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The Effect of Low-Intensity Shock Wave Therapy on Moderate Erectile Dysfunction: A Double-Blind, Randomized, Sham-Controlled Clinical Trial

Dimitrios Kalyvianakis, Ioannis Mykoniatis, Nikolaos Pyrgidis et al.

Correspondence: Nikolaos Pyrgidis (email: nikospyrgidis@gmail.com).

Full-length article available at auajournals.org/10.1097/JU.0000000000002684.

Study Need and Importance: The role of low-intensity shock wave therapy in patients with moderate erectile dysfunction remains uncaptured. In this context, we performed the first double-blind, randomized, sham-controlled trial to evaluate the efficacy and safety of low-intensity shock wave therapy exclusively in patients with moderate vasculogenic erectile dysfunction.

What We Found: Twelve sessions of low-intensity shock wave therapy twice weekly for 6 weeks with a treatment protocol of 5,000 impulses, 0.096 mJ/mm^2 energy flux density and 5 Hz frequency using the ARIES 2^{TM} device are highly effective in patients with moderate vasculogenic erectile dysfunction and previous good or partial response to phosphodiesterase type 5 inhibitors. Compared to sham therapy, the proportion of participants attaining a minimal clinically important difference in the International Index of Erectile Function–Erectile Function domain, as well as the mean change from baseline in the International Index of Erectile Function–Erectile Function domain and in the "yes" responses to question 3 of Sexual Encounter Profile diaries significantly improved at 1 and 3 months after low-intensity shock wave therapy (see Table).

Limitations: Due to the single-center design of our study and the eligibility criteria restricted to patients with moderate erectile dysfunction, we included a rather small number of patients. Additionally, the relatively short followup duration of our study did not permit us to assess the long-term efficacy of low-intensity shock wave therapy, as well as the duration of the positive effect of low-intensity shock wave therapy in patients with moderate vasculogenic erectile dysfunction. Importantly, since we applied a specific low-intensity shock wave therapy protocol, our results may not be extrapolated to other low-intensity shock wave therapy generator systems or protocols.

Interpretation for Patient Care: Our findings suggest that low-intensity shock wave therapy is highly effective and safe in patients with moderate vasculogenic erectile dysfunction.

Table. *Comparison of changes from baseline in the International Index of Erectile Function–Erectile Function domain and question 3 of the sexual encounter profile diaries after low-intensity therapy versus sham therapy adjusted for baseline values*

Parameter	Mean±SD Low-Intensity Shock Wave Therapy	Mean±SD Sham Therapy	Mean Difference (95% CI)	Between-Group p Value
International Index of Erectile Function—erectile function domain:				
Baseline—1 mo	4.9±3	0.9±2	3.9 (2.7–5.2)	**<0.001**
Baseline—3 mos	5.7±2.3	1.2±1.6	4.4 (3.4–5.4)	**<0.001**
Sexual encounter profile question 3 (yes %):				
Baseline—1 mo	21±22	−2.1±15	19 (11–27)	**<0.001**
Baseline—3 mos	28±25	1.5±16	23 (14–32)	**<0.001**

The analysis of covariance (ANCOVA) was applied. Bold type indicates statistically significant p values.

THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000002684
Vol. 208, 388-395, August 2022
Printed in U.S.A.

THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

The Effect of Low-Intensity Shock Wave Therapy on Moderate Erectile Dysfunction: A Double-Blind, Randomized, Sham-Controlled Clinical Trial

Dimitrios Kalyvianakis,[1,2] Ioannis Mykoniatis,[1,2] Nikolaos Pyrgidis,[2]* Paraskeui Kapoteli,[1] Filimon Zilotis,[1] Agrippina Fournaraki[1] and Dimitrios Hatzichristou[1,2]

[1]First Department of Urology, G. Gennimatas Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
[2]Institute for the Study of Urological Diseases, Thessaloniki, Greece

Purpose: We conducted the first double-blind, randomized, sham-controlled trial evaluating the efficacy and safety of low-intensity shock wave therapy (LiST) exclusively in patients with moderate erectile dysfunction.

