

A single-centre result of two courses of low-intensity shockwave therapy (Li-SWT) in erectile dysfunction

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Abstract

The purpose of this study is to evaluate the results of two courses of low-intensity shock wave therapy (Li-SWT) in the treatment of patients with erectile dysfunction (ED). Between June 2015 and December 2020, diabetic and non-diabetic patients with ED treated with two Li-SWT courses were evaluated retrospectively among the data of 317 patients. The outcomes were evaluated using the International Index of Erectile Function-Erectile Function Domain (IIEF-EF) questionnaire values at baseline and 6 months post-treatment for each Li-SWT course with (0.09 mJ/mm²) 18000 shock waves. Successful treatment criteria for patients who also underwent physical examination and anamnesis before and after each course were IIEF-EF scores ≥ 26 during the 6 months follow-up. Forty-one patients with a mean age of 51.61 ± 11.80 years were included in the study. The mean IIEF-EF scores were 15.17 ± 3.75 at baseline, 21.61 ± 3.60 after the first course [mean difference(MD): -6.439 ; 95% confidence interval(CI), -7.138 – -5.740 ; $t = -18.621$; $p < 0.001$], and 25.27 ± 4.05 after the second course(MD: -3.658 ; 95% CI, -4.067 – -3.249 ; $t = -18.071$; $p < 0.001$). Evaluation of score increases in diabetic patients was also statistically significant for each course ($p < 0.001$). Our study shows that two courses of Li-SWT treatments are safe for both diabetic and non-diabetic patients with ED and effective for each course.

KEYWORDS

diabetes mellitus, erectile dysfunction, two courses of low-intensity shockwave therapy

1 | INTRODUCTION

Erectile dysfunction (ED) increases continuously with age and affects 30% of men above the age of 40 years worldwide and the rate varies from 35% to 90% due to different populations and ages among diabetic men as well. Endothelial injury, neuropathy, microvascular and fibrous-vascular alterations are basic pathological reasons for ED. Treatment of ED is so difficult, in all patients, especially in diabetic ones (Miner & Kim, 2015; Zhou et al., 2017).

Nonsurgical treatments include phosphodiesterase type 5 inhibitors (PDE5i), and intracavernosal injections of vasodilating agents (Carson & Lue, 2005). Although the PDE5i can afford temporary relief, it has several negative side effects, such as the need to plan sexual intercourse, headache, dizziness, a decrease in blood pressure

with serious effects when combined with nitrate preparations (Guo et al., 2009). Current medical treatments of ED cannot change the underlying pathophysiologic factors. Nowadays, ED treatment focused on regenerative therapies, such as low-intensity shockwave therapy (Li-SWT), to achieve a natural erection (Campbell et al., 2020). The effect mechanism of regenerative therapies in ED is related to the stimulation of cell proliferation, tissue regeneration, angiogenesis and the reversal of pathologic processes in the erectile tissue (Liu et al., 2019; Sokolakis et al., 2019). The European Association of Urology (EAU) guideline states that Li-SWT can be used in patients with mild organic ED or poor responsiveness to PDE5i with a weak recommendation force (Schoofs et al., 2019).

Even though it has been stated that Li-SWT treatment in ED can be well tolerated and effective, it is known that a specific treatment

protocol and long-term follow-up results are needed. Moreover, data about the two courses of Li-SWT in ED are also limited (Fojecki et al., 2018). The aim of this study is to evaluate the results of patients who had more than one course of Li-SWT, which is insufficient in the literature, and to answer the question of which patients can we recommend performing one more course Li-SWT.

