Linear Shockwave Therapy (LSWT) for Erectile Dysfunction

Clinical Data and Reports

RENOVA MORENOVA

April 2025

Table of Contents

Clinical Evaluation of Erectile Dysfunction Treatment Using Low-Intensity Shock Wave Therapy MORENOVA®
……..... 5
Jun Kato, Hajime Nakano, Akira Tsujimura
111th Annual Meeting of the Japanese Urological Association, April 2024

A Systematic Review of the Long-Term Efficacy of Low-Intensity Shockwave Therapy for Vasculogenic Erectile Dysfunction
……..... 16
Brunckhorst O, Wells L, Teeling F, Muir G, Muneer A, Ahmed K
International Urology and Nephrology, 51(5):773–781, May 2019

Effect of Low-Dose PDE5i and Low-Energy Shock Wave on Acute Phase of Peyronie's Disease
……..... 25
Lu M
The Journal of Urology, 201(4S):e953–e254, May 2019

A Phase 2 Randomized Trial To Evaluate Different Dose Regimens of Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction: Clinical Trial Update
……..... 26
Katz JE, Molina ML, Clavijo R, Prakash NS, Ramasamy R
European Urology Focus, 4(3):336–337, April 2018

Doppler Test in Penis Flaccid State to Assess Erectile Dysfunction Severity and Shockwave Treatment Outcomes
……..... 28
Gatkin M, Sopotov A
World Meeting on Sexual Medicine, Lisbon, March 2018

Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis
……..... 29
Zhihua vLu, vGuiting Lin, Amanda Reed-Maldonado, Chunxi Wang,
Yung-Chin Lee, Tom F. Lue
Accepted May 31, 2016

Twelve-Month Efficacy and Safety of Low-Intensity Shockwave Therapy for Erectile Dysfunction in Patients Who Do Not Respond to Phosphodiesterase Type 5 Inhibitors
……..... 45
Amado Bechara, MD, PhD, Adolfo Casabé, MD, Walter De Bonis, MD, and Pablo Gomez Ciciclia, MD

Sex Med 2016;-:e1ee8

Safety and efficacy of low intensity shockwave (LISW) treatment in patients with erectile dysfunction ……..... 56

A. Ruffo, M. Capece, D. Prezioso, G. Romeo, E. Illiano, L. Romis, G. Di Lauro, F. Iacono

Int. Braz. J. Urol., 2015

Linear Shock Wave Therapy in the Treatment of Erectile Dysfunction……... 63

M. Pelayo-Nieto, E. Linden-Castro, A. Alias-Melgar, D. Espinosa-Pérez Grovas, F. Carre˜no-de la Rosa, F. Bertrand-Noriega, R. Cortez-Betancourt

Actas Urol Esp. 2015

Long Term Efficacy of Low Intensity Linear Focused Shockwave Therapy for Vascular Erectile Dysfunction Patients: 20 months follow-up…….. 67

A. Casarico, P. Puppo

22nd National Congress of the Italian Urological Association, Bologna, May 2015

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 ……..... 72

A. Bechara, A. Casabé, W. De Bonis, J. Nazar

Archivos Españoles de Urología, April 2015

Initial Experience with Linear Focused Shockwave Treatment for Erectile Dysfunction: a 6-Months Follow-Up Pilot Study…….……... 81

Y. Reisman, A. Hind, A. Varaneckas, I. Motil

Internation Journal of Impotence Research, October 2014

Safety and Efficient Duration of Linear Focused Shockwave Treatment for Erectile Dysfunction – A 12 months Follow-up Pilot Study…… 86

Y. Reisman

16th World Meeting on Sexual Medicine, Sao Paulo, October 2014

Initial Clinical Experience of Linear Focused, Low Intensity Shockwave for Treatrment of ED Patients with Different Severity Symptoms……..... 88

N. Cruz, A. Morales

16th World Meeting on Sexual Medicine, Sao Paulo, October 2014

Low intensity shock wave (LISW) treatment (Renova) in order to improve male sexual function: A preliminary data on 42 patients……..... 90

F. Iacono, A. Ruffo, D. Prezioso, G. Romeo, E. Illiano, L. Romis, G. Di Lauro

16th Congress of the European Society for Sexual Medicine (ESSM), Istanbul, February 2014

Low Intensity Linear Focused Shockwave Therapy: a New Treatment to Improve the Quality of Life of Vascular Erectile Dysfunction Patients……. 92

P. Puppo, A. Casarico

21st National Congress of the Italian Urology Association, Rome, June 2014

The Effect of Low Intensity Shockwave Therapy on the Erectile Function of Smokers and Non-smokers - Initial Report with a Dedicated System…….....……. 95

P. Puppo, A. Casarico

30th Italian society of Andrology Congress (SIA), Maratea, May 2014

Linear Low Intensity Shockwaves Treatment of Vasculogenic ED – First Results……..... 97

I. Motil, T. Šramkova

102nd Annual Meeting of the Japanese Urological Association (JUA), Kobe, April 2014

Efficacy and Safety of Linear Focused Shockwaves for Erectile Dysfunction (RENOVA) – A Second Generation Technology.....…. …… 99

Y. Reisman, A. Hind, A. Varaneckas, I. Motil

2nd Biennial Meeting of the Middle East Society for Sexual Medicine (MESSM), Dubai, November 2013

Efficacy and Safety of Linear Focused Shockwaves for Erectile Dysfunction (RENOVA) – A Second Generation Technology..... ……..... 101

Y. Reisman, A. Hind, A. Varaneckas, I. Motil

12th Congress of Latin American Society for Sexual Medicine (SLAMS), Cancun, August 2013

Line Focused Shock Wave for Erectile Dysfunction – a different technological approach……..... 103

A. Hind, O. Saleh, Y. Abu Asbeh

5th Pan Arab Congress of Sexual Medicine, Dubai, April 2013

Clinical Evaluation of Erectile Dysfunction Treatment Using Low-Intensity Shock Wave Therapy MORENOVA®: A Study of 59 Cases

Jun Kato[1], Hajime Nakano[1], Akira Tsujimura[2]

Abstract:

This study investigates the efficacy of low-intensity shock wave therapy (MORENOVA®) for treating erectile dysfunction (ED) in 59 patients who presented with ED as their chief complaint at the East Ekimae Clinic Shinbashi in Tokyo, Japan.

Patient Background and Methods: The patients had an average age of 54.2 ± 13.26 years, ranging from their 20s to their 70s (maximum age of 78). The study included patients with no underlying health conditions prior to treatment, as well as those with various chronic conditions such as hypertension. MORENOVA® was conducted according to standard procedures, with evaluations of the patient's EHS (Erection Hardness Score) and SHIM (Sexual Health Inventory for Men) scores before treatment, and one and three months after treatment. EHS quantifies erection hardness, while SHIM is used to assess overall erectile function. In addition to these assessments, patients were asked to provide free-form feedback regarding their impressions and opinions after the therapy.

Results and Conclusion: One month after therapy, the average SHIM score improved from 11.4 to 16.7 ($p<0.01$), while the average EHS improved from 1.9 to 2.8 ($p<0.01$). After three months, the SHIM score improved from an average of 10.5 to 15.0 ($p<0.01$), and the EHS improved from 1.9 to 2.6 ($p<0.01$). The improvements in SHIM score and EHS were statistically significant at both one- and three-months post-treatment. Similar treatment effects were observed across different age groups and among patients with underlying health conditions. Of the 34 responses to the AI-analyzed post-treatment feedback, 70% were positive. This study strongly suggests that low-intensity shock wave therapy is a promising treatment option for ED across diverse age groups and patients with underlying health conditions. Future research should focus on exploring the relationship between patient background, underlying health conditions, and treatment efficacy, as well as evaluating the long-term sustainability of treatment effects over 6 months and 1 year.

Key Words: Erectile Dysfunction (ED), Low-Intensity Shock Wave Therapy for ED, MORENOVA®, Erection Hardness Score (EHS), Sexual Health Inventory for Men (SHIM)

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Introduction:

MORENOVA® is a cutting-edge medical device developed by DIREX, an Israeli company renowned for its advanced technology in the field of urology. It was designed specifically for the treatment of erectile dysfunction (ED) and is based on clinical results that suggest shock waves (pressure waves traveling faster than the speed of sound) can contribute to the improvement of ED. DIREX leveraged its expertise in shock wave therapy for kidney stone lithotripsy and adapted it for ED treatment, resulting in this groundbreaking medical device.

MORENOVA® is a compact version of the older RENOVA®, and while the fundamental principle remains the same, it utilizes low-intensity shock waves on the penis and perineum. Renova has been implemented in over 70 countries and boasts over 100,000 treatment cases. The therapy itself is relatively painless, takes about 20 minutes, and has not been associated with any side effects, making it a promising new strategy in ED treatment.

As shown in Figures 1-A & 1-B, the linear shock waves from MORENOVA® are a type of low-intensity shock wave therapy (ESWT = Extracorporeal Shockwave Therapy). The treatment involves delivering a total of 1,800 shock waves (900 from each of the two applicators) with an energy density of 1.8 mJ/mm² to the sides of the penis and the perineum. This stimulates endothelial cells within penile blood vessels, promoting angiogenesis[1)]. Improved blood flow to the penis leads to the delivery of adequate blood supply necessary for erection, thereby enhancing erectile function. It is also possible to combine MORENOVA® treatment with ED medication.

There is no standard protocol for the frequency of treatments[2)], however, this study followed the protocol recommended by DIREX, which entails five sessions conducted 2-3 times per week. Contraindications and exclusions for MORENOVA® are listed in Table 2.

Methods:

The study included 59 patients (average age: 54.1 ± 13.2 years) who presented with erectile dysfunction (ED) as their chief complaint at the East Ekimae Clinic Shinbashi from May 2022 to March 2024. Patients were included in the study if they met the eligibility criteria, did not have contraindications or exclusions to MORENOVA® treatment, and consented to participate in the clinical study. Participants received five treatment sessions over a period of two to five weeks.

Patient evaluation was based on age, underlying health conditions, duration of ED, and pre- and post-treatment SHIM (Sexual Health Inventory for Men) and EHS (Erection Hardness Score) scores (both in Japanese versions[3)]). This observational study did not restrict the use of ED medications during the study period. The study was conducted retrospectively, in compliance with the Helsinki Declaration and Good Clinical Practice (GCP) guidelines. It was approved by the local ethics committee (Ethics Committee of Juntendo University Urayasu Hospital, approval number E23-0445). Statistical significance was assessed using appropriate statistical methods (paired t-

test). Additionally, patients were asked to provide free-form feedback on their impressions and opinions about the therapy one month after the treatment.

Results:

Figure 2 shows the age distribution of the participants. The most common age group was the 50s, accounting for 32.2%, followed by the 60s at 30.5%, the 40s at 18.6%, the 20s and 30s at 10.2%, and the 70s (with a maximum age of 78) at 8.5%.

Figure 3 displays the duration of ED experienced by participants as part of the patient background. The majority of cases (71.0%, or 42 participants) had experienced ED for one to three years. Four cases (7%) had been experiencing ED for 10 to 14 years.

Figure 4 shows the breakdown of underlying health conditions among the participants. A total of 18 participants (30.5%) were receiving treatment for an underlying condition, with hypertension being the most common (33.3%), followed by dyslipidemia, diabetes, and hyperuricemia as the primary conditions.

Figures 5 shows the changes in SHIM score and EHS one month after treatment. The SHIM score improved significantly from 11.4 to 16.7 ($p<0.01$), and EHS also improved significantly from 1.9 to 2.8 ($p<0.01$).

Figures 6 shows the SHIM score and EHS three months after treatment. Although the number of cases decreased to 30 at three months, the SHIM score improved significantly from 10.5 to 15.0 ($p<0.01$), and EHS improved significantly from 1.9 to 2.6 ($p<0.01$). This demonstrates that the improvements were maintained even three months after treatment.

Furthermore, Figures 7 and Figure 8 display the changes in SHIM score and EHS by age group. While there was a trend of decline in the scores at three months across all age groups, the improvements achieved from before treatment were maintained.

Table 4a-4c contain free-form feedback and impressions about the treatment from participants. An AI analysis of the responses from 34 participants showed that 70% provided positive feedback (as shown in Figure 9).

Discussion:

The prevalence of erectile dysfunction (ED) has been rising worldwide[4)], including in Japan, where it has become a national health concern. The age distribution in this study (Figure 2) spanned from patients in their 20s to the oldest patient being 78 years old, with the majority of patients being in their 50s and 60s. Around 71% of patients had been suffering from ED for a relatively short duration of one to three years, while five patients were in their 70s, including one patient who had been receiving ED treatment for 10 to 14 years.

In terms of medication, 67.8% (40/59) of the patients were either currently using or had

previously used ED medications, while 18.6% (11/59) had never used ED medications (some had discontinued use due to side effects). Regarding underlying conditions (Figure 4), 30.5% (18/59) of the patients had comorbidities, with hypertension being the most common (33.3%). Although the use of antihypertensive medications was not thoroughly analyzed, a variety of medications were reported, with amlodipine being the most commonly used. The potential impact of medication-induced ED should be considered in future research.

Additionally, dyslipidemia and diabetes each accounted for 16.7% (2/18) of cases, and patients were typically prescribed statins or SGLT2 inhibitors. One case was managed with self-administered insulin injections. Other comorbidities included atrial fibrillation (post-ablation) and benign prostatic hyperplasia, indicating that some patients had multiple underlying conditions.

Future research should investigate the impact of various comorbidities (e.g., HbA1C levels) on the efficacy of MORENOVA® treatment. The improvements in SHIM score and EHS observed one month after treatment (Figures 5 and 6) were significant, with continued significant improvements observed three months post-treatment (Figures 7 and 8), despite the reduction in the number of respondents from 59 to 30.

The limited number of cases in this study may have affected the results, but the sustained improvement in EHS across almost all age groups is notable. It will be important to assess whether these improvements persist over longer periods, such as six months or a year.

Another study by Kurosawa et al.[5] assessed the efficacy of low-intensity shock wave therapy products (ED1000 and Renova) in 76 and 484 cases, respectively. A multivariate analysis identified age as the only factor influencing EHS (P=0.009), suggesting RENOVA® is recommended for patients under 70 years old.

In this study, improvements were observed even in patients over 70 years old (albeit only five patients), but a larger sample size might reveal similar trends to those of previous studies. Lastly, AI analysis of free-form feedback from 34 patients one-month post-treatment revealed that 70% of patients reported positive experiences (Figure 9).

Despite the limited sample size and observational period, the study suggests consistent efficacy of MORENOVA® treatment across age groups, ED duration, and the presence of comorbidities. The sustained improvements in EHS scores even three months post-treatment indicate the potential for long-term efficacy of this treatment method.

In conclusion, MORENOVA® shows promise as a new option in the treatment of erectile dysfunction (ED). It may offer an alternative for patients who experience a reduction in efficacy with ED medications, as well as for those who cannot continue ED medication due to side effects or contraindications. Long-term clinical trials and comparative studies with other ED treatment methods are crucial and are expected to clarify MORENOVA®'s positioning in the treatment of ED.

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Fig 1 -A

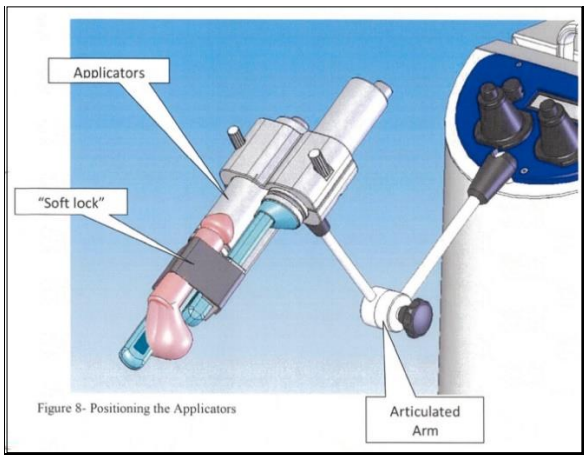

Fig 1 -B

1. Individuals with a history of radical prostatectomy or extensive pelvic surgery.
2. Patients with venous leak erectile dysfunction.
3. Those with abnormal bleeding tendencies or coagulation disorders, such as an international normalized ratio (INR) greater than 3.
4. Patients with hemophilia (A and B).
5. Individuals experiencing localized bleeding.
6. Those who have undergone pelvic area surgery or radiation therapy within the last 12 months.
7. Patients with a history of cancer treatment within the last 12 months or those in the recovery phase.
8. Those with neurological or psychiatric conditions that impact erection.
9. Individuals with penile deformities or abnormalities (e.g., Peyronie's disease) during erection.
10. Patients with local wounds, dermatitis, infections, or tumors in the penile, scrotal, or inguinal regions.
11. Those with implants within the penis (including penile prostheses).
12. Other medical history or conditions that the physician deems necessary for exclusion.

