

Extracorporeal Shockwave Therapy Combined with Drug Therapy in Chronic Pelvic Pain Syndrome : A Randomized Clinical Trial

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Purpose: Chronic prostatitis/ chronic pelvic pain syndrome (CP/CPPS) is a nonspecific pelvic pain in the absence of signs of infection or other obvious local pathology for at least three of the last 6 months. Evidence for treatment approach is limited. So the aim of this study is to investigate the effect of extracorporeal shock wave therapy (ESWT) combined with pharmacotherapy in the treatment of CP/CPPS.

Materials and Methods: In this randomized clinical trial, 31 patients with CP/CPPS were investigated in two groups: the intervention group (n=16) was treated with a combination of an alpha-blocker, an anti-inflammatory agent, a muscle relaxant and a short course of antibiotic in combination with 4 sessions of focused ESWT (a protocol of 3000 impulses, 0.25 mJ/mm² and 3 Hz of frequency). The control group (n=15) received the aforementioned pharmacotherapy with 4 sessions of sham-ESWT. Follow-up was performed 4 and 12 weeks following ESWT by using the Visual Analogue Scale (VAS), International index of Erectile function (IIEF) 5, National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) and International Prostate Symptom Score (IPSS) questionnaires. Post void residual (PVR) urine and maximum flow rate (Qmax) were also assessed in both groups.

Results: The patients mean age was 43.7 ±12.6 years. In both groups, the mean scores of NIH-CPSI (total and sub-domains) and VAS showed statistically significant improvements after 4 and 12 weeks compared to the baseline ($P < .001$). In the intervention group, IPSS (mean difference: 4.25) and Qmax (mean difference: 2.22) were also significantly improved ($P < .001$). There was a significant improvement in NIH-CPSI (mean difference: 1.1) and VAS scores (mean difference: 1.1) in the intervention group as compared to the control group ($P < .01$). Qmax, PVR and IIEF score were not statistically different in the two groups.

Conclusion: ESWT in combination with pharmacotherapy could improve the treatment outcome in patients with CP/CPPS.

Keywords: chronic pelvic pain syndrome; erectile dysfunction; extracorporeal shock wave therapy; pain management; prostatitis

INTRODUCTION

Chronic Prostatitis /Chronic Pelvic pain syndrome (CP/CPPS) is the most frequent urological disorder in men younger than 50 and the third most common urological finding in men over 50 years old.⁽¹⁾ According to the national institute of health (NIH), chronic pelvic pain syndrome (CPPS) is a chronic or persistent pain that lasts 3 months in the last 6 months and is perceived in structures related to the pelvis which is associated with symptoms suggestive of lower urinary tract, sexual, bowel or pelvic floor dysfunction and causes negative emotional and cognitive consequences.

(2,3)

The prevalence of CPPS is between 3–10 % that affects nearly 15% of all urologic outpatient visits.^(4,5) Despite its high prevalence and its impact on quality of life (QOL), the pathogenesis of the CPPS is hardly understood. Numerous etiologies are proposed including infection, pelvic floor hyperactivity, local chemical alterations, neurologic components (central sensitization), and perfusion disturbances.^(6,7) It is important to exclude other genital and pelvic disorders present with pelvic pain before the diagnosis of CPPS.⁽⁸⁾ The determination of the severity of the disease, its

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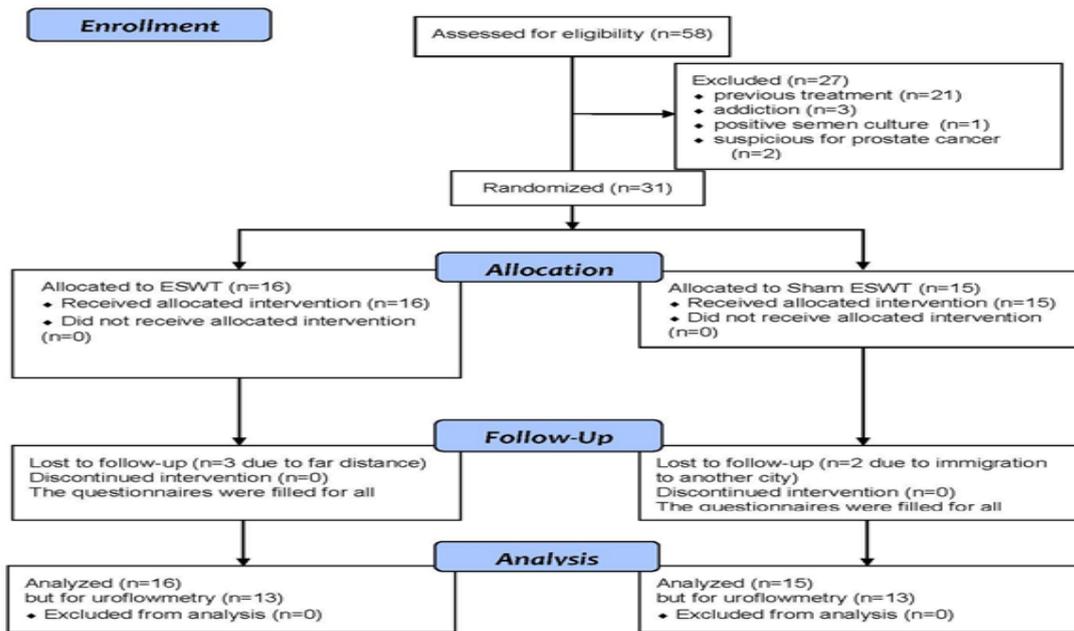


