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Comparison of the efficacy of low-intensity shock wave therapy and its combination with platelet-rich plasma in patients with erectile dysfunction

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Abstract

We aimed to compare the efficacy of low-intensity shock wave therapy (Li-SWT) alone and its combination with platelet-rich plasma (PRP) in the treatment of patients with erectile dysfunction (ED). Between January 2015 and October 2020, patients who did not benefit from the use of phosphodiesterase type 5 inhibitors (PDE5i; 5 mg/day) for at least 3 months and underwent Li-SWT or Li-SWT with PRP were evaluated retrospectively. There were 93 patients who were subjected to Li-SWT only (Group 1) and 91 patients subjected to Li-SWT with PRP (Group 2). Analysis of the International Index of Erectile Function-Erectile Function Area (IIEF-EF) scores showed a significant increase in both the groups post-treatment (Group 1: from 14.33 ± 4.39 to 23.8 ± 4.37, $p = .001$; Group 2: from 17.82 ± 3.44 to 26.3 ± 2.55, $p = .001$). When the increase in the IIEF-EF scores was compared pre- and post-treatment between the groups with respect to the ED grades, there was no statistically significant difference between them. Furthermore, while the intravaginal ejaculatory latency time (IELT) in successfully treated patients of Group 1 remained the same, Group 2 presented 1.5–3.5 times (mean, 2.4) prolongation. Their mean IELT score showed an increase from 2.2 (0.8–3.5) min to 5.3 (2.8–10.5) min. Our study shows that combination treatment of Li-SWT with PRP injections is not only safe for patients with ED, but also effective and safe in prolonging the IELT.

KEYWORDS

erectile dysfunction, intravaginal ejaculatory latency time, low-intensity shockwave therapy, platelet-rich plasma

1 | INTRODUCTION

The occurrence of erectile dysfunction (ED) increases with age and affects 30%–65% of men above the age of 40 years worldwide. Current medical treatment of ED includes intracavernosal injections and administration of phosphodiesterase type 5 inhibitors (PDE5i). The new strategies for medical treatment in ED focus on achieving a natural erection by restoring the erectile penile tissue. Even though the application of regenerative therapies in humans is limited, the use of low-intensity shock wave therapy (Li-SWT) and platelet-rich plasma (PRP) is well known (Campbell et al., 2020).

It is known that penile Li-SWT promotes angiogenesis and regeneration of the neuronal nitric oxide synthase positive nerves, endothelium and smooth muscle cells in rat models with diabetes and pelvic neurovascular injury (Li et al., 2016; Qiu et al., 2013). Although there is insufficient data on this subject in the literature, the European Association of Urology (EAU) guidelines recommended Li-SWT for patients with mild organic ED or poor responsiveness to PDE5i with a weak force (EAU Guidelines, 2020).

Platelets contain various growth factors (GFs), such as platelet-derived GF, epithelial GF, insulin-like GF, vascular endothelial GF and basic fibroblast GF. These GFs play an important role in natural wound healing, vascular remodelling and inflammatory and immune responses (Galliera et al., 2012). PRP is a well-described, platelet-based treatment that is prepared by the centrifugation of the patient's own blood (Drury et al., 2021). The application of PRP to the site of the cavernous nerve (CN) injury has neuromodulatory effects on the regeneration of the CN and recovery of the erectile function (Campbell et al., 2020; Ding et al., 2009). A recent study reported intracavernous PRP treatment in ED cases to be efficient and reliable. Although the mean International Index of Erectile Function-Erectile Function Area (IIEF-EF) values increased significantly, the ED grades of the patients remained the same (Taş et al., 2021).

Potential beneficial effects of Li-SWT in ED involve stimulation of cell proliferation, tissue regeneration and angiogenesis, similar to those of PRP (Clavijo et al., 2017; Galliera et al., 2012; Lu et al., 2017). The results of regenerative therapies, especially those regarding the combination treatment of Li-SWT and PRP in humans, are insufficient. We aimed to compare of the efficacy of Li-SWT alone and its combination with PRP in patients with ED.

