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ARTICLE

Clinical Research

# Evaluation of a low-intensity shockwave therapy for chronic prostatitis type IIIb/chronic pelvic pain syndrome: a double-blind randomized sham-controlled clinical trial

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## Abstract

**Background** Currently, there is no efficacious treatment method for chronic prostatitis type IIIb/chronic pelvic pain syndrome (CP/CPPS). Aim of the study was to investigate and compare the efficacy and safety of low-intensity shockwave therapy (LiST) vs. sham treatment in CP/CPPS patients.

**Methods** Patients with CP/CPPS diagnosis were randomized in this prospective, sham-controlled, double-blind study either to the active groups (Group B, C) who received 5000 shockwaves per session with energy flux density 0.1 mJ/mm$^2$ or to the sham group (Group A) who received 5000 shockwaves from a visually identical sham probe. All groups underwent six sessions (once/week). LiST effects on pain, micturition, quality of life (QoL), and erectile function were evaluated at 4, 12, and 24 weeks after treatment. The parameters were investigated using validated questionnaires. Uroflowmetry and post void residual calculation were performed at baseline and at 4- and 12-week FU visit. Prostate mpMRI and PSA measurement were performed at baseline and 12-week FU visit.

**Results** Overall, 45 men were randomized to the active ($n = 30$) and sham groups ($n = 15$). Regarding impact of LiST in National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) total, pain, and QoL subdomains scores a clear and persistent in all FU timepoints improvement was found compared to sham treatment. NIH-CPSI urinary subdomain, International Prostate Symptom Score [IPSS], PSA, and mpMRI-PIRADS scores did not differ between the two groups. The mean difference between the LiST and sham group in the change of the NIH-CPSI pain-domain score (Q1–4) from baseline to 12 weeks after final treatment which was 3.3 (95% CI, 1.8, 4.7). Perineal LiST was easy and safe to perform without anesthesia or any side-effects.

**Conclusions** LiST seems to be a safe and effective treatment option for CP/CPPS, considerably improving pain and quality of life. Lack of any side-effects, and the potential for repetition make LiST a promising treatment choice for CP/CPPS patients.

## Introduction

Despite its high prevalence and its increasing morbidity, which is comparable to that of diabetes mellitus, Crohn's disease or the condition after a heart attack [1], no standardized or unanimous accepted treatment is available, so far, for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Common pharmacological interventions, as well as numerous non-pharmacological interventions have been proposed but their efficacy, as monotherapies, remains controversial due to low-quality published evidence, while in certain cases their reported side-effects may predominate over their potential treatment effect [2, 3]. Recently, a multimodal therapeutic approach by using phenotype driven choices has been proposed as a promising treatment solution for this very difficult-to-treat syndrome [4, 5]. Moderate intensity shockwave therapy has been proposed for pain reduction in CP/CPPS patients due to its analgesic,

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anti-inflammatory, and anti-spastic effects [6]. Interestingly, even though perineal shockwave therapy efficacy and safety have been previously reported both in randomized clinical trials (RCTs) and meta-analyses [2, 7–10], these evidence have failed, so far, to derive a guideline recommendation supporting the application of shockwave therapy for the treatment of CP/CPPS [11, 12]. Moreover, low-intensity shockwave therapy (LiST) has never been tested. In this scope, aim of our study was to further investigate and compare the efficacy and safety of LiST vs. sham treatment in CP/CPPS patients, using an alternative treatment protocol to control treatment-associated pain.

## Material and methods

### Study design

The study was a double-blind randomized sham-controlled clinical trial performed at the CP/CPPS outpatient clinic of an academic hospital. Study protocol was reviewed and approved by the institutional ethics board and registered at clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT03543761). This randomized clinical trial was undertaken according to Consolidated Standards of Reporting Trials (CONSORT) statement [13] (Appendix 1). All participants gave written informed consent before being enrolled. Patients were recruited from June 2018 to June 2019 and the final results were obtained in January 2020.

### Participants

The predefined inclusion criteria for participation in the clinical trial were: (i) age between 18 and 60 years old, (ii) diagnosis of with CPPS (type IIIB) according to National Institutes of Health (NIH) classification causing pain or discomfort in the perineal or pelvic region for at least a 3 [3] month period within the last 6 [6] months without clear abnormalities on urological examination, (iii) NIH-Chronic Prostatitis Symptom Index (CPSI) total score of more than 15 and pain-domain >4, (iv) Patient's unrestricted capability to consent and comply to the protocol.

The predefined exclusion criteria were: (i) presence of infection in urine and/or sperm, (ii) history of prostate, bladder, or urethral cancer, (iii) history of prostate or pelvic surgery, pelvic radiation, systemic, or chemotherapy intravesical chemotherapy, (iv) Unilateral orchialgia without pelvic symptoms, active urethral stricture or bladder stones, or any other urological condition associated with lower urinary tract symptoms, any neurological disease or disorder affecting the bladder, (v) PI-RADS score 4–5 in the baseline prostate multi-parametric MRI (mpMRI), (vi) prostatic specific antigen (PSA) >4 and/or positive (suspicious for malignancy) digital rectal examination (DRE).

At screening the diagnosis of CPPS (type IIIB) was based on full medical history, clinical examination, the NIH-CPSI questionnaire, 2-glass test, semen culture, and uroflowmetry with residual urine measurement. In order bacterial and type IIIA prostatitis to be excluded during 2-glass test, a diagnostic method previously proved to have strong concordance with the gold standard 4-glass test [14], one 10-cc urine sample was collected before and one after prostate massage. These samples were analyzed for signs of inflammation (leukocytes) and cultured to detect bacteria, if present. Prostate cancer was ruled out clinically (by DRE), serologically (by PSA testing) and by imaging (mpMRI) at baseline.

The CONSORT flow diagram [13] is shown in Fig. 1a.