Table 1

Number of Subjects by Age Group

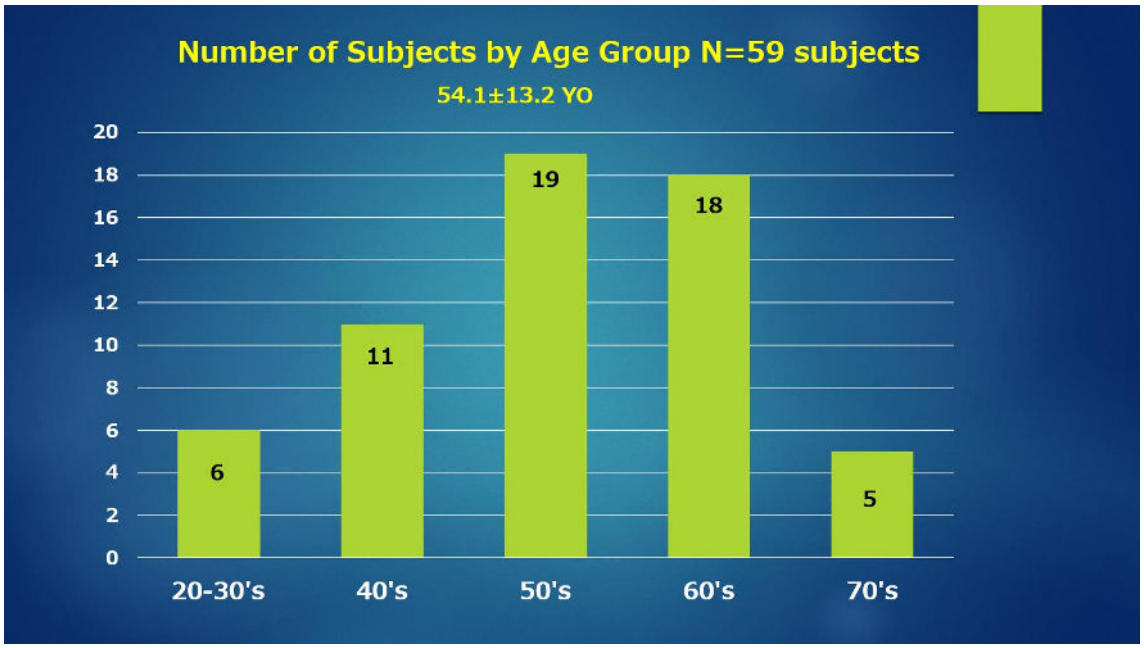

Fig.2

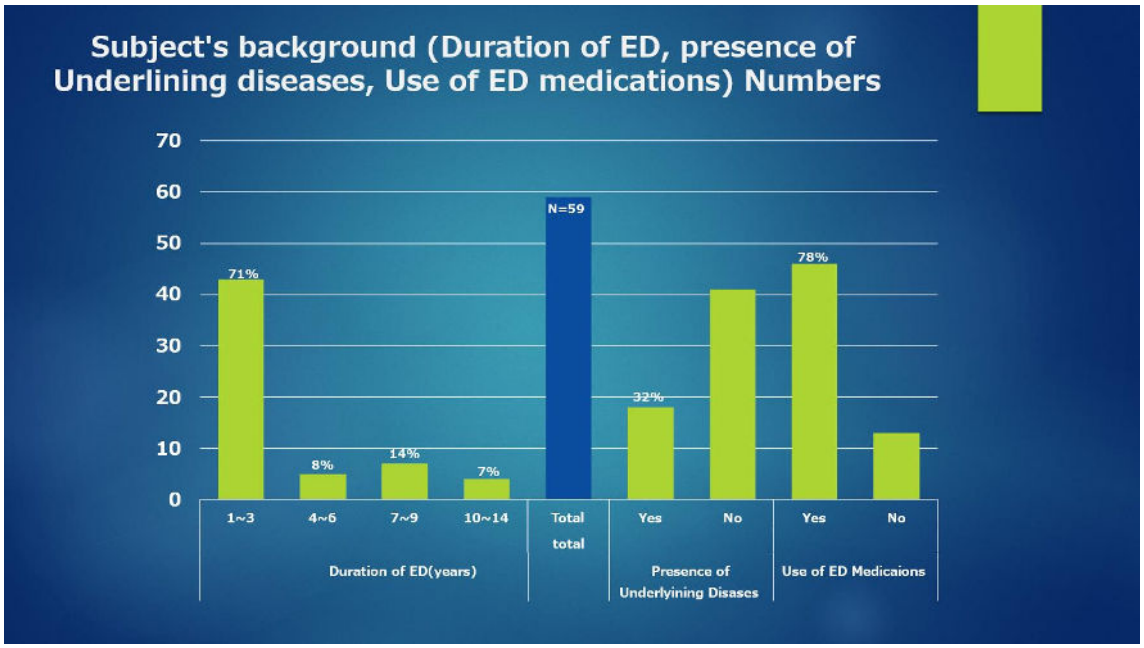
Subject's background (Duration of ED, presence of Underlining diseases, Use of ED medications) Numbers
70
60
50
40
30
20
10
0
71%
8%
14%
7%
N=59
32%
78%
1~3
4~6
7~9
10~14
Total
total
Yes
No
Yes
No
Duration of ED(years)
Presence of Underlyining Disases
Use of ED Medicaions

Fig. 3

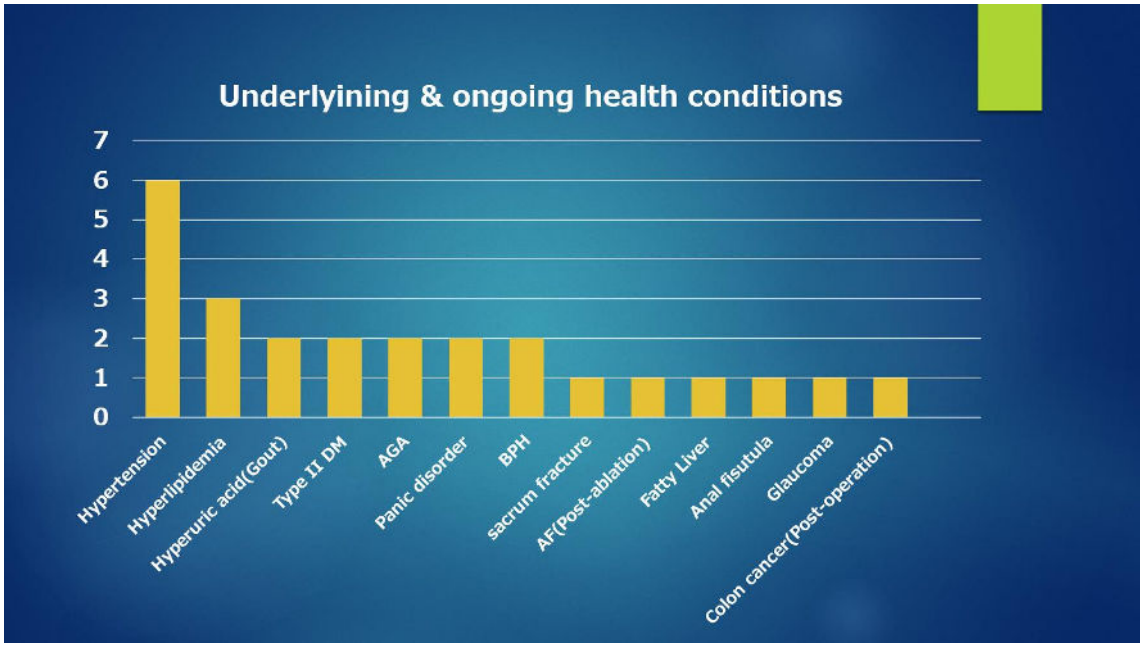
Underlyining & ongoing health conditions
7
6
5
4
3
2
1
0
Hypertension
Hyperlipidemia
Hyperuric acid(Gout)
Type II DM
AGA
Panic disorder
BPH
sacrum fracture
AF(Post-ablation)
Fatty Liver
Anal fisutula
Glaucoma
Colon cancer(Post-operation)

Fig.4

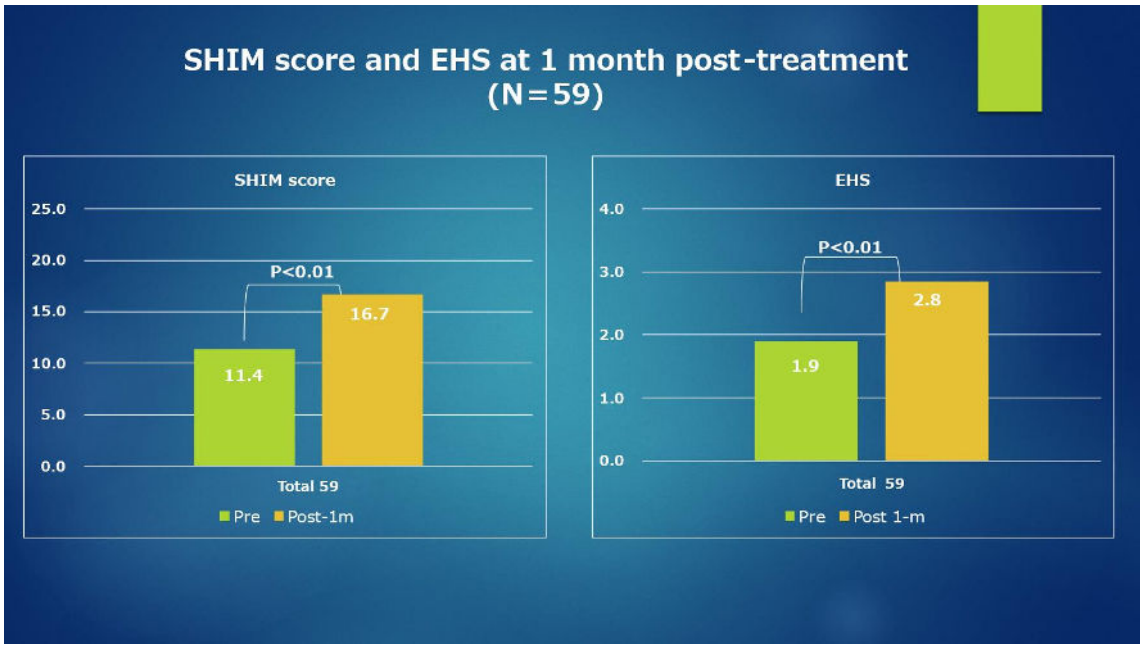
SHIM score and EHS at 1 month post-treatment
(N=59)
SHIM score
25.0
20.0
15.0
10.0
5.0
0.0
P<0.01
11.4
16.7
Total 59
Pre
Post-1m
EHS
4.0
3.0
2.0
1.0
0.0
P<0.01
1.9
2.8
Total 59
Pre
Post 1-m

Fig. 5

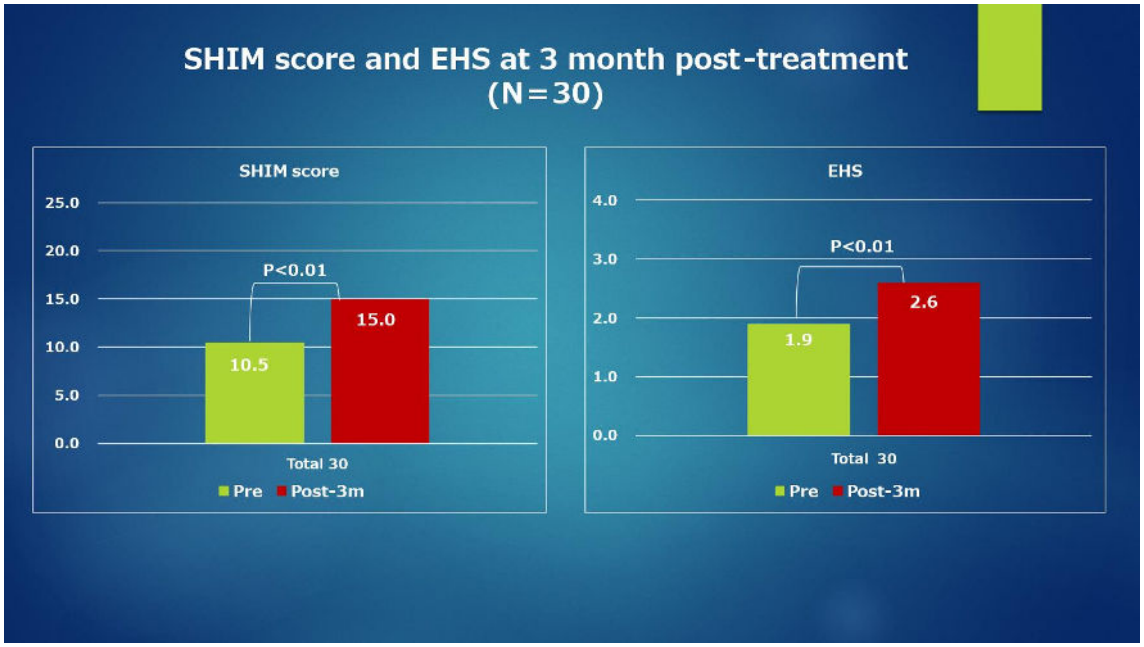
SHIM score and EHS at 3 month post-treatment
(N=30)
SHIM score
25.0
20.0
15.0
10.0
5.0
0.0
P<0.01
10.5
15.0
Total 30
Pre
Post-3m
EHS
4.0
3.0
2.0
1.0
0.0
P<0.01
1.9
2.6
Total 30
Pre
Post-3m

Fig.6

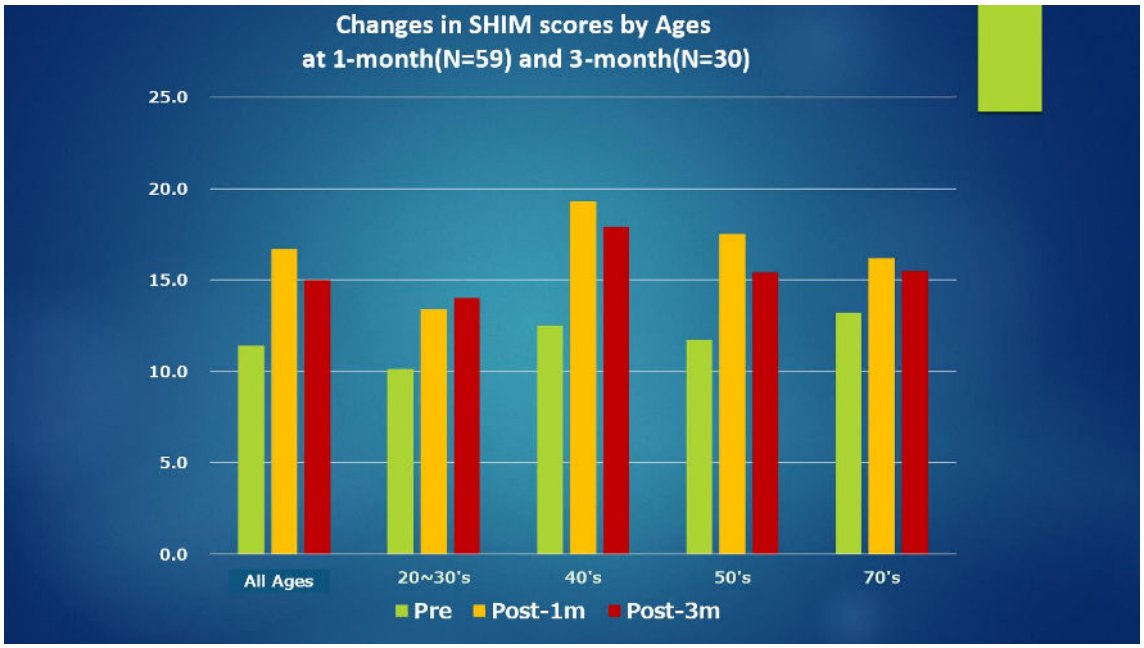
Changes in SHIM scores by Ages
at 1-month(N=59) and 3-month(N=30)
25.0
20.0
15.0
10.0
5.0
0.0
All Ages
20~30's
40's
50's
70's
Pre
Post-1m
Post-3m

Fig.7

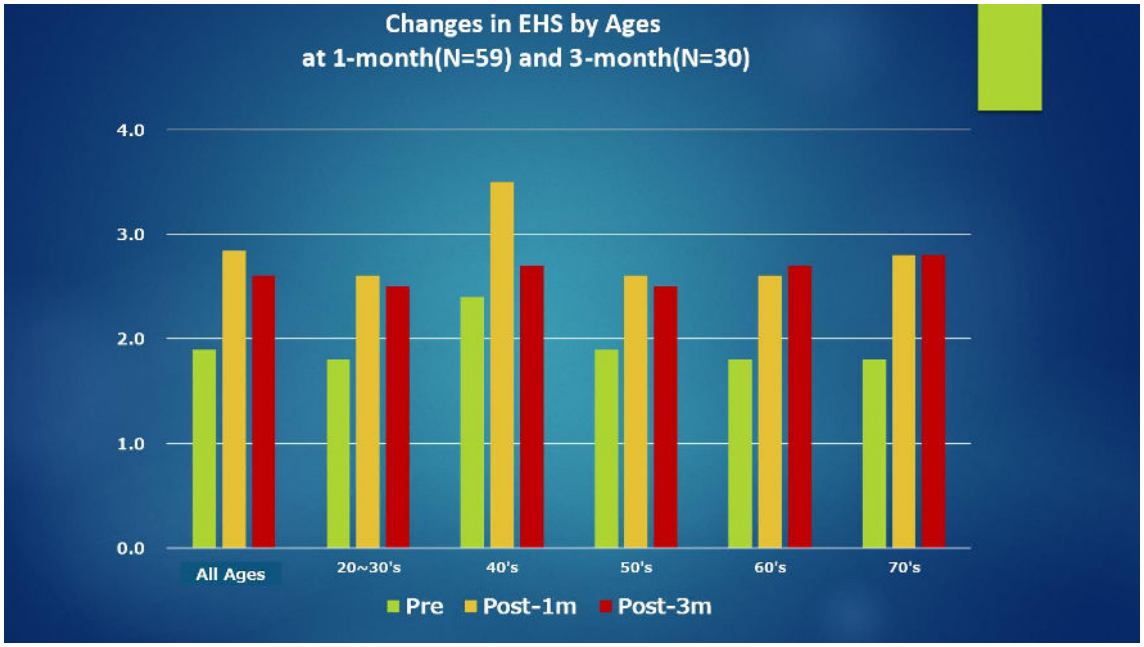
Changes in EHS by Ages
at 1-month(N=59) and 3-month(N=30)
4.0
3.0
2.0
1.0
0.0
All Ages
20~30's
40's
50's
60's
70's
Pre
Post-1m
Post-3m

Fig. 8

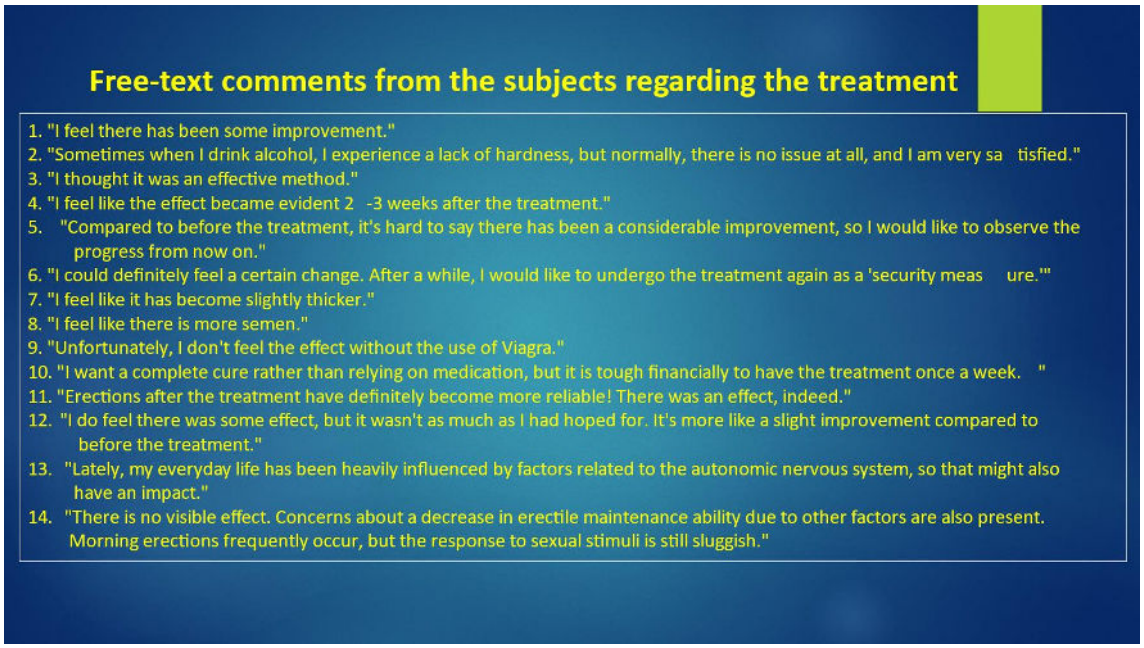

Table-4a

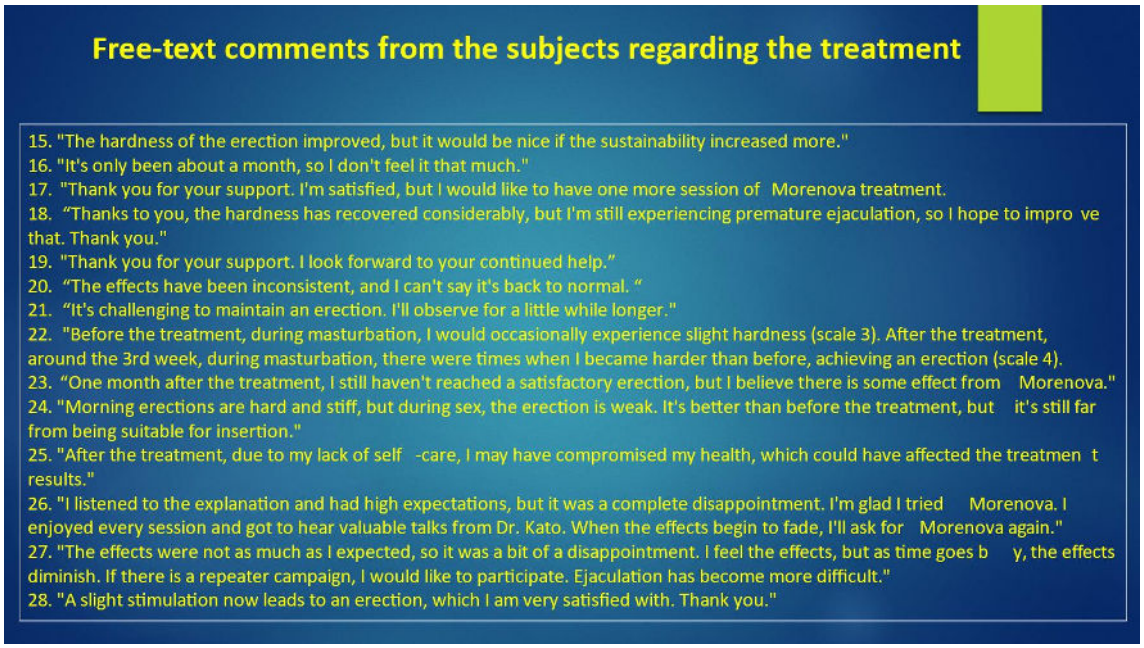

Table-4b

Free-text comments from the subjects regarding the treatment

29. "Due to various reasons, I haven't been able to practice until September, which is unfortunate, but my condition has imp roved considerably."
30. "There was a certain effect, but it doesn't feel like one session was enough."
31. "I didn't really feel much of an effect."
32. "No particular change."
33. "The process has been satisfactory, and I would consider another treatment if it's reasonably priced.
34. "Before the treatment, I felt quite old, but now I feel somewhat better. I'm curious about how much more improvement a repeat treatment might bring."

