Comparison of the effects of extracorporeal shock wave therapy and a vacuum erectile device on penile erectile dysfunction: a randomized clinical trial

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Abstract
Background: This randomized clinical trial (October 2012–December 2013) compared extracorporeal shock wave therapy (ESWT) and a vacuum erectile device (VED) for management of erectile dysfunction (ED).

Methods: Consecutive Chinese patients (20–55 years) with ED, abnormal nocturnal penile tumescence and rigidity (NPTR), and international index of erectile function-5 items (IIEF-5) score <22 were randomized to receive ESWT or VED (twice weekly, 4 weeks). Primary outcomes were treatment efficacy and success rate 4 weeks after completion of therapy. Secondary outcomes included changes in IIEF-5 score, sex encounter profile (SEP) score, erection hardness score (EHS) and NPTR assessments 4 weeks post-therapy. All enrolled patients (n=30 per group) completed the study. At baseline, age, IIEF-5 score, SEP score, EHS, and NPTR assessments were similar between groups.

Results: Four weeks post-therapy, IIEF-5 score increased in the ESWT (15.03±3.00 vs. 11.60±2.28) and VED (15.10±3.06 vs. 11.53±2.27) groups, as did SEP score, EHS, and NPTR measures (all P < .05). Efficacy in the ESWT and VED groups was excellent in 10% and 13.3%, respectively, and moderate in 63.3% and 53.3%, respectively. Treatment success rate in the ESWT and VED groups was 73.3% and 67.7%, respectively.

Conclusion: VED use and ESWT have comparable efficacies in the treatment of ED in Chinese patients.

Abbreviations: ED = erectile dysfunction, EHS = erection hardness score, ESWT = external shock wave therapy, GAQ = global assessment questionnaire, ICI = intracavernous injection, IIEF-5 = international index of erectile function 5 items, MPR = maximal percentage of penile rigidity, NO = nitric oxide, NPTR = nocturnal penile tumescence and rigidity, PDE5i = phosphodiesterase type-5 inhibitors, SEP = sex encounter profile, TTEE = total time of effective erection, VED = vacuum erectile device.

Keywords: efficacy, erectile dysfunction, extracorporeal shock wave therapy, vacuum erectile device

1. Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve and maintain an erection sufficient to permit satisfactory sexual performance.[1] ED occurs most commonly in men aged 40 to 70 years, and its prevalence has been reported to vary from around 10% to 52% depending on the study design and the precise definition used. [2-3] Furthermore, the prevalence of ED increases steeply with age.[1,2] In western countries, the annual incidence of ED is ~25 to 30 per 1000 men.[4,5] Risk factors associated with ED include cardiovascular disease, hypertension, diabetes mellitus, lower urinary tract symptoms, prostate cancer, depression, and smoking.[6,7] ED may severely influence the physical and psychological health of the men it affects and has a significant impact on the quality of life of patients and their sexual partners.[8,9]

A variety of noninvasive and invasive treatment options are available for ED. Phosphodiesterase type-5 inhibitors (PDE5i), such as sildenafil, vardenafil, tadalafil, and avanafil, are currently the first-line therapy for ED.[10,11] These drugs enhance blood flow to the penis through nitric oxide (NO)/cyclic guanosine monophosphate signaling pathways. However, PDE5i agents are effective in only ~60% of patients and are associated with adverse effects such as headache, flushing, and dyspepsia.[12,13] In addition, the use of PDE5i agents is associated with a high treatment cost. Alternative therapies for ED include intracavernous injections (ICI) with vasogenic agents (such as prostaglandin E1), phentolamine, vasoactive intestinal polypeptide, papaverine, and atrazine), intraurethral pharmacotherapy with prostaglandin E1 suppositories, vascular surgery, and surgical implantation of a penile prosthesis.[10,11] However, none of these treatment options are first-line therapies because of...
their invasive nature and other disadvantages. Although gene therapy and stem cell transplantation are currently being investigated as novel potential treatments for ED, they have yet to be successfully developed into therapies for routine use in the clinic.[10,11]

In recent years, there has been considerable research interest in the development of simple, effective, and noninvasive alternatives to PDE5i agents. A vacuum erectile device (VED) utilizes negative pressure to distend the corporal sinusoids and increase blood flow to the penis,[14,15] essentially achieving the same effect as a PDE5i. Several studies have reported that a VED, used either alone or in combination with a PDE5i, can exert a useful therapeutic effect in various types of ED.[16–18] Another recently developed treatment modality for ED is extracorporeal shock wave therapy (ESWT), which utilizes acoustic waves to exert transient mechanical forces on tissues that lead to biological changes such as angiogenesis and neovascularization.[14,19] Numerous clinical investigations have demonstrated that ESWT is well tolerated and has good clinical efficacy in the treatment of ED.[20–22]

