Original Article

# Efficacy and safety of low-intensity pulsed ultrasound (LIPUS) combined with tadalafil in the treatment of severe erectile dysfunction: a retrospective cohort study

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**Background:** Low-intensity pulsed ultrasound (LIPUS) is an effective and safe treatment for mild to moderate erectile dysfunction (ED). This study aimed to investigate the efficacy and safety of combining LIPUS with tadalafil in treating severe ED.

**Methods:** The data from 27 patients treated with LIPUS alone (group A) and 21 patients treated with a combination of LIPUS and daily 10 mg tadalafil (group B) were retrospectively analyzed. The LIPUS regimen consisted of twice-weekly treatments for 4 consecutive weeks. The treatment was considered effective if the change in International Index of Erectile Function-Erectile Function Domain (IIEF-EF) score after treatment was greater than or equal to the minimal clinically important difference (MCID) (the MCID for severe ED is 7 points). The effectiveness, IIEF-EF score, erectile hardness score (EHS), peak systolic velocity (PSV), end diastolic velocity (EDV), and adverse events were evaluated before treatment, 4 weeks after treatment, and 12 weeks after treatment.

**Results:** Compared to pre-treatment, both groups showed significant improvement in IIEF-EF score and EHS at 4 and 12 weeks after treatment ($P<0.001$), with no statistically significant difference between the two time points ($P>0.05$). The effective rate did not significantly differ between group A (9/27, 33.3%) and group B (10/21, 47.62%) at 4 weeks or between group A (9/27, 33.3%) and group B (12/21, 57.14%) at 12 weeks after treatment ($P=0.32$, $P=0.10$). However, in patients without comorbidities, the effective rate of group B (12/18, 66.67%) was higher than that of group A (9/25, 36.00%) at 12 weeks after treatment ($P=0.047$). After LIPUS treatment, the PSV level significantly increased and the EDV level significantly decreased compared with before treatment ($P<0.05$). No adverse events were reported.

**Conclusions:** The study suggests that LIPUS has a therapeutic effect on severe ED patients, especially those without comorbidities. It may have a synergistic or overlapping effect with phosphodiesterase type 5 inhibitors (PDE5Is) on severe ED patients without comorbidities.

**Keywords:** Erectile dysfunction (ED); low-intensity pulsed ultrasound (LIPUS); color duplex doppler ultrasonography (CDDU); severe; tadalafil

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## Introduction

Erectile dysfunction (ED) is a common male sexual dysfunction disease, which seriously affects the intimate relationship between patients and their partners, and has a significant impact on their quality of life and physical and mental health because the penis cannot achieve sufficient erection during sexual activity (1,2). A study has shown that the prevalence of ED in Asia can reach 22.4–69.2% (3). According to the latest National Health and Morbidity Survey data in Malaysia, the prevalence of moderate to severe ED among males aged ≥18 years is 31.6% (4). Some guidelines indicate that at the current stage, the non-surgical treatment methods for ED mainly cover oral phosphodiesterase type 5 inhibitors (PDE5Is) and intracavernous injection (ICI) (5,6). PDE5Is have brought a boon to many ED patients due to its good safety and therapeutic effect, but there are still some limitations in clinical practice (7). A considerable number of patients have various adverse reactions such as headache, blood pressure reduction, and facial flushing, and 42.3% of ED patients are ineffective in PDE5Is treatment (8). Many patients are worried about dependence and withdrawal of drugs or want to choose alternative treatments (9). ICI is a one-time induction of penile erection, which cannot achieve the purpose of radical ED (10). In addition, it can cause local pain during or after injection. Inflatable penile prosthesis (IPP) can be considered for ED patients who are ineffective with PDE5Is and ICI, but its clinical use is limited due to its high cost and the occurrence of postoperative complications (11). It is clear that these schemes treat patients symptomatically and cannot correct the pathological mechanism of ED, thus failing to completely cure ED.

