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*Original Research Article*

# The Effective Dose of Low Intensity Extracorporeal Shock Wave Therapy on Patients with Vasculogenic Erectile Dysfunction

Ahmed Fathy Samhan. PhD PT

Physical Therapy Department, New Kasr El-Aini Teaching Hospital, Faculty of Medicine, Cairo University, Egypt.
Physical Therapy and Health Rehabilitation Department, College of Applied Medical Sciences, Salman bin Abdul-Aziz University, Saudi Arabia

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## ABSTRACT

**Introduction:** Vasculogenic erectile dysfunction (VED) is defined as inability to get or keep an erection firm enough for sexual intercourse due to diseases such as diabetes mellitus and atherosclerotic vascular occlusive disease.
**Aim of Study:** To evaluate the most effective and ideal dose (100, 200, 300 shocks per time) of Low-intensity extracorporeal shock wave therapy (Li-ESWT) in treatment of VED and each dose has the long lasting effects.
**Methodology:** Study Design: A prospective, randomized controlled study. Sample size: 30 Patients; Each group-10. Study setting: Physical therapy clinic, College of Applied medical Sciences, Salman bin Abdulaziz University, Saudi Arabia. Duration of Study: 12 months. Patients received 100, 200, 300 shocks per time of Li-ESWT, for group 1, 2, and 3 respectively and were applied 3 sessions per week for one month (12 sessions). Outcome measures: 5-item version of International Index of Erectile Function (IIEF-5) questionnaire and penile Doppler ultrasonography (PDU) which have been collected pre-treatment, post-treatment and follow-up (three months).
**Results:** The results of both outcome measures, showed that there were significant improvement in VED post-treatment, and after 3 months later in the 3 groups of study which mean all doses are effective but there were a difference in effectiveness as the most improvement was in 300 shocks per time, which showed also more long acting effects.
**Conclusion:** 300 shocks per time might be ideal Li-ESWT dose for VED, and had long lasting effects.
***Keywords:*** Vasculogenic Erectile Dysfunction, Low-intensity Extracorporeal Shock Wave Therapy, penile Doppler ultrasonography

## INTRODUCTION

Erectile dysfunction (ED) is not a life-threatening medical problem for men but profoundly affects their quality of life (QOL), and is defined as an inability to achieve and maintain an erection satisfactory for sexual intercourse. [1] According to the underlying causes, ED can be classified as psychogenic, endocrinologic, neurogenic, and vasculogenic. Vasculogenic erectile dysfunction (ED) is defined as inability to get or keep an erection firm enough for sexual intercourse due to diseases such as diabetes mellitus and atherosclerotic vascular occlusive disease. [2]

ED often affects males over 40 years old. The prevalence of ED in males under 40 years old is about 1% to 10%, whereas it is 50% in the 40 to 70-year-old. The etiologies of ED can be complex and overlapping, but the primary organic cause for ED is vascular origin, and is related to inadequate arterial inflow during arousal, impaired cavernosal smooth muscle relaxation, or veno-occlusive dysfunction. [3] It has been proven that ED and coronary artery disease (CAD) share pathways. One of the basic mechanisms playing a role in the pathophysiology of vasulogenic ED is endothelial dysfunction, which develops as a result of reduction in the synthesis and bioavailability of nitric oxide (NO) and subsequent atherosclerosis. Atherosclerosis leads to an impairment of the blood flow required for normal erection. [4]

A physical examination is recommended to identify information of value such as Peyronie's plaques, atrophic testes in hypogonadism, uncontrolled hypertension and neurological disorders. [5] Standardized questionnaires such as the International Index of Erectile Function (IIEF) are useful for assessing the severity of ED and satisfaction after treatment. [6] The penile Doppler ultrasonography (PDU) is a diagnostic modality useful in determining vasculogenic ED as well as its severity. [7]

The current non-surgical treatment of ED mainly consist of oral phosphodiesterase type 5 inhibitors (PDE5is) and/or intracavernosal injections of vasodilating agents. These treatments are very effective and safe with rare adverse effects. However, they all share the same major drawback: they do not alter the underlying pathophysiology of the erectile mechanism. [8] Unfortunately, surgical treatment for ED had relatively poor results as it was effective in only about 50% of all cases and it was restricted to young men with traumatic arterial occlusion, and the data on long-term outcome were limited. [9]

