

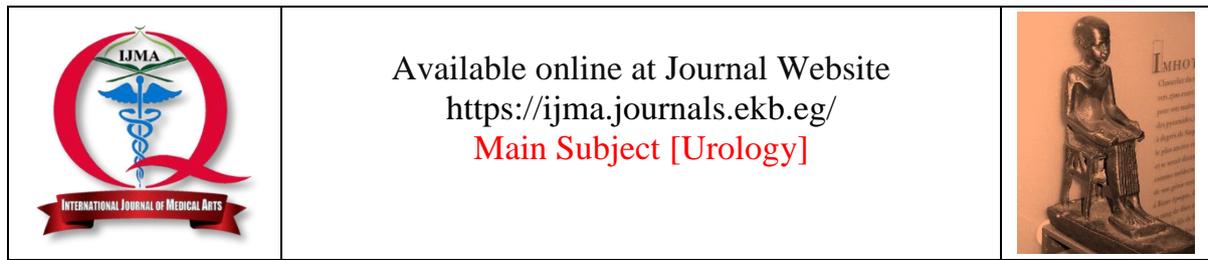
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Original Article

Extracorporeal Shockwave Therapy in The Treatment of Mild Erectile Dysfunction: The Outcome in The Treatment of Naïve Patients and In Patients Intolerant Phospho-Diesterase Type 5 Inhibitors

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ABSTRACT

Article information

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Background: Extracorporeal shockwave therapy [ESWT] has been introduced as a novel therapeutic approach for treating erectile dysfunction [ED] and has shown promising results

The aim of the work: This study aims to evaluate the outcome of using ESWT on naïve patients with mild erectile dysfunction among patients who do not respond to or comply with the use of phosphodiesterase type 5 [PDE5] inhibitors.

Patients and Methods: This prospective interventional study included 150 patients diagnosed with erectile dysfunction divided into two groups: a naïve patient's group [75 patients] and a non-compliant to PDE5 inhibitors group [75 patients]. Erectile function was assessed using the Arabic version of the International Index of Erectile Function [IIEF] and the Erectile Hardness Scale [EHS].

Results: The IIEF scores increased from 14.19 ± 2.54 preoperatively to 22.23 ± 5.85 postoperatively in naïve patients, and from 13.72 ± 2.79 to 21.82 ± 5.72 in the non-compliant group. The EHS scores increased from 2.27 ± 0.34 to 3.43 ± 0.64 in naïve patients and from 2.18 ± 0.34 to 3.58 ± 0.58 in the non-compliant group. While IIEF and EHS scores increased postoperatively compared to preoperatively, there was no statistically significant difference between the naïve and non-compliant groups regarding pre- and postoperative IIEF and EHS assessments [$P > 0.05$].

Conclusion: Both treatment-naïve patients with mild ED and those who respond to but do not comply with PDE5 inhibitors may benefit from extracorporeal shockwave therapy, a noninvasive approach that appears effective and safe.

Keywords: Extracorporeal shockwave; Erectile Dysfunction; International index of erectile function.



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INTRODUCTION

The inability to get or keep an erection long enough for sexual satisfaction [greater than three months] is called erectile dysfunction [ED]. Its incidence ranges from 13% to 21% across all age categories, according to reports [1].

As an independent risk factor, ED is known to become more common as people get older. Erection problems can also be caused by diseases that impact the penile arteries, nerves, hormone levels, corporal endothelium, smooth muscle tissue, or tunica albuginea. In addition to hypertension and hyperlipidemia, other risk factors include diabetes, obesity, smoking, and heavy alcohol use [2].

Penile erection function is dependent on intra-cavernosal smooth muscle relaxation. As a result, the corpora cavernosa can accommodate a greater volume of blood, which in turn constricts the emissary veins and reduces venous output [3].

The process is controlled by the hypothalamic paraventricular and medial preoptic nuclei. Through the cavernosal nerves, the impulses travel. The erectile process is initiated by nitric oxide from cavernous nerve terminals and maintained by nitric oxide from endothelial cells. The intra-cavernosal smooth muscle tissue relaxes in the presence of low intracellular calcium, leading to an increase in arterial flow and simultaneous veno-occlusive activity. After all of this has taken place, the corpora will receive very little blood flow, resulting in a firm erection. Erectile dysfunction can be caused by pathology that arises from any of the aforementioned processes [4].