### Study protocol

After primary screening visit, all patients receiving other treatments for CP/CPPS underwent a 2-week washout period. All eligible patients were randomly assigned in a 2:1 ratio, to either active LiST or sham treatment. Participants agreed not to receive any other CP/CPPS treatment during the study period.

Patients were assessed by the NIH-CPSI, the International Prostate Symptom Score [IPSS], the International Index of Erectile Function-Erectile Domain (IIEF-ED) and the clinical phenotype system status [urinary, psychosocial, organ specific, infection, neurologic/systemic, tenderness, and sexual dysfunction (UPOINTS)] at baseline and 4, 12, and 24 weeks after their final treatment session. All questionnaires were completed by the patients at the aforementioned time points. PSA measurement and mpMRI of the prostate were performed at screening and at 12-week FU visit. Maximum urinary flow rate (Qmax) measured by uroflowmetry and post void residual (PVR) measured by ultrasound were recorded at baseline and at 4- and 12-week FU visits. At each treatment or FU visit any form of adverse event was reported and also degree of treatment-induced pain was assessed by a pain visual analog scale (VAS) score at the end of each treatment visit. Study protocol is depicted in Fig. 1b.

### Randomization/allocation concealment/blinding

On visit 2 (V2), all eligible patients were randomized by the study coordinating center with a computer-generated randomization sequence in a 2:1 ratio. To ensure allocation concealment and minimize bias, the coordinating center created three 15-patient groups (A, B, and C) via a web-based registration system. Each group was attributed to a unique probe designed to deliver either shockwave energy

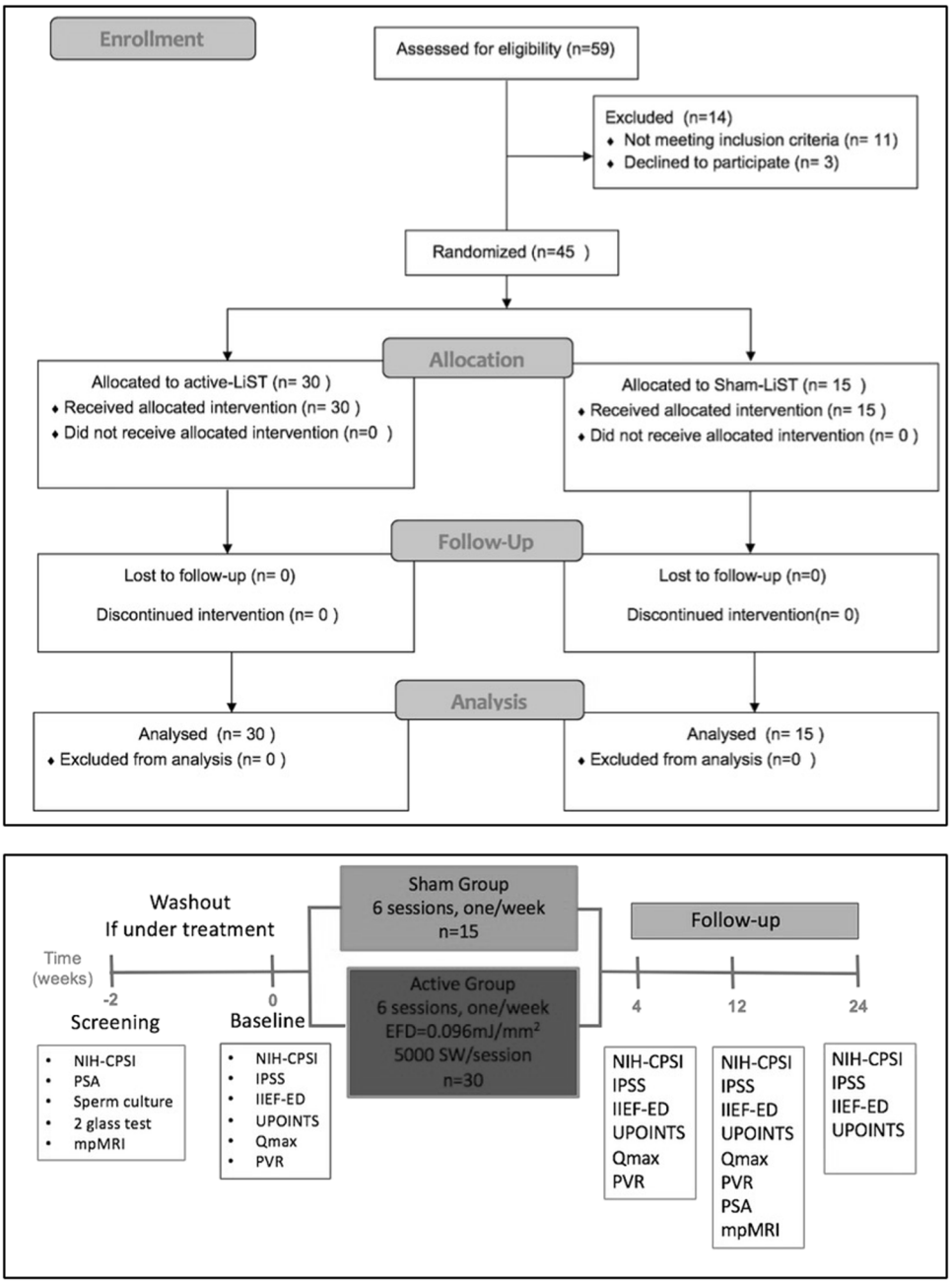


**Fig. 1 Patient enrollement proccess and study design.** **a** CONSORT flow diagram. **b** Study protocol.

or sham treatment. If only two groups were created, the person applying would have used the one probe more times than the other, violating the double-blind design of our trial. The sham probe had been specially manufactured in order to be identical to both active probes generating the same noise and vibration but without delivering any shockwave energy.

Overall, the double-blind character of the study was ensured as the participants and the clinicians applying the LiST sessions were unaware of which treatment protocol (active or sham) each group received.