In recent years, low energy shock wave therapy (LESWT) has been proven in a large number of literatures to significantly improve erectile function in patients with organic ED (12-15). Because of its non-invasiveness, good tolerability, and the potential to reverse the pathophysiology of ED, LESWT has been recommended as the first-line treatment for ED by the European Association of Urology (EAU) and the International Society of Sexual Medicine (ISSM) (16). However, most studies have focused on mild and moderate ED, while studies on severe ED are fewer, and the outcomes are different (9,17). As another important form of promising therapeutic sound, low-intensity pulsed ultrasound (LIPUS) has also been proven to significantly improve erectile function in patients with mild and moderate ED (18). As a new type of ED treatment device, as stated by the Asia-Pacific Society of Sexual Medicine, it is recommended as a highly promising non-invasive alternative therapy for the treatment of ED (13). However, the treatment outcomes for clinically more difficult severe ED patients are unknown. At the same time, the efficacy of LIPUS combined with PDE5Is in such patients is still unknown, and further exploration should be conducted. Therefore, the aim of this study was to investigate the efficacy and safety of LIPUS alone and LIPUS combined with tadalafil in the treatment of severe ED through a retrospective cohort study. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-154/rc).

### Highlight box

**Key findings**

- Low-intensity pulsed ultrasound (LIPUS) has a therapeutic effect on severe erectile dysfunction (ED) patients, especially those without comorbidities. It may have a synergistic or overlapping effect with phosphodiesterase type 5 inhibitors (PDE5Is) on severe ED patients without comorbidities.

**What is known and what is new?**

- LIPUS is an effective and safe treatment for mild to moderate ED.
- To our knowledge, this is the first study to evaluate the efficacy and safety of LIPUS and LIPUS combined with tadalafil 10mg once daily in the treatment of patients with severe ED. Our results show that LIPUS still has a certain improvement effect in the treatment of severe ED patients, especially for patients without comorbidities, without obvious adverse events, and lasts for at least 3 months. LIPUS and PDE5Is have synergistic or overlapping effects in patients with severe ED without comorbidities. At the same time, the effect of LIPUS was confirmed for the first time in terms of penile hemodynamics.

**What is the implication, and what should change now?**

- LIPUS still has a certain therapeutic effect on severe ED patients, especially for patients without complications. However, for patients with severe ED and comorbidities, the effect still requires a larger sample size for further research. LIPUS and PDE5Is have synergistic or overlapping effects on patients with severe ED without comorbidities, and the specific mechanisms need to be further studied. More prospective and well-designed randomized controlled studies are needed to further verify their effects in the future.

## Methods

### *Patient data*

The medical records of 27 patients with severe ED who received LIPUS treatment (group A) and 21 patients

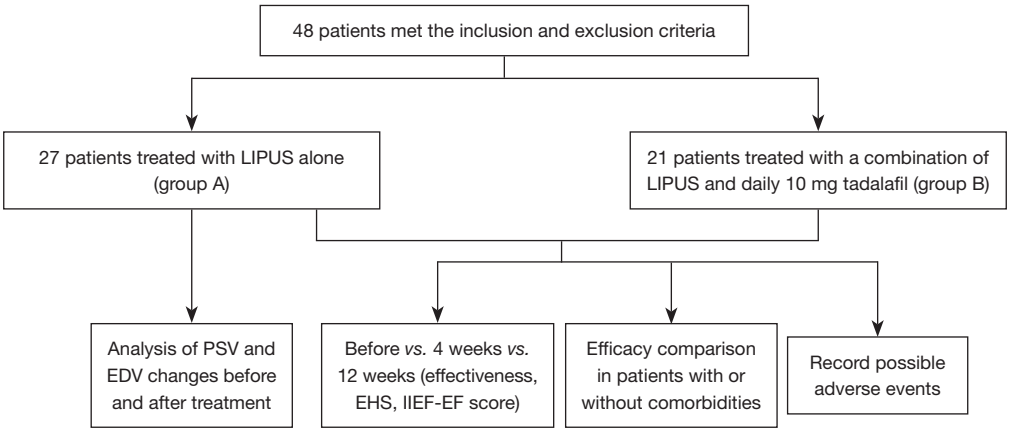


**Figure 1** Patient enrollment and evaluation metrics. LIPUS, low-intensity pulsed ultrasound; PSV, peak systolic velocity; EDV, end diastolic velocity; EHS, erectile hardness scale; IIEF-EF, International Index of Erectile Function-Erectile Function Domain.