To date, there have been no clinical trials directly comparing the clinical efficacies of ESWT and a VED in the management of ED. We hypothesized that both therapies would be effective in the treatment of ED and that a direct comparison of the efficacies of the 2 treatment approaches would provide insight that would help guide clinicians and patients in future decision-making regarding alternative therapies to PDE5i agents. Therefore, the aim of the present randomized clinical trial was to make a preliminary comparison of the efficacies of ESWT and a VED in the management of ED in patients in China.

2. Materials and methods

2.1. Patients and study design

This randomized, parallel (2-arm) clinical trial prospectively recruited consecutive patients with ED seen at the Department of Infertility and Sexual Medicine, Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China between October 2012 and December 2013. The inclusion criteria were: age 20 to 55 years; a diagnosis of ED made based on the diagnostic criteria of the Guidelines on Erectile Dysfunction published by the European Association of Urology[23] and the Guidelines on Erectile Dysfunction published by the Chinese Andrology Association; abnormal nocturnal penile tumescence and rigidity (NPT); international index of erectile function 5 items (IEF-5) score <22; and had not received previous treatment for ED with a VED, ESWT, or a PDE5i. Subjects were excluded from enrollment if any of the following criteria applied: previous prostatic surgery, diabetes mellitus, hypertension, trauma, penile anatomic abnormality, unstable spinal cord injury, psychiatric illness, chronic hemolologic disease with an obvious clinical manifestation, history of malignancy in the previous 5 years, or recent administration of an anti-androgen or androgen. Patients were also excluded if they had received any treatment for ED during the previous 7 days, including oral medications, a VED, ICI, and intraurethral pharmacotherapy.

Owing to the preliminary nature of this study, there was no a priori calculation of sample size based on power calculations. There were no important changes to the methods after trial commencement. This study was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-Sen University, and written informed consent was obtained from each patient before their enrollment in the study. The study was performed in accordance with the principles of the Declaration of Helsinki.

2.2. Grouping

The patients were randomized into 2 equal groups: an ESWT group (to receive treatment with ESWT) and a VED group (to receive treatment with a VED). The random allocation sequence was produced by a random number generator in SPSS 17.0 for Windows (SPSS Inc, Chicago, IL). Implementation of the random allocation sequence was achieved using sequentially numbered, opaque, sealed envelopes. The study authors generated the random allocation sequence, enrolled participants, and assigned participants to interventions. Neither the patient nor the investigators were blinded to the interventions after assignment.

2.3. Interventions

Patients in the ESWT group were treated using ESWT delivered with an LGT-2500B shockwave therapy device (Longest Technology Co. Ltd., Guangzhou, China) operated by a nurse. The shockwaves were delivered to 3 points on the penile shaft and 2 points on the bilateral crus penis (diagram 1). Delivery of shockwaves to the testes, spermatic cords or urethra was avoided to prevent injury. Three hundred shocks were delivered to each of the 5 treatment points at an energy density of 1 bar (100 kPa) and a frequency of 2 Hz. Each patient was treated twice per week (with an interval of at least 2 days) for 4 consecutive weeks. Following the end of each treatment session, the patients were allowed to leave after 15 minutes of rest provided they had no discomfort.

Patients in the VED group were treated using an SW-3501 male sexual dysfunction therapeutic apparatus (Sanwe Medical Science and Technology Co. Ltd., Jiangsu, China). An appropriately sized vacuum bottle was selected in accordance with the penis size to ensure good air tightness. The intensity of the vacuum pressure was 250 mmHg. Each treatment session lasted 15 minutes, and each patient was treated twice per week for 4 consecutive weeks. The patients were allowed to leave 15 minutes after the end of each treatment session provided they were experiencing no discomfort.

2.4. Outcome measures

The outcome measures were evaluated 4 weeks after the completion of each therapy, that is, the total follow-up time from the start of treatment was 8 weeks.

