Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population

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SRINI VS, REDDY RK, SHULTZ T, DENES B. Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. *Can J Urol* 2015;22(1):7614-7622.

Introduction: *Erectile dysfunction (ED) has been shown to be associated with a number of physical conditions and affects not only physical but also psychosocial health. Currently oral, on-demand phosphodiesterase type 5 inhibitors (PDE5i) are preferred first line treatment. Though effective, these drugs have limitations and are associated with significant non-compliance, side effects and do not reverse the underlying pathology. Non-invasive low intensity shockwave therapy (LISWT) has been shown to significantly improve erectile function in men previously PDE5i dependent. We describe our experience and results with this therapy in an Indian population of men with ED. This study assessed the efficacy of low intensity extracorporeal shockwave therapy (LI-ESWT) on Indian men with organic ED who had previously responded to PDE5i.*

Materials and methods: *All the patients underwent a 1 month PDE5i washout period. Men were randomized to receive either 12 sessions of LI-ESWT (n = 95) or placebo/sham therapy (n = 40). Before the first treatment, erectile function and penile hemodynamics were assessed to substantiate a vascular etiology for the ED. Outcomes were assessed using Erection Hardness Score (EHS), International Index of Erectile Function-Erectile Function Domain (IIEF-EF domain) and Clinical Global Impression of Change (CGIC) scores at 1, 3, 6, 9 and 12 months post-treatment.*

Results: *We found a significant increase in the EHS and IIEF-EF Domain scores from visit 1 to follow up 5 (12 months) in the treated group compared to the placebo group. By 1 month after treatment there were highly significant differences between the LI-ESWT and placebo groups ($p < 0.0001$). Out of 60 men in the LI-ESWT group who completed the study, 47 (78%) men at FU1 and 43 (71%) at FU5 who were initially unable to achieve spontaneous erections hard enough for penetration (EHS ≤ 2) were able to do so (EHS ≥ 3) compared to none in the placebo group. The treatment was well tolerated and none of the men experienced treatment related discomfort or reported any adverse effects from the treatment.*

Conclusions: *In this double-blind, placebo-controlled study, LI-ESWT demonstrated a positive long term clinical effect with improvement in erectile function of Indian men with vasculogenic ED who were prior responders to PDE5i therapy. The efficacy and tolerability of this treatment, coupled with its long term benefits and rehabilitative characteristics, make it an attractive new therapeutic option for men with vasculogenic erectile dysfunction.*

Key Words: erectile dysfunction, low intensity, penis, hemodynamics, shockwaves

Introduction

There are several therapeutic options available for treating men with erectile dysfunction (ED) with phosphodiesterase type 5 inhibitors (PDE5i) currently first line therapy for men with vasculogenic ED. While these have proven to be safe and effective, they have limited utility as most need to be dosed on demand in close proximity to sexual activity and do not provide long term benefit.[1] Gene and stem cell therapies are examples of treatment strategies with the potential to address the underlying pathophysiology with the goal of restoring spontaneous erectile function, rather than provide on-demand palliative treatment.[2,3]

Low intensity extracorporeal shockwave therapy (LI-ESWT) has recently been introduced as a treatment

Accepted for publication December 2014

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modality for ED. In 1990 Young and Dyson demonstrated that therapeutic ultrasound could promote angiogenesis by enhancing the expression of vascular endothelial growth factor.[4-6] That finding led to the investigation of low intensity or low energy shockwaves in the treatment of coronary artery disease,[7] non-healing bone fractures,[8] calcifying tendonitis[9] and diabetic foot ulcers.[10] Vardi in 2010 demonstrated that LI-ESWT treatment to be an effective treatment strategy for ED in a mostly European population of men with vasculogenic ED.[11,12] Recently, Qiu et al investigated the effect of LI-ESWT on ED of streptozotocin (STZ) induced diabetes mellitus rat model. The researchers found out that LI-ESWT can partially ameliorate DM-associated ED by promoting regeneration of neuronal nitric oxide synthase (nNOS)-positive nerves, endothelium, and smooth muscle in the penis. These beneficial effects are thought to be mediated by recruitment of endogenous MSCs.[13]

As it has been reported that there are differences between Asian and European men in penile length and the underlying etiologies of ED,[14] we report herein our initial experience on the efficacy and safety of LI-ESWT for the treatment of ED in an Asian population.