## Shockwave therapy application

Patients were treated with a low-energy shockwave generator (ARIES 2 and Smart Focus probe; Dornier MedTech GmbH, Wessling, Germany). Active Groups (Group B and C) underwent sessions (one/week) with active LiST probe following a treatment protocol of 5000 SW/session, energy flux density (EFD) = 0.096 mJ/mm$^2$ (energy level 7) and frequency = 5 Hz. Sham Group (Group A) underwent six sessions (one/week) with sham LiST probe following the same treatment protocol as the patients of active groups.

Perineal LiST application was performed with the patient in the supine position and with the hip abducted and flexed, giving the therapist free access to the urogenital diaphragm. The probe was applied with ultrasound gel perpendicular to the perineal body targeting the painful areas of the prostatic and perineal region. Each treatment session lasted ~20 min without local or systemic analgesia needed. Experienced investigators (F.Z. and I.M.) applied the treatment protocol.

The final LiST EFD = 0.096 mJ/mm$^2$ was selected based on a pilot study that we conducted 1 month prior to the inception of the present RCT. In 15 CP/CPPS patients, three EFD levels (0.25, 0.15, and 0.096 mJ/mm$^2$) were gradually applied. Starting from the highest and most widespread in previous relevant studies energy level (EFD = 0.25 mJ/mm$^2$) 11 out of 15 patients (73.3%) experienced a bothering treatment-induced pain (mean VAS score = 4.13). At EFD = 0.15 mJ/mm$^2$ 3 out of 15 patients (20%) experienced a bothering treatment-induced pain (mean VAS score = 2.59). When we tested EFD = 0.096 mJ/mm$^2$ no patient experienced a bothering treatment-induced pain (mean VAS score = 0.45).

## Outcomes

### Primary outcome

The difference between the LiST and sham group in the change of the NIH-CPSI pain-domain score (Q1–4) from baseline to 12 weeks after final treatment.

### Secondary outcomes

- The difference between the LiST and sham group in the change of the NIH-CPSI pain-domain score (items 1–4) from baseline to 4 and 24 weeks after final treatment.
- The difference between the LiST and sham group in the change of the following parameters from baseline to 4, 12, and 24 weeks after final treatment:
  (i) Total NIH-CPSI score (items 1–9), (ii) NIH-CPSI Urinary domain score (items 5–6), (iii) NIH-CPSI Quality of life domain score (items 7–9), (iv) IIEF-ED score, (v) IPSS score, (vi) Qmax and PVR, (vii) Number of positive domains in UPOINTS phenotype system.
- The difference between LiST and sham group in the mean pain VAS score after six LiST sessions.
- Changes in mpMRI before and 12 weeks after treatment.
- Adverse events rate in all patients.

### Sample size calculation

Primary endpoint of the study, according to which the sample size was calculated, was the change in NIH-CPSI pain subdomain score from baseline to 12-week FU visit. Given the data from previous RCTs [7–9], we assumed conservatively that for the CPSI-pain subdomain, the sham group will improve by 1 point, and the active group will improve by 4 points, with a standard deviation (SD) of 3 points. Therefore, for 80% power and a 2-sided significance level of 0.05, we required 12 sham: 24 active participants to show a 3-point clinical significance difference between the two treatment groups. Assuming a 20% dropout, we recruited 15 sham: 30 active participants.

## Statistical analysis

Continuous variables are demonstrated as mean with standard deviation (SD) or as median with interquartile range ($Q_1$–$Q_3$), while frequencies with percentages for categorical variables *n* (%). Independent samples *t*-test and the nonparametric test of Mann–Whitney were used in order to compare the continuous variables among treatment groups. To assess group mean differences in the changes from baseline in all continuous variables, analyses of covariance was used with change from baseline at follow-up as dependent variable and baseline value of the dependent variable and treatment group as covariates. Test of normality was conducted using Shapiro–Wilk test as well as histograms, P–P and Q–Q plots. Relationships with a *p* value ($p$) < 0.05 were considered as statistically significant. All reported *P* values are two-sided. Data were analyzed in the Statistical Package for the Social Sciences 25.0 (SPSS Inc., Chicago, IL, USA) and R statistical software (Version 3.6.2).

# Results

Overall, 45 men were randomized to the active ($n = 30$) and sham groups ($n = 15$). The mean age of patients in the active and sham groups were 42.2 ± 10.1 and 46.1 ± 10.7 years, respectively. Baseline characteristics of the participants are summarized in Table 1. In the baseline evaluation the means of all study's parameters were not statistically different for the two groups.

## NIH-CPSI total, pain, and QOL subdomains scores

With respect to within-group data analysis, NIH-CPSI total, pain, and QOL subdomains scores and also the score of question#4 of NIH-CPSI (assessing specifically pain severity) were significantly improved in the active group in all FU timepoints compared to baseline ($p < 0.05$). On the contrary, the sham group showed a transient significant improvement only for the pain subdomain and only at the 4-week FU visit (Table 2). Regarding between-group analysis, the values of the above parameters were significantly different in favor of the active LiST group in all FU timepoints (Table 2 and Fig. 2a, b). Moreover, when the changes from baseline to 4,