Materials and Methods: Seventy patients were randomized to 12 sessions of LiST (35) or sham therapy (35) twice weekly. Patients were evaluated at 1 and 3 months after completion of treatment. The proportion of participants attaining minimal clinically important difference (MCID) in the International Index of Erectile Function–Erectile Function (IIEF-EF) and the effect of LiST on erectile function, as well as on safety, were the study outcomes.

Results: At 3 months, MCID was attained by 27 (79%) patients in the LiST group compared to 0 patients in the sham group. The risk difference between the 2 groups was 79% (95% confidence interval [CI]: 66–93, p <0.001) and the baseline-adjusted mean between-group-difference in the IIEF-EF was 4.4 points (95% CI: 3.4–5.4, p <0.001). At 1 month, MCID was attained by 20 (59%) patients in the LiST group compared to 1 (2.9%) patient in the sham group. The risk difference between the 2 groups was 56% (95% CI: 38–73, p <0.001) and the baseline-adjusted mean between-group-difference in the IIEF-EF was 3.9 points (95% CI: 2.7–5.2, p <0.001).

Conclusions: Twelve sessions of LiST twice weekly for 6 weeks with a treatment protocol of 5,000 impulses, 0.096 mJ/mm^2 energy flux density and 5 Hz frequency are highly effective in patients with moderate erectile dysfunction. Still, further long-term randomized studies are warranted to corroborate our findings.

Abbreviations and Acronyms

ED = erectile dysfunction
IIEF-EF = International Index of Erectile Function–Erectile Function
LiST = low-intensity shock wave therapy
MCID = minimal clinically important difference
PDE5 = phosphodiesterase type 5
RCT = randomized controlled trial
SEP = Sexual Encounter Profile

Key Words: extracorporeal shockwave therapy, erectile dysfunction, randomized controlled trial

Accepted for publication March 19, 2022.

Support: The LiST device was provided by Dornier MedTech GmbH, Wessling, Germany. The Institute for the Study of Urological Diseases supported the trial. The funding institution reviewed only the design and conduct of the study. The funder had no role in the collection, management, analysis and interpretation of the data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication. Wolters Kluwer, the publisher of The Journal of Urology®, made this article accessible online by all without charge through the PubMed Central (PMC) repository.

Conflict of Interest: Dimitrios Hatzichristou is a speaker and investigator for Dornier MedTech GmbH.

Author Contributions: All authors participated in the drafting, writing and editing of the manuscript. All gave final approval and agree to be accountable for all aspects of work, ensuring integrity and accuracy.

Submission History: This paper was presented at the ESSM2022 Virtual Meeting on February 19, 2022.

* Correspondence: Institute for the Study of Urological Diseases, Alois 16, Pilaia, Thessaloniki, Greece (telephone: 0030 6982 14 2006; FAX: 0030 2310 99 2543; email: nikospyrgidis@gmail.com).

THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000002684
Vol. 208, 388-395, August 2022
Printed in U.S.A.

Erectile dysfunction (ED) is highly prevalent in the general population and is typically classified, based on its severity, into mild, mild-to-moderate, moderate and severe.[1] Low-intensity shock wave therapy (LiST) is considered among the acceptable treatment modalities and is recommended as first-line treatment in the European guidelines for well-selected patients with vasculogenic ED.[2] The available randomized controlled trials (RCTs) that paved the way for this recommendation were performed in patients with different levels of ED severity and were, therefore, underpowered to determine the separate efficacy rate of LiST in patients with mild, mild-to-moderate, moderate or severe ED.[3]

The lack of direct evidence regarding the efficacy of LiST in patients with different levels of ED severity is reflected by multiple guideline recommendations which postulate, based on nonrandomized studies, that LiST may be predominantly effective in patients with mild or mild-to-moderate vasculogenic ED.[4] However, it should be highlighted that indirect evidence suggests that LiST may also be safe and effective in patients with moderate or severe vasculogenic ED.[5,6] These contradictory findings have fueled the debate about the characteristics and severity of symptoms that LiST responders should display.[7]

Based on the previous notion, although patients with moderate ED are the largest group of patients who require treatment of ED,[8] the efficacy of LiST in this group remains uncaptured. In this scope, we conducted the first double-blind, randomized, sham-controlled trial aiming to evaluate the efficacy and safety of LiST exclusively in patients with moderate vasculogenic ED.