Materials and methods

Screening, inclusion and exclusion criteria

We screened men in our ED outpatient clinic between September 2009 and September 2011who had a history of ED for at least 6 months and who were responders to PDE5is. A total of 165 men underwent screening, which included a complete medical history and physical examination, penile Doppler, nocturnal penile tumescence (NPT), International Index of Erectile Function (IIEF), International Index of Erectile Function-Erectile Function Domain Score (IIEF-EF domain) and erection hardness score (EHS). All subjects were required to discontinue PDE5i during the study period. For study inclusion each participant had to have an IIEF-EF domain score of < 18 following a 4 week PDE5i washout period (time V1 = baseline taken just before the first visit). Written informed consent was obtained before entering the study. The study protocol was reviewed and approved by our institution's ethics review board. Men were excluded if they had undergone radical prostatectomy, received pelvic radiotherapy or hormonal therapy, were receiving treatment for a psychiatric condition, or had any anatomical, neurological or hormonal abnormalities.

Since the mean age for men presenting with ED in the Indian population tends to be younger than in the West, and psychogenic causes for ED are more common than in younger than older patients, to ensure that our study group did not include men with psychogenic ED, we used penile Doppler to confirm an underlying organic basis for the ED at study entry.

Based on Doppler findings 30 patients were excluded, leaving 135 enrolled in the study. Inclusion and exclusion criteria are summarized in Table 1.

Study protocol

Substantiation of non-psychogenic ED

At the screening visit (Sx) the penile hemodynamics of each male were evaluated with real time ultrasonographic color Doppler (GE LOGIQ P6 machine) using a high frequency transducer (8 MHz linear vascular probe.[15,16] In the flaccid state, cavernosal diameter, cavernosal

TABLE 1. **Study selection criteria**

Inclusion criteria	**Exclusion criteria**
ED of more than 6 months.	Prior history of prostatectomy or pelvic radiotherapy.
Positive response to PDE5i.	Any cause of ED other than vascular-related.
IIEF-EF domain score of 6 ≤ 18.	Any unstable medical, psychiatric, spinal cord injury, penile anatomical abnormalities.
Non-neurological pathology.	Clinically significant chronic hematological disease.
Stable heterosexual relationship for more than 3 months.	Cardiovascular conditions that prevent sexual activity. H/o heart attack, stroke or life-threatening arrhythmia within the previous 6 months. Cancer within the past 5 years. Anti-androgen treatment (oral or injectable). Use of any treatment for ED within 7 days of screening.

ED = erectile dysfunction; PDE5i = phosphodiesterase type-5 inhibitors, IIEF-EF =International Index of Erectile Function – Erectile Function

arteries, deep dorsal vein and their flow velocities were measured using an 8 MHz GE LOGIQ P6 linear probe, with Doppler frequencies of 4.4 MHz and a CW Doppler with transmitting frequencies of 8-10 MHz. The patients were given oral sildenafil 100 mg, and 60 minutes later the cavernosal diameter, cavernosal arteries, deep dorsal vein were assessed and their flow velocities measured. The patients were than provided with visual sexual stimulation for 10 minutes to achieve a full or maximum erection. The above measurements were then repeated 70 and 80 minutes post-sildenafil. Patients were considered eligible to participate in the study if peak systolic velocity (PSV) was < 30 cm.

Randomization

All 135 participants underwent a 4 week PDE5i washout period. At baseline, prior to first visit (study time V1), the men were randomized 3:1 into two groups: those randomized to LI-ESWT (treatment group) and those randomized to sham therapy (placebo group).

Treatment and follow up periods

Each subject then began the 9 week treatment period which involved two LI-SWT treatment sessions per week for 3 weeks, repeated after a 3 week no treatment interval. Four outcome evaluation measures were examined, each in a separate analysis. Two separate analyses were performed assessing change in IIEF-EF domain scores, as follows:

1) IIEF-EF domain score change: these were evaluated as change of scores against V1 (baseline) for each of the six succeeding visits, and directly across all seven visits.
2) Total IIEF score change: these were evaluated across visits Sx, V1, V7 and FU1.
3) EHS score: these were evaluated across all seven visits.
4) CGIC score: these were evaluated across the six post-baseline visits.

The details of the changes in IIEF-EF domain scores, the erection hardness scores and the clinical global improvement change scale (CGICS) are shown in Table 2.

TABLE 2. **Scoring details**

IIEF-EF domain score	
≤ 5	no attempts at intercourse
6-10	severe ED
11-16	moderate ED
17-21	mild to moderate ED
22-25	mild ED
≥ 26	"normal" erectile function
Erection hardness score	
Grade 1 – tumescence but no rigidity	
Grade 2 – tumescence with minimal rigidity	
Grade 3 – rigidity sufficient for sexual intercourse	
Grade 4 – fully rigid erection	
Clinical global improvement – change scale	
1 – very much improved	
2 – much improved	
3 – minimally improved	
4 – no change	
5 – minimally worse	
6 – much worse	
7 – very much worse	

ED = erectile dysfunction

LI-ESWT procedure in treatment group

Standard commercial ultrasound gel was applied to the penis. The penis was stretched manually and the shockwaves were delivered to the distal, mid and proximal penile shaft, and to the left and right crura using a specialized focused shockwave probe Omnispec ED1000 (Medispec Ltd., Yehud, Israel).[4,5] As the depth of the shockwaves reaches both corpora, treatment was applied to only one side of the penile shaft. Three hundred shocks at an energy density of 0.09 mJ/mm^2 and a frequency of 120 shocks per minute were delivered at each of the five treatment points. Each treatment session lasted approximately 15 minutes. No, topical, local or systemic analgesia was administered.