**Table 1** Baseline characteristics of the study participants.

| | Active group | Sham group | *p* value |
|---|---|---|---|
| *N* (%) | 30 (66.7) | 15 (33.3) | – |
| Age (years) | 42.2 (10.1) | 46.1 (10.7) | 0.238 |
| Height (cm) | 179.4 (7.1) | 174.3 (5.4) | 0.018 |
| Weight (Kg) | 85.4 (13.1) | 74.6 (9.5) | 0.007 |
| Body mass index (Kg/m$^2$) | 26.5 (3.7) | 24.6 (3.0) | 0.087 |
| Number of previous CP/CPPS treatments | | | |
| 0–1 | 0 | 0 | 1 |
| 2–3 | 24 | 11 | 0.472 |
| >3 | 6 | 4 | 0.297 |
| PI-RADS score | 2 (2–2) | 2 (2–2) | 0.350 |
| PSA (IQR) | 0.73 (0.45–1.39) | 0.76 (0.58–1.28) | 0.736 |
| NIH-CPSI total score (SD) | 24.6 (4.7) | 23.9 (5.8) | 0.678 |
| NIH-CPSI pain score (SD) | 12.6 (2.2) | 12.5 (2.2) | 0.962 |
| NIH-CPSI urinary score (SD) | 3.4 (2.8) | 3.0 (3.1) | 0.637 |
| NIH-CPSI QOL score (SD) | 8.6 (1.1) | 8.4 (1.2) | 0.578 |
| IPSS (IQR) | 6.5 (2.8–14.5) | 4 (2–16) | 0.699 |
| IIEF-ED (IQR) | 23.5 (20.0–28.3) | 28 (21–28) | 0.474 |
| Positive UPOINTS domains (IQR) | 3 (2–3) | 3 (2–3) | 0.345 |
| QMAX (IQR) | 18.4 (15.7–25.3) | 20.1 (12.8–23.0) | 0.773 |
| PVR (IQR) | 21.1 (13.8–44.7) | 20.1 (10.8–81.8) | 0.923 |

*IIEF-ED* International Index of Erectile Function-Erectile Domain, *IPSS* International Prostate Symptom Score, *QOL* quality of life, *PVR* post void residual, *NIH-CPSI* National Institute of Health-Chronic Prostatitis Symptom Index, *SD* standard deviation, *IQR* interquartile range.

12, and 24-week FU values were compared between the two groups a clear superiority of LiST vs. sham treatment was reported for NIH-CPSI pain subdomain score which was the primary outcome of our study, but also for the other parameters ($p < 0.001$) (Table 3). The number of men achieving a minimal clinically important difference (MCID) in NIH-CPSI total score (defined as ≥6 points decrease) was significantly higher for the active group in all FU timepoints ($p < 0.001$). In the 6-month FU visit 50% (15/30) of men in the active group maintained a MCID vs. no patient in the sham group (Table 4).

## NIH-CPSI urinary subdomain score, IPPS, Qmax, and PVR

The within and between-group data analysis showed no improvement of the subjective urination-related parameters (NIH-CPSI urinary subdomain score, IPPS) after LiST or sham treatment. Moreover, a statistically significant exacerbation of IPPS in the 24-week FU visit compared to baseline (8 vs. 6.5, $p < 0,05$) (Table 2) and in the change from baseline to 12-week FU values compared to sham group (0.60 vs. −0.87, $p = 0.021$) were reported for the active group (Table 3). Regarding objective urination-related parameters (Qmax and PVR) no statistically significant difference was found between groups in all FU timepoints with the exception of greater decrease regarding PVR volume reported from baseline to 12-week FU for the LiST group (14,5 vs. 0.74, $p = 0.033$) (Table 3).

## IIEF-ED and UPOINTS phenotype system

IIEF-ED score was improved for LiST group in the 4- and 12-week FU compared to baseline ($p < 0.05$) (Table 2). Moreover, the change from baseline to all FU timepoints was statistically significant higher for the LiST group (Table 3). Nevertheless, there was no statistical difference in IIEF-ED between the groups for all study timepoints (Table 2). Regarding UPOINTS phenotype system a greater decrease in the number of positive domains was reported in LiST group compared to sham group (Tables 2 and 3). An analytic report of the percentage of positive UPOINTS domains for the active and sham group for all study timepoints is presented in Appendix 2. The comparison of the percentage of baseline positive UPOINTS domains between the patients with and without MCID in the NIH-CPSI at the 6-monh FU visit revealed a significant statistical difference only for the Tenderness (T) and Sexual dysfunction (S) domains (Appendix 3).

## mpMRI and PSA findings

Regarding changes in mpMRI of the prostate the median PI-RADS score was 2 for both groups in baseline and at 12-week FU visit revealing no difference both in within and between groups analysis ($p = 0.963$). Similarly, no significant difference from baseline values and between groups was found also for the 12-week FU visit PSA values ($p = 0.478$) (Table 2).

## Safety

No hemorrhagic adverse effect associated with LiST, such as hematuria, hemospermia, or ecchymosis was seen in any of the patients during the study period. Regarding treatment-induced perineal pain, a statistically significant higher mean pain VAS score was reported for the LiST group (0.333 vs. 0.167, $p < 0.001$). However the very low score values for both groups prove that the LiST is actually a painless method. In general, no other form of adverse

