

ARTICLE



Long-term effects of combination treatment comprising low-intensity extracorporeal shockwave therapy and tadalafil for patients with erectile dysfunction: a retrospective study

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This study retrospectively examined the effects of low-intensity extracorporeal shockwave therapy and tadalafil on erectile dysfunction patients. 116 patients got low-intensity extracorporeal shockwave therapy twice weekly for 3 weeks, 5 mg of tadalafil daily for 3 weeks, and adjuvant therapy for 6 months. Group A (1 year), Group B (2 years), Group C (3 years), and Group D (4+ years) were treated patients' follow-up groups. The patients' International Index of Erectile Function-5 (IIEF-5) scores were gathered at the start of treatment via face-to-face interviews and at the end of follow-ups by telephone conversations. IIEF-5 scores and the minimal clinically significant differences were the main outcomes. Mean follow-up length, age, and IIEF-5 scores of the patients were 2 ± 1.16 years, 47.34 ± 12.65 years, and 12.09 ± 3.66 points, respectively. Compared to baseline, treatment increased the median IIEF-5 scores of patients in groups A, B, C, and D by 7 [3–12], 6 [0–8], 7 [1–9], and 6.5 [2.5–10] points, respectively ($p = 0.001$). 71%, 63%, 65.8%, and 65% of treated patients in groups A, B, C, and D met the minimal clinically significant differences criteria ($n = 77$). Mild disease patients were 9.14 times more likely to respond to treatment than severe illness patients (OR, 9.14; 95% CI, 1.28–65.46; $P = 0.02$). Low-intensity extracorporeal shockwave therapy and 5 mg of tadalafil can treat erectile dysfunction for up to 4 years with sustained outcomes. This treatment is optimal for mild illnesses.

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INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance [1]. This condition is frequently observed in men in their forties who have vascular risk factors [2, 3], and it significantly impacts their quality of life [4]. Phosphodiesterase-5 inhibitors (PDE5Is) are the primary treatment for men with ED [5].

Nevertheless, they can cause adverse effects and reduce the frequency of natural sexual intercourse. Furthermore, other treatment modalities may be necessary as they are not effective for all ED patients [6].

The conventional treatments for ED, such as PDE5Is, vacuum devices, and intracavernous therapy, share the same limitations. Firstly, they do not address the underlying pathophysiology, unlike penile prosthesis implantation, as their effects are not permanent. Secondly, they must be applied at a suitable time before sexual intercourse. Thirdly, they are invasive, expensive, and may not be successful for some ED patients [7–11]. These limitations can lead to dissatisfaction among patients and treatment abandonment [12, 13]. Thus, it is essential to explore novel and effective treatment options with minimal side effects. In 2010, Vardi et al. conducted a pivotal well-designed study that demonstrated that low-intensity extracorporeal shockwave therapy (Li-ESWT) has beneficial effects and can enhance erectile function with minimal side effects [14, 15]. These findings have been corroborated by an

animal study [16] and meta-analyses [17, 18]. However, the long-term effects of Li-ESWT in combination with PDE5Is on men with ED have not been adequately explored. In this retrospective, observational study, we assessed the effect of 4 years of treatment combining Li-ESWT and tadalafil on ED patients.

MATERIALS AND METHODS

Study design and patients

This retrospective, observational study was conducted at a single center, following the principles of the Declaration of Helsinki for research involving human subjects, and with approval from the institutional review board (approval number: ESH/GOEK2022/1). Formal informed consent was not obtained due to the retrospective nature of the study. The study enrolled 116 participants with erectile dysfunction (ED), diagnosed based on initial symptoms, medical workup results, sexual history, and International Index of Erectile Function-5 (IIEF-5) questionnaire scores [19, 20] self-reported by patients.

All patients, including those with no response to phosphodiesterase-5 inhibitors (PDE5Is) and those without psychogenic disorders, received the same treatment protocol consisting of six sessions of low-intensity extracorporeal shockwave therapy (Li-ESWT) combined with 5 mg of tadalafil daily for 3 weeks. Adjuvant therapy with 5 mg of tadalafil daily was then prescribed for 6 months. Patients were followed up and their sexual and medical histories, physical examination, and laboratory test results were recorded. No additional treatment was given to patients after the 6-month adjuvant treatment with tadalafil.

