THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH & REVIEWS

# The Role of the Low-Intensity Extracorporeal Shockwave Therapy on Penile Rehabilitation After Radical Prostatectomy: A Randomized Clinical Trial

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## ABSTRACT

**Background:** Erectile dysfunction (ED) after radical prostatectomy (RP) still represents a major issue. Considering the benefits recently described regarding the application of low-intensity extracorporeal shockwave therapy (LiESWT) in vasculogenic ED, questions arise about its role in the scenario of penile rehabilitation.

**Aim:** To compare the early introduction of phosphodiesterase-5 inhibitor (PDE5i) with a combination therapy enrolling both early PDE5i use and LiESWT in patients submitted to RP.

**Methods:** This study is a randomized clinical trial, open-label, with 2 parallel arms and an allocation ratio of 1:1. The study was registered in ReBEC (*ensaiosclinicos.gov.br*) Trial: RBR-85HGCG. Both arms started tadalafil at a dose of 5 mg/day right after the removal of the transurethral catheter, and the experimental group received 2,400 shocks/session-week distributed on 4 different penile regions. The full treatment consisted of 19,200 impulses across 8 weeks.

**Outcomes:** The primary clincal end point was $\geq$4-point difference favoring the experimental group considering the mean International Index of Erectile Function short form (IIEF-5) at last follow-up. Any statistical difference in the IIEF-5 score between the arms was stated as the primary statistical end point.

**Results:** Between September 25, 2017, and December 3, 2018, 92 men were enrolled in the study. At last follow-up, we assessed 77 patients, 41 in the control group and 36 in the intervention group. A difference between groups was detected when accessing the final median IIEF-5 score (12.0 vs 10.0; $P = .006$). However, the primary clinical endpoint considering a difference $\geq$4-point between the arms has not been reached. When performing an exploratory analysis comparing the proportion of those individuals with an IIEF-5 score $\geq$17, no difference between groups was noted (17.1% vs 22.2%; $P = .57$).

**Clinical Implications:** So far, the benefits arising from LiESWT for penile rehabilitation after RP have been uncertain.

**Strengths & Limitations:** This is the first trial assessing the role of LiESWT on erectile function after RP. Our study protocol included only one session per week for the experimental group, raising a query if a more intensive application could achieve better results once a statistically significant difference was found between groups. We discontinue the PDE5i use at the last session, which may have interfered in the penile vascular rehabilitation, maybe compromising the results too.

**Conclusion:** After therapy with 19,200 impulses therapy across 8 weeks, we found an improvement of the IIEF-5 score, but it was not enough to be considered clinically significant. More studies are warranted before any recommendation on this topic. **Baccaglini W, Pazeto CL, Corrêa Barros EA, et al. The Role of the Low-Intensity Extracorporeal Shockwave Therapy on Penile Rehabilitation After Radical Prostatectomy: A Randomized Clinical Trial. J Sex Med 2020;XX:XXX–XXX.**



**Key Words:** Prostate Cancer; Erectile Dysfunction; Erectile Function; Penile Rehabilitation; Shockwave

Received August 13, 2019. Accepted December 23, 2019.

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https://doi.org/10.1016/j.jsxm.2019.12.024

## INTRODUCTION

Loss of erectile function (EF) after radical prostatectomy (RP) still represents a major issue. A penile rehabilitation, to improve EF, has been suggested through early introduction of phosphodiesterase-5 inhibitor (PDE5i) and/or with intracavernous injection of vasoactive agents and vacuum device therapy.[1−3] Erectile dysfunction (ED) after RP is mainly due to lesions in the neurovascular bundles. This may occur by partial or total sectioning, by stretching (the most common), or by thermal lesion of the nervous fibers, leading to a neuropraxia.[1] Thus, a multifactorial mechanism, beyond a neurologic cause, should be related to the post-RP ED.