Placebo treatment

Patients allocated to the placebo group were treated with a placebo probe supplied by the manufacturer. The placebo probe was identical in appearance and made the same sound as the treatment probe, but contained a metal plate to block the transmission of the shockwave energy from being applied to the penis. Since the appearance, sound and vibration of the probes used in both groups were similar, and the treatment is painless, both the operator and the subject were blinded to treatment randomization.

Follow up

We characterized seven distinct phases of the treatment course, Figures 1a and 1b: Sx is the first (screening) visit at which the patient undergoes penile Doppler, NPT, IIEF score, IIEF-EF domain and EHS. Visit 1 (V1) is the randomization visit where baseline IIEF score, IIEF-EF

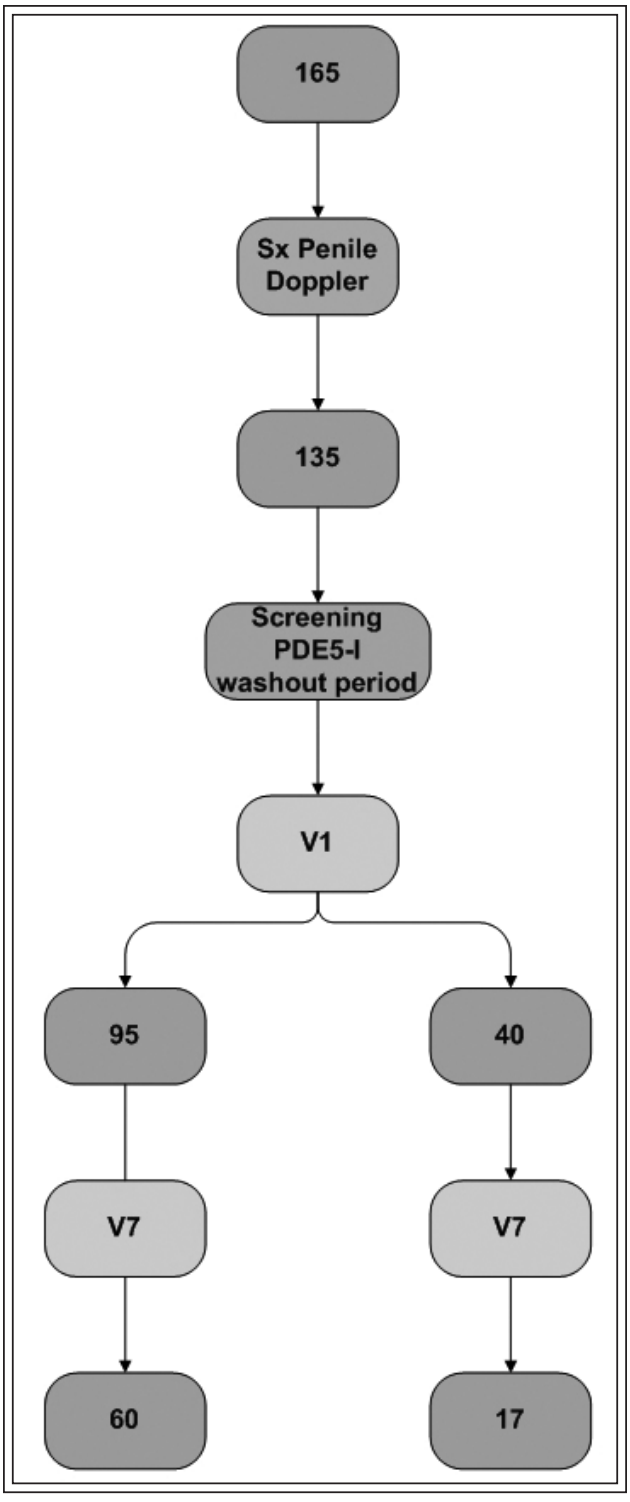

Figure 1a. Trail screen failure and dropout flowchart.

domain and EHS were assessed and the patients were randomly allocated to either the treatment or placebo groups. Visit 7 (V7) occurs after six treatment sessions and a 3 week no-treatment interval period when the patient presents for the seventh session visit. Follow up 1 (FU1) is the first follow up which is carried out 1 month after the last treatment session. FU2, FU3, FU4 and FU5 are follow-ups after 3, 6, 9 and 12 months after the 12th session.