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Baseline and follow-up IIEF-5 questionnaire scores were recorded for each patient, with the latter obtained via a follow-up telephone call performed by a staff member from the clinic. Patients were divided into four groups based on the interval between treatment and the telephone call: group A (1-year follow-up), group B (2 years follow-up), group C (3 years follow-up), and group D (4 years or more follow-up).

Inclusion and exclusion criteria

This trial employed the following inclusion criteria: age above 18 years, absence of prior response to PDE5Is, diagnosis of non-psychogenic ED, and an ED history of less than 6 months.

The exclusion criteria included ED arising after radiation or chemotherapy of the pelvic organs, untreated hypogonadism, and hormonal, anatomical, and/or neurological defects. Patients who did not complete all treatments and those who received concurrent psychiatric treatments were also excluded. Patients whose IIEF-5 scores and satisfaction status could not be obtained were also excluded from the study.

Details of Li-ESWT

The patients were instructed to lie in a supine position on an examination table. A standard sonographic gel was applied to the penis, without the use of local analgesics. A specialized focused shockwave probe (Omnispec ED1000; Medispe Ltd., Yehud, Israel) that produces shocks with an energy density of 0.09 mJ/m² was used to administer shockwaves on the proximal, mid, and distal penile shaft, as well as on the right and left sides of the penis. At each of the five treatment points, three-hundred shocks were applied at a frequency of 160 shocks per minute.

Study endpoints and assessments

To evaluate ED severity, IIEF-5 scores with Turkish validation were utilized [20]. Although we did not have the IIEF-5 erectile function domain scores of the patients, we used IIEF-5 scores to detect minimal clinically important differences (MCIDs) [21]. Patients who showed clinically meaningful improvement in their IIEF-5 score at the end of the follow-up period were considered responders to treatment. Based on the baseline ED severity, increases in the IIEF-5 scores of 2 points for mild ED, 5 points for moderate ED, and 7 points for severe ED were deemed as MCIDs. In addition, overall patient satisfaction with the treatment was evaluated through yes/no questions.

Statistical methods

The Shapiro–Wilk test was utilized to assess the normality of continuous variables. Student's t-test was employed to compare two independent groups if the data was normal, while the Mann–Whitney U test was used for non-normal data. Non-normal measurements between two-time points were compared using the Wilcoxon test. For comparing numerical data among the four groups, a one-way analysis of variance was used for normal data, and the Kruskal–Wallis test was used for non-normal data. The chi-square test was utilized to examine the relationship between categorical variables. Multivariate binary logistic regression analysis was performed to calculate the adjusted odds ratios and 95% confidence intervals, and variance inflation factors were computed to prevent multicollinearity. During the univariate analysis, variables with $p < 0.10$ were included in the model. Statistical analysis was conducted using SPSS for Windows (version 24.0), with a p -value of ≤ 0.05 indicating statistical significance.

RESULTS

Patients

This study included 168 patients who visited our ED clinic between December 2017 and December 2021. During the screening, 52 men were excluded from the evaluation phase for various reasons, resulting in 116 patients being included in the study (Fig. 1). The study groups were comprised of 31, 27, 38, and 20 patients in groups A, B, C, and D, respectively. The patients' median age was 47 years (range, 19–71 years), and the mean follow-up duration was 2 years (± 1.16 years). Table 1 displays patient demographics and clinical characteristics, and Table 2 demonstrates that all traits assessed at baseline were homogenous in all groups.

Endpoint measures

In comparison to baseline values, treatment resulted in a significant increase in the median IIEF-5 scores by 7 points (range, 3–12 points), 6 points (range, 0–8 points), 7 points (range, 1–9 points), and 6.5 points (range, 2.5–10 points) in groups A, B, C, and D, respectively ($p = 0.001$). However, there were no significant differences in the changes in the median IIEF-5 scores between groups ($p = 0.611$) (Table 3). A clinically substantial improvement in IIEF-5 scores was observed in response to treatment ($n = 77$) using the MCIDs criteria, with 71%, 63%, 65.8%, and 65% of patients achieving the criteria in groups A, B, C, and D, respectively. No significant differences were observed in the proportions of patients achieving MCIDs between groups ($p = 0.928$) (Fig. 2). Patient satisfaction rates were 74.2%, 66.7%, 71.1%, and 80% in groups A, B, C, and D, respectively, with no notable variations between groups ($p = 0.775$). The response to

