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

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Abstract: **Low Intensity Shockwaves (LISW) are known to produce revascularization and have been in evaluation and in use to treat erectile dysfunction (ED). The present study is aimed to assess the safety and efficacy of a dedicated shockwave device (Renova) on Vasculogenic ED patients. Fifty seven patients with mild to severe ED were treated by Renova and their erectile function was evaluated by the IIEF-EF, SEP and GAQ questionnaires, at baseline and at 1 and 3 months post treatment. The average IIEF-EF increased significantly 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. No adverse events were reported during the treatment and the follow-up duration. In conclusion, it appears that the performance of Renova has made it the new advanced treatment for erectile dysfunction.**

Key words: Erectile dysfunction, extracorporeal shockwaves, low intensity shockwaves.

Introduction

Vasculogenic erectile dysfunction (ED) is defined as inability to get or keep an erection firm enough for sexual intercourse due to diseases such as diabetes mellitus and atherosclerotic vascular occlusive disease. Current methods for treating Vasculogenic ED aim at reducing symptoms instead of reversing the source of the disorder, which is in majority of patients is arterial or inflow disorders (Ref. 1). It has been demonstrated that shockwaves can enhance intrinsic angiogenesis and is used to treat ischemic heart disease (Ref. 2). Low-intensity shockwaves (LISW) have been evaluated for treating ED using a modified orthopedic device. The encouraging results that were seen in these studies were the first to show the effect of LISW on ED symptoms (Ref. 3-4). Recently published study conducted on rats with diabetes mellitus (DM) associated ED discovered that low-energy shockwave therapy (LESWT) significantly restored erectile function to levels almost similar to normal 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 (Ref. 5). The present study was aimed to assess the efficacy and safety of a new dedicated shockwave device, Renova, which was designed to achieve

substantially superior organ coverage compared to the existing devices.

Patients and methods

Study Protocol

This study was a multicenter open-label prospective pilot study, conducted at 4 sites.

This study consisted of a screening phase, treatment phase and a 3 months follow-up phase. At screening phase, patients had an extensive medical and sexological history evaluation and physical examination. Inclusion criteria were heterosexual men in stable heterosexual relationship for at least 3 months, aged 20-80, with vascular ED (according to physician judgment) for at least 6 months, International Index of Erectile Function- Erectile Function Domain (IIEF-EF) score of 6 to 25 (Ref. 7). Recruited patients were both responders and non-responders 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 anti-androgens, 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 (Ref. 7-8). Global Assessment Questions (GAQ, Ref. 9) were used at follow-up as well. The IIEF-EF questionnaire is widely accepted as the best method to verify ED progress. It includes 6 questions regarding erectile function, and its score range is 1-30 points. The SEP questionnaire includes 2 questions: 1) Over the past 4 weeks, were you able to insert your penis into your partner's vagina? 2) Over the past 4 weeks, did your erection last long enough for you to have successful intercourse? There are 2 possible answers: Yes or No. The GAQ questionnaire includes 2 questions: 1) Over the past 4 weeks, has the treatment you have been taking improved your erectile function? 2) If yes, has the treatment improved your ability to engage in sexual activity over the past 4 weeks? Similar to the SEP questionnaire, there are 2 possible answers: Yes or No.

At all study endpoints, patients were evaluated while under the same conditions in terms of pharmacotherapy as they were at baseline evaluation.

Patients committed to avoid using any ED treatment other than PDE5-I oral medication throughout the study duration.

The treatment consisted of four weekly treatment sessions. During each session 3600 shocks of 0.09mJ/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 (4 sessions) each area has received 3600 shocks of 0.09mJ/mm^2.

Follow-ups were conducted at 1 and 3 months post treatment and were consisted of adverse events report, IIEF-EF, SEP and Global Assessment Questions (GAQ). The primary success criterion, regarding to efficacy, was defined as an increase of IIEF-EF score from baseline to the second follow up (3 months post treatment) according to the severity of the symptoms by the minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale (Ref. 6) as described in table 1.

IIEF-EF Baseline Score	Success Factor
6-10	improvement of 7 points or more
11-16	improvement of 5 points or more
17-25	improvement of 2 points or more

Table 1 - The success criteria of this study according to Rosen et al (Ref. 6)

Treatment device

As being the first dedicated shockwave system for ED, Renova (Direx Group Ltd) differs from other shockwave devices in several aspects. Instead of generating shockwaves that converge on a single focal point and requires moving the shockwave source to multiple positions along the penis, Renova is based on Linear Shockwave Therapy (LSWT) which enables generation of a 70mm long and 40mm depth treatment area along the target organ. In addition, Renova enables efficient positioning when attempting to apply to the crura. Renova's electromagnetic generator delivers shockwaves with a maximum energy density of 0.09mJ/mm^2, meaning, they deliver 10% of the pressure used for disintegrating kidney stones. Shocks are delivered at a maximum rate of 300 PPM (5 Hz), therefore, a treatment session of 3600 shocks lasts approximately 15 minutes.