The suggested method for treating erectile dysfunction is with phosphodiesterase-5 inhibitors [PDE5I], intravenous injections, or intraurethral alprostadil injections. Yet, there are negative side effects linked to them [5].

The addition of extracorporeal shockwave therapy [ESWT] to the treatment options for erectile dysfunction has been greeted with promising results [6].

Forty years ago, ESWT was first used in medical practice [7]. The fields of urology, traumatology, and orthopedics make extensive use of ESWT. In contrast to the current on-demand pharmacological treatment, ESWT can enhance penile blood circulation, which may lead to spontaneous erections [8].

It was once thought that penile extracorporeal shockwave therapy may cure erectile dysfunction. Possible positive outcomes associated with erectile dysfunction include fostering cell proliferation, regenerating tissues, and increasing blood vessel formation, which in turn promotes the regrowth of neurons, endothelium, and smooth muscle cells that produce nitric oxide [9].

It appeared that endogenous mesenchymal stem cells were recruited to mediate the impact. Also, ESWT is improving a neurovascular injury in the pelvis by encouraging angiogenesis [10].

The aim of this study is to evaluate the outcome of using of Extracorporeal shockwave therapy [ESWT] on naïve patients with mild Erectile dysfunction [ED] refers to the inability to achieve or maintain an erection.

PATIENTS AND METHODS

Our prospective interventional study included 150 patients diagnosed with erectile dysfunction attending at the Urology and andrology clinics of Al-Azhar University Hospital [Damietta]. Our study followed the Helsinki declaration principals. Ethical approval was obtained from the Institutional review board of Al-Azhar University. Written informed consent was obtained from every patient at the time of recruitment. Patients was divided into two groups; Naïve patients' group, and non-compliant to PDE5 inhibitors group. We included the patients according to the following criteria:

The inclusion criteria for this study included patients over 20 years of age who were in stable relationships, had mild erectile dysfunction [ED] persisting for a minimum of 6 months, and were previously untreated with PDE5 inhibitors despite being responsive to them

The exclusion criteria comprised individuals with unstable psychiatric disorders, unaddressed hormone abnormalities, clinically significant medical conditions such as diabetes and hypertension, presence of any tumors in the pelvic or penile region, a background of advanced pelvic surgery or non-nerve-sparing irradiation like radical prostatectomy, and penile structural abnormalities like penile chordee.

Data collection

Complete medical, Surgical, and psychosexual history was taken from every patient. General

and local genital examinations were done also at the time of recruitment.

Erectile function was assessed by using the Arabic version of the international index of erectile function [11] and by Erectile hardness scale [EHS] [12]. The IIEF Questionnaire was developed to address the need for a self-report measure of both erectile function and sexual function that can be given under guidance of a clinician.

The IIEF Questionnaire presents the quality of male sexual function in terms of five domain scores: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. This questionnaire consists of only five questions and each IIEF-5 item is scored on a five-point ordinal scale where lower values represent poorer sexual function. Thus, a response of 0 for a question was considered the least functional, whereas a response of 5 was considered the most functional.

The possible scores for the IIEF5 range from 1 to 25 [one question has scores of 1 – 5], and a score above 21 was considered as normal erectile function and at or below this cutoff, ED. According to this scale, ED is classified into four categories based on IIEF-5 scores: severe [1 – 7], moderate [8 – 11], mild to moderate [12 – 16], mild [17 – 21], and no ED [22 – 25].

Patients were treated with Li-ESWT twice weekly for three weeks, and repeated again after three weeks rest period.

Low-intensity extracorporeal shock wave [5,000 SWs, energy intensity of 0.09 mJ/mm²] was applied to 8 treatment points [500 SWs each] through an applicator, four along the penile shaft [proximal and distal LT and RT 1000 sws] and two at the crural and sub glanular levels. All patients were assessed by the IIEF and EH scale 6 weeks postoperative.