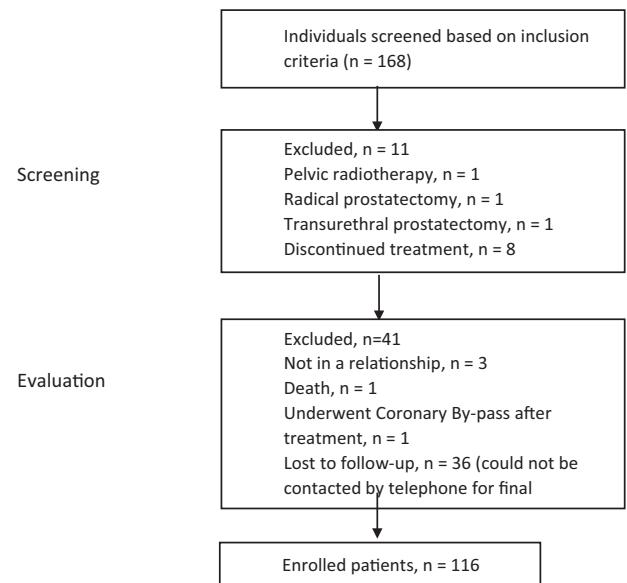


Fig. 1 Consort diagram.

Table 1. Descriptive statistics for demographic and clinical characteristics of the patients.

Demographic and clinical characteristics	Descriptive statistics (n = 116)	
	Mean \pm SD	Median (Min–Max)
Age (years)	47.34 \pm 12.65	47 (19–71)
BMI (kg/m ²)	26.72 \pm 3.72	26.22 (16.48–37.65)
Follow-up length (years)	2 \pm 1.16	2 (0.33–4.10)
Baseline IIEF-5 score	12.09 \pm 3.66	12 (5–20)
IIEF-5 score at the end of follow-up	18.41 \pm 5.68	20 (5–25)
	N (%)	
Smoker	25 (21.6)	
Diabetes mellitus	25 (21.6)	
Hypertension	31 (26.7)	

Values are presented as mean \pm standard deviation, median (minimum–maximum), or number (n) (%). BMI body mass index, DM diabetes mellitus, HT Hypertension, IIEF-5 International Index of Erectile Function-5.

Table 2. Comparisons of demographic and clinical characteristics among the groups.

	Group A (n = 31) n (%)	Group B (n = 27) n (%)	Group C (n = 38) n (%)	Group D (n = 20) n (%)	P
Smoking	7 (22.6)	6 (22.2)	7 (18.4)	5 (25)	0.943
DM	5 (16.1)	8 (29.6)	10 (26.3)	2 (10)	0.299
HT	8 (25.8)	8 (29.6)	8 (21.1)	7 (35)	0.693
Disease severity (IIEF-5 scores)					0.427
5–7 (severe)	6 (19.4)	2 (7.4)	5 (13.2)	0 (0)	
8–11 (moderate)	10 (32.3)	9 (33.3)	10 (26.3)	5 (25)	
12–16 (mild to moderate)	13 (41.9)	14 (51.9)	16 (42.1)	11 (55)	
17–21 (mild)	2 (6.5)	2 (7.4)	7 (18.4)	4 (20)	
Age (years) (Mean ± SD)	47.81 ± 13.08	48.52 ± 12.73	46 ± 12.83	47.55 ± 12.26	0.874
BMI (kg/m ²) Median [25–75%]	25.9 [24.4–27.1]	26.5 [24.1–29.4]	26.1 [23.3–28.4]	25.1 [23.3–29.8]	0.694
Baseline IIEF-5 score Median [25–75%]	11.0 [8–13]	12.0 [10–15]	12.0 [11–15]	13.0 [11.5–15]	0.084

BMI body mass index, DM diabetes mellitus, HT hypertension, IIEF-5 International Index of Erectile Function-5.

Significant set at 0.05 level; Chi-square test for categorical data, one-way ANOVA test for data, Kruskal–Wallis test for non-normal data. Values are presented as mean ± standard deviation, median (minimum–maximum), or number (n) (%).

Table 3. Improvements in IIEF among follow-up groups.

	Follow-up groups				P*
	Group A Median [25–75%]	Group B Median [25–75%]	Group C Median [25–75%]	Group D Median [25–75%]	
Baseline IIEF-5 scores	11.0 [8–13]	12.0 [10–15]	12.0 [11–15]	13.0 [11.5–15]	0.084
Follow-up IIEF-5 scores	20 [15–22]	20 [11–23]	20 [15–22]	22 [16.5–23.0]	0.644
Changes in IIEF-5 scores	7 [3–12]	6 [0–8]	7 [1–9]	6.5 [2.5–10]	0.611
Within groups P [#]	0.001	0.001	0.001	0.001	

IIEF-5 International Index of Erectile Function-5.