Main outcome measures (primary end point)

We used the IIEF-EF domain to assess erectile function. Treatment success was defined as a 5-point or greater improvement in the IIEF-EF domain between V1 and FU1 (also FU5), as this correlates with an improvement in erectile function by at least one severity category. The secondary outcome measures were defined as significant increases in the CGIC and an increase in EHS from ≤ 2 at V1 to ≥ 3 at FU1 and FU5.

Results

Statistical analysis

JMP (SAS Institute, Cary, NC, USA) and R statistical software were employed for analyses. Specifically for Friedman's test and associated post-hocs, Galili's R program[17] was employed. Patients in the placebo-treated went through only three phases of the study and followed for 3 months, (V7, FU1, FU2). Comparisons with the shockwave-treated group at later time points were thus limited.

The demographic and medical characteristics of the treatment and placebo groups are shown in Table 3.

For IIEF-EF domain and total IIEF statistics, change scores were constructed for each patient for each stage, with reference to V1, i.e. Delta IIEF-EF domain V7 is the change score at V7 minus V1, and Delta IIEF-EF domain FU1 is FU1-V1.

The distributions of the data indicated the use of non-parametric statistics, therefore, separate Wilcoxon tests were performed at each stage. Summarized inference from one way ANOVA, Wilcoxon test and 2 sample test – normal approximation, Table 4.

Besides basic distributional analysis of demographic and outcome factors, we conducted longitudinal analyses of four outcome parameters over either six or seven visits. The non-parametric distributions of the total IIEF and IIEF-EF domain change scores, and the ordinal scales used for RS and GCI necessitated the use of Friedman's ANOVA, a rank-based non-parametric procedure for repeated measures, along with multiplicity-corrected, pairwise (between all stage pairs) post-hoc tests. Friedman's test does not allow for missing data, and imputation, LOCF, or other data "recovery" strategies are not appropriate for this study. Box plots and parallel coordinate plots (individual response plots) were also produced.

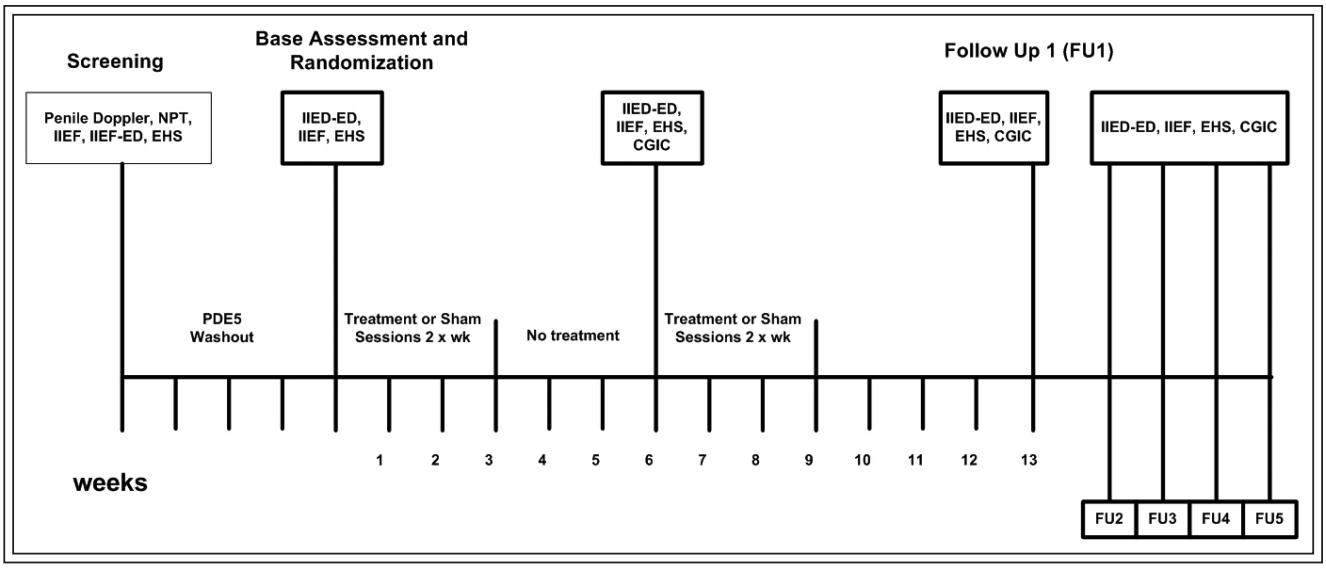

Figure 1b. Study flowchart.

