LSWT

Linear Shockwave Therapy for Erectile Dysfunction

Clinical Data and Reports

September 2018

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Twelve-Month Efficacy and Safety of Low-Intensity Shockwave Therapy for Erectile Dysfunction in Patients Who Do Not Respond to Phosphodiesterase Type 5 Inhibitors

Amado Bechara, MD, PhD, Adolfo Casabé, MD, Walter De Bonis, MD, and Pablo Gomez Ciciclia, MD

ABSTRACT

Introduction: Low-intensity shockwave therapy (LISWT) has recently emerged as a promising method in the treatment of erectile dysfunction (ED).

Aim: To assess the long-term results of the effectiveness and safety of LISWT in patients with ED who are non-responders to phosphodiesterase type 5 inhibitor (PDE5i) treatment.

Methods: This open-label, longitudinal, and observational study investigated an uncontrolled population of 50 consecutive patients whose ED was unresponsive to PDE5i treatment. Patients were treated with a four-session LISWT protocol. During active treatment and follow-up, all patients remained on their regular high on-demand or once-daily PDE5i dosing schedules.

Main Outcome Measures: Effectiveness was assessed according to the International Index of Erectile Function erectile function domain, questions 2 and 3 of the Sexual Encounter Profile, Erection Hardness Scale, and Global Assessment Question scores at baseline and at 3, 6, 9, and 12 months after treatment. Patients were considered responders whenever they showed improvement in erection parameters in all four assessments and responded positively to the Global Assessment Question. Adverse events were recorded. Statistical variables were applied and findings were considered statistically significant at a P value less than $< .05$.

Results: Eighty percent (mean age ¼ 64.8 years) completed the 12-month follow-up. Positive response rates were 60% of available subjects at the end of the study and 48% of the intent-to-treat population. After the 12-month follow-up, 91.7% of responders maintained their responses. No patient reported treatment-related adverse events.

Conclusion: LISWT in patients with ED unresponsive to PDE5i treatment was effective and safe in 60% of patients treated. The efficacy response was maintained for 12 months in most patients.

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Key Words: Low-Intensity Extracorporeal Shockwave Therapy; Erectile Dysfunction; Phosphodiesterase Type 5 Inhibitor

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INTRODUCTION

Erectile dysfunction (ED) is a medical entity that is highly prevalent in men older than 50 years whose history of vascular risk factors (VRFs) has been a common denominator in the origin of this symptom.[1]

Many studies have stressed the status of ED as a potential indicator of cardiovascular disease, although other clinical trials have found a high incidence of ED in men with VRFs such as metabolic syndrome, diabetes, and hypertension.[2,3]

Since 1998, the phosphodiesterase type 5 inhibitor (PDE5i) has introduced a change in the treatment paradigm for patients with ED because approximately 60% of patients can recover their erectile function and lead a satisfactory sex life.[4]

Despite the effectiveness of PDE5i in the treatment of ED, 40% to 50% of patients—depending on the etiology of the dysfunction—do not respond to this drug therapy, even after optimization approaches such as treatment combinations have been implemented.[5e10]

For some years, low-intensity shockwave therapy (LISWT) has been implemented for the treatment of ED and to optimize the response to PDE5i.

A shockwave is a wave of abrupt pressure (vibration move- ment) produced by an object that travels faster than the speed of sound (<10 ns) producing external pressure differences and Increased temperature.[11]

Since the 1980s, shockwaves of different intensities have been used therapeutically in medicine. High-intensity shockwaves (pressure ¼ 450 bar) have been implemented in the treatment of urolithiasis, medium-intensity shockwaves (pressure ¼ 200 bar) in the treatment of arthralgia, tendinitis, and bursitis, and more recently LISWT (pressure ¼ 80 bar) in the treatment of ED.

Young and Dyson[12] discovered that therapeutic ultrasound encourages angiogenesis by enhancing the expression of vascular endothelial growth factor. Nurzynska et al[13] reported that shockwaves have a positive influence on the proliferation and differentiation of cardiomyocytes, smooth muscle, and endo- thelial cell precursors, with a more obvious effect in cells from a normal heart than from a pathologic heart.

After these initial reports, LISWT was implemented in the treatment of chronic myocardial ischemia and diabetic foot ulcers, among other applications.[14e18]

The idea of applying LISWT to the penis stemmed from a study with animals that proved that the energy of shockwaves applied to the myocardium of pigs ameliorates ischemia-induced myocardial dysfunction.[14] By extrapolating these findings to ED, it was presumed that shockwaves applied to the penis might increase blood flow and improve endothelial function through the stimulation of angiogenesis in the corpus cavernosum.

The mechanism of action is still not completely elucidated. However, low-intensity energy has been shown to induce the production of a physiologically significant amount of non-enzymatic nitric oxide and activate intracellular cascade pathways that trigger the release of angiogenic factors.[19]

In this way, shockwaves produce mechanic stress and micro- trauma at the cellular level, thus generating a series of biological cascades that favor the release of angiogenic factors leading to neovascularization.

In vivo and in vitro evidences have proved that shockwaves enhance the expression of growth factors related to angiogenesis, increase mRNA and vascular endothelial growth factor cellular levels and its receptor, Flt-1, and induce neovascularization, increase blood supply, and significantly increase angiogenic markers.[14e17]

In that regard, Qiu et al[20] found that shockwave therapy significantly restored erectile function in rats with streptozotocin- induced diabetes mellitus to levels similar to those exhibited by healthy controls, thus validating the animal model as comparable to prior clinical trials performed in humans. According to trial results, improvements in erectile function might be attributable to the positive effects afforded by the shockwaves on endothelial and smooth muscle regeneration in the penis. These effects appear to be mediated by the recruitment of endogenous smooth muscle cells.

Interestingly, the results recently published by Assaly- Kaddoum et al[21] showed that LISWT significantly improved erectile function in Goto-Kakizaki rats to the same extent as sildenafil. Furthermore, the effects of LISWT were potentiated with sildenafil. Nevertheless, this was not mediated by a mechanism dependent on nitric oxide and cyclic guanosine monophosphate and the investigators encouraged further investigation of the mechanism of action of these devices.

The first observation studies in patients who responded poorly to PDE5i therapy reported on the efficacy and safety of LISWT devices, especially in patients with ED of vascular origin and in those with a poor response to PDE5i treatment.[22,23]

Recently, Kitrey et al[24] performed a sham-controlled evaluation of penile LISWT effect in 58 patients unable to achieve sexual intercourse using a PDE5i. In the LISWT and sham groups, 54.1% and 0% of patients, respectively, achieved an erection hard enough for vaginal penetration. According to changes in the International Index of Erectile Function erectile function domain (IIEF-EF) score, treatment was effective in 40.5% of men who received LISWT but in none in the sham group.

AIM

Based on these findings, the aim of this study was to assess the effectiveness and safety of LISWT after 12 months in the treatment of ED in patients with a history of vascular disease or associated VRFs with a low response to PDE5i treatment.

METHODS

This study was an open-label, longitudinal, observational, and independent study designed to evaluate the safety and efficacy of LISWT in an uncontrolled population of sexually active men with ED unresponsive to PDE5i treatment and associated VRFs.

This study consisted of a screening phase, a treatment phase, and a 12-month follow-up phase. At the screening phase, patients had an extensive medical and sexological history evaluation and a physical examination.

The inclusion criteria involved sexually active men with ED that was unresponsive to PDE5i treatment and exhibited VRFs (eg, diabetes, hypertension, dyslipidemia, and coronary artery disease). Patients with untreated hypogonadism or a history of pelvic surgery and patients with ED of neurologic origin (resulting from prostatectomy, pelvic surgery, or spinal cord injury) were excluded.

Patients were considered non-responders to PDE5i if they, after completing all optimization measures commonly suggested (correct dose optimization of PDE5i, correction of risk factors, improvement in sexual stimuli, and correction of testosterone levels, and proper patient dietary training, especially with the use of short-acting PDE5i), had an IIEF-EF score lower than 26 points when using these drugs.[10,11]

Fifty consecutive patients with ED fulfilled the inclusion criteria and accepted the invitation to participate. During LISWT and follow-up, these patients continued with PDE5i treatment at the maximum dose or with a daily dose under the same treatment protocol. Only those patients who completed the 12-month follow-up were considered for result analysis.

Severity of ED was classified into five categories according to the IIEF-EF score.[25]

The following evaluation criteria were used: IIEF-EF to assess ED severity, questions 2 and 3 from the Sexual Encounter Profile (SEP2 and SEP3) to assess penetration and erection sustain- ability, the Erection Hardness Score (EHS), and a Global Assessment Question (GAQ): Has the treatment improved the quality of your erections?[26e29]

Improvement of the IIEF-EF score was defined as an increase from baseline to follow-up (12 months after treatment) according to the minimal clinically differences suggested by Rosen et al.[30]

The criterion for treatment success according to the EHS was a score of 3 or 4. Assessment measurements were taken face to face before treatment and 3, 6, 9, and 12 months after LISWT completion (Figure 1).

Patients were considered responders to LISWT whenever they showed improvement in erection parameters in all four assess- ments (IIEF-EF, SEP2, SEP3, and EHS) and responded positively to the GAQ at 3, 6, 9, and 12 months after treatment. Adverse events were recorded.

This trial was performed using Renova NR, an extracorporeal LISWT device (Direx Argentina, Buenos Aires, Argentina). This equipment uses linear shockwaves and, unlike previous models, spans the entire area of the organ (up to 70 mm) and thus can apply shockwaves with greater precision at the penile crura and corpus cavernosum.[31]

The subjects started the treatment right after inclusion in the study because they continued their respective current PDE5i therapies.

According to previously published studies, the treatment consisted of applying 14,400 shockwaves during a period of 4 weeks. In each session, the patient received 3,600 shockwaves of 0.09 mJ/mm^2: 1,800 were applied to the penis (900 to each corpus cavernosum) and 1,800 were applied to the perineum (900 to each crus). The areas that received treatment were the same at each session. All sessions were performed without anesthesia in an outpatient setting and each lasted 20 minutes.[31]

The study was conducted according to Good Clinical Practices and the Declaration of Helsinki, it was approved by the local research ethics committee, and all patients signed an informed consent form.

Variables of demographic characteristics of responders and non- responders were calculated using the Mann-Whitney test and Fisher exact test. Efficacy variables were assessed using the Friedman test, and individual comparisons were assessed with the Bonferroni- Dunn method. Statistical variables were applied and findings were considered statistically significant at a *P* value less than .05.

Main Outcome Measures

Effectiveness was assessed using the IIEF-EF, SEP2 and SEP3 diaries, EHS, and GAQ at baseline and at 3, 6, 9, and 12 months after treatment.

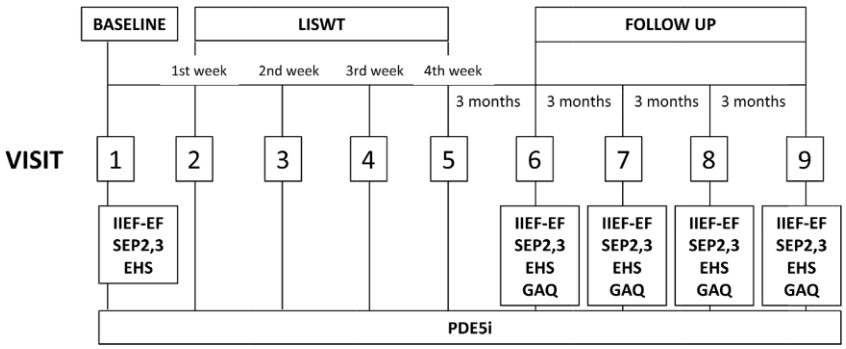


Figure 1. Study flowchart. EHS ¼ Erection Hardness Scale; GAQ ¼ Global Assessment Question; IIEF-EF ¼ International Index of Erectile Function erectile function domain; LISWT ¼ low-intensity shockwave therapy; SEP2 and 3 ¼ questions 2 and 3 of Sexual Encounter Profile.

RESULTS

Eighty percent of patients (40 of 50) completed the treatment and 12-month follow-up. Ten patients with similar demographic characteristics were excluded from the study because of loss to the first follow-up.

Median age was 64.8 years and duration of ED was 70.5 months.

Table 1. Demographic characteristics of patients (responders and non-responders to low-intensity shockwave therapy)

	Responders (n ¼ 24)	Non-responders (n ¼ 16)	*P* value
Age (y), mean (range)	65 (50e82)	64.4 (48e82)	.8902*
Duration of ED (mo)	64.4	77.8	.4385*
Range (mo)	12e132	8e120	
Vascular risk factors, n (%)			
Hypertension	14 (58.3)	11 (68.8)	.7397†
Diabetes mellitus	3 (12.5)	7 (43.8)	.0588†
Dyslipidemia	11 (45.8)	9 (56.3)	.7475†
Coronary artery disease	10 (41.7)	7 (43.8)	.9999†
Severity of ED according to IIEF, n (%)			
Severe	4 (16.7)	6 (37.5)	.1592†
Moderate	12 (50)	4 (25)	.1881†

Mild to moderate	4 (16.7)	4 (25)	.6905†
Mild	4 (16.7)	2 (12.5)	.9999†

ED ¼ erectile dysfunction; IIEF ¼ International index of Erectile Dysfunction. *Mann–Whitney test. †Fisher exact test.

The positive response rate was 60% of available subjects at the end of the study and 48% of the intent-to-treat population.

Sixty percent of patients (24 of 40) showed improvement in efficacy parameters in all four assessments (IIEF-EF, SEP2, SEP3, and EHS) and responded positively to the GAQ. These changes were significant from the first follow-up (3 months after treatment).

By the third month after treatment, 91.7% of responders to LISWT (22 of 24) maintained efficacy parameters up to the last follow-up visit 12 months after treatment.

No statistically significant difference was found for age, duration of ED, comorbidities, and dysfunction severity when comparing responders to LISWT (24 of 40) with non-responders to LISWT (16 of 40; Table 1).

In responders to LISWT, the increase in results obtained through the IIEF-EF score was statistically significant from the 3-month assessment after treatment, reaching a mean of 9.3 points and of 9.1 points by 12 months after treatment (Figure 2).

From 3 months after treatment to the end of follow-up monitoring, significant changes were encountered in the responder group for the EHS and SEP2 and SEP3, with a response rate of almost 80% of attempts (Figure 2).

Improvements in the IIEF-EF score were higher whenever ED was more severe, with changes of 13, 10.5, 6.8, and 4.5 points for patients with severe, moderate, mild to moderate and mild ED, respectively (Table 2).

Thirteen patients reached a score of at least 26 points in the IIEF-EF score, and the degree of severity decreased in nine and remained unchanged in two.

DISCUSSION

This study evaluated a group of patients with ED and associated VFRs who responded poorly to PDE5i therapy in a 12-month pilot study. Erectile function was recovered in 60% of patients after treatment with linear-focused LISWT.

Most randomized, double-blinded, sham-control trials have reported the efficacy of LISWT in patients with ED.[32e34]

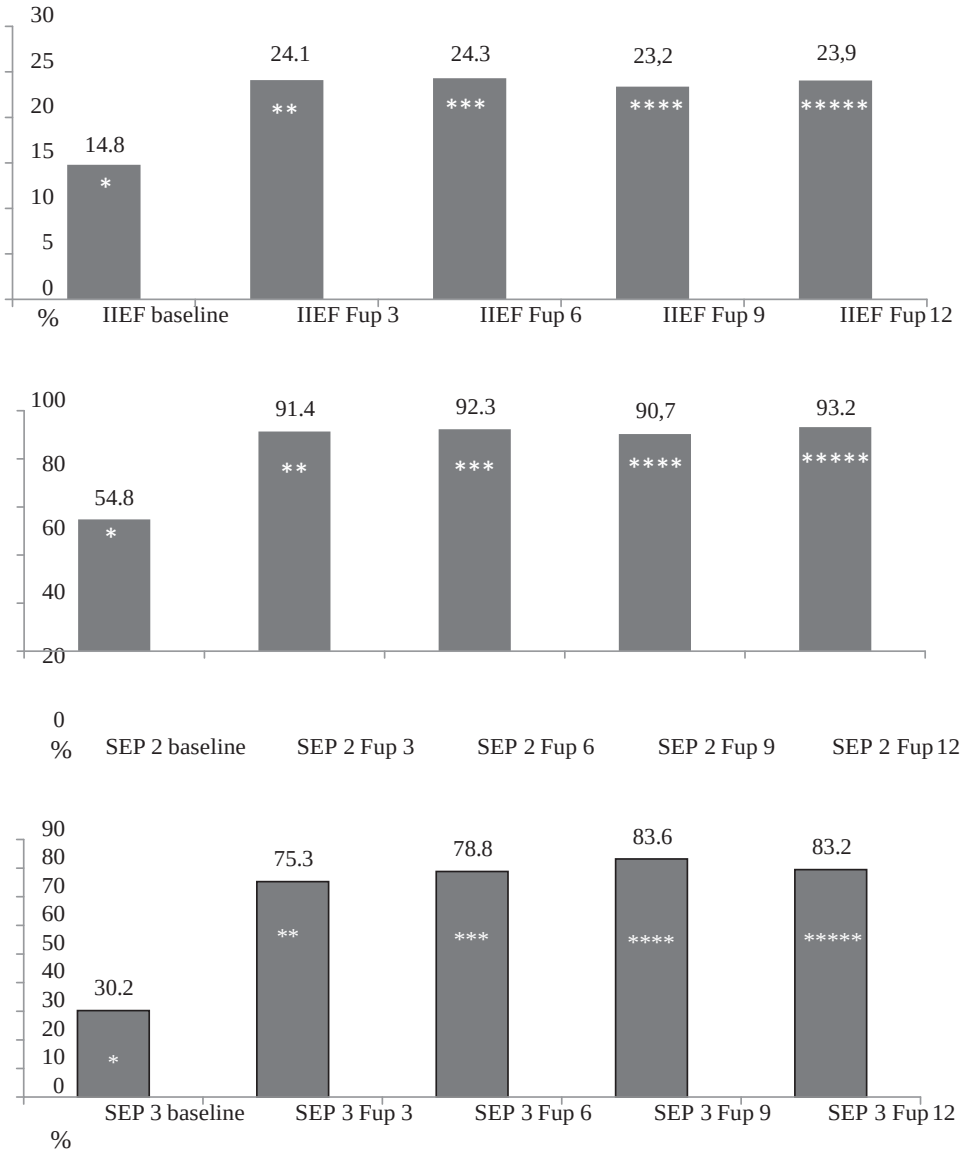
Vardi et al[32] presented the first randomized, double-blinded, sham-control trial that demonstrated that LISWT had a positive short-term clinical and physiologic effect on the erectile function of men who respond to oral PDE5i therapy. They found a significantly greater increase in the IIEF-EF score in the treated group than in the sham-treated group. In addition, physiologic penile hemodynamic significantly improved in the treated group but not in the sham group (maximal postischemic penile blood flow ¼ 8.2 vs 0.1 mL/[min $ dL], $P < .0001$) assessed using plethysmography.

However, Yee et al,[33] using a similar treatment scheme to the one used in the study by Vardi et al[32] and implementing the same shockwave therapy system (Omnispec ED1000; Medispec Ltd, Germantown, MD, USA), did not find significant statistical evidence in the IIEF score and EHS score in a group of 28 patients under LISWT treatment compared with a sham-treated group of 30 patients. Nevertheless, they found a significant difference in patients with severe

ED according to the Sexual Health Inventory for Men and concluded that LISWT has clinical efficacy in this subgroup of patients.

More recently, Srini et al,[34] in a randomized double-blinded trial with active treatment and sham therapy, reported a positive long- term efficacy in patients with vasculogenic ED treated with linear- focused shockwaves, just as Vardi et al[32] had (Omnispec ED1000).