Since the mid-1990s, extracorporeal shockwave therapy (ESWT) has been successfully used in physical therapy field in treatment of joint pain, tendonitis, and bursitis. [10] Low-intensity extracorporeal SW therapy (Li-ESWT) was used both in vitro and in vivo studies and the results shown that this energy can stimulate angiogenesis. The idea of applying Li-ESWT to the penis came from animal studies in which Li-ESWT was applied to the myocardium of pigs, where it has been reported that there was an improvement in ischemia induced myocardial dysfunction. [11] Extrapolating these findings to ED, LI-ESWT of the penis would improve penile blood flow and endothelial function by stimulating angiogenesis in the corpora. [12]

The aim of the present study was to evaluate the most effective and ideal dose (100, 200, 300 shocks per time) of Li-ESWT in treatment of VED and each dose had the long lasting effects.

## MATERIALS AND METHODS

### *Subjects*

This study was carried out on 30 patients with VED, the mean age was 46.83±4.81. The study was designed as a prospective, randomized, controlled study with pre-treatment, post-treatment and follow-up (three months after finishing) evaluation. The data were collected between 2013 and 2014 at outpatient physical therapy clinic, Applied Medical Sciences College, Salman Bin Abdulaziz University, Saudi Arabia. Institutional Ethical Committee Clearance and written informed consent was taken from participants. Subjects were assigned randomly into 3 groups of equal number 10 for each, patients received 100, 200, 300 shocks per time of Li-ESWT, for group 1, 2, and 3 respectively using a

computer generated table of random numbers.

Inclusion criteria were: men between 40 and 55 years of age with a history of VED for at least 6 months, each man had to have an IIEF-5 questionnaire score between 11 and 19. PDU showing the mean of both cavernosal peak systolic volume (PSV) values of 30 cm/s or less post-stimulation that revealing the patient had arterial insufficiency. [13] Each patient agreed to discontinue PDE5is during the entire study period. Exclusion criteria were: patient had undergone radical prostatectomy, received pelvic radiotherapy or hormonal therapy. Patients were receiving ongoing treatment for a psychiatric condition, or had any anatomical, neurological or hormonal abnormalities.

***Outcome Measures***

There were 2 outcome measures, IIEF-5 questionnaire and cavernosal PSV measured by PDU which have been collected pre-treatment, post-treatment and follow-up (three months).

International Index of Erectile Function (IIEF-5) questionnaire

Erectile dysfunction was evaluated through the shortened version of the IIEF-5 questionnaire. All patients were asked to complete the Arabic version of IIEF-5 questionnaire. Each item was scored from 1 to 5. The final score was calculating and ED grading was determined according to Rosen et al, 1999: absent ED (score: 22–25), mild ED (score: 17–21), mild to moderate ED (score: 12–16), moderate ED (score: 8–11), and severe ED (score: 5–7). [14]

***The penile Doppler ultrasonography (PDU)***

Throughout this study PDU was performed using a duplex Doppler device with ultrasound scanning which performed using a high resolution digital Hitachi Hi Vision 6500 Ultrasound Machine that uses a Windows XP-based operating system, fitted with EUP-L53S 5-10 MHz, Linear probe in all patients, following an intra-cavernosal injection of 50 mg of papaverine and the patients were left alone to prevent the loss of concentration for sexual arousal and were asked to maintain the best possible erection by tactile stimulation. Using a standard penoscrotal approach, cavernous artery waveforms were evaluated at 5, 10, and 20 minutes, and peak systolic velocity (PSV) was recorded. The Doppler angle was maintained between 30° and 60° during the examinations. The mean of both cavernosal PSV values were less than 30 cm/s which diagnosed as arterial insufficiency and PSV more than 30 cm/s had nonvascular etiology of ED or normal values. [15]

***Treatment Procedures***

***Group 1:*** Ten VED patients were treated by the Storz Duolith Li-ESWT system (Storz Medical AG, Switzerland) with probe's diameter of 30 mm. The probe was used with a standard commercial gel normally used for ultrasonography without any local anesthetic effect on the penis or the perineum before, during and after the intervention. Patient was comfortably in supine position and the penis was manually stretched and the probe was delivered to the distal, mid and proximal penile shaft, and the left and right crura. Since the depth of SW reached both corpura, treatment was delivered on one side of the penile shaft only. The treatment protocol consisted of 3 treatment sessions per week (day after day) for one month. At each treatment session, Li-ESWT was applied on the penile shaft and crus for 100 shocks per time with an energy density of 0.09 mJ/mm² [16] and an emission frequency of 4Hz at 5 different penile anatomical sites mentioned before (each area received 100 shocks).

