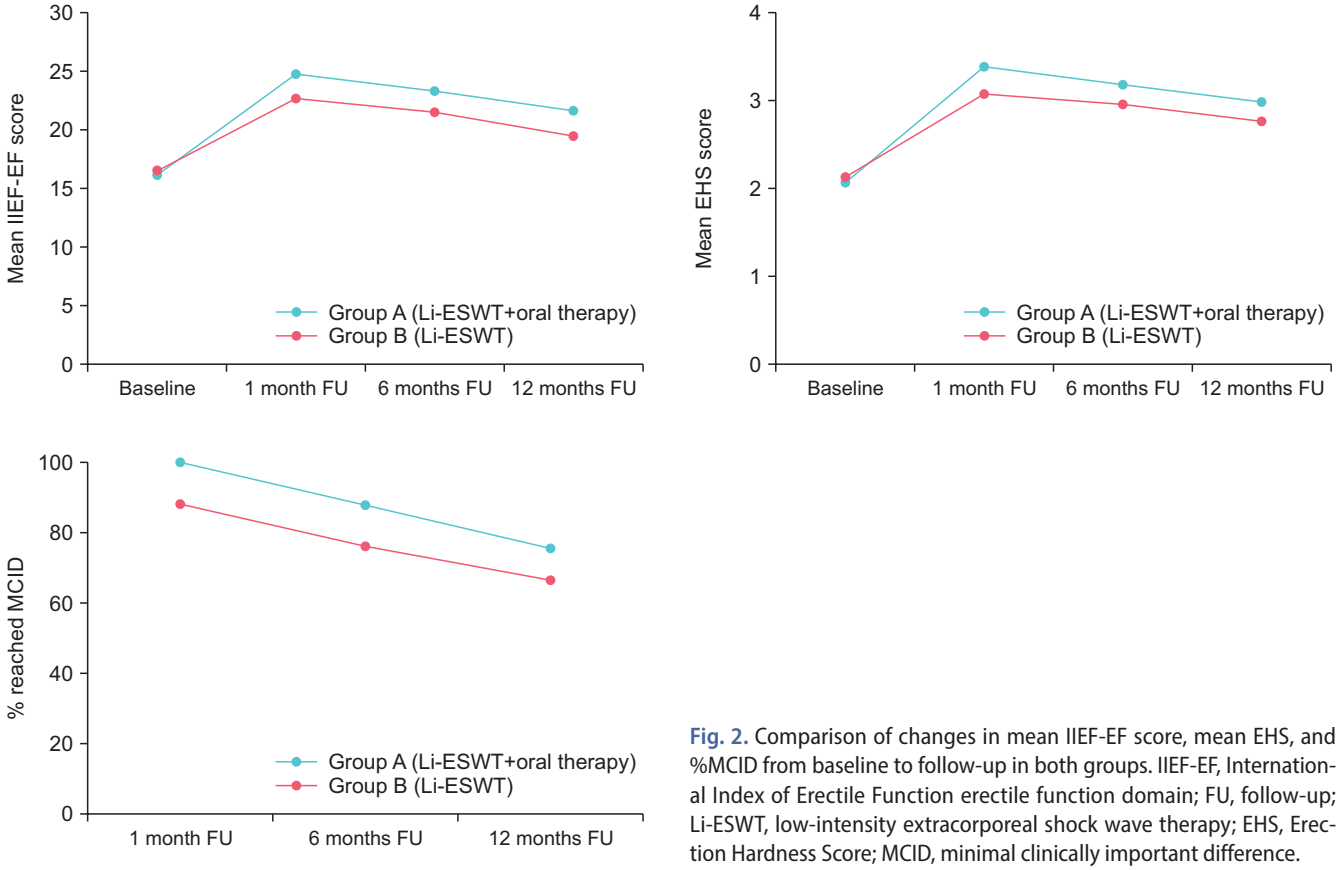

Fig. 2. Comparison of changes in mean IIEF-EF score, mean EHS, and %MCID from baseline to follow-up in both groups. IIEF-EF, International Index of Erectile Function erectile function domain; FU, follow-up; Li-ESWT, low-intensity extracorporeal shock wave therapy; EHS, Erection Hardness Score; MCID, minimal clinically important difference.

