Long-term Restoration of the Penile Microcirculation in Patients with Vasculogenic Erectile Dysfunction with Low-Intensity Shock Wave Treatment

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Abstract

Background: Vasculogenic erectile dysfunction is a prevalent disease that can be treated using low-intensity shock waves (LI-SWT).
Aim: The aim of this study was to determine the most effective treatment plan and combination of factors leading to the desired result.
Methods: 261 patients were randomly selected, including 19 who underwent sham treatment and gave written consent to undergo LI-SWT. The ages of the patients ranged from 23 to 75 years old and they were divided into three groups. One group received treatment every day (24), another group received treatment twice a week for three weeks (167), and the third group received treatment twice a week with a one-week break (70). All patients filled out questionnaires and underwent penile triplex ultrasonography with ultrasound detection of penile arteries and penile blood flow velocity (PBFV) at baseline, immediately after treatment termination, and six months later. Additionally, 144 out of 261 patients were followed up after 12 and 24 months. The study used IBM SPSS Statistics, ver. 23.0 to compare treatment type effects with other criteria such as the duration of erectile dysfunction, patient age, intensity/frequency of treatment procedures, Erectile Hardness Score (EHS), International Index of Erectile Function domain (IIEF-ED) score, concomitant diseases, metabolic disorders, environmental factors, habits, sexual activity, and different treatment options in the past.
Results: Investigations showed that the improvement in IIEF5 and EHS scores was mostly subjective, while the velocity changes after treatment with simultaneous improvement of artery detection were more objective. These changes interacted with the disease duration, the number and frequency of the procedures, different comorbidities, etc. Artery visualization and velocity increase over time, from screening level to improved measures after treatment termination, 6, 12,24 months with improvement tendency. The study also found that the frequency of treatment provided affected the artery visualization dynamics data and that there were statistically significant interactions between the frequency of the provided treatment, different comorbidities, and disease duration in velocity measures.
Conclusions: Overall, improvement was detected in all three groups, and such improvement was not related to different treatment strategies. Additionally, the study found that LI-SWT was a safe and feasible treatment option resulting in clinical improvement rates during long-lasting follow-up. **(TCM-GMJ December 2023; 8 (2):P25-P28)**

Keywords: Vasculogenic ED**;** Low-Intensity Shock Wave Treatment; Penile Arterial Flow Improvement.

Introduction

Erectile dysfunction, or ED, is a condition where a man is unable to achieve or maintain an erection that is sufficient for successful sexual intercourse. It can have a significant impact on a person's quality of life and relationships, regardless of nationality (1,2). ED affects an estimated 150 million people worldwide and can be an indication of systemic macrovascular disease. Endothelial dysfunction, which impairs blood flow, is believed to be the underlying cause of vasculogenic ED, coronary artery disease (CAD), and peripheral artery disease (PAD). Because risk factors for atherosclerosis, such as smoking, diabetes, hyperlipidemia, and obesity, are prevalent in people with ED, metabolic factors likely play a crucial role in linking the two disorders (3,4). The vasculogenic origin of ED can be diagnosed with Doppler studies of the penile arterial vessels. Low-intensity shock wave treatment (LI-SWT) is the recommended curative option for vasculogenic erectile dysfunction, according to the EAU Guidelines.

A groundbreaking study conducted by Vardi et al in 2010 demonstrated the efficacy of LI-SWT in treating ED, indicating a physiological impact on cavernosal hemodynamics. This innovative method has replaced other established non-surgical treatments such as PDE5i, ICI, and VED, which are on-demand treatments. The majority of research on vasculogenic ED is based on the assessment of IIEF5 or IIEF5 and EHS, with different sources of measurements of erectile function by EDITS scores (5,6,7,8,9). Several papers investigate different options regarding different sources of energy applied to the penile shift, and some explore the efficacy of different shock wave machines (6,9). In 2019, Campbell et al. evaluated the first randomized controlled trials meta-analysis exploring LI-SWT as a treatment modality strictly for ED. They analyzed data from seven RCTs with 607 patients and found a statisti-

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cally significant increase in IIEF-EF of 4.23 in the treatment group compared to the sham group at the one-month follow-up. Five of the seven trials provided data on the proportion of patients with baseline EHS <2 who improved to EHS >3 at one-month post-treatment.