***Group 2:*** Ten VED patients were treated by Li-ESWT as an identical fashion of group 1 with the same treatment protocol but with 200 shocks per time with an energy density of 0.09 mJ/mm² and an emission frequency

of 4Hz at 5 different penile anatomical sites (each area received 200 shocks).

***Group 3:*** Ten VED patients were treated by Li-ESWT as an identical fashion of the other two groups with the same treatment protocol but with 300 shocks per time with an energy density of 0.09 mJ/mm² and an emission frequency of 4Hz at 5 different penile anatomical sites (each area received 300 shocks).

***Post-Study Follow-up***

After 3 months from the end of the treatment procedures for the 3 groups, a follow-up intervention of IIEF-5 questionnaire and cavernosal PSV measured by PDU were performed to investigate each dose of Li-ESWT (100,200, 300 shocks per time), and the long lasting effect in treatment of VED.

***Statistical Analysis***

All statistics were calculated by using the statistical package of social sciences (SPSS) version 16. Descriptive statistics (mean and standard deviation) were computed for all data. One way repeated measures of ANOVA using Greenhouse-Geisser test was used to assess the difference within each group in IIEF-5 questionnaire and cavernosal PSV. Also, Bonferroni test was used to determine the significant difference between time of evaluation (pre-treatment and post-treatment, pre-treatment and follow-up, post-treatment and follow-up). Analysis of variance test (ANOVA) was used for age, duration of ED in months, IIEF-5 questionnaire and cavernosal PSV between groups.

## RESULTS

The mean ages of all subjects was 46.83±4.81, in group 1 was 47.00±4.88, in group 2 was 47.20±5.16, and in group 3 was 46.30±4.88 with p-value of 0.914. The mean duration of ED in months of all subjects was 16.83±8.35, in group 1 was 16.70±8.56, in group 2 was 17.00±8.87, and in group 3 was 16.80±8.51 with p-value of 0.997. Both p-values mean no significant difference between the 3 groups, so there was a homogenous between the 3 groups.

The mean changes in IIEF-5 questionnaire of the 3 groups are summarized in table 1.

In group 1, there was a statistically significant difference within group in IIEF-5 questionnaire (F= 22.104, P=0.001). Pairwise comparison test using Bonferroni correction revealed that an improvement in patients suffering from VED from pre-treatment, post-treatment and follow-up time (14.00±2.36 ,17.60±3.13, and 20.00±3.56, respectively) with $p < 0.05$ between pre-treatment & post-treatment and pre-treatment & follow-up which mean a significant difference. There was non-significant difference $p > 0.05$ in post-treatment & follow-up time which revealed that the improvement of VED was the same after finishing treatment by 3 months. In group 2, there was a statistically significant difference within group (F= 16.820, P=0.001). Pairwise comparison test using Bonferroni correction revealed that an improvement in patients suffering from VED from pre-treatment, post-treatment and follow-up time (14.80±2.66,19.80±2.20, and 20.60±3.47 respectively) with $p < 0.05$ between pre-treatment & post-treatment, pre-treatment & follow-up which mean a significant difference. There was non-significant difference $p > 0.05$ in post-treatment & follow-up time which revealed that the improvement of VED was the same after finishing treatment by 3 months. In group 3, there was a statistically high significant difference within group (F= 128.895, P=0.001). Pairwise comparison test using Bonferroni correction revealed that a high improvement in patients suffering from VED from pre-treatment, post-treatment and follow-up time (13.60±2.32, 22.60±1.17, and 24.20±0.79 respectively) with $p < 0.05$ between pre-treatment & post-treatment,

pre-treatment & follow-up and post-treatment & follow-up time which revealed that the improvement of VED was continued after finishing treatment by 3 month.

Comparison between the 3 groups of the study revealed that there were non-significant differences in mean changes of IIEF-5 questionnaire pre-treatment (p=0.544) and there was a high significant differences post-treatment and follow-up time ($p < 0.05$). Pairwise comparison test using Bonferroni correction post-treatment revealed that non-significant difference from group 1, group 2 ($p = 0.128$), significant difference between group 2 & group 3 (p=0.035), and high significant difference between group 1 & group 3 (p=0.001) which mean group 3 was the best group in improvement of VED post-treatment. Pairwise comparison test using Bonferroni correction follow-up time revealed that non-significant difference from group 1, group 2 ($p = 1.00$), significant difference between group 2 & group 3 ( p=0.030), and significant difference between group 1 & group 3 (p=0.001) which mean group 3 was the best group in improvement of VED after finishing treatment by 3 month. Fig.1 demonstrates the mean values difference of IIEF-5 questionnaire pre-treatment, post-treatment and follow-up time in the 3 groups.

