Original article

Extracorporeal shock wave treatment for non-inflammatory chronic pelvic pain syndrome: a prospective, randomized and sham-controlled study

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Keywords: *extracorporeal shock wave; chronic prostatitis; pain*

Background Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a clinical syndrome characterized by pain in the perineum, pelvis, suprapubic area, or external genitalia and variable degrees of voiding and ejaculatory disturbance. The analgesic effect of extracorporeal shock wave treatment (ESWT) was an interesting phenomenon with an unclear mechanism discovered by chance in the applications for urolithiasis, on which ESWT has become an increasingly popular therapeutic approach as an alternative option for the treatment of a number of soft tissue complaints. In this study, we aimed to evaluate the feasibility and efficacy of ESWT in non-inflammatory (IIIB) CP/CPPS.

Methods Men diagnosed with IIIB CP/CPPS were randomized to either ESWT (group 1, *n*=40) or the control (group 2, *n*=40). Group 1 received 20 000 shock wave impulses in 10 sessions over a two-week period, whereas group 2 received only a sham procedure. The total scores and sub-domain scores of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) for both groups were assessed at baseline, mid-treatment, end-point, and 4-week and 12-week follow-up visits.

Results The mean total NIH-CPSI score of group 1 was significantly decreased from baseline at all post-treatment time points (P <0.01 for all). Decreases in pain domain and quality of life (QOL) scores were also significant. In group 2, no significant decreases of total NIH-CPSI score and pain domain score were found at all post-treatment time points. At the end-point of treatment, 71.1% of group 1 exhibited perceptible improvement in total NIH-CPSI compared with 27.0% of group 2 (P <0.001); additionally, 28.9% of group 1 exhibited clinically significant improvement compared with 10.8% of group 2 (P <0.01). Moreover, a greater number of patients in group 1 at 4-week and 12-week follow-up were rated as responders (perceptible and clinically significant response) compared with group 2.

Conclusion ESWT exhibits a potentially therapeutic role in the treatment of CP/CPPS.

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Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a disabling condition and a prevalent urologic problem in 10%–14% of adult men of all ages and ethnic origins.[1] As many as 50% of men are affected by this condition at some points during their lifetimes.[2] As early as 1980, the National Ambulatory Care Survey reported twenty office visits per 1000 men per year for symptoms compatible with CP/CPPS.[3]

The etiology for CP/CPPS has not been fully elucidated, yet a wide range of diagnostic tests and therapies are offered clinically. Thus, pathogenesis, diagnosis, and treatment options remain a challenge for most urologists. Progress has been made over the past decade toward further understanding of this benign entity. Chronic infection, inflammation, neuropathy, pelvic floor muscle dysfunction, autoimmune disease, and neurobehavioral disorders are among the postulated etiologies, although no single factor is thought to be the cause. Standard therapies for CP/CPPS include antibiotics, anti-inflammatory agents, 5-α reductase inhibitors, and α-1 blockers.[1-3] However, numerous patients face frustration from the inadequate effects of treatment following multiple repeated attempts to cure this disorder. Recently, multi-modal treatment approaches and the utilization of complementary and alternative medicine (CAM) strategies, defined in accordance with a group of diverse medical and health care systems, practices, and products not presently considered part of conventional medicine, have been suggested as potential treatment options for CP/CPPS, biofeedback, acupuncture, hyperthermia, and phytotherapy for example.[4]

Extracorporeal shock wave therapy (ESWT), a minimally invasive technology, has long been used successfully in lithotripsy for the elimination of urinary calculi as a standard urological procedure.[5] The analgesic side effects of ESWT are an interesting phenomenon, although the underlying mechanisms are unclear, which were discovered upon application for urolithiasis by chance, independent of high or low-dose energy, and ESWT has

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since become an increasingly popular therapeutic approach as an alternative option for the treatment of a number of soft tissue complaints.[6-8] Currently, most investigators agree that microbial infection does not play a significant role in CP/CPPS, particularly in the non-inflammatory type (category IIIB), and findings of recent studies have strongly suggested that IIIB CP/CPPS is the result of or associated with pelvic floor abnormalities.[9] Tension myalgia related to the pelvic floor muscles, i.e., levator ani and short external rotators, potentially leads to non-inflammatory CP/CPPS.[9,10] Based on these findings, we hypothesized that the analgesic effect of shock waves could potentially be useful for pain reduction in CP/CPPS patients. We conducted this study in order to test the safety and efficacy of ESWT in the treatment of this complex disorder.