Table-4c

Based on AI analysis (ChatGPT) of the feedback from 34 participants, 70% of the responses were positive.

Positive:
Individuals reported feeling the effects of the treatment and expressed satisfaction. Some mentioned improvements in their condition and believed the treatment was effective. Many were interested in receiving additional treatments and repeated sessions.

Neutral:
Some individuals noted that there was some effect, but they were not fully satisfied. Others mentioned feeling somewhat disappointed or having no particular change in their condition.

Negative:
A few individuals expressed that they did not feel any effect from the treatment and felt disappointed. Some mentioned financial concerns, making it difficult for them to pursue additional treatments. Others still struggled with maintaining erections and found the treatment did not fully address their issues.

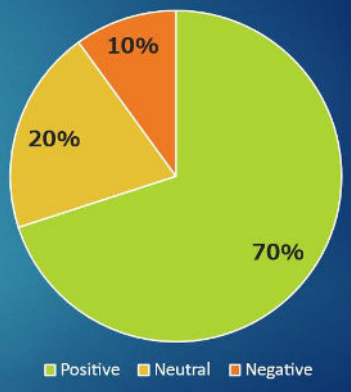

Fig.9

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UROLOGY - REVIEW

A systematic review of the long-term efficacy of low-intensity shockwave therapy for vasculogenic erectile dysfunction

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Abstract

Purpose To look at the evidence base for LISWT as a treatment modality for vasculogenic erectile dysfunction, focusing on the long-term outcomes at over 6 months following treatment.

Methods A systematic literature search was conducted utilising MEDLINE and Scopus databases from 2010 to September 2018 by two independent reviewers. Outcome measures extracted for long-term efficacy included International Index of Erectile Function scores and Erection Hardness Scores. Subgroup analysis for LISWT effectiveness included age, PDE5i responsiveness, presence of vascular co-morbidities and smoking status.

Results The search identified eleven studies, representing a total of 799 patients. Nine studies found a significant improvement in erectile function after LISWT at 6-month follow-up (median IIEF-EF improvement in 5.3 at 6 months). However, of five studies assessing erectile function at 12 months; two identified a plateauing of results, with three a deterioration (IIEF-EF score changes of − 2 to 0.1 from 6 months). Erectile function did, however, remain above baseline results in all of these studies. Subgroup analysis revealed increasing age to reduce the response to LISWT treatment. Whilst ED severity, PDE5i responsiveness and co-morbidities potentially influence effectiveness, results are still inconsistent.

Conclusions LISWT may be a safe and acceptable potential ED treatment with demonstrated benefits at 6 months. There is some question regarding efficacy deterioration beyond this, but there is still a demonstrated benefit seen even at 12 months post treatment. However, quality of evidence remains low with larger multiinstitutional studies required, standardising confounders such as shockwave administration and oral medication use.

Keywords Erectile dysfunction · Vasculogenic impotence · Extracorporeal shockwave therapy

Introduction

Atherosclerosis of penile arteries and endothelial dysfunction, known as vasculogenic erectile dysfunction (ED), is the cause of ED in 40% of men over the age of fifty [1]. There is currently no known long-lasting or curative treatment for vasculogenic ED [2]. At present both AUA and EAU guidelines for

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the treatment of vasculogenic ED recommend initial lifestyle changes to address modifiable risk factors, followed by oral phosphodiesterase 5 inhibitors (PDE5is) as first line medical management. However, only 80% of patients respond to PDE5is as its mechanism of action requires both intact nerves and a basic level of endothelial function [3]. PDE5is are contraindicated in patients using nitrate therapy, so a significant proportion of patients with Vascular ED are forced into second and third line treatment options [4]. Alternative treatment options to PDE5is include vacuum erection devices which are simple to use but have variable patient satisfaction rates [5], intracavernosal injections and topical prostaglandin E1 analogues (Alprostadil). Patients unresponsive to first and second line treatments may progress to surgical management with penile prosthesis [4].

The precise mechanism of action of low-intensity shockwave therapy (LISWT) is not fully understood; however, it is believed that the compression and subsequent negative pressures created from the shockwave energy, the so-called cavitation phenomenon, is an important factor [6]. These tensile forces lead to shear stress on cell membranes which have been shown to have the potential to treat the underlying cause of vascular ED by prompting increased expression of vascular endothelial growth factor (VEGF) [7], recruitment of perivascular stem cells and recruitment of endothelial progenitor cells [8], resulting in neovascularisation of penile arteries. Furthermore, shockwaves may also improve nerve regeneration as seen in animal studies, due to a hypothesised increasing in the ability of injured axons to repair and Schwann cell proliferation [9] which may be useful in ED caused by neurovascular aetiologies. LISWT is unlike any of the currently offered treatment options as it could provide men with a natural erection by treating the underlying pathophysiology, rather than treating the symptoms.

However, the evidence for its use is still debated at present, lacking Food and Drug Administration (FDA) approval for ED, and is still considered experimental by organisations such as the Sexual Medicine Society of North America. Additionally, there has so far largely been a focus on the short-term efficacy of LISWT as a treatment mobility. This review of the literature therefore aimed to:

1. Assess the current evidence base focusing on the long-term outcomes at over 6 months of using LISWT as a treatment modality for vascular ED.
2. Identify if any cohorts of patients with demonstrated improved long-term efficacy of treatment after LISWT

Materials and methods

This review was performed following guidelines defined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10]. The review was prospectively registered, PROSPERO registration number: CRD42018112789.

Study eligibility criteria

Original research articles utilising LISWT to treat vasculogenic ED, with a minimum follow-up period of 6 months for their cohorts, were included. Study types included were randomised controlled trials (RCTs) as well as prospective and retrospective single arm experimental studies. Exclusion criteria were articles not utilising either International Index of Erectile Function-Erectile Function Domain (IIEF-EF) or Erection Hardness Score (EHS) as an outcome parameter and studies published before 2010 (the first trial for LISWT in vasculogenic ED was conducted in 2010 [2]). Furthermore, animal studies, case studies, reviews, studies using LISWT for non-vasculogenic ED and studies unavailable in the English language were all excluded from the review.

Information sources and search

Electronic databases, MEDLINE (via PubMed) and Scopus, were systematically searched for research articles from January 2010 to September 2018. A combination of MeSH terms and key terms was used ('Low-Intensity Shockwave Therapy' OR 'Pulsed Ultrasound' OR 'Low Intensity Ultrasound' OR 'Shockwave' OR 'Shock wave') AND ('Erectile Dysfunction' OR 'ED' OR 'Sexual Dysfunction'). In addition, a thorough reference review of identified articles was conducted, to ensure that all relevant articles were included. The grey literature was searched via abstracts on Scopus and ongoing clinical trials in Cochrane Library and ClinicalTrials.gov, with authors contacted for any available preliminary data.

Study selection

The search was conducted independently by two reviewers (OB and LW) to identify potentially relevant articles. Title and abstract screening was conducted, with full-text articles subsequently screened along inclusion criteria for inclusion into qualitative analysis. Discrepancies between reviewers were discussed until 100% agreement was achieved.

Data collection and data items

Data extraction was independently conducted by two reviewers (OB and LW). Specific data were extracted from

all studies such as study type, number of participants, participant demographics and LISWT treatment regimen. The primary outcome measure extracted for clinical efficacy included erectile function measures such as IIEF-EF or EHS scores after LISWT at long-term follow-up of over 6 months. This included both raw questionnaire score improvements, percentage improvements and also study defined success rates as per score improvements. Additionally, subgroup analysis of LISWT effectiveness was conducted via assessment of population cohorts including age, PDE5i responsiveness, presence of vascular co-morbidities and smoking status.

Risk of bias in individual studies and across studies

The internal validity of each individual article was assessed using the Cochrane Risk of bias tool and with further qualitative analysis for randomised controlled trials and non-randomised studies, respectively [11]. Non-randomised studies were assessed qualitatively by authors critically appraising the methodology, as per definitions in Online Resource 1. Bias across studies was assessed via the GRADE tool in order to provide a recommendation from our review for each individual outcome measure [12].

Results

Study selection

A total of 521 articles were identified through the literature search. Duplicate removal and initial screening excluded 434 articles. Of the 87 full-text articles assessed for eligibility, a final eleven articles were included in the review (Fig. 1).

Study characteristics and result synthesis

Of the eleven articles, five were RCTs and six were non-randomised (Table 1). Three of the RCTs were placebo-controlled; the others compared two different treatment groups. The total number of patients investigated across all studies was 799 patients.

Long-term efficacy of LISWT

Nine studies of the eleven studies [2, 13–20] found a statistically significant increase in erectile function utilising either IIEF or EHS scores after LISWT at over 6-month follow-up (median IIEF-EF score improvement from baseline at 6 months 5.3, range 2.6–10.7). None of these studies demonstrated a decrease in erectile function below baseline post intervention (Fig. 2). However, the results from two randomised, sham-controlled studies, Fojecki et al. and Olsen et al., did not reach the authors' set threshold for significance at follow-ups of over 6 months [21, 22]. The effects of LISWT were followed up for 24 months in one study, 12 months in four studies and 6 months in the remaining six studies. When assessing studies with follow-ups of greater than 6 months, there appeared to be limited improvement in IIEF scores beyond this time period (change in IIEF-EF scores of between −2 and 0.1). No studies identified an ongoing improvement at 12 months when compared to 6 months with two studies demonstrating plateauing of IIEF scores [15, 18]. Three studies showed there was a gradual diminishing effect of effectiveness of LISWT beyond 6 months; however, scores remained at above baseline erectile function in all cases [13, 16, 21]. The largest of these studies demonstrating a gradual decline was conducted by Kitrey et al. This prospective single-armed trial of 156 patients demonstrated an initial response rate of 63.5% at 1 month, decreasing to 42.9% at 12 months and declining to just 34% at 2-year follow-up.

Effect of LISWT on specific population cohorts

Subgroup analysis demonstrated conflicting findings between studies. Whilst the majority of studies have not been powered to draw conclusions based on specific subgroups, trends in results were seen. Age, PDE5i responsiveness, presence of vascular co-morbidities and smoking status have all been proposed to impact the efficacy of LISWT treatment.

Two out of three studies assessing age specifically identified a reduced effectiveness of LISWT with increasing age [14, 17]. These studies identified that younger age was a statistically significant predictor for improved treatment responsiveness and increasing age (> 65 years) and vascular co-morbidities shortened the duration of LISWT effects in comparison to younger, healthier patients. However, in contrast the study conducted by Bechara et al. saw no statistically significant difference in age, duration of ED or co-morbidities when comparing LISWT responders to non-responders [18].

ED severity appears to have contrasting effects on efficacy. Whilst the study conducted by Bechara et al. identified that patients with severe ED responded better to LISWT with the greatest IIEF-EF point increase, Kitrey and colleagues found that the duration of treatment effect was reduced in patients with severe ED at 24-month follow-up [13, 18]. Additionally, when considering duration of ED symptoms, Reisman et al. identified a negative effect on LISWT responsiveness with increasing duration of symptoms, finding the average ED duration to be 3.5 years longer in LISWT non-responders than responders [20]. PDE5i response was seen to be important in a

Table 1 Overview of Studies Included

Study	Follow-up duration (Months)	N. of participants	Study design	Baseline IIEF Score for inclusion	Stable heterosexual relationship > 3 m	PDE5i responsive?	Shockwave exposure	Shockwave administration location	Shockwave delivery	Sig. improvement using LISWT at > 6 months?
Bechara 2016 [17]	12	40	Prospective Single-Arm Trial	< 26	Not stated	N	F: Once per week D: 4 weeks	Each Corpora cavernosum and perineum (each crus)	*TSWPS*: 3,600, *SWD*: 900 (per corpora), 900 (per crus) *EFD*: 0.09 mJ/mm^2, *F*: not given	Y
Fojecki 2018 [20]	12	126	Double-Blinded Sham-Controlled Randomised Trial	< 25	Y	Not stated	F: Once per week D: 5 weeks (just group A) 4-week break	Each corpora cavernosum and perineum (each crus)	*TSWPS*: 600 *SWD*: 300 (2 corpora), 150 (per crus) *EFD*: 0.09 mJ/mm^2, *F*: 5 Hz	N
Hisasue 2016 [16]	6	56	Prospective Single-Arm Trial	Not stated (EHS of 1 or 2)	Not stated	Not stated	F: Twice per week D: 3 weeks, 3-week break and 3 weeks	Three sites on one side of penile shaft, two on crura	*TSWPS*: 1500, *SWD*: 300 (3 penile sites and per crus) *EFD*: 0.09 mJ/mm^2, *F*: 120/min	Y
Kalyvianakis 2018 [13]	6	42	Randomised, 2-parallel-arm, open-label study	< 26	Not stated	Not stated	F: Once or Twice per week dependent on Group D: 12 weeks, (Phase 1: 6 weeks, Phase 2: 6 weeks)	Back and forth movement of probe from glans to pubis on each side	*TSWPS*: 5000 *SWD*: 1000 (per corpora and 2 penile site), 500 (per crus) *EFD*: 0.05 mJ/mm^2, *F*: 8 Hz	Y
Kalyvianakis 2017 [14]	12	46	Double-Blinded Sham-Controlled Randomised Trial	6–21	Y	Y (at least partial)	F: Twice per week D: 3 weeks, 3-week break and 3 weeks	Three locations on penile shaft, two on crura	*TSWPS*: 1500, *SWD*: 300 (3 penile sites and per crus) *EFD*: 0.09 mJ/mm^2, *F*: 160 pulses/min	Y
Kitrey 2018 [12]	24	156	Prospective Single-Arm Trial	Not stated	Not stated	Mixed	F: Twice per week D: 3 weeks, 3-week break and 3 weeks	Five treatment points on penile shaft	*TSWPS*: 1500, *SWD*: 300 (5 penile sites) *EFD*: 0.09 mJ/mm^2, *F*: 120 pulses/min	Y

Table 1 (continued)

Study	Follow-up duration (Months)	N. of participants	Study design	Baseline IIEF Score for inclusion	Stable heterosexual relationship > 3 m	PDE5i responsive?	Shockwave exposure	Shockwave administration location	Shockwave delivery	Sig. improvement using LISWT at > 6 months?
Olsen 2015 [21]	6	105	Double-Blinded Sham-Controlled Randomised Trial	< 20	Y	Y	F: Once per week D: 5 weeks	Three positions on each corpora cavernosum individually	*TSWPS*: 3000, *SWD*: 500 (3 per corpora) *EFD*: 0.15 mJ/mm^2, *F*: 5 Hz	N
Pelayo-Nieto 2015 [18]	6	15	Prospective Single-Arm Trial	12–16	Not stated	Not stated	F: Once per fortnight D: 8 weeks	Two points on cavernosa and each crus	*TSWPS*: 5,000, *SWD*: 900 (per corpora), 1600 (per crus) *EFD*: 0.09 mJ/mm^2, *F*: 5 Hz	Y
Reisman 2014 [19]	6	58	Prospective Single-Arm Trial	6–25	Y	Mixed	F: Once per week D: 4 weeks	One site on each corpora cavernosum and crus	*TSWPS*: 3600, *SWD*: 900 (per corpora and crus) *EFD*: 0.09 mJ/mm^2, *F*: not given	Y
Srini 2015 [15]	12	135	Double-Blinded Sham-Controlled Randomised Trial	< 18	Y	Y	F: Twice per week D: 3 weeks, 3-week break and 3 weeks	Five treatment points unilaterally on penile shaft	*TSWPS*: 1500, *SWD*: 300 (5 penile sites) *EFD*: 0.09 mJ/mm^2, *F*: 120/min	Y
Vardi 2010 [2]	6	20	Prospective Single-Arm Trial	5–19	Not stated	Y	F: Twice per week D: 3 weeks, 3-week break and 3 weeks	Three points on penile shaft and each crura	*TSWPS*: 1500, *SWD*: 300 (3 penile sites and per crus) *EFD*: 0.09 mJ/mm^2, *F*: 120/min	Y

D duration, *EFD* energy flux density, *F* frequency, *LISWT* low-intensity shockwave therapy, *SWD* shockwave delivery, *TSWPS* total shockwaves per session