2 | MATERIALS AND METHODS

2.1 | Patients

Between January 2015 and December 2020, the data a total of 317 patients who underwent Li-SWT treatment for ED were evaluated retrospectively. Forty-one patients, who had been treated with 2 courses of Li-SWT 6 months apart, were included in the study among fifty-seven patients. None of the patients did use PDE5i during the treatment and follow-up. The exclusion criteria were glycated haemoglobin levels >7 ng/ml ($n = 6$), hypogonadism (testosterone levels <4 ng/mL) ($n = 2$), non-adjusted cardiac and antihypertensive medications with consultations ($n = 4$), history of radical pelvic surgery ($n = 1$), not followed up ($n = 1$), and data unavailability ($n = 2$).

A urologist recorded the sexual history of the patients and performed a genitourinary physical examination, and evaluated the blood testosterone levels. The erectile function of patients was determined according to the International Index of Erectile Function-Erectile Function Domain (IIEF-EF) questionnaire (Cappelleri et al., 1999). ED grading was made following; 0–10 points were severe ED, 11–16 points were moderate ED, 17–21 points were mild-moderate ED, 22–25 points were mild ED and 26–30 points were normal Erectile Function.

In our clinical routine that all patients with ED are informed about different treatment options according to current treatment guidelines, detailed information is also provided about outcomes and complications.

2.2 | Methods

All patients included in this study had been subjected to a total of two courses of Li-SWT apart six months. One course consisted of five implementations about 7 ± 2 days apart. In each implementation, 1800 shockwaves (SW) (0.09 mJ/mm²) were applied to the distal penile shafts and 1800 SW to the perineal corpus cavernosum. Thus, in total, 18,000 SW were applied to each patient at the end of one course. The treatment was administered in an outpatient setting without anaesthesia, wherein the application areas were the same, and each implementation lasted approximately 20 min (Reisman et al., 2015).

The SW were applied with a Linear Renova (Initia Ltd. Petah Tikva), a second-generation electromagnetic energy source Li-SWT device that could penetrate the tissue up to 70 mm.

In the study, in which the probe was supported manually without the use of any stabilisers or additional accessories to ensure an effective tissue contact, the applications were performed by the same urologist throughout the entire process.

2.3 | Outcome criteria of patients

For evaluation of each Li-SWT course, the IIEF-EF questionnaire values, physical examination and anamnesis were performed, at the beginning and 6 months follow-up but, Doppler USG was not. Successful treatment criteria for patients were IIEF-EF scores ≥ 26 during the 6 months follow-up.

This study was approved by Çukurova University Clinical Research Ethics Committee (Approval no. 115;10.01.2021).

2.4 | Statistical analysis

Statistical Product and Service Solutions version 22.0 (SPSS Inc.) software was used for statistical analysis. Continuous variables are presented as means \pm standard deviations. Independent *t*-tests were performed for these variables; *p*-values <0.05 were considered statistically significant. The distribution normality of our data was demonstrated by 'Skewness and Kurtosis' values in the range of $+1.5$ – -1.5 (Tabachnick & Fidell, 2013).

3 | RESULTS

Forty-one patients who underwent two courses of Li-SWT were included in the study. Eighteen of them had DM. The mean age of patients was 51.61 ± 11.80 years. After two courses of Li-SWT, the 25 successfully treated patients' mean age was 49.84 ± 11.01 ; however, the 16 patients with a mean age of 54.38 ± 12.80 years old could not be treated successfully. The difference in ages was statistically significant ($p < 0.001$). Table 1 shows the descriptive statistics for demographics and patients' characteristics. The Li-SWT courses were well tolerated in all cases, and no systemic complications or local complications (such as penile pain, skin reactions, Peyronie's Disease and haematuria) were noted during the treatment or follow-up.