METHODS

Patients

We conducted a 14-week, randomized, single-blinded study from August 2009 to May 2011 to investigate the symptomatic improvement in men with IIIB CP/CPPS who received either ESWT or sham treatment and were refractory to conventional therapies. Patient diagnosis was based on clinical history of disease, the NIH-CPSI questionnaire, physical examination, urinalysis, uroflowmetry with residual urine measurement, transrectal ultrasonography of the prostate, four-glass test, and semen culture. Inclusion criteria included: age of over 18 years, pelvic pain or discomfort defined as pain in the bladder, groin, genitals, or lower abdomen and/or perineal or perianal areas without clear abnormalities on urological examination for a minimum of three months, NIH-CPSI total score greater than 15 and pain domain score greater than four, and the ability to communicate, understand, and comply with the requirements of the study. Exclusion criteria included chronic urethritis, urinary stones, bacterial or inflammatory CP/CPPS, seminal vesiculitis, bladder cancer, prostate cancer, urethral strictures, neurogenic bladder dysfunction, restricted mobility, and antimicrobial or anti-inflammatory medication within the four weeks prior to enrollment in our study. Patients were also excluded from the analysis if they had a documented history of prostatic intraepithelial neoplasia on biopsy, serum prostate-specific antigen levels in excess of 4 ng/ml, history of prostate surgery or radiotherapy, acute urinary retention, or an indwelling catheter.

All recruited patients were informed of treatment methods and written informed consent was obtained from each patient; ethical approval for the study was obtained from the ethics review board of Tongji Medical College, Huazhong University of Science and Technology (HUST).

Study design

Patients enrolled in this study were blinded to group allocation and were randomized to receive either shock wave treatment (group 1) or sham treatment (group 2) using the closed-envelope method. All patients had received prior treatment that consisted of antibiotics, anti-inflammatories, plant extracts, alpha1-blockade, 5-alpha-reductase inhibitors, antimuscarinics, anxiolytics, and neuromodulation agents. Two weeks prior to the study, patients halted all medications used to control their specific prostatic symptoms. Throughout the study, patients received no drugs that could influence the results, such as antibiotics, anti-inflammatories, antidepressants, or pain relievers.

ESWT

The patients in group 1 received 20 000 extracorporeal shock wave impulses in 10 sessions over a period of two weeks. Patients reclined in an adjustable chair, and their testicles were pushed forward gently during the procedure. Shock waves were applied directly to the perineal area in which the pain was localized (from anus to scrotum). Ultrasound gel was used as a coupling agent, and the applicator of the ESWT unit (HB-ESWT-01, Haibin Medical Equipment Co. Ltd., China) was held perpendicular to the treatment surface throughout the treatment. During the initial impulses, patients were instructed to adjust the applicator in order to feel the shock waves target the localized region of pain (Figure 1). The starting energy density was 0.06 mJ/mm^2 and the frequency of 2 Hz was used for all the treatments. The energy density was gradually increased until it reached the maximum possible tolerable pain level reported by the patient. This energy density was recorded during the first session and used in all subsequent sessions. Patients in group 2 were treated by sham ESWT, which was conducted by setting the energy level to 0 (no shock wave energy transmission), under conditions identical to group 1.

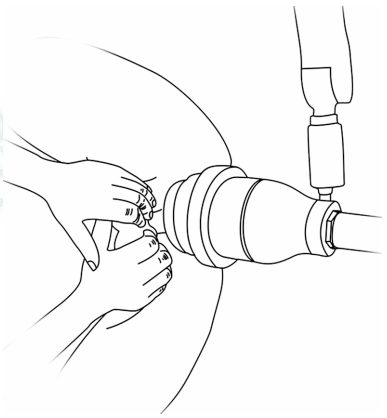

Figure 1. Patient position and delivery of shockwaves.