METHODS

Study Design

We performed this RCT at the outpatient andrology department of our institution. The study protocol was predefined, approved by the corresponding Institutional Review Board (IRB No. 5142/02_04_18) and registered at ClinicalTrials.gov (NCT03518983). Our findings were reported based on the CONSORT statement.[9,10] All individuals were recruited from June 2018 to January 2021 and their final followup results were obtained in July 2021.

Selection Criteria

The predefined inclusion criteria comprised: 1) sexually active male patients 40-70 years old in a stable, heterosexual relationship for more than 3 months, 2) presence of vasculogenic ED (defined after medical history by experienced clinicians) for at least 6 months, 3) regular use of any phosphodiesterase type 5 (PDE5) inhibitor with good or partial response to treatment (defined as at least 5/10 successful sexual intercourse attempts), 4) presence of moderate vasculogenic ED after a 1-month washout from PDE5 inhibitors, documented with an 11−16 score in the International Index of Erectile Function−Erectile Function (IIEF-EF), 5) agreement to suspend any ED treatment for the duration of the study, 6) agreement to attempt sexual intercourse, without prior intake of alcohol or recreational drugs, at least 4 times every month for the duration of the study and document the outcome of each attempt using the Sexual Encounter Profile (SEP) diaries.

The predefined exclusion criteria comprised: 1) any history of trauma, major surgery or radiation to the pelvis, 2) any history of priapism, penile fracture or major penile surgery, 3) presence of Peyronie's disease or other anatomical disorders restricting sexual intercourse, 4) abnormal serum testosterone levels (<300 ng/dl or >1,197 ng/dl), 5) presence of any severe or unregulated medical or psychiatric disease precluding participation to the study, 6) allergy to the ultrasound gel, 7) partners of patients with self-reported sexual dysfunction or other medical conditions restricting sexual activity, 8) pregnant, breastfeeding or younger than 18 years old partners of patients.

Recruitment, Randomization and Blinding

All patients presenting to our outpatient clinic who were regular PDE5 inhibitor users and were willing to undergo treatment with LiST monotherapy were initially screened by 2 certified urologists on sexual medicine. They underwent a detailed medical and sexual history, an extensive physical examination and necessary laboratory tests to establish vasculogenic ED diagnosis and to exclude other causes of ED, such as psychogenic, neurogenic, iatrogenic or endocrine. Subsequently, those patients willing to participate in the study underwent a 1-month washout period from any PDE5 inhibitor or other ED treatments. In this 1-month period, they were requested to attempt sexual intercourse at least 4 times and document outcomes in the SEP questionnaire (a validated, self-reported diary of 5 yes-no questions that patients completed after each sexual intercourse attempt). SEP dairies were then evaluated and all patients completed the IIEF.[11]

Patients fulfilling the eligibility criteria underwent randomization, based on a computer-generated simple randomization sequence, in a 1:1 ratio to 12 sessions of LiST or sham therapy twice weekly for 6 weeks. To preserve allocation concealment, the coordinating team performed the assignment of all patients to each group via a web-based registration system. Each group was attributed to a unique probe designed to deliver either LiST or sham therapy. To ensure the double-blind design of the trial, the sham probe was specially manufactured to be identical to the LiST probe and to generate the same noise and vibrations during treatment without delivering any shock wave energy. After completion of the study, the manufacturer revealed the function of each probe. Therefore, physicians, staff collecting data and patients were blinded to group allocation throughout the course of the study.