**Table 2** Comparative data within and between groups.

| | Baseline | FU 1 (week 4) | FU 2 (week 12) | FU 3 (week 24) |
|---|---|---|---|---|
| NIH-CPSI total score (SD) | | | | |
| Active group | 24.6 (4.7) | 16.0 (4.9)* | 16.5 (5.3)* | 18.0 (5.4)* |
| Sham group | 23.9 (5.8) | 21.7 (6.6) | 22.3 (6.6) | 22.9 (5.5) |
| *p* value for between groups | 0.678 | **0.002** | **0.003** | **0.007** |
| NIH-CPSI Pain score (SD) | | | | |
| Active group | 12.6 (2.2) | 7.2 (2.1)* | 7.9 (2.3)* | 9.0 (2.0)* |
| Sham group | 12.5 (2.2) | 10.7 (3.0)* | 11.1 (2.6) | 11.4 (1.9) |
| *p* value for between groups | 0.962 | **<0.001** | **<0.001** | **<0.001** |
| NIH-CPSI Urinary score (SD) | | | | |
| Active group | 3.4 (2.8) | 3.5 (2.6) | 3.4 (2.4) | 3.6 (2.4) |
| Sham group | 3.0 (3.1) | 3.2 (2.8) | 3.4 (2.7) | 3.4 (2.5) |
| *p* value for between groups | 0.637 | 0.753 | 0.967 | 0.794 |
| NIH-CPSI QOL score (SD) | | | | |
| Active group | 8.6 (1.1) | 5.3 (1.7)* | 5.2 (2.1)* | 5.5 (2.3)* |
| Sham group | 8.4 (1.2) | 7.8 (1.7) | 7.8 (1.8) | 8.1 (1.6) |
| *p* value for between groups | 0.578 | **<0.001** | **<0.001** | **<0.001** |
| Question #4 CPSI (SD) | | | | |
| Active group | 6.1 (0.5) | 3.0 (0.4)* | 3. 1 (0.4)* | 3.6 (0.5)* |
| Sham group | 5.9 (0.4) | 5.8 (0.5) | 6.0 (0.4) | 6.1 (0.3) |
| *p* value for between groups | 0.774 | **<0.001** | **<0.001** | **<0.001** |
| IPSS score (IQR) | | | | |
| Active group | 6.5 (2.8–14.5) | 6.5 (3–13.5) | 6 (3–13) | 8 (5–14)* |
| Sham group | 4 (2–16) | 5 (3–15) | 6 (3–16) | 6 (5–16) |
| *p* value for between groups | 0.699 | 0.894 | 0.698 | 0.646 |
| IIEF-ED score (IQR) | | | | |
| Active group | 23.5 (20.0–28.3) | 27 (25–29)* | 27.5 (25.8–28.0)* | 27 (25.8–28.0) |
| Sham group | 28 (21–28) | 27 (23–29) | 26 (23–29) | 26 (23–28) |
| *p* value for between groups | 0.474 | 0.459 | 0.307 | 0.185 |
| Median UPOINTS (IQR) | | | | |
| Active group | 3 (2–3) | 1 (1–2)* | 2 (1–2)* | 2 (1–2)* |
| Sham group | 3 (2–3) | 2 (1–3) | 2 (1–3) | 2 (2–3) |
| *p* value for between groups | 0.345 | 0.070 | **0.032** | **0.025** |
| Median QMAX (IQR) | | | | |
| Active group | 18.4 (15.7–25.3) | 21.9 (14.0–30.9) | 18.1 (13.1–24.4) | – |
| Sham group | 20.1 (12.8–23.0) | 19.3 (15.6–25.7) | 20.5 (15.7–26.1) | – |
| *p* value for between groups | 0.773 | 0.300 | 0.647 | |
| Median PVR (IQR) | | | | |
| Active group | 21.1 (13.8–44.7) | 31.5 (16.0–45.7) | 15.3 (6.6–30.7)* | – |
| Sham group | 20.1 (10.8–81.8) | 33.1 (14.5–55.5) | 30.3 (10.7–55.7) | – |
| *p* value for between groups | 0.923 | 0.516 | 0.079 | |
| Median PI-RADS (IQR) | | | | |
| Active group | 2 (2–2) | – | 2 (2–2) | – |
| Sham group | 2 (2–2) | – | 2 (2–2) | – |
| *p* value for between groups | 0.350 | | 0.930 | |
| Median PSA (IQR) | | | | |
| Active group | 0.73 (0.45–1.39) | – | 0.69 (0.40–1.54) | – |
| Sham group | 0.76 (0.58–1.28) | – | 0.79 (0.52–1.04) | – |
| *p* value for between groups | 0.736 | | 0.478 | |

The bold *p* values represent statistical significance.

*IIEF-ED* International Index of Erectile Function-Erectile Domain, *IPSS* International Prostate Symptom Score, QOL quality of life, *PVR* post void residue, *NIH-CPSI* National Institute of Health-Chronic Prostatitis Symptom Index, *SD* standard deviation, *IQR* interquartile range, *FU* follow up.

*$p < 0.05$ versus Baseline.

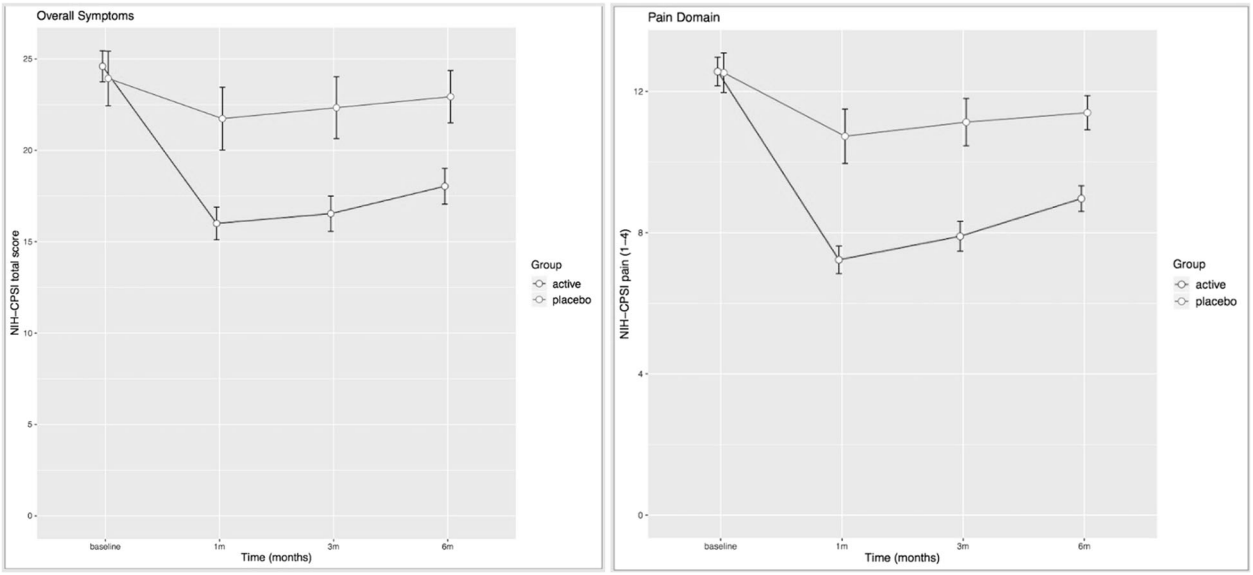


**Fig. 2 NIH-CPSI total score values for active and sham group in all timepoints. a**, **b** NIH-CPSI pain subdomain score values for active and sham group in all timepoints.

event was reported during the treatment and follow-up period.