In a narrative review of all published studies, Gruenwald et al[35] found that 60% to 75% of treated patients who responded to PDE5i therapy could eliminate their dependency on those drugs and achieve an erection and vaginal penetration and that 72% of non-responders to PDE5i before undergoing LISWT became responders and achieved vaginal penetration.



Friedman test: * vs ** , *vs ***, * vs ****, * vs ***** p<0,05

Figure 2. Evolution of changes in IIEF-EF score, SEP2, and SEP3 in responders to LISWT (n ¼ 24). *P* < 0.05 by Friedman test (*baseline vs **Fup 3, vs ***Fup 6, vs ****Fup 9, vs *****Fup 12). Fup 3 ¼ 3-month follow-up; Fup 6 ¼ 6-month follow-up; Fup 9 ¼ 9-month follow-up; Fup 12 ¼ 12-month follow-up; IIEF-EF ¼ International Index of Erectile Function erectile function domain; SEP2 and 3 ¼ questions 2 and 3 of the Sexual Encounter Profile.

These investigators used a compact electrohydraulic system fitted with a targeted shockwave source (Omnispec ED1000). Unlike the system used for the present patients, Gruenwald et al[35] had to stretch the penis and manually apply the transducer to it proximally, medially, and distally and then apply it to the peri- neum. With this operator-dependent method, the selected treat- ment protocol consisted of two sessions per week for a period of 3 weeks and was repeated after a treatment-free interval of 3 weeks.

Table 2. IIEF-6 changes according to severity of ED before and 12 months after treatment with shockwaves of low intensity

ED severity	n	Baseline IIEF-6 score, mean ± SD	Follow-up 12-mo IIEF-6 score, mean ± SD	IIEF-6 improvement points	P value
Severe	4	9 ± 1.155	22 ± 3.651	13	.029
Moderate	12	12.8 ± 1.328	23.3 ± 4.619	10.9	.0001
Mild to moderate	4	18.5 ± 1.291	25.3 ± 4.113	6.8	.002
Mild	4	22.8 ± 0.500	26.3 ± 4.193	4.5	.3429
Total	24	14.7 ± 4.757	23.9 ± 4.303	9.2	.0001

ED ¼ erectile dysfunction; IIEF-6 ¼ International index of Erectile Dysfunction.

Chung and Cartmill,[36] in an open-label prospective study of 30 patients with ED, assessed the efficacy and safety of an electromagnetic shockwave unit of higher energy density (0.25 mJ/mm2) previously used in the treatment of tenosynovitis and tendinitis (Duolith SD1 Ultra; Storz Medical AG, Tägerwilen, Switzerland). Treatment duration consisted of two sessions per week for a period of 6 uninterrupted weeks. Sixty percent of patients showed an improved erectile response according to the IIEF-5 and the Erectile Dysfunction Inventory of Treatment Satisfaction index 6 weeks after treatment, and this effect remained for 4 months.

The present trial was performed using the Renova NR. Its design makes it operator independent: its transducer can deliver shockwaves after being secured to the penis and the perineum; thus, the operator does not need to hold the device. The trans- ducer spans an area of 70 mm, which allows effective application to each corpus cavernosum. LISWT involves a very small amount of energy (0.09 mJ/mm^2), equivalent to 10% of the energy used by conventional lithotripters for the treatment of urinary tract stones.

The efficacy of the Renova NR reported by other investigators was an average improvement of more than four points in the IIEF-EF score, thus going beyond the minimal important dif- ferences proposed by Rosen et al[30] to consider a treatment of ED effective.

Reisman et al,[31] in a multicenter study with a larger number of patients and 6-month follow- up, reported 81% efficacy, whereas Ruffo et al[37] reported 76% efficacy in a group of 31 patients and 3-month follow up.

Currently, no available study has directly compared the efficacy of these three different LISWT methods. In the present study, improvements in IIEF-EF, SEP2, SEP3, and EHS scores became evident from the first through the third follow-ups after treatment, with statistically significant values that were main- tained to the end of the follow-up phase in 90% of patients.

It is worth pointing out that, unlike what has been reported by other investigators, the present study considered a patient responsive to LISWT when he showed improvement in efficacy in all four assessments and responded positively to the GAQ and not just the IIEF score alone, which reinforces the result of this study. It is well known that changes in IIEF imply only an improvement in score but does not necessarily guarantee a patient's successful or complete sexual intercourse. In contrast, many men consult for the correction of erections insufficient for penetration, yet they are not fully satisfied. Sixty percent of the present patients achieved and

maintained an erection after penetration, and they were satisfied with the improvement of their penile rigidity after treatment. This might better explain the lower efficacy compared with other studies.

Factors such as patient age and duration of ED did not influence the results.

An interesting aspect to consider is that patients continued their regular treatment and PDE5i drug throughout LISWT, thus eliminating the resulting bias of suspending and resuming oral treatment as described in other trials. Therefore, each patient was compared with himself before and after shockwave therapy concurrently with PDE5i treatment.

This study has several limitations that are important to consider. First, its lack of a placebo group prevents a proper comparison of the effects of LIWST. As mentioned earlier, other trials have shown significant differences between active and placebo treatments.[24,32e34] Second, this research extended through a follow-up period of 12 months and sustained the patients' response; thus, there was no placebo treatment, which tends to be brief and not sustained over time, although this aspect has not been fully elucidated. Third, 10 patients were not included in the results owing to lack of follow-up. If one assumes that those 10 patients dropped out because of lack of response or were disappointed with the results, then this could constitute a serious bias when interpreting the results. If this were the case, then the response rate would be of 48% instead of 60%. This value seems more realistic given the weight of the results presented by Kitrey et al[24] who obtained approximately 50% recovery in non-responders to PDE5i therapy in a prospective, randomized, double-blinded, sham- controlled study. If the lack of placebo is considered an important bias, then it should be considered representative of a "real-life" setting.

In contrast, whenever independent pilot studies are conduct- ed, the number of patients included tends to be small, and the results cannot be generalized. Nevertheless, however limited the data and the experiences reported in the literature thus far, one can consider these data quite promising.

There is no certainty that these improvements were due to the vascular changes suggested by other investigators because this study had an observational design of clinical practice; patients did not undergo any penile vascular study such as a Doppler evalu- ation that can show changes in the cavernosal arteries.

There are many uncertainties to LISWT: the published liter- ature is not multicentric and usually has a small number of patients and short follow-up time. It is not clear whether the number of sessions and treatments was sufficient. It does not define the best profile of patients who might benefit from this treatment. The mechanism of action is not clear.

Nevertheless, LISWT has a good safety profile, with no adverse events reported. The effectiveness in clinical and empirical practice is high. This new treatment modality seems promising to optimize treatments of ED, especially in patients with associated VRFs.

The main contribution of this study is adding more data using LISWT with only four sessions and a second-generation device in patients with ED unresponsive to PDE5i and associated VRFs followed for 1 year.

Despite the enthusiasm over these results, it is necessary to have a larger number of long-term multicentric placebo- controlled studies that can prove the efficacy and safety of this innovative treatment tool, thus avoiding false expectations and unnecessary medical expenses.

CONCLUSIONS

Extracorporeal LISWT in patients with ED unresponsive to PDE5i treatment was effective and safe in 60% of patients. The efficacy response was maintained for 12 months in most

patients. Large-scale, multicentric, long-term, randomized, sham- controlled studies are needed to determine the benefits of this new line of treatment for ED.

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Safety and efficacy of low intensity shockwave (LISW) treatment in patients with erectile dysfunction

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ABSTRACT

The primary goal in the management strategy of a patient with ED would be to determine its etiology and cure it when possible, and not just to treat the symptoms alone. One of the new therapeutic strategies is the use of low intensity extracorporeal shockwave (LISW) therapy. The mechanism of shockwave therapy is not completely clear. It is suggested that LISW induces neovascularization and improvement of cavernosal arterial flow which can lead to an improvement of erectile function by releasing NO, VEGF and PCNA.

Materials and Methods: 31 patients between February and June 2013 with mild to severe ED and non-Phosphodiesterase 5 inhibitors responders were enrolled. Patients underwent four weekly treatment sessions. During each session 3600 shocks at 0.09mJ/mm^2 were given, 900 shocks at each anatomical area (right and left corpus cavernosum, right and left crus). Improvement of the erectile function was evaluated using the International Index of Erectile Function (IIEF-EF), the Sexual Encounter Profile (SEP) diaries (SEP-Questions 2 and 3) and Global Assessment Questions (GAQ-Q1 and GAQ--Q2).

Results: At 3-month follow-up IIEF-EF scores improved from 16.54±6.35 at baseline to 21.03±6.38. Patients answering 'yes' to the SEP-Q2 elevated from 61% to 89% and from 32% to 62% in the SEP-Q3. A statistically significant improvement was reported to the Global Assessment Questions (GAQ-Q1 and GAQ-Q2).

Conclusion: In conclusion, we can affirm that LISW is a confirmed therapeutic approach to erectile dysfunction that definitely needs more long-term trials to be clarified and further verified.

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INTRODUCTION

Erectile dysfunction (ED) is the main complaint in male sexual medicine and is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Although ED is a benign disorder, it may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of patients and their partners (1).

ED seems to affect 52% of 40-70-year-old men (2). Advances in basic and clinical research on ED during the past 15 years have led to the development of a variety of new treatment options, including pharmacological agents for intracavernous, intraurethral, and oral use and the use of vacuum erection devices (1).

Oral therapies have changed the diagnostic and therapeutic approach to ED becoming a major tool in treating ED. In fact, phosphodiesterase-5

inhibitors (PDE5-i) in the late 1990s and early 2000s completely revolutionized the field of sexual medicine becoming the most popular treatment and the first-line monotherapy for ED (3).

Unfortunately, they are limited for being used before the sexual act and do not modify the physiologic mechanism of penile erection (4).

After the initial enthusiasm of the use of the PDEi, the psychological impact–artificiality of erections and planning for sexual intercourse as well as a not proven curative effect (5) have slightly limited the use of these drugs, leaving the field open to the development of new therapies to treat or maybe cure patients with ED. Furthermore, the frequently reported side-effects of PDE5i, such as headache, dyspepsia, muscular pains, and hot flushes can affect a normal sexual intercourse (6).

The primary goal in the management strategy of a patient with ED would be to determine its etiology and cure when possible, and not just the treatment of symptoms. One of the new therapeutic strategies is the use of low intensity extracorporeal shockwave (LISW) therapy.

Shockwaves (SWs) are longitudinal acoustic waves that travel in the speed of water in ultrasound through body tissue and that carry energy (7). SWs have been widely used in urology to treat urinary stone disease (8), and less often in Peyronie's disease (9) or chronic pelvic pain syndrome (CPPS) in males (10).

The mechanism of action of low-intensity shock waves (LISW) is still not very clear. Many authors suggested that LISW improves erectile function increasing cavernous blood flow and inducing a neovascularization (11). Neovascularization is promoted by the expression of angiogenesis-related growth factors, such as endothelial nitric oxide synthase (NOS), vascular endothelial growth factor (VEGF), and endothelial cell proliferation factors, e.g., proliferating cell nuclear antigen (PCNA) (12).

The aim of our study is to evaluate the improvement of erectile function after therapy with LISW in men affected by mild to moderate ED.

MATERIALS AND METHODS

Study population

31 patients between February and June 2013 with mild to severe ED, and non-Phosphodiesterase 5 inhibitors responders were assessed for this study. Only 2 (6.4%) underwent treatment with PDE5-i in the last four weeks before starting the treatment (Table-1). They all signed an informed consent.

Inclusion criteria were: good general health, ED for at least six months, IIEF-EF between 7 to 24 (=mild to moderate).

Exclusion criteria included: neurological pathology, past radical prostatectomy or extensive pelvic surgery, recovering from cancer during the last year, any unstable medical, psychiatric disorder, spinal cord injury, penile anatomical abnormalities, clinically significant chronic hematological disease, anti-androgens or radiotherapy treatment of the pelvic region.

The medical and psychosexual history of all patients were evaluated at baseline to detect comorbidities. Table-2 summarizes the patients' organic co--morbidities: cardiovascular diseases in 7 pts (22%), hypertension in 18 pts (58%), diabetes in 12 pts (38%) and abnormal total serum cholesterol in 13 pts (41%).

Table 1 - The pretreatment characteristics of population.

Variable	Patients	P value
Age (years)		0.39
Mean±SD	59.93±12.16	
N.of subjects analysed	31	
Time suffering from ED (yrs)		0.50
Mean±SD	3.66±4.57	
N.of subjects analysed	31	
Treatment with PDE5-I in the last 4 weeks (%)	6.45	0.12
Proportion	2/31	

Table 2 - Analysis of self-reported measures at baseline , 1-month and 3-month follow up by treatment cohort.

Variable	Baseline	Follow-up 1 month	p value	Follow-up 3 months	P value
IIEF – EF	16.54±6.35	21.13±6.31	P=0.0075	21.03±6.38	p=0.0096
SEP-Q_2 (%)	61 (yes)	86 (yes)	P=0.0292	89 (yes)	P=0.0112
	38 (no)	13 (no)		10 (no)	
		2 drop-out			
SEP-Q_3 (%)	32 (yes)	58 (yes)	P=0.0402	62 (yes)	P=0.0207
	67 (no)	41 (no)		37 (no)	
		2 drop-out			

(IIEF-EF): International Index of Erectile Function; **(SEP-Q2):** Sexual Encounter Profile-Q2; **(SEP-Q3):** Sexual Encounter Profile-Q3

Study design

This is a pilot clinical study evaluating safety and efficacy of LISW treatment (performed with Renova ®) on symptomatic ED patients versus baseline.

Study schedule

a) screening

Patients were visited (visit 1) and those who were using PDE5-i had to go to a flush-out period of three weeks before starting the treatment. Furthermore, they committed to refrain from usage of PDE5-i during the duration of the treatment session.

b) Treatment

Patients underwent four weekly treatment sessions. During each session 3600 shocks at 0.09 mJ/mm2 were given. Shocks were applied at the penis shaft at right corpus cavernosum and left corpus cavernosum, right crus and left crus, 900 shocks at each area.

The treatment areas were the same for every session, so that at the end of the full treatment (four sessions) each area received 3600 shocks at an average 0.09mj/mm. We used this protocol under the guidance of Direx Group LTD.

LISW utilize low energy-0.09mJ/mm^{2-}-equivalent to 10% of the energy used by conventional kidney stone lithotripters in the treatment of urinary tract stones. This device generates a low intensity shockwave focused along a line of 70mm and hence is able to apply shockwaves to the corpora cavernosa and crura effectively.

For the past 3 years, a similar LISW technique has been used in different sites using the same level of energy density to treat ED (13). Shockwaves are created by a special generator and are focused using a specially designed shockwave applicator apparatus. The shockwaves are delivered through the applicator covering the entire corpora cavernosa of the penis.

The treatment does not inflict pain and does not require any anesthesia or sedation.

Each session lasts approximately 30 minutes.

c) Primary efficacy objective

To evaluate the increase of number of points in the International Index of Erectile Function (IIEF-EF) questionnaire from baseline (visit 1) to 1 and 3 months after treatment regarding the severity of the symptoms according to minimal clinically important differences in the erectile function domain of the IIEF scale (14). The IIEF-EF was chosen as primary clinical efficacy assessment tool in this study. It has been reported to be brief and reliable, psychometrically sound, and easy to administer in both research and clinical settings. It is available (and cross-culturally validated) in 10 languages and demonstrates adequate sensitivity and specificity for detecting treatment-related changes in erectile function (15).

d) Secondary efficacy objective

To study the clinical efficacy of LISW in terms of improvement in sexual activity leading to optimal penetration at 1 and 3 months post-treatment by using the Sexual Encounter Profile

(SEP) diaries (SEP-Questions 2 and 3). Patients recorded efficacy information after each sexual encounter by answering the two yes/no questions of the test: SEP Question 2:"Were you able to insert your penis into your partner's vagina?" and SEP Question 3:"Did your erection last long enough for you to have successful intercourse?".

In addition, patients underwent further evaluation with the Global Assessment Question (GAQ) by answering the two yes/no questions of the test: (GAQ-Q1) "Over the past four weeks has the treatment you have been taking improved your erectile function?" and (GAQ-Q2) "If yes, has the treatment improved your ability to engage in sexual activity over the past four weeks".

Statistical analysis

Statistical analysis was performed by the program Statistical Package for Social Sciences for Windows, version 11.5.1 (SPSS Inc., Chicago, IL, USA), using X^2 test and T-student for categorical data comparisons.

RESULTS

All patients had mild to severe ED at least six months, were non PDE-5i responders, with a mean age of 59.93±12.16 years. Median follow-up was of 3 months (range 2-5 months). Global patient perceptions after treatment with LISW significantly improved. Indeed IIEF--EF score showed significant improvement (baseline 16.54±6.35 vs 21.13±6.31 after 1 month P=0.0075; baseline 16.54±6.35 vs 21.03±6.38 after 3 months p=0.0096) (Table-2; Figure 1-3). About 86% (P=0.0292) and 89% (P=0.0112) of patients answered with a positive answer to SEP Q2 question ("Were you able to insert your penis into your partner's vagina?") 1 month and 3 months after treatment, respectively, versus 61% positive answers pre-treatment (Table-2). SEP Q3 question ("Did your erection last long enough for you to have successful intercourse?") was answered positively by 58% (P=0.0402) 1 month after LISW treatment and 62% (P=0.0207) after 3 months. After 1 month of treatment there were two drop-outs (Table-2). Table-3 shows patients' satisfactions of treatment with GAQ-Q1 ("Over the past four weeks has the treatment you have been taking improved your erectile function?") and GAQ-Q2 questions ("If yes, has the treatment improved your ability to engage in sexual activity over the past four weeks"). Regarding the individual answers for the GAQ questions, we noticed that 89% and 62% of patients at 1 and 3 months respectively answered "Yes" to the GAQ-Q1 while in the same period 79% and 76% of patients answered "Yes" to the