with severe ED who received tadalafil 10 mg once daily combined with LIPUS treatment (group B) at Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University (Nanjing, China) from June 2020 to December 2023 were retrospectively analyzed (*Figure 1*). Baseline information regarding age, medical history, body mass index (BMI), years of education, International Index of Erectile Function-Erectile Function Domain (IIEF-EF) score, erectile hardness scale (EHS), and comorbidities was obtained before treatment. Two experienced andrologists evaluated the clinical history, auxiliary examinations, and scale data. The treatment of all patients was carried out by the same physician. The number of standard cases determines the sample size. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Boards of Nanjing Drum Tower Hospital did not require formal approval for conducting the study as we utilized completely anonymous retrospective data. All patients consented to the collection and use of their data in the database for research purposes.

**Inclusion criteria**

In this study, patients with severe ED (score ≤10) were screened based on the IIEF-EF (15). (I) The age of ED patients was ≥20 years old; (II) the ED history was at least 3 months; (III) the International Erectile Index Score (IIEF-EF) was ≤10; (IV) the patients had a fixed sexual partner, and could maintain a normal sexual relationship, at least trying to have sex once a week.

**Exclusion criteria**

(I) The patients with psychological ED or mental disorders; (II) the patients with abnormal genital anatomy; (III) the ED patients with abnormal sex hormone examination results; (IV) the ED patients with previous pelvic trauma, surgery, or radiotherapy; (V) the patients with hemorrhagic diseases or abnormal coagulation function; (VI) the patients with inflammation, ulcer, tumor, or other lesions at the treatment site, or the patients with prostatitis; (VII) the patients with incomplete follow-up data; (VIII) known tadalafil-related adverse events. The general information of the two groups of patients is shown in *Table 1*.

### *Study design*

This was a single-center, retrospective cohort clinical study. The treatment lasted for 1 month. Group A was treated with LIPUS, and group B was treated with tadalafil 10 mg once daily combined with LIPUS treatment. The LIPUS therapeutic device (model: WBL-ED, Beijing Wanbeili Medical Instrument Co., Ltd., Beijing, China) was used in the outpatient treatment room, twice a week for 4 weeks. The main parameters were: the ultrasonic frequency was 1.7 MHz, the pulse duration was 200 μs, the duty ratio was 1:4, and the sound intensity of the treatment probe was 200 mW/cm$^2$. The treatment area included the left and right penile shaft and crus, a total of four parts, each part was treated for 5 minutes, and each treatment lasted for 20 minutes.

 

**Table 1** Basic information of the two groups of ED patients

| Characteristic | Group A (n=27) | Group B (n=21) | P value |
|---|---|---|---|
| Age (years) | 37.00±12.85 | 34.05±7.26 | 0.35 |
| Duration (months) | 30.07±26.35 | 33.62±36.56 | 0.70 |
| BMI (kg/m$^2$) | 21.93±2.63 | 22.20±2.86 | 0.74 |
| Education years | 12.00±2.09 | 11.71±1.95 | 0.63 |
| IIEF-EF score | 6.30±3.15 | 4.43±3.01 | 0.88 |
| EHS | 1.89±0.58 | 1.81±0.75 | 0.68 |
| Comorbidities | 2 (7.41) | 3 (14.29) | 0.64 |
| Diabetes | 1 (3.70) | 1 (4.76) | |
| Hypertension | 1 (3.70) | 2 (9.52) | |

Values are presented as mean ± standard deviation or n (%). Group A: treated with LIPUS alone; Group B: treated with a combination of LIPUS and daily 10 mg tadalafil. ED, erectile dysfunction; BMI, body mass index; IIEF-EF, International Index of Erectile Function-Erectile Function Domain; EHS, erectile hardness scale.