3.1 | Evaluation of mean IIEF-EF scores

The mean IIEF-EF scores of patients were 15.17 ± 3.75 at baseline, 21.61 ± 3.60 after the first course [mean difference (MD): -6.439 ; 95% confidence interval(CI), -7.138 – -5.740 ; $t = -18.621$; $p < 0.001$], and 25.27 ± 4.05 after the second course (MD: -3.658 ; 95% CI, -4.067 – -3.249 ; $t = -18.071$; $p < 0.001$) (Table 2). The results show that the first course provided an improvement of 6.44 and also the second course that was 3.65 points. The power of positive correlation between the baseline and after first course scores was 0.82

TABLE 1 Demographic characteristics of patients

| | The study population <i>n</i> = 41 | Patients with DM <i>n</i> = 18 | Patients with non-DM <i>n</i> = 23 |
|---|------------------------------------|--------------------------------|------------------------------------|
| Age years ^a | 51.61 ± 11.80 | 51.50 ± 11.66 | 51.69 ± 12.16 |
| Duration of ED years ^a | 4.54 ± 2.75 | 5.25 ± 2.50 | 4.02 ± 2.10 |
| Hypertension ^b | 9 (21.9) | 4 (22.2) | 4 (17.4) |
| Diabetes mellitus ^b | 18 (43.9) | 18 (100) | |
| Cardiovascular diseases ^b | 8 (19.5) | 4 (22.2) | 4 (17.4) |
| Benign prostatic hyperplasia ^b | 14 (34.1) | 6 (33.3) | 8 (34.8) |
| Peyronie's disease ^b | 3 (7.3) | 2 (11.1) | 1 (4.3) |
| Morbid obesity ^b | 2 (4.9) | | 2 (8.7) |
| Penile hypoesthesia ^b | 2 (4.9) | | 2 (8.7) |
| Pelvic trauma ^b | 1 (2.4) | | 1 (4.3) |

Abbreviations: BMI, Body Mass Index; ED, Erectile dysfunction.

^aData are expressed as mean ± standard deviation,

^bData are expressed as frequency (%).

TABLE 2 Pre- and post-treatment mean IIEF-EF scores of Li-SWT Courses

| | First Course Li-SWT | Second Course Li-SWT | <i>p</i> value |
|--|---------------------|----------------------|----------------|
| Mean IIEF-EF scores (<i>n</i> = 41) | | | |
| Baseline | 15.17 ± 3.75 | 21.61 ± 3.60 | 0.001 |
| 6th month | 21.61 ± 3.60 | 25.27 ± 4.05 | 0.001 |
| Mean IIEF-EF scores of patients with DM (<i>n</i> = 18) | | | |
| Baseline | 13.94 ± 3.87 | 20.72 ± 4.31 | 0.001 |
| 6th month | 20.72 ± 4.31 | 23.94 ± 4.78 | 0.001 |
| Mean IIEF-EF scores of patients with non-DM (<i>n</i> = 23) | | | |
| Baseline | 16.13 ± 3.42 | 22.30 ± 2.83 | 0.001 |
| 6th month | 22.30 ± 2.83 | 26.30 ± 3.09 | 0.001 |

Note: Bold values indicate statistical significance (*p* < 0.05).

Abbreviations: DM, Diabetes Mellitus; IIEF-EF, International Index for Erectile Function Area Index; Li-SWT, Low-intensity shockwave therapy.

and also the power of positive correlation was 0.95 between the first and second courses. Both *p*-values were significant with <0.05. The comparison of IIEF-EF score increases with the previous one was statistically significant for each course in all patients.

The mean age of non-diabetic patients was 51.69 ± 12.16 years. Their mean scores were 16.13 ± 3.42 at baseline, 22.30 ± 2.83 after the first course (MD: -6.174; 95% CI, -6.860: -5.488; *t* = -18.675; *p* < .0001) and 26.30 ± 3.09 after the second course (MD: -4.000; 95% CI, -4.583: -3.416; *t* = -14.227; *p* < .0001) (Table 2). The results show that the first course provided an improvement of 6.17 and also the second course that was 4.00 points. The power of positive correlation between the baseline and after first course scores was 0.89 and also the power of positive correlation was 0.90 between the first and second courses. Both *p*-values were significant with <0.05.