Figure 1 - IIEF-EF score at baseline and after 1 month follow-up

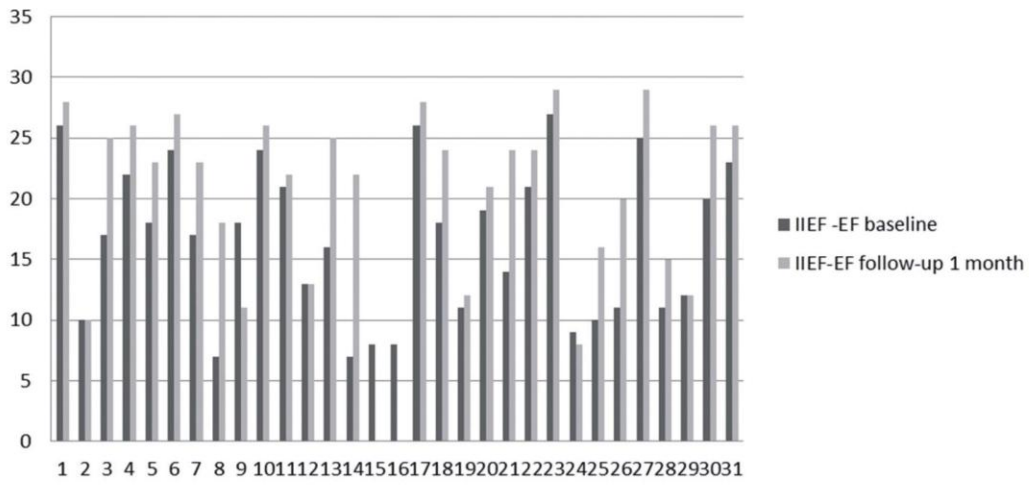


Figure 2 - IIEF-5 score at baseline and after 3 month follow-up

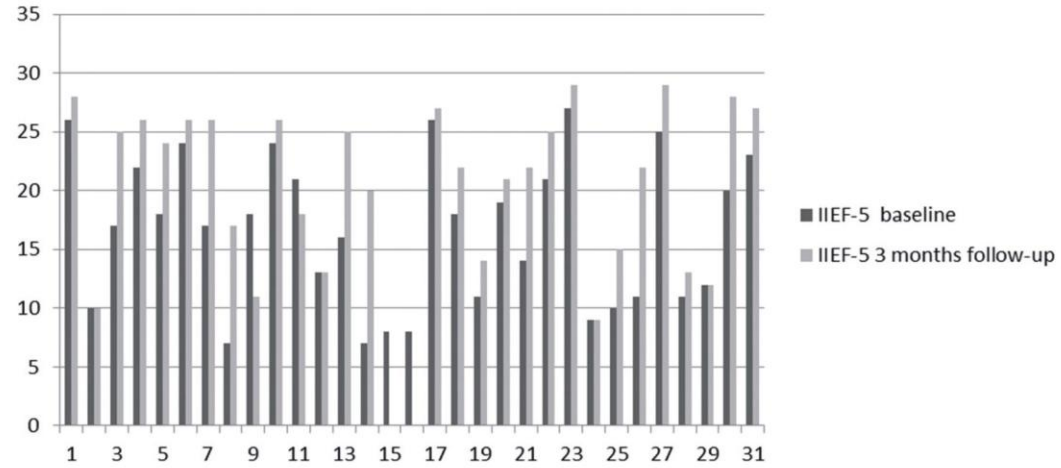
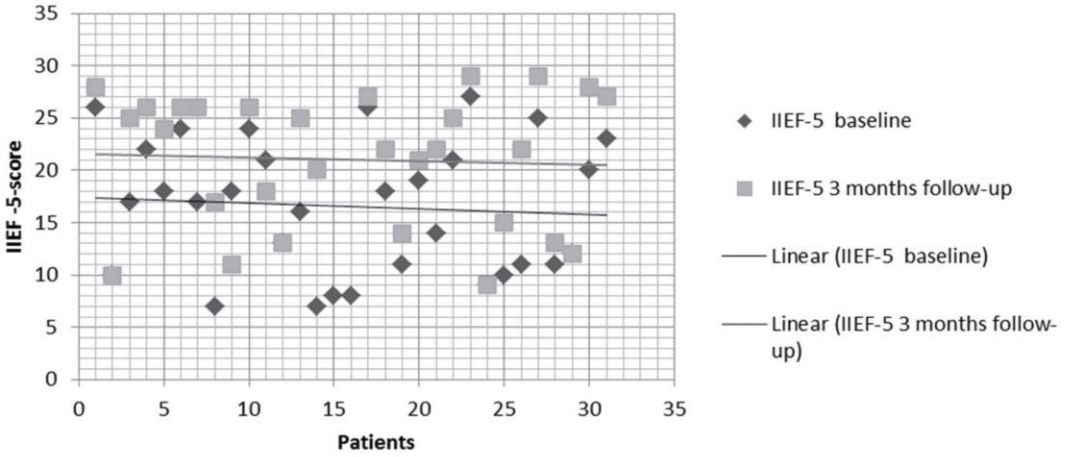


Figure 3 - Dispersion date IIEF score baseline and 3 month follow-up



GAQ-Q2 demonstrating success with the treatment (Table-3).

No adverse events were reported during and following treatment.

DISCUSSION

According to others author's data LISW appears to be significantly effective for increasing erectile function thanks to the improvement in penile hemodynamics (13, 11). By releasing neo--angiogenic factors and subsequent neovascularization of the treated tissue, LISW therapy leads to tissue regeneration (16). In fact, it has been shown that this low intensity energy acts on vascularization inducing a non-enzymatic production of physiologic amounts of nitric oxide (17). Nitric oxide (NO), the smallest known signaling molecule, is produced by three isoforms of NO synthase (NOS; EC 1.14.13.39). Neuronal NOS (nNOS, NOS I) is

Table 3 - Analysis of self-reported measures at 1-month and 3-month follow up by treatment cohort.

Variable	Follow-up 1 Month	Follow-up 3 Month	P value
GAQ-Q_1 (%)	89 (yes)	62 (yes)	P=0.141
	10 (no)	38 (no)	
	2 droup-out	2 droup-out	
GAQ-Q_2 (%)	79 (yes)	76 (yes)	P=0.7259
	20 (no)	24 (no)	
	2 droup-out	2 droup-out	

(GAQ-Q1): Global Assessment Question- Q1; **(GAQ-Q2):** Global Assessment Question- Q2

constitutively expressed in central and peripheral neurons and in some other cell types. Its functions include synaptic plasticity in the central nervous system (CNS), central regulation of blood pressure, smooth muscle relaxation, and vasodilatation via peripheral nitrergic nerves. Nitrergic nerves are of particular importance in the relaxation of corpus cavernosum and penile erection (18). In corpus cavernosum nNos-derived NO activates guanylyl cyclase which synthesizes cyclic GMP (cGMP) from GTP which in turn is the basis for the pro--erectile function of PDE5 inhibitors (19).

The most important isoform is eNOS, which keeps blood vessels dilated, controls blood pressure, and has numerous other vasoprotective and anti-atherosclerotic effects inhibiting DNA synthesis, mitogenesis, and proliferation of vascular smooth muscle cells as well as smooth muscle cell migration. eNOS is mostly expressed in endothelial cells and synthesizes NO in a pulsatile manner (20).

eNOS appears to be a homeostatic regulator of numerous essential cardiovascular functions: in fact, eNOS-derived NO causes vasodilation in all types of blood vessels by stimulating soluble guanylyl cyclase and increasing cyclic GMP in smooth muscle cells that regulates the activity of calcium channels as well as intracellular contractile proteins that affect the relaxation of corpus cavernosum smooth muscle (21). Qiu et al. reported that LISW can partially ameliorate Diabetes Mellitus (DM)-associated ED in rat model by promoting regeneration of nNOS-positive nerves, endothelium, and smooth muscle in the penis. These beneficial effects appear to be mediated by recruitment of endogenous mesenchymal stem cells (MSCs) (22). Wang and colleagues discovered that LISW stimulates the expression of angiogenesis-related growth factors, such as endothelial nitric oxide synthase (eNOS) and vascular endothelial growth factor (VEGF), and endothelial cell proliferation factors, such as proliferating cell nuclear antigen (PCNA).

The eNOS and VEGF began to rise in as early as one week and remained high for 8 weeks, then declined to baseline in 12 weeks; whereas the increase of PCNA and neo-vessels began in 1 week and persisted for 12 weeks and longer (12).

The effect of LISW on intracellular VEGF levels in human umbilical vein endothelial cells (HUVECs) has also been reported by Nishida et al. (23), who found that LISW significantly increased the expression of VEGF mRNA and its receptor, Flt-1. Their studies on the effects of LISW on a porcine model of chronic myocardial ischemia also showed that VEGF expression was significantly upregulated in the ischemic myocardial cells after treatment inducing neovascularization and improving myocardial perfusion (24).

Furthermore, it has been proved that SW therapy improved symptoms and myocardial perfusion in patients with severe coronary artery disease without any complications or adverse effects (24-26).

Regarding erectile dysfunction, Vardi et al. have been the first ones to believe in the use of

LISW to improve male sexual function (27). In the first randomized, double-blind, sham-controlled study, they demonstrated a positive short-term clinical and physiological effect on the erectile function of men who respond to oral PDE5Is (28). In another trial they reported an improvement in penile hemodynamics and endothelial function, as well as IIEF-EF domain score in severe ED patients who were poor responders to PDE5Is.

In this paper we demonstrated the efficacy of LISW in the medical management of ED. Our data show a statistically significant improvement of IIEF-EF score (5 points) and an increase of SEP and GAQ scores after treatment.

Limitations of this study are the lack of a sham controlled arm and the relatively low number of participants.

CONCLUSIONS

LISW has a well-documented positive clinical and physiological effect on erectile function. The preliminary data at 1 and 3 months follow-up are very encouraging and indicate a therapeutic success of this second generation technology for treating ED with linear low-intensity shockwaves. We also noticed that this treatment is feasible and easy to administer and with no side effects reported. Clearly, we cannot assure the long-term efficacy of LISW, so further studies are needed in order to strengthen these results and to assess whether is possible to repeat cyclically the treatment.

CONFLICT OF INTEREST

None declared.

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CASUISTRY

Linear shock wave therapy in the treatment of erectile dysfunction☆

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KEYWORDS
Erectile dysfunction;
Vasculogenic erectile dysfunction;
Linear shock wave;
Linear shock wave therapy

Abstract
Introduction: Linear shock wave therapy (LSWT) is a new noninvasive therapy that uses low-intensity shock waves to induce local angiogenesis promising modality in the treatment of erectile dysfunction (ED).
Objective: To evaluate the effectiveness of LSWT in men with vasculogenic erectile dysfunction (ED), in a Tertiary Care Center.
Material and methods: Included 15 men aged 45–70 years, sexually active with mild and moderate vascular ED evaluated with the International Index of Erectile Function (IIEF). The study was conducted in three stages: screening, treatment and results. Treatment stage: 4 weekly sessions LSWT (RENOVA®) 5000 waves (.09 mJ/mm^2). Erectile function was assessed with IIEFF-EF, SEP (Sexual Encounter Profile) and GAQ (Global Assessment Questions) at one and six months after treatment.
Results: The rate of success was 80% (12/15). Patients with mild ED (6/15) 40% and moderate ED (9/15) 60%. We found a positive association between IIEF-Basal (average 14.23 pts) and IIEF at one month and six months after therapy (19.69 pts) a difference of 5.46 pts ($p < .013$).
Conclusions: The feasibility and tolerability of this treatment, and rehabilitation potential features, make it this an attractive new treatment option for patients with ED.
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PALABRAS CLAVE
Disfunción eréctil;
Disfunción eréctil vasculogénica;
Ondas de Choque Lineal;
Terapia de Ondas de Choque Lineal

Terapia de ondas de choque lineales en el tratamiento de la disfunción eréctil

Resumen
Introducción: La terapia de ondas de choque lineales (LSWT) es una nueva terapia no invasiva que utiliza ondas de choque de baja intensidad para inducir la angiogénesis local controlada y mejorar significativamente la función eréctil.
Objetivo: Evaluar la eficacia de la LSWT en hombres con disfunción eréctil vasculogénica (DE) en un centro de atención de tercer nivel.

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Material y métodos: Se incluyeron 15 hombres de edades comprendidas entre 45 y 70 años, sexualmente activos con DE vascular leve y moderada, evaluados con el índice internacional de función eréctil (IIEF). El estudio se realizó en 3 etapas: detección, tratamiento y seguimiento. Recibieron 4 sesiones de LSWT semanales (RENOVA®) 5.000 ondas (0,09 mJ/mm^2). La función eréctil se evaluó con IIEFF-EF, Perfil del encuentro sexual (SEP) y Cuestionario de evaluación global (GAQ) al mes y a los 6 meses después del tratamiento.
Resultados: La tasa de éxito fue del 80% (12/15). Pacientes con DE leve 40% y DE moderada 60%. Se encontró una asociación positiva entre el IIEF-basal (promedio 14,23 pts) y IIEF un mes y 6 meses después del tratamiento (19,69 pts) una diferencia de 5,46 puntos (p < 0,013).
Conclusiones: La factibilidad y tolerabilidad de este tratamiento, y sus características potenciales de rehabilitación, hacen que pueda ser una nueva opción terapéutica atractiva para pacientes con DE.
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Introduction and clinical scenario

Erectile dysfunction (ED) is the persistent inability to achieve and maintain the erection sufficient to permit satisfactory sexual intercourse.[1] Vasculogenic ED is due to diseases such as diabetes mellitus, hypertension, hyperlipidemia, smoking, or vascular occlusive disease.[2,3] Although ED is a benign disorder, it affects physical, mental, and social health and has a significant impact on quality of life of men and their partners.[4] LWST stimulates the expression of angiogenesis-related growth factors, such as endothelial nitric oxide synthase, vascular endothelial growth factor, and endothelial cell proliferation factors. Also LWST induces neovascularization and cell proliferation.[5] LWST could improve penile blood flow and endothelial function by stimulating angiogenesis in the penis.[6] This technology is becoming a new modality in the treatment of patients with ED.

Clinical cases

We evaluated 15 men, with vasculogenic ED, between 45 and 70 years of age sexually active (sexual activity with a partner or manual stimulation) with mild to moderate vasculogenic ED. Patients were assessed with the International Index of Erectile Function (IIEF-EF). The study was conducted in three stages, from June to December 2013. The first stage consisted of screening, including complete medical history and physical examination. The second stage was the treatment, which in turn was carried out in two phases, the first phase is called ''physical therapy'' in which all patients received 4 sessions with LSWT (RENOVA®) 5000 waves of 0.09 mJ/mm^2, 300 intensity waves/min (5 Hz), 40 mm deep, in four areas (cavernosum right, left waves on each side 900, and left and right crus waves 1600 on each side); each session lasting 20 min with an interval of one week between each session.

The treatment is performed on an outpatient basis without using any anesthetic. The second phase of treatment consisted of ''rehabilitation'' at home between sessions (sexual activity with a partner or manual stimulation); and finally, the third stage of the study, evaluating the clinical results using IIEF, EHS (Erection Hardness Score), SEP (Sexual Encounter Profile), GAQ (Global Assessment Questions) at one month and six months after treatment.

We analyzed quantitative and qualitative variables such as age, body mass index (BMI), smoking history, diabetes mellitus, hypertension, ischemic heart disease, Basal IIEF (Grade ED), EHS, SEP, years with ED. The statistical analysis is done with GraphPad Prism 6.0 and SPSS 19 statistics using the following tests: Student *t* distribution (*t*), Pearson correlation (*r*), (*p*).

Results

Fifteen men with a mean age of 59.6 years (45–70) with mild to moderate ED were enrolled. 40% of patients (6/15) had mild ED, and 60% had moderate ED (9/15). Patients with mild ED had a basal IIEF-EF average of 18 points, and 13 points for patients with moderate ED. Treatment efficacy was evaluated with IIEF-EF, GAQ, and SEP.

Success of treatment was defined as an increase of >2 points and >5 points in groups of mild and moderate, respectively (9). No adverse effects occurred. The rate of success was 80%. We found a positive association between the basal IIEF (average 14.23 pts) and IIEF after one month and six months (19.69 pts) with a difference of 5.46 pts ($p < 0.013$) (Table 1).

Patients with mild ED 83% (5/6) had improvement >2 pts; and patients with moderate ED 78% (7/9) had an increase of >5 pts ($p < 0.56$).

We found no association between minor age (mean 59.6 years) and treatment success, (7/15) 46% of patients were >60 years, all these (7/7) had a positive response to treatment, and (8/15) 54% patients were <60 years in this group, 62% (5/8) were successful with the treatment ($p < 0.01$).

We observed that patients who had 1–5 years with ED 60% (9/15) showed an improvement of 4 points in 67% (6/9) of patients, ($p < 0.20$); and we did not find an association between the IPSS (average 9 points) and the success of treatment ($p = 0.0712$).

We analyzed the influence of the smoking index on the response to the treatment. Patients had a smoking index <20 and >20, and there is a negative association ($p < 0.05$) between these groups, 73% (11/15) of patients had a smoking index (SI) <20, 92% (10/11) of them were successful with

Table 1 Results of sexual function questionnaires before and 1 month after low-intensity extracorporeal shockwave therapy.

Test Score	Baseline Score	Score 1 mo after treatment	p value
IIEF	15 (11–18) pts	20 (11–23) pts	$p < 0.013$
EHS	2 (2–3) pts	4 (2–4) pts	$p < 0.01$
SEP III	7 patients	12 patients	$p = 0.0013$
GAQ	–	12 patients	

IIEF: International Index of Erectile Function 21–25 points = normal, 16–20 = mild erectile dysfunction, 11–15 = moderate erectile dysfunction, 5–10 = severe erectile dysfunction. EHS: 0 = the penis enlarges, 1 = the penis enlarges, but not flabby, 2 = the penis hardens, but not enough for penetration, 3 = the penis is hard enough for penetration but not completely hard, 4 = the penis is completely hard and stiff. SEP: Sexual Encounter Profile; GAQ: Global Assessment Questions.

the treatment, and only 50% (2/4) of patients with a SI >20 showed improvement.

There is no influence between obesity and treatment response in these patients, according to the BMI. Overweight 73% (11/15) and obese 27% (4/15) patients, in the obese patients group had 50% (2/4) success with the treatment, the trend is that there is no association between obesity and no improvement in IIEF ($p = 0.15$).

Diabetic patients were 53% (8/15), of which 62% (5/8) had a favorable response to treatment, and 47% (7/15) of non-diabetic patients were successful with the treatment.

During the study, we compared the strength of erection with baseline and post-treatment level, finding that 53% (8/15) of patients had EHS <2, and of these, 33% (3/8) showed improvement with treatment ($p < 0.01$) (Table 2).

In reviewing the responses on the GAQ, in our study we found that 80% (12/15) of patients responded ''yes'', therefore we consider it a successful treatment for these patients (Table 1).

Discussion

All treatments available for ED improve sexual function and the quality of erections, but they are not curative. The search for a cure for ED is the next step, and it should be the goal in the coming years. Scientific evidence casts controversial results, so efficiency will be demonstrated in LSWT double-blind controlled studies.

We selected measurement tools validated and accepted as the IIEF and EHS, these questionnaires have a high degree of sensitivity and specificity for detecting changes in the mechanism of erection associated to the treatment.[7–9]

The results in our study show that EHS was >3 in 80% of patients after LSWT. It is a remarkable improvement in patients, and it is noteworthy that it was achieved without using any medication. Subjective evaluation of erectile function coincides with the fact that LWST has an effect on the mechanism of erection by improving blood flow to the penis.[10] It is suggested that successful LSWT for mild to moderate ED is defined as an increase >2 and >5 points in the IIEF.[11]

Table 2 Patient characteristics and the effect of low-intensity extracorporeal shockwave therapy on the International Index of Erectile Function score.

Patient characteristics	No. Patient that improve IIEF	p value
ED grade		
Mild	(5/6)	$p < 0.56$
Moderate	(7/9)	
Age		
<60 years	(5/8)	$p < 0.01$
>60 years	(7/7)	
ED duration		
>3 years	(6/6)	$p < 0.20$
<3 years	(6/9)	
Smoking index		
>20	(2/4)	$p < 0.05$
<20	(10/11)	
Quality of life		
QoL >15	(10/10)	
QoL <15	(2/5)	$p = 0.19$
Body mass index		
>30	(2/4)	$p = 0.009$
<30	(10/11)	
Diabetes mellitus		
Diabetic patients	(5/8)	
Non-diabetic Patients	(7/7)	$p = 0.1$
Trust to achieve and maintain erection		
Q15 >3	(10/10)	
Q15 <3	(2/5)	$p = 0.19$

SEP evaluates sexual encounters with two questions; SEP-2 in the past 4 weeks, were you able to penetrate your partner?, SEP-3 Have you had an erection long enough for you to have successful intercourse? The GAQ questionnaire evaluates treatment; GAQ-1 in the past 4 weeks, Has the treatment you have been following improved erectile function?, GAQ-2 if the response to GAQ-1 is YES, Has the treatment improved its ability to engage in sexual activity during the past 4 weeks? In reviewing the responses to these questionnaires, in our study we found that 80% of patients responded ''yes'', so it is considered a successful treatment for these patients.

