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Comparative Efficacy of Low-Intensity Extracorporeal Shockwave Therapy with/without Daily Tadalafil for Erectile Dysfunction Stratified by Severity: A Prospective Multi-center Study

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Abstract

Tadalafil administration and low-intensity extracorporeal shockwave therapy (Li-ESWT) are both effective treatments for erectile dysfunction (ED), but the option of monotherapy or combination therapy for patients with varying severities of ED remains uncertain. This study aimed to compare the efficacy of Li-ESWT monotherapy versus Li-ESWT combined with daily tadalafil across different ED severity subgroups. A total of 188 men aged 18–60 years with ED were enrolled from three clinical centers between June 2018 and March 2020. Demographic data, International Index of Erectile Function-5 (IIEF-5), erectile hardness score (EHS), Clinical Global Impression scale (CGI), and minimal clinically important difference (MCID) were collected. Li-ESWT was delivered using the Renova system with standardized parameters (once weekly for a total of four sessions). Patients in the combination therapy group received 5 mg of tadalafil daily for one continuous month during the Li-ESWT treatment period. Statistical analyses compared pre- and post-treatment outcomes within and between groups. The study population comprised 53 patients in the Li-ESWT monotherapy group and 135 in the combination therapy group. Compared to baseline, IIEF-5 scores improved by 2.92 ± 2.57 points with Li-ESWT monotherapy and by 4.60 ± 4.24 points with combination therapy. In patients with moderate to severe (Mo-Se) ED, combination therapy yielded significantly higher IIEF-5 scores (13.26 ± 5.59 vs. 9.65 ± 3.38, p = 0.001) and higher EHS scores (2.70 ± 0.78 vs. 2.30 ± 0.73, p = 0.042) compared to monotherapy at the 3-month follow-up. Compared with Li-ESWT group, the combination group demonstrated significantly higher “improved” response rates in both CGI (58.3% vs. 40.0%, p = 0.045) and MCID (56.2% vs. 20.0%, p = 0.004) assessments in Mo-Se ED patients. Both Li-ESWT monotherapy and combination therapy with tadalafil are effective treatments for ED. The combination strategy appears to offer superior clinical benefits for patients with Mo-Se ED, whereas monotherapy may be sufficient for those with mild ED. Future large-scale, long-term studies are needed to further validate the value of tailoring treatment selection based on ED severity.

Introduction

Erectile dysfunction (ED) is a prevalent condition that affects male ability to achieve and maintain an erection sufficient for sexual activity. Traditional treatments for ED include oral medications such as phosphodiesterase type 5 inhibitors (PDE5i), intracavernosal injections, urethral alprostadil suppositories, vacuum erection devices, and penile prosthesis implants. Recently, novel therapies such as low-intensity extracorporeal shockwave therapy (Li-ESWT), stem cell therapy (SCT), and platelet-rich plasma (PRP) have emerged as potential treatment options[1]. According to the European Association of Urology (EAU) guidelines, Li-ESWT and PDE5i are recommended as conventional therapies for ED due to their minimal invasiveness[2]. PDE5i, particularly tadalafil characterized as a longer duration of action, has been extensively validated as an effective treatment for ED, significantly improving the International Index of Erectile Function-5 (IIEF-5) scores[3]. Moreover, daily administration of 5 mg tadalafil over 12 weeks has been shown to enhance both psychological outcomes and vascular rehabilitation in relation to ED treatment[4,5]. Li-ESWT has also been demonstrated to significantly improve IIEF-5 and Erection

Hardness Score (EHS), with therapeutic efficacy observed in both short-term (3 months) and long-term (6–12 months) follow-ups[6]. However, the choice of the most appropriate therapy for ED should consider patient preference, individual response to treatment, and the severity of ED. Given the high costs associated with Li-ESWT and the potential side effects of tadalafil, determining the optimal treatment approach for varying severities of ED remains unresolved and warrants further investigation. In this study, we aim to compare the efficacy of Li-ESWT monotherapy with Li-ESWT combined with daily tadalafil in patients with mild and moderate to severe (Mo-Se) ED, respectively. Our objective is to establish an optimal therapeutic strategy for ED that balances effectiveness with minimal treatment burden.