Evaluations

The efficacy of ESWT was evaluated by measuring the changes in the NIH-CPSI and individual domains of the NIH-CPSI at the following time points: one week before treatment (baseline), one week after the initial treatment (mid-point), two weeks after the initial treatment (endpoint), four weeks after the endpoint (4-week follow-up), and 12 weeks after the endpoint (12-week

follow-up). Adverse events associated with the therapy were monitored and documented throughout the study.

Post hoc responder analysis

Based on previous reports examining NIH-CPSI responders, descriptive post hoc analysis was performed. Responders were defined as men who experienced a decrease of six or more points in total NIH-CPSI compared to baseline, reflecting a 25% decrease in total NIH-CPSI compared to baseline (perceptible improvement), or 12 points, reflecting a 50% decrease in total NIH-CPSI compared to baseline (clinically significant improvement).

Statistical analysis

An independent third party, blinded to the treatment groups, analyzed the data. The statistical analysis software system, version 15.5 (SPSS Inc., USA) was used for the analysis. We summarized data using mean and standard deviations for the continuous variables and frequency tables for the categorical variables. Differences between pre-treatment and post-treatment scores for the total NIH-CPSI score and individual domains of the NIH-CPSI questionnaire were evaluated using matched, paired *t*-tests. The comparison of the efficacy between the two groups was performed using an unpaired *t*-test. To compare the efficacy between the two groups, Pearson's chi-square analysis was used. Statistical significance for all tests was considered at $P < 0.05$.

RESULTS

Patient disposition and demographics

Of the 225 men screened for this study, 80 were eligible according to the inclusion/exclusion criteria and were enrolled in the study following informed consent. Patients were randomized according to the closed-envelope method into either group 1 (ESWT, n=40) or group 2 (sham operation, n=40). Seventy-five (93.8%) patients completed the study and were evaluable, and five patients withdrew from the study. One patient who was randomized to group 1 did not return, without reason, after the first session of ESWT, and three patients who were randomized to group 2 did not continue the study due to noncompliance with study protocol. One patient who was randomized to group 1 was lost to follow-up without reason, although he completed all ESWT sessions. The remaining 75 patients (38 in group 1, and 37 in group 2) were entered for analysis. The baseline characteristics and NIH-CPSI data of these patients are shown according to study group in Table 1; the baseline data for the two groups were comparable with no evident differences between the two groups at baseline.

Efficacy of ESWT

Regarding within-group data comparison, the mean total NIH-CPSI score of group 1 was significantly decreased from baseline at all post-treatment time points (P <0.01

Table 1. Baseline characteristics by individual treatment groups

Parameters	Group 1	Group 2
Age (years)	48.7±12.1	46.3±10.2
Symptom duration (months)	16.2±5.2	15.4±3.1
NIH-CPSI score	30.5±4.7	29.3±4.1
Pain domain	15.6±2.4	14.7±2.7
Urinary score	4.4±1.1	4.7±1.3
Quality of life	10.5±1.7	9.9±2.1
Qmax (ml/s)	17.6±6.7	16.2±5.7
Prostate volume (ml)	14.5±2.3	13.7±1.9
Serum PSA (μg/ml)	1.2±0.8	1.3±0.8