TABLE 3. **Demographic and medical characteristics of treatment and placebo groups**

Item	Finding
PME	There are no differences in the degree of premature ejaculation (PME) in either group, p = 1.00.
DM	There are no differences in rates of diabetes mellitus (DM) in the two groups, p = 0.276.
HTN	There is significantly more hypertension (HTN) in the shockwave-treated group (21/95, or 22.11%) than in the placebo-treated group (2/40, or 5%), p = 0.0219.
IHD	There is significantly more ischemic heart disease (IHD) in the placebo-treated group (10/40, or 25%) than in the shockwave-treated group (3/95, or 3.16%), p = 0.0003.
SMOKING	There are no differences in smoking between the groups, p = 0.18.
ALCOHOL	There are more drinkers of alcohol in the placebo-treated group (19/40, or 47.5%) than in the shockwave-treated group (22/95, or 23.16%), p = 0.0074.
LIPIDS	There are more lipid patients in the placebo-treated group (19/40, or 47.5%) than in the shockwave-treated group (19/95, or 20%), p = 0.0017.

TABLE 4. **Summary of changes between baseline, visit 7 and follow up 1**

Item analyzed	Inference
DELTA IIEF-EF DOMAIN Between V7 and V1	Greater changes for shockwave treatment than for placebo treatment at stage1, $p < 0.0001$. Multiplying the p value by two still yields a highly significant difference, $p < 0.0001$.
DELTA IIEF-EF domain between FU1 and V1	Greater changes for shockwave treatment than for placebo treatment at stage 1, $p < 0.0001$. Multiplying the p value by two still yields a highly significant difference, $p < 0.0001$.

A. Shockwave group

IIEF-EF domain change scores relative to V1 baseline scores (n = 60)

Friedman's test indicated overall differences between change scores, $p < 0.0001$. Protected pairwise comparisons indicate many differences between change scores at different stages. A trend for good significance was evidenced at $p < 0.10$, Figure 2a.

IIEF-EF scores over all seven stages (n = 60)

In order to allow direct comparisons with the baseline (V1) level, raw IIEF-EF domain scores were compared across all seven phases of the study. Friedman's test indicated overall differences between changes scores, $p < 0.0001$. Protected pairwise comparisons indicate many changes were noted at $p < 0.10$, Figure 2b.

EHS score over all seven stages (n = 60)

EHS scores, an ordinal assessment measure, were compared across all seven stages. Friedman's test indicated overall differences between erection hardness scores, $p < 0.0001$. Protected pairwise comparisons indicate many differences between scores at different stages. A trend for significance was evidenced at $p < 0.10$, Figure 3a.