The mean age of diabetic patients was 51.50 ± 11.66 years. Their mean scores were 13.94 ± 3.87 at baseline, 20.72 ± 4.31 after the first course (MD: -6.600; 95% CI, -8.965: -4.235; *t* = -6.312;

p < .0001) and 23.94 ± 4.78 after the second course (MD: -2.700; 95% CI, -3.379: -2.021; *t* = -9.000; *p* < .0001) (Table 2). The results show that the first course provided an improvement of 6.78 and the second course was 3.22 points. The power of positive correlation between the baseline and after first course scores was 0.76 and also the power of positive correlation was 0.98 between the first and the second courses. Both *p*-values were significant with <0.05.

3.2 | Evaluation of successful outcome with IIEF-EF scores ≥26

According to ED grades, successful treatment results are summarized in 3 columns in Table 3. The patients' initial ED grades before treatment are shown in the first column. Patients whose IIEF-EF scores increase to the range of 22–25 (mild ED grade) after the first course are also shown in the second column. Finally, the number of patients with an IIEF-EF score of ≥26 after two courses of Li-SWT, whose treatment was considered successful, is shown in the third column of Table 3.

Twenty-five (61%) patients with ED were successfully treated with two courses of Li-SWT. At the end of the first course, none of the patients had IIEF-EF scores ≥26 but, twenty-seven of 41 patients increased to mild ED grade. Twenty-three (85%) of these twenty-seven patients were treated successfully at the end of the two courses (Table 3).

According to initial ED grades, 15/18(83.3%) patients with mild to moderate ED, and 10/16(62.5%) with moderate ED had been treated successfully with two courses of Li-SWT. The number of severe ED grades was higher in diabetic patients than in non-diabetic patients and, none of them could be successfully treated by the two courses of Li-SWT (Table 3).

Twenty-three of 27 patients (85%) who had increased to mild ED at the end of the first course were successfully treated by the second course. The evaluation of successful treatment rates was 56% patients with DM versus 65% with non-DM.

TABLE 3 According to baseline ED grades, the number of patients at the end of the first course with mild ED and the end of two courses successfully treated patients

| Baseline ED Grades | Number of patients | | End of First Course Patients with Mild ED (IIEF-EF = 22-25) | | End of Two Courses Patients with successfully treatment (IIEF-EF \geq 26) | |
|--------------------|--------------------|--------|---|--------|---|--------|
| | DM | Non-DM | DM | Non-DM | DM | Non-DM |
| Severe | 5 | 2 | 0 | 0 | 0 | 0 |
| Moderate | 7 | 9 | 5 | 5 | 6 | 4 |
| Mild-Moderate | 6 | 12 | 6 | 11 | 4 | 11 |

Abbreviations: DM, Diabetes Mellitus; ED, Erectile dysfunction; IIEF-EF, International Erectile Function-Erectile Function Area Index; IIEF-EF \geq 26, Successfully treated patients; IIEF-EF=22-25, Patients with Mild ED grade.

4 | DISCUSSION

Our study showed that each Li-SWT course provided a statistically significant increase in IIEF-EF scores. This study is very important in terms of demonstrating the efficacy and safety of more than one course of Li-SWT, and it has also been shown that patients who cannot gain normal erectile function with a single course can recover with the second course.

Although, many questions remain unanswered regarding the mechanism of action, the ideal treatment protocol, many recent studies about Li-SWT implementations in ED present exciting positive results about the possibility of restoring erectile tissue based on blood flow Doppler assessments (Sokolakis et al., 2019; Sokolakis & Hatzichristodoulou, 2019). The study of Kalyvianakis D et al. confirmed the beneficial effect of one-course Li-SWT on penile haemodynamics and the beneficial effect of this treatment up to 12 months. They reported, the IIEF-EF minimal clinically important differences [75% vs. 25%; $p = .008$], and mean peak systolic velocity increasing [4.5 vs. 0.6 cm/s; $p < .001$], in the Li-SWT groups (Kalyvianakis & Hatzichristou, 2017). In contrast, the objective penile Doppler ultrasonography criteria for the evaluation of the etiological diagnosis and follow-up were not used in this study. Even if the IIEF-EF scores correlate with Doppler USG, all questionnaires used in the examination of ED should be interpreted carefully as answers may be affected by certain daily events, including stress, social problems, and self-consciousness. Similar to the current studies, we may advise evaluating with both the IIEF-EF questionnaire and as objective criteria Doppler ultrasound to examine the increasing erectile capacity. Because the relationship between the increase in IIEF-EF scores and angiogenesis/nerve regeneration is also not clear (Sokolakis & Hatzichristodoulou, 2019).