Statistical analysis

Statistical analysis was performed with SPSS statistical software, version 25 [IBM, Chicago, Illinois, USA]. The normality of the data was tested by the Kolmogorov-Smirnov test. Qualitative data were presented as numbers and percentages and were compared by the Chi square test, while quantitative data were presented as mean and standard deviations and were compared by the

independent t test. As a result, the p-value was considered significant at the level of <0.05.

RESULTS

A total number of 150 ED patients were included in this study. Table 1 showed the demographics and baseline clinical characteristics of the studied patients, in which the two groups were relatively comparable and the difference was not significant statistically [$P > 0.05$ for all variables].

As regards the PSV, EDV and IR, the PSV, and IR were increased postoperatively in both groups. Also, the EDV was decreased postoperatively. Despite of increased PSV and IR and decreased EDV post-operative than pre-operative but there is no statistically significant difference was found between naïve patients with mild Erectile dysfunction and patients' non-compliant to phosphodiesterase type 5 inhibitors regarding pre and postoperative PSV, EDV and IR assessment [$P > 0.05$] [Table 2].

In terms of the IIEF, it was increased from 14.19 ± 2.54 in naïve patients preoperatively to 22.23 ± 5.85 postoperatively, and also increased from 13.72 ± 2.79 in non-compliant to PDE5 inhibitors patients preoperatively to 21.82 ± 5.72 postoperatively. According to the EHS, it was increased from 2.27 ± 0.34 in naïve patients preoperatively to 3.43 ± 0.64 postoperatively, and also increased from 2.18 ± 0.34 in non-compliant to PDE5 inhibitors patients preoperatively to 3.58 ± 0.58 postoperatively [Table 3].

Despite of increased IIEF and EHS post-operative than pre-operative but there is no statistically significant difference was found between naïve patients with mild Erectile dysfunction and patients' non-compliant to phosphodiesterase type 5 inhibitors regarding pre and postoperative IIEF and EHS assessment [$P > 0.05$].

As regards the success rate, Table 4 showed overall success rate of 67.3% among all the studied population no statistically significant difference was found between naïve patients with mild Erectile dysfunction and patients' non-compliant to phosphodiesterase type 5 inhibitors regarding success rate [73.3% vs 61.3%] [$P > 0.05$].

Table [1]: Comparison of demographics and clinical data among the study groups

	Naïve patients		Non-compliant to PDE5 inhibitors		Test of sig.	
	[n = 75]		[n = 75]		t/x ²	P value
Age, years						
Mean ± SD	32.44 ± 4.72		33.96 ± 4.95		1.925	0.056
Range	42 – 73		41 – 74			
Duration, months						
Mean ± SD	31.85 ± 3.76		33.18 ± 5.52		1.725	0.087
Range	6 – 45		10 – 50			
Smoking	No.	%	No.	%		
Yes	26	34.7%	29	38.7%	0.258	0.611
No	49	65.3%	46	61.3%		
Clinical variables	Mean	SD	Mean	SD		
SBP mmHg	120.32	3.60	119.18	3.43	1.918	0.057
DBP mmHg	66.13	3.19	65.60	3.61	0.921	0.358
Pulse beat/min	74.03	4.06	75.40	4.36	1.924	0.056
HbA1C%	5.49	0.50	5.62	0.69	-1.276	0.204
Serum cholesterol [mg/dl]	201.17	37.53	196.48	40.41	-0.712	0.478
Testosterone [ng/dl]	4.43	1.48	4.64	1.71	-0.777	0.438
Prolactin [µg/l]	10.58	3.27	10.74	3.20	-0.770	0.293
Urea [mg/dl]	35.49	8.50	35.62	9.69	-0.084	0.933
Creatinine [mg/dl]	0.97	0.53	0.95	0.41	-0.712	0.478
AST [U/l]	24.43	5.48	25.64	4.71	-1.401	0.164
ALT [U/l]	29.18	4.27	27.74	5.20	-1.791	0.076

Table [2]: Comparison of PSV, EDV and IR [pre and postoperative assessment] among the studied groups