## Discussion

Management of men suffering from CP/CPPS is one of the most controversial and challenging issues in office urology. The disease is characterized by various clinical phenotypes, incompletely understood pathophysiologic mechanisms, different and subjective diagnostic tools and multiple treatment options with inadequate efficacy rates and potential side-effects [4]. These facts inevitably lead to a frequently expressed frustration from both patients and treating physicians. Therefore, an easily applied treatment modality with proved high efficacy and safety is urgently needed.

Shock wave therapy may improve CP/CPPS symptoms and especially pain through several mechanisms, such as nociceptors hyperstimulation, passive muscle tone reduction, nitric oxide synthesis induction, increase of local microvascularisation and interruption of nerve impulses [7, 15–17].

These aforementioned potentially beneficial properties of moderate intensity shockwave therapy for CP/CPPS treatment have also been demonstrated in clinical level in previous studies [6–9, 18–21] (Appendix 4). In the vast majority of these studies an EFD = 0.25 mJ/mm$^2$ was applied. In our study, we tried to assess the efficacy and safety of an alternative and more "patient friendly" (regarding treatment-induced pain), energy protocol using LiST with EFD = 0.096 mJ/mm$^2$.

Most of the results reported by the present study are in harmony with the aforementioned published data. Regarding impact of LiST in NIH-CPSI total, pain, and QOL subdomains scores we found a clear and persistent in all FU timepoints improvement compared to sham treatment. Parameters regarding which all the previous sham-RCTs reported similar results [7–9, 22] (Appendix 4). The significant improvement in QOL subdomain is most likely a natural consequence of the significant improvement in pain and taking into account that pain intensity represent the strongest independent predictor of QOL for CP/CPPS patients [23]. In this point, it must be highlighted that recently a correct critique was expressed upon the validity and capability of NIH-CPSI pain-domain score to accurately report the effect of a CP/CPPS treatment on pain symptom. This composite score, by examining too many variables (location, frequency, and severity of pain) can be easily biased [24]. So, the most valid endpoint now accepted in the field for such studies is the VAS or NRS pain severity score (captured as Question #4 of the CPSI) and this is the reason we included separately the results of CPSI Question #4 in Tables 2 and 3. We must also underline that according to more modern definitions it is now believed that subjects must achieve at least a >4–6 point decrease in CPSI pain-domain score instead of the CPSI total score to be clinically significant. By using this definition 10 out of 30 active patients achieved MCID in the 6-month follow-up.

Regarding voiding symptoms, no change after LiST was noticed, compared both to baseline and to sham group values according to NIH-CPSI urinary domain scores and moreover a slight exacerbation was recorded according to

**Table 3** Comparisons of changes from baseline to 4, 12, and 24-week FU visit in outcomes adjusted for baseline values and treatment group.

| | | Active group mean (SE) | Placebo group mean (SE) | Mean difference (95% CI) | *p* value |
|---|---|---|---|---|---|
| NIH-CPSI total score | Baseline—week 4 | 8.5 (0.77) | 2.3 (1.1) | 6.2 (3.5, 8.9) | **<0.001** |
| | Baseline—week 12 | 8.0 (0.82) | 1.7 (1.2) | 6.3 (3.4, 9.2) | **<0.001** |
| | Baseline—week 24 | 6.4 (0.82) | 1.2 (1.2) | 5.2 (2.4, 8.2) | **0.001** |
| NIH-CPSI (1–4) | Baseline—week 4 | 5.3 (0.43) | 1.8 (0.61) | 3.5 (2.0, 5.0) | **<0.001** |
| | Baseline—week 12 | 4.7 (0.41) | 1.4 (0.58) | 3.3 (1.8, 4.7) | **<0.001** |
| | Baseline—week 24 | 3.6 (0.36) | 1.2 (0.52) | 2.4 (1.2, 3.7) | **<0.001** |
| NIH-CPSI (4) | Baseline—week 4 | 3.1 (0.24) | 0.1 (0.16) | 3 (1.6, 4.0) | **<0.001** |
| | Baseline—week 12 | 3 (0.21) | −0.1 (0.13) | 3.1 (1.7, 4.6) | **<0.001** |
| | Baseline—week 24 | 2.5 (0.26) | −0.2 (0.1) | 2.4 (1.2, 3.7) | **<0.001** |
| NIH-CPSI (5–6) | Baseline—week 4 | −0.05 (0.12) | −0.17 (0.17) | 0.12 (−0.29, 0.53) | 0.556 |
| | Baseline—week 12 | −0.03 (0.16) | −0.35 (0.23) | 0.32 (−0.25, 0.89) | 0.264 |
| | Baseline—week 24 | −0.20 (0.18) | −0.33 (0.25) | 0.13 (−0.48, 0.74) | 0.664 |
| NIH-CPSI (7–9) | Baseline—week 4 | 3.3 (0.31) | 0.69 (0.43) | 2.61 (1.5, 3.6) | **<0.001** |
| | Baseline—week 12 | 3.4 (0.35) | 0.66 (0.50) | 2.74 (1.5, 3.9) | **<0.001** |
| | Baseline—week 24 | 3.1 (0.38) | 0.33 (0.53) | 2.77 (1.5, 4.1) | **<0.001** |
| IPSS | Baseline—week 4 | 0.48 (0.33) | −0.42 (0.46) | 0.90 (−0.24, 2.04) | 0.117 |
| | Baseline—week 12 | 0.60 (0.36) | −0.87 (0.50) | 1.5 (0.23, 2.72) | **0.021** |
| | Baseline—week 24 | −1.1 (0.82) | −0.38 (1.2) | −0.72 (−3.6, 2.1) | 0.611 |
| IIEF-ED | Baseline—week 4 | −3.1 (0.43) | −1.0 (0.61) | −2.1 (−3.60, −0.59) | **0.007** |
| | Baseline—week 12 | −3.3 (0.45) | −0.92 (0.63) | −2.4 (−3.95, −0.82) | **0.004** |
| | Baseline—week 24 | −3.3 (0.43) | −1.2 (0.60) | −2.1 (−3.64, −0.65) | **0.006** |
| UPOINTS | Baseline—week 4 | 1.2 (0.13) | 0.53 (0.18) | 0.67 (0.21, 1.13) | **0.005** |
| | Baseline—week 12 | 1.3 (0.14) | 0.46 (0.20) | 0.84 (0.35, 1.33) | **0.001** |
| | Baseline—week 24 | 1.1 (0.14) | 0.28 (0.20) | 0.82 (0.32, 1.30) | **0.002** |
| Qmax | Baseline—week 4 | −1.9 (1.3) | −0.01 (1.9) | −1.89 (−6.6, 2.8) | 0.414 |
| | Baseline—week 12 | 1.5 (1.3) | −1.1 (1.8) | 2.6 (−1.9, 7.0) | 0.256 |
| PVR | Baseline—week 4 | 1.2 (4.0) | −4.1 (5.6) | 5.3 (−8.6, 19.1) | 0.450 |
| | Baseline—week 12 | 14.5 (3.6) | 0.74 (5.1) | 13.8 (1.1, 26.3) | **0.033** |