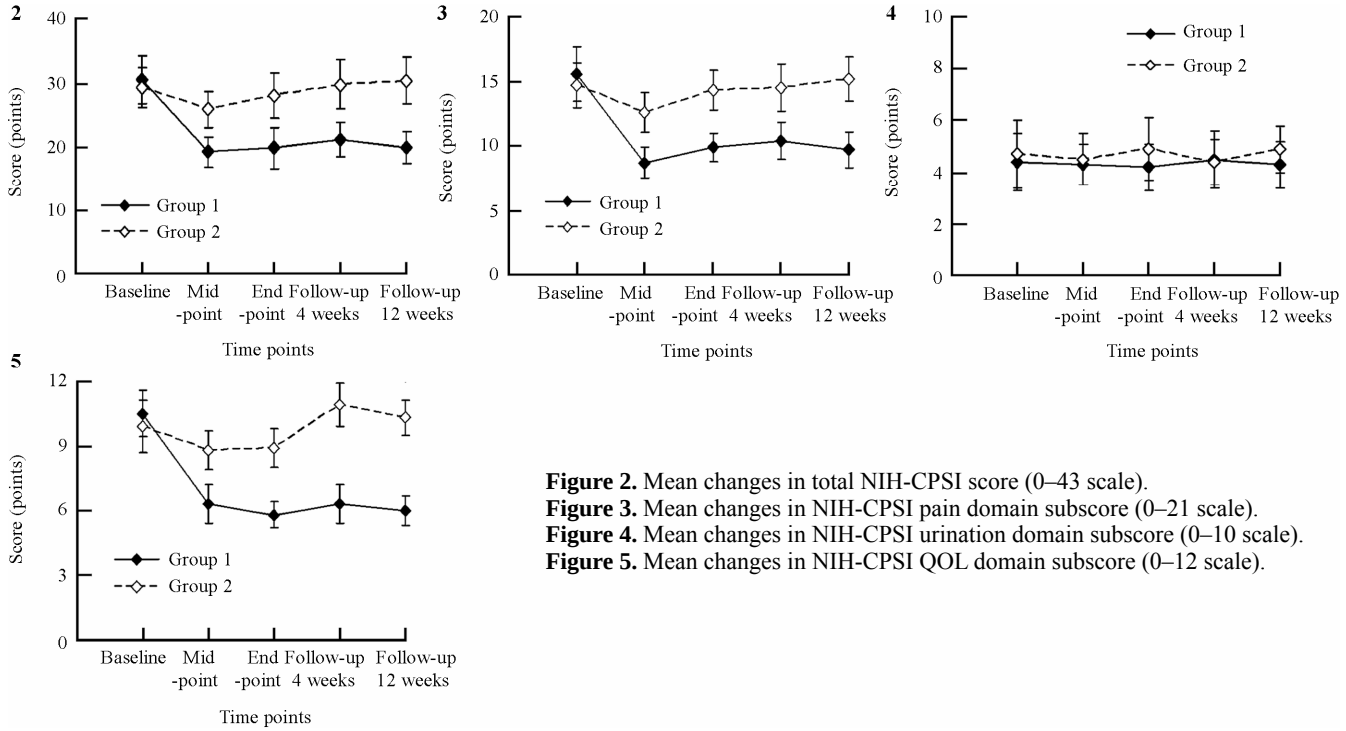

Figure 2. Mean changes in total NIH-CPSI score (0–43 scale).
Figure 3. Mean changes in NIH-CPSI pain domain subscore (0–21 scale).
Figure 4. Mean changes in NIH-CPSI urination domain subscore (0–10 scale).
Figure 5. Mean changes in NIH-CPSI QOL domain subscore (0–12 scale).

for all). The decreases that were observed in the scores of pain domain and quality of life (QOL) were also significant. No significant changes were found in the scores of urination domain at all time points. Regarding group 2, significant decreases of total NIH-CPSI score and pain domain scores were found only at the mid-point of treatment (Figures 2–5).

With respect to between-group comparisons, the total NIH-CPSI scores in group 1 were significantly lower compared with group 2 at all time points post-treatment (P <0.05 for all). Pain scores and QOL scores at all post-treatment time points demonstrated significant differences between the two groups, whereas there was no significant difference between two groups regarding urination scores (Figures 2–5).

Safety of ESWT

ESWT was well tolerated, and there were no adverse events or side effects reported, nor any anesthetics utilized, throughout this study.