### *Evaluation of efficacy and observation indicators*

(I) The treatment was considered effective if the change in IIEF-EF score after treatment was greater than or equal to the minimal clinically important difference (MCID) (the MCID for severe ED is 7 points) (19); (II) the erectile hardness of patients was evaluated by EHS; (III) the cavernous artery peak systolic velocity (PSV) and end diastolic velocity (EDV) were measured by color duplex doppler ultrasonography (CDDU) before and after treatment to evaluate the vascular function of patients' penis (20). The detection methods were as follows: (I) prostaglandin E1 was injected into the cavernous body of the penis and erection was induced under sexual stimulation; (II) obtain ultrasound images of the left and right cavernous arteries to evaluate PSV and EDV. Examples of results are shown in *Figure 2*; (III) adverse events were recorded. The main measure of effectiveness was the rate of response observed after 12 weeks. Additional

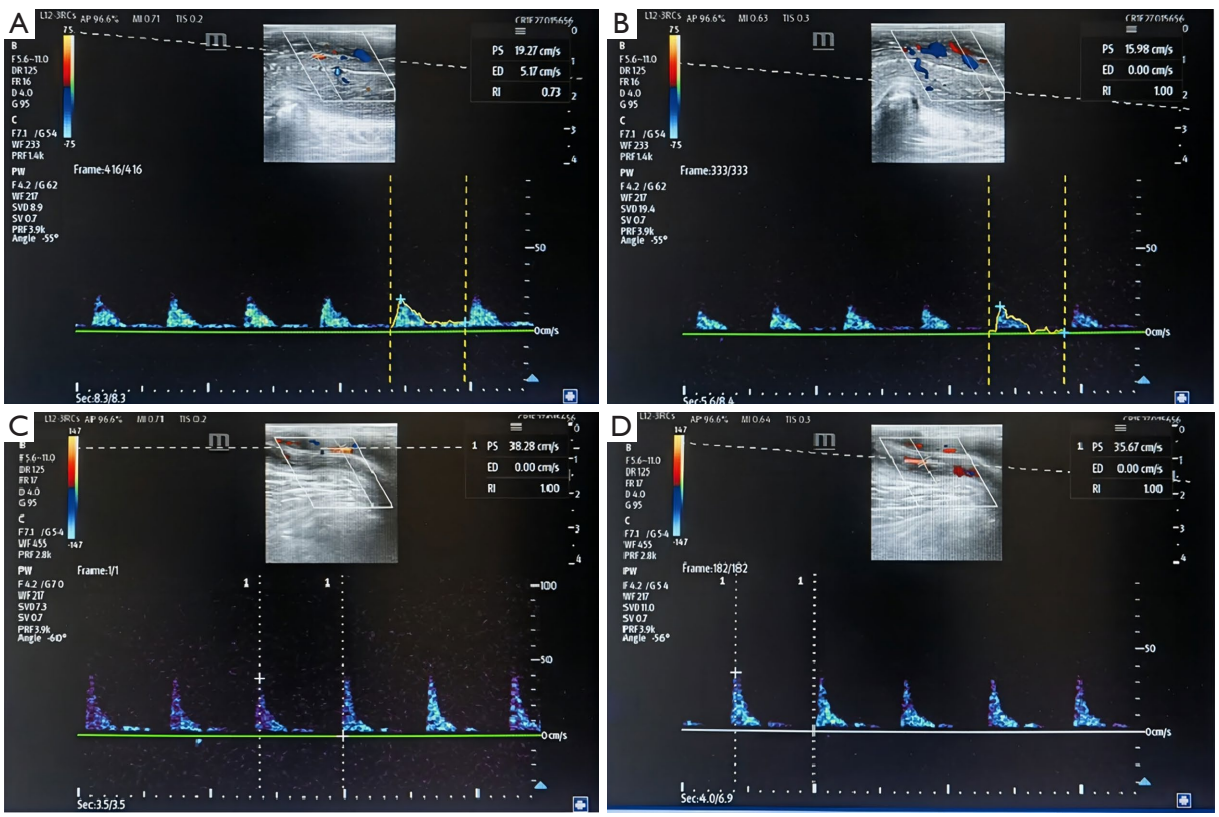


**Figure 2** Changes in left and right PSV and EDV before and after LIPUS treatment. (A) PSV and EDV of the left cavernous artery before treatment; (B) PSV and EDV of the right cavernous artery before treatment; (C) PSV and EDV of the left cavernous artery after treatment; (D) PSV and EDV of the right cavernous artery after treatment. PSV, peak systolic velocity; EDV, end diastolic velocity; LIPUS, low-intensity pulsed ultrasound.