The mean changes in cavernosal PSV in cm/s of the 3 groups are summarized in table 2.

The results of the other variable cavernosal PSV in cm/s in group 1, there was a statistically significant difference within group (F= 74.983, P=0.001). Pairwise comparison test using Bonferroni correction revealed that an improvement in cavernosal PSV from pre-treatment, post-treatment and follow-up time (18.60±1.71,25.50±3.75, and 29.40±4.95, respectively) with $p < 0.05$ between pre-treatment & post-treatment, pre-treatment & follow-up and post-treatment & follow-up which mean a significant difference. In group 2, there was a statistically significant difference within group (F=157.782, P=0.001). Pairwise comparison test using Bonferroni correction revealed that an improvement in cavernosal PSV from pre-treatment, post-treatment and follow-up time (19.10±2.18,28.10±2.20, and 32.00±1.41 respectively) with $p<0.05$ between pre-treatment & post-treatment, pre-treatment & follow-up and post-treatment & follow-up which mean a significant difference. In group 3, there was a statistically high significant difference within group (F=206.116, P=0.001). Pairwise comparison test using Bonferroni correction revealed that a high improvement in patients suffering from VED from pre-treatment, post-treatment and follow-up time (18.60±2.59, 32.80±1.55, and 35.00±0.82 respectively) with $p < 0.05$ between pre-treatment & post-treatment, pre-treatment & follow-up and post-treatment & follow-up time which mean a significant difference.

Comparison between the 3 groups of the study revealed that there were non-significant differences in mean changes of cavernosal PSV pre-treatment (p=0.842) and there was a high significant differences post-treatment and follow-up time ($p<0.05$). Pairwise comparison test using Bonferroni correction post-treatment revealed that non-significant difference from group 1, group 2 (p=0.15), significant difference between group 2 & group 3 ( p=0.003), and high significant difference between group 1 & group 3 (p=0.001) that mean group 3 was the best group in cavernosal PSV after finishing the treatment. Pairwise comparison test using Bonferroni correction follow-up time revealed that non-significant difference from group 1, group 2 ($p = 0.189$), non-significant difference between group 2 & group 3 (p=0.101), and significant difference between group 1 & group 3

(p=0.001) which mean group 3 was the best group in improvement of VED after finishing treatment by 3 month. Fig.2 demonstrates the mean values difference of cavernosal PSV in cm/s pre-treatment, post-treatment and follow-up time in the 3 groups.

**Table 1:** IIEF-5 questionnaire pre-treatment, post-treatment and follow-up time between the 3 groups.

| Time of evaluation | Mean ± SD | | | |
|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | p-value |
| Pre-treatment | 14.00±2.36 | 14.80±2.66 | 13.60±2.32 | 0.544 |
| Post-treatment | 17.60±3.13 | 19.80±2.20 | 22.60±1.17 | 0.001 |
| Follow-up | 20.00±3.56 | 20.60±3.47 | 24.20±0.79 | 0.006 |
| p-value | 0.001 | 0.001 | 0.001 | |

**Table 2:** Cavernosal PSV in cm/s measured by penile Doppler ultrasonography (PDU) pre-treatment, post-treatment and follow-up time between the 3 groups.

| Time of evaluation | Mean ± SD | | | |
|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | p-value |
| Pre-treatment | 18.60±1.71 | 19.10±2.18 | 18.60±2.59 | 0.842 |
| Post-treatment | 25.50±3.75 | 28.10±2.77 | 32.80±1.55 | 0.001 |
| Follow-up | 29.40±4.93 | 32.00±1.41 | 35.00±0.82 | 0.001 |
| p-value | 0.001 | 0.001 | 0.001 | |