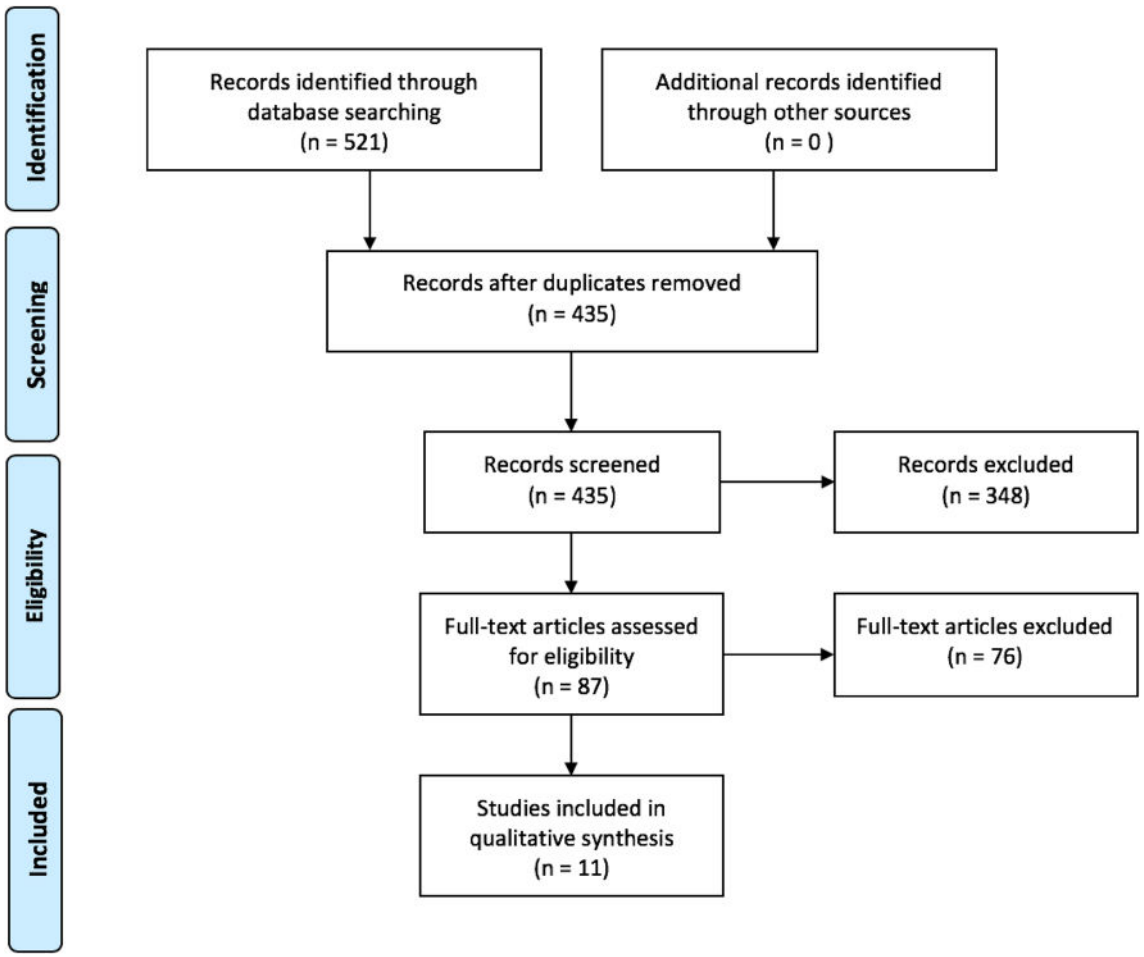

Fig. 1 PRISMA flow chart for article selection

single study where PDE5i responders were statistically more likely to receive benefit from LISWT, with longer duration of efficacy in this cohort [14].

Two studies assessed the effect of vascular risk factors on LISWT effectiveness. In a comparison of patients with at least one vascular co-morbidity (cardiovascular disease, hypertension, high cholesterol), to those with none, Reisman et al. identified lower success rates in those with co-morbidities (76.2% vs 93.7%, respectively) [20]. Smoking status was seen to negatively impact the success of LISWT in one study, with patients possessing a smoking index of less than 20 having a statistically significant chance of improving erectile function (91% vs. 50%) [19]. Finally, the presence of diabetes demonstrated mixed results. Whilst one study demonstrated success rates which were 25% lower in diabetic patients, with shorter duration of treatment effects [20], Pelayo-Nieto et al. contrastingly identified that diabetic patients demonstrated an improved clinical response to LISWT (62% vs 47%) [19].

Quality assessment of articles

There are still limited number of studies assessing long-term follow-up after LISWT with predominantly non-randomised trials present. Risk of bias assessment of randomised trials (Online Resource 2) showed the largest concern to be regarding selection bias, introduced by attrition of study participants. Whilst higher attrition rates are expected due to the longer follow-up in our selected articles, unusually high dropout rates in some studies such as Srini and Fojecki et al. (over 20%) which was identified to be more heavily weighted towards the placebo or the 5-week treatment group [16, 21]. This could skew results towards those receiving the treatment, generating false-positive results. Additionally, the five randomised trials demonstrated small numbers of total participants, with all being single centre trials. There are finally concerns regarding the sham or double blinded nature of the trials. It is difficult to ensure true blinding in these circumstances with many of the trials identifying no benefit at all

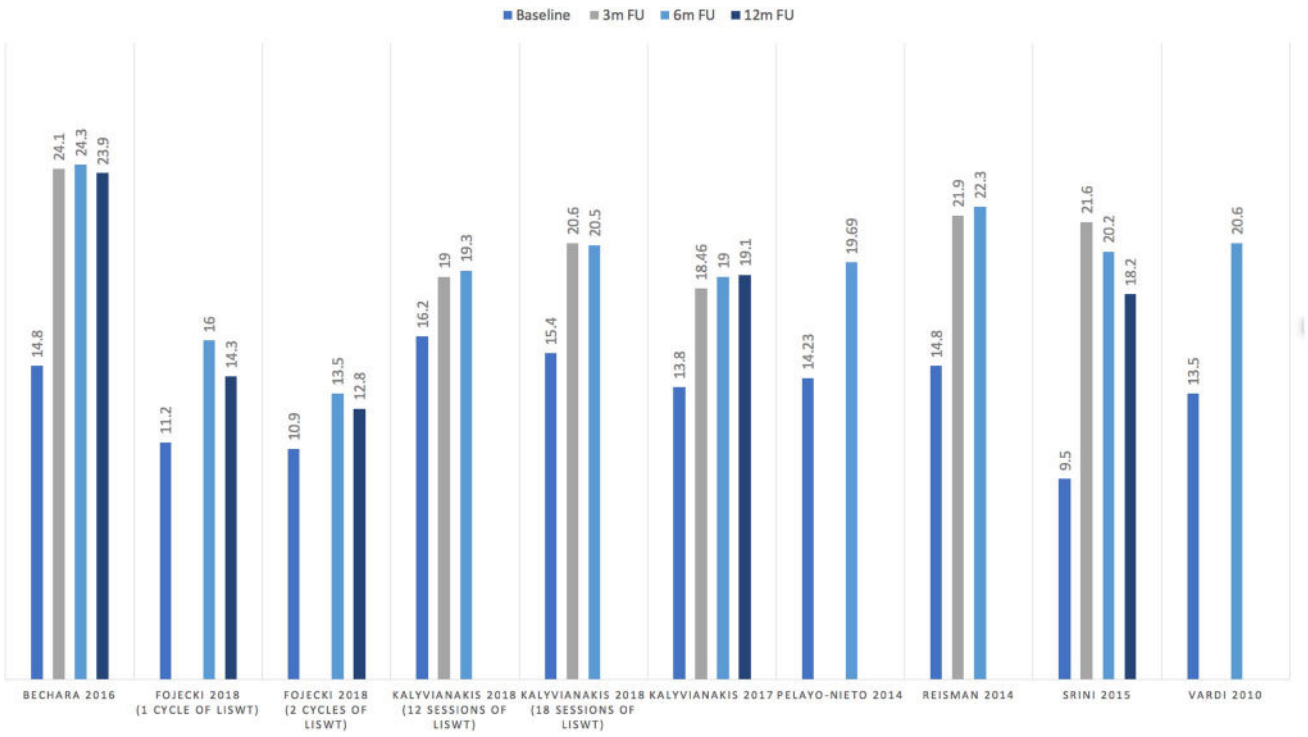

Fig. 2 Long-term efficacy of LISWT based on IIEF-EF scores at baseline, 3, 6 and 12 months

from sham treatment which is unexpected as some placebo effect is expected.

PDE5i use prior and during treatment is currently variable. Whilst the majority of studies included a 4-week 'washout period' without PDE5i use, this was not consistent across all studies, with additional variation surrounding ongoing PDE5i use and timing of restarting this. Four studies allowing participants to resume PDE5i use from 1-month post-LISWT [2, 17, 20, 21], and one study keeping patients on treatment throughout entire treatment duration [18]. This is important as this produces as a confounder which may explain differences in long-term efficacy post-LISWT. Finally, an extremely large variation in administration protocols was identified. Individual studies varied significantly in terms of shockwaves delivered per session, time between sessions and even sites of administration as demonstrated in Table 1. This presents a limitation towards external validity of the studies in view of effect sizes for long-term erectile function post-LISWT.

Comment

This systematic review assesses the long-term effect of LISWT at over 6 months on vasculogenic ED patients. Out of the eleven papers identified, nine demonstrated a statistically significant improvement in erectile function at 6-month follow-up. However, these studies show that beyond 6 months there is no ongoing improvement in erectile function seen. Three out of five studies demonstrated a gradual decline in erectile function with two showing a plateauing of results. However, it is important to note that IIEF-EF scores in all studies remained significantly above baseline functional scores, demonstrating benefit even at 12-month post-treatment. This is likely secondary to the ongoing underlying vascular progression of disease, with LISWT having no impact on comorbidities or progressive atherosclerotic disease affecting the cavernosal tissue [13]. Assessment of the overall quality of the evidence for long erectile function improvement via the GRADE protocol demonstrates that current recommendation for use remains low at present (Online Resource 3). This is due to the predominantly non-randomised evidence base currently present with trials presenting small patient numbers, single institutions and methodological concerns regarding the double-blind sham trials.

Subgroup analysis assessing individual cohorts of patients for LISWT effectiveness yielded varying results. Two studies suggest that younger patients may be more likely to benefit from prolonged benefits in erectile function. This is hypothesised to be secondary to less structural cavernosal and ultra-structural damage present, with greater VEGF receptor activity resulting in a greater biological response from treatment [14, 17]. This has led to suggestions that LISWT may have a role in early intervention, or

even prophylactic treatment in high-risk patients, thereby preventing irreversible vascular changes [14, 23]. However, at present the objective evidence for this is non-existent. Similarly, it would be expected that patients with severe ED would see a reduced effectiveness of treatment secondary to increased ultra-structural damage. Whilst previous findings in short-term follow-up have supported this [24], our review has identified conflicting evidence in the long term, with no clear relationship of ED severity or duration to clinical efficacy.

The evidence assessing cardiovascular co-morbidities and risk factors on treatment effect in the long term is limited. There is contrasting evidence assessing diabetic patients with further review certainly needed. Furthermore, whilst smoking and presence of other cardiovascular risk factors appear to negatively impact the efficacy of treatment, these results are restricted to a single study only in the long term [20]. Similarly, whilst PDE5i responders and naïve patients have previously been identified as positive predictive markers for treatment success in short term studies [24], this cannot be determined for long-term studies yet. Only a single study demonstrated improved efficacy; however, this was not statistically significant. Therefore, at present there is no concrete evidence for any subgroup identified as a predictive marker for long-term successful treatment.

This is the first review, to our knowledge, to specifically assess the long-term efficacy of LISWT for vasculogenic ED. It provides important evidence to demonstrate that there appears to be a lasting effect of erectile function improvement at 6 months for patients which either plateau or may gradually deteriorate towards 12 months post-treatment. This is clinically important, providing urologists evidence for treatment, but additionally offers evidence for frank discussion regarding expectations of erectile function beyond 6-month post-treatment. However, as previously mentioned due to varying study methodologies this review highlights to researchers further areas of research to increase the evidence base surrounding LISWT use.

Whilst there is clinically relevant data currently available, there are several concerns regarding current methodology of identified trials which require standardisation in future studies. It is clear larger studies which are multi-institutional and multi-national are required in the first instance to increase external validity of results. Further to this, PDE5is use prior and post-treatment is extremely variable in the literature. Whilst a washout period and limited PDE5i use may improve the results obtained, it could be argued that future research should focus on more real-life applicability by maintenance of medical therapy concurrently to LISWT. Additionally, future research must standardise administration of LISWT, in particular with regard to the device utilised, treatment delivery in terms of sessions and duration as well as location of administration with current positioning widely varied in the studies identified. In terms of outcome measures utilised, there is a need for greater objective parameters through penile haemodynamic studies concurrently to subjective measures such as IIEF-EF and EHS scores, which can be heavily influenced by other factors such as sexual partners, lifestyle, life events, psychology and comorbidities [13]. Finally, this review has identified a need for longer follow-up at 12 months and beyond to assess the ongoing longevity of treatment efficacy.

As is the case with any systematic review, this review has its limitations. These are largely arising from the data set available with limitations in the number of trials which are available with few randomised studies identified assessing long-term outcomes specifically. Additionally, several methodological concerns and variations as previously mentioned are present. This is particularly true when considering treatment administration and concurrent therapy, meaning that generalisability of results must be considered, and hence, standardised recommendations could not be made. When this variability in methodology was combined with the lack of randomised trials reporting standardised outcome measures such as IIEF-EF and the large heterogeneity of results seen when statistical pooling of randomised studies was attempted, meant that any meaningful statistical assessment of data via a meta-analysis was not feasible. Finally, there is always the possibility of missed studies which could affect current recommendation; however, the risk of this was minimised via a comprehensive search strategy and searching both grey and current literature.

Conclusions

This systematic review identifies that LISWT offers a treatment modality which improves erectile function, with results lasting to over 6 months. There appears to be some limitation of ongoing benefit beyond this at 12 months with either plateauing or even reduction in functional outcomes at this time. Increasing age appears to reduce responsiveness to LISWT treatment in long-term follow-up studies. Furthermore, ED severity, PDE5i responsiveness and co-morbidities may also influence its effectiveness; however, results are inconsistent at present. Whilst LISWT may be a safe and acceptable long-term ED treatment modality, it is clear further investigation is still needed through larger and more standardised trials to improve its evidence base.

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Compliance with ethical standards

Conflict of interest All other authors have no conflicts of interest to make.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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Effect of Low-dose PDE5i and Low-energy Shock Wave on Acute Phase of Peyronie's Disease

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Objective

To investigate the efficacy and safety of low-dose PDE5i and low-energy shock wave (Li-SWT) in the treatment of acute phase of Peyronie disease (PD).

Methods

Twenty patients with acute PD within 6 month onset were collected. The patients were 26-52 years old with an average of 41.6 years. The patients were randomly divided into two groups, 12 of which were orally administered with 5 mg of tadalafil every night for 3 months; the other 8 received 4 times of Li-SWT.

Li-SWT uses the Renova shock wave therapy device with an energy density of 0.09mJ/mm2, each time 3200 times in the penile plaque, 900 times in the left and right penile shaft, and once a week for 4 consecutive treatments as a cycle. All patients underwent ultrasound or MRI, penile bending angle measurement, improvement of subjective symptoms, and IIEF-5 scale before and after treatment.

Results

In the low-dose PDE5i group, the symptoms were improved (8/12) and the low-energy shock wave (Li-SWT) was also improved (5/8). The IIEF5 score in the PDE5i group improved from 12.8 to 17.5 and from 13.4 to 18.3 in the Li-SWT group, without significant difference between the two groups. The subjective symptoms of pain and discomfort were also improved in both groups. But the plaque size and penile curvature did not change significantly in both groups. In the PDE5i group, 2 patients had mild dizziness and back pain, while there was no obvious adverse reaction in Li-SWT group.

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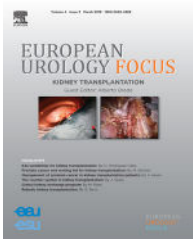

Clinical Case Discussion

A Phase 2 Randomized Trial To Evaluate Different Dose Regimens of Low-intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction: Clinical Trial Update

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Internationally, several trials have investigated the efficacy of low-intensity extracorporeal shockwave therapy (LI-ESWT) for the treatment of erectile dysfunction (ED). These trials have included varying treatment protocols, with the delivery of between 6000 and 18 000 therapeutic shockwaves over a period of 6–10 wk. However, the results have thus far been equivocal [1–4]. It is noteworthy that multiple meta-analyses have demonstrated a significant improvement in ED with LI-ESWT, as measured via International Index of Erectile Function (IIEF) scores [5,6]. Nonetheless, the US Food and Drug Administration (FDA) has not approved LI-ESWT for ED in the USA.

In this clinical trial update, we report the results from a phase 2 clinical trial at the University of Miami investigating LI-ESWT using the MoreNova shockwave generator developed by DirexGroup (Canton, MA, USA). We are specifically investigating treatment protocols requiring fewer shockwaves over a shorter duration of time. The study is listed on ClinicalTrials.gov as NCT03067987. In brief, we recruited 80 men with ED. Our inclusion criteria were: men aged 30–80 yr with a baseline IIEF-EF score of 11–25, total testosterone 300–1000 ng/dl, no history of neurologic or psychiatric disease or pelvic surgery or radiation, no anatomic malformations, and hemoglobin A1c $\leq$7.0%. We did not exclude patients suspected of having psychogenic ED. We used RedCap software to register patients according to an embedded randomization schema developed by Stata (StataCorp, College Station, TX, USA), in which a block design was used to randomize the patients in a 1:1 allocation ratio to receive one of two treatment protocols. Importantly, men already taking a phosphodiesterase-5 inhibitor (PDE5i) were assigned a washout period of 4 wk before beginning the study and remained without PDE5i for the duration of the study.

Group A is undergoing five treatments of 720 shockwaves given over five consecutive days. Group B receives six treatments of 600 shockwaves given every other day over 2 wk. Each group receives a total of 3600 shockwaves. The device delivers electromagnetic shockwaves in linear segments, circumferentially around the penis, with an energy intensity of ~0.09 mJ/mm (Fig. 1). Subjects are assessed using both the IIEF and Erection Hardness Score (EHS) questionnaires at baseline and at 1, 3, and 6 mo after treatment. One-way repeated-measures analysis of variance (ANOVA) is used to calculate within-group differences in response to treatment. We also calculate the percentage of patients who reach the minimal clinically importance difference (MCID), which is an increase in IIEF of $\geq$2 for patients with baseline mild ED (IIEF score of 17–25), and $\geq$5 for patients with baseline moderate ED (IIEF score of 11–16) at the end of 6 mo [7]. Two-way repeated-measures ANOVA is used to determine whether there was a significant difference between groups A and B.

Thus far, 78/80 patients have begun the trial, of whom 21 have completed their treatment, eight in group A and

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Fig. 1 – The MoreNova shockwave generator used for this trial.

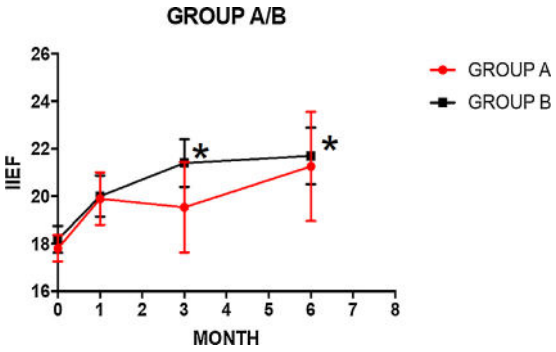

Fig. 2 – International Index of Erectile Function (IIEF) scores for groups A and B at baseline and at 1, 3, and 6 mo after treatment. * Statistically significant change from baseline.