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Table 2. Results of outcome measures in the two study groups

	Total	IIEF-EF baseline	IIEF-EF at 1 month FU	IIEF-EF at 6 months FU	IIEF-EF at 12 months FU	EHS baseline	EHS at 1 month FU	EHS at 6 months FU	EHS at 12 months FU	Reached MCID at 1 month FU	Reached MCID at 6 months FU	Reached MCID at 12 months FU
Overall												
Group A (Li-ESWT+oral therapy)	41	16.0±4.0	24.8±3.4	23.3±4.6	21.6±5.5	2.07±0.72	3.39±0.59	3.17±0.67	2.98±0.72	41 (100.0)	36 (87.8)	31 (75.6)
Group B (Li-ESWT)	42	16.5±4.1	22.7±4.2	21.5±4.5	19.5±4.9	2.12±0.80	3.07±0.78	2.95±0.76	2.76±0.73	37 (88.1)	32 (76.2)	28 (66.7)
p-value		0.28	0.007	0.037	0.034	0.38	0.019	0.08	0.08	0.011	0.084	0.18
Mild ED (IIEF-EF score 18–25)												
Group A (Li-ESWT+oral therapy)	18	20.1±1.7	27.1±1.6	26.8±1.9	25.8±2.0	2.67±0.48	3.78±0.43	3.61±0.50	3.44±0.51	18 (100.0)	18 (100.0)	18 (100.0)
Group B (Li-ESWT)	19	20.6±1.6	26.2±1.2	25.3±1.4	23.2±1.1	2.79±0.42	3.63±0.50	3.53±0.51	3.21±0.42	19 (100.0)	19 (100.0)	19 (100.0)
p-value		0.18	0.03	0.004	<0.0001	0.21	0.17	0.32	0.07	NS	NS	NS
Moderate ED (IIEF-EF score 11–17)												
Group A (Li-ESWT+oral therapy)	23	12.9±1.7	23.0±3.4	20.6±4.3	18.3±5.2	1.61±0.50	3.10±0.51	2.83±0.58	2.61±0.66	23 (100.0)	18 (78.3)	13 (56.5)
Group B (Li-ESWT)	23	13.1±1.6	19.9±3.6	18.4±3.8	16.4±4.6	1.56±0.59	2.61±0.66	2.48±0.59	2.39±0.72	18 (78.3)	13 (56.5)	9 (39.1)
p-value		0.34	0.002	0.036	0.098	0.378	0.003	0.024	0.142	0.009	0.058	0.119
Age ≤50 y												
Group A (Li-ESWT+oral therapy)	23	18.0±3.5	26.6±2.1	25.5±3.6	24.1±4.5	2.43±0.59	3.74±0.45	3.48±0.59	3.30±0.70	23 (100.0)	22 (95.7)	20 (87.0)
Group B (Li-ESWT)	21	18.4±3.7	25.2±2.4	23.9±3.2	22.1±2.9	2.57±0.68	3.57±0.51	3.33±0.66	3.19±0.51	21 (100.0)	20 (95.2)	18 (85.7)
p-value		0.36	0.022	0.064	0.045	0.23	0.12	0.21	0.28	NS	NS	NS
Age >50 y												
Group A (Li-ESWT+oral therapy)	18	13.5±3.1	22.4±3.4	20.6±4.3	18.4±5.2	1.61±0.61	2.94±0.42	2.78±0.55	2.56±0.51	18 (100.0)	14 (77.8)	11 (61.1)
Group B (Li-ESWT)	21	14.6±3.6	20.2±4.2	19.2±4.5	16.9±5.1	1.67±0.66	2.57±0.68	2.57±0.68	2.33±0.66	16 (76.2)	12 (57.1)	10 (47.6)
p-value		0.16	0.042	0.164	0.185	0.38	0.02	0.15	0.12	0.012	0.085	0.2

Values are presented as mean±standard deviation or number (%).

IIEF-EF, International Index of Erectile Function erectile function domain; FU, follow-up; EHS, Erection Hardness Score; MCID, minimal clinically important difference; Li-ESWT, low-intensity extracorporeal shock wave therapy; ED, erectile dysfunction; NS, not significant.

years). These results are presented in Table 2.