P* = Kruskal–Wallis test, P[#] = Wilcoxon test.

treatment was not associated with the baseline IIEF-5 score, age, smoking status, or ED severity ($p = 0.053$, $p = 0.082$, $p = 0.086$, and $p = 0.094$, respectively) (Table 4). However, after controlling for the impact of other factors, patients with moderate ED responded to treatment 9.14 times better than those with severe ED (odds ratio, 9.14; 95% confidence interval, 1.2–0.02). No adverse effects were observed at the Li-ESWT treatment sites. Eight patients (4.76%) were unable to complete the treatment regimen due to adverse effects of tadalafil, with five experiencing back pain and three experiencing headaches.

DISCUSSION

Current urological guidelines recommend PDE5Is as the first-line treatment for patients with erectile dysfunction (ED), but these drugs have limitations. First, PDE5Is have palliative and transient effects as they do not address the underlying pathology of ED. Second, PDE5Is may not be effective for patients with severe ED, despite positive outcomes in many studies. Third, adverse effects are associated with PDE5I use. Moreover, patients must plan sexual activity and take the medication in advance, which can lead to dissatisfaction and treatment discontinuation [22–24].

To address the limitations of PDE5Is and provide curative and non-invasive therapy for ED, low-intensity extracorporeal shock-wave therapy (Li-ESWT) has gained attention in andrological practice as a promising treatment option in recent years [14]. While numerous studies report positive and long-lasting effects of Li-ESWT on the IIEF-5 erectile function domain scores, some investigations suggest that the effects may diminish over time,

and the therapy may not be effective for patients with severe ED [25].

Li-ESWT has been shown to stimulate the release of angiogenic factors, such as vascular endothelial growth factor, endothelial nitric oxide synthase, and proliferating cell nuclear antigen, resulting in the promotion of tissue regeneration and neoangiogenesis, and improving the local blood supply and hemodynamics. In addition, Li-ESWT has been found to partially treat peripheral neuropathy, endothelial dysfunction, and pathological fibromuscular alterations in the corpus cavernosum [26]. Li-ESWT also enhances the synthesis of cGMP, the second messenger underlying smooth muscle relaxation required for erection [16], and its combination with PDE5Is could result in a synergistic effect to increase its influence on erectile function. Several studies have explored the effects of combining Li-ESWT with PDE5Is on IIEF-5 erectile function scores in men with ED and found that the combination is more effective than either treatment alone [27–29].

Our findings demonstrate a significant improvement (approximately 6 to 7 points) in median IIEF-5 scores of patients with ED who received our treatment regimen compared to baseline values of all groups, with no significant differences between groups. The improvement in median IIEF-5 scores remained stable for up to 4 years or more, and 65% of patients remained responders for this duration. Our study suggests that the long-term administration of tadalafil, both during the Li-ESWT period and as an adjuvant treatment (for 6 months), may have long-lasting beneficial effects on IIEF-5 scores. Our results suggest that the use of such a combination of Li-ESWT and PDE5Is for the treatment of ED should be investigated by well-designed clinical studies.