Table 1 – Baseline characteristics for the two study groups.

Parameter	Group A	Group B
Age (yr)	60.8 ± 4.1	48.3 ± 4.3
Testosterone (ng/dl)	514.5 ± 52.0	466.8 ± 34.6
Hemoglobin A1c (%)	5.3 ± 0.1	5.6 ± 0.2
International Index of Erectile Function score	18.3 ± 1.2	17.6 ± 1.0
Erection Hardness Score	2.6 ± 0.3	2.7 ± 0.1

13 in group B. No side effects arising from the treatment were reported. Baseline characteristics are reported in Table 1. For group A there was no significant difference in mean IIEF or EHS scores at the different time points (Fig. 2). Nevertheless, 62.5% of the men achieved MCID according to IIEF scores. For group B, mean IIEF scores differed significantly between the time points. Post hoc tests using Bonferroni correction revealed that LI-ESWT elicited an increase in IIEF scores from baseline beginning at 3 mo (21.4 ± 1.3 vs 17.6 ± 1.0; $p = 0.009$) and continuing at 6 mo (21.8 ± 1.2 vs 17.6 ± 1.0; $p = 0.028$; Fig. 2). Furthermore, mean EHS scores differed significantly between all time points. However, post hoc tests using the Bonferroni correction revealed no statistically significant increases between specific time points. Similar to group A, 61.5% of men in group B achieved MCID. In addition, there was no statistically significant difference between groups A and B.

Preliminary results from our study provide further evidence that LI-ESWT is an effective and durable noninvasive treatment modality for ED. It is important to note that the findings were only significant for the group B treatment protocol; however, this is probably secondary to a greater number of group B patients having completed the trial at the time of this update. Therefore, our preliminary data demonstrate that a reduced treatment protocol with 3600 shockwaves delivered over 2 wk is effective for the treatment of mild to moderate ED. As more patients complete the trial, we will determine whether 1 wk of therapy is equally effective. In addition, since there is no sham group, we are unable to control for any placebo effect. Nonetheless our results are consistent with research in other countries, demonstrating a moderate clinically significant improvement in ED with LI-ESWT.

In conclusion, it has been shown that LI-ESWT is safe and effective as a treatment modality for ED. It has not been approved by the FDA as more studies in the USA are needed. LI-ESWT is best used for mild to moderate ED, is potentially more durable than PDE5i and less invasive than IPPs, and may play a major role in the future of ED treatment.

Conflicts of interest: Ranjith Ramasamy was provided with a MoreNova shockwave device by DirexGroup (the product manufacturer) and received support from the Barton Weiss Men's Health Initiative. The remaining authors have nothing to disclose.

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DOPPLER TEST IN PENIS FLACCID STATE TO ASSESS ERECTILE DYSFUNCTION SEVERITY AND SHOCKWAVE TREATMENT OUTCOMES

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M.D. M. Gatkin, M.D. A. Sopotov

Introduction :

It would be convenient to have a method to evaluate objectively the outcomes of Low Intensity Shockwave Treatment (LIST) or ED. Flow Mediated Dilation was used and recently TRIMIX cavernous injection showed correlation of IIEF improvement with Doppler test. Our objective was to perform an initial Pilot Study in order to check whether we could use Doppler test in the flaccid penis and avoid cavernous injection. From February to September 2017, we treated 36 patient with Vascular Erectile Dysfunction (ED) by Renova Linear Low Intensity Shockwave treatment(LIST) and performed a Ultrasound Doppler procedure test of the cavernous deep penile artery , in the flaccid state .

Aim

We performed the following :
a) Collecting anamnesis data, identifying diseases, filling of IIEF-5 (SHIMS) score .
b) Physical examination for definition of genital status, the presence of possible anomalies and deformities of the external genitalia.
c)Laboratory tests included: determination of fasting glycemia,total Testosterone and PSA levels **d)** Doppler Spectral Power (DPS) of the cavernosal deep penile artery , in the flaccid state , without any pharmacological forced dilatation .

The average age of the patients was 56 years.
The average duration of ED is 11 months.
Average Score IIEF-5 is 13 (Mild to Moderate)
Co-morbidities : arterial hypertension (compensated) , insulin-dependent diabetes mellitus.

Method

The patient was placed on a gynaecological chair, in a warm and relaxed atmosphere (to avoid stress or anxiety which could influence the DSP tests)
Ultrasound Doppler transducer was pointed at the right and left Crus.
Doppler test included peak systolic velocity (PSV)) and Resistivity Index (RI)
We divided the 36 patients into 3 groups, based on the following parameters:

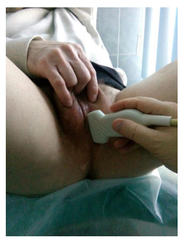
Group I : Mild severity (12 Patients),
Group II: Mild To Moderate (14 patients)
Group III: Severe (10 patients)

Follow up after 4 weeks

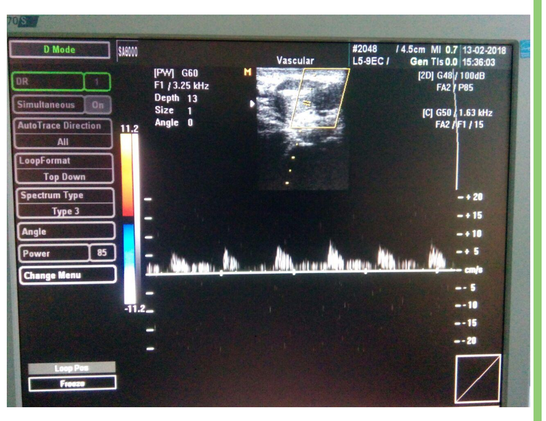
Treatment :

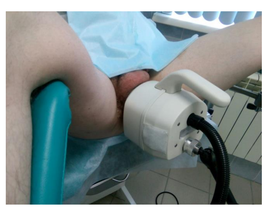
Group I : LIST with the Renova (1 session once a week - 4 weeks);
Group II: Same as I but adding PDE5-I (Tadalafil 5 mg once daily for 28 days).
The follow-up at 1 month
Group III : Same as I but adding PDE5-I (Tadalafil 5 mg once daily for 28 days).

Doppler measurement method



Taking the DSP test from left and right Crura



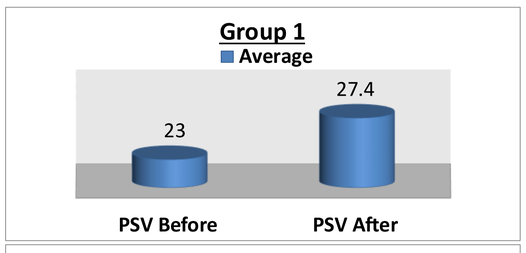


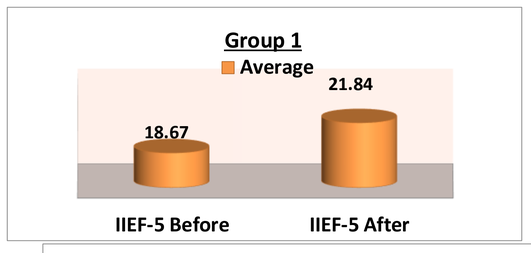
Treatment Procedure with LIST Renova. (left and right side of Crura)

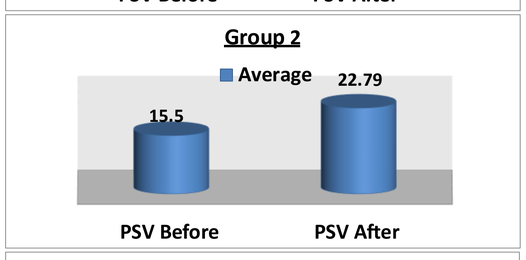
Treatment Procedure with LIST Renova. (left and right side of corpus cavernous)

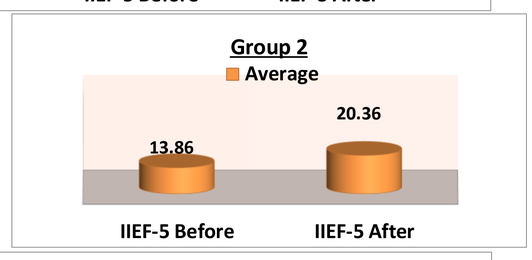
Results

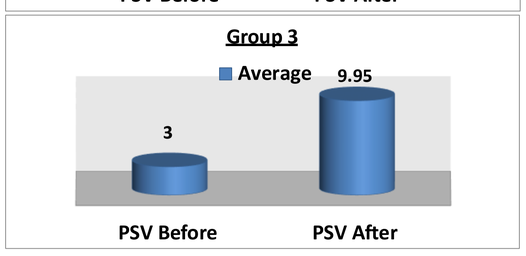
		PSV Before	PSV After	R.I. Before	R.I After	IIEF-5 Before	IIEF-5 After
Group I	Average	23	27.4	0.86	0,87	18.67	21.84
	Standard Deviation	1.6	1,24	0,07	0,07	1.67	5.8
Group II	Average	15.5	22.79	1.01	0.98	13.86	20.36
	Standard Deviation	3.3	2.91	0.04	0.04	1.75	2.21
Group III	Average	3	9.95	0.13	0.98	7.3	12.8
	Standard Deviation	4.9	6	0.35	0.41	2.16	3.19

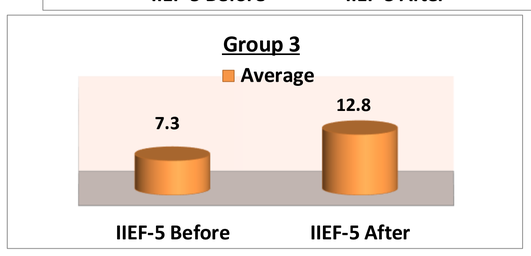


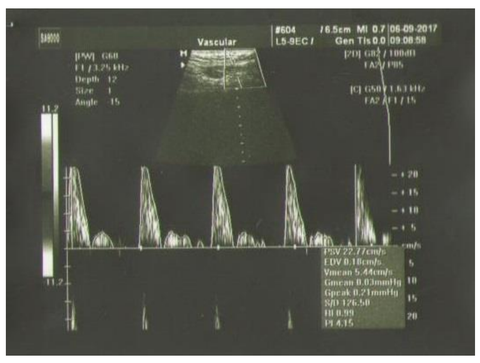




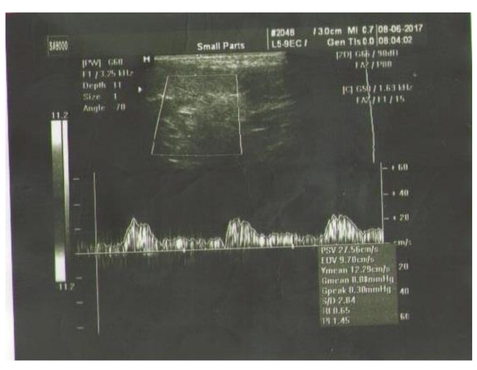




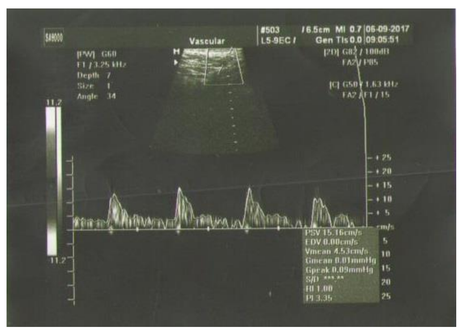




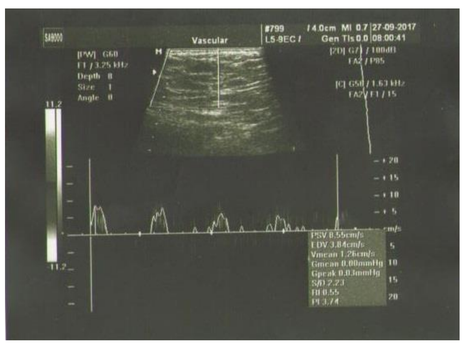
DSP test. PSV 22.7cm/s



DSP test. PSV 27.5cm/s



DSP test. PSV 15.16cm/s



DSP test. PSV 8.55cm/s

Group I had excellent results in IIEF improvement, increase of PSV and reduction of RI.
Similar results in Group II with Tadalafil.
Group III had poor results.

Conclusion

Our experience shows the potential of using DPS and RI in flaccid penis for diagnosis and treatment assessment of results of LIST with Renova
This is an initial Pilot and additional studies have to be performed to asses the potential of this method .

Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis

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Abstract

Context: As a novel therapeutic method for erectile dysfunction (ED), low-intensity extracorporeal shock wave treatment (LI-ESWT) has been applied recently in the clinical setting. We feel that a summary of the current literature and a systematic review to evaluate the therapeutic efficacy of LI-ESWT for ED would be helpful for physicians who are interested in using this modality to treat patients with ED.
Objective: A systematic review of the evidence regarding LI-ESWT for patients with ED was undertaken with a meta-analysis to identify the efficacy of the treatment modality. *Evidence acquisition:* A comprehensive search of the PubMed and Embase databases to November 2015 was performed. Studies reporting on patients with ED treated with LI- ESWT were included. The International Index of Erectile Function (IIEF) and the Erection Hardness Score (EHS) were the most commonly used tools to evaluate the therapeutic efficacy of LI-ESWT.
Evidence synthesis: There were 14 studies including 833 patients from 2005 to 2015. Sev- en studies were randomized controlled trials (RCTs); however, in these studies, the setup parameters of LI-ESWT and the protocols of treatment were variable. The meta-analysis revealed that LI-ESWT could significantly improve IIEF (mean difference: 2.00; 95% confidence interval [CI], 0.99–3.00; $p < 0.0001$) and EHS (risk difference: 0.16; 95% CI, 0.04–0.29; $p = 0.01$). Therapeutic efficacy could last at least 3 mo. The patients with mild- moderate ED had better therapeutic efficacy after treatment than patients with more severe ED or comorbidities. Energy flux density, number of shock waves per treatment, and duration of LI-ESWT treatment were closely related to clinical outcome, especially regarding IIEF improvement.
Conclusions: The number of studies of LI-ESWT for ED have increased dramatically in recent years. Most of these studies presented encouraging results, regardless of variation in LI-ESWT setup parameters or treatment protocols. These studies suggest that LI-ESWT could significantly improve the IIEF and EHS of ED patients. The publication of robust evidence from additional RCTs and longer-term follow-up would provide more confi- dence regarding use of LI-ESWT for ED patients.
Patient summary: We reviewed 14 studies of men who received low-intensity extra- corporeal shock wave treatment (LI-ESWT) for erectile dysfunction (ED). There was evidence that these men experienced improvements in their ED following LI-ESWT.

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1. Introduction

Phosphodiesterase type 5 inhibitors (PDE5-Is) are currently the most widely used treatments for male erectile dysfunction (ED); however, these medications merely treat ED symptoms. They do not correct the underlying penile pathophysiology, such as vascular lesions secondary to diabetes mellitus, structural lesions secondary to trauma, or neurologic injury secondary to prostatectomy, that is responsible for the ED [1]. A novel method to prevent the deterioration of erectile function due to these pathophysiologic processes is desper- ately needed. Based on studies generated from other clinical fields, low-intensity extracorporeal shock wave treatment (LI- ESWT) has been used to treat ED for almost 10 yr, and encouraging results have been reported.

Since the 1980s, when it was first introduced for renal lithotripsy, shock wave therapy has been rapidly adopted all over the world for different disease processes, producing either destructive effects or promoting regenerative effects. The shock wave is a kind of acoustic wave that carries energy and that, when propagating through a medium, can be targeted and focused noninvasively to affect a distant selected anatomic region. When LI-ESWT is applied to an organ, the shock waves interact with the targeted tissues and induce a cascade of biological reactions. This results in the release of growth factors, which in turn triggers neovascularization of the tissue with subsequent improve- ment of the blood supply [2]. LI-ESWT has been used to treat musculoskeletal disorders [3], myocardial infarction [4],

nonhealing wounds [5], and ED [6].

Improvements in both International Index of Erectile Function (IIEF) and Erection Hardness Score (EHS) have been reported after using LI-ESWT for patients with ED. At the beginning of research into LI-ESWT, most studies were retrospective and included few patients. In the past 2 yr, well-designed prospective studies have been conducted and concluded that LI-ESWT is a feasible noninvasive method for improving male ED.

We performed a systematic review of the current body of literature investigating the application of LI-ESWT for ED. Our goal was to analyze the available data to determine the efficacy of LI-ESWT for ED.

2. Evidence acquisition

2.1 Search strategy

We performed a systematic search of PubMed and Embase databases for studies on LI-ESWT and ED. The search terms were *shock wave AND (erectile dysfunction OR IIEF OR EHS)*. We investigated the current studies of LI-ESWT for patients with ED, the therapeutic efficacy of LI-ESWT for patients with ED, and the relationship of therapeutic efficacy and different setup parameters and protocols.

2.2 Inclusion and exclusion criteria

All clinical studies that investigated the efficacy of LI-ESWT for ED were included regardless of study design. Both

randomized controlled trials (RCTs) and cohort studies were included. No limitation was placed on PDE5-I consumption during the LI-ESWT treatment period or on the severity of ED. The follow-up data were abstracted from these studies. If more than one study was published by a medical center, only the last report was included in our review. All literature reviews, editorial comments, background, animal models, and case reports were excluded.

2.3 Data extraction and synthesis

The abstracts were independently reviewed by three authors (Z.L., G.L., T.F.L.) to determine eligibility for inclusion. The basic details of the study, setup parameters of the LI-ESWT machine, treatment protocols, assessment tools, and *p* values were abstracted manually from each of the studies (G.L., Z.L.), and the data were verified (T.F.L.).

2.4 Study outcomes

Fourteen studies were included in our review. Seven studies were RCTs and were included for meta-analysis. The patients were distributed in different areas of the world, and there were no overlaps of populations among the studies. Details are shown in Table 1 and Supplementary table.

2.5 Meta-analysis

The abstracted data were analyzed with RevMan 5.3 software (Cochrane Collaboration, London, UK). The risk of bias in the included studies was assessed by the Cochrane Collabora- tion's tool. The proper effect sizes and statistical analysis methods were chosen according to different data types and evaluation purposes. For continuous variables, weighted mean difference (MD) and a 95% confidence interval [CI] were used. For discontinuous variables, risk difference (RD)

and a 95% CI were used. For the heterogeneity test between studies, the I^2 test was used. The data without significant heterogeneity ($p > 0.05$, $I^2 \leq 50\%$) were analyzed by the fixed-effects model. The data with heterogeneity that could

not be explained were analyzed by the random-effects model. The data that could not be analyzed were described. The results of the meta-analysis are presented in forest plots. Publication bias is presented in funnel plots.

3. Evidence synthesis

A Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) flow chart of screening and selection results is shown as Figure 1.

