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Research Article

Safety and efficacy of extracorporeal shockwave therapy on chronic prostatitis/chronic pelvic pain syndrome: a prospective, randomized, double-blind, placebo-controlled study

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ABSTRACT

Purpose: This study aimed to investigate the efficacy and safety of extracorporeal shock wave therapy (ESWT) over an 8-week period in individuals diagnosed with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) compared to a control group.

Materials and methods: This prospective, double-blind, placebo-controlled study enrolled 46 participants diagnosed with CP/CPPS, who were randomly assigned to either the treatment group or the control group in a 2:1 ratio. In the treatment group, ESWT was administered at the perineum once a week for 8 weeks. CP/CPPS-related symptoms were assessed using the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH–CPSI). Pain and erectile function were measured using the Visual Analogue Scale (VAS) and the International Index of Erectile Function-Erectile Function (IIEF-EF).

Results: The primary efficacy assessment variable, the change in NIH–CPSI total score at 4 weeks after the end of the 8-week treatment compared to baseline, was significantly improved ($P = 0.0225$) in the treatment group (-11.27 ± 8.39) compared to the control group (-5.44 ± 5.73). Regarding the secondary efficacy assessment variables, the treatment group showed significant decreases compared to the control group in change in NIH–CPSI total score ($P = 0.0055$) at the end of the 8-week treatment compared to baseline, along with significant decreases in pain and quality of life scores, as well as VAS assessments at the end of the 8-week treatment and 4 weeks after the end of treatment ($P < 0.05$). Moreover, in the evaluation conducted to assess improvement in sexual function, the treatment group showed a significant increase compared to baseline than the control group in the IIEF total score at 4 weeks after the end of the treatment ($P = 0.0364$). No patients experienced severe side effects related to ESWT during the therapeutic period or the follow-up duration.

Conclusions: The efficacy assessment in this clinical trial indicates that extracorporeal shock wave therapy is expected to have a symptomic improvement effect on CP/CPPS.

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1. Introduction

Chronic prostatitis is a prevalent urological condition that affects men worldwide and poses a substantial challenge due to its diverse etiology and limited treatment options. The National Institute of Health (NIH) classifies chronic prostatitis into four categories, with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) being the most common, with a whole-life prevalence of approximately 9% to 16% among males.[1]

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CP/CPPS, characterized by persistent pelvic pain and lower urinary tract symptoms with or without white blood cells in prostatic fluid, urine, and semen, presents a significant challenge. Conventional treatments involve an array of approaches, such as the use of alpha-blockers, antibiotics, and hormonal therapy, administered over approximately 8 weeks.[2] Erectile dysfunction—including ejaculatory pain—is also common, with phosphodiesterase type 5 often prescribed, but there are currently clear limitations to the pharmacologic treatment of CP/CPPS beyond the issue of side effects.[3,4] The National Institutes of Health Chronic Prostatitis Collaborative Research Network has emphasized the need to develop innovative strategies to treat this common condition, particularly for patients for whom existing treatments have failed.

Extracorporeal Shock Wave Therapy (ESWT) has emerged as a promising frontier in chronic prostatitis management. Initially employed for lithotripsy, ESWT has since shown therapeutic potential in various medical domains. Recent studies suggest its efficacy in noninflammatory CP/CPPS (type IIIb) in particular, where it offers a noninvasive and targeted intervention.[5,6] However, limited studies have included inflammatory CP/CPPS (type IIIa).

This study aims to explore the use of magnetic-type unifocal ESWT as a novel treatment modality for CP/CPPS, providing insights into its underlying mechanisms, clinical outcomes, and potential advantages.

2. Material and methods

This prospective, randomized, double-blind, and placebo-controlled clinical study was structured to include participants who were confirmed to have CP/CPPS (both types IIIa and b). Participants were randomly assigned to either the ESWT (Impo88) treatment group or the placebo group in a 2:1 ratio.