The early use of PDE5i was supposed to improve penile rehabilitation, protecting and preventing permanent endothelial lesion.[4] However, the evidence addressing this method is weak, and the reported success rate ranges from 35 to 75%—when a nerve-sparing procedure was performed.[5,6] Therefore, on a panorama where the classical modalities still limited in achieving the rehabilitation, any attempt to enhance these results matters.

Recent evidence has shown that low-intensity extracorporeal shockwave therapy (LiESWT) may improve EF. In patients with vasculogenic ED, for example, it occurs inducing neovascularization and, consequently, enhancing the penile perfusion, which in turn might convert PDE5i nonresponders to responders.[7−9] In addition, some studies in neuro-injury disease models have shown LiESWT neuroprotective and neurodegenerative effects.[10,11] An investigation study compared autologous nerve graft with and without LiESWT use in an experimental model of sciatic injury. They demonstrated advanced functional recovery in animals treated with LiESWT.[12] So, it emerges the doubt if the LiESWT application might have a role after RP. Therefore, we propose a study to access the LiESWT effects on EF after RP. The primary end point was to compare the early introduction of PDE5i with a combination of early PDE5i and LiESWT in patients submitted to RP.

## MATERIALS AND METHODS

This study was a randomized clinical trial, open-label, with 2 parallel arms and an allocation ratio of 1:1. The study protocol was reviewed and approved by our local ethics committee. The study was registered in ReBEC (*ensaiosclinicos.gov.br*) Trial: RBR-85HGCG. All participants gave written informed consent before entering the study.

### Inclusion and Exclusion Criteria

Every candidate to RP from our institution was considerate as a potential participant. Thus, they have been recruited preoperatively during the consultation to check the eligibility in accordance with baseline data. In addition, the participants were evaluated in consultation after 1 week of the RP to verify if they are still eligible and to apply the informed consent. All patients underwent open RP or laparoscopic RP by urologists in a teaching hospital. Individually, information regarding the International Index of Erectile Function short form (IIEF-5),[13,14] comorbidities, smoking status, and PDE5i use were assessed. The inclusion criteria are as follows: patients aged $\leq$75 years presenting preoperatively an IIEF-5 score >20 (with or without the use of PDE5i), to be in a stable heterosexual relationship for at least 3 months, undergoing bilateral nerve-sparing RP as per the surgical team. After the first initial cases, we decided to modify the inclusion criteria based on IIEF-5 to IIEF $\geq$18 to better represent the sample in our setting. In addition, the participants should agree to discontinue PDE5i use at the end of the protocol for the last assessment of erectile rehabilitation. Exclusion criteria were as follows: patients submitted to pelvic radiotherapy or androgen deprivation therapy, patients with uncontrolled psychiatric condition (depressive mood), patients that presented major postoperative complication in accordance with Clavien-Dindo classification[15] (CD $\geq$ III), patients with ED due to endocrine disease (such as hypogonadism or uncontrolled diabetes mellitus) or those who lost to follow-up.

### Study Protocol

Those participants who met the eligibility criteria were randomized to and divided into 2 groups—experimental and control groups—in a ratio of 1:1. Both arms started tadalafil at a dose of 5 mg/day right after the removal of the transurethral catheter, which occurred between the 7th and 10th postoperative days. All patients received 5 mg tadalafil tablets (7 per week) which were dispensed weekly at each follow-up visit. Patients were monitored in regard continence status (measured by pad/day), sexual function (by history), possible adverse effects of medication, need of additional treatments, as well as any stressful event. The follow-up was scheduled on different days for the groups. The application of the LiESWT (8-week period) began at the V1 (the 6th week after the RP) in those allocated in the experimental group. These applications were performed by 2 researchers (R.Y.S.R. and A.N.) at an isolated room of the research center. Some specific adverse effects that could be related to the LiESWT (such as hematomas, local pain, and neuropraxia) were assessed. Furthermore, at V9, 7 days after the last application (14th week), both group participants were asked to stop the PDE5i during the next 2 weeks (washout period). Therefore, at V10 (the last follow-up), 21 days after last LiESWT application (experimental group) and 16th postoperative week (control group), the final IIEF-5 score was assessed without PDE5i use (Figure 1).