Study Protocol

All sessions were performed by a LiST or a sham generator (ARIES 2^{TM} and Smart Focus probe) provided by Dornier MedTech GmbH, Wessling, Germany. Treatment was applied in the supine position without anesthesia. Patients allocated to LiST received during each session 5,000 impulses along the penis at an energy flux density of 0.096 mJ/mm^2 and a frequency of 5 Hz (level 7 at the

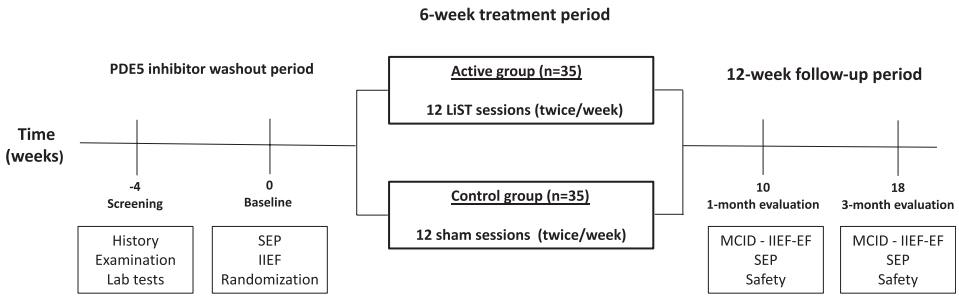

Figure 1. Study protocol.

ARIES 2 generator). More specifically, 2,000 impulses were delivered to the corpora cavernosa, 2,000 to the crura cavernosa and 1,000 to the penile hila based on a protocol developed by our research team.[12–14]

At 1 and 3 months after completion of the 12-session treatment, all participants were requested to proceed for additional clinical evaluations. Any PDE5 inhibitors or other ED treatments were prohibited throughout the whole followup period. All participants returned their SEP diaries for the last month and completed the IIEF-EF at both followup evaluations. Question 3 of the SEP diaries ("Did your erection last long enough for you to have sexual intercourse?") was evaluated. For each sexual attempt, a yes response to this question was scored with 1 and a no response was scored with 0. Subsequently, the percentage of successful sexual attempts based on the total number of attempts was estimated. Accordingly, the minimal clinically important difference (MCID), defined as an improvement in the IIEF-EF by at least 5 points, was also documented.[15] The detailed study protocol is depicted in Figure 1.

Study Outcomes and Sample Size Estimation

The primary outcome of our study was the proportion of patients in each group attaining MCID based on the IIEF-EF at 3 months after completion of the treatment protocol. Secondary outcomes included: 1) the proportion of patients in each group attaining MCID based on the IIEF-EF at 1 month after completion of treatment protocol, 2) the mean change from baseline in the IIEF-EF between the 2 groups at the 1- and 3-month evaluations after completion of treatment protocol, 3) the mean change from baseline of the proportion of yes responses to question 3 of the SEP diaries between the 2 groups at the 1- and 3-month evaluations, 4) any treatment-related adverse events.

Based on RCTs recruiting patients with moderate ED, we supposed that at the 3-month evaluation the proportion of patients attaining an MCID based on the IIEF-EF in the LiST group would be 60% and in the sham group 25%.[6,16] Assuming an 80% statistical power and a 5% 2-sided type I margin of error, we estimated, based on the χ^2 test, a sample size of 30 participants per group. Considering an approximately 20% dropout rate, we recruited a total of 70 participants.

Statistical Analysis

The proportions of patients attaining an MCID in the IIEF-EF at 1 and 3 months between the 2 groups were compared with the χ^2 test. The absolute risk difference with the corresponding 95% CIs was also estimated. To compare the mean change from baseline between the 2 groups in the IIEF-EF and in the proportion of yes responses to question 3 of the SEP diaries, we applied the analysis of covariance (ANCOVA) adjusting only for the baseline value of each variable. All statistical analyses were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria) and 2-sided p values lower than 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics and Followup

A total of 70 patients with moderate ED were randomized to LiST (35) or sham therapy (35). The median age of the included participants was 57 years (IQR: 52.6) and their median duration of ED was 48 months (IQR: 33.8). No statistically significant differences were detected between the 2 groups in terms of their baseline characteristics (Table 1). All included participants received the allocated intervention and completed the treatment protocol of 12 LiST or sham therapy sessions twice weekly for 6 weeks. Apart from mild discomfort during the application of therapy, no other treatment-related adverse events were reported.