**Table 2** IIEF-EF score, EHS and effective rate at different time points before and after treatment

| Indicator | Before treatment | | 4 weeks after treatment | | 12 weeks after treatment | |
|---|---|---|---|---|---|---|
| | Group A (n=27) | Group B (n=21) | Group A (n=27) | Group B (n=21) | Group A (n=27) | Group B (n=21) |
| IIEF-EF score | 20.80±2.30 | 13.73±1.75 | 24.57±2.71* | 20.61±4.14* | 24.91±2.43* | 21.49±3.47* |
| EHS | 1.89±0.577 | 1.81±0.75 | 2.59±0.64* | 2.52±0.87* | 2.59±0.57* | 2.62±0.67* |
| Efficient | – | – | 9 (33.33) | 10 (47.62) | 9 (33.33) | 12 (57.14) |
| Effectiveness in patients with comorbidities | – | – | 0 (00.00) | 0 (0.00) | 0 (00.00) | 0 (0.00) |
| Effectiveness in patients without comorbidities | – | – | 9/25 (36.00) | 10/18 (55.56)$^{\&}$ | 9/25 (36.00)$^{\&}$ | 12/18 (66.67)$^{\&\#}$ |

Values are presented as mean ± standard deviation or n (%). Group A: treated with LIPUS alone; Group B: treated with a combination of LIPUS and daily 10 mg tadalafil. "–" indicates no data. Compared with before treatment, *P<0.05. Compared with Group A, $^{\#}$P<0.05. Compared with effectiveness in patients with comorbidities, $^{\&}$P<0.05. IIEF-EF, International Index of Erectile Function-Erectile Function Domain; EHS, erectile hardness scale; LIPUS, low-intensity pulsed ultrasound.

measures of effectiveness included enhancements in IIEF-EF, EHS, PSV, and EDV assessments.

### *Follow-up*

The patients were scheduled for follow-up appointments at the hospital during the 4th and 12th week after completing their treatment. In cases where patients were unable to attend in-person, telephone follow-ups were conducted.

### *Statistical analysis*

We employed the statistical program for social sciences (SPSS) software version27.0 (SPSS Inc., Chicago, IL, USA) to describe and analyze the data. Categorical variables were expressed as frequency and rate, and difference analysis was performed using the $\chi^2$ test or Fisher's exact test. Continuous variables were expressed as mean ± standard deviation, and between-group difference analysis was performed using the two independent sample *t*-test, and intra-group difference analysis was performed using the paired *t*-test. In all analyses, P<0.05 was considered statistically significant.

## Results

### *Baseline conditions of the two groups of patients*

From June 2020 to December 2023, a total of 48 patients were screened. Among them, 27 patients were treated with LIPUS alone (group A) and 21 patients were treated with a combination of LIPUS and daily 10 mg tadalafil (group B). The last follow-up date was March 10, 2024. The characteristics of the baseline patients are reported in *Table 1*. There were no significant differences in age, ED duration, BMI, education, IIEF-EF score, EHS, and comorbidities between the two groups (P>0.05).

### *IIEF-EF scores and EHS follow-up of the two groups of patients*

Compared with before treatment, IIEF-EF score and EHS follow-up of patients in the two groups were significantly improved at 4 and 12 weeks after treatment (P<0.001), and there was no statistically significant difference between 4 and 12 weeks after treatment (P>0.05). According to the MCID in IIEF-EF score, there was no statistically significant difference in effective rate between group A (9/27, 33.3%) and group B (10/21, 47.62%) at 4 weeks, as well as group A (9/27, 33.3%) and group B (12/21, 57.14%) at 12 weeks after treatment (P=0.32, P=0.10). However, in patients without comorbidities, there was a statistically significant difference in effective rate between group A (9/25, 36.00%) and group B (12/18, 66.67%) at 12 weeks (P=0.047). In addition, the effective rate of patients without comorbidities in both groups was higher than that of patients with comorbidities (*Table 2*).