The initial trend indicators help us identify risk factors that contribute to negative results. We consider that monitoring should be extended to obtain long-term results, and so far there are no reports of long-term results.

Conclusions

Our short-term results are encouraging, but they demand a long-term evaluation. Based on our results, LSWT can be effective and safe for the treatment of vasculogenic ED. The feasibility and tolerability of this treatment make it an attractive new treatment option for patients with vasculogenic ED.

Conflict of interest

The authors declare that they have no conflict of interest.

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EFFECTIVENESS OF LOW-INTENSITY EXTRACORPOREAL SHOCK WAVE THERAPY ON PATIENTS WITH ERECTILE DYSFUNCTION (ED) WHO HAVE FAILED TO RESPOND TO PDE5I THERAPY. A PILOT STUDY

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Summary.- *Low-intensity extracorporeal shock wave therapy (LIESWT) of the penis has recently emerged as a promising modality in the treatment of ED.*

OBJECTIVES: The objective of this paper is to assess the effectiveness and safety of LIESWT on patients with ED who have failed to respond to PDE5i treatment.

METHODS: Open label, prospective, longitudinal observational study. The study involved an uncontrolled population of 25 patients. The treatment consisted in applying 20,000 shock waves during a period of four weeks. In each session the patient received 5000 shock waves of 0.09 mJ/mm2: 1800 were applied on the penis (900 on each corpus cavernosum), and 3200 were applied on the perineum (1600 on each crus). During the active treatment and follow-up phases, all patients remained on their regular high on demand or once-a-day dose PDE5i schedules.

Main Outcome Measures: Effectiveness was assessed by IIEF-6, SEP2, SEP3 and GAQ. Patients were considered to be responders whenever they improved on all three erection assessment parameters and respond positively to the GAQ at three months post-treatment. Adverse events were recorded. Statistical variables were applied and findings were considered to be statistically significant whenever the P value was < 0.05.

RESULTS: Eighty percent (median age 63) of the patients (20/25) completed the study. Five patients were lost to follow-up and were excluded from the analysis.

Sixty percent (60%) of the patients responded to the treatment, improved the 3 efficacy evaluating parameters and responded positively to the GAQ. The increase in mean IIEF-6 score was of 9 points after the third post-treatment month. There were no patients reporting treatment-related adverse events.

CONCLUSIONS: LIESWT for men with ED and that are PDE5i non-responders was safe and effective and restoring PDE5i response in more than 50% of patients. A large-scale multicenter study is required to determine the benefits of this treatment for ED.

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Keywords: *Low Intensity Extracorporeal Shock Wave Therapy. Erectile dysfunction. PDE5i.*

Resumen.- *Las LISW son una novedosa modalidad de tratamiento en pacientes con disfunción eréctil (DE).*

OBJETIVO: Evaluar la efectividad y seguridad de las LISW en varones con DE no respondedores a IPDE5.

MÉTODO: Estudio naturalístico, prospectivo, longitudinal, observacional que incluyo una población de 25 pacientes no respondedores a dosis máxima de IPDE5. El tratamiento consistió en aplicar 20000 LISW durante 4 semanas (4 sesiones). En cada sesión el paciente recibió 5000 ondas de choque de 0,09 mJ/mm^2. 1800 aplicadas en el pene (900 en cada cuerpo cavernoso) y 3200 en el periné (1600 en la raíz derecha e izquierda cavernosa). Durante el tratamiento y fases de seguimiento se mantuvo igual dosis de IPDE5 como venía siendo tratado. Los cambios sobre la erección fueron evaluados utilizando el Índice Internacional de la Función Eréctil-6 (IIEF-6) y las preguntas 2 y 3 del Perfil de Encuentro Sexual (SEP). Complementariamente se agregó una pregunta sobre eficacia global del tratamiento (GAQ). Consideramos respondedor al paciente que mejoraba significativamente los 3 parámetros de rigidez y que respondiera afirmativamente a la GAQ, 3 meses pos-tratamiento. Fueron aplicadas variables de cálculo para considerar una significancia estadística con una p< 0,05.

RESULTADOS: El 80% de los pacientes (20/25) completaron el estudio. La mediana de la edad fue de 63 años. Cinco fueron excluidos del análisis por perdida de seguimiento. Del grupo evaluado, 12 (60%) mejoraron los 3 parámetros de erección y respondieron afirmativamente a la GAQ. El incremento promedio del IIEF-6 fue de 9 puntos. Ningún evento adverso fue reportado.

CONCLUSIONES: LISW en varones con DE no respondedores a IPDE5 fue eficiente y seguro, restaurando la respuesta a los IPDE5 en más de la mitad de los pacientes. Estudios multicéntricos, controlados y con mayor número de pacientes confirmaran el beneficio de esta nueva línea de tratamiento.

Palabras clave: *Terapia de ondas de choque de baja intensidad. Disfunción eréctil. IPDE5.*

INTRODUCTION

The treatment of erectile dysfunction (ED) has evolved considerably over the last decade, following the introduction of type 5 phosphodiesterase inhibitors (PDE5i), which have become the first line of treatment for this complaint.

Despite the effectiveness of these drugs, a number of patients ranging from 40% to 50% (depending on the etiology of their disease) do not respond to drug therapy even after optimization approaches such as treatment combinations have been implemented (1-5).

The second and third lines of treatment are the self-injection of vasoactive drugs and penile prosthestic implants, which many patients are reluctant to accept.

Recently, two observational and one controlled trial have been published reported efficacy and safety of low-intensity extracorporeal shock wave therapy (LI-ESWT), particularly for patients with ED of vascular origin who are PDE5i non-responders (6-8).

Young and Dyson discovered that therapeutic ultrasound encourages angiogenesis by enhancing the expression of vascular endothelial growth factor. (9). Nurzynska et al. demonstrated that shock waves have positive influence on both the proliferation and the differentiation of cardiomyocytes, smooth muscle and endothelial cells precursors, with a more obvious effect being evident in the cells from normal heart than in those taken from pathologic hearts (10).

From these initial reports, LI-ESWT was implemented in the past decade in the treatment of chronic myocardial ischemia, diabetic foot ulcers, among other applications (11-15).

LI-ESWT involves a very small amount of energy (0.09 mJ/mm2), equivalent to 10% of the energy used by conventional lithotripters for the treatment of urinary tract stones.

Initially, LI-ESWT systems essentially involved orthopedic extracorporeal shock wave therapy devices delivering targeted energy (7).

The mechanism of action is still not completely elucidated. However, it has been shown that low-intensity energy induces the production of a physiologically significant amount of non-enzymatic nitric oxide and activates the intracellular cascade pathways that trigger the release of angiogenic factors (16).

Based on the above assumptions, the aim of this study has been to evaluate the effectiveness and safety of low-intensity extracorporeal shock wave therapy on patients with ED that are PDE5i non-responders.

AIM

To assess the effectiveness and safety of low-intensity extracorporeal shock wave therapy on patients with Erectile Dysfunction (ED) who have failed to respond to PDE5i treatment

METHODS

This was a prospective, longitudinal, observational and independent study, designed to evaluate the safety and efficacy of LI-ESWT in a population uncontrolled sexually active men with erectile dysfunction and associated vascular risk factors (VRFs) are PDE5i non responders.

The inclusion criteria involved sexually active ED male patients who were non-responders to oral PDE5i therapy and exhibited vascular risk factors (VRFs) (e.g., diabetes, hypertension, dyslipidemia and coronary artery disease). Patients with untreated hypogonadism or a history of pelvic surgery, as well as patients with ED of neurological origin (resulting from prostatectomy, pelvic surgery or spinal cord injury) were excluded.

They were considered non-responders to PDE5 inhibitors those patients who after completing all optimization measures commonly suggested manifested not achieve and / or maintain erections sufficient for penetration and had an International Index of Erectile Function 6 questions (IIEF-6) under action of these drugs <26 points (17,18).

The study involved a total population of 25 patients. During the active treatment and follow-up phases, all the patients remained on their regular high on demand or once-a-day dose PDE5i schedules (Table I).

The following evaluation criteria were used: the International Index of Erectile Function Questionnaire (IIEF-6) to assess ED severity (19); questions 2 and 3 from the Sexual Encounter Profile (SEP2 and SEP3) to assess penetration and erection sustainability; and a Global Assessment Question (GAQ): Does the treatment has improved the quality of your erections?.

The severity of ED was classified into five categories according to the IIEF-6 score: no ED -score 26 to 30-, mild -score 22 to 25-, mild to moderate

Table I. Study design and procedures.

	VISIT 1 Screening (Baseline)	VISIT 2 1st week of treatment	VISIT 3 2nd week of treatment	VISIT 4 3rd week of treatment	VISIT 5 4th week of treatment	VISIT 6 1st month evaluation	VISIT 7 3rd month evaluation
PDE5i	X	X	X	X	X	X	X
Medical history	X						
Physical Examination	X	X	X	X	X	X	X
LSWT		X	X	X	X		
IIEF-EF, SEP 2-3	X					X	X
GAQ						X	X
Treatment		X	X	X	X		
Adverse Effects		X	X	X	X	X	X

-score 17 to 21-, moderate -score 11 to 16-, and severe -score 6 to 10- (17).

The evaluation criteria were assessed before treatment as well as one month and three months after treatment completion. Patients were always evaluated while on PDE5i therapy.

After the treatment the patients were considered to be responders whenever they improved on all three assessment erection parameters and to respond positively to the GAQ at three months post-treatment.

This trial was performed using RENOVA NR, a LI-ESWT device manufactured by Direx Group. The treatment consisted in applying 20,000 shock waves during a period of four weeks (four sessions). In each session, the patient received 5000 shock waves of 0.09 mJ/mm2: 1800 were applied on the penis (900 on each corpus cavernosum), and 3200 were applied on the perineum (1600 on each crus). The treatment areas were the same in all four sessions. All sessions were performed without anesthesia and in an outpatient setting, and each lasted 20 minutes.

The study was conducted according to Good Clinical Practices and the Helsinki Declaration, it was approved by the local Research Ethics Committee, and all the patients signed an informed consent form.

Considering the number of patients included and the rate of loss to follow for the calculation of the variables of demographic characteristics of responders and non-responders and the efficacy variables, medians were compared using nonparametric tests as Mann-Whitney test and the Wilcoxon test Match respectively. A $p< 0.05$ was considered statistical significance

RESULTS

Eighty percent (80%) of the patients (20/25) completed the study. Five patients were lost to follow-up and were excluded from the analysis.

The median age and the duration of ED were 63 years and 42 months respectively (Table II). Additional demographic details are shown in Table II.

Erectile dysfunction as per the IIEF-6 score was severe in 20% of the patients, moderate in 40%, mild to moderate in 35%, and mild in 5%. The mean age of the patients was 54.3, 62.3, 63.4 and 58, respectively, for severe, moderate, mild to moderate and mild ED. ED duration as related to ED severity was 28.5, 66, 60 and 36 months for severe, moderate, mild to moderate and mild patients, respectively.

Table II. Baseline data of the patients.

n	20
Median Age	63
Age range (years)	46-78
Median ED duration (months)	42
Range (months)	12-132
Cardiovascular risk factors	n (%)
Hypertension	11 (55 %)
Diabetes Mellitus	11 (55 %)
Dyslipidemia	5 (12,5 %)
Coronary artery disease	5 (12,5 %)

Sixty percent (60%) of the patients (12/20) responded to the treatment, improved the 3 parameters for evaluating efficacy and responded positively to the GAQ. The baseline characteristics of the patients that responded and failed to respond to the therapy are shown in Table III.

The increase in the IIEF-6 score in responders patients was statistically significant as from the first-month evaluation, and attained a mean of 9 points after the third month post-treatment (Figure 1).

Improvements on the IIEF score were more dramatic whenever ED was more severe, with changes of 14, 10.8 and 5.8 points for patients with severe, moderate and mild-to-moderate ED respectively. Four patients reached a score equal to or higher than 26 points in the IIEF, and the degree of severity dropped in the remaining patients (Table IV).

Towards the end of the study, significant changes were encountered in the responder group with regard to questions 2 and 3 of the Sexual Encounter Profile. In the non-responder group of patients, the changes in these two questions were not statistically significant (Figure 2).

15 of 20 patients (75 %) stated that the therapy had improved their erectile response.

There were no patients reporting treatment-related adverse events.

DISCUSSION

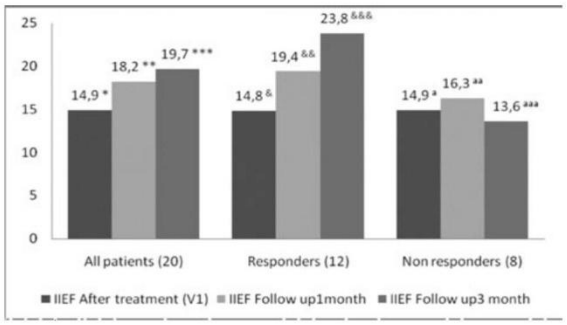
Erectile dysfunction, a highly prevalent complaint in men over 50, can almost always be traced back to a history of vascular risk factors (19).

Many studies have emphasized the status of ED as a potential indicator of cardiovascular disease later in life, while other clinical trials have found a high rate of ED in men with vascular factors such as metabolic syndrome, diabetes and hypertension (20, 21).

Table IIII. Demographic characteristics of patients (both responders and non-responders).

Patients	Responders	Non-responders
n	12	8
Median Age (years)	56.5*	60**
Age range (years)	46-78	62-65
Median ED durations (months)	36&	30 &&
Range (months)	12-132	6-120
Cardiovascular risk factors	**n (%)**	**n (%)**
Hypertension	6 (50 %)	5 (62.5 %)
Diabetes Mellitus	7 (58 %)	4 (50 %)
Dyslipidemia	2 (42 %)	3 (37.5)
Coronary artery disease	4 (33.3 %)	1 (12.5)
ED Severity according to the IIEF	**n (%)**	**n (%)**
Severe	1 (8.3 %)	3 (37.5 %)
Moderate	6 (50 %)	2 (25 %)
Mild to Moderate	5 (41.7 %)	2 (25 %)
Mild	0 (0 %)	1 (12.5 %)

*Mann Whitney test: * vs ** P > 0.05; & vs && P > 0.05*
ED::Erectile dysfunction



* vs ** P < 0.05	& vs && P < 0.05	a vs aa P < 0.05
* vs *** P < 0.05	& vs &&& P < 0.05	a vs aaa P > 0.05
** vs *** P > 0.05	&& vs &&& P < 0.05	aa vs aaa P > 0.05

Figure 1. Evolution of changes in IIEF-6 score after the first and third month of treatment.

Introduced in 1998, PDE5i have changed the treatment paradigm for patients with ED as a result of this therapy, approximately 60 % of patients can recover their erectile function and lead a satisfactory sex life as a result (22).

The choice of PDE5i and their dose regimen are specific to each patient. However, some patients are all too hastily considered to be non-responders because of prescription dosage errors. With the right dose optimization, an increase in sexual stimuli, a correction of testosterone levels and proper patient dietary training whenever short-acting PDE5i are used, around one-third of non-responders succeed in recovering their erectile function (18).

However, despite these measures, about 40 % of men fail to achieve an adequate response to PDE5i, and must resort to second or third-line options; others abandon all treatment possibilities altogether when they realize that they are not responding to oral therapy.

For some years now, low-intensity extracorporeal shock wave therapy has been implemented to optimize the response of PDE5i.

Qiu X et al have demonstrated that shock wave therapy significantly restored erectile function in rats with streptozotocin-induced diabetes mellitus, to levels similar to those exhibited by healthy controls, thus validating the animal model as comparable to prior clinical trials performed on humans. According to trial results, improvements in erectile function might be attributable to the positive effects afforded by the shock waves on endothelial and smooth muscle regeneration in the penis. These effects appear to be mediated by the recruitment of endogenous smooth muscle cells (23).

Vardi et al presented the first randomized, double-blind, sham-controlled study that demonstrated that low-intensity extracorporeal shock wave therapy has a positive clinical and physiological short-term effect on erectile function for patients that are PDE5i responders (8).

These experts used a compact electrohydraulic system fitted with a targeted shock wave source (Omnispec ED1000, Medispec Ltd, Germantown, MD, USA). Unlike the system we used on our patients, they had to stretch the penis and manually apply the transducer to it proximally, medially and distally, and then apply it to the perineum. With this operator-

Table IV. Changes in ED severity following shock wave treatment concurrently with PDE5I therapy (responders patients).

	Before treatment	After treatment
	n (%)	n (%)
Severe Erectile dysfunction (ED)	1 (8.3)	0 (0)
Moderate ED	6 (50)	0 (0)
Mild to Moderate ED	5 (41.7)	4 (33.3)
Mild ED	0 (0)	4 (33.3)
No ED	0 (0)	4 (33.3)

dependent method, the selected treatment protocol consisted of two sessions per week over a period of three weeks, and was repeated after a treatment-free interval of three weeks.

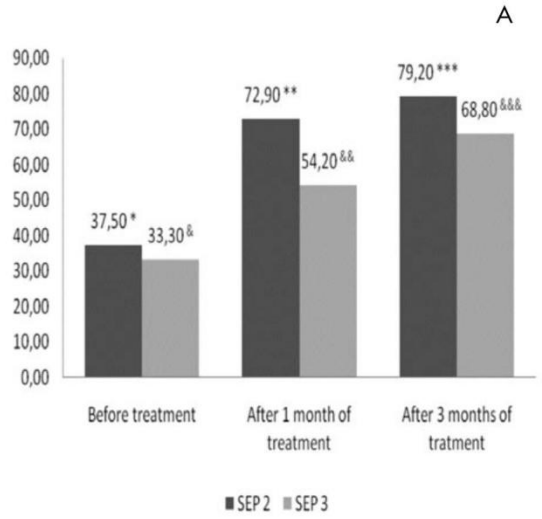
It is worth pointing out that, unlike the group of patients presented by Vardi et al (6), those patients included in this presentation were only non-responder patients to oral therapy at the maximum dose, and only after having indicated and verified that all optimization indications had been fulfilled. PDE5i were never suspended, and they continued with their regular scheme throughout the four-week treatment with LISW, as well as during the follow up period of 1to 3 months.

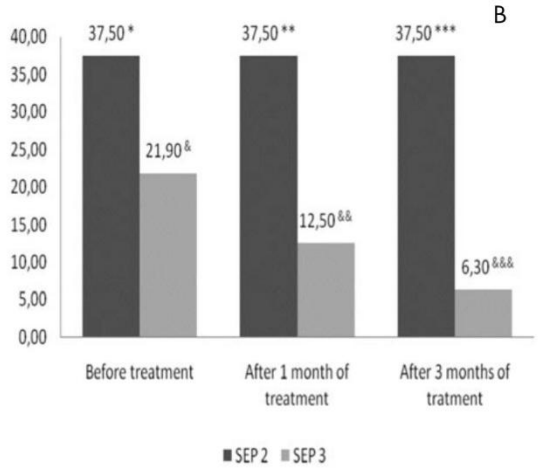
As mentioned before, the device selected for our trial (Renova NR), is manufactured by Direx Group, and involves a special LI-ESWT technology. This operator-independent system is fitted with a transducer that is capable of delivering shock waves all along the penis, spanning an area of 70mm and thus eliminating the need for penis manipulation. Furthermore, the transducer does not even need to be held by the operator, as it can be secured to the perineum.

Study design was as suggested by the manufacturer, i.e. four weekly sessions, each lasting 20 minutes.

In our trial, improvements in the IIEF-6 score were evident as early as the first month after treatment completion, but the four efficacy parameters became clearly apparent as of the third month after treatment completion, with an average improvement of 9 points in the IIEF.