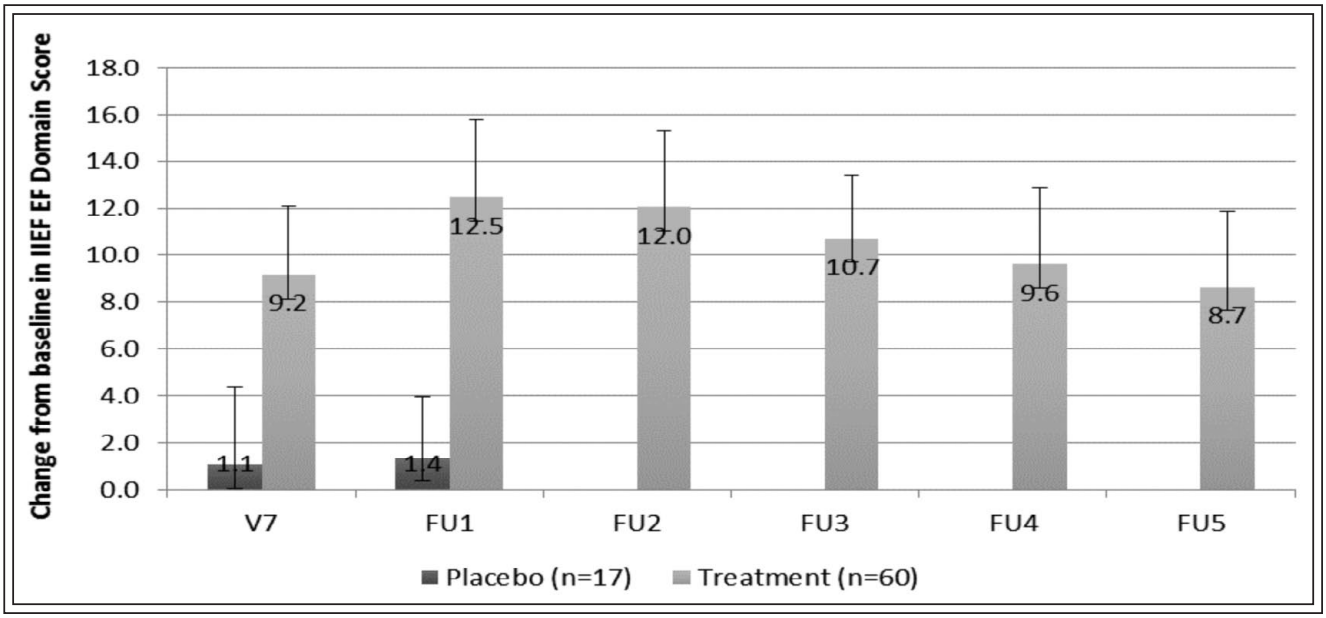

Figure 2a. Improvement of IIEF-EF domain change scores from baseline.

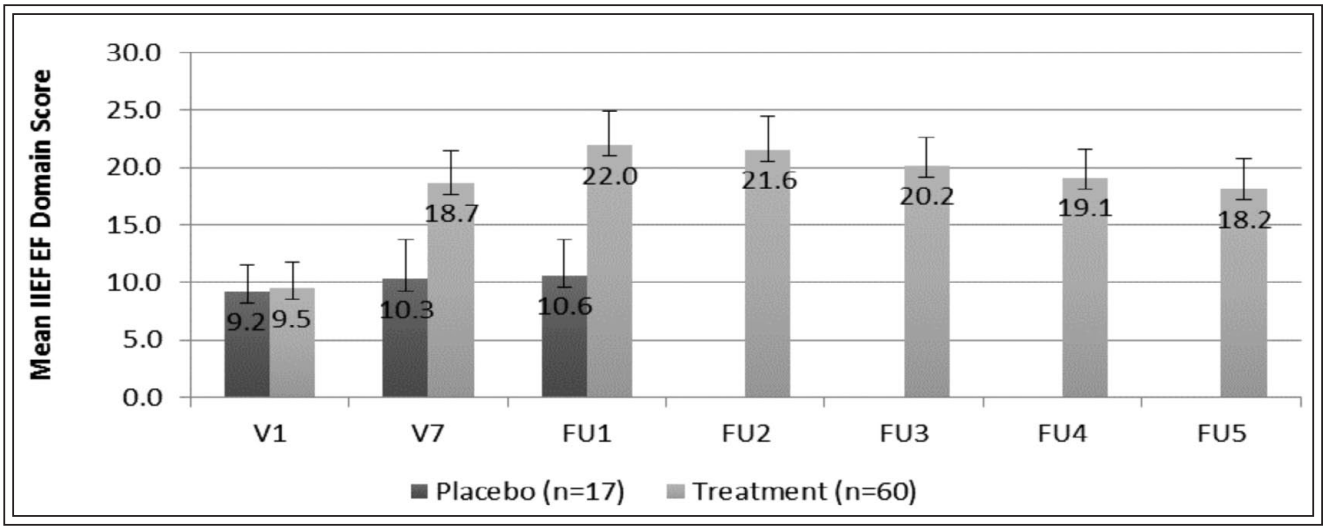

Figure 2b. IIEF-EF domain scores.

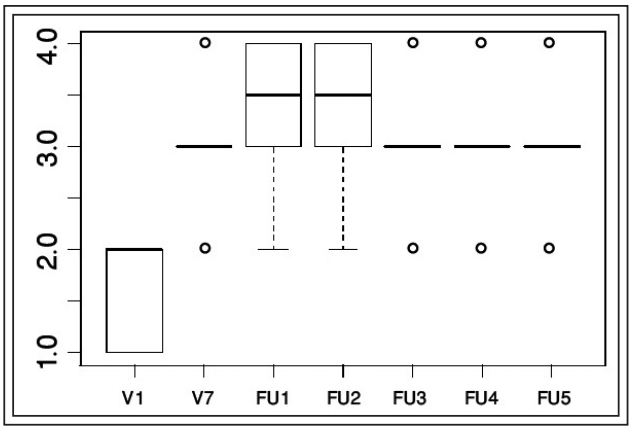

Figure 3a. EHS score over six post-baseline stages.

GCI score over six post-baseline stages

GCI scores, an ordinal assessment measure, were compared across six post baseline phases. Friedman's test indicated overall differences between GCI scores, $p < 0.0001$ (data not shown).

B. Comparisons between shockwave and placebo-treated groups

Contingency table/Fischer's exact probability test was applied between treated group and placebo.

Patient characteristics

Of 135 patients 95 received shockwave treatment and 40 were subjected to sham treatment (placebo group). Their characteristics are shown in Table 3, which shows the age comparison.