	Naïve patients		Non-compliant to PDE5 inhibitors		Test of sig.	
	[n = 75]		[n = 75]		t/z	P value
Pre-operative	Mean	SD	Mean	SD		
PSV [cm/s]	25.89	5.52	26.12	5.19	-0.254	0.800
EDV [cm/s]	5.65	2.64	5.72	2.88	-0.150	0.881
IR	0.73	0.07	0.74	0.08	-0.787	0.433
Post-operative	Mean	SD	Mean	SD		
PSV [cm/s]	42.73	7.88	41.22	8.32	1.103	0.272
EDV [cm/s]	1.93	1.24	1.88	1.28	0.235	0.815
IR	0.92	0.06	0.91	0.07	0.908	0.366

Table [3]: Comparison of IIEF_EF and EHS [pre and postoperative assessment] among the studied groups

	Naïve patients		Non-compliant to PDE5 inhibitors		Test of sig.	
	[n = 75]		[n = 75]		t/z	P value
Pre-operative	Mean	SD	Mean	SD		
IIEF_EF	14.19	2.54	13.72	2.79	1.042	0.299
EHS	2.27	0.34	2.18	0.43	1.374	0.172
Post-operative	Mean	SD	Mean	SD		
IIEF_EF	22.23	5.85	21.82	5.72	0.419	0.676
EHS	3.43	0.64	3.58	0.58	1.453	0.149

Table [4]: Comparison of outcome [success rate] among the study groups

	Naïve patients		Non-compliant to PDE5 inhibitors		Total		Test of sig.	
	[n = 75]		[n = 75]		[n=150]		t/x ²	P value
Successful outcome	N	%	N	%	N	%		
Yes	55	73.3%	46	61.3%	101	67.3%	2.455	0.117
No	20	26.7%	29	38.7%	49	32.7%		

DISCUSSION

This study's primary objective was to evaluate the effectiveness of extracorporeal shockwave therapy [ESWT] in treating moderate erectile dysfunction [ED] in individuals who had previously no treatment experience with ESWT and who had responded well to medication but were not using phosphodiesterase type 5 [PDE5] inhibitors. Because there was no significant difference regarding statistics between the groups in terms of age, duration of illness, smoking, vital signs [blood pressure and pulse], laboratory data [HbA1c, serum cholesterol, testosterone and prolactin level], renal functions [urea and creatinine] and liver functions [AST and ALT], the current study registered two groups that were well-matched in terms of baseline data in order to eliminate the effect of any confounding factor that may affect the final outcome.

The results demonstrated that both groups of patients—naïve patients with mild erectile dysfunction and patients who were not compliant with PDE5 inhibitors—reached similar levels of success when treated with extracorporeal shockwave therapy, which led to a notable rise in peak systolic velocity [PSV] and resistive index [RI] and a lessening of end-diastolic velocity [EDV]. Not only did penile hemodynamics noticeably improve, but erectile capability also saw a positive impact.

Despite the lack of research comparing the results of extracorporeal shockwave therapy for mild erectile dysfunction in naïve patients with non-compliant PDE5 patients, multiple studies have shown that this therapy is effective in treating erectile dysfunction.

A randomized controlled trial [RCT] conducted by **Shendy et al.** ^[8], examined the efficacy of low-intensity extracorporeal shockwave therapy [Li-ESWT] in treating erectile dysfunction in diabetic patients. In this trial, which included 21 participants, the researchers compared the Doppler indices taken before and after the treatment and found a significant rise in PSV and RI [$p < 0.05$], but no significant decrease in ESV [$p \geq 0.05$]. A marked improvement in penile hemodynamics, as seen by a substantial increase in PSV, paralleled the good effect on erectile capacity.

According to **Kalyvianakis et al.** ^[9], who conducted a 2-phase study comparing the safety and effectiveness of 6 and 12 treatment sessions over a 6-week period and investigating the effects of repeat treatment after 6 months, PSV significantly increased in both groups after treatment [$P < .001$]. EDV and RI, on the other hand, showed improvements in both groups but did not show a statistically significant difference between them. Because of this, penile hemodynamic improvements after 6 and 12 sessions of treatment over the course of 6 weeks were similar. In addition, extracorporeal shockwave therapy significantly increased penile blood flow, according to assessments of penile hemodynamics ^[12].