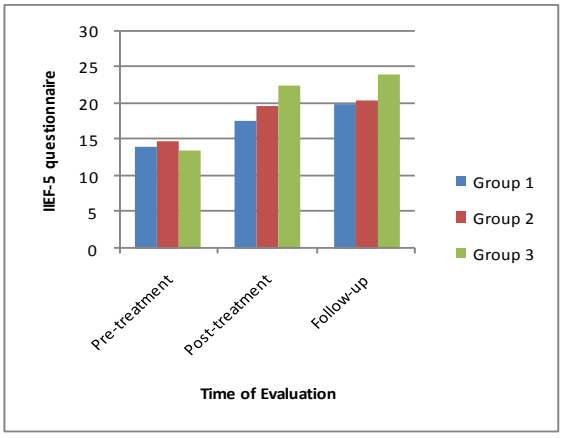


**Figure 1:** IIEF-5 questionnaire pre-treatment, post-treatment and follow-up time between the 3 groups.

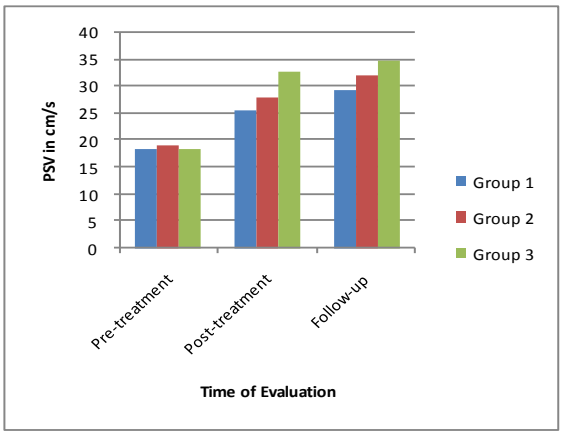


**Figure 2:** Cavernosal PSV in cm/s pre-treatment, post-treatment and follow-up time between the 3 groups.

## DISCUSSION

The present study was a prospective, randomized controlled trial done on 30 patients who had VED and assigned into 3 groups of equal number 10 for each, patients received 100 shocks each time of Li-ESWT (group 1), patients received 200 shocks each time of Li-ESWT (group 2), and patients received 300 shocks each time of Li-ESWT (group 3) The purposes of this study were to assess the most effective and ideal dose (100, 200, 300 shocks per time) of Li-ESWT in treatment of VED and each dose had the long lasting effects.

The underlying mechanism of SWs, and its biological action is not completely understood, it is theorized that the tissue is 1st compressed due to the +ve pressure from the energy that is carried by the SW and 2nd expands due to the tensile properties of the tissue. [17] Nishida et al., 2004, explained this phenomenon as a cavitation because it resembled a micrometer-sized violent collapse of bubbles. [11] Because the physical forces that are generated by cavitation are more localized, it is thought that SW induces a localized stress on cell membranes in the same way that shear stress affects endothelial cell membranes. [18] This stress

then expels angiogenic factors, such as increased local nitric oxide (NO) production through the increased activity of endothelial NO synthase (eNOS) and neuronal NOS (nNOS), platelet derived growth factor, and vascular endothelial growth factor (VEGF). [19] Shock waves have been reported also to cause membrane hyperpolarization, activation of the Ras signaling pathway, [20] non-enzymatic synthesis of NO, [21] and induction of stress fibers and intercellular gaps. [22]

In the present study, Li-ESWT, as physical therapy modality, was used to cure VED as other currently available treatments for ED enhance erectile function by improving the quality of erections, and none are curative. The findings of this study were supported by a variety of previous studies conducted LI-ESWT in both animals and humans.

In vitro and animal study by Wang et al., 2003, explained that LISWs stimulate endothelial cell proliferation with the expression of eNOS, VEGF, and proliferating nuclear antigen. [23] The angiogenic markers increased after 1 week and continued to rise for 8 weeks, while the processes of neovascularization and cell proliferation started 4 weeks and persisted for more than 12 weeks. The same group also reported that LI-ESWT stimulated neovascularization of the tendon-bone junction in dogs [24] and rabbits. [23]

Qiu et al., 2013, investigated the effects of LI-ESWT on erectile function in diabetes mellitus rats using a protocol that is similar to the one used to treat men with ED. They found much less nNOS-containing nerves in the dorsal nerves of the penis, around the dorsal arteries, and in the corpora cavernosa. nNOS-containing nerves, endothelial and smooth muscle cells, and mesenchymal stem cells (MSCs) were more abundant in the LI-ESWT group. [25] Such findings support the notion that the mechanism of the therapeutic action of LI-ESWT is the recruitment of MSC, which was postulated by Chen et al., 2004. [26]