Materials and methods

Study design and patients

The study was a prospective, multi-center, non-randomized controlled trial designed to evaluate the efficacy of Li-ESWT and tadalafil in patients with ED. Consecutive ED patients aged 18–60 years old were enrolled from three andrology centers including Renji hospital, Shanghai Jiao Tong University School of Medicine, the First Affiliated Hospital of Anhui Medical University and Guangdong Province Hospital of Chinese Medicine from June 2018 to March 2020. ED patients who had a complaint of erectile problems at least 6 months were enrolled from andrology outpatient in the hospitals.

Those willing to participate in the study accepted a 1-month washout from any ED treatment. After 1-month period without ED treatments, patients with ED met the screening criteria were allocated in monotherapy Li-ESWT or Li-ESWT combined with daily tadalafil 5 mg. Monotherapy group consisted of ED patients received Li-ESWT once a week with a four-week treatment session in total. Combination therapies group ED men who underwent therapy with tadalafil 5 mg once daily bedtime for 4 weeks and Li-ESWT with a four-week treatment session. This study had been registered on the Chinese Clinical Trial Registry (No. ChiCTR-INR-17013804), and approved by Renji Hospital Ethics Committee (2018 – 119) with written informed consent obtained following Helsinki Declaration revisions. Written informed consent was obtained from all participants prior to enrollment.

Screening Procedures and Inclusion/Exclusion Criteria

The screening process and criteria are illustrated in Fig. 1. Participants were included if they met the following conditions: (1) They reported having a relatively stable sexual partner and had engaged in sexual intercourse within the past four weeks. (2) They completed a subjective assessment of erectile function. (3) Those diagnosed with ED had IIEF-5 score of ≤ 21 and EHS of ≤ 3. Exclusion criteria were as follows: (1) A history of problematic sexual behavior, specific medical conditions (e.g., physical disability, trauma, pelvic surgery), severe psychological disorders, or use of medications affecting erectile function.

(2) Invalid or incomplete questionnaire responses. (3) Failure to complete the Li-ESWT sessions or the full follow-up period.

ED classification

ED diagnosis: IIEF-5 ≤ 21 and EHS ≤ 3. Mild ED was defined as 12 ≤ IIEF-5 ≤ 21, and moderate to severe ED was defined as 5 ≤ IIEF-5 ≤ 11[7].

Li-ESWT

Patients were treated with a low-energy shockwave device (RENOVA, Direx Group) configured at 0.09 mJ/mm², 5 Hz (300 shocks/min), and 40 mm penetration depth. A total of 1,600 shocks were delivered to each penile crus and 900 shocks to each corpus cavernosum, for a bilateral total of 5,000 shocks per session. Every session lasted approximately 20 minutes.

Outcomes

The primary endpoint was the between-group difference in IIEF-5 and EHS at 3 months post-treatment. Secondary endpoints included: (1) the between-group difference in “improved” responses on the Clinical Global Impression (CGI) scale, (2) the proportion of participants achieving the minimal clinically important difference (MCID) in erectile function (defined as ≥ 5-point increase in IIEF-5) at 3 months, and (3) any treatment-related adverse events.

Sample size estimation

Based on the past studies at the time of design present control study, we hypothesized that the IIEF-5 would increase by 5 points in the Li-ESWT + tadalafil group, and by 3 points in the mono-therapy Li-ESWT group at the 3-month evaluation[8,9]. Thus, we set α=0.05 (2-sided significance level) and (1-β)=80% (80% power to detect a mean difference of 2 ± 2.2) in the calculation formula $N = \left(\frac{Z_{\alpha/2} + Z_{\beta}}{\Delta / \sigma} \right)$ (σ =2.2).

Considering the different unequal design and assuming a dropout rate of about 10%, 67 patients in the combination group and 17 in the monotherapy group were the minimum sample size in the two groups.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median (minimum, maximum). Group comparisons of normally distributed data were performed with one-way ANOVA, non-normally distributed data with the Kruskal-Wallis test, and categorical variables with the χ^2 test. All analyses were run in SPSS 29.0. Statistical significance was set at $p < 0.05$.