Efficacy – IIEF-EF domain change scores

Improvement as measured by IIEF was greater in men with severe ED than in men with moderate ED at all time-points, except at FU3, where there was a numerical trend but did not reach significance. Both the moderate and severe ED groups improved by an average of at least 7 points at 1 year follow up (FU5) compared to baseline values (V1). Improvement at 12 months follow up was smaller than at first month after treatment (FU1) but similar to visit seven – V7 (no statistically significant difference).

In the placebo group there was no statistical improvement – either when comparing the moderate with the severe group, or with the severe group compared to baseline. No placebo effect was observed, which may be a reelection of the strict selection and rigorous screening to exclude men with psychogenic etiology (57% were screened out or dropped-out before visit 1). For screen failure and dropout rate please refer to Figure 1a. The placebo group (n = 17 and n = 14 / 40 followed / recruited) was followed only until FU-1 (6 months post-last treatment).

Efficacy – Erection hardness change score, Figure 3b

All of the patients in the treatment group had EHS ≤ 2 at visit 1. At FU1 (1 month post-final treatment) 90% of the treated patients (54/60) reported functional erections defined as EHS ≥ 3 and were able to achieve vaginal penetration. At FU1, 100% of the patients in the treatment group had an improvement in their EHS by at least one grade. At FU1 all patients reported an EHS ≥ 2. Fifty percent of the patients achieved EHS of 4 (fully rigid), 40% had EHS = 3 (penile rigidity

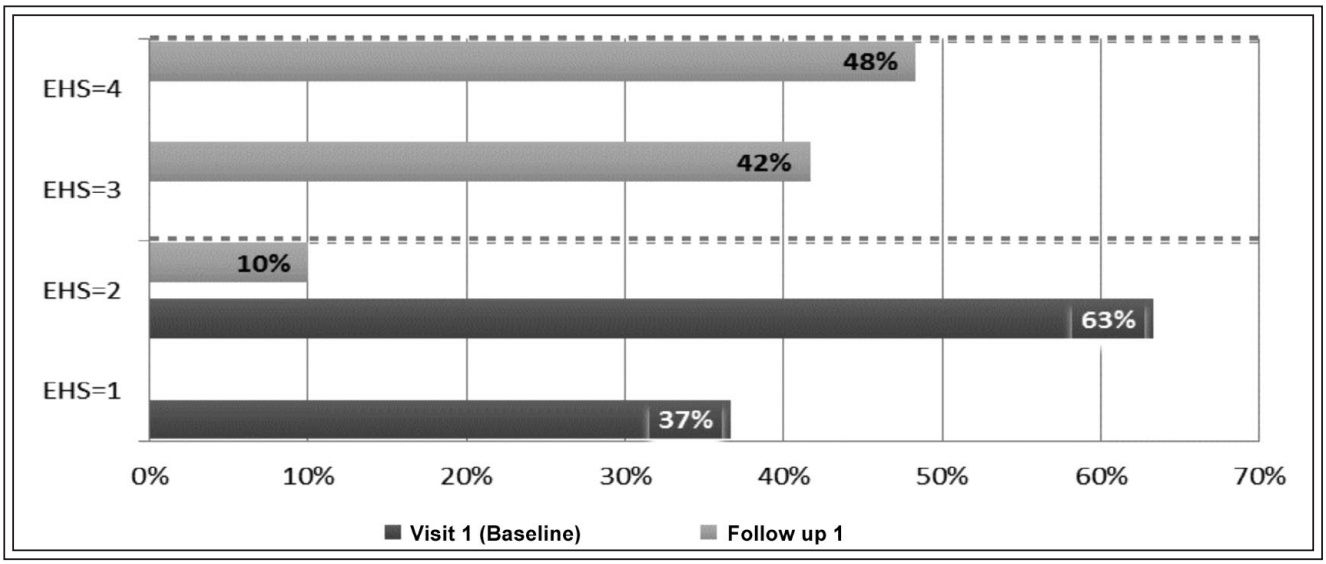

Figure 3b. Erection hardness scores.

that allowed vaginal penetration but not completion of successful intercourse); only 10% improved by only one grade (EHS 1 to EHS 2); 73% (44/60) improved EHS by two grades. In the placebo group there was a slight decrease in EHS at the follow ups. At FU5, four patients from the treatment group regressed to EHS ≤ 2, however, 83% (50/60) reported EHS ≥ 3 erections. This correlated with the regression seen both in IIEF-EF domain and CGIC. This regression or loss of efficacy was minimal and not significant.

Adverse events

The low intensity shockwave energy used in this study (0.09 mJ/mm^2) was not associated with any reported pain or discomfort. There were no reports of ecchymoses or hematuria.