DISCUSSION

The introduction of sildenafil has revolutionized the treatment of ED, and oral drugs belonging to the PDE5is class are still the first-line therapy. Although very effective, oral therapy is burdened by various complications and limitations: it is an on-demand therapy that reduces the spontaneity of intercourse by forcing patients to plan their sexual activity. Furthermore, these drugs cause adverse effects, are expensive, have contraindications, and are not effective in all patients. All these elements lead a considerable proportion of men to abandon oral therapy. Thus, the main limitation of oral therapy remains that it is not a lasting and definitive cure for ED. Other types of treatments for ED such as intracavernous therapy and the implantation of a penile prosthesis have not been completely successful owing to their invasiveness and high costs [20,21].

Li-ESWT was introduced precisely with the aim of overcoming the limits of oral therapy: to make the pathologic processes underlying ED reversible and, above all, to be a definitive therapeutic approach with stable and lasting results. Despite these exciting initial promises, only a few studies in the literature have published long-term results and the outcomes are conflicting. In fact, some articles report that the effects of the shock waves wear off over time, whereas others suggest that the benefits are unchanged or only slightly reduced after 1 year [7-11]. In particular, in the study published by Fojecki et al. [8], only half of the treated patients showed persistence of therapeutic goals after 1 year.

Li-ESWT actually represents only one of the many tools available in the arsenal of therapies for ED, and substantial evidence demonstrates how the concept of "multimodal therapy," i.e., the concomitant administration of various synergistic treatments, has been successfully applied in the field of sexual medicine [22,23]. In designing this study, we hypothesized a potential synergistic effect of the concomitant administration of Li-ESWT, L-arginine 2,500 mg, and tadalafil 5 mg. It is in fact known that one of the main mechanisms by which shock waves induce angiogenesis is the activation and upregulation of the expression of both types of the NO synthase enzyme: the eNOS present in endothelial cells and the nNOS inside of neuronal cells. Both of these forms of the NOS enzyme use L-arginine as the only precursor to produce NO. In addition, Li-ESWT also increases the production of cGMP, the second messenger underlying smooth muscle relaxation essential for erection, and the degradation of cGMP is inhibited by tadalafil [6]. On the basis of these molecular mechanisms, some studies already published have suggested a synergistic effect of shock waves with PDE5is [12]. It has also been demonstrated by both our group and other authors that there is a synergistic effect when PDE5is are administered together with L-arginine [14-16].

Most of the published studies have used Li-ESWT as a salvage treatment for patients affected by severe ED to make them responsive to oral therapy [13,24,25]. However, the European Association of Urology also recommends the use of Li-ESWT in individuals with mild ED as an alternative first-line therapy in well-informed patients who desire a curable option [2]. In our protocol we intended to reserve shock waves for this type of patient who had the potential to be cured definitively and be able to return to spontaneous sexual activity. Furthermore, this therapeutic scheme was designed not only to enhance and make the effects of Li-ESWT more lasting but also to ensure the patient a gradual return to spontaneous relations by gradually abolishing oral therapy. It is for this reason that we prescribed daily tadalafil 5 mg for 3 months and daily L-arginine 2,500 mg for 6 months in the study group. All our patients reported a statistically significant improvement in erectile function in terms of both IIEF-EF and EHS scores ($p<0.0001$). The increase in both scores was statistically significant at all follow-up visits at 1, 6, and 12 months ($p<0.0001$). However, we found that the beneficial effects of Li-ESWT persisted for up to 1 year from the last application but tended to decrease in intensity. Men enrolled in group A reported a greater increase in IIEF-EF and EHS scores and longer-lasting benefits. Our results are in line with other studies in the literature that describe a potential curative effect of chronic therapy with tadalafil 5 mg, based on the fact that the benefits of this type of treatment persist even after its cessation [26,27]. Furthermore, as already published in other studies, we found that the degree of response to treatment and the duration of benefits were greater in younger men and in patients affected by mild ED [5,11]. In particular, the increase in the mean IIEF-EF score considered at 12 months in patients included in group B older than 50 years was less significant ($p=0.049$).

Overall, in both groups we found a low incidence of minor adverse effects. Some patients experienced a stinging sensation during Li-ESWT, especially at the perineal level, but we never needed to reduce the energy density and in no case was treatment interrupted because of the onset of side effects. Only one patient treated with oral therapy discontinued treatment for muscle pain. Conversely, a considerable number of 94 individuals who met the inclusion criteria refused to be enrolled in this study for the following reasons:

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cost of treatment, lack of time, poor motivations, satisfaction with oral therapy, and distance. Similarly, 10 patients already recruited did not complete the allocated treatment for the same reasons. These data show that Li-ESWT requires strong motivation and that oral therapy is still preferred by many patients for its simplicity, effectiveness, and immediacy.