The bold *p* values represent statistical significance.

*IIEF-ED* International Index of Erectile Function-Erectile Domain, *IPSS* International Prostate Symptom Score, *QOL* quality of life, *PVR* post void residue, *NIH-CPSI* National Institute of Health-Chronic Prostatitis Symptom Index, *SE* standard error, *CI* confidence interval, *FU* follow up.

**Table 4** Percent of patients who achieved MCID (≥6 point reduction in total NIH-CPSI score).

| | Active *N* (%) | Sham *N* (%) | Difference (95% CI) | Active vs. sham *P* value |
|---|---|---|---|---|
| 4-week FU | 23/30 (76.7%) | 2/15 (13.3%) | 63.3% (33.1–78.3%) | <0.001 |
| 12-week FU | 18/30 (60.0%) | 1/15 (6.7%) | 53.3% (24.2–69.7%) | <0.001 |
| 24-week FU | 15/30 (50.0%) | 0/15 (0.0%) | 50.0% (23.6–66.9%) | 0.001 |

*MCID* minimally clinical important difference, *NIH-CPSI* National Institute of Health-Chronic Prostatitis Symptom Index, *FU* follow up.

IPSS scores from baseline to 6-month values. Findings were confirmed objectively also by the nonsignificantly altered values of Qmax and PVR after LiST. However, our results must be interpreted with caution as it seems that participants in our study had only mild urinary symptoms and normal Qmax and PVR values at the baseline evaluation and probably the margin for improvement was very small. Conflicting data of previous RCTs [7, 8, 18, 25] (Appendix 4) regarding urination behavior highlight the need for further phenotypically directed studies about the impact of LiST in this crucial for CP/CPPS patients symptom domain.

Positive results were reported by Zimmermann et al. regarding LiST effect on erectile function of CP/CPPS patients[7] (Appendix 4). This improvement could be attributed to the assumption that QOL amelioration

achieved by LiST in CP/CPPS patients has a positive impact on their sexual function. Moreover, application of LiST in the area of crura of the corpus cavernosum during transperineal approach for CP/CPPS treatment may positively effect erectile function [26]. Nevertheless, in our results no statistical difference in IIEF-ED between the groups for all study timepoints was reported highlighting that more high-quality data are needed in order to clarify the effect of LiST on erectile function of CP/CPPS patients.

Our data, revealing a durable efficacy of LiST up to 24-week FU visit, is not consistent with the study by Moayednia et al. [18]. Moreover, Al Edwan et al. [20] reported efficacy of LiST in refractory cases of CP/CPPS at least for 1 year after treatment (Appendix 4). However, a trend for exacerbation of LiST efficacy was shown in our study raising the question whether efficacy would have been retained statistically significant in a longer FU period. Moreover, the possibility of a retreatment protocol seems valuable in order to assess further improvement. Thus, further studies with long-term FU periods and LiST retreatment studies are crucial for further development of this promising treatment approach.

The major strength of our study is certainly the design of the study as randomized, double-blind sham-controlled trial. Another strength lies in the fact that all of our included patients have previously failed in at least two other pharmaceutical or non-pharmaceutical CP/CPPS treatment modalities (Table 1). Nevertheless, our results are limited by the single-center character of the study, the empirical choice of LiST protocol and the relatively short FU period. Moreover, sample size was not adequate for clinical useful subgroup analyses. Future studies may randomize patients based on UPOINT phenotype and duration of CP/CPPS symptoms.

LiST represent a fast, painless, easily applied, and potentially repeatable outpatient local therapy characterized by proven mid-term efficacy and the lack of any systemic side-effects such the ones caused by other available CP/CPPS treatments. Thus, could be a potential valuable treatment option in physicians therapy armamentarium. Further phenotypically directed studies with adequate sample sizes and long-term FU comparing different generators, different LiST protocols and the efficacy of LiST retreatment are needed to determine which will be the most effective LiST protocol and who will be the most suitable candidates for receiving it.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.