### Intervention—LiESWT in the Experimental Group

A commercially available gel, which is used to sonography, was applied in the genital area; subsequently, the penis was stretched manually with the patient in a lithotomy position. Using Renova (DIREX Group), the impulses were applied on the penile shaft and crura bilaterally without anesthesia in an outpatient setting. The LiESWT device used is based on linear therapy that enables

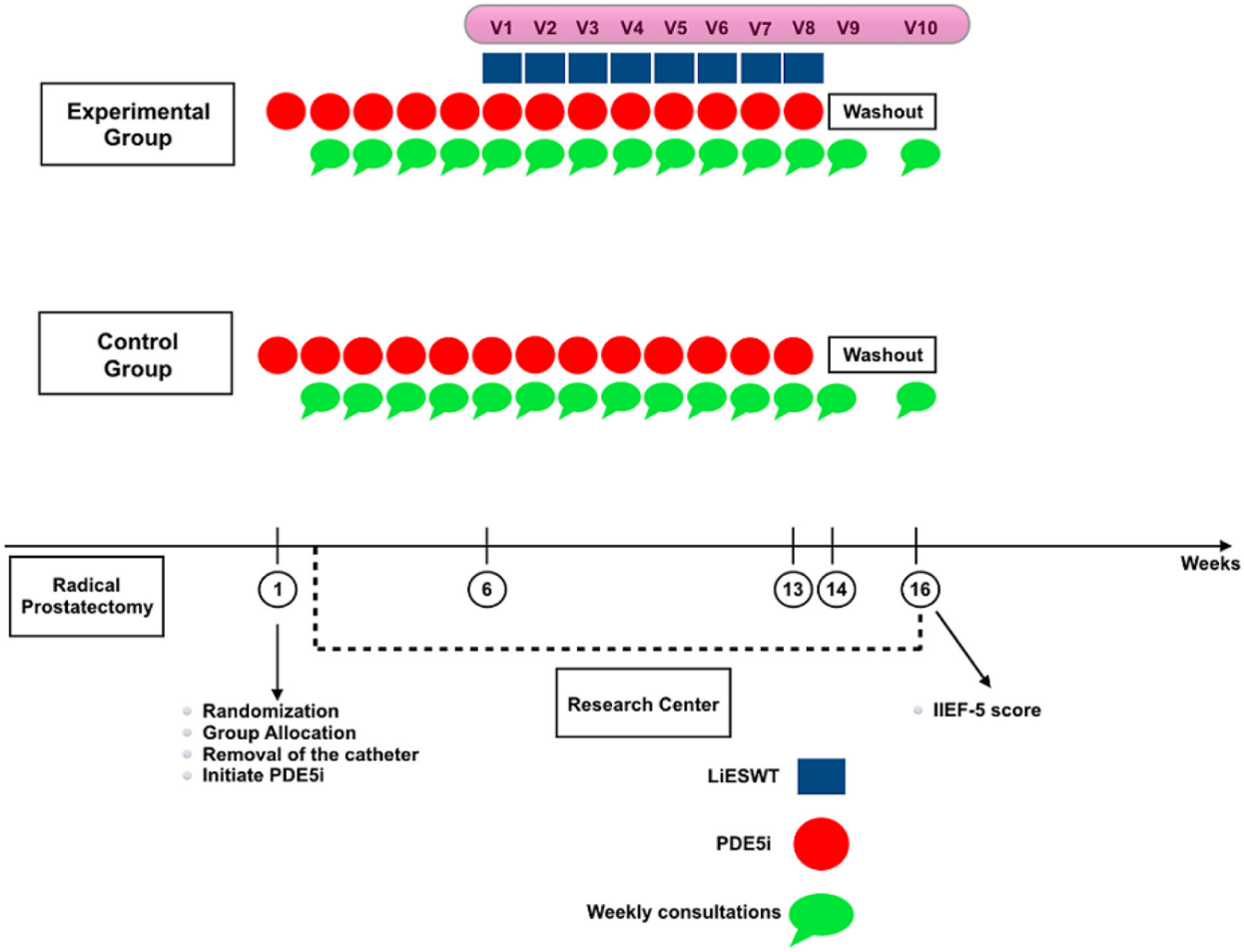


**Figure 1.** Study protocol. Figure 1 is available in color online at www.jsm.jsexmed.org.

focusing shockwaves on a 70 mm long and 10 mm wide treatment area. Each impulse reaches one target area depth of 40 mm, resulting in a focal volume of 9.4 $cm^3$. Besides, the maximum energy density produced is 0.09 mJ $mm^2$, which corresponds to ~10% of that used for the kidney stone treatment. Thus, the patients received per session 600 pulses on each region described (total: 2,400 shocks/session). The shocks were emitted at a maximum frequency of 300 pulses/min (5 Hz), which required an interval of ~8 min for each session. The full treatment consisted of 19,200 impulses across 8 weeks. Despite previous studies with Renova reporting a dosage of 900 pulses per region, no specific recommendation addressing our scenario was found when our study had started. We considered that more than 1 dosage per week is too intense for patients after RP.

## Outcome Measures

The IIEF-5 questionnaire was the selected instrument to evaluate EF preoperatively and at the end of the follow-up. We defined 2 primary end points: a clinical end point and a statistical end point. The primary clinical end point was defined as a difference of at least 4 points favoring the experimental group considering the final mean IIEF-5 score (V10). This specific cutoff has been proven to represent the minimal clinically important difference (MCID) in the EF domain of the IIEF scale.[16] In addition, the mean difference in the IIEF-5 score between groups was stated as a primary statistical end point. The rate of patients reaching orgasm and the erectile hardness score at last follow-up were established as secondary end point. Adverse effects were accounted for and classified in accordance with the CD classification. Continence status was established as the use of 0−1 pad/day and was also evaluated.

## Sample Size

The sample size calculation was based on the assumption of a 4-point of difference between the final IIEF-5 means (estimated as MCID) and considering a standard deviation (SD) of an outcome variable of 7.0 (calculated based on a previous pilot study).[16] In addition, we considered a power of 0.90 and $\alpha$ (2-sided) of 0.05 with a 30% estimation of dropout resulting in a sample size of 92 for this study.

## Randomization

To the randomization, a numeric, random sample displayed in a table was created in a ratio of 1:1 using the R statistical package