After completion of the treatment protocol, all participants were requested to proceed to the followup evaluations. One patient in the active (due to

Table 1. *Baseline characteristics of the study participants*

Baseline Characteristics	LiST		Sham Therapy	
No. pts	35		35	
Median yrs age (IQR)	54	(47—63)	61	(52—64)
Median kg/m^2 body mass index (IQR)	28	(25—31)	28	(25—31)
No. smoking (%)	13	(37)	11	(31)
No. hypertension (%)	14	(40)	13	(37)
No. diabetes (%)	8	(23)	7	(20)
No. hyperlipidemia (%)	8	(23)	12	(34)
No. coronary heart disease (%)	7	(20)	9	(26)
Median ng/dl testosterone (IQR)	490	(409—556)	445	(384—556)
Median mos ED duration (IQR)	68	(35—124)	48	(32—97)
Median IIEF on PDE5 inhibitors (IQR)	55	(53—61)	57	(53—61)
Median IIEF—EF on PDE5 inhibitors (IQR)	22	(20—25)	23	(21—25)
Median IIEF after washout (IQR)	42	(39—44)	42	(37—45)
Median IIEF-EF after washout (IQR)	14	(13—16)	15	(13—16)
Median % yes SEP question 3 (IQR)	25	(0—25)	25	(25—25)

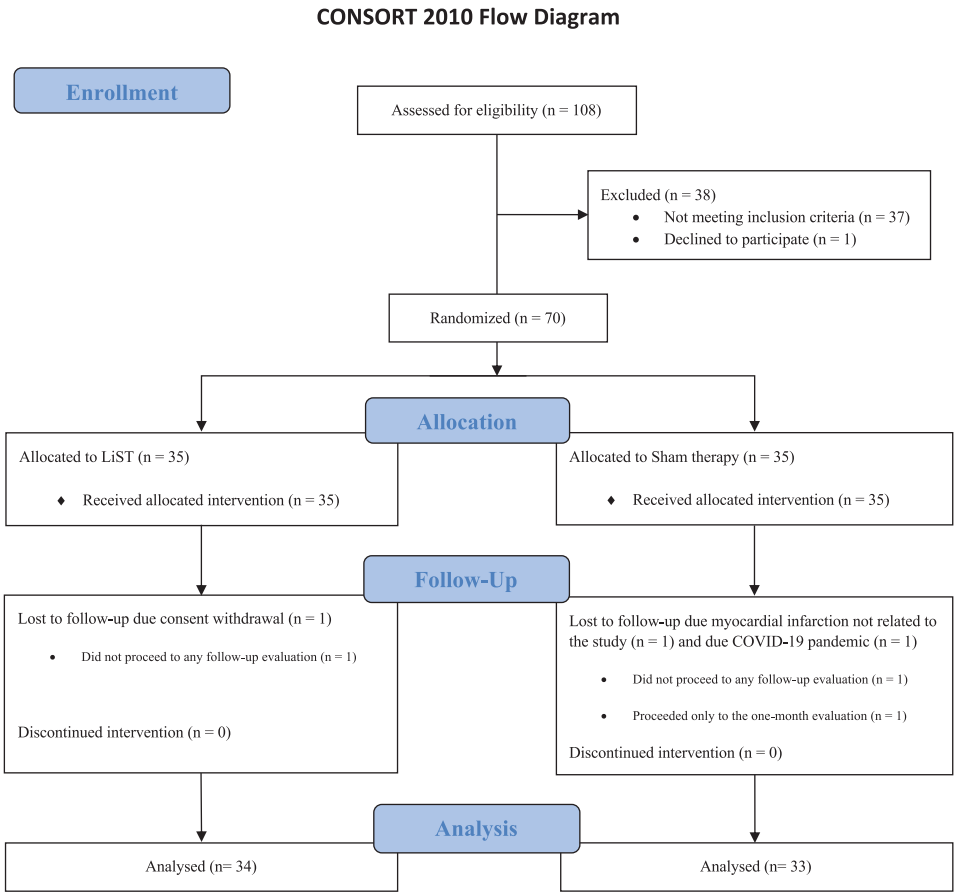

Figure 2. Study flowchart.

consent withdrawal) and 1 in the control group (due to myocardial infarction not related to the study) did not proceed to any followup evaluation. Additionally, 1 patient in the control group proceeded only to the 1-month evaluation (due to the COVID-19 pandemic). The step-by-step CONSORT flowchart is depicted in Figure 2.