Patients were eligible for inclusion if they exhibited symptoms of CP/CPPS for a minimum of 3 months and showed no evidence of infection in urinary and seminal culture studies. The exclusion criteria for this study were as follows: 1) initiation of another treatment method at the study's commencement; 2) CP/CPPS following lower urinary tract localization studies; 3) prior prostate surgery (radical prostatectomy, transurethral prostatectomy, etc.); 4) prostate-specific antigen (PSA) levels exceeding 4 ng/mL; 5) history of pelvic surgery; 6) pelvic radiation therapy; 7) any other urological condition associated with lower urinary tract symptoms, such as urethral stricture or bladder stones, or any neurological disease; 8) individuals with cardiac disease, cardiac arrhythmias, recipients of cardiac assistance devices, orthopedic metallic implants, urological prostheses (penile prostheses), and medical devices involving the insertion of artificial structures into the human body, such as artificial urethral sphincters; and 9) noncompliance with the study protocol. Participants were also disqualified if their PSA levels exceeded 4 ng/mL during the initial screening, and a prostate biopsy was preferably conducted to rule out potential prostate cancer risk. The screening process for CP/CPPS included a comprehensive medical history, physical examination, NIH-Chronic Prostatitis Symptom Index (NIH–CPSI) questionnaire, PSA measurement, microscopic analysis, and microbiological culture before and after prostate massage, along with examination of prostate secretions.

If the trial device or the control device was used with a participant at least once, then that participant was included in the safety set for safety evaluation.

2.1. Assessments

Impo88 is a magnetic-type unifocal ESWT device that has been approved by the Ministry of Food and Drug Safety (Product Approval Number: 15-203). It is configured to deliver a total of 3,000 pulses in a single session over 8 weeks, with 500 pulses applied to six designated points within the anal region at intervals of 3 Hz and an energy level of 0.25 mJ/mm^2. The treatment protocol was designed with reference to previously published studies on the treatment of prostatitis using ESWT.[7,8] During the treatment, the subjects were able to confirm that the therapy was in progress as the shockwaves generated audible sounds. The control group used a placebo device that produced similar sounds during the therapy, but which did not actually deliver any energy, thus resulting in no therapeutic effect. Fig. 1 shows the treatment area of the six different anatomic sites at the perineum and the shape of the treatment device. Given the broader and deeper focal zone of this device, it was feasible to produce a wide spectrum of focused shock waves in the prostate from the perineal region without encountering any challenges.

2.2. Outcome measurement

Clinical symptoms in patients were assessed using the NIH–CPSI score, International Index of Erectile Function-Erectile Function (IIEF-EF) score, and Visual Analogue Scale (VAS) score. NIH–CPSI scores were used to examine CP/CPPS-related complaints. The IIEF-EF score served as an indicator of potency function. Pain intensity was gauged through the VAS score. The primary endpoint involved evaluating the average changes in NIH–CPSI total score between baseline and 4 weeks after the end of the 8 weeks of treatment, comparing the two groups (the treatment group (Impo88) and the placebo). Secondary endpoints encompassed changes in the NIH–CPSI total score between baseline and immediately following the end of the 8 weeks of treatment, and they were compared for both groups. Moreover, changes in NIH–CPSI pain score, NIH–CPSI urinary score, NIH–CPSI quality of life (QoL) score, IIEF-EF, and VAS were compared for both groups immediately after and 4 weeks after the end of treatment. Any adverse events were also recorded to evaluate the safety of ESWT.

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation. The independent samples *t*-test and Mann–Whitney tests were used to compare continuous variables between the two groups. Paired *t*-tests or Wilcoxon signed-rank tests were used to compare variables within each group. Analyses of covariance were conducted to assess the group mean differences in changes from baseline among all continuous variables. The change from baseline at follow-up served as the dependent variable, with the baseline value of the dependent variable and treatment group serving as covariates. Statistical analysis was conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) with $P < 0.05$ set as the threshold for statistical significance.

3. Results

From December 2021 to May 2023, 46 participants successfully completed the study. Out of 60 potential candidates, three dropped out during the screening phase, with the remaining safety set comprising 57 individuals who had used the trial device at least once. Among them, 38 were randomly assigned to the ESWT treatment group, and 19 were randomly assigned to the placebo group. Within the ESWT treatment group, eight participants dropped out, ultimately leaving 30 participants in the treatment group who completed the study as planned. Meanwhile, in the placebo group, three individuals dropped out, thus leaving 16