### *Follow-up of PSV before and after LIPUS treatment*

There were 6 patients with complete pre- and post-treatment penile CDDU examination data for LIPUS

**Table 3** PSV and EDV before and after LIPUS treatment

| Indicator | Before treatment (n=6) | After treatment (n=6) | P value |
|---|---|---|---|
| Left PSV (cm/s) | 33.29±11.70 | 45.74±5.66 | 0.01 |
| Right PSV (cm/s) | 29.81±13.24 | 39.71±7.49 | 0.047 |
| Left EDV (cm/s) | 5.88±5.22 | 1.00±2.44 | 0.048 |
| Right EDV (cm/s) | 6.24±5.74 | 0.19±0.46 | 0.04 |

Values are presented as mean ± standard deviation. PSV, peak systolic velocity; EDV, end diastolic velocity; LIPUS, low-intensity pulsed ultrasound.

treatment. After treatment, the PSV level of the patients was higher than that before treatment (left PSV: 45.74±5.66 *vs.* 33.29±11.70 cm/s; right PSV: 39.71±7.49 *vs.* 29.81± 13.24 cm/s), and the difference was statistically significant (P=0.01, P=0.047). Meanwhile, the EDV level of the patients after treatment was lower than that before treatment (left EDV: 1.00±2.44 *vs.* 5.88±5.22 cm/s; right EDV: 0.19±0.46 *vs.* 6.24±5.74 cm/s), and the difference was statistically significant (P=0.048, P=0.04) (*Table 3*, *Figure 2*).

### *Adverse events*

No local bleeding, purpura, pain, numbness, tingling, or other adverse events occurred in the 48 patients during treatment and follow-up.

## Discussion

To our knowledge, this is the first study to evaluate the efficacy and safety of LIPUS and LIPUS combined with tadalafil 10mg once daily in the treatment of patients with severe ED. Our results show that LIPUS still has a certain improvement effect in the treatment of severe ED patients, especially for patients without comorbidities, without obvious adverse events, and lasts for at least 3 months. LIPUS and PDE5Is have synergistic or overlapping effects in patients with severe ED without comorbidities. At the same time, the effect of LIPUS was confirmed for the first time in terms of penile hemodynamics, with a significant increase in PSV and a significant decrease in EDV after treatment compared to baseline levels. This may be due to the improvement of penile pathological structure after LIPUS treatment, thereby improving the blood flow supply of the penile artery and venous occlusion function.

As well known, penile erection is closely related to vascular, nerve, endocrine system, as well as muscle and connective tissue (21). Testosterone plays an important role in the development and treatment of ED. According to the American Urological Association, the testosterone concentration should be tested in all men with ED to determine whether there is testosterone deficiency. Moreover, men with ED and testosterone deficiency who are considering using PDE5Is to treat ED should be informed that these drugs may be more effective if combined with testosterone therapy (22). The pathophysiology of ED is multifaceted, but mainly related to vascular diseases associated with reduced endothelial function (23). Both have similar risk factors, such as diabetes, hypertension, and hyperlipidemia (21). A study has found that hypertension, metabolic syndrome, and cardiovascular events are independently associated with severe ED (23). The causes of vascular endothelial dysfunction are chronic inflammation and oxidative stress (23). At the same time, a significant proportion of such patients have no response or less response to PDE5Is (24). Therefore, new treatment methods need to be explored for such patients.