3.1 The current studies of low-intensity extracorporeal shock wave treatment for erectile dysfunction

A total of 14 studies involving 833 patients were included in this review. All of the studies were published between 2005 and 2015. These studies were performed by different medical centers in different countries. Most of these ED patients had an organic etiology, such as a vascular lesion [7,8], a nerve injury [9], or a lesion of the cavernous body of

Table 1 – Current studies of low-intensity extracorporeal shock wave treatment for erectile dysfunction patients

Study	Year of publication	Country	Disease	Setup of LESW		Protocol of LESW treatment			Follow-up, mo	Evaluation tools for ED	*p* value of IIEF after LI-ESWT	Study design
				Total treatment treatment	No. of sites of courses, wk	No. of pulses each each week	No. of treatments mJ/mm^2	Energy density, treatment				
Olsen et al [19]	2015	Denmark	ED	0.15	3000	1	6	5	1, 3, 6	IIEF-5, EHS	0.67	RCT
Frey A	2015	Denmark	ED after RP	NA	3000	2	3	6	1, 12	IIEF-5	0.0049	Cohort study
Bechara et al [15]	2015	Argentina	ED	0.09	5000	1	4	4	3	IIEF-6, SEP2, SEP3, GAQ	NA	Cohort study
Chung and Cartmill [7]	2015	Australia	ED	0.25	3000	2	4	6	1, 4	IIEF-5, EDITS, overall satisfaction score	<0.05	Cohort study
Pelayo-Nieto et al [8]	2015	Mexico	ED	0.09	5000	1	4	4	1, 6	IIEF, SEP, GAQ	0.013	Cohort study
Hisasue	2015	Japan	ED	0.09	1500	2	5	9	1, 3, 6	IIEF, EHS, MPCC	<0.05	Cohort study
Srini et al [16]	2015	Indian	ED	NA	NA	NA	NA	NA	1, 3, 6, 9, 12	IIEF-EF, EHS, CGIC	0.0001	RCT
Yee et al [18]	2014	Hong Kong	ED	0.09	1500	2	5	9	1	IIEF-ED, EHS,	0.001	RCT
Palmieri et al [10]	2012	Italy	ED + PD	0.25	2000	1	NA	4	3, 6	IIEF, quality of life	<0.05	Cohort study
Vardi et al [17]	2012	Israel	ED	0.09	1500	2	5	9	1	IIEF, EHS, penile blood □ow	0.0322	RCT
Zimmermann et al [14]	2009	Austria	ED + chronic pelvic pain	0.25	3000	1	NA	4	1, 3	IIEF	0.034	RCT
Chitale et al [11]	2010	UK	ED + PD	NA	3000	1	NA	6	3, 6	IIEF	0.249	RCT
Poulakis et al [12]	2006	Germany	ED + PD	0.17	2000	1	NA	5	1, 3, 6	IIEF-5	0.205	RCT
Skolarikos et al [13]	2005	Greece	ED + PD	NA	3000	NA	NA	6	3, 12	IIEF-5	0.06	Cohort study

CGIC = Clinical Global Impression of Change; ED = erectile dysfunction; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; EHS = Erectile Hardness Score; GAQ = Global Assessment Questionnaire; IIEF = International Index of Erectile Function; LI-ESWT = low-intensity extracorporeal shock wave treatment; MPCC = maximal penile circumferential change; NA = not available; PD = Peyronie's disease; RCT = randomized controlled trial; RP = radical prostatectomy; SEP = Sexual Encounter Profile.

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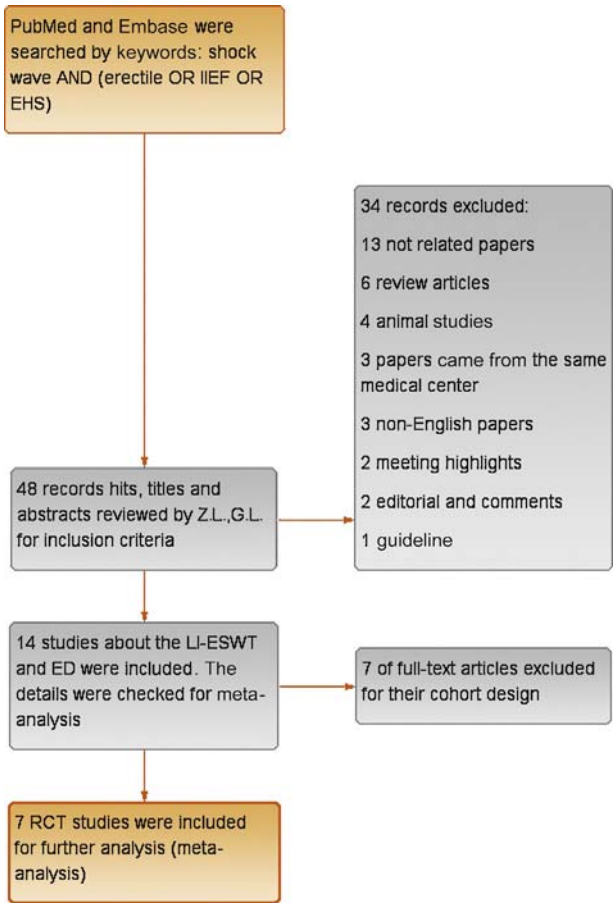


Fig. 1 – The search terms were *shock wave AND (erectile OR IIEF OR EHS)*. Forty-eight records were enrolled. After review, 14 studies about low-intensity extracorporeal shock wave treatment and erectile dysfunction were included. Seven were randomized controlled trials and were included in the meta-analysis.
ED = erectile dysfunction; EHS = Erection Hardness Score; IIEF = International Index of Erectile Function; LI-ESWT = low-intensity extracorporeal shock wave treatment; RCT = randomized controlled trial.

the penis (Peyronie's disease [PD]) [10–13]. One study focused on ED patients with chronic pelvic pain [14]. Most of the studies prohibited the usage of PDE5-Is during the treatment course. Some RCTs even set a washout period for patients who had taken PDE5-I before they started LI-ESWT. Only three studies did not limit the use of PDE5-Is during the treatment [10,11,15]. One of these studies was included for meta-analysis because of its RCT design.

Of the 14 included studies, 7 were RCTs, and the remaining 7 were cohort studies (Table 1). According to the conventions of evidence-based medicine, RCTs provide level 1 evidence, the highest level of evidence. Consequent- ly, the seven RCTs were included for meta-analysis.

The setup parameters of LI-ESWT were different among studies. The energy flux density (EFD) varied from 0.09 to 0.25 mJ/mm^2, and the number of shock wave pulses of each treatment was between 1500 and 5000. In most of the studies, LI-ESWT directed treatment at multiple sites on the penis during each treatment. The treatment course of most studies was not longer than 6 wk, and only three studies had a longer treatment course of 9 wk.

The IIEF was the prevailing assessment tool for ED patients, and all studies in our analysis provided the IIEF before and after LI-ESWT. This made it possible to perform further meta-analysis. Another frequently used assessment tool was the EHS, which was provided by five studies. Other tools, such as the Sexual Encounter Profile, the Global Assessment Questionnaire, maximal penile circumferential change, and the Clinical Global Impression of Change, were not used consistently throughout multiple studies and so were not used for further meta-analysis.

3.2 The quality evaluation of the studies and analysis for the risk of bias

The Cochrane Collaboration's tool was used for assessing the quality of the study and the risk of bias. The RCTs reported that the patients were assigned randomly into LI- ESWT or control groups without describing the process of randomization [16,17]. Most studies did not describe how the physicians were blinded to the study participants. When the patients in the control group received the sham treatment, the LI-ESWT output energy would need to be reduced to zero, thus it would be difficult to keep the physician blinded to this change. Only the study by Yee et al [18] reported the details of how the double blinding was

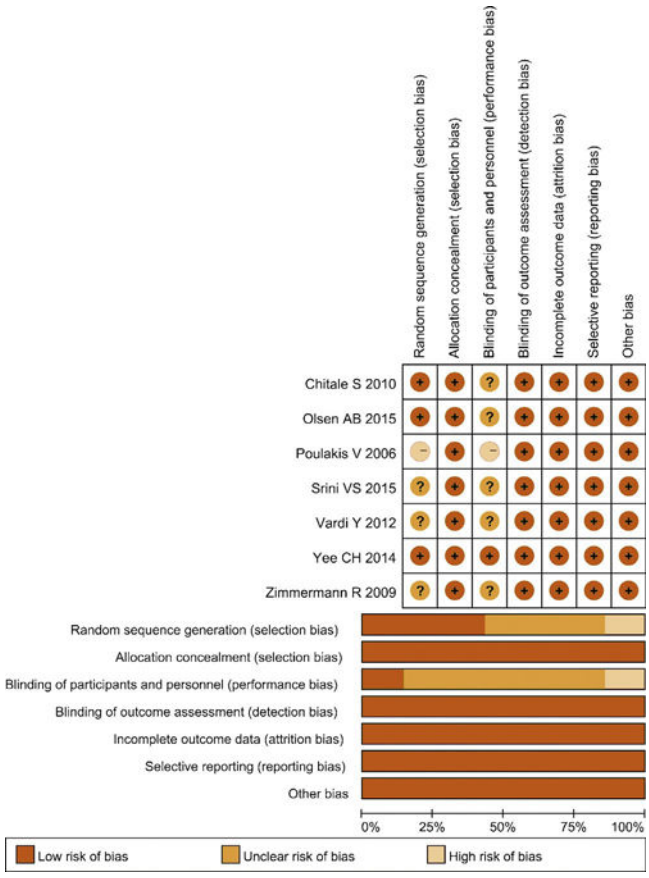


Fig. 2 – There were seven randomized controlled studies included in our meta-analysis. The quality of studies was assessed with the Cochrane Collaboration's tool. This revealed that 57.1% of the studies had an unclear risk of bias in randomization, and only 16.7% of studies had good blinding for both patients and doctors.

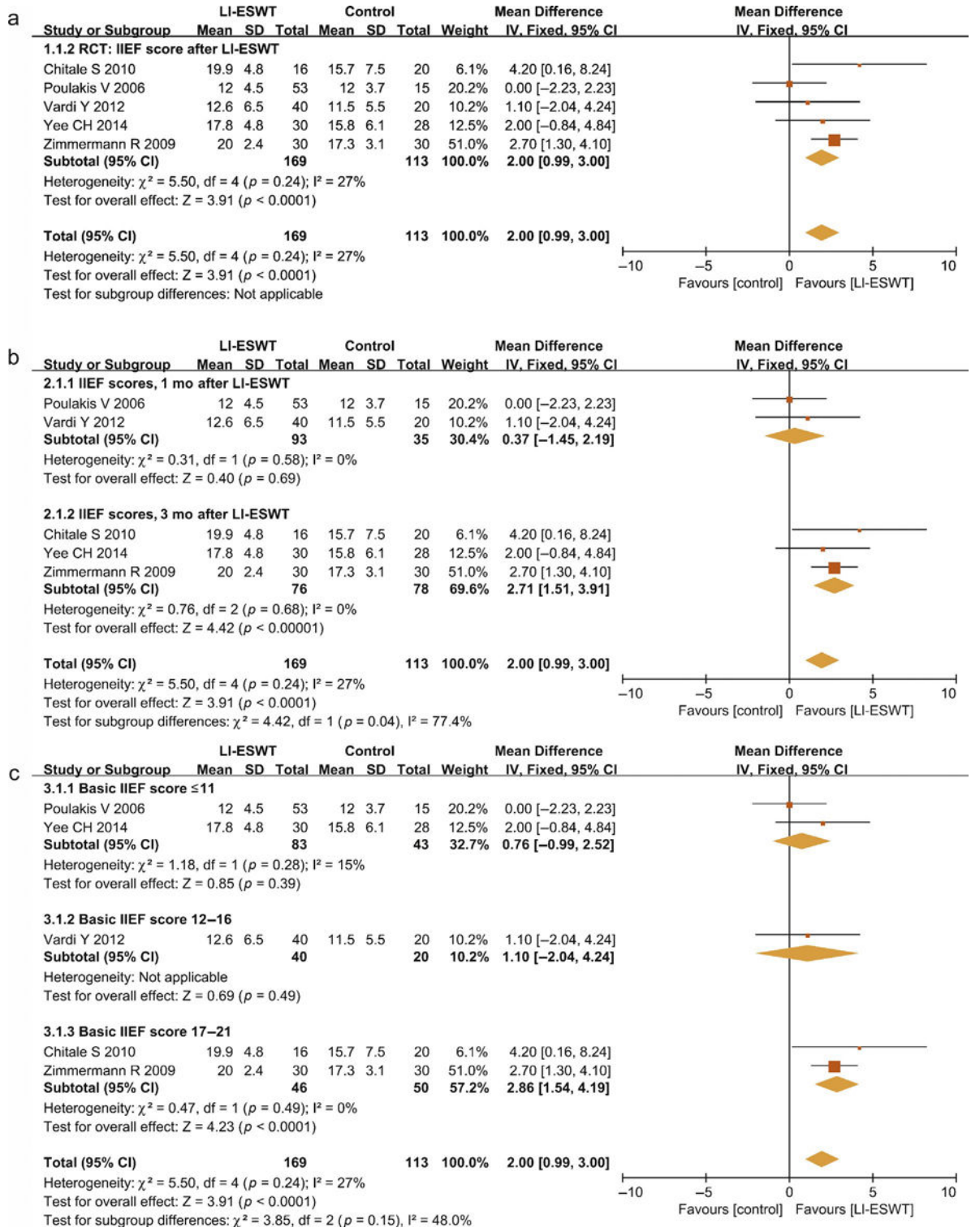


Fig. 3 – Clinical outcomes. (a) Although some studies did not prove that low-intensity extracorporeal shock wave treatment (LI-ESWT) could increase International Index of Erectile Function (IIEF), the meta-analysis results showed that LI-ESWT could improve IIEF significantly (mean difference [MD]: 2.00; 95% confidence interval [CI], 0.99–3.00; $p < 0.0001$). (b) Subgroup analysis: The studies that assessed the IIEF at 1 mo did not reveal a significant improvement (MD: 0.37; 95% CI, S1.45 to 2.19; $p = 0.69$). However, the studies assessing IIEF at 3 mo showed significant improvement (MD: 2.71; 95% CI, 1.51–3.91; $p < 0.0001$). (c) The IIEF in the group with mild erectile dysfunction (ED) increased significantly (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$), but in the severe and moderate groups, it did not ($p = 0.39$ and $p = 0.49$, respectively). (d) The studies of ED patients without any comorbidities revealed a significant increase of IIEF (MD: 2.36; 95% CI, 1.19–3.53; $p < 0.0001$) compared with the studies recruiting ED patients with Peyronie's disease. (e) The IIEF of patients in the group with LI-ESWT plus phosphodiesterase type 5 inhibitors improved more significantly (MD: 4.20; 95% CI, 0.16–8.24; $p = 0.04$).

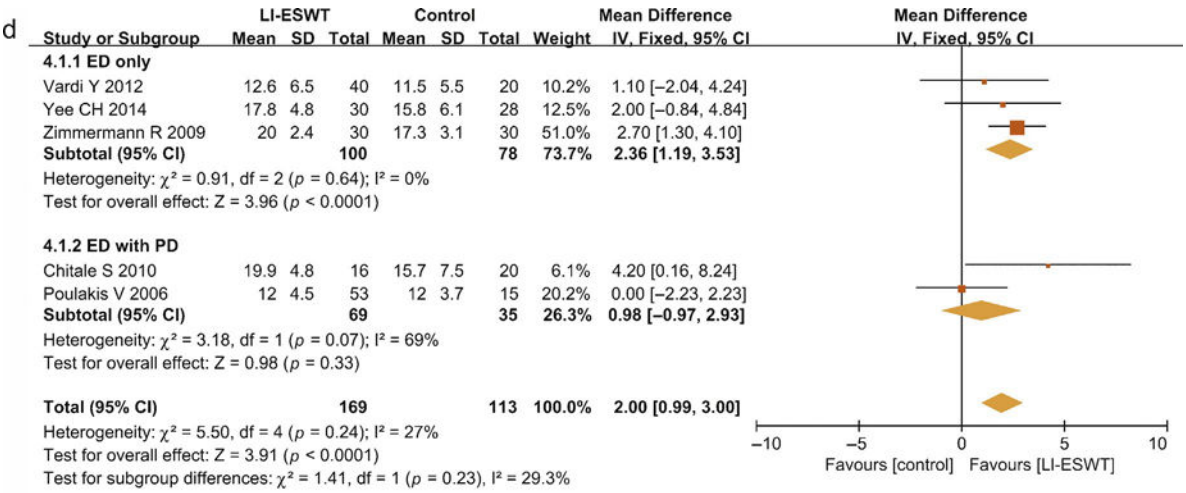
CI = confidence interval; ED = erectile dysfunction; IIEF = International Index of Erectile Function; IV = inverse variance; LI-ESWT = low-intensity extracorporeal shock wave treatment; PD = Peyronie's disease; PDE5-I = phosphodiesterase type 5 inhibitor; RCT = randomized controlled trial; SD, standard deviation.

ensured. Figure 2 shows that 57.1% studies had an unclear risk of bias in randomization and that only 16.7% of studies had good blinding for both patients and doctors.

3.3 The evaluation of the therapeutic efficacy of low-intensity extracorporeal shock wave treatment for patients with erectile dysfunction

The IIEF, the prevailing assessment tool for ED patients, was available for abstraction from five RCTs. The data included mean value and standard deviation of the IIEF and the number of patients in the treatment and control groups. The studies by both Yee et al [18] and Poulakis et al [12] concluded that the IIEF did not increase significantly in the treatment group compared with the control group; the p values were 0.156 and 0.205, respectively. The remaining three RCTs reported that the IIEF increased significantly in the LI-ESWT group compared with the control group [11,14,17]; the p value was <0.05. The overall meta-analysis of the data revealed that LI-ESWT improved the IIEF significantly overall in the treatment groups (MD: 2.00; 95% CI, 0.99–3.00; $p < 0.0001$) (Fig. 3a).

Subgroup analysis was performed. Figure 3b shows that Poulakis et al [12] and Vardi et al [17] assessed IIEF at 1 mo after LI-ESWT and that the IIEF did not increase significantly (MD: 0.37; 95%CI, —1.45 to 2.19; $p = 0.69$). Three other studies, however, assessed IIEF at 3 mo after treatment and found that the IIEF increased significantly (MD: 2.71; 95% CI, 1.51–3.91; $p < 0.0001$). In Figure 3c, the studies were divided into three groups by the IIEF before LI-ESWT—Ç11, 12–16, and 17–21—corresponding to severe, moderate, and mild ED, respectively. The meta-analysis showed that the IIEF of patients in the mild ED group increased significantly after LI-ESWT (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$). The patients in the severe and moderate groups did not show a significant increase in IIEF ($p = 0.30$ and $p = 0.49$). In Figure 3d, the studies were divided into two groups: the ED group and the ED with PD group. The subgroup analysis showed that the patients in the ED group improved significantly in IIEF (MD: 2.36; 95% CI, 1.19–3.53; $p < 0.0001$). The patients in the ED with PD group had no significant improvement in IIEF ($p = 0.33$). Finally, the studies were divided into two groups by usage of PDE5- Is. Figure 3e shows that the IIEF increased in both groups but



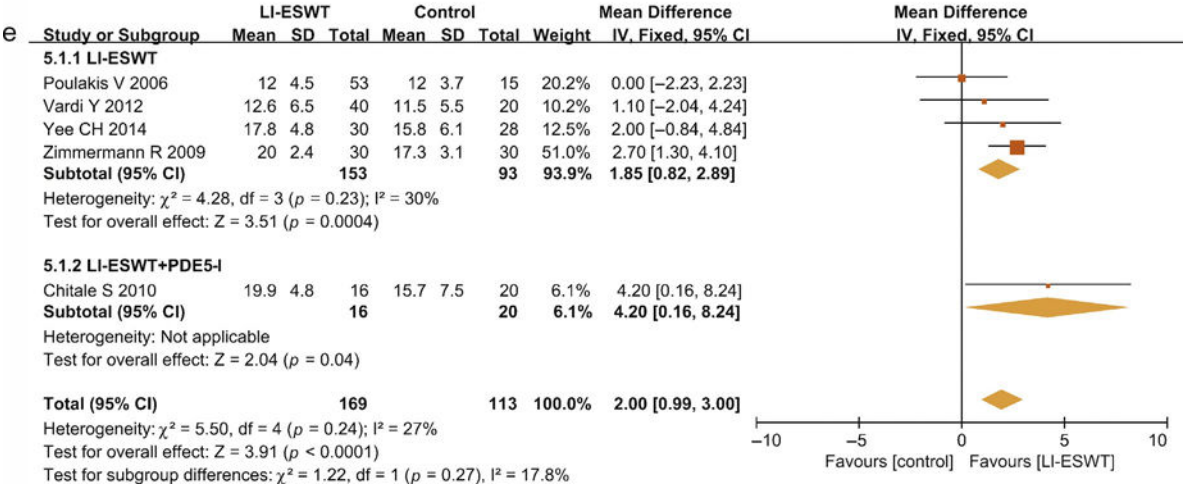


Fig. 3. (*Continued*).

increased more significantly in the group with LI-ESWT combined with PDE5-I use (MD: 4.20; 95% CI, 0.16–8.24;

$p = 0.04$).