Kalyvianakis et al. investigated the impact of energy flux density used on low-intensity shockwave therapy in four different groups of patients. They found no statistically significant differences in the change of all outcome measures assessing erectile function between different sessions frequency (10).

In 2021, Chung et a.l issued the first publication evaluating the clinical outcomes of LI-SWT at a minimum 5-year follow-up in an open-label single-arm prospective study of men with vascular ED. The mean follow-up period was 69.9 months, and the study found a sustained overall satisfaction rate subsequent to follow-up. There were minor time-limited adverse events reported, but no significant adverse events were observed.

Unfortunately, studies dedicated to the assessment of the results of treatment and restoration of impaired blood flow based on objective criteria are missing. The purpose of our study was to develop objective criteria for assessing the efficacy of treatment. We compared two or three different parameters, such as disease duration, penile arterial flow velocity, and artery detection by ultrasound at different times after treatment termination. Through multivariate statistical comparison, we were able to identify the objective characteristics of the restoration of erectile function.

Methods

Our unit treated 632 patients with vasculogenic ED from December 2014 till February 2022. Out of those, 261 patients were randomly selected and gave written consent to participate in the study, including 19 who underwent sham-controlled treatment. The age of the patients ranged from 23 to 75 years. We used Storz Medical Duolith SD1 Ultra for performing Li-ESWT. 19 patients underwent sham treatment, and out of those, 15 had Li-SWT after 2-3 months. All patients received 6 procedures with 3000 shocks, with energy density ranging from 0.15 to 0.25 mJ/mm2, and frequency of 4.0 Hz. According to the treatment scheme, all patients, including 242 from the main group and 19 from the sham-controlled group, were divided into 3 groups: those receiving treatment every day (24), twice a week for 3 weeks (167), and twice a week with a 1-week break (70). All patients, including the sham group, completed questionnaires and underwent investigations at baseline, immediately after treatment termination, and after 6 months. 144 out of 261 patients were followed up after 12 and 24 months. Our study design differed from previous investigations by detecting penile arteries during ultrasound investigations and using a special scoring system: 0 for not visible, 1 for poorly visible, 2 for moderately visible, and 3 for well visible. We also estimated the blood flow velocity in these arteries. Accordingly, all patients underwent penile triplex ultrasonography by the same investigator with ultrasound detection of penile arteries and penile blood flow velocity (PBFV) across different time points. We conducted IBM SPSS Statistics, ver. 23.0 to compare treatment type effects with other criteria, such as the duration of the erectile dysfunction, age of the patients, the intensity/frequency of the performed treatment procedures, Erectile Hardness Score (EHS), International Index of Erectile Function domain (IIEF-ED) score, concomitant diseases, metabolic disorders, environmental factors, habits, sexual activity, and different treatment options in the past.

Results and discussion

Through our research, we were able to identify several key objective characteristics that can be used to evaluate the effectiveness of a treatment. While changes in the IIEF5 and EHS scores can be observed during treatment and follow-up, they are largely subjective. However, changes in velocity after treatment, as well as improvements in artery detection, can be considered objective indicators. These features can be influenced by factors such as the duration of the disease, the number and frequency of procedures, and any comorbidities present.

The statistical analysis revealed an overall main effect of frequency of the provided treatment (without taking into account disease duration, side of the impairment of the penile arterial vessels) on the improvement of artery visualization ($F(1.89, 447.07) = 408.895$, $p < .001$, $h2=0.634$) and velocity ($F(1.58; 372.37) = 89.89$, $p < .001$, $h2=0.278$). Artery visualization increases over time, from screening level (1.3 ± 0.06) to improved measures after treatment termination (1.96 ± 0.43) and 6 months (2.342 ± 0.004). The same conformity revealed velocity data: velocity measures are different for screening (15.07 ± 0.63), after treatment (21.45 ± 0.52), and after 6 months (23.67 ± 0.75) groups with improvement tendency.