The European Association of Urology (EAU) guideline on ED states that Li-SWT can be used with a weak recommendation force for patients with mild organic ED or poor responders to PDE5i. In contrast, in the American Urological Association (AUA) guideline, Li-SWT stands as an investigational recommendation, not an approved treatment option (Schoofs et al., 2019). Hence, we think there is a requisite need for more studies to understand the effect of more than one Li-SWT course in ED with different grades.

In our study, weekly 3600 SWs in a total of five weeks were applied to each patient at one course.

The number of SWs delivered with the linear probe was calculated based on the report of positive outcomes in ED of the previous three trials applied by an electromagnetic device (Renova, Direx Systems GmbH).

Same as our study Bechara et al. and Reisman et al. treated their patients with weekly 3600 SWs and 0.09 mJ/mm², a total of four weeks (Bechara et al., 2016; Reisman et al., 2015). Pelayo-Nieto et al. applied the same energy level; however, their treatment protocol consisted of four treatments of weekly 5000 SWs (Pelayo-Nieto et al., 2015). And also, the outcome evaluation criteria IIEF-EF questionnaire was similar to them.

We applied the SW with a Linear Renova (Initia Ltd. Petah Tikva), a second-generation electromagnetic energy source Li-SWT device. Although the studies reported the heterogeneities about different production types (piezoelectric, electromagnetic, electrohydraulic) and delivery devices (linear, focused) of SWs (Clavijo et al., 2017; Fojecki et al., 2017; Lu et al., 2017; Sokolakis et al., 2019), a recent study about the efficacy of Li-SWT for the treatment in ED stated the good tolerability and the similar efficacy of different SW devices/probes; on the other hand, it emphasized the needs of a specific treatment protocol and long-term follow-up results (Campbell et al., 2019).

The optimal number of treatments in Li-SWT still needs to be investigated. In our results, considering the IIEF-EF scores and the number of patients successfully treated, it was revealed that two courses of treatment were better than one course of treatment. In contrast, Fojecki et al. reported that two courses (10 implementations \times 600 = 6.000 SWs) of Li-SWT were not superior to one course (5 implementation \times 600 = 3.000 SWs). In other words, at the 6th and 12th months, follow-up results of 6000SWs are not superior to 3000 (Fojecki et al., 2017). The inconsistency of results between this report and ours may be due to the SW numbers applied because we applied 18.000 SWs for each course.

Many randomised, double-blind, sham-controlled study results for one course of Li-SWT implementation can be found in the literature (Fojecki et al., 2017; Kitrey et al., 2016; Olsen et al., 2015; Sokolakis & Hatzichristodoulou, 2019; Vardi et al., 2012). Srimi et al.

found significant increases in the IIEF-EF questionnaire, the results of 12th month follow-up after focused Li-SWT (Srini et al., 2015) were similar to our first course 6th month's.

If we perform more than one course of Li-SWT in ED, we will absolutely have new questions to answer. Firstly, how should we decide on the second course? What are the objective criteria for whom the second course should be performed? Additionally, is it safe to perform the second course? First of all, our study showed that performing the second course is safe and tolerable because no patient during treatment and follow-up reported penile pain, skin reactions, Peyronie's Disease or haematuria. This result is compatible with the currently limited literature (Fojecki et al., 2018).