Patients Attaining MCID

Regarding the primary outcome, 27 (79%) patients attained an MCID in the LiST group compared to 0 patients in the sham group ($p < 0.001$) at the 3-month followup evaluation. Therefore, at the 3-month evaluation 79% (95% CI: 66–93) more patients treated with LiST attained an MCID in the IIEF-EF scale compared to sham therapy. At the 1-month followup evaluation, 20 (59%) patients attained an MCID in the LiST group compared to 1 (2.9%) patient in the sham group ($p < 0.001$). Therefore, at the 1-month evaluation 56% (95% CI: 38–73) more patients treated with LiST attained an MCID in the IIEF-EF scale compared to sham therapy. The proportion of patients attaining an MCID after each treatment, as well as the corresponding comparisons between the 2 groups, are displayed in Table 2 and the raw data of all participants in the supplementary Table (https://www.jurology.com).

Effect of LiST on Erectile Function

At the baseline evaluation, the 2 groups did not display any significant differences in the IIEF-EF ($p = 0.41$) and in the proportion of "yes" responses to question 3 of the SEP diaries ($p = 0.07$). A statistically significant improvement in both scores was demonstrated at the followup evaluations after LiST compared to sham therapy. Adjusting for the baseline values, LiST resulted in a statistically significant improvement of the IIEF-EF both at the

Table 2. *Patients attaining MCID in the IIEF-EF at the 1- and 3-month followup evaluations*

Patients with MCID in the IIEF-EF	No. LiST/Total No. (%)	No. Sham Therapy/Total No. (%)	% Risk Difference (95% CI)	Between-Group p Value
1 mo	20/34 (59)	1/34 (2.9)	56 (38, 73)	**< 0.001**
3 mos	27/34 (79)	0/33 (0)	79 (66, 93)	**< 0.001**

The chi-squared (χ^2) test was performed for all comparisons. Bold type indicates statistically significant p values.

Table 3. *Absolute between-group difference of LiST versus sham therapy in the IIEF-EF and SEP question 3 at all time points*

Parameter	Baseline	1 Mo	3 Mos
Mean±SD IIEF-EF:			
LiST	14±1.7	19±3.3	20±2.4
Sham therapy	14±1.6	15±2	16±2.2
p Value for between groups		**<0.001**	**<0.001**
Mean±SD SEP question 3 (Yes %):			
LiST	20±16	41±18	48±22
Sham therapy	25±12	23±14	26±16
p Value for between groups		**<0.001**	**<0.001**

The 2-sample t-test was performed for between-group comparisons. Bold type indicates statistically significant p values.

1-month (3.9 points, 95% CI: 2.7−5.2, p <0.001) and at the 3-month (4.4 points, 95% CI: 3.4−5.4, p <0.001) followup evaluations compared to sham therapy. Similarly, adjusting for the baseline values, LiST resulted in a statistically significant improvement of the proportion of "yes" responses to question 3 of SEP diaries both at the 1-month (19%, 95% CI: 11−27, p <0.001) and at the 3-month (23%, 95% CI: 14−32, p <0.001) followup evaluations compared to sham therapy. The corresponding measures and comparisons are presented in Tables 3 and 4, whereas the effect of treatment over time on a patient level is illustrated in Figure 3.

DISCUSSION

The present RCT indicates that 12 sessions of LiST twice weekly for 6 weeks are highly effective in patients with moderate vasculogenic ED and previous good or partial response to PDE5 inhibitors. Compared to sham therapy, the proportion of participants attaining an MCID in the IIEF-EF, as well as the mean change from baseline in the IIEF-EF and in the "yes" responses to question 3 of SEP diaries, significantly improved at 1 and 3 months after LiST. As expected from previous RCTs, no treatment-related adverse events occurred after LiST.