In a recent report featured at the Congress of the Latin American Society for Sexual Medicine, Reisman et al presented a prospective, multicentric, open-label pilot study which was conducted at four





A. Wilcoxon matched pairs test

* vs **	p<0.05
* vs ***	p<0.01
** vs ***	p>0.05
& vs &&	p>0.05
& vs &&&	p<0.05
&& vs &&&	p>0.05

B. Wilcoxon matched pairs test

* vs **	p>0.05
* vs ***	p>0.05
** vs ***	p>0.05
& vs &&	p>0.05
& vs &&&	p>0.05
&& vs &&&	p>0.05

Figure 2. Evolution of changes in SEP 2 and SEP 3 after treatment in responders (A) and nonresponders (B).

sites and involved 52 patients with mild to severe ED. The patients were treated with the same device as the one used in this trial, with results assessed using IIEF-EF, SEP 2-3 and GAQ at one and three months post-treatment. Success was defined as an increase in the IIEF-EF score between baseline and the second follow-up. Significant changes were reported for 78.8% of the patients in the IIEF score, which exhibited a 6.8 increase (24).

It should be noted that in contrast with Reisman's report, in our trial patients had to exhibit changes across all four PDE5i response enhancement variables (IIEF6, SEP2, 3 and GAQ) –i.e., not just the IIEF score- in order for them to be considered treatment responders. This adds robustness to our results, as numeric changes in the IIEF score alone do imply improvement, but do not necessarily guarantee complete or successful intercourse. In our results, not all patients improved their IIEF6, had better SEP 2 and SEP 3 and many of those who claimed that the treatment had improved (GAQ), not reflected in the IIEF or SEP 2 or SEP3.

In addition, four out of twelve responders in our trial (33 %) attained normal IIEF values, and the rest experienced a decrease in symptom severity (Table V).

Finally, once shock wave therapy was completed and while still on PDE5i treatment, patients in the responder population successfully completed intercourse in 70% of their sexual encounters as shown in figure 2 (SEP 2, 3). This figure is similar to the one exhibited by different PDE5i efficacy reports (25-27).

Our study has several limitations. First, its lack of a placebo group prevents a proper comparison of the effects of shock wave therapy.

Another limitation of this study is the short follow-up phase (three months after treatment), which added to the lack of a placebo group, prevents us from knowing whether the changes are temporary or permanent, or derived from a placebo effect.

Importantly, each patient was compared with himself before and after shock wave therapy concurrently with PDE5 inhibitors. These were patients that had remained unresponsive to oral therapy even after the introduction of optimization measures.

Whenever independent pilot studies are conducted, the number of patients included tends to be small, and the results cannot be generalized. Nevertheless, we believe that, however limited the experiences reported in the literature so far allow us to take these preliminary data into consideration, while being cautious about its interpretation. We hope that these data will be to be confirmed by multicenter sham control studies on a larger group of patients and involving a longer follow-up phase.

In our group of patients, neither age nor ED duration had an influence on the results (Table II). However, and although changes in the IIEF were directly proportional to ED severity, the group of VRFs and severe ED patients responded less in percentage terms (25%) (Table III). This observation is consistent with the importance of defining whether the number of sessions or shock waves should be increased or repeated over time depending on ED severity. Gruenwald et al report that a second round of LI-ESWT was beneficial in 25 patients with partial or unsatisfactory results after the first session (28).

CONCLUSIONS

According to our results, low-intensity extracorporeal shock wave therapy for patients with ED and vascular risk associated who are poor PDE5i responders, was safe and effective. This approach will thus enable the optimization and restoration of PDE5i response in more than 50% of patients. A large-scale multicentric study is required to determine the benefits of this new line of treatment for ED.

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ORIGINAL ARTICLE

Initial experience with linear focused shockwave treatment for erectile dysfunction: a 6-month follow-up pilot study

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Low-intensity shockwaves (LISW) are known to produce revascularization and have been in evaluation and in use to treat erectile dysfunction (ED). The present single-arm pilot study is aimed to assess the safety and efficacy of a dedicated shockwave device (Renova) on vasculogenic ED patients. Fifty-eight patients with mild to severe ED were treated by LISW and their erectile function was evaluated by the International Index of Erectile Function–Erectile Function Domain (IIEF–EF), Sexual Encounter Profile and Global Assessment Questions questionnaires, at baseline and at 1, 3 and 6 months post treatment. The average IIEF–EF increased significantly from 14.78 at baseline to 21.93 at 3 months post treatment and stabilized at 22.26 at 6 months post treatment. Out of 58 patients, 47 (81%) had a successful treatment. No adverse events were reported during the treatment and the follow-up duration. In conclusion, it suggests that the performance of LISW could add a new advanced treatment for ED.

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INTRODUCTION

Vasculogenic erectile dysfunction (ED) is defined as inability to get or keep an erection firm enough for satisfying sexual intercourse and is maybe originated by diseases, such as diabetes mellitus (DM) and atherosclerotic vascular occlusive disease. Current methods for treating vasculogenic ED aim at reducing symptoms instead of reversing the source of the dysfunction, which in the majority of the patients is due to arterial or inflow disorders.[1] It has been demonstrated that shockwaves can enhance intrinsic angiogenesis and are used to treat ischemic heart disease.[2] Low-intensity shockwaves (LISW) have been evaluated for treating ED in both pilot and randomized sham-controlled studies. The encouraging results that were seen in these studies were the first to show the effect of LISW on ED symptoms,[3–4] but have never been evaluated elsewhere. Recently published study conducted on rats with DM-associated ED showed that low-energy shockwave therapy (LESWT) significantly restored erectile function to levels almost similar to normal levels of controls. The therapeutic efficacy of LESWT is possibly mediated by increased recruitment of mesenchymal stem cells (MSCs) that promote the regeneration of DM-damaged erectile tissues.[5]

The present study was aimed to assess the safety and efficacy of a new dedicated shockwave device, 'Renova', which was designed to achieve substantially superior organ coverage, compared with the existing devices and hence produces positive results with a shorter protocol in a multicenter study.

SUBJECTS AND METHODS

Study protocol

This study was a multicenter open-label prospective pilot study, conducted at four sites. It was conducted in accordance with the principles of the Declaration of Helsinki of World Medical Association. Patients gave their written informed consent before participation in the study. This study consisted of a screening phase, treatment phase and a 6-month follow-up phase. At screening phase, patients had an extensive medical and sexological history evaluation, as well as a physical examination. Inclusion criteria were heterosexual men in stable heterosexual relationship for at least 3 months, aged 20–80 years, with vascular ED (according to physician judgment) for at least 6 months, International Index of Erectile Function–Erectile Function Domain (IIEF–EF)[6] score of 6–25 points. Recruited patients were both responders and nonresponders to phosphodiesterase type 5 inhibitors (PDE5-i). The exclusion criteria were hormonal, neurological or psychological pathology, past radical prostatectomy, any unstable medical or psychiatric condition, spinal cord injury, penile anatomical abnormalities, clinically significant chronic hematological disease, usage of antiandrogens, recovering from cancer in the past 5 years or radiotherapy in pelvic region.

At baseline and follow-up visits IIEF–EF and Sexual Encounter Profile (SEP)—questions 2 and 3 questionnaires were used.[7–8] Global Assessment Questions[9] (GAQ) were used at follow-ups as well. The IIEF–EF questionnaire is widely accepted as the best method to verify ED progress. It includes six questions regarding erectile function and its score range is 1–30 points. Safety was assessed at each treatment and follow-up visits, by answering questions regarding side effects and pain as part of the case report form (CRF). Patients were instructed to inform the investigators if any side effects occur.

Almost all of the patients were using PDE5-i during baseline evaluation. No PDE5-i were used 3 weeks prior to treatment, during shockwave treatment, and until the first follow-up, 1 month post treatments. Answering the questionnaires at the 3 and 6 months post-treatment follow-ups was made, whereas the patients were using PDE5-i, as was done in previously done studies.[3] At all follow-up sessions, patients were instructed to return to the exact PDE5-i consumption as at baseline, as shown in Figure 1. Patients committed to avoid using any ED treatment other than PDE5-i oral medication throughout the study duration.

The treatment consisted of 4 weekly treatment sessions. During each session 3600 shocks of 0.09 mJ mm^2 were applied. Shocks were applied at the penis shaft at right corpus cavernosum and left corpus cavernosum, and at the crura at right crus and left crus, 900 shocks at each area. The treatment areas were the same for each session, so that at the end of the full treatment (four sessions) each area has received 3600 shocks of 0.09 mJ mm^2.

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Figure 1. The use of PDE5-I throughout the study.

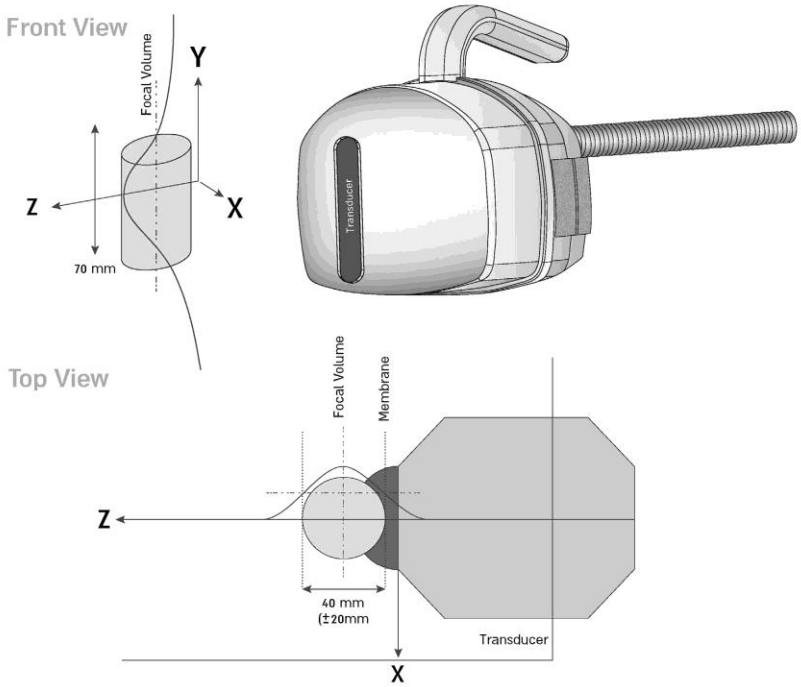

Figure 2. Qualitative view of the shockwave intensity changes.

Follow-ups were conducted at 1, 3 and 6 months post treatment and were consisted of adverse events report, IIEF–EF, SEP and GAQ questionnaires. The primary success criterion, regarding to efficacy, was defined as an increase of IIEF–EF score from baseline to the third follow-up (6 months post treatment) according to the initial ED severity: >2-point increase for mild symptoms; >5 points for moderate symptoms; and >7 points for severe symptoms.[6]

Treatment device

Renova (Direx Group) is the first dedicated shockwave system for ED. Instead of generating shockwaves that converge on a single focal point and require moving the shockwave source to multiple positions along the penis, Renova is based on linear shockwave therapy (LSWT) that enables focusing shockwaves on a 70 mm long and 10 mm width treatment area along the target organ. The shockwaves penetrate into the treated organ to a 40 mm depth and therefore their focal volume is 9.4 cm^3. Figure 2 described qualitatively how shockwaves intensity changes in *z* axis. The prolonged shape of the transducer (Figure 3) enables effective positioning when applying to the crura by its direct contact to the groin. Renova's electromagnetic generator delivers shockwaves with a maximum energy density of 0.09 mJ mm^2, meaning, they deliver 10% of the pressure used for disintegrating kidney stones. Shocks are delivered at a maximum rate of 300 pulses min^{-1} (PPM; 5 Hz), therefore, the net treatment time of a session of 3600 shocks lasts ~15 min.

Figure 3. Renova's transducer: its prolonged shape enables effective positioning when applied to the crura.

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Statistical analysis

Patients' demographic variables were summarized by descriptive statistics. The average score of each questionnaire and its s.d. was calculated at baseline and at 1-, 3- and 6-month follow-up. Student's *t*-test were used at significance level of < 0.05.

RESULTS

Fifty-eight middle-aged men (mean: 56.75 ± 9.91 years, range: 33–84 years) with vasculogenic ED were recruited for this study: 20 patients were treated at Men's Health Clinic, Amstelland Hospital, Amsterdam; 17 were treated at the Urology and Andrology Center, Red Crescent Hospital, Ramallah; 11 were treated at Amber Clinic, Klaipėda; and 10 were treated in Urologickaambulance.cz, Brno. Patients' characteristics were similar in all sites, excluding the patients in Brno, who had a longer duration of ED and a lower success rate than the rest of the sites. The selection of patients in the Lithuanian site was made with patients who had a milder average of clinical signs.

Twenty-five patients (43.1%) suffered from cardiovascular disease, 41.4% (24 patients) had diabetes, 39.7% (23 patients) suffered from hypertension and 46.6% (27) had high cholesterol level. Fifty patients (86.2%) were PDE5-i responders. In all, 37.9% of patients were smokers, 19.0% were past smokers and 43.1% have never smoked. Table 1 describes patients' background diseases with an emphasis on some of the main risk factors for vasculogenic ED.

Patients' baseline IIEF–EF score ranged between 6 and 25 points with an average of 14.8. Table 2 summarizes the effect of low-intensity extracorporeal shockwave therapy on the IIEF–EF scores, according to the baseline ED severity.

A moderate negative Pearson correlation coefficient of −0.62 was found between the duration of ED and success of treatment. Figure 4 describes the change in the IIEF–EF score between baseline and the follow-ups at 1, 3 and 6 months post treatment, according to the duration of ED. The percentage of patients who have answered 'Yes' to questions 2 and 3 of the SEP was calculated at baseline and at 1-, 3- and 6-month follow-up and is presented in Figure 5.

The percentage of patients who have answered 'Yes' to questions 1 and 2 of the GAQ was calculated at 1-, 3- and 6-month follow-up; for question 1, the percentages were 74.14%, 82.76% and 89.66%, respectively. For question 2, the percentages at 1-, 3- and 6-month follow-up were 63.79%, 68.97% and 75.86%, respectively.

Table 1. Patients' comorbidities with an emphasis on some of the main risk factors for vasculogenic ED: cardiovascular diseases; diabetes; hypertension; and high cholesterol

Disease	*Cardiovascular disease*	*Diabetes*	*Hypertension*	*High cholesterol*
Prevalence (%)				
27.6				
19.0	✓	✓	✓	✓
10.3				✓
10.3	✓	✓		
8.6		✓		
8.6		✓		✓
6.9		✓	✓	✓
1.7	✓	✓	✓	
1.7	✓			✓
1.7		✓	✓	
1.7	✓	✓		
1.7	✓			

Table 2. The results of the IIEF–EF, before and at 6 months following low-intensity extracorporeal shockwave therapy

Baseline ED severity	*Number of patients*	*PDE5-i responders*	*Baseline IIEF–EF AVG ± s.d.*	*IIEF–EF improvement points AVG ± s.d.*	*% Success*	*P-value*
Severe	13	69.23%	8.5 ± 1.2	8.5 ± 6.3	61.54	< 0.001
Moderate	22	86.36%	13.3 ± 1.8	8.3 ± 5.1	77.27	< 0.001
Mild to moderate	18	94.44%	18.6 ± 1.5	6.8 ± 3.0	94.44	< 0.001
Mild	5	100.00%	23.6 ± 1.3	3.6 ± 0.5	100.00	< 0.001
Total	58	86.2%	14.8 ± 4.8	7.5 ± 4.7	81.03	< 0.001

Abbreviations: ED, erectile dysfunction; IIEF–EF, International Index of Erectile Function–Erectile Function Domain; PDE5-i, phosphodiesterase type 5 inhibitors. Two-tailed *t*-test was performed on the IIEF–EF scores of each group of ED severity before Renova treatment and at 6-month follow-up.

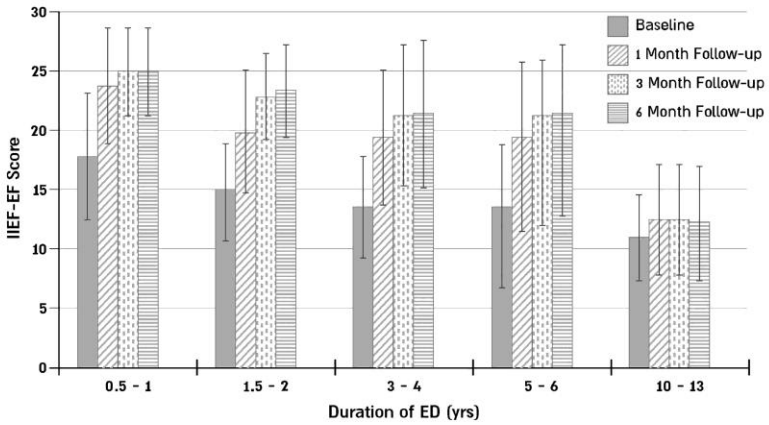

Figure 4. The change in the IIEF–EF score between baseline and the follow-ups at 1, 3 and 6 months post treatment, in accordance with the ranges of ED duration. The error bars indicate the s.d. of each group.

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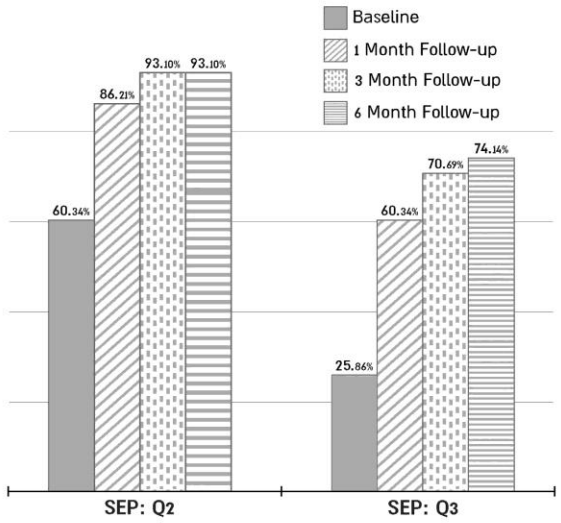

Figure 5. the average results of SEP questions 2 and 3 at the baseline and at each follow-up. The percentages represent the fraction of patients who have answered 'Yes' to each of these questions.

The difference between the IIEF–EF scores and the SEP answers, from baseline to the third follow-up was remarkable and has a statistical significance, with a *P*-value of < 0.001.

LISW treatment has succeeded in $>80\%$ of the cases (47 patients). Among the successful patients, the average IIEF–EF score increase was nine points.

When comparing diabetic patients and nondiabetic patients, the success rate of the latter group was 25% higher (70.83% and 88.24%, respectively). In all, 41.4% of patients in this study were diabetic (24 patients) and there was no significant difference between age and ED duration of the diabetic and nondiabetic patients (57.45 and 56.25 years, 2.90 and 2.96 years, respectively). This may indicate on better suitability of this treatment to nondiabetic patients.

Among the 58 patients, 4 patients stopped using PDE5-i during follow-up as they had no need for it.

No adverse events or complications were reported during and following treatment.

During the treatment period and thereafter, no use of analgesics was needed.

DISCUSSION

This study is the first study that shows a successful treatment with LISW for vascular ED in a multicenter manner, which is not connected to the previous publications and from different sites than the previous publications.[3–4]

When compared with previously described studies, in which PDE5-i were used, the results of this study are in line, with similar success rates.[3–4]

This study included patients with mild to severe ED symptoms, whereas 22.4% of patients had severe symptoms, 37.9% moderate, 31.0% mild to moderate and 8.6% mild. The average baseline IIEF–EF was 14.8 points, which represents moderate ED symptoms.

When comparing the success rate between groups of other comorbidities, no strong correlation was found. Owing to the small sample size, more research is required.