Mixed-model ANOVA gave the possibility to assess independent variables' interaction effects on measured parameters. The statistical treatment of artery visualization dynamics data shows an interaction between the frequency of the provided treatment and side (deteriorated right or left penile artery) ($F(1.773, 418.47) = 5.58$, $p = .006$, $h2=0.023$), but without the significant main effect of the side as an independent factor alone ($F(1,236) = 1.226$, $p = .269$, $h2=0.005$). The fact that the frequency of the provided treatment interacts significantly with the Side gives the possibility to discuss the view that visualization may improve differently in Right and Left Penile Arteries across the measurement time points**.** In all cases we have revealed a little bit higher measurements (row data) for Left (for screening -1.43 ± 0.07; After treatment termination - 2 ± 0.07; After 6 months - 2.35 ± 0.05) than for Right (1.18 ± 0.07; 1.9 ± 0.73; 2.3 ± 0.06 correspondingly) side. Finally, we have better improvement of visualization for the left side too: for the Right side mean difference between screening and after 6-month measurements is 1.15 ± 0.006 and for the Left side 0.91 ± 0.058 ($p<0.05$ for both cases).

In the case of the Velocity study there is no interaction between the frequency of the provided treatment and Side and no statistically significant differences between Right and Left artery measurements, but Left artery results are higher (21.25±0.8) than Right side measurements (18.83±0.93)(P=0.11). In Velocity measures statistically significant interactions were revealed between frequency of the provided treatment and Disease Duration. The breakdown of velocity measures gave the possibility to interpret this interaction. As we know velocity increases through the treatments (screening, after treatment termination, after 6 months). At the screening level, there were significant differences between '>10 years' and <6 months' (p=0.004), '1 year' (p=0.012), and '2 years' (p=0.047) disease history groups. After treatment termination velocity was increased in all mentioned groups and continued increasing after 6 months too. The better increase in comparison to screening level was revealed in '<6 months', '1 years' and '2 years' disease history groups (mean differences 9.56 ±1.39, 8.2±0.67, 7.8±0.69 correspondingly; p<0.001). After 6 months, in comparison to the screening level, a higher increase was observed in the same disease history groups (mean differences - 10.83±2.2, 10.8±1.06; 11.62±1.09 correspondingly). But in the '>2 years', '>5 years', and '>10 years' groups there were no significant differences from the 'after treatment termination' period (2.13±0.95, p=0.077; 1.74±1.23, p=0.48; 1.76±2.85, p=0.99). Consequently, the subjects with disease duration >2 years, > 5 years, and > 10 years of history reveal statistically significant improvement during the treatment period.

There were no Velocity differences between Right and Left measures in total and in each disease duration group, but splitting the data by Disease Duration with Side and making multiple pairwise comparisons revealed some statistically significant results**.** It is very interesting that in Right position Velocity doesn't differ by disease duration history groups (exception is differences between '2 years' and '>2 years'), but in Left side group there were statistically significant differences between '>2 years', '>5 years' and '>10 years' groups in comparison to '<6 months' (mean differences – 9.52±2.75, p=0.01; 11.73±2.9, p=0.001; 20±4.6, p<0.001 correspondingly) and '1 years' groups (mean differences 5.62±1.75, p=0.023; 7.84±2.07, p=0.003; 16.12±4.11, p=0.002). So, Disease duration has different effects on the velocity of the Right (F(5, 236)=3.87; p=0.002) and Left (F(5,236) =7.54; p<0.01) side. The clearest and statistically significant differences (F(1,236)=4.96; p=0.027) between Right and Left measures revealed in a group with a 1-year disease history (mean differences 4.37±1.9; p<0.05).