In this study, Twenty-three of 27 patients (85%) who had increased to mild ED at the end of the first course were successfully treated by the second course. As a result, if we try to answer the question of "how should we decide on the second course? What are the objective criteria for whom the second course should be performed?", we may recommend a second course of Li-SWT to the patients who increased to mild ED at the end of one course. It means that if the patient was with mild ED, one Li-SWT course might be recommended, whether primer or had been treated previously with one course of Li-SWT. This recommendation is also compatible with EAU guidelines (Schoofs et al., 2019).

In the evaluation of patients with DM, each Li-SWT course significantly increased the IIEF-EF scores. The successful treatment ratio of diabetics with the others was 56% versus 65%. Similar to our results, a recent study confirms that Li-SWT is safe and effective, and treating a diabetic ED is harder than also non-diabetic patients (Zhou et al., 2017).

A recent study showed that important factors affecting the success of Li-SWT were age, diabetes, hypertension, smoking, obesity, hyperlipidaemia, pre-treatment Sexual Health Inventory for Men (SHIM) score and ED duration (Adelaeim et al., 2021). Additionally, a meta-analysis comments that ED is an indicator of endothelial dysfunction due to preceding vascular events and increasing age (Dong et al., 2011). Similarly, the age of successfully treated patients in this study was significantly younger than others.

Similar to the literature, to reduce vascular risk factors that increase with aging, we advised our patients, making lifestyle changes (Esposito et al., 2010; Giugliano et al., 2004).

It is important to remember that differences in the numbers of SWs and the lack of a standardised implementation protocol might cause conflicting results. Obviously, dose-finding studies that define the appropriate protocol settings for different devices must be conducted since these details were neglected in previous trials (Fode et al., 2017).

The future aim of Li-SWT research with controlled and prospective clinical trials should be to accurately determine the adequate number of SWs for patients with different degrees of ED. The recommendation of EAU guidelines in ED, 'Li-SWT can be used in patients with mild organic ED or poor responders to

PDE5i', is compatible with our results (Schoofs et al., 2019). We hope that future studies will explain the effectiveness of more than two courses of Li-SWT for successful treatment, especially in severe ED degrees.

4.1 | Strengths & Limitations

The strength of our study is that it is the second study investigating the efficacy of two Li-SWT courses (Fojecki et al., 2018). Although it is known that there is no difference in the efficacy of linear probes and focused probes (Campbell et al., 2019), the use of a linear probe, absence of standardised SW number, absence of objective penile Doppler ultrasonography criteria for evaluating the etiological diagnosis and follow-up, and the retrospective study design with a small group is the limitations of this study.

Because this study was performed with a small group, we were unable to evaluate the treatment success of two courses of Li-SWT in all degrees of ED with substantial evidence.

4.2 | Safety

Whether repeated Li-SWT courses might result in fibrotic plaques in corpora cavernosa and, ultimately, the development remains uncertain (Hatzichristodoulou et al., 2013). In one trial, Peyronie's Disease occurred in a case receiving two courses of Li-SWT. However, no long-term complaints had been reported; it was determined to be coincidental and not related to the SW effects (Fojecki et al., 2018). Likewise, in this study, the development of new PD did not occur in any patient after treatment. Additionally, no irritative urinary symptoms were noticed, or no intracutaneous reactivity occurred.

5 | CONCLUSION

The results of this study demonstrated that two courses of Li-SWT (0.09 mJ/mm², 36000 SWs) in both diabetic and non-diabetic patients with ED were better than one course (0.09 mJ/mm², 18000 SWs) at 6th months of the treatment. We advise the second course for achieving successful treatment only to the patients 'whose IIEF-EF scores increase to the mild ED grade after one course'.

The two courses of Li-SWT treatment were not only safe but also effective. Large-scale, placebo-controlled prospective studies with more than one course Li-SWT application are needed to confirm our results.

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CONFLICT OF INTEREST

No conflict of interest was declared by the author.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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