## References

1. Schaeffer AJ, Datta NS, Fowler JE, Krieger JN, Litwin MS, Nadler RB, et al. Overview summary statement. Diagnosis and management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Urology 2002;60:1–4.
2. Franco JV, Turk T, Jung JH, Xiao Y-T, Iakhno S, Garrote V, et al. Non-pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome. Cochrane Database Syst Rev. 2018;1:CD012551.
3. Franco JV, Turk T, Jung JH, Xiao Y-T, Iakhno S, Tirapegui FI, et al. Pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome. Cochrane Database Syst Rev. 2019;10:CD012552.
4. Magistro G, Wagenlehner FME, Grabe M, Weidner W, Stief CG, Nickel JC. Contemporary management of chronic prostatitis/chronic pelvic pain syndrome. Eur Urol. 2016;69:286–97.
5. Doiron RC, Shoskes DA, Nickel JC. Male CP/CPPS: where do we stand? World J Urol. 2019;37:1015–22.
6. Zimmermann R, Cumpanas A, Hoeltl L, Janetschek G, Stenzl A, Miclea F. Extracorporeal shock-wave therapy for treating chronic pelvic pain syndrome: a feasibility study and the first clinical results. BJU Int. 2008;102:976–80.
7. Zimmermann R, Cumpanas A, Miclea F, Janetschek G. Extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome in males: a randomised, double-blind, placebo-controlled study. Eur Urol. 2009;56:418–24.
8. Vahdatpour B, Alizadeh F, Moayednia A, Emadi M, Khorami MH, Haghdani S. Efficacy of extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome: a randomized, controlled trial. ISRN Urol. 2013. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3755541/.
9. Zeng X-Y, Liang C, Ye Z-Q. Extracorporeal shock wave treatment for non-inflammatory chronic pelvic pain syndrome: a prospective, randomized and sham-controlled study. Chin Med J. 2012;125:114–8.
10. Yuan P, Ma D, Zhang Y, Gao X, Liu Z, Li R, et al. Efficacy of low-intensity extracorporeal shock wave therapy for the treatment of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and meta-analysis. Neurourol Urodyn. 2019;38:1457–66.
11. Engeler D, Baranowski PA, Berghmans B, Borovicka J, Cottrell AM, Dinis-Oliveira P, et al. EAU Guidelines 2018. EAU Guidelines Office, Arnhem, The Netherlands. 2018.
12. Capogrosso P, Frey A, Jensen CFS, Rastrelli G, Russo GI, Torremade J, et al. Low-intensity shock wave therapy in sexual medicine-clinical recommendations from the European Society of Sexual Medicine (ESSM). J Sex Med. 2019;16:1490–505.
13. Schulz KF, Altman DG, Moher D. CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
14. Nickel JC, Shoskes D, Wang Y, Alexander RB, Fowler JE, Zeitlin S, et al. How does the pre-massage and post-massage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? J Urol. 2006;176:119–24.
15. Mariotto S, Cavalieri E, Amelio E, Ciampa AR, de Prati AC, Marlinghaus E, et al. Extracorporeal shock waves: from lithotripsy to anti-inflammatory action by NO production. Nitric Oxide. 2005;12:89–96.
16. Wess OJ. A neural model for chronic pain and pain relief by extracorporeal shock wave treatment. Urol Res. 2008;36:327–34.

17. Marszalek M, Berger I, Madersbacher S. Low-energy extracorporeal shock wave therapy for chronic pelvic pain syndrome: finally, the magic bullet? Eur Urol. 2009;56:425–6.
18. Moayednia A, Haghdani S, Khosrawi S, Yousefi E, Vahdatpour B. Long-term effect of extracorporeal shock wave therapy on the treatment of chronic pelvic pain syndrome due to non bacterial prostatitis. J Res Med Sci J Isfahan Univ Med Sci. 2014;19:293–6.
19. Guu S-J, Geng J-H, Chao I-T, Lin H-T, Lee Y-C, Juan Y-S, et al. Efficacy of low-intensity extracorporeal shock wave therapy on men with chronic pelvic pain syndrome refractory to 3-as therapy. Am J Mens Health. 2018;12:441–52.
20. Al Edwan GM, Muheilan MM, Atta ONM. Long term efficacy of extracorporeal shock wave therapy [ESWT] for treatment of refractory chronic abacterial prostatitis. Ann Med Surg. 2017;14:12–17.
21. Pajovic B, Radojevic N, Dimitrovski A, Vukovic M. Comparison of the efficiency of combined extracorporeal shock-wave therapy and triple therapy versus triple therapy itself in Category III B chronic pelvic pain syndrome (CPPS). Aging Male J Int Soc Study Aging Male. 2016;19:202–7.
22. Salama AB, Abouelnaga WA. Effect of radial shock wave on chronic pelvic pain syndrome/chronic prostatitis. J Phys Ther Sci. 2018;30:1145–9.
23. Tripp DA, Curtis Nickel J, Landis JR, Wang YL, Knauss JS. CPCRN Study Group. Predictors of quality of life and pain in chronic prostatitis/chronic pelvic pain syndrome: findings from the National Institutes of Health Chronic Prostatitis Cohort Study. BJU Int. 2004;94:1279–82.
24. Nickel JC. Chronic prostatitis/chronic pelvic pain syndrome: it is time to change our management and research strategy. BJU Int. 2020;125:479–80.
25. Rayegani SM, Razzaghi MR, Raeissadat SA, Allameh F, Eliaspour D, Abedi AR, et al. Extracorporeal shockwave therapy combined with drug therapy in chronic pelvic pain syndrome: a randomized clinical trial. Urol J. 2020;17:185–91.
26. Kalyvianakis D, Memmos E, Mykoniatis I, Kapoteli P, Memmos D, Hatzichristou D. Low-intensity shockwave therapy for erectile dysfunction: a randomized clinical trial comparing 2 treatment protocols and the impact of repeating treatment. J Sex Med. 2018;15:334–45.