



Low Intensity Shock Wave Treatment for Erectile Dysfunction—How Long Does the Effect Last?

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Purpose: We studied the long-term efficacy of penile low intensity shock wave treatment 2 years after an initially successful outcome.

Materials and Methods: Men with a successful outcome of low intensity shock wave treatment according to the minimal clinically important difference on the IIEF-EF (International Index of Erectile Function-Erectile Function) questionnaire were followed at 6, 12, 18 and 24 months. Efficacy was assessed by the IIEF-EF. Failure during followup was defined as a decrease in the IIEF-EF below the minimal clinically important difference.

Results: We screened a total of 156 patients who underwent the same treatment protocol but participated in different clinical studies. At 1 month treatment was successful in 99 patients (63.5%). During followup a gradual decrease in efficacy was observed. The beneficial effect was maintained after 2 years in only 53 of the 99 patients (53.5%) in whom success was initially achieved. Patients with severe erectile dysfunction were prone to earlier failure than those with nonsevere erectile dysfunction. During the 2-year followup the effect of low intensity shock wave treatment was lost in all patients with diabetes who had severe erectile dysfunction at baseline. On the other hand, patients with milder forms of erectile dysfunction without diabetes had a 76% chance that the beneficial effect of low intensity shock wave treatment would be preserved after 2 years.

Conclusions: Low intensity shock wave treatment is effective in the short term but treatment efficacy was maintained after 2 years in only half of the patients. In patients with milder forms of erectile dysfunction the beneficial effect is more likely to be preserved.

Key Words: penis, erectile dysfunction, extracorporeal shock wave therapy, treatment outcome, risk factors

Low intensity extracorporeal shock wave therapy is a new treatment modality for ED. The efficacy of this technique using various types of energy (electrohydraulic, electromagnetic or piezoelectric), several protocols and devices has already been published. The short-term results of most studies are encouraging.^{1–8} LIST is

effective even in patients with severe ED in whom the response to PDE5Is has stopped.⁹ While the mechanism of action is not fully understood, animal studies have shown that the shear stress exerted by this energy induces the release of angiogenic factors and results in revascularization.^{10,11} Since one of the underlying causes of ED is

Abbreviations and Acronyms

CVD = cardiovascular disease

CVRF = cardiovascular risk factors

DM = diabetes mellitus

ED = erectile dysfunction

IIEF-EF = International Index of Erectile Function-Erectile Function

LIST = low intensity shock wave treatment

MCID = minimal clinically important difference

PDE5I = phosphodiesterase type 5 inhibitor

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poor cavernous blood flow, it was theorized that by triggering neovascularization LIST could potentially improve cavernous flow.

LIST introduced a new concept in ED treatment. It is a modality that is not targeted to the symptom. It is aimed to modify the underlying pathological process that causes ED and may include regenerative elements, eg neovascularization of cavernous tissue and improved endothelial function. Therefore, data on the long-term efficacy of LIST are crucial to make this modality clinically relevant.

The aim of this study was to evaluate the long-term effect of LIST in patients with clinical success 1 month after the end of treatment. The question of the long-term durability of LIST is raised in every discussion with patients who are candidates for this treatment.

METHODS

During the last 5 years we have followed all of our patients who underwent LIST for ED. A heterogeneous group of patients treated with penile LIST during previous clinical studies comprised this cohort, including men with a large range of baseline ED severities such as CVRF, CVD and DM. Responders and nonresponders to PDE5Is were included. Although these patients participated in different studies, the treatment protocol and evaluation methods were identical in all. Our protocol consisted of 12 treatment sessions, including twice weekly for 3 weeks, 3 weeks with no treatment and an additional 3 weeks with 2 sessions per week.^{1,4,5,9} LIST was applied to 5 treatment points along the penis. A total of 1,500 shock waves was applied at 0.09 mJ/mm² and 120 shocks per minute.

Success at 1 month was determined according to strict predesignated criteria, including the change in the score of the IIEF-EF domain questionnaire from baseline before treatment according to the MCID,¹² ie an increase of at least 7, 5 and 2 points for severe, moderate and mild ED, respectively. All included patients were followed at the clinic at 3 and 6 months. Later followup visits were performed by a physician or a nurse at the clinic or by telephone interview, including the IIEF-EF questionnaire, at 12, 18 and 24 months.

As the outcome measure of failure we used the IIEF-EF domain scores. Our point of reference was the successful result achieved 1 month after the last treatment session. A decrease in the IIEF-EF score to below the expected success score according to MCID criteria was considered failure.

Statistical analysis was performed with SPSS®, version 21.0. Data are presented as mean $\pm$ SD or the number and percent unless otherwise specified. Groups were compared with 1-way ANOVA. The Student t-test was used to analyze continuous variables and the chi-square test was used for categorical variables. Multivariable binary logistic regression analysis was performed to determine the association of variables of interest with the probability of a successful response to LIST during the 24-month followup. Statistical significance was considered at $p < 0.05$.