2 | MATERIALS AND METHODS

2.1 | Patients

Between January 2015 and October 2020, 218 patients who were with <26 IIEF-EF score after the use of daily 5 mg of tadalafil for at least 3 months and underwent a course of either Li-SWT alone (Group 1) or Li-SWT and PRP combination (Group 2) in the same period were evaluated retrospectively. In other words, ED patients who were unable to achieve a penile erection that would allow satisfactory sexual activity despite the daily using 5 mg PDE5i were included in this study. The exclusion criteria were glycated haemoglobin levels >7 ng/ml ($n = 14$), hypogonadism (testosterone levels <4 ng/ml; $n = 3$), nonadjusted cardiac and antihypertensive medications with consultations ($n = 5$), history of pelvic surgery ($n = 5$), history of degenerative neurological disorders ($n = 1$), not followed up ($n = 4$) and data unavailability ($n = 2$). A urologist recorded the sexual history of the patients and intravaginal ejaculatory latency time (IELT), performed a genitourinary physical examination and evaluated the metabolic hormonal levels. Thirty-four patients in group 1 and 26 in group 2 had been suffering from premature ejaculation, in the period of healthy sexual life before the appearance of ED complaints, within less than 3 min. The erectile function of patients was determined according to the IIEF-EF questionnaire (Cappelleri et al., 1999).

In our clinical routine, all patients with ED are informed in detail regarding the different treatment options, results and complications according to the current treatment guidelines. The patients in this study made their own treatment decision between Li-SWT alone and combination therapy of Li-SWT and PRP. Furthermore, all patients were using PDE5i before the treatment, and they continued its use during the treatment and follow-up.

2.2 | Li-SWT application in both groups

All patients included in this study had been subjected to Li-SWT for one course, consisting of five implementations about 7 ± 2 days apart. In each implementation, 1,800 shockwaves (SW) (0.09 mJ/mm^2) were applied to the distal penile shafts and 1,800 SW to the perineal corpus cavernosum. Thus, in total, 18,000 SW was 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.), a second-generation electromagnetic energy source Li-SWT device that could penetrate the tissue up to 70 mm. All implementations were conducted by the same urologist. The probe was manually supported without using any stabilisers or additional accessories to ensure an effective tissue contact.

2.3 | Preparation and injection process of PRP in Group 2

In patients subjected to PRP combination with Li-SWT, a venous puncture was performed in the clinic. A total of 30 ml of whole blood was drawn from the patients and filled in two PRP sets that were self-gelled and citrated (Ycellbio PRP, Ycellbio Medical Co. Ltd.). The sample was centrifuged at 3,700 ×g for 10 min, and the supernatant was separated from the remaining blood sample. Two kits yielded approximately 12–16 ml of injectable PRP (Matz et al., 2018). A local anaesthetic cream was applied to the target skin, at least 20 min before each PRP injection. The administration in Group 2 was performed via very small-sized injection needles within 3–5 min after the PRP preparation. Each PRP injection was administered 10–14 days apart (Taş et al., 2021), three times in one course. Approximately 3–4 ml of PRP was injected in each one of the four regions: one intracavernosal and three subcutaneous areas (both right and left lateral neural lines and dorsal balanic submucosal region; Figure 1).

2.4 | Outcome criteria of patients

The outcomes were evaluated using the IIEF-EF questionnaire and IELT values at baseline and 6 months post-treatment, while the patients continued using PDE5i (5 mg/day). The short-term clinical results of Li-SWT application alone and the combination treatment were evaluated separately for both groups and compared. Additionally, physical examination and anamnesis were conducted before and after implementation of each course. Successful