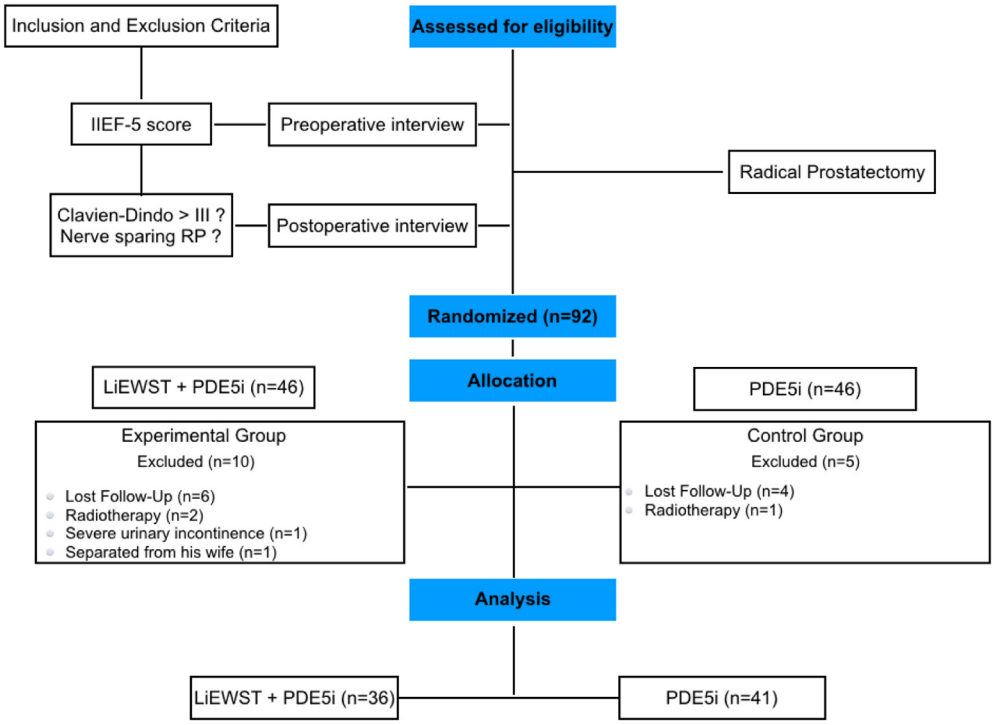


**Figure 2.** Flow diagram. Figure 2 is available in color online at www.jsm.jsexmed.org.

v.3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). Afterward, the random order was applied to the participants in sequence as they entered the trial. The sequence was generated by one author (C.L.P.), the process of allocation was made by other 2 authors (F.T. and L.M.) as well as the interventions that were applied by 2 other authors (A.N. and R.Y.S.R.) who were not involved in the first 2 steps.

## Statistical Analysis

The data were analyzed using statistical software (SPSS 21, IBM Software). The continuous variables were presented and analyzed in accordance with the normality. So, parametric (mean ± SD) and nonparametric data (median; IQR) were tested with t-test and Wilcoxon test, respectively. The t-test was applied when comparing groups concerning the final IIEF-5 means as well. The pretreatment and post-treatment moments were examined with a paired t-test. To the categorical variables (displayed as frequency and percentages), the chi-square test was adopted. Finally, considering baseline and final IIEF-5 values, an analysis of covariance was performed. The $P$ value $< .05$ was considered significant.

# RESULTS

Between September 25, 2017, and December 3, 2018, 92 men were enrolled in the study (Figure 2). 10 (21%) patients of the experimental group and 5 (11%) patients of the control group were excluded. Of these, 10 were lost to follow-up (6 in the experimental and 4 in the control group), 3 needed adjuvant radiotherapy (2 in experimental and 1 in the control group), 1 developed severe urinary incontinence with associated dermatitis and had to stop the application, and one separated from his wife.

Patient demographic and clinical characteristics were similar in the 2 trial groups (Table 1). The data collection cutoff date for the analysis was March 19, 2019. Approximately 83% of patients (82.9% vs 83.3%; $P = .962$) in both groups were continent at the last assessment. No differences between postoperative complication CD I-II (12.2% vs 11.1%; $P = .882$) and CD III-IV (none) were accounted (Table 2). At baseline, the median IIEF-5 score was 22.0 and 21.0 in the experimental and the control groups, respectively ($P = .510$). A difference between groups was detected when accessing the final IIEF-5 score (12.0 vs 10.0; $P = .006$); however, it was not enough to meet the primary clinical outcome. The analysis of covariance confirmed that there is an effect of LiESWT in the mean IIEF-5 score after treatment controlled for the IIEF-5 score before treatment [$F(1,74) = 4.366$; $P = .040$] (control: 10.3 ± 0.8 vs experimental: 12.7 ± 0.8; $\Delta = 2.4$; 95% CI: 0.1−4.6; $P = .04$). The pretreatment IIEF-5 score had no effect on post-treatment score values ($P = .692$).

An exploratory analysis was made comparing the proportion of those individuals who reached an IIEF-5 score $\geq 17$ (at 10th protocol visit). No difference between groups was noted (17.1% vs 22.2%; $P = .57$). In addition, no adverse event was detected during LiESWT treatment until the last follow-up.

# DISCUSSION

Since 2010, LiESWT has been investigated in the clinical setting for the treatment of organic ED with conflicting results.