Statistical analysis

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

Results

57 middle aged men (mean: 56.9 ± 9.9 yr, range: 33-84 yr) with Vasculogenic ED were recruited for this study. 43.9% (25 patients) have suffered from cardiovascular disease. 86.0% (44 patients) were PDE5-I responders. Table 2 summarizes the patients' demographic characteristics in division to baseline ED severity. Patients' baseline IIEF-EF score ranged between 6 and 25.

There was no decrease of scores between 1 and 3 months follow-up. Tables 3 and 4 summarize the effect of low-intensity extracorporeal shockwave therapy on the IIEF-EF, SEP and GAQ scores and show the change in these scores from baseline to 3 months post treatment.

No adverse events were reported during and following treatment.

Baseline ED Severity	Age	Cardiovascular disease	Response to PDE5-I
Severe	64.2±5.2	53.8%	69.2%
Moderate	57.8±10.7	68.2%	86.4%
Mild to Moderate	52.2±7.8	17.6%	94.1%
Mild	48.6±10.3	0.0%	100.0%
Total	**56.9±9.9**	**43.9%**	**86.0%**

Table 2 - Patients' demographic characteristics

Baseline ED Severity	Number of Patients	Baseline IIEF-EF		IIEF-EF Improvement Points		% Success
		Range	Average	Success Criterion	Results	
Severe	13	6-10	8.5±1.2	7	8.2±5.9	61.5%
Moderate	22	11-16	13.3±1.8	5	7.7±4.5	77.3%
Mild to Moderate	17	17-21	18.6±1.5	2	5.7±2.1	100.0%
Mild	5	22-25	23.6±1.3	2	3.8±0.8	100.0%
Total	**57**	**6-25**	**14.7±4.9**	**6.9±4.2**		**82.5%**

Table 3 – The results of the International Index of Erectile Function- Erectile Function domain (IIEF-EF), prior to and 3 months following low-intensity extracorporeal shockwave therapy. Success is determined according to table 1.

Baseline ED Severity	SEP 2		SEP 3		GAQ 1	GAQ 2
	Baseline	Follow-up	Baseline	Follow-up	follow-up	Follow-up
Severe	23.1%	76.9%	7.7%	53.8%	76.9%	61.5%
Moderate	45.5%	95.5%	9.1%	50.0%	72.7%	54.5%
Mild to Moderate	94.1%	100.0%	47.1%	100.0%	100.0%	100.0%
Mild	100.0%	100.0%	80.0%	100.0%	100.0%	100.0%
Total	**59.6%**	**93.0%**	**26.3%**	**70.2%**	**84.2%**	**73.7%**

Table 4 – The percentages of "Yes" answers to the Sexual Encounter Profile (SEP) questions and the Global Assessment Questions (GAQ) prior to and at 3 months following low-intensity extracorporeal shockwave therapy. The last questionnaire deals with the treatment; therefore it was used only after treatment.

Discussion

As seen in table 3, Renova treatment has succeeded in 47 out of 57 cases, meaning 82.5% success. Among the successful patients, the average IIEF-EF score increase was 8 points. When reviewing the baseline IIEF-EF scores of failed patients, it appears that their average score is 11.4, which is lower than the general baseline IIEF-EF score in more than 20%. Success rate for more severe cases is lower than the general success rate. When considering the numerical change in IIEF-EF, only 5 patients (8%) 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, since they are referring directly to the patient's ability to perform successful intercourse.

When reviewing the individual answers for the GAQ questions, it appears that 73% of the patients (42 patients) have answered both of these questions with "Yes". Since these questions are intended to evaluate the treatment, these results indicate on a successful treatment.

Conclusions

The results of this study indicate success of this second generation technology for treating ED with linear low-intensity shockwaves. This study shows that Initial follow up data from almost 60 patients demonstrate a clear therapeutic success in over 80% of patients. Pain is tolerated by 100% of

the treated patients and no side effects have been recorded, demonstrating the suitability of this treatment to millions of men who find themselves limited by the currently available solutions. Possible changes in the protocol should be investigated, such as adjusting the number of treatment session to the baseline ED severity.

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