To our knowledge, we provide the first RCT exploring the efficacy of LiST in a homogenous group in terms of baseline characteristics and ED severity. We selected patients with moderate ED, as they may predominantly benefit from the tissue regenerative properties of LiST. In particular, most patients with moderate ED opt for PDE5 inhibitors and initially respond well to oral treatment.[17] However, in many cases these patients develop severe ED due to progression of the underlying ED pathophysiology.[18] Therefore, patients with moderate ED may be an ideal population for the application of regenerative treatment modalities in an attempt to delay ED progression.[19]

Indeed, our findings indicate that patients with moderate ED may benefit from the regenerative properties of LiST. We also aimed to contextualize the magnitude of LiST efficacy in patients with moderate ED. The number of participants attaining MCID and the corresponding IIEF-EF improvement were higher compared to previous studies.[20−22] However, the fact that all available RCTs on the field enrolled patients with different degrees of ED did not permit them to provide robust outcomes.[23] Nevertheless, the ED severity of each patient is crucial when selecting LiST as a treatment modality.[24] Therefore, the present sham-RCT was tailored to showcase LiST as a valuable addition to the health care provider's armamentarium for the management of moderate vasculogenic ED. Of note, our findings are also in line with previous studies performed by our research team, applying the same LiST protocol.[13,25]

A plethora of basic-research studies have suggested that LiST induces shear stress and endothelial damage which, in turn, leads to neoangiogenesis and remodeling of the corporal tissue.[26] LiST may improve erectile function by activating a regeneration cascade in the erectile tissue, vessels and nerves and by reversing the pathological processes of ED.[27] Still, the exact pathophysiological mechanism of LiST remains unknown, which further discourages clinicians from accepting LiST as a first-line treatment modality for ED.[28] Studies exclusively in patients with mild, mild-to-moderate or severe ED may cover this gap in the literature. Similarly, high-quality and predominantly multicenter cohort studies are mandatory to determine the duration of the positive effect of LiST.[29] Based on the previous notion, further studies evaluating the role of LiST as part of a combination treat-

Table 4. *Comparison of changes from baseline in the IIEF-EF and SEP question 3 after LiST versus sham therapy unadjusted and adjusted for the baseline value, with ANCOVA applied*

Parameter	Mean±SD LiST	Mean±SD Sham Therapy	Unadjusted Mean Difference (95% CI)	Adjusted Mean Difference (95% CI)	Adjusted between-Group p Value
IIEF-EF:					
Baseline—1 mo	4.9±3	0.9±2	4 (2.8 to 5.3)	3.9 (2.7 to 5.2)	**<0.001**
Baseline—3 mos	5.7±2.3	1.2±1.6	4.5 (3.5 to 5.5)	4.4 (3.4 to 5.4)	**<0.001**
SEP question 3 (Yes %):					
Baseline—1 mo	21±22	−2.1±15	23 (14 to 33)	19 (11 to 27)	**<0.001**
Baseline—3 mos	28±25	1.5±16	27 (16 to 37)	23 (14 to 32)	**<0.001**

Bold type indicates statistically significant p values.