In recent years, LESWT has attracted extensive attention and research enthusiasm among scholars as a non-invasive, user-friendly, well-tolerated, non-obvious adverse reactions, and potentially radical treatment of ED (25). The principle of LESWT in the treatment of ED is not yet fully clear, but it is mainly believed to be related to the repair of vascular endothelial cells in the penile cavernous body, the promotion of penile vascular endothelial neoplasia, the improvement of penile hemodynamics, and the restoration of normal penile histology (26). A large number of literatures have confirmed that LESWT can significantly improve the erectile function of mild and moderate ED (26). LIPUS, as another important form of microenergy medicine, is also considered an ideal therapeutic approach for ED patients to obtain spontaneous erectile function

(18,27). LIPUS is a low-intensity mechanical energy that can be transmitted to tissues and cells in the form of high-frequency sound waves to produce biological effects. There is no clear study on its specific molecular mechanism (13). The principle of LIPUS resides in depending on the physical properties like the thermal effect and cavitation effect of ultrasonic waves (28). Without causing damage to the cells, it absorbs and activates the dormant stem cells for tissue repair, and subsequently generates biological effects that facilitate the formation of new blood vessels and nerves. Compared with LESWT, LIPUS has an extremely small thermal effect due to its low intensity and pulse output mode, and its non-thermal effect is typically considered capable of inducing therapeutic changes in tissues (16). Lei *et al.* (29) confirmed that LIPUS has an improvement effect on the pathological structure of the penile cavernous body in animal studies. In the study of Liu *et al.* (30), LIPUS and adipose-derived stem cells were combined to treat diabetic ED rats, and the results showed that LIPUS enhanced the angiogenic effect of adipose-derived stem cells. In terms of clinical research, Cui *et al.* (18) conducted LPUST treatment twice a week for 4 weeks on 80 patients with mild to moderate ED. The effective rate was 54/80 (67.50%) at 12 weeks, which was significantly higher than that of the sham operation control group 8/40 (20.00%), indicating that LIPUS has good efficacy for patients with mild to moderate ED. This is consistent with the conclusions of previous meta-analyses supporting the application of LESWT in patients with mild to moderate ED (31,32). In human clinical trials, the publicly accessible data regarding LIPUS is extremely scarce. The clinical evidence for the application of LIPUS in the treatment of ED is progressively accumulating, and it is supposed to exert a comparable biological effect to LESWT (13).

There are still many unknown aspects of LESWT in the treatment of ED at this stage. There is no clear answer to the question of which specific ED patients benefit from the treatment (25,26,33). The treatment effect of severe ED is also poorly understood, and different outcomes are even obtained (9,17,34). Gruenwald *et al.* (9) treated 29 patients with severe ED and poor PDE5Is response with LESWT, and the follow-up tests showed that the IIEF-ED scores of the patients were significantly improved, 72.4% achieved EHS ≥3, and the penile hemodynamics were significantly improved. Kitrey *et al.* (34) found that after LESWT treatment, about half of the patients with severe ED could achieve grade III or higher penile hardness with the assistance of PDE5Is, which showed that LESWT still plays a certain improvement effect in the treatment of severe ED patients. However, Ergün *et al.* (17) found that after LESWT treatment in 63 diabetic patients with severe ED and no response to PDE5Is, the patients' response to PDE5Is did not change, and none of them achieved an erection sufficient for sexual intercourse. The difference in outcomes may be related to the population included, and some studies did not include the evaluation of MCID, which may weaken the clinical significance of the results (14,35). In our study, we evaluated the effect of LIPUS treatment and LIPUS combined with PDE5Is treatment in 48 patients diagnosed with severe ED by IIEF-EF. The results showed that LIPUS still had a certain therapeutic effect in patients with severe ED. Although the differences in EHS between the two groups at each time point after treatment were not statistically significant (P>0.05), among the patients without comorbidities, at 12 weeks, the effective rate of the combined treatment group was higher than that of the LIPUS treatment alone group (P=0.047). This suggests that LIPUS and PDE5Is have a synergistic or superimposed effect in the treatment of patients with severe ED without comorbidities, but the specific mechanism needs further study. In addition to the above results, we also found a very interesting phenomenon. With the passage of time, there was a delayed improvement in effective rate in the LIPUS group, although the results were not statistically significant. This suggests that the repair of penile vascular endothelial function achieved through LIPUS is time-dependent. This is similar to the mechanism and results of LESWT in the treatment of ED reported in the literature (36).