The current study found that low intensity extracorporeal shockwave therapy improved penile hemodynamics as measured by penile Doppler parameters among 20 men with erectile dysfunction who had undergone kidney transplantation [mean age = 53.7 years]. The discrepancy may be attributed to the different inclusion criteria used in the two studies.

The results of this study demonstrated that both groups of patients—naïve patients with mild erectile dysfunction and patients who were not compliant with phosphodiesterase type 5 inhibitors—saw a significant improvement in their International Index for Erectile Function erectile function domain [IIEF-EF] score and Erectile health score [EHS] after receiving extracorporeal shockwave therapy.

This study's findings are in agreement with those of **Shendy et al.** ^[8], which demonstrated a substantial rise in IIEF-EF in the group that received shockwave therapy [$p < .001$], in contrast to the control group [$p = 0.194$]. When the post-treatment IIEF was compared between both groups, the shockwave therapy group had a significantly higher value [$p < 0.001$].

Ladegaard et al. ^[13] also looked at penile rehabilitation using Li-ESWT in a placebo-controlled trial for males who had erectile dysfunction after robotic nerve-sparing radical prostatectomy, which is in line with the present study. Twenty patients had shockwave therapy and eighteen people acted as controls out of a total of thirty-eight people that were enrolled.

At 4 and 12 weeks, the shockwave group showed a notable improvement in IIEF-5 and EHS. After 12 weeks, there was a 3.45-point rise in the mean IIEF-5 score [$P = .026$] and a 0.5-point increase in the mean EHS score [$P = 0.019$].

Sramkova et al. [14] and the present study both used randomized, placebo-controlled clinical trials to assess the efficacy of extracorporeal shockwave therapy in the treatment of erectile dysfunction. At 4- and 12-weeks post-treatment, there was a statistically significant difference between the treatment and control groups in terms of erection quality as measured by the IIEF-5 [$p = 0.049$ and $p < 0.001$, respectively]. Additionally, there was a significant increase in EHS after week 12 [$p < 0.001$], and an increase after 4 and 12 weeks [$p = 0.030$ and $p < 0.001$, respectively].

Consistent with the current study, **Kalyvianakis et al.** [9] found that after six weeks of treatment, participants in the group that met twice a week for six sessions improved their IIEF-EF scores considerably more than those in the group that met once a week. Patients can get better sexual performance with 12 sessions twice weekly as opposed to 6 sessions once weekly, according to the study. A maximum of 18 sessions of shockwave therapy are permissible.

Additionally, a subset of diabetic individuals with erectile dysfunction [ED] who responded or did not respond to PDE5I were studied in **Srini et al.** [15] to determine the efficacy of low-intensity extracorporeal shock wave therapy [Li-ESWT]. Researchers discovered that Li-ESWT therapy helped patients who responded to PDE5I as well as those who did not. The results demonstrated that the shockwave group achieved a significant improvement in the IIEF-EF score regarding statistics. There was a 55% increase in the percentage of active PDE5 responders in the PDE5 non-responders' group following Li-ESWT. All the examined measures showed a statistically significant difference between the shockwave and sham groups, with shockwave being superior [$P < 0.001$].

However, a study conducted by **Fojecki et al.** [10] found that 126 patients with erectile dysfunction were randomly assigned to either a

sham treatment or low-energy extracorporeal shockwave therapy for a duration of 5 weeks. No improvement in erectile function was observed in the entire population in this trial. In addition, there was no discernible difference between the active and sham groups according to an analysis of PDE-5i responders. Still, keep in mind that we didn't intentionally power our trial to do this. Responders, non-responders, and treatment-naïve men were all part of this PDE-5i trial. Disagreement could arise since the number of sessions and the energy of the shockwave are different.

No statistically significant difference was discovered between naïve patients with moderate erectile dysfunction and patients' non-compliant to PDE5 inhibitors regarding success rate [73.3% vs 61.3%], according to the current study, which indicated an overall success rate of 67.3% among all the examined population [$P > 0.05$].