These results indicate that LI-ESWT increased the IIEF and improved the erectile function of ED patients. Accord- ing to the results of the current studies, the patients treated by LI-ESWT developed a good therapeutic effect by 3 mo. The patients who had mild or moderate ED and the ED patients who had no comorbidities benefited more from LI- ESWT than the patients with severe ED or with comorbid- ities.

Different LI-ESWT setup parameters, such as EFD and number of pulses, and different treatment protocols, including treatment frequency and length of course, resulted in differences in reported efficacy. The studies were divided into three groups according to EFD. The results

(Fig. 4a) showed that the studies using the highest EFD (>0.2 mJ/mm^2) reported significantly increased IIEFs (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$). The improvement of IIEF in this ED and PD subgroup was partially due to the

improvement of PD. After excluding this subgroup, we found that the improvement in IIEF was better in the group with EFD 0.09 mJ/mm^2 compared with EFD 0.1–0.2 mJ/ mm^2, although neither group reached statistical signifi- cance. Next, the studies were divided into two groups based on the number of shock waves delivered during each treatment. The results (Fig. 4b) showed that the studies administering more shock waves reported a significant increase in IIEF (MD: 2.86; 95% CI, 1.54–4.19' $p < 0.0001$) compared with the studies delivering fewer shock waves. To

compare different durations of treatment, the studies were divided into two groups according to duration of treatment of LI-ESWT. Figure 4c shows that the studies with a treatment course of <6 wk reported a significant increase in the IIEF (MD: 2.11; 95% CI, 0.98–3.25; $p = 0.0003$).

These results suggest that different setup parameters and different treatment protocols of LI-ESWT have sub- stantial influence on therapeutic efficacy. In summary, within the scope of this review, lower energy density,

increased number of pulses, and shorter treatment courses of <6 wk resulted in better therapeutic efficacy.

The EHS data were available for abstraction from four

RCTs. In the studies by Yee et al [18] and Olsen et al [19], EHS was reported at 3 mo after LI-ESWT. In the study by Yee et al, the EHS did not increase significantly. In subgroup analysis (Fig. 5), at 1 mo after LI-ESWT, the EHS increased significantly in three studies (RD: 0.47; 95% CI, 0.38–0.56; $p < 0.00001$). EHS did not improve as significantly after

3 mo as it did after 1 mo, but it still increased with statistical significance (RD: 0.16; 95% CI, 0.04–0.29; $p = 0.01$). These results indicate that LI-ESWT improves the erectile hard- ness of the penis for ED patients, especially at 1 mo after treatment, and that this improvement lasts for at least 3 mo.

3.4 Discussion

LI-ESWT has been used as a novel therapy for ED patients for the past 10 yr. Clinical studies and reports focused on this topic have increased dramatically in past 5 yr, especially in

2015. This implies that LI-ESWT as a therapeutic method for patients with ED has been increasingly adopted by both physicians and patients.

The IIEF is a patient-reported assessment that is purely subjective. In this review, we found that in some studies, patients in the control group also reported improvement of the IIEF [12,17,18]; however, patients in the LI-ESWT group improved more significantly than those in the control group. The range of improvement in the IIEF was from 5.3 to

7.6 points for the LI-ESWT group in our analysis [14,18]. It is undeniable that some studies revealed improvement with statistical significance; however, this improvement may have no significant clinical value. The minimal clinically important difference (MCID) of IIEF better assesses the true clinical efficacy of LI-ESWT. We recommend that, in the future, investigators use the MCID of IIEF as a more accurate and meaningful tool for evaluating the effect of LI-ESWT in the treatment of patients with ED [20].

The clinical outcome of LI-ESWT is closely related to the energy delivered to the target unit area, or EFD. The EFD used varied from 0.09 to 0.25 mJ/mm^2 among the studies included in our analysis. Based on this review, we could not determine the best EFD for ED therapy. Studies investigat- ing the use of LI-ESWT for various regenerative purposes have used varying energy densities. An investigation by Goertz et al showed that an energy density of 0.04 mJ/mm^2 could accelerate angiogenesis for skin burns [21]. The study by Abe et al revealed that an energy density of 0.1 mJ/mm^2 for a rat model of acute myocardial infarction suppressed ventricular remodeling and had a good anti-inflammatory effect [22]. The study by Tara et al found that an energy density of 0.11–0.21 mJ/mm^2 could encourage therapeutic angiogenesis for human ischemic tissues [23]. Ioppolo et al reported that for some musculoskeletal disorders, energy density could be increased to 0.3 mJ/mm^2 [24]. In the current review, most of the included studies used an energy density of 0.09 mJ/mm^2, which Vardi et al first reported in 2010 [17]. Most subsequent studies adopted this EFD and presented encouraging results. Additional studies and a longer duration of treatment are needed to establish whether therapeutic efficacy is positively correlated with energy density.

Some studies included in our review concluded that the biological efficacy of LI-ESWT was dosage dependent [25]. It seemed that more pulses would bring better biological efficacy. With this hypothesis in mind, some studies adopted multiple treatment sites, more frequent treatments, and longer courses of treatment. Meta-analysis showed that 3000 pulses per treatment brought more improvement than 1500 or 2000 pulses per treatment; however, more frequent treatment and longer treatment course did not improve erectile function significantly. The optimal treatment protocol remains to be defined. Whether there may be a plateau stage of treatment remains uncertain and requires further investigation. In addition, based on the premise that more treatment sites would produce better results, shock waves were delivered to multiple sites, such as the dorsal surface, both sides, and both crus of the penis. It seemed that more sites treated

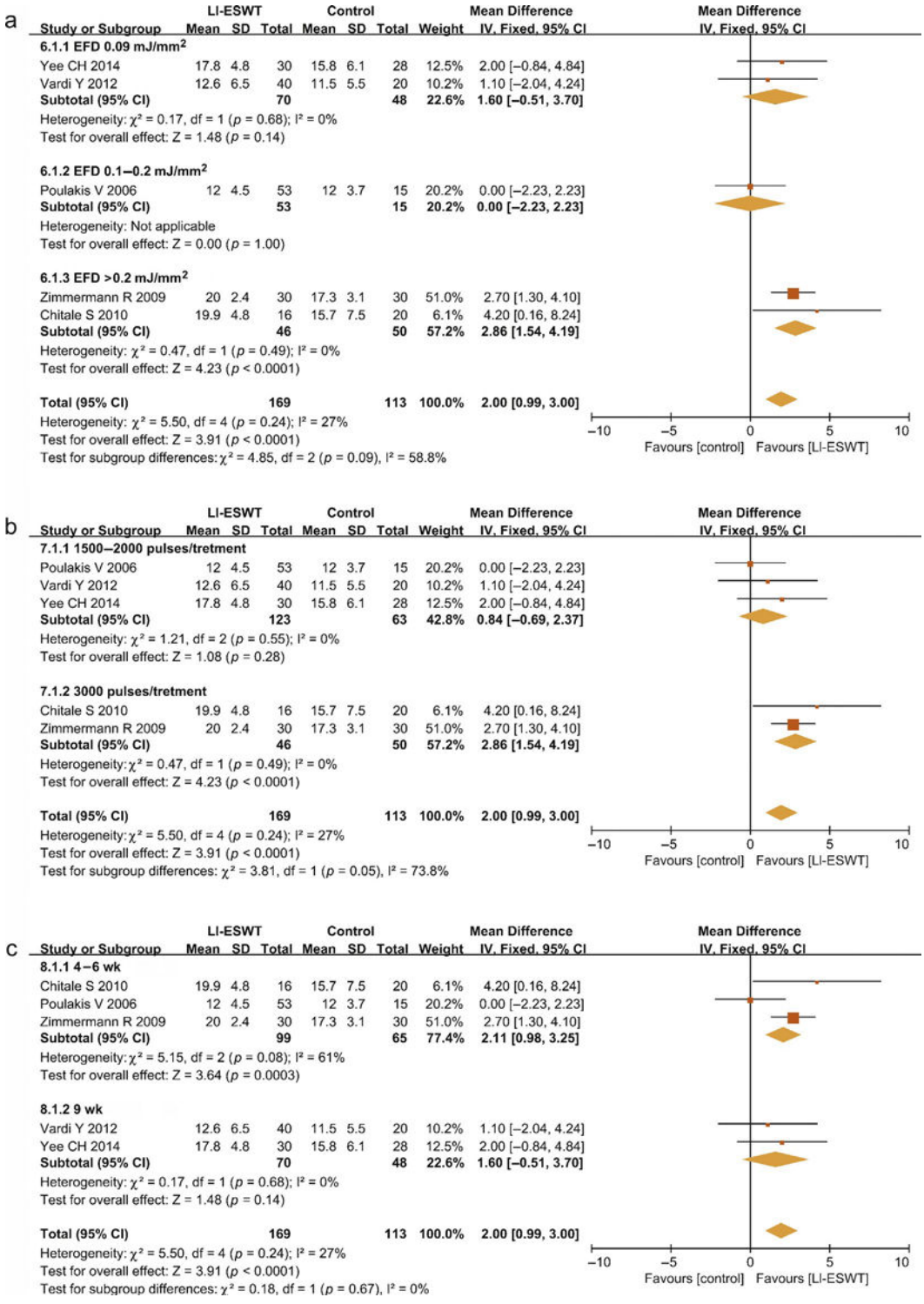


Fig. 4 – Relationship of energy dosage and treatment procedures. (a) The studies using higher energy flux density (EFD; >0.2 mJ/mm^2) resulted in significantly increased International Index of Erectile Function (IIEF; mean difference [MD]: 2.86; 95% confidence interval [CI], 1.54–4.19; $p < 0.0001$) in the erectile dysfunction (ED) and Payronie's disease groups. In ED-only groups, the improvement of IIEF was better for the group with EFD 0.09 mJ/mm^2 compared with EFD 0.1–0.2 mJ/mm^2, although it did not reach statistical significance. (b) The studies delivering more shock waves per treatment resulted in an increased IIEF (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$). (c) The studies with total course of treatment <6 wk revealed significant IIEF increase (MD: 2.11; 95% CI, 0.98–3.25; $p = 0.0003$) versus studies with longer courses of treatment (9 wk).
CI = confidence interval; EFD = energy flux density; IV = inverse variance; LI-ESWT = low-intensity extracorporeal shock wave treatment; SD, standard deviation.

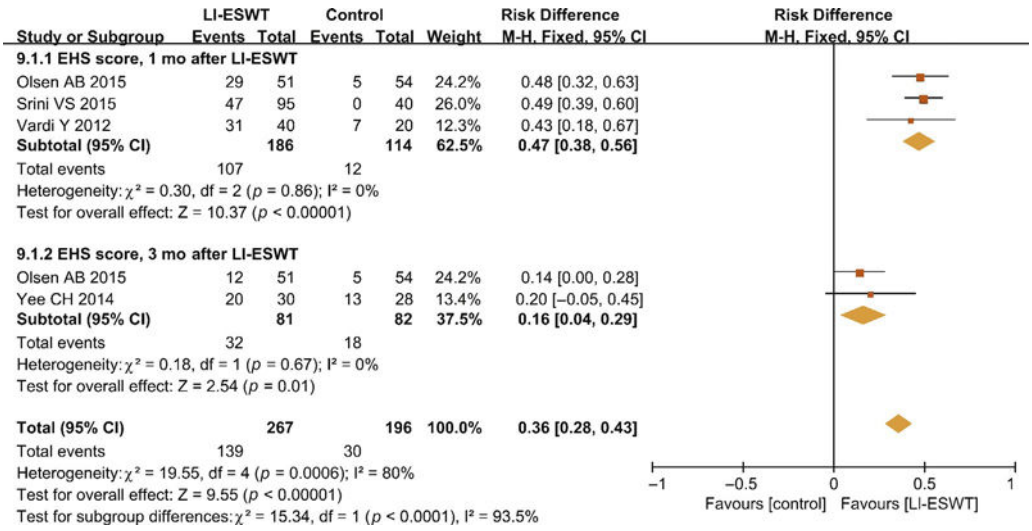


Fig. 5 – The Erection Hardness Score (EHS) increased significantly (risk difference [RD]: 0.47; 95% confidence interval [CI], 0.38–0.56; $p < 0.00001$) at 1 mo after treatment. Three months later, EHS slightly decreased but still improved with statistical significance (RD: 0.16; 95% CI, 0.04–0.29; $p = 0.01$). CI = confidence interval; EHS = Erection Hardness Score; LI-ESWT = low-intensity extracorporeal shock wave treatment; M-H = Mantel-Haenszel.

might produce better results. It is well known that shock waves can propagate 3–5 cm in human tissue [26]. It remains to be determined if it is necessary or beneficial to deliver treatment to multiple sites. This is also an area of potential future investigation.

The underlying mechanism of action of LI-ESWT is currently under investigation. According to recent reports, the effect is primarily related to the stimulation of cell proliferation, tissue regeneration, and angiogenesis [27,28]. In 2013, Qiu et al explored the therapeutic effect of LI-ESWT on a diabetic animal model and demonstrated that LI-ESWT can partially resolve diabetes mellitus–associated ED by promoting regeneration of neuronal nitric oxide synthase (nNOS)–positive nerves, endothelium, and smooth muscle in the penis [28]. Meanwhile, Liu and colleagues reported their results after treatment of a rat model of ED with LI-ESWT. The expression of some proteins, such as *a*-smooth muscle actin, von Willebrand factor, nNOS, and vascular endothelial growth factor, was upregulated [29]. In 2013, Siegfried and colleagues reported that LI-ESWT could stimulate the regeneration of injured nerve fibers. They believed that the potential mechanism of LI-ESWT was enhanced by neovascularization in the regenerating nerve and that VEGF and transforming growth factor *b* were associated with the process [30]. Very recently, it was reported that LI-ESWT improved erectile function in a rat model of pelvic neurovascular injury. Penile tissue compo- nents, especially vascular and neuronal tissue, demonstrated improved recovery after LI-ESWT therapy [27].

Several weaknesses contributed to the quality of the data provided. As shown in Table 1, five of seven studies published in 2015 were cohort studies. It is undeniable that these cohort studies have good study designs and robust data collection; each has an appropriate sample size and clear comparison. In evidence-based medicine, however, the evidence level of cohort studies is level 2, and thus they have lower power than RCTs, which provide level

1 evidence. To evaluate the efficacy of LI-ESWT more accurately, more RCTs with good study designs are needed. In addition, even in the RCTs that were included in this review, there were still some deficiencies. The details of randomization, the implementation of double blinding, the details of the treatment protocol, and the data from long- term follow-up are fundamental factors for assessing the quality of a study. As shown in Figure 2a and 2b, we found that most of the included RCTs did not describe the details of randomization or blinding, and the potential biases involved are unclear. If bias existed, it would have a great impact on the interpretation of the meta-analysis.

Most of the studies focused on the improvement of erectile function after LI-ESWT. Nevertheless, the potential impact of factors related to ED, such as age, hypertension, diabetes, hyperlipidemia, and coronary artery disease, are not discussed. Only four RCTs in our analysis provided the age data comparing the patients in the treatment and control groups [12,17–19]. No further investigation was performed to determine the influence of age on the efficacy of LI-ESWT. Three RCTs provided the profile of patient comorbidities, such as hypertension, diabetes, hyperlipid- emia, and coronary artery disease, but no further information was provided about the relationship between the clinical outcome of LI-ESWT and those comorbidities [17– 19]. In the future, more RCTs with stratification of age and comorbidities will help determine the influence of these factors on the efficacy of LI-ESWT for patients with ED.

With the aim of determining the efficacy of LI-ESWT alone and to avoid confusion, most of the included studies prohibited the usage of PDE5-Is during shock wave treatment. Nevertheless, because the goal of treatment is to maximize improvement of erectile function, a combina- tion of LI-ESWT and PDE5-Is may be the best choice. Gruenwald et al found that LI-ESWT effectively converted PDE5-I nonresponders to responders [31], and our results (Fig. 3e) support the use of LI-ESWT and PDE5-Is in

combination. Additional clinical trials are needed to further investigate this clinical question.

4. Conclusions

In recent years, LI-ESWT as a therapy for ED has attracted extensive attention. Studies of this topic have increased sharply, and most of these studies reveal encouraging results, such as improved IIEF and EHS and an effect that lasts up to 3 mo. The setup parameters and the treatment protocols are important for the therapeutic effects of LI-ESWT for patients with ED. The mechanism of LI-ESWT is to improve or even reverse the pathologic damage of tissue that causes ED. Additional studies are needed to explore the influences of age and comorbidities on response to LI-ESWT and to define the effects of LI-ESWT in combination with PDE5-Is. From our review, it is clear that LI-ESWT may have the potential to be the first-choice noninvasive treatment for patients with ED.

Author contributions: Tom F. Lue had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lue, Lin.
Acquisition of data: Lin, Lu, Lee, Wang.
Analysis and interpretation of data: Lu, Lee, Lin.
Drafting of the manuscript: Lu, Lin, Reed-Maldonado.
Critical revision of the manuscript for important intellectual content: Lin, Reed-Maldonado, Lue.
Statistical analysis: Lu, Lin.
Obtaining funding: Lue, Lin.
Administrative, technical, or material support: Wang, Lu.
Supervision: Lue.
Other (specify): None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j. eururo.2016.05.050.

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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

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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 ¼64.8 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

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]

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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 ¼450 bar) have been implemented in the treatment of urolithiasis, medium-intensity shockwaves (pressure ¼200 bar) in the treatment of arthralgia, tendinitis, and bursitis, and more recently LISWT (pressure ¼80 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 evalu- ation 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.