The primary outcome measures were treatment efficacy and treatment success rate assessed 4 weeks after the completion of the therapy. Treatment efficacy was defined as “excellent”, “moderate”, or “poor” based on assessments made using the IIEF-5, which is a brief scale to evaluate penile erectile function, sex encounter profile (SEP), which is a scale to assess sexual satisfaction, global assessment questionnaire (GAQ), which is a scale to investigate efficacy and erection hardness score (EHS), which is a scale to estimate penile rigidity according to 4 levels, which were evaluated before and 4 weeks after the completion of treatment. Efficacy was defined as excellent if all 4 of the following criteria were met: post-treatment IIEF-5 ≥22; SEP ≥4; GAQ ≥1; and EHS ≥3. Moderate efficacy was defined as: post-treatment IIEF-5 ≤21 but increased by ≥5 compared with the baseline; SEP ≥4; GAQ ≥1; and EHS ≥3. If the treatment effect did not meet the criteria for excellent or moderate efficacy, then
efficacy was defined as poor. Treatment success rate (%) was defined as: (number of cases of excellent efficacy + number of cases of moderate efficacy) / total number of cases × 100.

The secondary outcome measures were change in IIEF-5 score, change in SEP score, change in GAQ score, change in EHS, and 2 NPTR measures: change in the maximal percentage of penile rigidity (MPR) and total time of effective erection (TTEE). The NPTR evaluation was carried out before and 4 weeks after the completion of therapy using a RigiScan Plus Penile Rigidity Assessment System (version 5.02, Timm Medical Technologies, Eden, Priie, MN) to monitor the circumference and rigidity of the patient’s penis. The tip ring was placed on the penile shaft near the coronary sulcus, and the base ring was placed on the root of the penis. Each test was initiated by the patient at 10 PM and ended at 6 AM the following morning. The NPTR assessment was conducted on 2 consecutive nights at both baseline and follow-up, and the MPR and TTEE were each recorded as the better of the two values on the 2 consecutive nights. TTEE was defined as the total time for which the penile rigidity percentage was >60%.

There were no changes to the trial outcomes after the trial had commenced.

2.5. Statistical analysis
All analyses were performed using SPSS for Windows, version 17.0. Data are presented as the mean ± standard deviation (SD) or as number (percentage). Student t tests (continuous data) and χ² tests (categorical data) were used for the statistical comparisons. P < .05 was taken to indicate a statistically significant difference.

3. Results
3.1. Clinical characteristics of the patients included in the analysis
Of 69 patients screened for inclusion, 9 were excluded from the study (declined to participate, n = 5; did not meet the inclusion criteria, n = 3; and migration, n = 1). Therefore, a total of 60 patients were randomly allocated to the ESWT and VED groups (30 in each group). No patients discontinued the study or were lost to follow-up after randomization; therefore, 60 patients completed the entire study protocol and were included in the final analysis (Fig. 1).

The patient characteristics are presented in Table 1. At baseline, there were no significant differences between the ESWT
and VED groups in patient age, IIEF-5 score, SEP score, EHS, MPR, or TTEE.

3.2. Comparison of treatment outcomes between the ESWT and VED groups

In both the ESWT and VED groups, there were significant increases in IIEF-5 score, SEP score, EHS, MPR, and TTEE after treatment, as compared with the respective baseline values (all \( P < 0.001; \) Table 2).

With regard to the primary outcome measures, efficacy at 4 weeks after completion of therapy did not differ significantly between the 2 groups (Table 3). Excellent efficacy was observed in 3 of 30 patients (10%) in the ESWT group and 4 of 30 (13.3%) in the VED group; the corresponding values for moderate efficacy were 19 of 30 (63.3%) and 16 of 30 (53.3%). Treatment success rate was 73.3% in the ESWT group and 67.7% in the VED group. There were also no significant differences between the 2 groups in any of the secondary outcome measures, that is, IIEF-5 score, SEP score, EHS, MPR and TTEE at 4 weeks after completion of therapy (Table 3).

4. Discussion

The main finding of the present study is that treatment of ED for 4 weeks with either a VED or ESWT resulted in significant improvements in IIEF-5 score, SEP score, EHS, MPR, and TTEE at 4 weeks after completion of therapy (versus baseline). Furthermore, the efficacies of a VED and ESWT were comparable, with treatment success rates of ~70%. We conclude that both a VED and ESWT are good alternatives to PDE5i agents in the treatment of ED in Chinese patients.