Almost 28% of the patients didn't have any of the following vascular ED risk factors: cardiovascular disease; diabetes; hypertension; and high cholesterol. The success rate of patients who had at least one of the diseases listed above was 76.2%, whereas the success rate of patients without any of these diseases was 93.7%. There were no significant differences between the age, duration of ED and percentage of PDE5-i responders between patients with at least one of the listed disease and patients without any of these diseases (57.3 and 55.3 years, 3.0 and 2.7 years, 85.7% and 87.5%, respectively). The percentage of smokers was higher in the group of patients without any of the listed diseases (62.5%) compared with the second group (54.8%). Out of the first group, all patients who were nonsmokers (10.3% of all patients) succeeded in the treatment.

The ED duration of failed patients was on average longer than the ED duration of the whole group, with 6.4 and 2.9 years, respectively. As seen in Figure 3, the increase in IIEF–EF score decreases as the ED duration rises. Satisfactory success rates were shown in cases of ED that started up to 10 years previously, and even higher success rates were demonstrated on patients who recently noticed a decrease in erectile function. The average results are very disappointing for patients with ED for >10 years, so it seems this treatment is not adequate for such patients whereas average results are satisfactory for patients with ED for 5–6 years or less.

A comprehensive research is required for designing a modified protocol that would be suitable for cases of longtime ED.

When considering the numerical change in IIEF–EF, only six patients (10%) have not experienced any change in their erectile function.

When reviewing the change in SEP scores, a significant increase between baseline and follow-up is noticeable. These questions can indicate directly on the patients erectile function condition, as they are referring directly to the patient's ability to perform successful intercourse.

When reviewing the individual answers for the GAQ questionnaires, it appears that 75% of the patients (44 patients) have answered 'Yes' to both questions. As these questions are intended to evaluate the treatment, these results indicate a successful treatment and support the results found with the IIEF–EF scores.

When looking at the percentage of almost 7% of patients who stopped using PDE5-i after the treatment, this could perhaps be one of the next steps in the development of this treatment option, and might be a viable option for patients who are not satisfied with the effect of PDE5-i or that these drugs are contraindicated for them.

The specifically designed device, which has a specialized transducer that is configured to reach the exact treated areas, is able to treat a bigger area than other previously used devices and therefore enables a better adjustment to the patient's body, a shorter duration of treatment and a better coverage.

This pilot study on a small number of ED patients with a relatively short follow-up shows encouraging results. Large multicenter, long-term, randomized and sham-controlled studies are needed to be able to evaluate and define those patients who respond to this type of treatment. More data are also needed with regard to the possible long-term impact of shockwaves on penile tissue. More basic research is needed to be able to understand the mechanism of action of LISW on tissues.

CONCLUSIONS

The initial results of this pilot study suggest positive outcomes of this second generation technology for treating ED with linear low-intensity shockwaves. This study with 6 months follow-up from almost 60 patients is suggestive of a positive therapeutic efficiency in the majority of the patients. Pain is tolerated by 100% of the treated patients and no side effects have been recorded, demonstrating the potential of this technology, as a treatment option for men who are not satisfied by the currently available solutions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

Direx Group provided the treatment device (Renova), which generates linear focused shockwave.

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Safety and Efficient Duration of Linear Focused Shockwave Treatment for Erectile Dysfunction – A 12 months Follow-up Pilot Study

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Objective

The aim of this pilot study was to assess the safety, effectiveness and sustainable results of the Linear Focused Shockwave system Renova, for the treatment of Vascular Erectile Dysfunction patients.

Material and methods

Renova is a system that uses a Linear Low Intensity Shockwave technology. We have treated 20 patients with Vasculogenic ED; with an averaged International Index of Erectile Function (IIEF-EF) score of 12.35±3.16 (Range 7-18). The protocol consisted of 4 weekly sessions, in which a total of 3600 shockwaves were applied, divided into 4 areas; right and left crura, and right and left corpus cavernosum, 900 shockwaves in each site. The following questionnaires were used: IIEF-EF, Sexual Encounter Profile (SEP) and Global Assessment Question (GAQ), at baseline visit and 1, 3, 6 and 12 months post treatment. Success was defined as an increase in score from baseline to the 6 months post treatment follow-up, according to Minimal Clinical Improvement Criteria (Rosen et al.).

Results

At the 6 months follow-up, 18 patients out of 20 showed success (90%). Out of these 90%, **83.3% (15 patients) sustained the positive outcome for a period longer than 12 months** after the end of treatment. The average IIEF-EF increased significantly from 12.35±3.16 at baseline to 20.65±2.64 at 6 months post treatment, and was 18.65±2.56 at the 12 month follow-up. Four patients (20%) who were non-responsive to Phosphodiesterase type 5

Inhibitors (PDE5i) at baseline became responsive after the treatment, and 2 patients (10%) successfully stopped using PDE5i. All 20 patients completed the last follow-up with an average of 14.5±1.08 months duration from the end of treatment. Among the successful patients, the average IIEF-EF score increase was 8.3 points. No side effects were reported.

Conclusions

With a success rate of 90% after 6 months, and an 83.3% sustainable positive effect after 1 year, the results of this pilot study suggest that this treatment is probably effective for at least 1 year. No anaesthesia or analgesia was needed, and no adverse effects were recorded, making it a potential good alternative for current available treatments.

The above paper abstract was presented at the *16th World Meeting on Sexual Medicine*, on October 11th 2014, Sao-Paulo, Brazil.

Long Term Efficacy of Low Intensity Linear Focused Shockwave Therapy for Vascular Erectile Dysfunction Patients: 20 months follow-up

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Objective

Erectile dysfunction is a common medical disorder that primarily affects men older than 40 years of age [1]. Phosphodiesterase type 5 inhibitors (PDE5i) are considered as first-line therapy as they increase arterial blood flow leading to smooth muscle relaxation, vasodilatation and penile erection [2]. The limitation in the efficacy of PDE5i is that a 'critical amount' of NO is necessary for these drugs to work. Therefore, in cases of impairment in NO synthesize or release or in cases of destruction of NO, PDE5i cannot cure erectile dysfunction (ED) symptoms [3].

Lately, studies have started to evaluate the effect of low intensity shockwave (LISW) to treat ED on PDE5i responders and non-responders patients [4-8].

The current study evaluated how the therapy by a new device ('RENOVA', Direx Group) using low-intensity linear focused shockwave, exerts effective and sustainable results at long term follow-up on patients who suffer from ED of vascular origin and experience full, partial or no response at all to PDE5i.

Materials and Methods

This study was conducted in an outpatient clinic from March to December 2013. Eligible patients were those suffering from Vasculogenic ED for at least 6 months, and their International Index of Erectile Function score (IIEF-EF, [9]) was between 9 and 25 (while on PDE5i). Patients who had hormonal, neurological or psychological pathology or had undergone radical prostatectomy were excluded.

During the treatment period and 3 weeks prior to it, no PDE5i were used.

The treatment consisted of 4 weekly sessions. Shockwaves were delivered with a maximum energy of 0.09mJ/mm2; therefore, no anesthesia was required. At the end of the full treatment a total of 20000 SW had been delivered (6400 shocks at each crura, 3600 shocks at each corpus).

Erectile function was evaluated by means of IIEF-EF, questions 2-3 of the Sexual Encounter Profile (SEP), questions 1-2 of the Global Assessment Questions (GAQ) and the Erection Hardness Score (EHS), at baseline and at 1, 3 and 6 months post treatment. Success was defined as positive answer to both SEP questions and both GAQ questions, EHS of 3 or higher and an increase of IIEF-EF score from baseline to the third follow up (6 months post treatment) according to the severity of the symptoms [10].

Out of 25 patients enrolled to this study, 24 finished the full treatment series. The mean age of these patients was 62.58 ± 8.32 (45-74) years and the mean duration of their ED was 4.84 ± 4.46 (1-20) years. 52% were smokers, 26% had diabetes, 58% had high cholesterol levels, 37% had a cardiovascular disease and 47% had hypertension. 75% of the patients had a positive response to PDE5i.

At the end of the treatment and during the follow-up period patients were using PDE5i as needed.

14 patients out of 19 patients who had a successful result in all evaluation parameters at 6 months follow-up were evaluable for long-term follow up (15-21 months; mean 19.8 months) They completed again all the questionnaires.

Results

At 6 months follow-up the overall percentage of patients who achieved positive outcomes at all 4 evaluation questionnaires was 79%.

33% of the PDE5i non-responders (2/6) and 94% of the responders (17/18) achieved positive outcomes at all 4 evaluation questionnaires.

44.4% of the responders stopped using PDE5i at 6 month follow-up. None of the patients have reported on pain during or after treatment. No adverse events were reported.

11/14 patients (78.5%) who had a successful result at 6 months FU, and were evaluable for long-term FU, maintained the advantage gained.

2 patients, PDE5i non responders, continued to respond to PDE5i. Their IIEF at long term FU was respectively 19 (+1) and 23 (-2).

9 patients, PDE5i responders, lost 4 points combined at IIEF-6 (5 patients with unchanged scores, 1 patient dropped from 29 to 27, 1 patient gained 1 point from 26 to 27, 1 patient

dropped from 25 to 23 and the last patient dropped from 27 to 26); SEP and GAQ were unchanged; EHS was reduced from 4 to 3 in only 1 patient and was maintained at 4 in 4 patients.

5 out of these 9 patients had successful intercourses without PDE5i or used them occasionally.

3/14 patients (21.4%) did not maintain the advantage gained at the long term FU. IIEF (while on PDE5i), was 20/24/21, 15 points lower (-9/-2/-4) than at 6 months FU; SEP was unchanged (2); EHS was 1 point lower (from 4 to 3) in 1 patient; GAQ dropped from 2 to 0 in all 3 patients.

Discussion

This pilot study was designed for assessing the long term efficacy of a novel device for the treatment of erectile dysfunction, based on an original technology that enables the delivery of low-intensity shockwaves onto a long focal area. The subjects in this study included also patients with multiple co-morbidities, different degrees of response to PDE5i and wide range of ED severities. The results of this study demonstrate a possible alternative treatment for some of the patients who did not respond to first-line oral pharmacotherapy and thanks to this treatment may avoid turning to other therapy options which are less convenient to use. In parallel, these data imply on a potential mean to eliminate the need for PDE5i which may significantly improve patients' quality of life.

At 6 months FU, an overall success in 79% of the patients was shown, that was maintained by 78.5% of these at longer FU (19.8 months mean). 55% of PDE5i responders (at baseline evaluation) continued to have successful intercourses without use of PDE5i or using them occasionally.

Conclusion

A growing number of men develop vascular erectile dysfunction because of multiple comorbidities such as diabetes, hypertension, heart disease, dyslipidemia or smoke. PDE5i, alprostadil injections, vacuum constriction devices and surgical treatment are symptomatic therapies and do not help patients to achieve spontaneous erections. Moreover medications are contraindicated in some conditions and may have side effects. LISWT, is a promising, minimally invasive therapy without side-effects that induce the release of endothelial nitric oxide synthase, vascular endothelial growth factors and proliferating cell nuclear antigen and thus enhance neovascularization of the penis.

The long-term follow up shows that the vast majority of patients who achieved a positive result from treatment with 20000 low intensity linear shock waves, delivered in 4 weekly sessions, continues to maintain the advantage gained after 19.8 months.
The effect of treatment wanes gradually only in 21.4% of the patients.
There is a need for further research to determine if modifications in the treatment protocol (number and intensity) of low-intensity linear focused shockwave could make the positive effect last longer and if an additional treatment could be useful for patients who did not have or lost a successful result from the treatment.

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The above paper abstract was presented at the *22nd National Congress of the Italian Urological Association*, on May 24th 2015, Bologna, Italy.

Initial Clinical Experience of Linear Focused, Low Intensity Shockwave for Treatment of ED Patients with Different Severity Symptoms

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Objective

The aim of this clinical experience was to assess the feasibility of the application of Linear Focused Low Intensity Shockwaves (Renova Direx Group) as an alternative or complementary treatment for Vascular ED patients with different degrees of symptom severity.

Material and methods

The treatment was offered in a routine natural way in 2 medical centers: 46 patients in Malaga (series A), and 35 in Sevilla (Series B). The treatment was composed of 4 weekly sessions, in which shockwaves were applied into 4 areas: right and left crura, and right and left corpus cavernosum, with 900 shockwaves in each site (Total 14400). No need for anesthesia, sedation or painkillers and each session's treatment time was 20 minutes. The evaluation was done using the IIEF-EF, SEP and GAQ questionnaires, at baseline visit, 1 month and 3 months post treatment.

Results

The average IIEF-EF increased significantly from 19.94 and 14.03 at baseline to 23.92 and 18.53 at 3 months post treatment. A number of patients stopped using PDE5-i; 30.77% and 23.53% respectively. SEP 2 increased from 88.89% and 43.48% to 100% and 66.67%. The SEP 3 increased from 38.89% and 27.59% to 78.75% and 57.89%.

At baseline, the use of PDE5-i for sexual intercourses was needed by 77.78% and 85.19% of patients, and was reduced to 53.85% and 35.29% at 3 months post treatment. No side effects were recorded.

Conclusions

The results of both series at 3 months show a consistent and global improvement in IIEF-EF, SEP 2 and SEP 3 parameters. Since the baseline symptoms severity of patients in series B was much higher compared to series A, the end results obtained in series B are consistently lower compared to series A.

This would imply that the outcome of the treatment is related to the baseline symptoms severity, meaning that in average, patients with more severe ED symptoms will improve, but will not reach the final level of improvement that can be obtained by mild to moderate patients.

In our experience the Linear-Focused Low Intensity Shockwave treatment is a valid alternative or complement to current available treatments.

The above paper abstract was presented at the *16th World Meeting on Sexual Medicine*, on October 11th 2014, Sao-Paulo, Brazil.

Efficacy and Safety of Linear Focused Shockwaves for Erectile Dysfunction (RENOVA) – A Second Generation Technology

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Introduction

Recent studies have demonstrated that low intensity shockwaves have a therapeutic effect on ED of vascular origin.

Objective

The present study was aimed to assess the efficacy and safety of a dedicated shockwave device, Renova, which was designed to achieve substantially superior organ coverage.

Material and Methods

52 patients with mild to severe ED were treated by Renova as part of a multi-center, open-label, prospective pilot study, conducted at 4 sites. Patients underwent 4 weekly treatment sessions by a Renova that generates line focused shockwaves. Patients' erectile function was assessed by the IIEF-EF, SEP and GAQ questionnaires at baseline and at 1 and 3 months post treatment. Success was defined as an increase of IIEF-EF score from baseline to the second follow up according to the severity of the symptoms at baseline.

Results

The average IIEF-EF greatly increased from 14.7 at baseline to 21.4 at 1 month and 3 months post treatment. **Out of 52 patients, 41 (79%) had a successful treatment.** No adverse events were reported during the treatment and the follow-up duration. Main outcomes are presented in the following table:

Age	**Baseline IIEF-EF**	**Improvement in IIEF-EF**	**P value**	**% Success**
57.2 ± 10.1	14.7 ± 4.9	6.8	<0.0001	78.8%

Conclusions

The results of this study indicate success of the second generation technology for treating ED with linear low-intensity shockwaves. Initial follow up data demonstrate a therapeutic success in almost 80% of patients. No side effects have been recorded, demonstrating the suitability of this treatment in an office setting.

The above paper abstract was presented at the *12th Congress of the Latin American Society for Sexual Medicine*, on August 29th 2013, Cancun, Mexico.

Low intensity shock wave (LISW) treatment (Renova) to improve male sexual function: A preliminary data on 42 patients

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Objective

The aim of our study is to investigate the safety and efficacy of Low intensity Extracorporeal shock wave therapy LI-ESWT (Renova) in the treatment of erectile dysfunction.

Methods

We enrolled 47 patients with erectile dysfunction (ED). They underwent four weekly sessions using a dedicated device (Renova) for the management of erectile dysfunction. The treatment included four weekly sessions. During each treatment session, LI-ESWT was applied at four different anatomical areas, right and left corpus cavernosum and right and left crus penis (900 shocks, 0.09 mJ/mm2 intensity at 240 shocks/min at each site for a total of 3600 shocks). Patients were followed at one month after treatment. Two self-administered questionnaires: International Index of Erectile Function-Erectile Function (IIEF-ED), Sexual Encounter Profile (SEP- Questions 2 and 3) were given to patients to assess their sexual function pre and post treatment.

Results

Five patients dropped out of treatment, so forty-two patients (mean age was 59.2 years) were evaluated. At one month follow-up, we noticed a statistically significant improvement in IIEF-ED domain scores in treated patients (from a mean of 12+/- 4.8 at baseline to 23.5+/- 5.3, $p<0.05$). **SEP-Q2 and SEP-Q3 success rates improved from 57% to 84% and from 24% to 76% respectively.** No side effects were reported.

Conclusion

(LI) ESWT improves male sexual function inducing neovascularization in the treated tissues by stimulating the expression of angiogenesis-related growth factors, such as endothelial nitric oxide synthase, vascular endothelial growth factor, and endothelial cell proliferation factors, such as proliferating cell nuclear antigen. This therapy shows a statistically significant clinical improvement of erectile function without any side effect or contraindication. In our opinion further studies are needed even to assess the possibility to repeat the treatment cyclically or in association with PDE5-i or with nutraceutical composite.

The above paper abstract was presented at the *16th Congress of the European Society for Sexual Medicine (ESSM)*, on February 1st 2014, Istanbul.

Low Intensity Linear Focused Shockwave Therapy: a New Treatment to Improve the Quality of Life of Vascular Erectile Dysfunction Patients

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Objective

Erectile dysfunction is a common medical disorder that primarily affects men older than 40 years of age. Phosphodiesterase type 5 inhibitors (PDE5i) are considered as first-line therapy as they increase arterial blood flow leading to smooth muscle relaxation, vasodilatation and penile erection. The limitation in the efficacy of PDE5 inhibitors is that a 'critical amount' of NO is necessary for these drugs to work. Therefore, in cases of impairment in NO synthesize or release or in cases of destruction of NO, PDE5 inhibitors cannot cure erectile dysfunction (ED) symptoms.

The correlation between potency and quality of life was established by a study on 1680 men seeking medical attention in a free screening program at three different locations in the USA. Unsurprisingly, it was reported that potent men have a better quality of life than impotent men.

Lately, studies have started to evaluate the effect of low intensity shockwave (LISW) to treat ED on PDE5i responders and non-responders patients.

The current study evaluated how the therapy by a new device ('RENOVA', Direx Group) using low-intensity linear focused shockwave affects the quality of life of patients who suffer from ED of vascular origin and experience full, partial or no response at all to PDE5 inhibitors.

Methods and results

This study was conducted in an outpatient clinic over a period of 10 months. Eligible patients were those who have been suffering from Vasculogenic ED for at least 6 months, and their International Index of Erectile Function score in the erectile function domain (IIEF-EF) was between 9 and 25. Patients who had hormonal, neurological or psychological pathology or have undergone radical prostatectomy were excluded.

The treatment consisted of 4 weekly sessions; in each session 4 areas were treated consecutively: left and right sides of the Crura and the Corpora Cavernosa. Shockwaves were delivered with a maximum energy of 0.09mJ/mm^2; therefore, no anesthesia was required. During the treatment period (22 days) and 3 weeks prior it, no phosphodiesterase type 5 inhibitors (PDE5-I) were used.

Erectile function was evaluated by means of IIEF-EF, questions 2-3 of the Sexual Encounter Profile (SEP), questions 1-2 of the Global Assessment Questions (GAQ) and the Erection Hardness Score (EHS), at baseline and at 1, 3 and 6 months post treatment. Success was defined as positive answer to both SEP and GAQ questions, EHS of 3 or higher and an increase of IIEF-EF score from baseline to the third follow up (6 months post treatment) according to the severity of the symptoms.