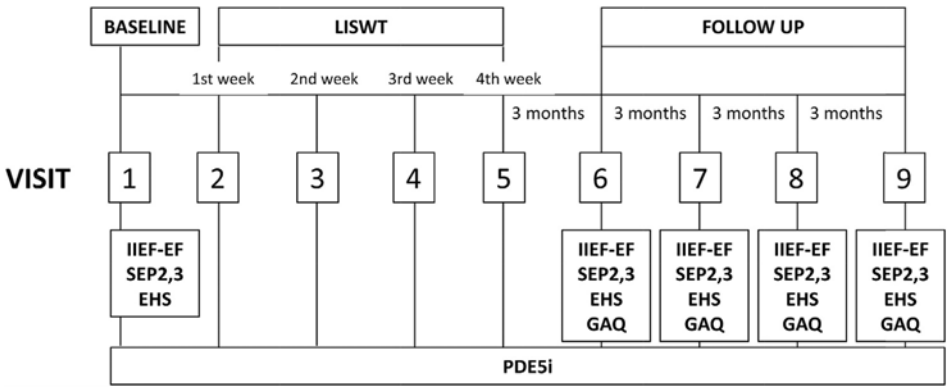


Figure 1. Study flowchart. EHS ¼Erection Hardness Scale; GAQ ¼Global Assessment Question; IIEF-EF ¼International Index of Erectile Function erectile function domain; LISWT ¼low-intensity shockwave therapy; SEP2 and 3 ¼questions 2 and 3 of Sexual Encounter Profile.

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 ¼24)	Non-responders (n ¼16)	*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, [redacted])			
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 [redacted] 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.

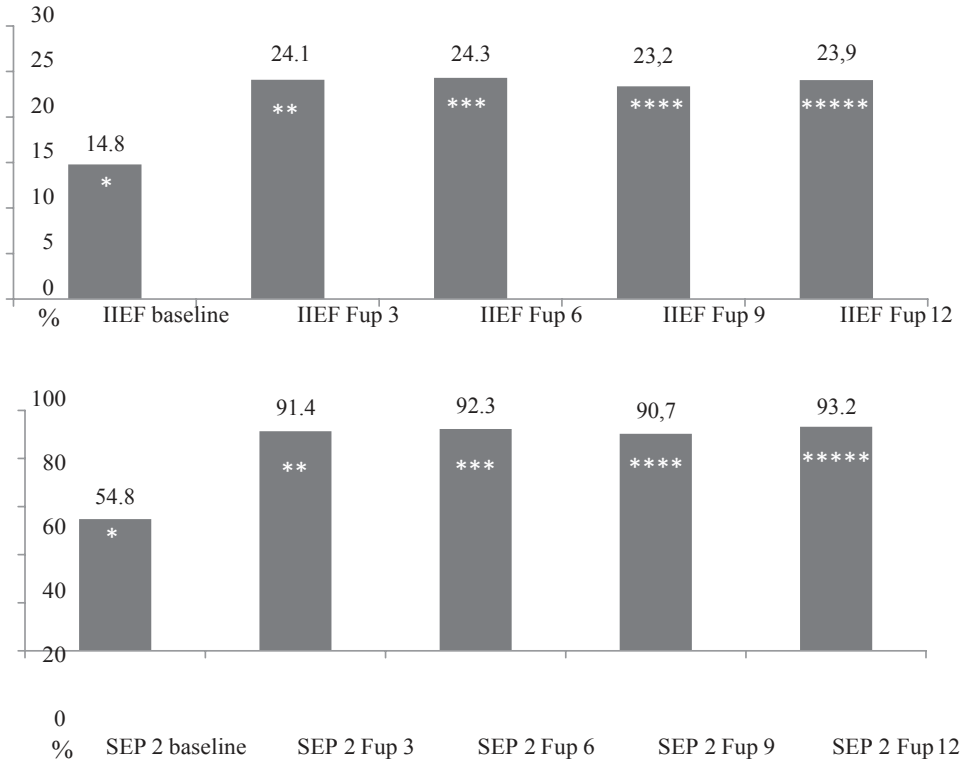
Most randomized, double-blinded, sham-control trials have reported the efficacy of LISWT in patients with ED.[32e34]

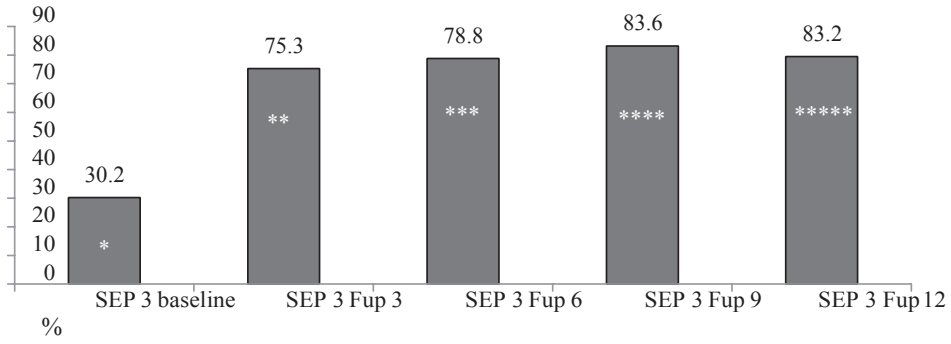
Vardi et al[32] presented the first randomized, double-blinded, sham-control trial that demonstrated that LISWT had a posi- tive short-term clinical and physiologic effect on the erectile function of men who respond to oral PDE5i therapy. They found a significantly greater increase in the IIEF-EF score 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 ¼8.2 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 ¼24). *P* < 0.05 by Friedman test (*baseline vs **Fup 3, vs ***Fup 6, vs ****Fup 9, vs *****Fup 12). Fup 3 ¼3-month follow-up; Fup 6 ¼6-month follow-up; Fup 9 ¼9-month follow-up; Fup 12 ¼12-month follow-up; IIEF-EF ¼International Index of Erectile Function erectile function domain; SEP2 and 3 ¼questions 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 differences 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 effi- cacy 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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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

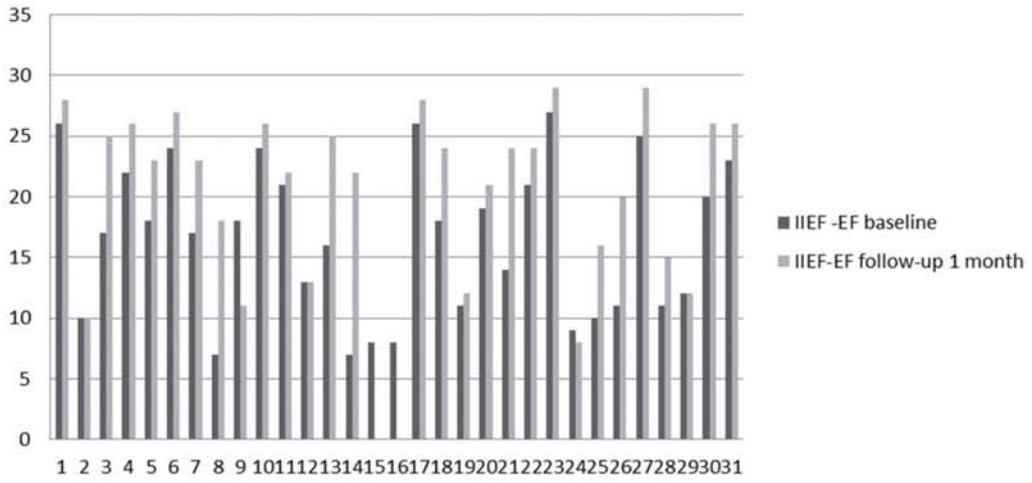


Figure 2 - IIEF-5 score at baseline and after 3 month follow-up

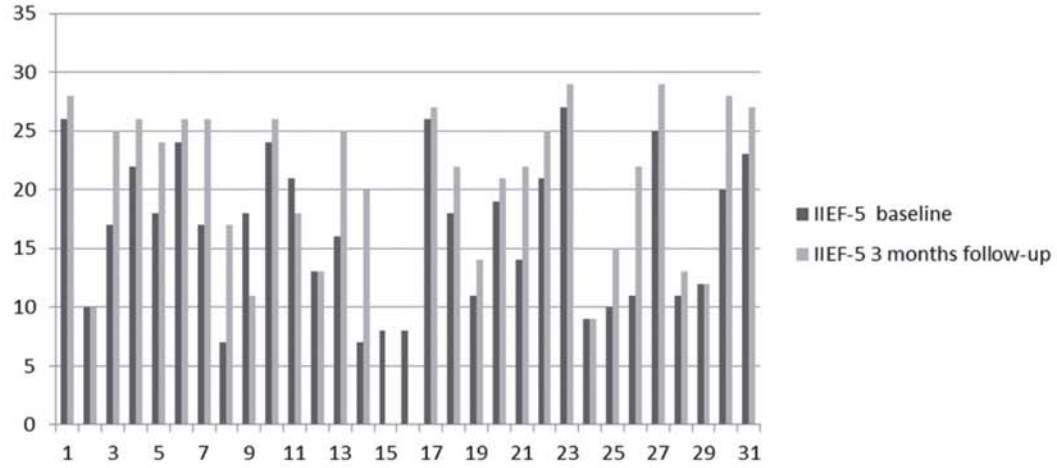
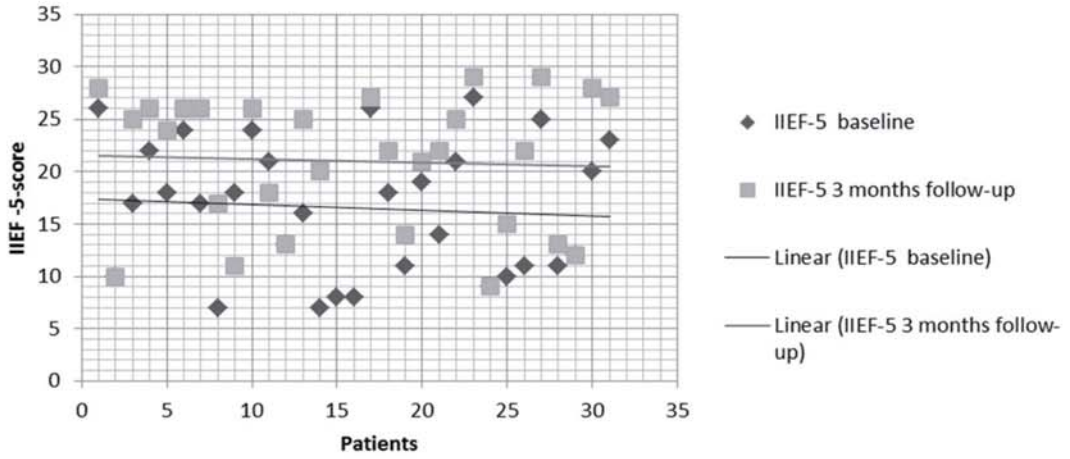


Figure 3 - Dispersion date IIEF score baseline and 3 month follow-up



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.

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.

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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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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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/mm². 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

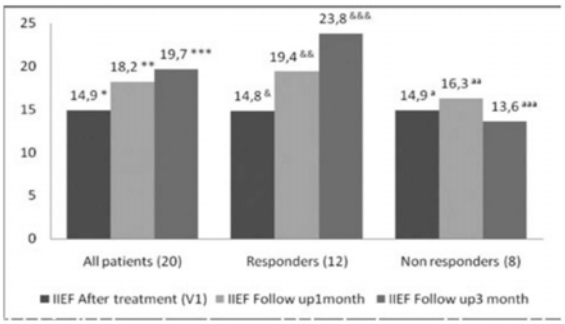
Erectile dysfunction, a highly prevalent complaint in men over 50, can almost always be traced back to a history of vascular risk factors (19).

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.

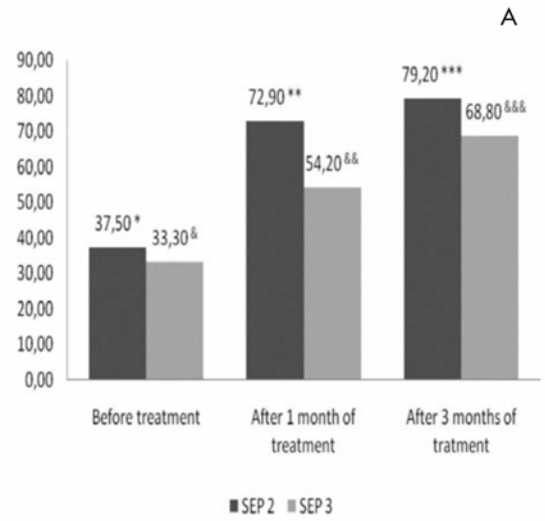
It is worth pointing out that, unlike the group of patients presented by Vardi et al (6), those patients included in this presentation were only non-responder patients to oral therapy at the maximum dose, and only after having indicated and verified that all optimization indications had been fulfilled. 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.

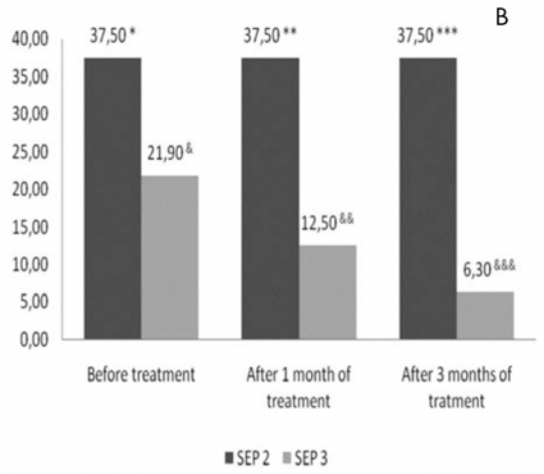
As mentioned before, the device selected for our trial (Renova NR), is manufactured by Direx Group, and involves a special LI-ESWT technology. This operator-independent system is fitted with a transducer that is capable of delivering shock waves all along the penis, spanning an area of 70mm and thus 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

Y Reisman[1], A Hind[2], A Varaneckas[3] and I Motil[4]

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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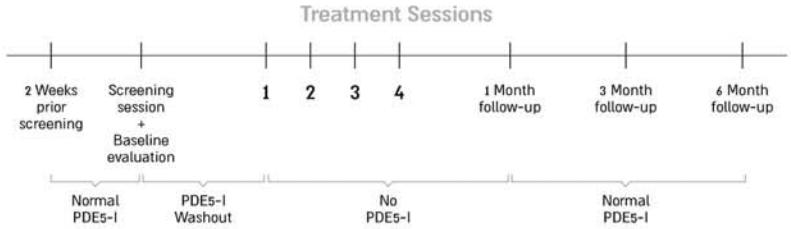

Figure 1. The use of PDE5-I throughout the study.

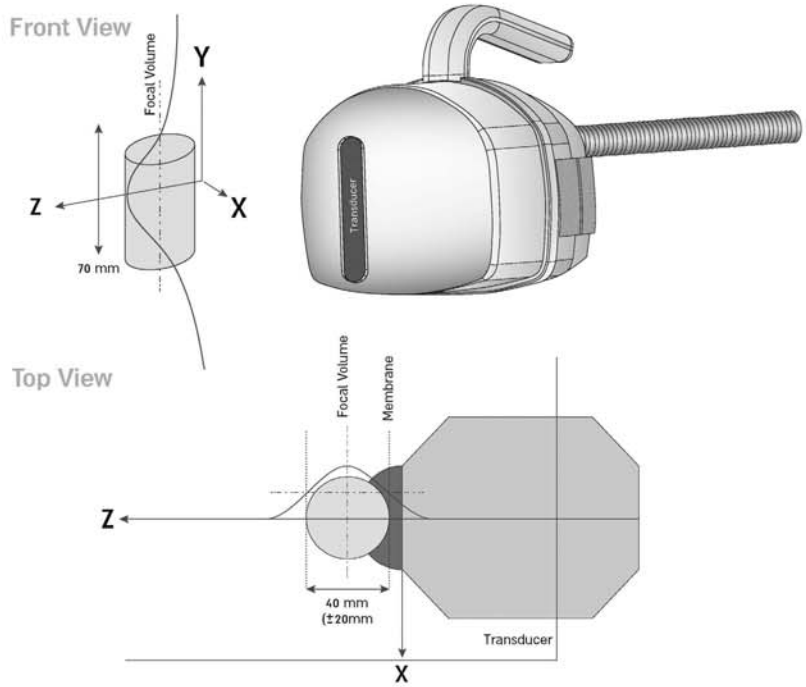

Figure 2. Qualitative view of the shockwave intensity changes.

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.

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.

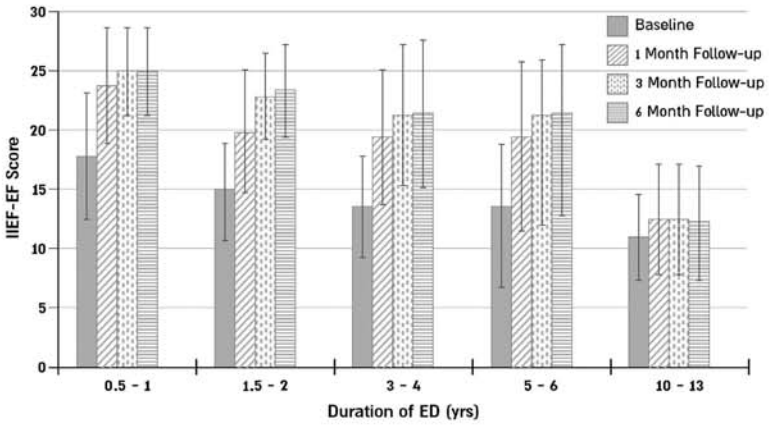

Figure 4. The change in the IIEF–EF score between baseline and the follow-ups at 1, 3 and 6 months post treatment, in accordance with the ranges of ED duration. The error bars indicate the s.d. of each group.

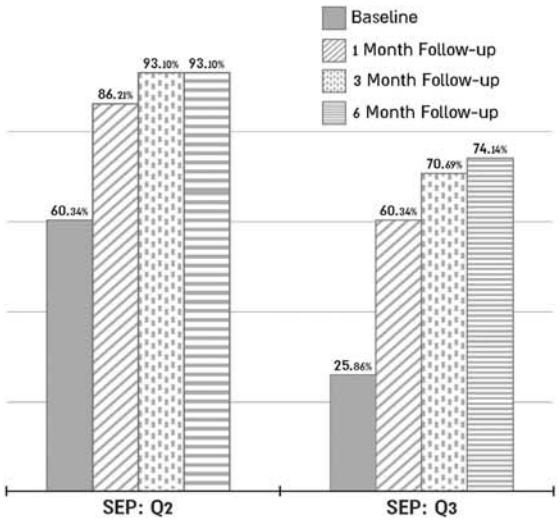

Figure 5. the average results of SEP questions 2 and 3 at the baseline and at each follow-up. The percentages represent the fraction of patients who have answered 'Yes' to each of these questions.

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.

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.

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.

16th CONGRESS OF THE EUROPEAN SOCIETY FOR SEXUAL MEDICINE
joint by the 12th Congress of the European Federation of Sexology
29 January – 1 February 2014 | Istanbul, Turkey

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.

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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.

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.

Middle East Society for Sexual Medicine

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.

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.

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

LSWT – CLINICAL DATA AND REPORTS

	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.