RESULTS

All 156 patients treated with our standard LIST protocol were considered for this study. Median age of the cohort was 59.1 years (range 27 to 81), 73 patients (46.8%) had DM and 128 (82.1%) had CVD or CVRF. Of the men 55% had severe ED, defined as an IIEF-EF score of 10 or less. Table 1 lists detailed patient characteristics.

Of these cases 99 (63.5%) responded to treatment and were considered successful according to the mentioned criteria. Patients who did not respond to LIST were referred to other treatments or received a second round treatment. Two patients with initial success were lost to followup after 18 months. In these patients treatment was considered to have failed at the 24-month visit.

During the 2-year followup we found that the clinically effective response decreased with time. We started with 99 positive responders (63.5%) at 1 month and ended with only 53 (34%) at 2 years (fig. 1). The response was maintained 2 years after the end of treatment in 53% of the patients in whom therapy was initially successful at 1 month.

We investigated several parameters to define the group of patients prone to a shorter successful response to LIST. Among the parameters that were tested were patient age, DM, ED severity, time of ED, the PDE5i response, CVD and CVRF (table 2). On univariate analysis patients with severe ED before LIST and patients with DM were prone to earlier failure. The response was maintained after 24 months in only 20 of the 49 patients (40.8%) with severe ED in whom LIST was initially successful compared to 33 (66%) of the remaining patients (table 2).

Severe ED at baseline was a significant risk factor on multivariable binary logistic regression analysis. Figure 2 shows a comparison of severe and nonsevere ED cases. A specific group of interest, that is patients who were PDE5i nonresponders at baseline, were also prone to earlier failure during followup, although it was not statistically significant.

Table 1. Patient baseline characteristics

	Overall	LIST	
		Responders	Nonresponders
No. pts	156	99	57
Mean $\pm$ SD age	59.1 $\pm$ 10.1	58.2 $\pm$ 10.6	60.6 $\pm$ 9.1
Mean $\pm$ SD ED duration (mos)	64.6 $\pm$ 49	60.3 $\pm$ 46	72 $\pm$ 55
No. ED severity (%):			
Mild	21 (13.5)	17 (17.2)	4 (7)
Moderate	49 (31.4)	33 (33.3)	16 (28.1)
Severe	86 (55.1)	49 (49.5)	37 (64.9)
Mean $\pm$ SD IIEF-EF (points)	10.7 $\pm$ 4.4	11.1 $\pm$ 4.4	10 $\pm$ 4.4
No. PDE5i responders (%)	88 (56.4)	61 (61.6)	27 (47.4)
No. CVD or CVRF (%)	128 (82.1)	80 (80.8)	48 (84.2)
No. DM (%)	73 (46.8)	41 (41.4)	32 (56.1)

Groups were compared by 1-way ANOVA with Student t-test used for continuous variables and chi-square test used for categorical variables (p not significant).

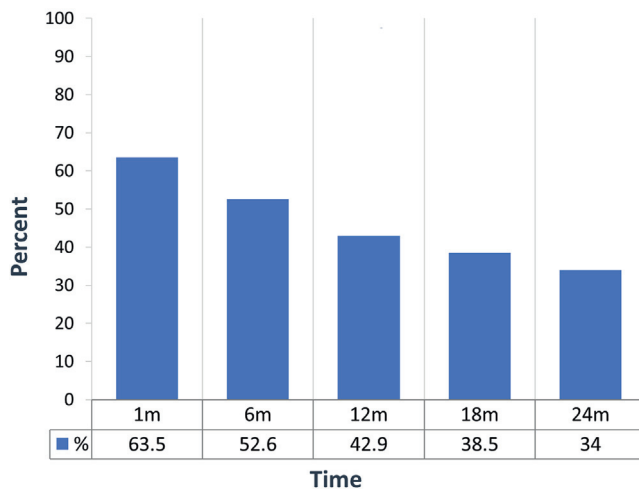


Figure 1. Percent of patients in whom improvement was maintained with time. *m*, months.

All patients with DM and severe ED at baseline in whom success was initially achieved lost the effect of LIST during the 2-year followup. On the other hand, patients with milder forms of ED and without diabetes had a 76% chance that the beneficial effect of LIST would be preserved after 2 years.

DISCUSSION

Although the results of the current study are limited to a relatively small cohort, they clearly show a gradual decrease in the effect of LIST on erectile function with time. The results indicate that patients with more severe disease at baseline had a higher probability of treatment failure at 2 years. Patients with DM were also prone to earlier failure, although DM was not an independent risk factor on multivariate analysis. Patients with severe ED and with diabetes had probably the worst prognosis as the initial positive response was not maintained in any patient in this group after 2 years.