Out of 25 patients who were enrolled to this study, 24 have finished the full treatment series. The mean age of these patients was 62.58 ± 8.32 (45-74) years and the mean duration of their ED was 4.84 ± 4.46 (1-20) years. 52% were smokers, 26% had diabetes, 58% had high cholesterol levels, 37% had a cardiovascular disease and 47% had hypertension. 74% of the patients had a positive response to PDE5 inhibitors.

All patients were instructed to use PDE5 inhibitors during the 4 weeks prior baseline evaluation. At the end of the treatment and during the follow-up period patients were using PDE5 inhibitors as needed.

At the most recent follow-up of each patient, 40% of the PDE5i non-responders and 78% of the responders achieved positive outcomes at all 4 evaluation questionnaires. 42.8% of the responders stopped using PDE5 inhibitors at 6 month follow-up. Out of these patients, 83% achieved positive outcomes at all 4 evaluation questionnaires. **The overall percentage of patients who achieved positive outcomes at all 4 evaluation questionnaires was 70%.** None of the patients have reported on pain during or after treatment. No adverse events were reported.

Discussion

This pilot study was designed for assessing the efficacy of a novel device dedicated for the treatment of erectile dysfunction and based on an original technology that enables the delivery of low-intensity shockwaves onto a long focal area. The subjects in this study included also patients with multiple co-morbidities, different degrees of response to PDE5 inhibitors and wide range of ED severities. The results of this study demonstrate a possible alternative treatment for some of the patients who did not respond to first-line oral pharmacotherapy and thanks to this treatment may avoid turning to other therapy options which are less convenient

to use. In parallel, these data imply on a potential mean to eliminate the need for PDE5 inhibitors which may significantly improve patients' quality of life. In order to establish the overall effect of this treatment on the quality of life of ED patients, a larger study with longer follow-up duration is required.

The above paper abstract was presented at the *21st National Congress of the Italian Urology Association*, on June 2014, Rome, Italy.

Linear Low Intensity Shockwaves Treatment of Vasculogenic ED – First Results

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Introduction and Objectives

ED is significantly associated with: increased age, diabetes, cardiovascular disease, hypertension, depression, smoking, medications, and has a multifactorial etiology with physical and psychological factors.

The treatment options currently offered to patients are: drugs that reversibly inhibit penile-specific PDE5 and enhance the nitric oxide–cyclic GMP pathways of cavernous smooth muscle relaxation, vacuum constriction device, intraurethral and intracorporeal alprostadil, or surgical treatment-implantation of penile prosthesis.

Our aim was to assess the safety and efficacy of a unique Linear Shockwave Therapy for Vasculogenic ED patients in a prospective trial (PT).

Materials and Methods

22 men with vasculogenic ED completed this open-label, prospective pilot study. In order to compare our own results (22 men) we included the outputs of 3 other European LSWT centers. Finally, an overall of 69 (22+47) patients with mild to severe ED were treated using the Renova device and were evaluated.

The evaluation of success was made according to the IIEF-EF questionnaire, which was filled at baseline, and 1, 3 and 6 months post treatment.

Results

The average IIEF-EF increased significantly from 14.7 at baseline to 21.6 at 1 month and 3 months post treatment. **82% of patients had a successful treatment.** No adverse events were reported during the treatment and the follow-up duration.

Conclusions

We have been able to prove that Linear SWT is an effective therapeutic option for men with erectile dysfunction of vasculogenic origin. Moreover the efficacy of linear application of low-intensity extracorporeal shock waves is superior to former non-linear methods.

The above paper abstract was presented at the *102nd Annual Meeting of the Japanese Urological Association (JUA)*, on April 21st 2014, Kobe, Japan.

Efficacy and Safety of Linear Focused Shockwaves for Erectile Dysfunction (RENOVA) – A Second Generation Technology

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Introduction

Vasculogenic erectile dysfunction (ED) which is caused by arteriosclerosis can be treated by a variety of therapies that aim at reducing ED symptoms. Low-intensity shockwaves (LISW) were discovered as an enhancing factor to angiogenesis for treating ischemic heart disease. In addition, LISW therapy demonstrated significantly the restoration of erectile function in diabetic rats. The present study evaluates the therapeutic effect of LISW produced by an innovative device on patients with erectile dysfunction.

Objective

The present study was aimed to assess the safety and efficacy of a dedicated shockwave device, 'Renova', which was designed to achieve substantially superior organ coverage.

Material and Methods

57 patients with mild to severe ED were treated by Renova as part of a multi-center, open-label, prospective pilot study, conducted at 4 sites. Patients underwent 4 weekly treatment sessions by a novel machine (Renova) that generates line focused shockwaves at 4 treated areas: right and left crus and right and left corpus cavernosum. Each treatment session lasted approximately 15 minutes, did not required anesthesia and did not cause any pain or adverse

effects. Patients' erectile function was assessed by the IIEF-EF, SEP and GAQ questionnaires at baseline and at 1 and 3 months post treatment. Success was defined as an increase of IIEF-EF score from baseline to the second follow up according to the severity of ED symptoms at baseline.

Results

The average IIEF-EF score has greatly increased from 14.7 at baseline to 21.6 at 1 month and 3 months post treatment. **Out of 57 patients, 47 (82%) had a successful treatment.** Among the successful patients, the average IIEF-EF score increase was 8 points. No adverse events were reported during the treatment and the follow-up duration.

Conclusions

The results of this study indicate success of the second generation technology for treating ED with linear low-intensity shockwaves. Initial follow up data from almost 60 patients demonstrate a clear therapeutic success in 82% of patients.

The above paper abstract was presented at the *2nd Biennial Meeting of the Middle East Society for Sexual Medicine*, on November 2013, Dubai.

Sociedad Mexicana de Urologia
Colegio de Profesionistas, A.C.

Initial Experience Using Linear Shockwave Therapy (RENOVA®) in the Treatment of Erectile Dysfunction

Dr. Pelavo-Nieto, Marcela

Sociedad Mexicana de Urologia (SMU) National Congress

Mexico, November 2013

Título:
Experiencia Inicial (15 casos) con el uso de Terapia de Ondas de Choque Lineales (RENOVA ®) en el Tratamiento de Disfunción Eréctil, Centro Médico Nacional 20 de Noviembre ISSSTE.

Autores:
Pelayo-Nieto, Marcela; Linden-Castro, Edgar; Alias-Melgar, Alejandro; Espinosa-Perezgrovas Daniel; Bertrand-Noriega, Federico, Ordoñez-Campos Eduardo; Guerra-Zepeda, Luis; Cortez-Betancourt, Roberto; Morales-Covarrubias, Jesús; Carreño-De la Rosa, Fernando; Sánchez-Neave, Ernesto.

Servicio de Urología, Centro Médico Nacional 20 de Noviembre, ISSSTE, México, D.F.

Resumen

Introducción: La Terapia de Ondas de Choque Lineales (LSWT) es una nueva terapia no invasiva que utiliza ondas de choque de baja intensidad para inducir la angiogénesis local controlada y mejorar significativamente la función hemodinámica del órgano sexual masculino. **Objetivo:** Reportar nuestra experiencia (15 casos) con el uso de Terapia de Ondas de Choque Lineales como tratamiento para DE. **Material y Métodos:** Estudio piloto, prospectivo, transversal, en el que se incluyeron 15 hombres de 45-70 años de edad, sexualmente activos con DE vasculogénica leve y moderada evaluados con el Índice Internacional de Función Eréctil (IIEF-EF). El estudio se realizó en tres etapas: screening, tratamiento y seguimiento. Recibieron 4 sesiones semanales de LSWT (RENOVA®) 5000 ondas de 0.09 mJ/mm2, y su función eréctil fue evaluada con IIEFF-EF, SEP (Perfil de Encuentro Sexual) y GAQ (Preguntas de Valoración Global) a uno y tres meses posteriores al tratamiento. **Resultados:** El 40% de los pacientes con DE leve y 60% con DE moderada. Observamos que la tendencia de éxito en nuestro estudio fué del 78%. Encontramos una correlación entre el IIEF- Basal (promedio 14.23 pts) y el IIEF a un mes (19.69 pts) y tres meses , diferencia (5.46 pts) con una distribución t (1.7445) *(p<0.013)*. **Conclusiones: Verificamos que** la LSWT tiene un efecto positivo clínico a corto plazo en hombres con DE.Seguimientos a largo plazo de la LSWT mostrara la posibilidad d ser una alternativa eficaz y segura para el tratamiento de DE. La factibilidad y tolerabilidad de este tratamiento, y sus características potenciales de rehabilitación, hacen que pueda ser una nueva opción terapéutica atractiva para pacientes con DE.

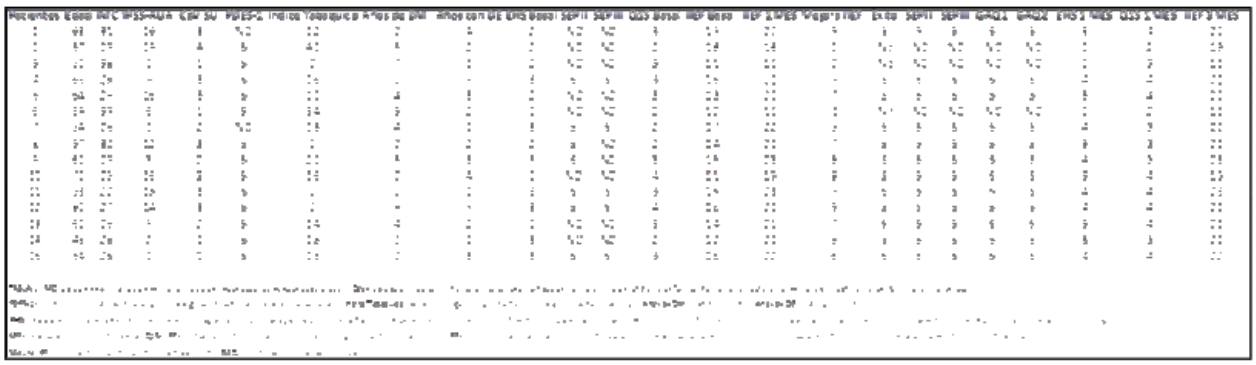
Palabras clave: Disfunción eréctil, Ondas de Choque Lineal, Disfunción eréctil vasculogénica.

Abstract

tratamiento de pacientes con DE. Existe poca evidencia científica sobre la eficacia de LSWT, por lo que decidimos realizar un estudio piloto en la población mexicana con DE.

Objetivo:
Reportar nuestra experiencia (15 casos) con el uso de Terapia de Ondas de Choque Lineales como tratamiento para DE Vasculogénica en el Centro Médico Nacional 20 de Noviembre, ISSSTE.

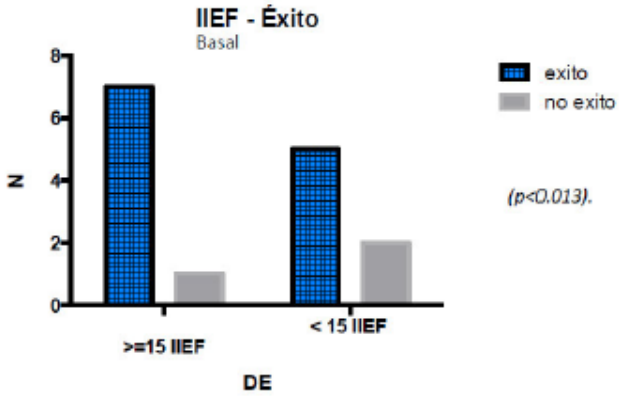
Material y Métodos:
Se realizó un estudio piloto: Prospectivo, transversal. El Universo de estudio: Hombres sexualmente activos con DE Vasculogénica que acudan a valoración urológica al Centro Médico Nacional 20 de Noviembre, ISSSTE. El Tamaño de la muestra (n= 15 pacientes) a conveniencia. Se incluyeron hombres de 45-70 años de edad, sexualmente activos (actividad sexual con pareja) con DE vasculogénica leve y moderada evaluados con el Índice Internacional de Función Eréctil (IIEF-EF) Dominio A (11-20 puntos), pacientes respondedores y no respondedores a tratamiento con Inhibidores de Fosfodiesterasa tipo 5 (iPDE5) y que acepten participar en el estudio firmando consentimiento bajo información. No se incluyeron en el estudio a hombres con DE de origen neurológico (Esclerosis Múltiple, Enfermedad de Parkinson, tumores, discopatía, uremia, Polineuropatía, Cirugía de pelvis, retroperitoneo o prostatectomia radical); DE Anatómica o estructural (Enfermedad de Peyronie, Fractura de pene, curvatura congénita de pene, Micropene, Hipospadias, epispadias); DE Hormonal (Hipogonadismo, hiperprolactinemia, hiper o hipotiroidismo, Enfermedad de Cushing); DE Farmacológica (diuréticos, betabloquenates, antidepresivos, antipsicóticos, antiandrógenos, antihistamínicos, heroína, cocaína); DE Psicógena (falta de excitación sexual, trastornos de las relaciones íntimas, trastornos relacionados con el rendimiento o debida a angustia) y todos aquellos pacientes que no aceptaron participar en el estudio; abandonaron el estudio todos aquellos pacientes que decidieron no continuar del estudio; así como aquellos pacientes que hayan usado iPDE5 durante el tratamiento o 3 semanas o menos previas al inicio del tratamiento. Se analizaron variables cuantitativas y cualitativas como Edad, Índice de Masa Corporal (IMC), Puntuación Internacional de Síntomas Prostáticos (IPSS), Calidad de Vida según Síntomas Urinarios (CdV), Años con DE, Confianza que tiene en poder Lograr y Mantener una Erección (Q15- IIEF-5), Respondedor a iPDE5, Índice Tabáquico, Diabetes Mellitus, Hipertensión Arterial, Cardiopatía Isquémica , IIEF Basal (Grado de DE), EHS (Escala de firmeza de la Erección), SEP Basal (Perfil de Encuentro Sexual). El estudio se realizó en tres etapas, en el periodo comprendido entre Junio a Octubre 2013: la primera etapa consistió en el Screening, que incluye Historia clínica completa y exploración física. La segunda etapa del estudio fué el tratamiento, que a su vez se llevó a cabo en dos fases, en la primera fase la denominamos "fisioterapia" en la cual todos los pacientes recibieron 4 sesiones con LSWT (RENOVA®) 5000 ondas de 0.09 mJ/mm2, intensidad de 300 ondas/min (5Hz), 40 mm de profundidad, en cuatro áreas (cuerpo cavernoso derecho, izquierdo 900 ondas en cada lado, y crura derecha e izquierda 1600 ondas en cada lado); cada sesión con una duración de 20 min con intervalo de una semana entre cada sesión. El tratamiento se realizó de forma ambulatoria y no se requirió el uso de ningún tipo de anestesia. La segunda fase del tratamiento consistió en "Rehabilitación" en casa, entre una sesión y otra (actividad sexual con pareja o estimulación manual). Y por último, la tercera etapa del estudio , el Seguimiento a un mes y 3 meses posterior al tratamiento.
La función eréctil se evaluó con IIEF, EHS (Escala de firmeza de la Erección) SEP (Perfil de Encuentro Sexual), GAQ (Preguntas de Valoración Global) a un mes y tres meses posteriores al tratamiento. El Análisis Estadístico lo realizamos con GraphPad Prism 6.0 y SPSS statistics 19, utilizando las siguientes pruebas: Distribución t Student *(t)* , correlación de Pearson *(r)* y Correlación p *(p)*.



Resultados:

Se enrolaron quince hombres edad promedio 59.6 años (45-70) con DE leve-moderada. El 40% de los pacientes (7 pacientes) con DE leve y 60% (9 pacientes) con DE moderada. En los pacientes con DE leve, IIEF-EF basal promedio 18 puntos , DE moderada IIEF basal 13 puntos promedio. La eficacia del tratamiento fue evaluada con IIEF-EF, SEP y GAQ. Se definió como éxito al incremento de > 2 puntos y > 5 puntos en los grupos de DE leve y moderada respectivamente.[9] No se presentaron efectos adversos. Observamos que la tendencia de éxito en nuestro estudio fue del 78%.

Figura 1.

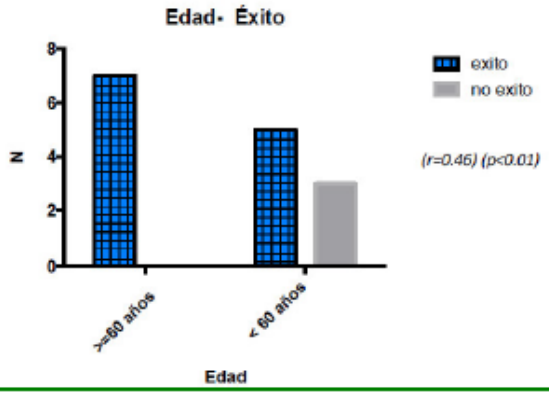


(p<0.013).

Encontramos una correlación entre el IIEF- Basal (promedio 14.23 pts) y el IIEF a un mes (19.69 pts) y tres meses , diferencia (5.46 pts) con una distribución t (1.7445) *(p<0.013).*

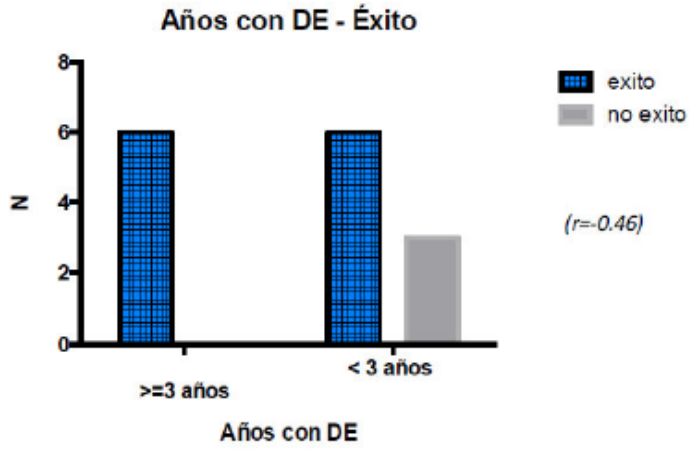
Se observó que el 53% de los pacientes tenían DE leve, y de éstos el 47% tuvo mejoría (>2 pts) , y de los pacientes con DE moderada (47%) solo el 33% de éstos tuvo un incremento >5 pts, *(r=-0-07) (p<0.01) (t=2.84).* (FIG.1) El estudio mostró que no existe correlación entre la edad (promedio 59.6 años) y el éxito del tratamiento *(r=0.46) (p<0.01)*, con el 47% de éxito promedio para los pacientes >60 años , y 33% de éxito en el tratamiento para los pacientes <60 años. (FIG.2).

Figura 2.



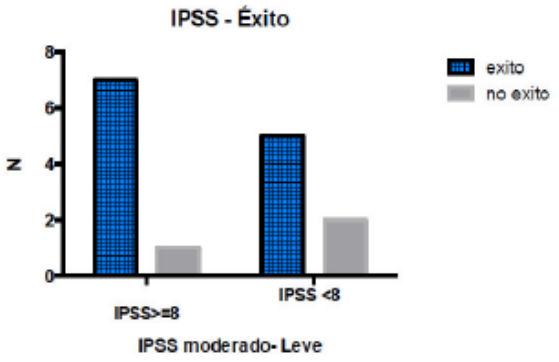
Observamos en nuestros pacientes que tenían de 1-5 años con DE (promedio 2.6 años), la tendencia fue que en aquellos pacientes con <3 años con DE (53.33%) presentaron una mejoría de 4 puntos promedio, una correlación negativa, es decir, entre menos años con DE tienen los pacientes mayor éxito presentaron con el tratamiento *(r=-0.46) (p<0.01)* . (FIG. 3).

