

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

Amado Bechara¹, Adolfo Casabé², Walter De Bonis³ and Julián Nazar⁴.

¹Jefe de Unidad de la División Urología del Hospital Durand. Buenos Aires, Argentina. Profesor de Urología de la UBA. Co-Director Médico del Instituto Médico Especializado (IME).

²Encargado del Sector Medicina Sexual de la División Urología del Hospital Durand. Co-Director Médico del IME Buenos Aires, Argentina.

³Urólogo de la División Urología del Hospital Durand y del IME. Buenos Aires, Argentina.

⁴Urólogo de la División Urología del Hospital Durand. Buenos Aires, Argentina.

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.



CORRESPONDENCE

Amado Bechara
Jefe de Unidad de la División Urología
del Hospital Durand.
Buenos Aires, (Argentina).

amadobechara@fibertel.com.ar

Accepted for publication: December 8th, 2014

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 incluyó 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 post-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 pérdida 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 prosthetic 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 1 st week of treatment	VISIT 3 2 nd week of treatment	VISIT 4 3 rd week of treatment	VISIT 5 4 th week of treatment	VISIT 6 1 st month evaluation	VISIT 7 3 rd 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 (%)
	<i>Hypertension</i>
	11 (55 %)
	<i>Diabetes Mellitus</i>
	11 (55 %)
	<i>Dyslipidemia</i>
	5 (12,5 %)
	<i>Coronary artery disease</i>
	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).

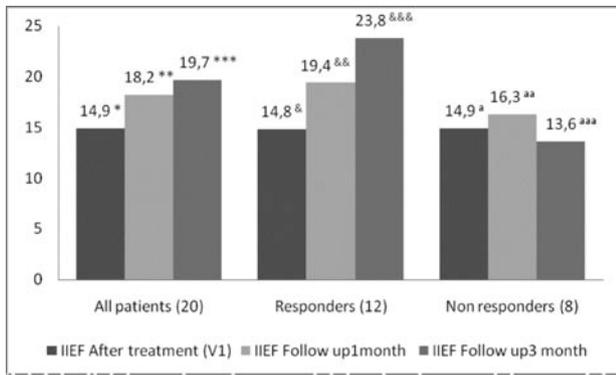
Many studies have emphasized the status of ED as a potential indicator of cardiovascular disease later in life, while other clinical trials have found a high rate of ED in men with vascular factors such as metabolic syndrome, diabetes and hypertension (20, 21).

Table III. 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 1 to 3 months.

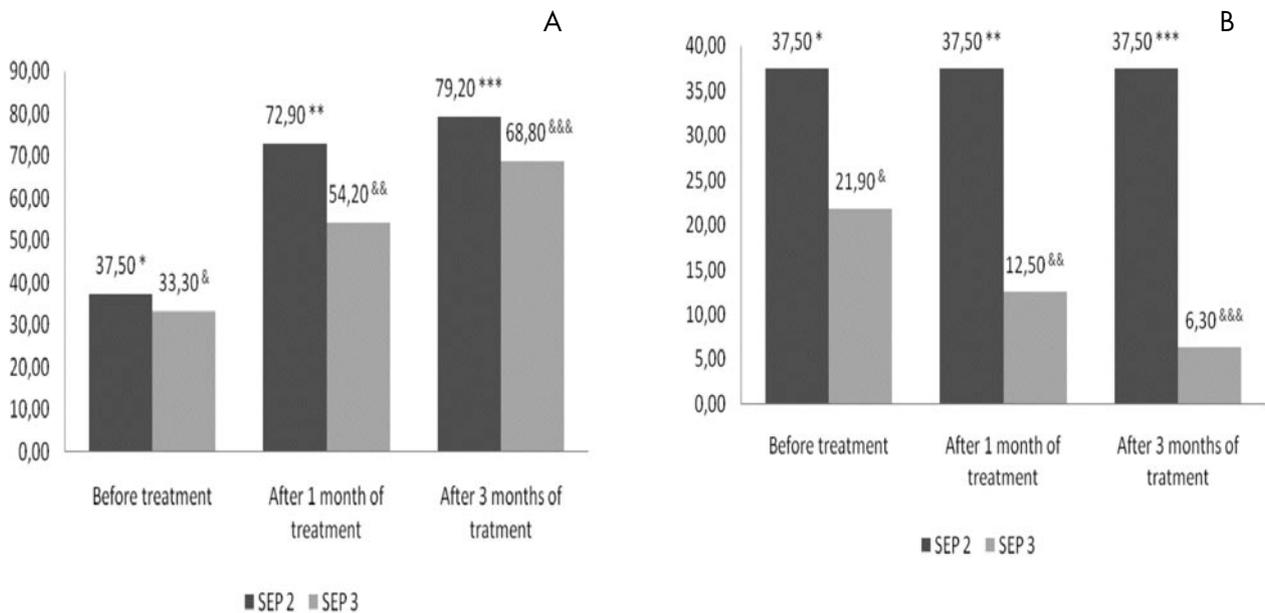
As mentioned before, the device selected for our trial (Renova NR), is manufactured by Direx Group, and involves a special LI-ESWT technology. This operator-independent system is fitted with a transducer that is capable of delivering shock waves

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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