Post hoc responder analysis

At the end-point of the study, 71.1% (27/38) patients in group 1 exhibited perceptible improvement in total NIH-CPSI compared with 27.0% (10/37) patients in group 2 (P <0.001), and 28.9% (11/38) patients in group 1 exhibited clinically significant improvement compared with 10.8% (4/37) in group 2 (P <0.01). Interestingly, these significant differences were maintained at the 4-week and 12-week follow-up time points, and additional patients were rated as responders (perceptible and clinically significant) in group 1 (63.2% (24/38) and 21.1% (8/38), respectively, at the 4-week follow-up time point, and 68.4% (26/38) and 23.7 % (9/38), respectively, at the 12-week follow-up time point) compared with patients in group 2 (5.4% (2/37) and 0 (0/37), respectively, at the 4-week follow-up time point, and 0 (0/37) and 0 (0/37), respectively, at the 12-week follow-up time point, P <0.05 for all).

DISCUSSION

CP/CPPS is a clinical syndrome characterized by pain in the perineum, pelvis, suprapubic area, or external genitalia, causing a variable degree of voiding and ejaculatory disturbance.[11] Currently, the exact etiology of CP/CPPS is not completely understood, and the optimal management of CP/CPPS remains unknown. In a primary-care setting in which QOL was measured, Turner et al[12] reported that a worse QOL was associated with greater pain and urinary symptoms, and that pain was more robustly associated with worse QOL compared to urinary symptoms. Recently, Tripp et al[13] also reported that pain intensity and urinary symptoms were independent predictors of QOL, with pain intensity representing the strongest predictor. These findings are highly suggestive that pain relief could significantly alleviate the overall symptoms of the condition we examined in this study, and improve the potential for effective treatment.

Over the past two decades, ESWT has been used to manage soft tissue pain in the vicinity of bone structure. The analgesic mechanisms and the specific biological effects of ESWT remain poorly understood and have not been extensively studied. Shock waves are regarded as mechanical, physical stimuli that produce extracellular cavitations when passing through human tissues. Cavitation may result in damage to local nerve endings and cell membranes; hence, the effect on transmission of pain signals.[14-16] Another explanation for the analgesic effect of ESWT is the gate-control theory. Krischek et al[17] reported that ESWT activates the small-diameter fibers and the serotonergic system, which ultimately modulates transmission through the dorsal horns.

Zimmermann et al[18] recently reported a similar, prospective trial that included 60 patients with CPPS treated by ESWT or sham treatment in which they found reduced pain and improved QOL in a significantly greater proportion of patients who underwent ESWT treatment. In this study, we utilized similar equipment and a different treatment regimen to evaluate the efficacy and safety of ESWT in treatment of IIIB CPPS. The results were similar to Zimmermann's study, and further demonstrated that trans-perineal ESWT significantly reduced the total NIH-CPSI, pain domain, and QOL domain compared to a control group up to a 12-week follow up time frame, which contributed greatly to the analgesic effect of ESWT. In comparison to Zimmermann's study,[18] relatively higher preliminary improvement rates of CPSI scores (68.4% in our study vs. 43.3% in Zimmermann's study) at the 12-week follow-up after ESWT, indicating that a comparative study regarding these differences is warranted to assess the effect of the differing ESWT regimens (interval, frequency, period, etc.) in the treatment of CP/CPPS. This result supports the hypothesis that the pelvic floor muscular dysfunctions (tension myalgia) may play a prominent role in the pathophysiology of CP/CPPS. Additionally, we noted that, regardless of pain or QOL subscore, a small proportion of patients exhibited no response to treatment, indicating that an underlying mechanism causing CP/CPPS could be involved in the etiology of this disease, and that ESWT, as a single-modality treatment, has limitations.

As a new approach to treat CP/CPPS, the safety of trans-perineal ESWT is another issue that requires serious consideration. Throughout our study, fortunately, there were no adverse events or side effects reported and no anesthetic deemed necessary, similar to previous report,[18] which further confirms the safety and ease of low energy ESWT in the treatment of soft tissue pain.

Psychological factors are closely related to the QOL of patients refractory with CP/CPPS;[19,20] thus, it is not

surprising that a very small proportion of patients in the sham-control group in our study exhibited a significant improvement in NIH-CPSI during early follow-up after ESWT, although this effect disappeared in late stages of follow-up. This interesting phenomenon suggests that the professional and systemic psychosocial interference can dramatically improve the treatment for some refractory cases of CP/CPPS.