Figura 3.



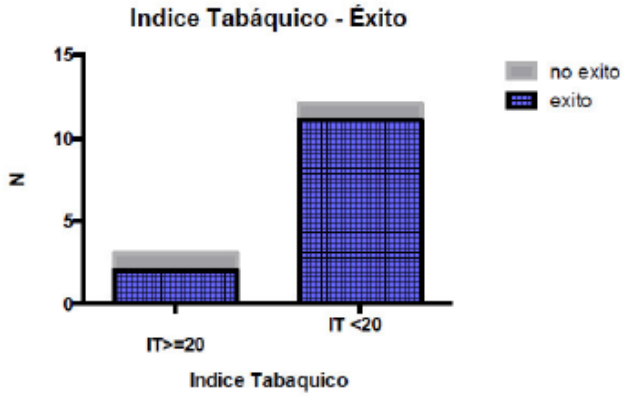
Analizamos el IPSS (promedio 9 puntos) y el éxito de tratamiento, sin observar correlación entre estas variables *(r=0.052) (t 0.0712) (p<0.01)* (FIG 4).

Figura 4.



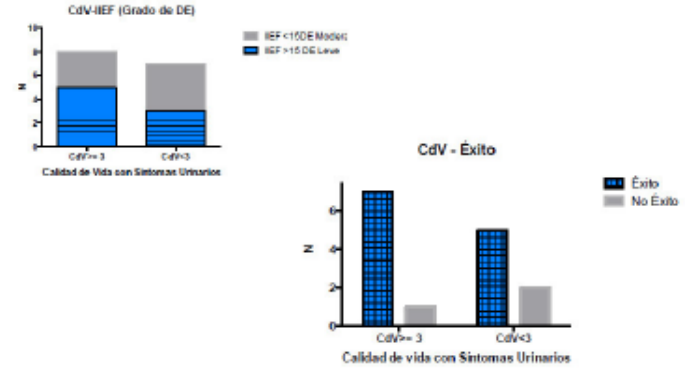
Un factor importante de daño microangiopático es el tabaquismo, por lo tanto comparamos la asociación de nuestros pacientes entre el Índice Tabáquico y la mejoría del IIEF con el tratamiento, y encontramos que existe una correlación negativa *(r= -0.47) (p<0.05) (t=0.02),* el 73% de los pacientes con Índice tabáquico <20, tuvo éxito con el tratamiento FIG.5

Figura 5.



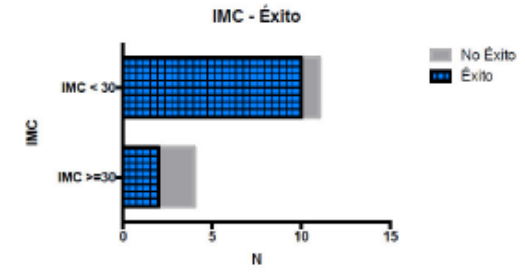
Interrogamos a nuestros pacientes para evaluar la CdV con los síntomas urinarios que presentan (IPSS), y observamos que no existe correlación entre el Grado de DE y la CdV con los Síntomas urinarios. El 33% de los pacientes con DE leve su CdV fue mas o menos satisfecha y el 20% de los pacientes con DE moderada. El 47% de los pacientes mas o menos satisfechos (CdV) tuvieron éxito con el tratamiento *(r=0.47) (p<0.05).* FIG. 6.

Figura 6.



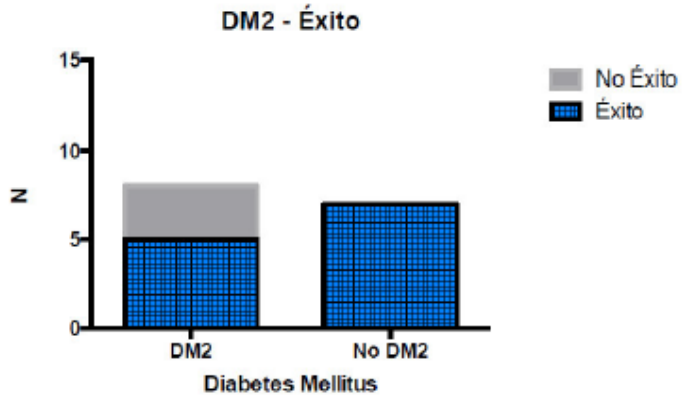
La obesidad es un factor de riesgo para DE, por lo que analizamos la influencia que existe entre la obesidad y la respuesta al tratamiento; se agruparon los pacientes según IMC (Sobrepeso 73 % y Obesos 27%), de los pacientes obesos el 50% tuvo éxito con el tratamiento, la tendencia es que no existe correlación entre obesidad y la mejoría del IIEF *(p<0.01) (t= 2.77) (r=0.45).* FIG.7.

Figura 7.



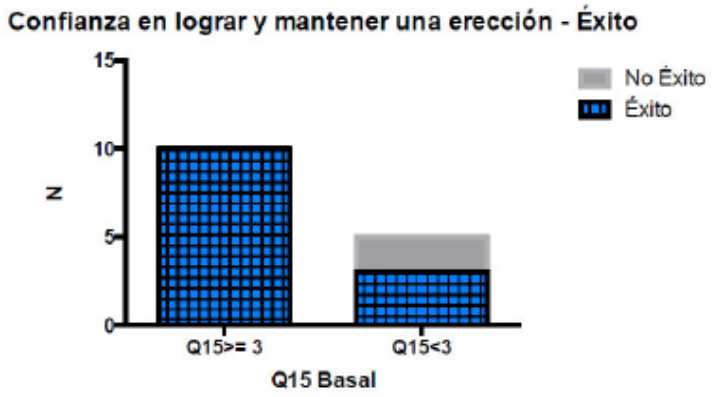
La relación en el número de años con DM2 (de los pacientes que padecen la enfermedad) con el éxito del tratamiento encontramos *(r= 0.09). (t=0.08).* El 53% de los pacientes son Diabéticos, de los cuales solo el 33% tuvo respuesta favorable con el tratamiento, y del 47% de los pacientes no diabéticos el 100% tuvo éxito con el tratamiento. FIG.8.

Figura 8.



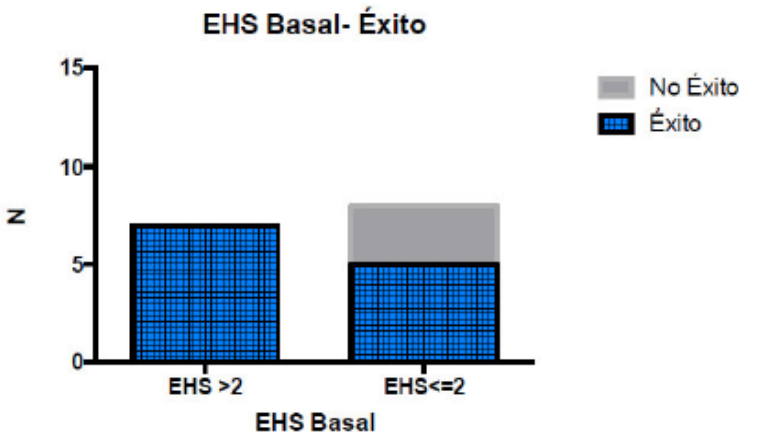
Analizamos la confianza que tiene el paciente en poder conseguir y mantener una erección antes y después del tratamiento, observando que el 67 % de los pacientes tenían confianza moderada, y de éstos el 100% presentó mejoría con el tratamiento. con EHS <3 los resultados fueron positivos, sin embargo solo el *(r=0.7456) (p<0.01)*. FIG. 9.

Figura 9.



Durante el estudio comparamos la firmeza de la erección con la escala basal y posterior al tratamiento, encontrando que el 53% de los pacientes tenían EHS<2, y de éstos el 33% presentaron mejoría con el tratamiento. (r=0.82) (p<0.01). FIG. 10.

Figura 10.



En la revisión de las respuestas en la Evaluación Global (GAQ) , en nuestro estudio encontramos que el 78% de los pacientes respondió "SI", por lo tanto consideramos un tratamiento exitoso para estos pacientes.

Discusión:

Todos los tratamientos disponibles para la DE mejoran la función sexual, mejorando la calidad de las erecciones, pero no son curativos. La búsqueda de una cura porción DE es el siguiente paso, y debe ser el objetivo en los próximos años. La evidencia científica arroja resultados controversiales, por lo que la eficacia del LSWT se demostrará con estudios controlados doble ciego. Nosotros seleccionamos herramientas de medición validadas y aceptadas como el IIEF y el EHS, estos cuestionarios tienen un alto grado de sensibilidad y especificidad para detectar cambios en el mecanismo de erección asociados al tratamiento. [11, 12, 14] Nosotros no utilizamos ultrasonografía doppler para evaluar los cambios hemodinámicos en el pene (flujo de la arteria cavernosa), ya que es operador dependiente y depende de la respuesta oportuna de los agentes vasoactivos y de la disposición del paciente. Aunque el ultrasonido doppler es un excelente estudio para evaluar la vascularidad del pene , podría ser un problema en la comparación de los cambios hemodinámicos del pene después del tratamiento. [10,15]. Los resultados en nuestro estudio muestran que el EHS fue >3 en el 78% de los pacientes después de LSWT. Es notable la mejoría en los pacientes , y también cabe mencionar que se logró sin usar ningún medicamento. La evaluación subjetiva de la función eréctil coincide, con que LWST ejerce un efecto en el mecanismo de la erección por la mejoría del flujo sanguíneo del pene. [8]. Las limitaciones de este estudio es la falta de un grupo control , y bajo numero de participantes; a pesar de las debilidades del estudio, los cambios en IIEF y EHS soportan la significancia clínica del tratamiento. Se propone que él éxito de LSWT para DE leve y moderada se define como el incremento >2 y > 5 puntos en el IIEF.[9] En el SEP evalúa la descripción del encuentro sexual con dos preguntas; SEP-2 ¿En las últimas 4 semanas, usted fue capaz de penetrar a su pareja?, SEP-3 ¿Usted tenía una erección suficiente tiempo para que pueda tener una relación sexual satisfactoria?; el GAQ es una evaluación global destinada a evaluar el tratamiento, GAQ-1 ¿En las últimas 4 semanas, el tratamiento que usted ha estado siguiendo mejoró su función eréctil?, GAQ-2 si la respuesta a GAQ-1 es SI, ¿El tratamiento ha mejorado su capacidad para participar en actividades sexuales durante las últimas 4 semanas?. En la revisión de las respuestas de estos cuestionarios, en nuestro estudio encontramos que el 78% de los pacientes respondió "SI", por lo tanto se considera un tratamiento exitoso para estos pacientes. Consideramos que una parte fundamental del tratamiento es la fase de "Rehabilitación" del tejido eréctil, ya que es lo que favorecerá que la angiogénesis por la liberación de crecimiento vascular producida por LSWT se vea traducida en la aparición de mejores erecciones. Los pacientes diabéticos con DE son considerados difíciles en la respuesta al tratamiento , sin embargo en nuestro estudio el 54% de los pacientes son diabéticos, y de éstos el 63% presentaron resultados favorables. La evaluación de la eficacia de LWST en este tipo de pacientes, con estudios aleatorios , doble ciego, con grupo control es ahora una necesidad para obtener mejores resultados.

Conclusiones:

Este estudio piloto fue diseñado para evaluar la eficacia y seguridad del uso de LSWT en el tratamiento de DE Vasculogénica en pacientes mexicanos. La respuesta a este tratamiento se definió como medida de éxito con diferencias clínicamente significativas en el dominio A (Función Eréctil) del IIEF y respuestas positivas del SEP y GAQ. La LSWT tiene un efecto positivo clínico a corto plazo en hombres con DE vasculogénica. Nuestro estudio muestra 78% de éxito con el tratamiento con LSWT ($p<0.013$) con significancia

clínica en la mejoría de la función eréctil, sin ningún efecto adverso hasta el seguimiento. Los indicadores iniciales de tendencias nos ayudan a identificar aquellos factores de riesgo que contribuyan para resultados negativos. Consideramos que el seguimiento debe ser ampliado para obtener resultados a largo plazo, ya que hasta el momento no hay reportes de resultados a largo plazo. En base al mecanismo fisiopatológico de la DE y al mecanismo de acción de LSWT, consideramos entonces, que en estudios posteriores se tome como variable la cantidad de erecciones y la calidad de las mismas que se presentan durante la fase de tratamiento(entre una sesión de LSWT y otra), ya que una posible teoría es que entre mayor número de erecciones y mejor calidad de las mismas, el mecanismo de acción de LSWT se favorece , sin embargo la respuesta favorable del tratamiento con LSWT se presenta hasta después de la 3 y 4 semana de tratamiento, por lo que sería interesante estudiar que resultados se presentarían con la combinación de LSWT e iPDE5. Nuestros resultados a corto plazo, son alentadores pero demandan una evaluación a largo plazo. Basado en nuestros resultados LSWT puede ser una alternativa eficaz y segura para el tratamiento de DE vasculogénica. La factibilidad y tolerabilidad de este tratamiento, y sus características potenciales de rehabilitación, hacen que sea ésta una nueva opción terapéutica atractiva para pacientes con DE vasculogénica.

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5th Pan Arab Congress of Sexual Medicine

Line Focused Shockwave for Erectile Dysfunction – A Different Technological Approach

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Introduction

During the last 2 years a new technology was introduced to treat Erectile Dysfunction. The treatment uses Low Intensity Shockwave which was shown to produce angiogenesis in order to improve the patient erectile function for patients of Vasculogenic origin ED. The initial treatments were done with conventional orthopedic treatment shockwave devices, and although results were encouraging, they have a series of limitations.

We are presenting our initial results with a new type of Low Intensity shockwave system that was specifically developed to treat ED.

Patients and Methods

Instead of focusing the shockwave into a focal point, like in any conventional lithotripter, Renova system (DirexGroup) shockwaves focalize along a 70mm line, with a dept of 40mm. This allows a perfect coverage of the full penis shaft and the crura. We use a short protocol of 4 weekly sessions, applying 900 shocks in each of the 4 following areas: right Crus, left Crus, right Corpus Cavernosum, left Corpus Cavernosum.

We have treated 20 patients and we have a follow up of the first 12 patients, both PDE5-I Responders and non Responders.

Results

IIEF-EF: International Index of Erectile Function – Erectile Function Domain

	Patient Initials	Baseline IIEF-EF	IIEF-EF at 1 month	IIEF Difference	Success /Failure
1	M I M	9	18	9	Success
2	H I S	8	8	0	Failure
3	N M M	8	8	0	Failure
4	J H S	17	24	7	Success
5	M N S	14	25	11	Success
6	O I S	19	25	6	Success
7	M M K	11	24	13	Success
8	A A D	6	19	13	Success
9	I H A	19	28	9	Success
10	A H	19	28	9	Success
11	S A	12	20	8	Success
12	A M H	17	24	7	Success
Average		**13.25**	**20.92**	**7.67**	**84%**

SEP- Sexual Encounter Profile

	Patient Initials	Baseline		Follow-up	
		SEP 2	**SEP 3**	**SEP 2**	**SEP 3**
1	M I M	NO	NO	YES	YES
2	H I S	NO	NO	NO	NO
3	N M M	NO	NO	NO	NO
4	J H S	YES	YES	YES	YES
5	M N S	YES	NO	YES	YES
6	O I S	YES	YES	YES	YES
7	M M K	NO	NO	YES	YES
8	A A D	NO	NO	YES	YES
9	I H A	YES	NO	YES	YES
10	A H	YES	YES	YES	YES
11	S A	NO	NO	YES	YES
12	A M H	YES	YES	YES	YES
Average		**50%**	**33%**	**83%**	**83%**

Comparative follow up: 1 and 3 months

	Patients Initials	Response to PDE5-I	IIEF Score			Results Comparison	Delta	Success
			Baseline	1month	3 months			
1	M I M	YES	9	18	18	Same	9	Yes
2	H I S	NO	9	8	8	Same	-1	No
3	N M M	NO	8	8	8	Same	0	No
4	J H S	YES	17	24	24	Same	6	Yes
5	M N S	YES	14	25	30	Improvement	16	Yes
6	O I S	YES	19	25	25	Same	6	Yes
7	M M K	YES	11	24	24	Same	13	Yes
8	A A D	NO	6	19	19	Same	13	Yes
9	I H A	YES	19	28	28	Same	7	Yes
10	A H	YES	19	28	28	Same	7	Yes
11	S A I	YES	12	20	20	Same	8	Yes
12	A M H	YES	17	24	24	Same	7	Yes

- Results at 1 and 3 month follow-up are essentially the same.
- Successful results are seen at 1 month post treatment.

Conclusions

- Initial results at 1 and 3 months show great progress in erectile function.
- Average IIEF-EF increased from 13.25 to 20.92 (57.86 % improvement).
- **84% Success according to success criteria**.
- All mild to moderate cases have succeeded.
- One severe case has improved while 2 severe cases failed.
- SEP and GAQ results have improved.
- No pain and no complications were reported.

The above paper abstract was presented at the *5th Pan Arab Congress of Sexual Health*, on April 20th 2013, Dubai.

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The Effect of Low Intensity Shockwave Therapy on the Erectile Function of Smokers and Non-smokers - Initial Report with a Dedicated System

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Introduction and Objective

The association between cigarettes smoking and erectile dysfunction (ED) was researched in many studies so far. The strongest relationship found was an adjusted odds ratio of 1.97 for incident ED in smokers compared with nonsmokers. Smoking appears to decrease pelvic and penile vascular flow. Moreover, atherosclerosis is possibly the most important vascular consequence of cigarette smoking. It was established that the effect of smoking on erectile function is related to impairment of endothelium dependent smooth muscle relaxation which is a key process leading to the dilation of vessels in the erectile tissue and an increased blood flow required for erection.

10 years ago, a study that examined the beneficial effects of Shockwaves on ischemia-induced myocardial dysfunction was published and revealed that shockwaves at energy level of 0.09mJ/mm² enhance coronary angiogenesis.

The present study examines the effect of a treatment by a new dedicated device delivering shockwaves at the same energy level and a long focal area adjusted to the male sexual organ, on patients suffering from vascular origin ED, both smokers and non-smokers.

Materials and Methods

25 patients with Vasculogenic ED were treated by the shockwave device, 4 times, once a week. 1600 shocks were applied to each Crus and 900 shocks were applied to each Corpus Cavernosum. No PDE5 inhibitors were used during the treatment and 3 weeks prior treatment. Erectile function was evaluated at baseline and at 1, 3 and 6 months post treatment by 4 self administered questionnaires: IIEF-6, SEP, GAQ and EHS. Success was defined as

positive answers to SEP and GAQ questions, EHS≥3 and a significant increase of IIEF-6 score according to the baseline ED severity.

Results

24 men with a mean age of 62.6 have finished treatment. 53% of them were smokers. There was no significant difference between ED duration, age and baseline IIEF-6 of smokers and non-smokers. Co-morbidities rates were higher in smokers than in non-smokers. The increase in IIEF-6 from baseline to the last follow-up was twice as large in the smokers than the non-smokers. **The overall success rate was 70% and 84% of patients answered "Yes" to both GAQ questions.** No adverse events were reported.

Conclusions

This pilot study shows that eventually this new treatment for vascular ED could be suitable to smoking patients and patients with vascular risk factors. More research is required for confirming the efficacy of this treatment on different populations.

The above paper abstract was presented at the *30th Italian society of Andrology Congress (SIA)*, on May 2014, Maratea, Italy.