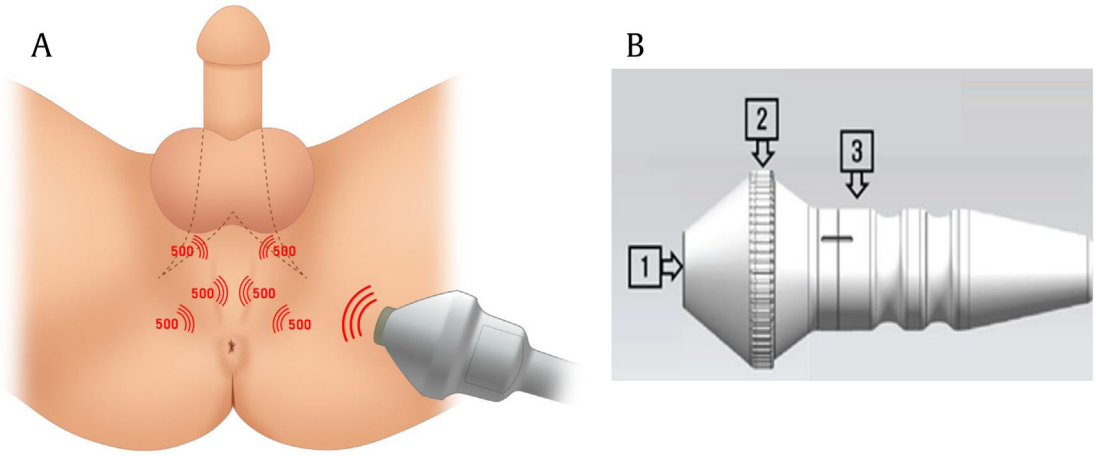


Fig. 1. Treatment sites on the perineum and picture of the treatment device (head portion). A. Six different sites of treatment for CP/CPPS using ESWT (Impo88). B. 1) Membranes in contact with skin, 2) for securing the membrane to the treatment area, 3) treatment part source handle. CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; ESWT, extracorporeal shock wave therapy.

participants in the placebo group who completed the study as intended. A CONSORT diagram of the study is shown in Fig. 2.

Table 1 presents the baseline characteristics of patients enrolled in the study, who are categorized into the ESWT group (N = 30) and the placebo group (N = 16). The comparison includes age (year), body mass index (kg/m^2), PSA (ng/mL), NIH–CPSI scores (total, pain, voiding, QoL domain), VAS, total International Prostate Symptom Score (IPSS) scores, and total IIEF-EF scores, and the *P*-values adjusted for baseline are provided. There were no statistically significant differences between the ESWT and placebo groups across all measured parameters, suggesting baseline comparability between the two groups. Patients with a previous history of medication use (antibiotics, alpha blockers, and analgesics) had stopped the medications for at least 2 weeks prior to ESWT as washout period.

Table 1
Baseline characteristics of the patients.

	ESWT group ($N = 30$)	Placebo group ($N = 16$)	*P*-value*
Age (yr)	39.20 ± 13.14	38.50 ± 14.58	0.8692
BMI (kg/m^2)	71.2 ± 4.3	72.1 ± 6.7	0.782
PSA (ng/mL)	0.89 ± 0.62	0.79 ± 0.74	0.181
History of medications for CP/CPPS			
Alpha-blockers	24	14	0.711
Antibiotics	15	8	0.066
Analgesics	27	15	0.834
NIH–CPSI total	24.73 ± 5.06	23.50 ± 5.47	0.4477
NIH–CPSI pain	11.43 ± 2.31	10.56 ± 4.29	0.4588
NIH–CPSI voiding	4.60 ± 2.50	4.19 ± 2.32	0.6575
NIH–CPSI QoL	8.70 ± 1.91	8.75 ± 1.95	0.9336
VAS	59.93 ± 16.49	47.00 ± 21.97	0.292
Total IPSS	12.13 ± 8.76	11.81 ± 7.49	0.9631
Total IIEF	35.70 ± 19.39	31.19 ± 19.27	0.419

P-value*: Compared between groups; *P*-value for ANCOVA adjusted for baseline, ESWT, extracorporeal shock wave therapy; BMI, body mass index; PSA, prostate-specific antigen; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; NIH–CPSI: National Institutes of Health-chronic prostatitis symptom index, QoL: Quality of Life, VAS: Visual Analogue Scale, IPSS: International Prostate Symptom Score, IIEF: International Index of Erectile Function.