The results of the current study showed that there were significant improvement in VED post-treatment with LI-ESWT, and after finishing treatment by 3 months in the 3 groups of the study which mean all doses of LI-ESWT are effective in treating ED but there were a difference in effectiveness as the most improvement was in group 3 (300 shocks per time), which showed also more long acting effect than the other two groups. The therapeutic effects increase with the increase of the dose. This finding supported by Liu et al., 2013, who investigate the therapeutic effect of different doses of LESWT on ED in streptozotocin (STZ) induced diabetic rats. Seventy five rats were randomly divided into 5 groups (normal control, diabetic control, 3 different dose LESWT treated diabetic groups). Twelve weeks later, different doses of LESWT (100, 200 and 300 shocks each time) treatment on penises were used to treat ED 3 times/week for 2 weeks. The erectile function was evaluated by ICP after 1 week, then the penises were harvested for histological study. The therapeutic effect might relate to treatment dose positively, and the maximal therapeutic effect was noted in the LESWT300 group. [27]

The results of the present study were supported by the results of previous studies. The 1st study of the efficacy of LESWT for ED in humans was conducted by Vardi et al., 2010. They evaluated the effect of LESWT on 20 males with ED who had previously responded to oral PDE5I. They recorded the IIEF score, nocturnal penile tumescence parameters, and penile and systemic endothelial function parameters before and after 3 weeks of treatment. A significant increase in the IIEF-ED domain was recorded in all subjects, and the duration of erection, penile rigidity, and

penile endothelial function improved significantly. At the 6-month follow-up, 10 of 20 subjects did not require PDE5I therapy. [28]

Vardi et al., 2012, investigated the clinical and physiological effects of LESWT on males with organic ED. Erectile function, penile hemodynamics, validated sexual function questionnaires, and veno-occlusive strain gauge plethysmography were assessed before and after LESWT or sham therapy. LESWT had a positive short-term clinical and physiological effect on the erectile function of males who responded to PDE5I therapy. About 50% of patients receiving LESWT developed idiopathic erection and could complete sufficient penetration without the help of a PDE5I. This trial also showed satisfactory feasibility and tolerability of LESWT. [16]

Palmieri et al., 2012, investigated the effects of LESWT plus tadalafil (5 mg/day) for managing patients with Peronie's disease and ED. The mean VAS score, mean IIEF score, and mean QOL score were reduced significantly in both LESWT group and ESWT plus tadalafil group, and the combination therapy lead to better outcomes, as expected. Thus, these results suggest that LESWT should be at least a component of any strategy for treating ED. [29]

Gruenwald et al., 2013, investigated LESWT as a possible treatment for patients with severe ED who responded poorly to PDE5I therapy. After treatment, the mean IIEF-ED scores increased and a significant improvement in penile hemodynamics was detected. [30]

This study is the 1st in using a new treatment protocol consisted of 3 treatment sessions per week (day after day) for one month without (no-treatment) interval as the previous studies as the patients prefer to complete the treatment without intervals, and also the 1st study to evaluate the therapeutic effect of different doses (100, 200, 300 shocks per time) of LI-ESWT in patients with VED. No severe adverse effects were reported during or after the study.

In the present study, more than one method of evaluation was used to find definite reasons about the effective and ideal dose (100, 200, 300 shocks per time) of Li-ESWT in treatment of VED and each dose has the long lasting effects. IIEF-5 questionnaire was a validated psychometric tool used to assess sexual function in men. The Arabic version of IIEF-5 proved to be reliable and valid method to evaluate patients with ED. [31] The penile Doppler ultrasonography (PDU) plays an important role in investigation of patients with ED, particularly when there has been a disappointing response to different treatment modalities. [32]

Different doses of LI-ESWT treatment could improve erectile function as there were significant improvement in IIEF-5 questionnaire scores which tended to normal values, and there were significant improvement in cavernosal PSV in cm/s measured by PDU as the values increased to normal. The maximal therapeutic effective dose was noted in the LI-ESWT (300 shocks per time group). Consequently, 300 shocks each time might be the ideal LI-ESWT dose for VED treatment.

## CONCLUSION

From our clinical observation, low intensity extracorporeal shock wave therapy with 300 shocks each time might be the ideal dose for vasculogenic erectile dysfunction patients, and had long lasting effects after finishing treatment as LI-ESWT treatment could improve 5-version of the International Index of Erectile Function questionnaire scores and cavernosal peak systolic velocity that measured by penile Doppler ultrasonography.

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