An earlier study by **Shendy et al.** [8] found that in the group that received shockwave therapy, 15 patients [71% of the total] were able to produce an erection strong enough for penetrative intercourse, while only 2 patients [9.5%] in the control group were able to do so [$p < 0.001$]. According to **Spivak et al.** [16], half of the subjects in the active group were successful after the sixth treatment, while 79.5% were successful after three treatments, 77.3% were successful after six treatments, and 65.9% were successful at twelve months' follow-up. After six treatments, 1 month, 6 months, and 12 months of follow-up, 17.6%, 35.3%, 23.5%, and 11.8% of participants in the placebo group reached MCID, respectively. There was a significant difference [$P < 0.05$] between the groups following the sixth treatment and throughout all follow-ups.

In addition, a study conducted by **Musa et al.** [17] examined the long-term effects, safety, and potential success factors of low-intensity shockwave lithotripsy [Li-SWT] in 52 men with erectile dysfunction [ED] who did not respond to oral PDE5 inhibitors. After 18 months of follow-up, 33 patients [63.5%] achieved an erection strong enough to penetrate, regardless of whether they were taking PDE5i or not [22 patients were still taking oral PDE5i]. After

using Li-SWT and oral PDE5i, the other 19 patients [36.5% of the total] did not improve.

When looking at the IIEF-EF score as a measure of success, the current study found that the active group had a rate of 37.9% and the sham group had a rate of 38.3% [P =.902]. Comparing the two groups, we find that the active group had a success rate of 3.5 percent and the sham group of 6.7 percent [P =0.369]. Disagreement could arise since the number of sessions and the energy of the shockwave are different.

Extracorporeal shock wave therapy has been validated as an effective treatment for erectile dysfunction in multiple meta-analyses and systematic reviews. Treatment plans with an energy density of 0.09 mJ/mm² and a pulse number of 1,500 to 2,000 are more beneficial to IIEF in ED patients, according to a recent systematic review and meta-analysis [18]. The trial included 16 RCTs with 1,064 participants. Patients experiencing moderate erectile dysfunction also showed a greater improvement in IIEF following extracorporeal shockwave therapy.

Dong et al. [19] included 7 studies with 522 participants. They found that compared to sham therapy, men treated with Li-ESWT had significantly better pooled mean IIEF-EF scores from baseline to follow-up [p <.00001]. The therapy group showed a substantial increase in changes to the IIEF-EF score [p<.00001]. In the therapy group, there was a substantial rise in EHS [p <.00001]. Mean IIEF scores improved for patients with mild to severe ED.

Moreover, a meta-analysis conducted by **Man and Li.** [20] included 9 trials with 637 patients. The results of the meta-analysis demonstrated that LI-ESWT has the potential to considerably enhance IIEF [p= 0.004] and EHS [p = 0.01]. It is possible that the therapeutic effect will last for at least three months [95% CI, 1.40-6.90; p = 0.003]. Energy density is lower [p = 0.01]. The therapeutic effectiveness was improved with a higher number of pulses [3000 pulses each session] and shorter total treatment durations [<6 weeks] [p = 0.02].

In a different meta-analysis, **Lu et al.** [21] considered 14 trials involving 833 patients and

found that LI-ESWT could considerably enhance IIEF [p < 0.0001] and EHS [p = 0.01]. Treatment may remain effective for at least three months. Compared to patients with severe ED or comorbidities, those with mild-moderate ED demonstrated superior therapeutic efficacy following treatment. Clinical outcomes, particularly improvements in IIEF, were correlated with energy flux density, the number of shock waves administered each session, and the length of time patients underwent LI-ESWT.

Conclusion: In naïve patients and patients who react to other treatments for moderate erectile dysfunction, but who do not comply with PDE5 inhibitors, the present study found that extracorporeal shockwave therapy is a safe, effective, and noninvasive alternative. PDE5 inhibitor non-compliant patients were treated with the same level of effectiveness as treatment naïve patients, who responded to the medication.

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