Results

Screening and participant flow are summarized in Fig. 1. Of 188 ED patients (mean age 36.47 ± 10.29 years) enrolled, 53 were allocated to Li-ESWT monotherapy and 135 to Li-ESWT + tadalafil combination therapy. Ten men (seven combination, three monotherapy) reported mild penile pain or discomfort during the first session. No further adverse events arose in patients who continued PDE-5 inhibitors. All participants completed the 1- and 3-month visits except two in the monotherapy arm and one in the combination arm.

Baseline characteristics did not differ between groups (Table 1). Both treatments improved IIEF-5 and EHS at 3 months (Fig. 2). Mean IIEF-5 increased by 2.92 ± 2.57 points after Li-ESWT and by 4.60 ± 4.24 points after combination therapy (Table 2). Among Mo–Se ED patients, combination therapy produced higher absolute scores than monotherapy at 3 months (IIEF-5: 13.26 ± 5.59 vs. 9.65 ± 3.38, $p = 0.001$; EHS: 2.70 ± 0.78 vs. 2.30 ± 0.73, $p = 0.042$) and a greater proportion of “improved” CGI response and MCID achievers (Table 3). In the mild or whole ED cohorts, however, between-group differences in IIEF-5, EHS and CGI “improved” rates were not significant (Table 2).

Discussion

In this study, weekly Li-ESWT plus daily 5 mg tadalafil for four weeks produced a significantly greater improvement in Mo-Se ED than Li-ESWT alone. In the mild-ED stratum, however, IIEF-5, EHS, MCID achievement and CGI “improved” rates did not differ between the two treatment groups. The stratified analysis demonstrates that combination therapy confers clinically meaningful benefits (MCID > 50%) exclusively in Mo-Se ED.

Accumulated evidence shows that Li-ESWT improves erectile function, with consistent gains in subjective scores (IIEF-EF/SHIM and EHS)[10,11] and objective nocturnal penile tumescence parameters[12]. Over the past decade, Li-ESWT has emerged as a non-invasive option for vasculogenic ED, and benefits have been maintained for ≥ 3 months in several trials[13–15]. Our data corroborate these findings that both IIEF-5 and EHS increased significantly 3 months after Li-ESWT. Pooled randomized controlled trials (RCTs) including men with all severity of ED report mean IIEF-EF increases by about 4 points, while retrospective series show about 3.5-point gains[13]. Our study showed that IIEF-5 increases by about 2.9 points after Li-ESWT monotherapy, which was in line with prior work. Li-ESWT produces only a modest

change in EHS, and this increment falls short of the accepted 1-point MCID[13], a pattern also seen in our cohort.

Li-ESWT has documented efficacy in mild-to-moderate ED[16,17], and pooled data suggest that men with less severe disease or fewer comorbidities gain more than those with severe ED[18,19]. Yet trials stratified by baseline severity are scarce, leaving the precise impact of therapy on mild or severe cohorts unclear. Li-ESWT promotes neovascularization, whereas daily tadalafil amplifies NO-cGMP signalling[20], together they may overcome the multifactorial pathophysiology of severe vasculogenic ED. For this reason, current guidelines advocate combination therapy for difficult-to-treat cases[21]. Recent pilot work indicates that Li-ESWT plus 5 mg tadalafil outperforms Li-ESWT alone in mild or mild-to-moderate ED[9,22], and 4-year follow-up shows sustained responses that are 9-fold more likely in mild than in severe cases[15]. Nevertheless, the added value of routine combination treatment across severity strata remains undefined. Our findings clarify this issue that combination therapy significantly improved IIEF-5, EHS and CGI in Mo-Se ED, but conferred no incremental benefit in mild ED. Li-ESWT monotherapy therefore appears sufficient for mild disease, whereas the combination should be reserved for Mo-Se cases. By limiting PDE5-i exposure and the number of Li-ESWT sessions, this risk-stratified approach maximises efficacy while minimising cost and side-effects, and may serve as an initial framework for patient selection in clinical practice.