At the same time, in order to further understand which specific ED patients benefit from treatment, we found that the treatment effect of severe ED patients with comorbidities (hypertension, diabetes) were lower than that of patients without comorbidities, regardless of LIPUS alone or combined with PDE5Is treatment. It should be pointed out that, in this study, due to the limited number of patients with comorbidities included, it seems that there is not sufficient driving force to summarize the impact of comorbidities on the treatment effect. In the follow-up, it is still necessary to increase the sample size to deeply analyze the role of LIPUS in severe ED patients with comorbidities.

CDDU can provide reliable information about penile hemodynamics. In our study, we collected data on the PSV and EDV of 6 patients with severe ED before and after LIPUS treatment. Before the treatment, the PSV was relatively low and the EDV was relatively high. After the treatment, the PSV significantly increased from the baseline

 

level, and the EDV significantly decreased. This might be attributed to the improvement of the penile pathological structure after LIPUS treatment, enhancing the penile arterial supply and venous occlusion function. This is the first time that the effect of LIPUS has been confirmed in terms of penile hemodynamics.

Although different LESWT settings and treatment regimens have been published, the optimal treatment strategy has yet to be determined. Since different frequency and total course of treatment may produce different biological effects, Xia *et al.* (37) compared the treatment effects of two different frequencies of LIPUS (2 times per week and 3 times per week, total 16 times) on mild and moderate ED, and the results showed no significant difference in the effects of the two regimens. In our study, all patients received LIPUS treatment twice a week, totally 8 times. This does not mean that this treatment regimen is optimal for patients with severe ED. The optimal effects of different frequencies and total courses of treatment need to be further studied. Meanwhile, as the patients in this study had severe ED, daily low-dose (2.5 or 5 mg) tadalafil oral administration was not adopted; instead, 10 mg tadalafil was chosen for daily oral administration. The efficacy and adverse reactions of tadalafil may hinge on the dose. Therefore, further high-quality studies are still needed in the future to explore and evaluate the effect and potential adverse reactions of LPUS regimens or higher doses of tadalafil.

This study has some limitations. Firstly, it is a retrospective study, which still needs to be confirmed by a multi-center prospective sham-controlled study. Secondly, some of the results were collected through telephone interviews. Thirdly, the sample size of this study is relatively small, somewhat limiting the interpretability of the data. However, considering that it was a single-center retrospective trial focused on patients with severe ED, we strongly believe that this study reports the first-round clinical data of LIPUS for such patients. Meanwhile, we plan to incorporate a larger sample in subsequent studies for analysis. Fourthly, although patients with abnormal sex hormone test results were excluded in this study, considering the mechanism of action of testosterone, the efficacy evidence in ED patients unresponsive to PDE5Is, and the mode of action of LIPUS, we plan to analyze testosterone concentration and the therapeutic effect of LIPUS in the future to further explore this method for treating ED. In addition, the response to PDE5Is was uncertain in the included population. At the same time, some patients may not have taken PDE5Is regularly according to the doctor's advice without reporting it, which may lead to result bias. Finally, the follow-up time of this study was only 3 months, which makes it impossible to evaluate the long-term efficacy. However, during the follow-up period, patients were strictly forbidden to use any other treatments for ED. For ethical reasons, we avoided asking patients with severe ED to refrain from all ED treatments for an extended period.

## Conclusions

In summary, our study found that LIPUS still has a certain therapeutic effect on severe ED patients, especially for patients without complications, and lasts for at least 3 months. There are no obvious adverse events. However, for patients with severe ED and comorbidities, the effect still requires a larger sample size for further research. LIPUS and PDE5Is have synergistic or overlapping effects on patients with severe ED without comorbidities, and the specific mechanisms need to be further studied. More prospective and well-designed randomized controlled studies are needed to further verify their effects in the future.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-154/rc

*Data Sharing Statement:* Available at https://tau.amegroups.com/article/view/10.21037/tau-24-154/dss

*Peer Review File:* Available at https://tau.amegroups.com/article/view/10.21037/tau-24-154/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-154/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Boards of Nanjing Drum Tower Hospital did not require formal approval for conducting the study as we utilized completely anonymous retrospective data. All patients consented to the collection and use of their data in the database for research purposes.



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