Discussion

Recently, the European Association of Urology issued the updated Male Sexual Dysfunction guidelines 2013, and included LI-ESWT as a possible modality for treating ED. The authors based their recommendation on animal study conducted on diabetic rat model[13] as well as reports of the clinical experience conducted on European males.[11,12] As there is some skepticism surrounding this treatment approach and the supporting scientific data is limited , we felt it was important to assess the efficacy and safety of LI-ESWT by conducting a randomized, double-blind, placebo-controlled study on an Indian population.

We chose to use assessment tools that are validated and widely accepted, including the IIEF and EHS. While validated in men receiving on demand PDE5i, these questionnaires have a high degree of sensitivity and specificity for detecting treatment related changes in the erectile function.[18-22] Since LI-ESWT is a non-pharmacological intervention whose effect is not related to the timing of the sexual encounter, we chose not to use questionnaires such as the sexual encounter profile.

The IIEF-EF domain scores of the treated men showed significant improved as early as FU1. Although significant, the improvement was not as great as the increases reported in the IIEF-EF domain scores that was reported for PDE5i.[23-28] However, these were not head to head studies and were conducted in different populations and this study made a rigorous attempt to exclude men with psychogenic ED. Unlike the initial sildenafil studies, which involved naïve cases, in our study required men to be PDE5i experienced with a positive response. Additionally, many of the original PDE5i studies included a mixed ED population, in contrast to our group of men who were restricted to have vasculogenic risk factors only. Our strict inclusion and exclusion criteria may also account for the lower (14%) placebo effect seen in this study compared to reported placebo effects as high as 45% in the initial PDE5i studies.[26] Later studies that excluded patients with psychogenic ED, and examined the effect of PDE5i on men with organic ED and cardiovascular risk factors, report placebo response rates comparable to what we report here.[26] It is possible that our empirical LI-ESWT protocol may not be ideal, and improved outcomes may be achieved by protocol modifications in the future.

Ease of definition and applicability make the EHS a valuable tool for simple clinical assessment. The EHS were consistent with IIEF scores and confirmed that more men in the treated group than in the placebo group were able to achieve erections sufficiently hard for penetration. However, the EHS is statistically ill suited for pre-post and two-group study designs such as ours. Further supporting our hypothesis that LI-ESWT improves penile hemodynamics is our finding that most of the treated men reported improvement in erectile function between treatment sessions 6 and 8, which should correspond to the time needed for LI-ESWT to induce the physiological changes. While the purpose of this study was to evaluate the early physiological effects of LI-ESWT on erectile function in men with vasculogenic ED our finding that the reported improvements in the IIEF-EF domain were maintained 3 months after the final treatment suggests that the physiological effect is maintained. This study is the first study to report detailed 1 year follow up results for men with vasculogenic ED undergoing LI-ESWT. We believe that future studies should include long term follow up to study and evaluate the durability of the effects of LI-ESWT on erectile function in men with ED.

The treatment protocol that was used in our current study and by others[12,13] to date is based on that described in the cardiology literature.[29,30] This is an empirical treatment protocol that has not been previously tested in pre-clinical animal models or human erectile tissue and, therefore, may eventually be modified as more protocols are studied. Although our final study population included only 60 men, it was sufficient to achieve our main goal of demonstrating the beneficial effect of LI-ESWT on erectile function. The dropout rate was high in the treatment group and not unexpectedly higher in the placebo group. We suspect that the length of the treatment (12 sessions), and the fact that in the treatment group subjects reported sufficient change only at visit 7-8, may have contributed to 37% (35/95) dropout rate. This was even more pronounced in the placebo group with 58% (23/40) dropout rate. This lack of patients' compliance to the protocol underscores the need to evaluate shorter protocols with perhaps fewer treatment sessions.

To date, adverse side effects have not been reported by others in patients undergoing high intensity penile shockwave therapy for the treatment of Peyronie's disease,[31-33] and while our subjects did not report any adverse effects to the treatment, the long term safety of LI-ESWT on penile tissues needs further investigation.

Conclusions

This is the first randomized, double-blind, placebo controlled study of the safety and efficacy of LI-ESWT on erectile function in men with ED in an Asian population. While the precise mechanism of action of LI-ESWT has not been established, our objective measurements suggest that this therapy works by improving penile hemodynamics. We also speculate that this treatment is unique in that it appears to provide long term rehabilitative benefits. Additional studies with long term follow up and modified treatment protocols are now needed to fully evaluate the efficacy of this new therapy and confirm our findings. We also encourage ongoing and additional basic science research to provide an understanding of the underlying mechanism of action. Our hope is that LI-ESWT will be incorporated as an effective and well tolerated non-invasive option into the armamentarium of treatments currently being used in the clinical management of men suffering from ED. □

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