ED is a common disease in men in modern society, and it dramatically affects the quality of a couple’s sexual life. In recent decades, PDE5i agents have become accepted as the first-line treatment for ED. However, these drugs are not effective in all patients, particularly those with diabetes-induced ED. Physical therapy with a VED has gained recent attention as an alternative to PDE5i agents, and the prevention of relative hypoxia in corporal tissue is considered to be the mechanism of its penile rehabilitation.\(^\text{[14]}\) Irrespective of neuronal dysfunction, a VED is able to draw blood into the penis, which improves its oxygen supply and thus promotes penile rehabilitation.\(^\text{[15,16]}\) The VED can produce an erection by creating a vacuum, and this state may be sustained for as long as the vacuum is maintained, which is important for patients who did not respond to a PDE5i\(^\text{[27]}\) and have similar clinical effects to an ICI regarding erectile hardness.\(^\text{[28,29]}\) Most previous investigations have reported that 70% of patients or more respond to a VED and that the IIEF score is elevated by ~2.5 to 3.1 points.\(^\text{[18,27–30]}\) This would be consistent with our data.

### Table 1
Comparison of baseline clinical characteristics between the ESWT and VED groups.

| Characteristic | ESWT group | VED group | \( P \) |
|---------------|------------|-----------|-------|
| Number of patients | 30         | 30        |       |
| Age, y | 34.10 ± 8.42 | 32.50 ± 7.75 | .447 |
| Range | 23–50       | 23–51     |       |
| IIEF-5 | 11.60 ± 2.80 | 11.53 ± 2.27 | .904 |
| SEP | 2.00 ± 0.33 | 2.07 ± 0.38 | .700 |
| EHS | 2.10 ± 0.24 | 2.10 ± 0.24 | 1.000 |
| NPTR | MPR (%) | 59.60 ± 12.12 | 60.60 ± 11.05 | .740 |
| TTEE, min | 34.83 ± 9.89 | 35.10 ± 10.00 | .918 |

Data presented as the mean ± standard deviation. Statistical comparisons made using Student t-tests. EHS = erection hardness score, ESWT = extracorporeal shock wave therapy, IIEF-5 = international index of erectile function 5 items, MPR = maximal percentage of penile rigidity during two consecutive nights of NPTR assessment, NPTR = nocturnal penile tumescence and rigidity, SEP = sex encounter profile, TTEE = total time of effective erection (i.e., the penis had a rigidity >60%) as the best value recorded during two consecutive nights of NPTR assessment, VED = vacuum erectile device.

### Table 2
Response to treatment in the ESWT and VED groups.

| Parameter | Before treatment | After treatment | \( P \) |
|-----------|-----------------|----------------|-------|
| IIEF-5 | 11.60 ± 2.80 | 15.03 ± 3.00 | 0.001 |
| SEP | 2.00 ± 0.33 | 3.47 ± 0.91 | 0.944 |
| EHS | 2.10 ± 0.24 | 3.00 ± 0.27 | .450 |
| NPTR | MPR (%) | 69.67 ± 9.40 | 71.13 ± 9.01 | .596 |
| TTEE, min | 46.53 ± 10.19 | 46.63 ± 10.76 | .971 |
| Efficacy | Excellent | 19 (63.3%) | 16 (53.3%) |       |
| Poor | 8 (26.7%) | 10 (33.3%) |       |

Data presented as the mean ± standard deviation or number (percentage). Intergroup statistical comparisons made using \( \chi^2 \) tests (efficacy) or Student t-tests (all other parameters). EHS = erection hardness score, ESWT = extracorporeal shock wave therapy, IIEF-5 = international index of erectile function 5 items, MPR = maximal percentage of penile rigidity during two consecutive nights of NPTR assessment, NPTR = nocturnal penile tumescence and rigidity, SEP = sex encounter profile, TTEE = total time of effective erection (i.e., the penis had a rigidity >60%) as the best value recorded during two consecutive nights of NPTR assessment, VED = vacuum erectile device.

### Table 3
Comparison of outcome measures between the ESWT and VED groups.

| Characteristic | ESWT group | VED group | \( P \) |
|---------------|------------|-----------|-------|
| IIEF-5 | 15.03 ± 3.00 | 15.10 ± 3.06 | .944 |
| SEP | 3.47 ± 0.91 | 3.67 ± 0.76 | .450 |
| EHS | 3.00 ± 0.27 | 2.97 ± 0.32 | .812 |
| NPTR | MPR (%) | 69.67 ± 9.40 | 71.13 ± 9.01 | .596 |
| TTEE, min | 46.53 ± 10.19 | 46.63 ± 10.76 | .971 |

Data presented as the mean ± standard deviation or number (percentage). Intergroup statistical comparisons made using \( \chi^2 \) tests (efficacy) or Student t-tests (all other parameters). EHS = erection hardness score, ESWT = extracorporeal shock wave therapy, IIEF-5 = international index of erectile function 5 items, MPR = maximal percentage of penile rigidity during two consecutive nights of NPTR assessment, NPTR = nocturnal penile tumescence and rigidity, SEP = sex encounter profile, TTEE = total time of effective erection (i.e., the penis had a rigidity >60%) as the best value recorded during two consecutive nights of NPTR assessment, VED = vacuum erectile device.
which showed an increase in IIEF-5 score of ~3.6 and a treatment success rate of ~68%.