3.1. Primary and secondary outcomes

The primary endpoint analysis showed that the changes in NIH–CPSI total score from baseline to 4 weeks after the end of treatment were −11.27 ± 8.39 points in the ESWT group

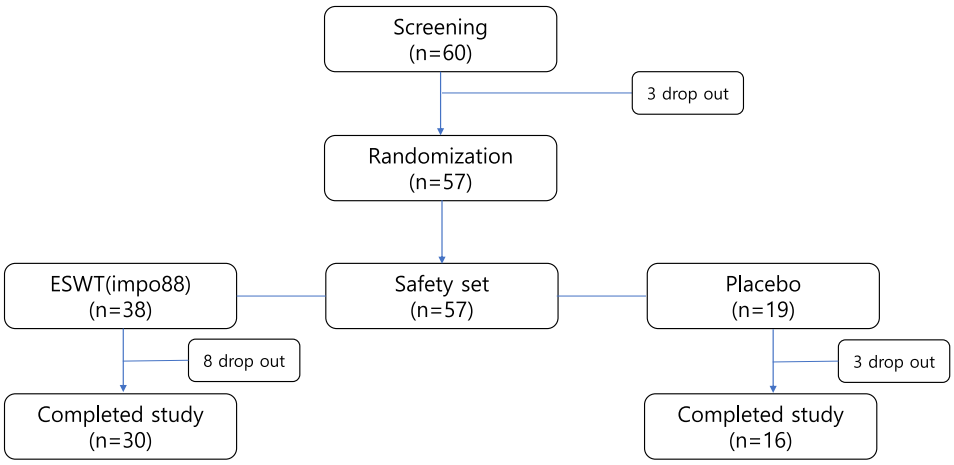


Fig. 2. CONSORT diagram of the study.

and −5.44 ± 5.73 points in the placebo group, thus representing a statistically significant difference in terms of symptom improvement ($P = 0.0225$).

The secondary endpoint analysis showed a statistically significant difference in the change from baseline to immediately after the end of treatment in the NIH–CPSI total score. The changes from baseline of NIH–CPSI pain, NIH–CPSI QoL, and VAS score showed significant differences when comparing between both groups immediately after and 4 weeks after the end of treatment, thus indicating the presence of significantly better symptom improvements in the ESWT group over the placebo group. Meanwhile, there were no statistically significant differences in the changes in NIH–CPSI voiding, Total IPSS score, or PSA, from baseline to immediately after and 4 weeks after the end of treatment. There was not a statistically significant difference between groups when comparing them in terms of total IIEF score from baseline to immediately after the 8 weeks of treatment, but there was a statistically significant difference in the change between groups at 4 weeks after the end of treatment. Table 2 summarizes the differences in the changes in variables from baseline to post-treatment.

Of the 57 volunteers that comprised the safety set by using the trial device at least once, there was one adverse event. Specifically, one (2.63%) of the 38 ESWT recipients reported a first-degree burn, but he wanted to continue in the study and was able to complete the protocol as scheduled without dropping out. The symptoms resolved after 1 week, and the patient did not complain of burn symptoms after the end of the study. There are no other adverse events—such as ecchymosis, perineal pain, gross hematuria, or hematospermia—were observed in any of the participants.

Fig. 3 depicts the trend of score changes in NIH–CPSI (total score, pain, and QoL domain) and VAS from baseline to immediately after and 4 weeks after the end of the 8 weeks of the treatment period.

Table 2
Differences in changes in variables from baseline to post-treatment.

	ESWT	Placebo	*P*-value*
Total NIH–CPSI			
△Immediately after	−10.37 ± 9.17	−4.31 ± 4.88	0.0055
△4 weeks after	−11.27 ± 8.39	−5.44 ± 5.73	0.0225
NIH–CPSI pain			
△Immediately after	−5.43 ± 4.85	−2.38 ± 3.65	0.0247
△4 weeks after	−6.23 ± 4.84	−3.19 ± 3.67	0.0333
NIH–CPSI voiding			
△Immediately after	−1.97 ± 2.62	−0.94 ± 1.34	0.1894
△4 weeks after	−2.00 ± 2.41	−1.00 ± 1.86	0.13
NIH–CPSI QoL			
△Immediately after	−2.97 ± 2.75	−1.00 ± 1.67	0.0133
△4 weeks after	−3.03 ± 2.59	−1.25 ± 2.05	0.0201
VAS			
△Immediately after	−36.33 ± 23.62	−12.00 ± 23.15	0.0017
△4 weeks after	−31.90 ± 29.34	−12.38 ± 19.11	0.0208
Total IPSS			
△Immediately after	−4.73 ± 8.20	−3.06 ± 3.09	0.9631
△4 weeks after	−4.60 ± 7.85	−2.88 ± 4.65	0.5712
Total IIEF			
△Immediately after	−0.37 ± 16.62	−4.00 ± 16.53	0.6031
△4 weeks after	2.60 ± 18.47	−3.44 ± 19.09	0.0364
PSA			
△Immediately after	−0.04 ± 0.28	−0.10 ± 0.39	0.7997
△4 weeks after	−0.08 ± 0.29	−0.07 ± 0.25	0.3746