**Table 1.** Patient demographic and clinical characteristics

| | Control group | Experimental group | P* |
|---|---|---|---|
| N | 41 | 36 | |
| Age (years), mean ± SD | 64.6 ± 5.3 | 64.6 ± 5.3 | .981 |
| BMI (Kg/m$^2$), mean ± SD | 25.9 ± 2.7 | 26.6 ± 3.6 | .340 |
| Hypertension (%) | 53.7% | 63.9% | .363 |
| Diabetes Mellitus (%) | 19.5% | 16.7% | .746 |
| Smoking | 4.9% | 8.3% | .539 |
| ASA ≥ 2 | 56.1% | 66.7% | .342 |
| PDE5i use | 2.4% | 8.3% | .238 |
| IIEF-5, median (IQR) | 22.0 (20.0–23.0) | 21.0 (19.0–23.8) | .510 |

ASA = American Society of Anesthesiologists score; BMI = body mass index; CI = confidence interval; PDE5i = phosphodiesterase-5 inhibitor; SD = standard deviation.
*Numerical variables were compared by Student's t-test and categorical variables by chi-square test.

In a pilot study, Vardi et al[17] launched the possibility of the LiESWT improve EF and to contribute to penile rehabilitation without the need for pharmacotherapy. In 2012, the same author described meaningful improvements in IIEF EF domain (IIEF-EF) in the LiESWT group when compared with the sham group (6.7 vs 3.0; $P = .032$).[18] The authors included only good responders to PDE5i, which was discontinued during the study period. In a third study, the same group addressed the role of LiESWT in PDE5i nonresponders and found a positive effect in IIEF-EF scores (8.8 vs 12.3; $P < .0001$). Besides that, several patients were converted to PDE5i responders.[7] Otherwise, 2 following randomized clinical trial did not reproduce these results. First, Yee et al[19] applied LiESWT to organic ED and showed no differences in either IIEF-5 (17.8 vs 15.8; $P = .156$) or erection hardness scale. Afterward, Olsen et al[20] randomized 105 patients to either LiESWT or sham therapy and presented no differences in the IIEF-ED score. Concerning the study protocols, the model used by Yee et al[19] was very similar to that in the study by Vardi et al[18] Study—9-week treatment period, comprised of 2 treatment sessions per week for 3 weeks that were repeated after a 3-week no-treatment interval. In addition, the LiESWT device was the same (Omnispec ED1000, Medispec Ltd, Yehud, Israel). Finally, a recent meta-analysis[21] presented a significant improvement in the pooled change in the IIEF-EF score (mean difference: 4.17 points; 95% CI: 0.5–8.3; $I^2 = 98.8\%$; $P < .0001$). All studies, except one, accumulated 18,000 impulses in the protocol. However, when analyzing these several previous studies, a common exclusion criterion was prior RP.

**Table 2.** Erectile function, continence, and complications of patients undergoing radical prostatectomy in the control and experimental arms

| | Control | Experimental | P* |
|---|---|---|---|
| N | 41 | 36 | |
| Final IIEF-5, median (IQR) | 10.0 (7.0–11.00) | 12.0 (9.3–15.8) | .006 |
| IIEF-5 ≥17 | 17.1% | 22.2% | .570 |
| CD 1-2 | 12.2% | 11.1% | .882 |
| CD 3-4 | 0.0% | 0.0% | ——— |
| Continence | 82.9% | 83.3% | .962 |

CD = Clavien-Dindo classification; IIEF-5 = International Index of Erectile Function short form assessed without PDE5i in accordance with the study protocol.
*The variables by chi-square test.

As far as we know, after reviewing the literature, our study represents the first randomized trial addressing the effects of LiESWT after RP.[22] Although we saw some evidence of improvement in IIEF-5 scores, the differences between groups did not meet the predefined MCID (ΔIIEF-5 ≥ 4) of the protocol. The erectile hardness score and proportion of patients reaching orgasm were ruled out from the protocol. We could not find any additional benefit for these tools after applying IIEF-5 in the protocol.