To evaluate the effectiveness of different treatment schemes we have compared 3 different (1 week, 3 weeks, and 5 weeks) shock wave approaches and assessed artery visualization and velocity dynamics for each approach and both (right and left) sides Statistical analysis of obtained row data didn't reveal any significant main effects of different strategies in artery visualization (F(2, 239)=1.538, p=0.217) and velocity ((F(2, 239)=2.396, p=0.093) studies overall. As in the case of the study of Disease Duration effects, in the cases of the different treatment plans, there were statistically significant within-groups main effects of Time on artery visualization (F(1,907; 455.849)=404.53, p<0.001, h2=0.629) and velocity (F(1.576; 372.374) =89.89, p<0.001, h2=0.276) improvement.

There were significant differences between different time points (screening, after treatment termination, and after 6,12,24 months) in total (in all treatment groups). It means that in all 3 different schemes of treatment: everyday treatment, twice per week for 3 weeks, and twice per week with a weekly break for 5 weeks, different dynamics of changes were not detected. In general, improvement was detected in all 3 groups and such improvement was not related to different treatment strategies

The main effects of the Side were non-significant too - there were statistically non-significant differences between the Right and Left Penile arteries for all study time (not taking into account Disease Duration or frequency of treatment procedures). Overall the results of the left and right penile arteries changes time dynamics were equal in all 3 different schemes of treatment.

Frequency of treatment procedures and Side Interaction was assessed and groups with different SWT schemes (SWT Main Effect) were compared - For artery visualization significant difference was revealed between 1 week and 5 weeks procedures (F(2,239)=3.01.p=0.05) at screening level only, but for the Velocity SWT Effect was non-significant**.**

This study found that SWT (shockwave therapy) had no significant effects on visualization and velocity at different levels of frequency for treatment procedures, including screening, after treatment termination, 6 months, and 12 months. In other words, there were no significant differences in the treatment effects on visualization and velocity at each time level.

However, the study did find that artery visualization improved over time for all SWT treatment schemes, from the screening level (1.3±0.06) to improved measures after treatment termination (1.96±0.43) and 6 months (2.342±0.004). The same trend was observed in velocity data, with velocity measures differing for screening (15.07±0.63), after treatment (21.45±0.52), and after 6 months (23.67±0.75) groups, with an overall trend towards improvement.

Interestingly, the study found that the number of treatments provided did not have an impact on the intensity or frequency of the procedures. This means that the increase and improvement in visualization and velocity were not dependent on the frequency of treatment sessions and developed in all cases. Our analysis of the data on artery visualization and velocity dynamics shows that the frequency of treatment procedures does not have any significant effect on the side. However, we have found that the improvement in visualization and velocity in the Right and Left Penile arteries is different across the measurement time points. We observed a statistically significant

difference between the measurements of the Right and Left Penile Arteries only when treatment procedures were given two times per week for the three-week treatment scheme.

Conclusions

Imagining of penile arteries and restoration of PBFV were dependent on age, disease duration, stage severity, concomitant diseases, and environmental factors. Hemodynamic changes after treatment termination in patients with shorter duration of the disease, younger age, and uncomplicated medical history, were "jump" type with further increase during follow-up. The changes were mainly on the left, which could be related to the additional supply of the left penile arteries by accessory branches of the pudendal artery (11). Statistical analysis of obtained row data didn't reveal any significant main effects of different Li-ESWT strategies on artery visualization. Statistically significant differences between right and left penile artery measurements only in patients of the second group were identified. The efficacy of Li-ESWT was multifactorial. PBFV was the objective criterion that improved during all treatment schemes and in all age groups but was restored after 3 weeks of treatment. Significant improvements in velocity and sexual life were in all patients with the absence of concomitant diseases, bad habits, and mild to moderate ED. In patients with severe ED penile velocity became stable after 6 months and stayed constant after 12 and 24 months. Results from Artery visualization and Velocity data give the possibility to evaluate the effectiveness of proposed treatment schemes and discuss the possibility of differentiating these improvements by lateralization and disease duration history.

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