The present study provides unique results not reported previously. First, it is one of the few articles publishing long-term results with 1 year of follow-up. Moreover, this is also the first study evaluating the long-term effects of Li-ESWT using a focal energy device provided by Storz Medical AG. Other authors who have published results with at least 1 year of follow-up used other equipment (Bechara et al., Renova Direx, Israel [7]; Fojecki et al., Richard Wolf, Knittlingen, Germany [8]; Kalyvianakis et al., Medispec, Gaithersburg, Maryland, USA [9]; Kitrey et al., miscellaneous system [11]), while investigators who used the same device as us reported results with a follow-up of up to 4 months (Palmieri et al., 1 month [13]; Ayala et al., 1 month [28]; Tsai et al., 3 months [25]; Chung and Cartmill, 4 months [24]; Olsen et al., 5 weeks [29]).

Overall, our results seem to be better than those published by other authors who used the Storz Medical AG device, but it is not possible to draw definitive conclusions because of the differences in the protocols and the characteristics of the patients treated. For example, Tsai performed 12 weekly applications at 0.15 mJ/mm^2 in patients with severe ED and reported that two-thirds of the patients were converted to PDE5i responders (EHS ≧3) [25]. Olsen's group evaluated our same type of patients (mild and moderate ED) but administered only five applications with a lower energy (0.15 mJ/mm^2). They found that 57% of the men with ED had an effect from Li-ESWT. Ayala et al. [28] performed only five sessions with a very low energy (0.10 mJ/mm^2) and provided retrospective results. Finally, Palmieri et al. [13] and Chung and Cartmill [24] used a protocol very similar to ours (6 biweekly sessions at 0.25 mJ/mm^2) but in patients refractory to oral therapy. Regarding the duration of the effects of Li-ESWT, our results are in line with those published by Bechara et al. [7], Srini et al. [10], and Kitrey et al. [11] who reported that the benefits persist with time but in some cases are reduced in intensity. Kalyvianakis et al. [9] found that the effects of 12 biweekly sessions not only persist over time but even increase, since they found a mean IIEF-EF score at 1 year higher than at the 1-, 3-, and 6-month follow-up visits. Probably the excellent results published by this study are attributed to the higher number and frequency of applications performed using maximum energy. Similarly, the poor outcomes found by Fojecki et al. [8] seem to be correlated with the lower energy delivered by using a device equipped with a piezoelectric linear handpiece.

In our opinion, our study has several strengths: it includes a high number of patients, it was conducted prospectively, it was randomized and single-blinded, and it evaluated outcomes with up to 1 year of follow-up, which has not been published before. However, we admit that the absence of a placebo group and the lack of evaluation of hemodynamic parameters could be considered as limitations. We suggest that future studies use our therapeutic protocol but with a greater number and a higher frequency of applications of Li-ESWT and also consider patients with severe ED unresponsive to medical therapy.

CONCLUSIONS

Adjuvant daily therapy with L-arginine 2,500 mg and tadalafil 5 mg was safe and effective in increasing the efficacy and the duration of benefits of Li-ESWT. The effects of Li-ESWT persisted for up to 1 year from the last application but tended to decrease in intensity. Results were better in younger men and in patients with mild ED.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Luigi Gallo, Stefano Pecoraro, and Pasquale Sarnacchiaro. Data acquisition: Luigi Gallo, Stefano Pecoraro, and Pasquale Sarnacchiaro. Statistical analysis: Pasquale Sarnacchiaro and Luigi Gallo. Data analysis and interpretation: Pasquale Sarnacchiaro and Luigi Gallo. Drafting of the manuscript: Luigi Gallo and Pasquale Sarnacchiaro. Critical revision of the manuscript: Luigi Gallo, Stefano Pecoraro, and Pasquale Sarnacchiaro. Administrative, technical, or material support: Luigi Gallo, Stefano Pecoraro, and Pasquale Sarnacchiaro. Supervision: Luigi Gallo, Stefano Pecoraro, and Pasquale Sarnacchiaro. Approval of the final manuscript: Luigi Gallo, Stefano Pecoraro, and Pasquale Sarnacchiaro.

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