Most of the study cohort comprised men with severe ED, including PDE5I nonresponders. This may explain the overall high long-term failure rate. Furthermore, initial success was defined by strict

Table 2. Univariate and multivariate analysis of possible risk factors for decrease in LIST effect

	No. Pts	No. 2-Yr Success (%)	p Value	
			Univariate	Multivariate
Overall	156	53 (34)		
Severe ED	86	20 (23.3)	0.002	0.001
PDE5i response	68	16 (23.5)	0.015	Not significant
DM pos	73	18 (24.7)	0.02	Not significant
ED more than 48 mos	78	22 (28.2)	Not significant	—
Age greater than 60	76	21 (27.6)	Not significant	—
Cardiovascular:			Not significant	—
Risk factors	128	41 (32)		
Disease	53	15 (28.3)		

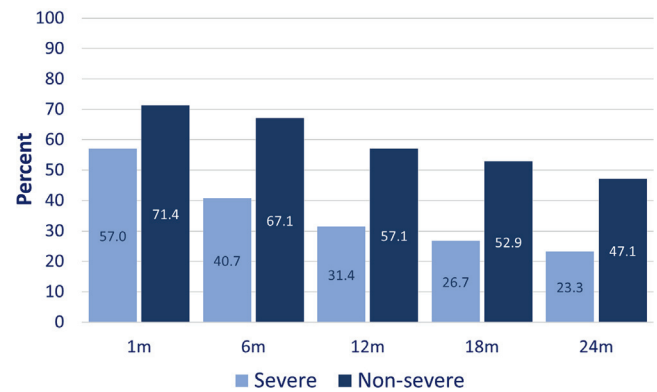


Figure 2. Maintenance of success with time according to ED severity. *m*, months.

MCID criteria, ie a change of at least 7 points in the IIEF-EF score in patients with severe ED. Using a different criterion such as an increase of only 5 points in the IIEF-EF score would probably have resulted in a higher success rate.

The apparent advantages of LIST, which is a noninvasive, nonpharmacological, easy to apply, painless and relatively inexpensive procedure, made it appealing. Consequently LIST was quickly accepted in clinical practice as a promising treatment option and it is even mentioned in EAU (European Association of Urology) guidelines.¹³ All of its advantages are relevant only if the effect is durable and preserved for a reasonable time. To date there is an increasing number of publications on LIST short-term efficacy but information on the long-term effect is lacking. To our knowledge this is the first study trying to answer this critical question.

Limited data are available on midterm followup. A study describing 1-year followup of shock wave therapy using similar protocol, device and evaluation measures showed a 71% success rate.¹⁴ Those results were similar to ours during 6-month followup and better than ours during 1-year followup. Bechara et al investigated the mid-term effect of LIST in a population of PDE5I nonresponders and found a surprisingly high 91.7% of patients in whom the positive response was maintained after 12 months.¹⁵ This difference can be attributable to different patient selection, a high dropout rate in the other studies and to our stricter criteria for a successful outcome.

A further limitation of the study is that some outcome data were collected through a telephone interview, including an indirect IIEF-EF questionnaire. Unfortunately we could not see all patients at the clinic for a formal visit including questionnaires. It is important to note that some patients probably used PDE5Is occasionally without reporting it, which may have biased the results.

The fading out phenomenon could simply be the result of the ongoing progress of the underlying pathology which initially caused ED. Since the systemic disease is not treated with penile LIST, the atherosclerotic effect continues to impair cavernous tissue and endothelial function during followup. The fact that the response to LIST was lost during 2-year followup in all patients with severe baseline ED and DM validates this logical assumption.

We should always bear in mind that performing a long-term study on a therapeutic effect for ED is challenging due to multiple intervening factors, eg a change in partners or in attitude regarding sex, personal crises, etc. Moreover, none of the participants was naïve to previous PDE5I treatment and they were always in the position to compare the effect of LIST to the effect of the previous PDE5I treatment.

The future of LIST as a reliable modality depends on our ability to improve its long-term efficacy mainly in patients with severe ED. This task will be achieved by animal and clinical studies on adjustments in the current treatment protocol to optimize immediate and long-term outcomes. These adjustments can include changing the total energy applied, improving local tissue penetration, modifying the number of treatment sessions and the duration of the treatment protocol, etc. A logical approach to improve long-term efficacy that should be investigated is to apply an additional shock wave therapy during followup. This could be performed routinely, ie as a maintenance therapy, or as an on

demand booster therapy when the effect starts to decrease.

In the meantime until further clinical data are available we should focus on improving patient selection. The LIST effect is better in the short term and more durable in the long term in patients with milder ED severity and fewer risk factors.

CONCLUSIONS

In patients who initially responded positively to LIST there is a gradual decrease in the effect on erectile function with time. Results indicate that patients with more severe disease at baseline have a higher probability of treatment failure at 2 years. Likewise patients with milder forms of ED have a better likelihood that the beneficial effect will be preserved after 2 years.

Long-term followup studies shed light on the true effect of LIST on erectile function. The reliability of this new physical therapy depends on its long-term efficacy. On one hand the long-term outcome reported in this study is relatively disappointing, mainly for patients with severe ED. On the other hand the lasting effect of LIST in a substantial group of patients revalidates the genuine restorative nature of this modality which cannot be attributed only to a placebo effect.

Further research is needed to optimize current treatment characteristics. In the meantime the data provided in this study can help us improve patient selection and better inform patients about the expected outcome.

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