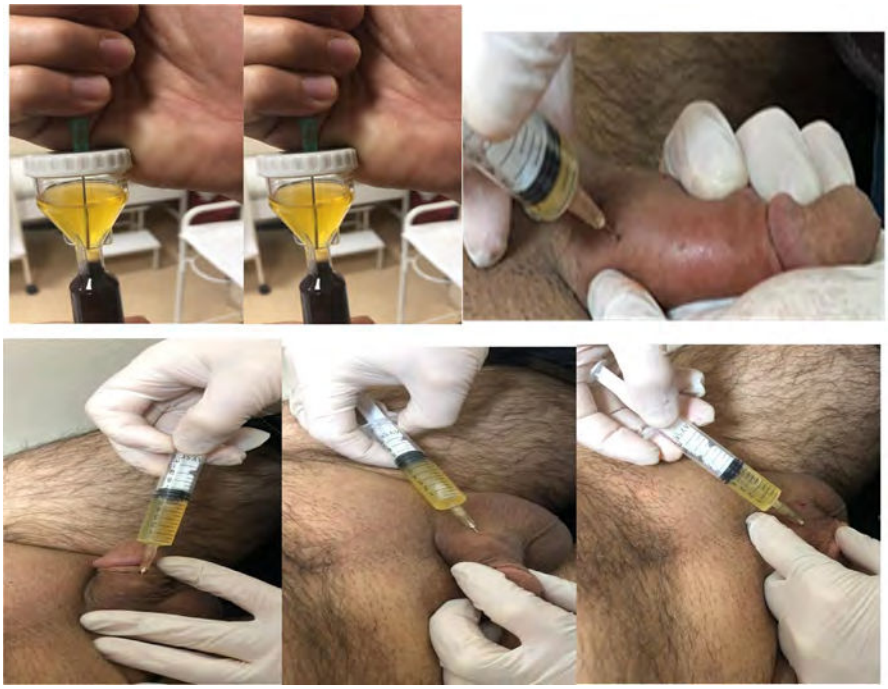

FIGURE 1 Approximately, 12–16 ml of injectable PRP which was yielded with two kits were injected with an insulin needle, 3–4 ml of its was applied in each one of the four regions: one intracavernosal and three subcutaneous areas (both right and left lateral neural lines and dorsal balanic submucosal region)

TABLE 1 Demographic and characteristics of the study population

	Group 1 Li-SWT ($n = 93$)	Group 2 Li-SWT+PRP ($n = 91$)	p value
Age years[a]	51.23 ± 11.36	46.9 ± 11.89	**.012**
Duration of ED years[a]	3.97 ± 2.97	3.97 ± 2.64	.999
Hypertension[b]	24 (25.8)	11 (12.1)	**.024**
Diabetes mellitus[b]	39 (41.9)	26 (28.6)	.065
Cardiovascular diseases[b]	27 (29)	20 (22)	.312
Benign prostatic hyperplasia[b]	20 (21.5)	11 (12.1)	.115
Peyronie disease[b]	8 (8.6)	3 (3.3)	.213
Hemorrhoid, Anal fissure[b]	3 (3.2)	5 (5.5)	.494
Usage of antiplatelets[b]	59 (63.4)	46 (50.5)	.101

Note: Bold values indicate statistical significance ($p < .05$).

[a]Data are expressed as mean ± standart deviation.

[b]Data are expressed as frequency (%).

treatment criteria for patients were IIEF-EF scores ≥26 during the 6-month follow-up.

This study was approved by Çukurova University Clinical Research Ethics Committee (Approval no. 80/36;08.31.2018 and 86/21;08.03.2019).

2.5 | Statistical analysis

Statistical Product and Service Solutions version 22.0 (SPSS Inc.) software was used for statistical analysis. Continuous variables are presented as means ± standard deviations. Independent *t* tests were performed for these variables; *p*-values <.05 were considered statistically significant.

3 | RESULTS

This study included 184 patients who underwent either Li-SWT (Group 1, $n = 93$) or Li-SWT with PRP (Group 2, $n = 91$).

The mean age (51.28 ± 11.43 vs. 46.7 ± 11.86 years) and hypertension ratio (25.8% vs. 12.1%) of Group 1 patients were significantly higher than that of the Group 2 patients ($p = .012$; $p = .024$). Table 1 shows the descriptive statistics for demographics and patients' characteristics. There was no statistically significant difference between the demographic characteristics of the two groups, except for the mean age of the patients.

The patients who did not initially benefit from treatment with 5 mg/day of PDE5i became responsive around the 3rd or 4th week of the treatment, and none of them suffered any side effects. PRP

injections and Li-SWT were well tolerated in all cases, and no systemic complications were noted during the treatment or follow-up. All patients in Group 2 reported a temporary pain at the injection site, and 24 (26.4%) of them had mild penile bruising after the injection despite the absence of bleeding diathesis.

3.1 | Evaluation of mean IIEF-EF scores

The IIEF-EF scores showed a significant increase in both the groups after treatment (Group 1: from baseline 14.33 ± 4.39 to 23.8 ± 4.37 6 months post-operatively, $p = .001$; Group 2: from baseline 17.82 ± 3.44 to 26.3 ± 2.55 6 months post-operatively, $p = .001$; Table 2).

The increase in the IIEF-EF scores was compared pre- and post-treatment with respect to the ED grades between the groups. Group 1 and Group 2 showed an increase of 9.62 ± 3.66 and 10.0 ± 1.41 in the severe ED group ($p = .890$), 10.39 ± 2.83 and 10.06 ± 1.71 in the moderate ED group ($p = .546$), 8.08 ± 1.59 and 7.78 ± 1.42 in the mild–moderate ED group ($p = .431$) and 7.0 ± 1.67 and 6.8 ± 1.01 in the mild ED group ($p = .739$), respectively. There was no statistically significant difference in the increase in the IIEF-EF scores between the groups with respect to the ED grades (Table 3).

TABLE 2 Pre&post treatment IIEF-EF scores of groups

	Group 1 Li-SWT ($n = 93$)	Group 2 Li-SWT+PRP ($n = 91$)	*p* value
Mean IIEF-EF scores			
Baseline	14.33 ± 4.39	17.82 ± 3.44	**.001**
6th month	23.8 ± 4.37	26.3 ± 2.55	**.001**

Note: Bold values indicate statistical significance ($p < .05$).