P-value*: Compared between groups; *P*-value for ANCOVA adjusted for baseline, ESWT, extracorporeal shock wave therapy; NIH–CPSI: National Institutes of Health-chronic prostatitis symptom index.
QoL, Quality of Life; VAS, Visual Analogue Scale; IPSS, International Prostate Symptom Score; IIEF, International Index of Erectile Function; PSA, prostate-specific antigen.

Table 3 shows the result of a comparative analysis conducted through multivariate analysis on the changes in total NIH–CPSI, total IPSS, total IIEF, and Global Efficacy Assessment Questions (GEAQ) score were observed at the end of the study for the CP/CPPS type IIIa to IIIb groups.

At the end of the study, the total IPSS and GEAQ scores showed significantly greater improvement in the CP/CPPS type IIIa group ($N = 15$) compared to the IIIb group ($N = 15$), while the total IIEF score showed significantly greater improvement in the CP/CPPS type IIIb group compared to the IIIa group.

4. Discussion

The management of CP/CPPS poses significant challenges in urology, as current treatments primarily focus on the symptoms without addressing the underlying causes. Shock wave therapy—the mechanisms of which are currently a matter of ongoing investigation—is considered to have promising potential to alleviate CP/CPPS symptoms through various pathways, including nociceptor hyperstimulation, the induction of nitric oxide synthesis, passive muscle tone decrease, the interruption of nerve impulses, and enhanced local microvascularization.[9,10]

In terms of the mechanism of action by which ESWT is effective for the treatment of CP/CPPS, Bae et al. reported—as the result of a preclinical study using the Impo88 device employed in the present clinical trial—that ESWT can regulate inflammatory pain in experimental CP/CPPS in Sprague Dawley male rats by down-regulating the NLRP3 inflammasome. Fundamentally, experimental prostatitis was shown to lead to overactivity in the TLR4-NFκB pathway compared to the normal and ESWT groups, while prostatitis-induced alterations in the BAX/BAK pathway was shown to be inhibited by ESWT.[11]

Comparing with a study by Alexander et al.[12] in which one group was treated with antibiotic monotherapy and another was treated with a combination of alpha-blockers for CP/CPPS, the total scores of NIH–CPSI were found to decrease by 6.2 ± 7.3 and 4.1 ± 6.1, respectively, after 6 weeks of treatment. Meanwhile, our study showed a better outcome with a decrease of 11.27 ± 8.39 points. In the NIH–CPSI pain domain, the monotherapy and combination groups in the prior study showed reductions of 1.8 ± 3.7 and 3.0 ± 4.6 points, respectively, while the Impo88 (ESWT) treatment group in our study showed a decrease of 6.23 ± 4.84 in this domain. In the monotherapy and combination groups from the previous study, the NIH–CPSI voiding (urinary) domain decreased by 1.1 ± 1.8 and 1.3 ± 2.1 points, respectively, while our study found a corresponding decrease of 2.00 ± 2.41 points in the Impo88 treatment group. Regarding the NIH-QoL domain, the monotherapy and combination groups showed respective reductions of 1.9 ± 2.4 and 1.3 ± 1.9 points, whereas the treatment group in our study showed a decrease of 3.03 ± 2.59 points. This leads to the conclusion that ESWT treatment utilizing Impo88 may be more effective than drug therapy in terms of improving the symptoms of CP/CPPS.

Considering the inconvenience involved with having to take a medicine daily, along with the potential side effects associated with antibiotics and alpha-blockers (such as low blood pressure, retrograde ejaculation, indigestion, etc.), ESWT is anticipated to hold significant potential for CP/CPPS treatment.