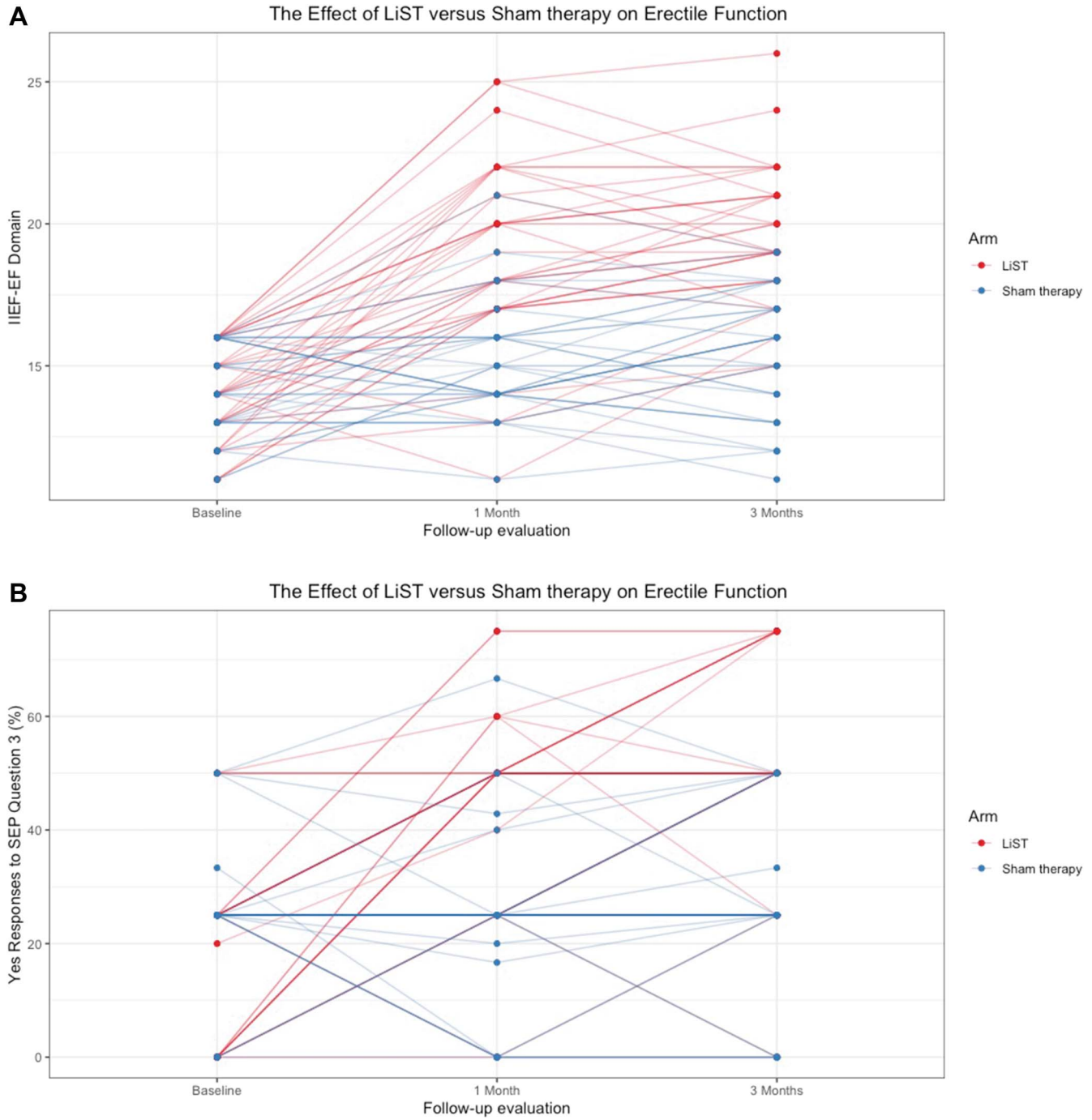

Figure 3. Parallel coordinate plots of patient-level data about the effect of LiST versus sham therapy on IIEF-EF (*A*) and "Yes" responses to SEP question 3 (*B*).

ment modality in patients with refractory ED are expected with great interest.[30]

It should be stressed that the findings of the present RCT were mitigated by some limitations. First of all, we did not apply any penile ultrasound measures to establish the vasculogenic origin of ED. Still, the fact that a low proportion of "yes" responses to question 3 of the SEP diaries was documented at baseline, as well as the fact that most included patients displayed comorbidities associated with vasculogenic ED, support its vasculogenic origin. Importantly, due to the single-center design of our study and due to our eligibility criteria restricted to patients with moderate ED, we included a rather small number of participants. Based on the previous notion, due to the relatively short followup duration of our study, the long-term efficacy of LiST, as well as the duration of the positive effect of LiST in patients with moderate vasculogenic ED, remain uncaptured. Moreover, since we applied a specific LiST protocol,

our results cannot be extrapolated to other LiST generator systems or protocols.

CONCLUSIONS

Our findings suggest LiST is highly effective and safe in patients with moderate vasculogenic ED. More than two-thirds of patients undergoing LiST twice weekly for 6 weeks presented an MCID based on the IIEF-EF scale. Compared to sham therapy, LiST significantly improved the proportion of participants attaining MCID in the IIEF-EF, as well as the mean IIEF-EF and SEP diaries scores at the 1- and 3-month followup evaluations. Still, further high-volume, multicenter RCTs with strict eligibility criteria and long-term followup are mandatory to corroborate our findings.

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