TABLE 3 Comparison of the mean IIEF-EF score increase between groups based on ED grades

	The mean IIEF-EF score increase		
	Group 1 Li-SWT ($n = 93$)	Group 2 Li-SWT+PRP ($n = 91$)	*p* value
Mild	7.0 ± 1.67	6.8 ± 1.01	.739
Mild to moderate	8.08 ± 1.59	7.78 ± 1.42	.431
Moderate	10.39 ± 2.83	10.06 ± 1.71	.546
Severe	9.62 ± 3.66	10.0 ± 1.41	.890

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

According to the initial ED grades in Group 1, 18/48 (37.5%) patients with moderate ED, 21/23 (91.3%) with mild-to-moderate ED and 6/6 (100%) with mild ED had post-treatment IIEF-EF scores ≥26. None of the patients with severe ED had IIEF-EF scores ≥26.

According to the initial ED grades in Group 2, 13/33 (39.4%) patients with moderate ED, 38/41 (92.7%) with mild-to-moderate ED and 15/15 (100%) with mild ED had post-treatment IIEF-EF scores ≥26. None of the patients with severe ED had IIEF-EF scores ≥26.

It was observed that the Li-SWT and PRP combination treatment did not contribute to the successful treatment ratios ($p = 1.000$; Table 4).

3.3 | Evaluation of IELT

Although the IELT in successfully treated patients of Group 1 remained the same, the Group 2 patients showed 1.5–3.5 times (mean, 2.4) prolongation. Their mean IELT showed an increase from 2.2 (0.8–3.5) min to 5.3 (2.8–10.5) min.

When the Group 2 patients were asked if they were willing to take more PRP injections to extend their IELT, all 66 successfully treated patients responded positively.

4 | DISCUSSION

Our study showed that the Li-SWT and PRP combination did not provide any additional benefit to the increase in the IIEF-EF scores, but it extended the IELT. However, this study is very important in terms of illustrating the effect of the Li-SWT and PRP combination treatment, and it is the first study in the literature on this subject.

TABLE 4 Comparison of the number of patients who were treated successfully, based on ED grades

	Group 1 Li-SWT ($n = 93$)		Group 2 Li-SWT+PRP ($n = 91$)		
	Number of patients before treatment	In post treatment, number of patients with IIEF-EF ≥26	Number of patients before treatment	In post treatment, number of patients with IIEF-EF ≥26	*p* values
Mild	6	6	15	15	
Mild to moderate	23	21	41	38	**1.000**
Moderate	48	18	33	13	**1.000**
Severe	16	0	2	0	

Current medical ED treatments provide symptomatic relief; hence, the new strategies of ED treatment focus on achieving a natural erection by restoring the erectile penile tissue with regenerative therapies. Even though the application of regenerative therapies in humans is limited, the use of Li-SWT and PRP is well known (Campbell et al., 2020). Although the mechanism of the treatment is unclear and a standardised treatment protocol is lacking, Li-SWT is known to be safe and effective in the treatment of ED (Adeldaeim et al., 2021; Campbell et al., 2019). Moreover, it is a recommended treatment option in the EAU guidelines for ED and in patients with mild vasculogenic ED or poor responses to PDE5i (EAU Guidelines, 2020). Furthermore, our successful treatment results with Li-SWT supported the recommendations of the EAU guidelines.

Usually, tadalafil is prescribed in optional doses of either 10 and 20 mg/day or 5 mg/day. Recent data have confirmed that 40% of men aged >45 years responded to treatment for combined ED and lower urinary tract symptoms/benign prostatic hyperplasia with tadalafil 5 mg once daily, showing symptom improvement after 12 weeks (EAU Guidelines, 2020). Our patients preferred the daily dose in order to have fewer side effects and to engage in continued sexual intercourse. All our patients who did not initially benefit from 5 mg/day PDE5i, despite its use for 3 months, reported that they became responsive around the 3rd or 4th week of the treatment with better erections. None of them suffered any side effects of PDE5i, because they had been using it in the past. Our recommendation of PDE5i use was compatible with that of current studies (Verze et al., 2020) to maximise the improvement in erectile function, and it was almost standard in Li-SWT application. Although the studies on the use of PRP in urologic disorders are limited, many clinical fields such as dermatology, ophthalmology and plastic surgery are using PRP to increase tissue regeneration, angiogenesis and wound healing as both primary and auxiliary treatment methods (Matz et al., 2018). In the pathophysiology of ED, endothelial dysfunction secondary to inflammation shows a significant occurrence rate; hence, the purpose of regenerative ED treatments is to improve the endothelial functions by facilitating the nitric oxide pathway (Assaly-Kaddoum et al., 2016; Vlachopoulos et al., 2006). Experimental studies demonstrate that the cellular mechanisms of PRP and Li-SWT that are activated in tissue regeneration and healing are similar (Liu et al., 2019; Namazi, 2011). Based on this literature, we aimed to evaluate and compare the IIEF-EF scores, post-treatment success rates and changes in IELT between the two groups.