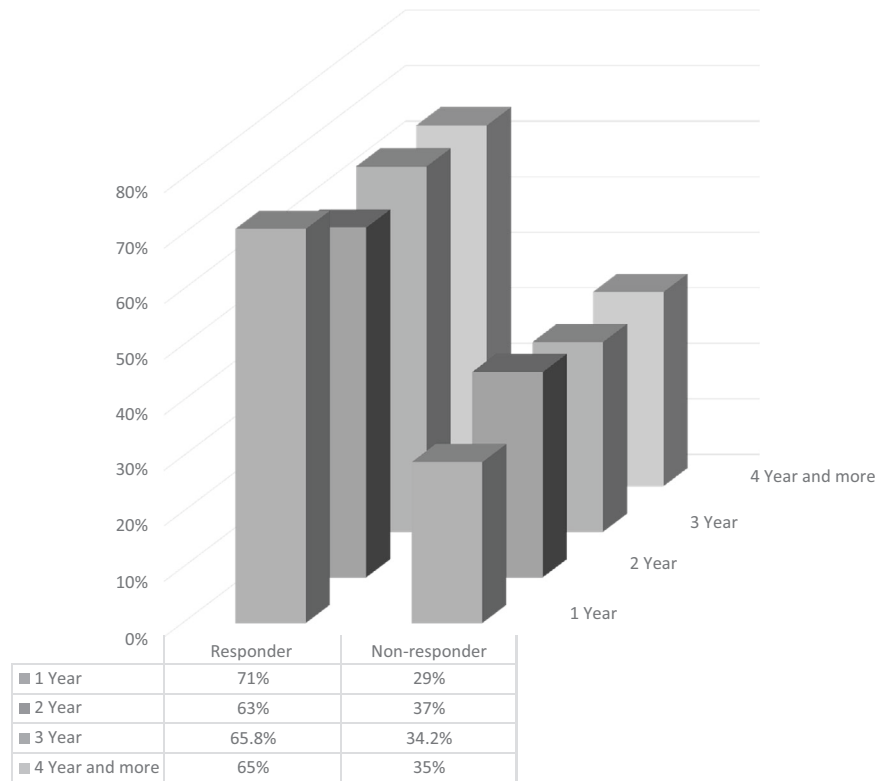


Fig. 2 Relationships between the treatment response and follow-up data.

Table 4. Relationship between treatment response and patient characteristics.

Patient characteristics	Responder (n = 77)	Non-responder (n = 39)	P
Age, years (Mean ± SD)	45.88 ± 12.27	50.25 ± 13.04	0.082
BMI, kg/m ²	Median [25–75%] 26.42 [24.02–29.41]	Median [25–75%] 26.15 [24.45–28.41]	0.730
Baseline IIEF-5 scores	12 [11–15]	11 [8–15]	0.053
Smoking			0.086
Yes	13 (16.9)	12 (30.8)	
No	64 (83.1)	27 (69.2)	
DM			0.215
Yes	14 (18.2)	11 (28.2)	
No	63 (81.8)	28 (71.8)	
HT			0.528
Yes	22 (28.6)	9 (23.1)	
No	55 (71.4)	30 (76.9)	
Severity of ED (IIEF-5 Score)			0.094
Sever (5–7)	6 (7.8)	7 (17.9)	
Moderate (8–11)	20 (26)	14 (35.9)	
Mild to moderate (12–16)	38 (49.4)	16 (41)	
Mild (17–21)	13 (16.9)	2 (5.1)	

BMI body mass index, DM diabetes mellitus, HT hypertension, IIEF-5 International Index of Erectile Function 5.

Significant set at 0.05 level; Chi-square test for categorical data, Student's t-test for normal data, Mann–Whitney U-test for non-normal data. Values are presented as mean ± standard deviation, median (minimum–maximum), or number (n) (%).

According to meta-analyses, patients with severe ED, hypertension, diabetes mellitus, longer ED durations, and no response to PDE5Is may not be good candidates for Li-ESWT [17, 18]. Our study found associations, although not significant, between response to treatment and baseline IIEF-5 score, age, smoking status, and ED severity. The strongest association was between ED

severity and response to treatment, with a 9.14-fold higher response rate for individuals with mild ED compared to those with severe ED. Therefore, patient selection is crucial for the success of LiESWT.

Patient satisfaction rates were high among those treated with our protocol, even after 4 years, and were similar to the

percentage of patients who were responders to treatment. However, further studies are needed to evaluate the long-term effects of this treatment on patient satisfaction.

It is important to note that patient safety was not compromised with only a small percentage of patients (4.76%) discontinuing treatment due to side effects caused by tadalafil. Although this study had some limitations such as the absence of a placebo group and a retrospective design, the sizable patient population and long follow-up period (4 years or more) make this study significant. Future studies should address the efficacy and safety of this combined treatment modality with larger samples and placebo-controlled designs.

CONCLUSIONS

The combination of daily 5 mg tadalafil and Li-ESWT as adjuvant therapy proved to be both safe and effective in treating ED patients who did not respond to PDE5Is. The beneficial effects of this combination persisted for at least 4 years after the last application, and the magnitude of improvement remained stable. While this treatment was effective for all patients regardless of ED severity, those with mild ED were the most suitable candidates.

DATA AVAILABILITY

The data generated during this study can be found within the published article and its supplementary files. The additional data are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Yurdaer Kaynak designed the study and contributed to data extraction. The study was written by Yurdaer Kaynak. Ilan Gruenwald contributed to the writing of the paper and editing. Both of them approved the final version and submitted the paper to the journal.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The study was done under ethical approval (approval number: ESH/GOEK2022/1).

ADDITIONAL INFORMATION

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