Although this study suggests the importance of treatment options for different degrees of ED, some limitations should be interpreted in the context. Firstly, non-randomized design and lack of sham-controlled Li-ESWT arm may introduce selection bias. Secondly, though this study from three centers, the sample size, especially the monotherapy group, was relatively small. The relatively limited sample size may lead to wide confidence intervals for all continuous outcomes and reduce the statistical power of subgroup analyses. Lastly, lack of penile ultrasound measures and short follow-up period could not verify the objective indicators improvement and long-term effect of the treatment plan.

Although the findings underscore the need to tailor therapy to ED severity, some limitations should be interpreted in the context. The non-randomized, open-label design and the absence of a sham-controlled Li-ESWT arm invite selection and performance bias. While three centers contributed, the modest overall sample, especially the small monotherapy cohort, produced wide confidence intervals and limited power for subgroup analyses. Finally, the lack of penile Doppler data and the brief 3-month follow-up preclude verification of objective hemodynamic improvement and long-term durability of either regimen.

In conclusion, both Li-ESWT monotherapy and combination therapy with tadalafil are effective in improving erectile function in ED patients. Li-ESWT monotherapy is sufficient for men with mild ED, while the addition of daily tadalafil yields superior outcomes in moderate-to-severe cases. These findings warrant confirmation in larger, multicentre trials designed to refine severity-based treatment algorithms.

Declarations

Conflicting Interests

The authors have no conflicts of interest to declare.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study had been registered on the Chinese Clinical Trial Registry (No. ChiCTR-INR-17013804), and approved by Renji Hospital Ethics Committee (2018-119) with written informed consent obtained following Helsinki Declaration revisions. All procedures were conducted in accordance with the institutional guidelines.

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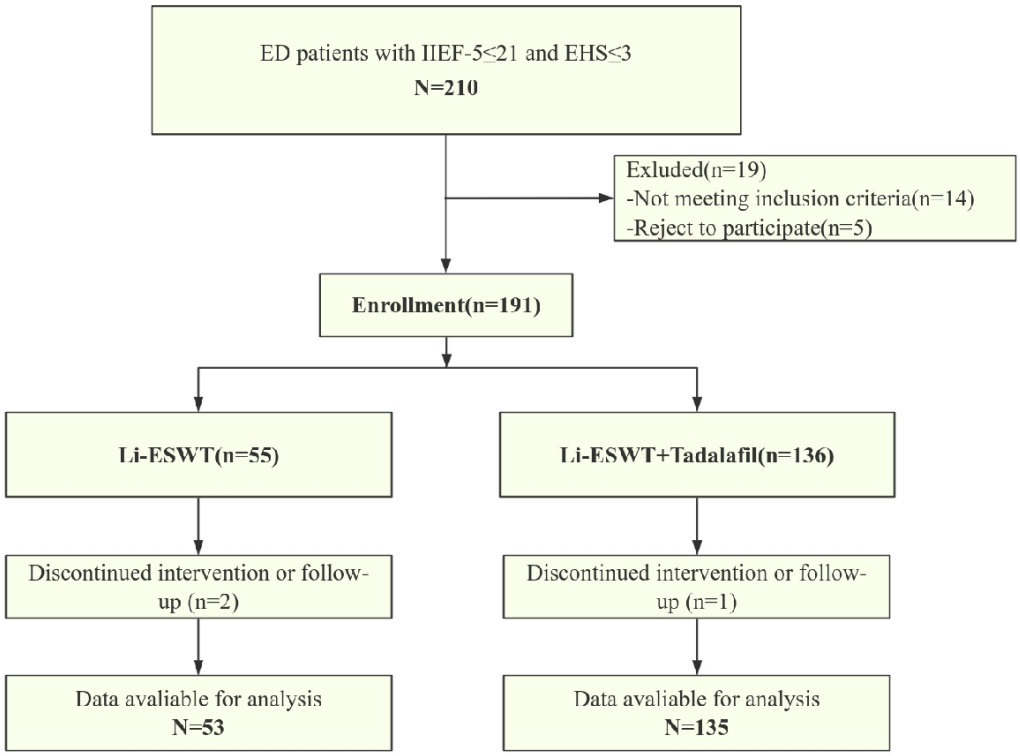
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Tables