In 2012, Wu et al. conducted an experimental study with a control group and animals with a neural crush injury. The PRP-treated group exhibited a significantly greater number of preserved myelinated cavernous neural axons at 1 month as compared to the non-PRP-treated group. These results support the conclusion that PRP increases the number of myelinated axons, thus facilitating the recovery of erectile function (Drury et al., 2021; Raheem et al., 2020). Similarly, the Group 2 patients in our study reported that in repeated PRP injections, the sensation of sensitivity and pain in the penile area increased as compared to the previous injection, despite application of the same local anaesthetic. Since the injections were administered along both lateral cavernosal and dorsal submucosal penile nerve line regions, we attributed the patients' feedback to an increase in the regional circulation and sensitivity due to the injections. Because the dorsal nerve of the penis is a somatosensory nerve that originates from the ventral rami of the S2–S4 spinal nerves, they have a direct connection to sexual function as they transmit afferent signals to the central nervous system (Kinter & Newton, 2020).

The results of up-to-date analysis on PRP use for ED and Peyronie's disease treatment reported in trials emphasised on limitations of small groups and short follow-up periods, with the lack of control groups and qualitative and quantitative analysis of PRP. Thus, it is important to mention that PRP therapy has the potential for treating male sexual dysfunction, but its safety is uncertain (Epifanova et al., 2020). In contrast, PRP is safe to use in ED.

A study conducted in January 2021 reported the tolerability, efficacy and reliability of PRP in ED. In that study, 31 patients (mean age, 54.41 ± 8.74 years) were evaluated using the IIEF-EF questionnaire after intracavernous autologous PRP administration three times at 15-day intervals. Although the mean IIEF-EF scores increased significantly ($p < .001$) from 18 to 20 after treatment, the mean value remained within the mild–moderate ED grade (scores between 17 and 21). Additionally, the post-treatment sexual satisfaction scores were significantly higher than the baseline values ($p = .002$). Although they reported a micro-fibrotic plaque in one patient during the follow-up after the third injection, they considered PRP safe (Taş et al., 2021). The presence of mild bruises at the PRP injection sites in some patients could be due to inattentive injection method or insufficient decompression after the procedure. Except for this local complication, we did not detect any fibrotic areas or systemic complications during the treatment and follow-up examinations.

Taş et al.'s (2021) study demonstrated that only PRP injections as a regenerative treatment approach in ED is effective but may be insufficient for complete healing. Similarly, our results suggest that PRP treatment in ED would require several PRP applications to achieve satisfactory IIEF-EF scores.

In our study, the statistically significant increase in the IIEF-EF scores 6 months post-treatment ($p = .001$) as compared to the baseline scores in each patient group is consistent with the literature indicating that Li-SWT applications are effective in ED treatment (Adeldaeim et al., 2021; Raheem et al., 2020).

4.1 | Strengths and limitations

The use of a linear probe, absence of standardised Li-SWT and PRP injection doses, absence of standardised injection sites and retrospective study design are the limitations of this study. Although it is known that there is no difference in the efficacy of linear probes and focused probes (Campbell et al., 2019), the lack of objective penile Doppler ultrasonography criteria for the evaluation of the etiological diagnosis and follow-up in ED was another limitation. Patients in group 2 who underwent combination treatment were younger and

had fewer comorbidities in general and also, the 6-month efficacy and the uncertain durability of the treatment represent other limitations. The strength of our study is that it is the first study investigating the efficacy of Li-SWT and PRP combination treatment in ED patients.

5 | CONCLUSION

This study showed that Li-SWT improves erectile functions and PDE5i treatment efficacy in PDE5i-refractory patients with ED. Additionally, the Li-SWT combination with PRP may not significantly benefit in terms of erectile function has been shown.

Combining Li-SWT with PRP injections was not only a safe treatment but also prolonged the IELT. Our PRP injection model may have a potential role in the treatment of patients with premature ejaculation.

Large-scale, placebo-controlled prospective studies with more number of PRP injections and LiSWT applications 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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