A previous clinical study showed that multifocal low-intensity ESWT (MESWT) led to symptomatic improvement in CP/CPPS in Asian men.[13] In that study by Kim et al. 30 patients were able to complete the study in total, and they were randomized in a 1:1 ratio to the treatment and control groups. Meanwhile, in our study, 46 participants were able to complete the study in total, and they were randomized in a respective 2:1 ratio to the treatment and control groups. The study by Kim et al. showed an improvement of

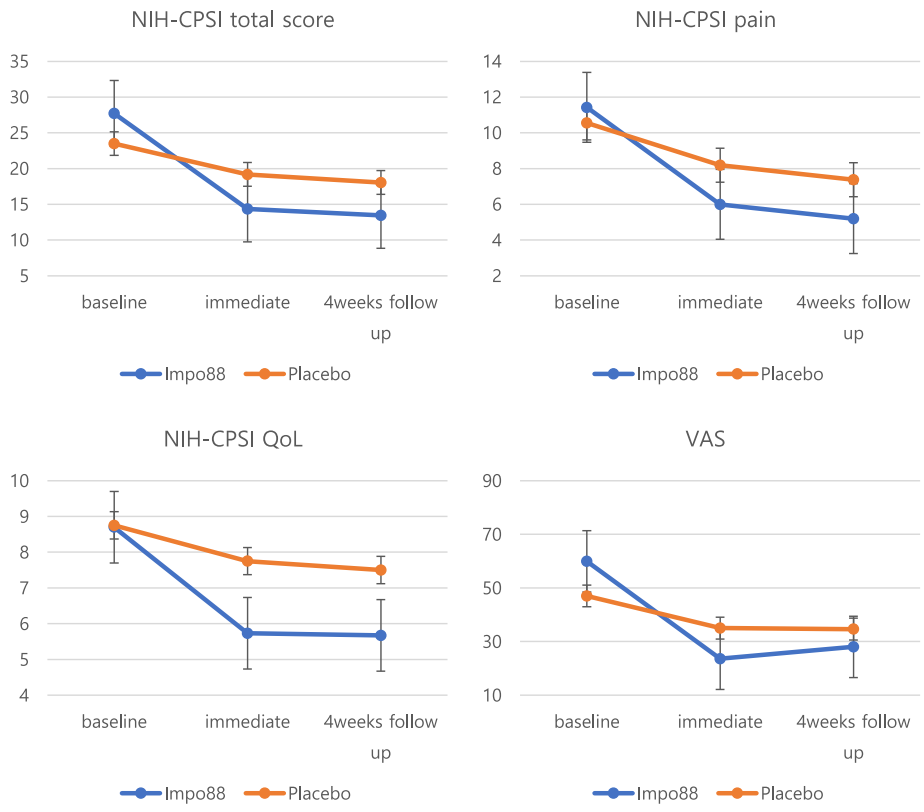


Fig. 3. Changes in NIH–CPSI (total score, pain, and QoL domain) and VAS. NIH–CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; QoL, quality of life; VAS, Visual Analogue Scale.

9.5 points in the NIH–CPSI total score after treatment compared to baseline. By slightly superior, our study showed significant improvement by approximately 11.27 points. Both studies showed significant improvements in the pain and QoL domains of NIH–CPSI, while neither study showed any significant changes in the voiding (urinary) domain of NIH–CPSI. Moreover, there were significant improvements in VAS scores in both studies, while there were no significant changes in PSA in either study.

A previous meta-analysis showed that ESWT led to average improvements of −3.93 on the NIH–CPSI pain domain, −1.79 on the urinary score, and −1.71 on the QoL domain.[3] While the mean improvements in this study were −6.23, 1.00, and −3.03, respectively, indicating that the treatment devices used in this study are more effective on average than those used in previous studies in terms of the pain and QoL domains.

The IIEF-EF total score, which was evaluated as a secondary outcome in the present clinical study, improved by 2.60 ± 18.47, thus showing a significant enhancement compared to baseline when compared to the related change in the placebo group. Among previous clinical trials examining the effectiveness of low-intensity ESWT in the treatment of erectile dysfunction, the maximum increase obtained was 5 points.[14] However, in this study, this observed improvement is deemed meaningful as a secondary benefit. Other previous clinical studies utilizing Li-ESWT to treat chronic pelvic pain syndrome also reported an improvement in the IIEF-EF total score,[5] meaning ESWT on the perineal area can have benefits in alleviating erectile function for CP/CPPS patients.