It is essential to highlight that among our inclusion criteria, there was no specific IIEF-5 score after surgery. All patients underwent systematic rehabilitation after RP regardless of EF status. Because the LiESWT have been scheduled very early after the RP, the application of the IIEF-5 score did not seem to be an appropriate tool to evaluate the EF. First, because its concept considers a 6-month period and because it assumes that the patient is having sexual relations, which is very unlikely to occur in the early postoperative period. Another concern was not over to apply the IIEF-5 questionnaire what might culminate in a common method bias.[23] Thus, we based our protocol on the idea that most patients would face at least a transient ED, and an early application of LiESWT, as it was postulated for the PDE5i, might lead us to a better result in EF. We highlight that until the last evaluation of IIEF5 (at V10), there may not have been enough time to contemplate on the partial or complete spontaneous EF recovery, which is seen in some patients. Regardless, it seems LiESWT does not have clinical effects in this setting. Moreover, perhaps the Expanded Prostate Cancer Index Composite—sexual domain could help this postoperative evaluation once it considers EF associated to urinary incontinence and in the context of postoperative convalescence.[24]

Similarly, Frey et al[25] proposed a pilot study to evaluate the LiESWT effect on post-RP ED. The median time after surgery was 24 months, and the participants were excluded from the analysis if they reported the use of any erectogenic aid during the study. Including 16 patients in the analysis, the median change in the IIEF-5 score was +3.5 points (9.5−14.5; $P = .004$) and +1.0 point (9.5−10; $P = .04$) at one and 12 months after the intervention, respectively. In parallel, the authors showed that only 2 patients were categorized as having no ED after LiESWT, and the majority of them achieved only marginal improvements. Accordingly, our study complements that first pilot one when comparing the LiESWT effects in different moments on the post-RP scenario, such as in a very early and late period, respectively. Moreover, both results lead us to suppose that the LiESWT efficacy may not be related to the period which it is applied after the RP once both studies presented very similar findings.

The role of LiESWT in penile rehabilitation was also assessed in men who underwent nerve-sparing radical cystectomy.[26] The patients were allocated in 3 groups: LiESWT group ($n = 42$), PDE5i group ($n = 43$), and control group—no intervention ($n = 43$). The application model was very similar to that in the study Vardi et al[17] and comprehended 18,000 impulses. After 9 months, a reassessment of the IIEF-EF showed similar scores between groups (24.4, 24.6, and 22.4, respectively; $P = .14$).

With regard to the use of PDE5i in our study, we decided to provide it to participants, as it represents a common practice for ED after RP, giving the study design greater reproducibility in clinical practice. Besides that, the effects of LiESWT in this setting were unknown. The LiESWT aims to increase the positive effects that already have been reached with the PDE5i and not necessarily replace it. Another reason was to reduce the risk of contamination of the sample because some patients could decide to take on their own during the study period. Finally, trials investigating this question are warranted, and so far, the existent evidence suggests benefits when combining LiESWT and PDE5i.[27]

Our study has some limitations. First, we used the machine Renova (DIREX Group), which does not have the sham probe making the blinding process unfeasible. Second, as mentioned previously, the early period after RP that we assessed the IIEF-5 could have limited the spontaneous recovery of EF. Third, we discontinue the PDE5i use at the last session, which may have interfered in the penile vascular rehabilitation. Fourth, some benefits of LiESWT could have disappeared after the washout period. However, unless in a continuous therapy model, the LiESWT method assumes that its application is discontinued at some point. Finally, our study protocol included only one session per week for the experimental group, raising a query if a more intensive application could achieve better results, once we found a statistically significant difference. However, we do not have a clear protocol when considering LiESWT after RP.

## CONCLUSION

This is the first trial assessing the role of LiESWT on EF after RP. After therapy with 19,200 impulses across 8 weeks, we were unable to demonstrate clinical benefits on the EF. However, a statistical difference was found between the study groups, which makes us wonder if a possible clinical benefit could be achieved in a longer follow-up. Therefore, more studies are warranted before any recommendation on this topic.

## ACKNOWLEDGMENTS

LiESWT shockwave machine was donated by RENOVA (DIREX Group).

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*Conflict of Interest:* The authors report no conflict of interest.

*Funding:* None.

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