Tables 1 to 3 are available in the supplementary files section

Figures

Figure 1 Study flow chart

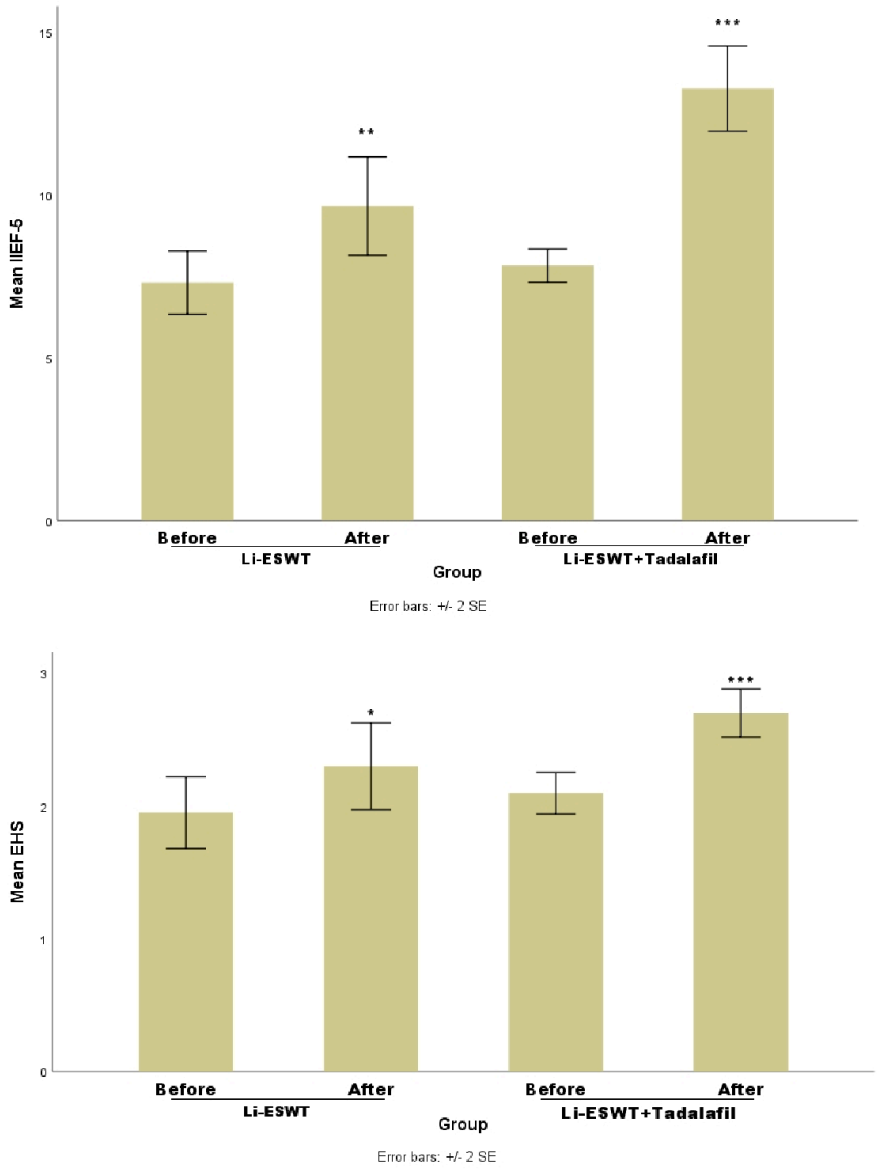


IIEF-5, International Index of Erectile Function 5; EHS, Erection Hardness Score; Li-ESWT, low-intensity extracorporeal shockwave therapy.

Figure 1

See image above for figure legend.

Figure 2 IIEF-5 and EHS before and after monotherapy and combination therapies.



IIEF-5, International Index of Erectile Function 5; EHS, Erection Hardness Score; Li-ESWT, low-intensity extracorporeal shockwave therapy.

Figure 2

See image above for figure legend.

Supplementary Files

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