The limitations of this study include the relatively small number of randomized patients and relatively short-term time period of follow-up. A multicenter study with a larger sample size, sham-controlled, and with longer-term follow up is warranted to elucidate the long-term effectiveness of ESWT and determine the duration of benefit that this treatment will offer and whether retreatment is necessary. In addition, the next step to future research will be to further elucidate the possible mechanisms of action of ESWT and to identify factors that influence the patient outcomes.

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REFERENCES

1. Mehik A, Hellstrom P, Lukkarinen O. Epidemiology of prostatitis in Finnish men: a population-based cross-sectional study. Br J Urol Int 2000; 86: 443-448.
2. Stamey T. Urinary tract infections in males. In: Stamey T, ed. Pathogenesis and treatment of urinary tract infections. Baltimore: Williams and Wilkins; 1980: 342-429.
3. Duloy AM, Calhoun EA, Clemens JQ. Economic impact of chronic prostatitis. Curr Urol Rep 2007; 8: 336-339.
4. Capodice JL, Bemis DL, Buttyan R, Kaplan SA, Katz AE. Complementary and alternative medicine for chronic prostatitis/chronic pelvic pain syndrome. Evid Based Complement Alternat Med 2005; 2: 495-501.
5. Chow GK, Streem SB. Extracorporeal lithotripsy. Update on technology. Urol Clin North Am 2000; 27: 315-322.
6. Mouzopoulos G, Stamatakos M, Mouzopoulos D, Tzurbakis M. Extracorporeal shock wave treatment for shoulder calcific tendonitis: a systematic review. Skeletal Radiol 2007; 36: 803-811.
7. Chow IH, Cheing GL. Comparison of different energy densities of extracorporeal shock wave therapy (ESWT) for the management of chronic heel pain. Clin Rehabil 2007; 21: 131-141.
8. Chung B, Wiley JP. Extracorporeal shockwave therapy: a review. Sports Med 2002; 32: 851-865.
9. Pontari MA, Ruggieri MR. Mechanisms in prostatitis/chronic pelvic pain syndrome. J Urol 2008; 179: 61-67.
10. Nadler RB. Bladder training biofeedback and pelvic floor myalgia. Urology 2002; 60 (6 Suppl): s42-s44.
11. Nickel JC. Clinical evaluation of the man with chronic prostatitis/chronic pelvic pain syndrome. Urology 2002; 60 (6 Suppl): s20-s23.
12. Turner JA, Hauge S, Von Korff M, Saunders K, Lowe M, Berger R. Primary care and urology patients with the male pelvic pain syndrome: symptoms and quality of life. J Urol 2002; 167: 1768-1773.
13. 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: 1279-1282.
14. Ogden JA, Alvarez RG, Levitt R, Marlow M. Shock wave therapy (Orthotripsy) in musculoskeletal disorders. Clin Orthop Relat Res 2001; (387): 22-40.
15. Ogden JA, Tóth-Kischkat A, Schultheiss R. Principles of shock wave therapy. Clin Orthop Relat Res 2001; 387: 8-17.
16. Delius M. Medical applications and bioeffects of extracorporeal shock waves. Shock Waves 1994; 4: 55-72.
17. Krischek O, Hopf C, Nafe B, Rompe JD. Shock-wave therapy for tennis and golfer's elbow: 1 year follow-up. Arch Orthop Trauma Surg 1999; 119: 62-66.
18. 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. Euro Urol 2009; 56: 418-424.
19. Nickel JC, Tripp DA, Chuai S, Litwin MS, McNaughton-Collins M, Landis JR; NIH-CPCRN Study Group. Psychosocial variables affect the quality of life of men diagnosed with chronic prostatitis/chronic pelvic pain syndrome. BJU Int 2008; 101: 59-64.
20. Zhang GX, Bai WJ, Xu T, Wang XF. A preliminary evaluation of the psychometric profiles in Chinese men with chronic prostatitis/chronic pelvic pain syndrome. Chin Med J 2011; 124: 514-518.

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