We have utilized color Doppler ultrasound to measure the diameter, blood flow velocity, and resistance index of the cavernous artery and demonstrated that the shear stress of the cavernous artery was higher during use of a VED. Experiments in animal models of ED have observed that a VED can exert an antihypoxic effect by enhancing the oxygen saturation of cavernous blood.[31] Additional experiments in rats have demonstrated that a VED may act through antihypoxic, antiapoptotic, and anti-inflammatory mechanisms, with effects that include decreased expression of hypoxia-inducible factor-1α, transforming growth factor-β1 and apoptotic indices, enhanced smooth muscle/collagen ratio and preserved α-smooth muscle actin, and endothelial NO synthase expression.[12] Thus, multiple interwoven mechanisms may contribute to the beneficial effects of a VED on ED.

ESWT has been widely used in the treatment of several diseases, including urolithiasis,[33] chronic motor system injury,[34] and Peyronie disease.[35] A shockwave is a type of mechanical acoustic wave with a high energy that produces a pressure impulse as it propagates through a medium.[11] The focus may be noninvasively adjusted, allowing a controllable amount of energy to be delivered at an expected position.[10] The focused waves interact with targeted deep tissues, initiating several biological changes,[37] including the breaking of fibrous adhesions, stimulation of capillary growth, and promotion of vascular endothelial cell hyperplasia.[14,19] In recent years, several controlled clinical trials have demonstrated beneficial effects of ESWT in patients with physical ED.[12,20,38–43] The response rates in previous studies were reported to range from 60% to 80%, with IIEF score increases of 3.5 to 9 points.[20,38,40,42,43] These findings are in good agreement with our observation that treatment success rate was 73% and that IIEF-5 score was increased by ~3.5 points after ESWT. It should be noted that some of the previous investigations utilized >1 course of ESWT and assessed IIEF at a different time during follow-up, which may have resulted in larger improvements in IIEF score than that seen in the present study.

The mechanisms underlying the beneficial effects of ESWT remain to be fully elucidated, although studies in animal models have shed some light on this. ESWT has been shown to significantly improve the erectile function of diabetic rats and increase the content of smooth muscle and endothelial cells[44] and to evoke a time- and treatment-dependent reduction in the ratio of intracavernosal pressure to mean arterial pressure, possibly owing to apoptosis and collagenization of corporal smooth muscle.[45] Studies using molecular biology techniques revealed that ESWT upregulated the expressions of α-smooth muscle actin, von Willebrand factor, neuronal NO synthase, and vascular endothelial growth factor and downregulated the expression of the receptor for advanced glycation endproducts in the corpus cavernosum.[66] We speculate that ESWT improves erectile function through a combination of actions, including prevention of fibrosis and apoptosis, enhancement of microcirculatory blood flow in local issue, and release of tissue factors such as endothelium-derived relaxing factor and various growth factors.

This study has several limitations. First, this was a single-center study; hence, the generalizability of the results to other regions of China or other countries remains to be established. Second, the patients and investigators were not blinded to the treatment used, which may have introduced a degree of bias. Third, the sample size was small, so it is possible that the study may have been underpowered to identify real differences between the 2 treatments. Fourth, the follow-up period was only 8 weeks in total, so we were unable to investigate the long-term benefits of the 2 treatments. Fifth, a detailed study of adverse events was not performed, which may have revealed an advantage of one therapy over the other despite the similar clinical efficacy. Indeed, ESWT is thought to be more convenient than a VED for long-term use and avoids potential complications such as penile hydrodema associated with VED use.[47] Sixth, we did not include PDE5i agents, established as the first-line option for ED, as a positive control. Seventh, the possible benefits of using combination therapy were not explored. Additional large-scale, multicenter, randomized clinical trials are needed to further investigate the merits of ESWT and VED use in the management of ED.

5. Conclusion

Both a VED and ESWT have good clinical efficacy in the management of ED in Chinese patients, and the therapeutic effect of ESWT is comparable to that of a VED. We suggest that both these therapies represent good alternatives to PDE5i agents in the treatment of ED.

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