The type IIIa, characterized by inflammatory CP/CPPS, shows a significant response in IPSS and GEAQ scores due to the anti-inflammatory effects of ESWT. As mentioned above, ESWT can downregulate the NLRP3 inflammasome and inhibit the TLR4-NFκB pathway, which are involved in the inflammatory process. This anti-inflammatory action likely leads to substantial symptom relief, thus resulting in greater improvements in IPSS and GEAQ scores.

And Type IIIb, or noninflammatory CP/CPPS, showed significant improvements in total IIEF scores, which could be due to the different underlying mechanisms of pain and erectile dysfunction in this group. ESWT might improve erectile function through enhanced local microvascularization and nerve regeneration. The absence of an active inflammatory process allows the therapy to focus more on repairing and improving the local blood flow and nerve function, leading to better outcomes in erectile function as reflected in the total IIEF scores.

The major strength of the current study is its prospective, randomized, double-blind, placebo-controlled design with a multicenter implementation. To our knowledge, this is also the first clinical study to include magnetic type unifocal ESWT in the treatment of both noninflammatory and inflammatory CP/CPPS (types IIIa and b) with more participants than have been included in previous studies.

Moreover, the device used in this study is a magnetic-type unifocal ESWT with a treatment depth of 80 mm. This is notably deeper than most other ESWT devices, which typically have a treatment depth of 50 mm. In a previous study that used a device with a 50-mm treatment depth,[15] the CPSI total score and VAS declined by 16.7% and 50%, respectively, after 12 weeks. Meanwhile, in our study, we observed respective improvements of 51.4% and 53.3%. In terms of IIEF-EF score, previous study showed an increase

Table 3
Multivariate logistic regression analyses comparing the changes in total NIH–CPSI, total IPSS, total IIEF, and GEAQ score observed at the end of the study for the CP/CPPS type IIIa and IIIb groups.

Variables	Coefficient (95% CI)	*P*-value
Total NIH–CPSI score	−0.242 (−3.343, 2.858)	0.877
Total IPSS score	3.575 (0.446, 6.703)	0.026
Total IIEF score	14.732 (4.043, 25.420)	0.007
GEAQ score	−0.272 (−0.529, −0.015)	0.038

NIH–CPSI: National Institutes of Health-chronic prostatitis symptom index. IPSS, International Prostate Symptom Score; IIEF, International Index of Erectile Function, GEAQ: Global Efficacy Assessment Questions, CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome.

of 5.3%, whereas our study showed an improvement of 7%. We believe that the treatment energy of the ESWT equipment in our study can penetrate deeper, thus applying a shockwave therapy to the neurovascular bundles on both sides of the prostate.

A limitation of this study is the relatively short follow-up period of 4 weeks postclinical treatment. Therefore, it was not possible to ascertain the duration of the treatment effect and how long it persists. It is also a limitation that the short study duration did not allow us to recruit enough subjects to compare types IIIa and IIIb. Moreover, future studies may consider exploring the combination of existing treatments, such as alpha-blockers, antibiotics, and NSAIDs with ESWT. Hence, there is a need for long-term follow-up studies that take various research approaches.

5. Conclusion

ESWT may be effective in the treatment of type III CP/CPPS, including noninflammatory and inflammatory types, and it can be safely used in patients who are difficult to treat with medication. Furthermore, the observed secondary improvement in IIEF-EF warrants further investigation in future research.

Conflicts of interest

All authors have no conflict of interest to declare.

Ethical statement

Ethical approval for the fulfillment of this study was granted by the Institutional Review Board (IRB) of Seoul St. Mary's Hospital and Korea University Guro Hospital (approval number: KC21DDDT0742) after receiving permission from the Korean Ministry of Food and Drug Safety. Informed consent was confirmed by the IRB, and before any procedures were executed, informed consent was obtained from each subject. This study was performed according to the principles of the Declaration of Helsinki and the ethical principles of Good Clinical Practice guidelines. The protocol was registered in Clinical Research Information Service (https://cris.nih.go.kr/cris, KCT identifier: KCT0009330).

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