Figure 1. CONSORT 2010 Flow Diagram

progression and treatment response can be assessed by means of reliable questionnaires such as International Prostate Symptom (IPSS) Score and National Institutes of Health-Chronic Prostatitis Index (NIH-CPSI).^(2,9,10) Unknown pathogenesis leads to limitations in the treatment of CPPS. The most common therapeutic approaches are α -receptor blockers, like tamsulosin, antibiotics which cover gram negative germs, analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and 5- α -reductase inhibitors used as mono- or combination therapy.⁽¹¹⁻¹³⁾

The second-line treatment protocols include physical therapy, trigger-point massage, electromagnetic treatment, acupuncture, prostate massage, and intraprostatic injection of botulinum toxin A.^(14,15)

There are many challenging issues in the management of patients with CPPS, such as the possibility of treatment failure by monotherapy or pharmacological side effects in long-term use.⁽¹⁶⁾

Although extracorporeal shock wave therapy (ESWT) has been successful for other indications such as orthopedic pain syndromes,⁽¹⁷⁾ there is limited evidence whether this approach is also effective for patients with CPPS. A number of mechanisms have been suggested including the increasing of local microvascularization, decreasing passive muscle tone, hyperstimulating nociceptors, interrupting the flow of nerve impulses, or influencing the neuroplasticity of the pain memory.^(18,19) ESWT is an outpatient procedure without significant side effects that can be simply applied.

According to the mentioned challenges in CPPS treatment and the fact that there is no conclusive data about the effectiveness of combining ESWT and drug therapy, we conducted a sham-controlled randomized clinical trial to study the effects of ESWT and oral pharmacological treatment combination therapy in patients with CPPS, which, to the best of our knowledge, has not been performed before.⁽²⁰⁾

MATERIALS AND METHODS

We performed this single-blind randomized controlled clinical trial from May 2017 to February 2018.

Inclusion and exclusion criteria

All patients with chronic prostatitis type IIIB/chronic pelvic pain syndrome who were referred to the urology clinic of Shohada-e-Tajrish hospital and met our inclusion criteria were enrolled in this study. The study inclusion criteria were as follows: patients older than 18 years of age diagnosed with type IIIB prostatitis (criteria according to NIH classification)⁽³⁾, patients with pain that lasted 3 months in the last 6 months without clear abnormalities upon urological examination and no evidence of bacteria in urinary and seminal fluid culture tests, and patients who were not addicted to drugs and narcotics.

The exclusion criteria of this study included being under treatment by another method at the beginning of the study, other diagnoses such as varicocele, hernia or prostate cancer during workup, PSA > 4, bleeding diathesis, history of urethral stricture or hematuria or urinary tract infection in the last year.

The diagnosis of patients was made by a single urologist based on a comprehensive history and physical examination including digital rectal examination, PSA measurement, urine analysis and culture, semen analysis and two-cup test.

A combination of an alpha blocker (tamsulosin 0.4mg daily), an NSAID (diclofenac sustained release 100mg daily), a muscle relaxant (baclofen 10mg/BD) for 12 weeks and a short term antibiotic (ofloxacin 300mg/BD for 2 weeks) were started for all patients. In this situation, no one was deprived from the treatment.

For each patient the questionnaires including IIEF5, IPSS and NIH-CPSI were completed and the degree of pain was assessed using VAS to achieve baseline char-

Table 1. Demographic and baseline data in both groups.

	Group	N	Mean	Std. Deviation	P Value
Age (years)	case	16	44.38	13.846	.77
	control	15	43.07	11.708	11.708
Marriage status (number of married)	case	16	8(50%)		1.00
	control	15	7(53.3%)		
Ejaculation per week	case	16	1.50	1.033	.4
	control	15	1.80	0.941	
Body Mass Index (Kg/m ²)	case	16	29.25	6.382	.98
	control	15	29.20	6.656	
Duration (months)	case	16	11.37	5.251	.95
	control	15	11.26	5.885	
IIEF ^a 5	case	16	16.38	6.131	.66
	control	15	15.47	5.153	
IPSS ^b	case	16	15.69	6.610	.90
	control	15	15.40	6.208	
NIH ^c pain part	case	16	13.06	6.298	.44
	control	15	14.67	5.052	
NIH urination part	case	16	4.75	2.817	.89
	control	15	4.87	1.767	
NIH QOL ^d part	case	16	7.69	2.750	.44
	control	15	8.33	1.759	
NIH total score	case	16	25.50	8.989	.42
	control	15	27.87	7.259	
PVR ^e (ml)	case	16	14.7500	9.83531	.72
	control	15	16.1333	11.84945	
Qmax (ml/s)	case	16	14.825	6.7752	.87
	control	15	15.233	7.0605	
VAS ^f	case	16	6.44	1.263	.94
	control	15	6.40	1.805	

^aIIEF: International Index of Erectile Function, ^bIPSS: International Prostate Symptom Score, ^cNIH: National Institute of Health, ^dQOL: Quality of Life, ^ePVR: Post Void Residue, ^fVAS: Visual Analog Scale

acteristics by a blind investigator.

We tried to have a consistent environment for participants and trained the participants well for rating the questionnaires to increase the reliability of our assessments. We also calculated the Cronbach's Alpha for

each questionnaire.

Uroflowmetry was also done to obtain maximum flow rate (Qmax) and post void residual urine (PVR). We used PC based Wireless Uroflowmeter by MMS from Netherland.

Table 2. Mean difference of variables before and after treatment in intervention and control groups after 4 and 12 weeks

	Intervention group			
	After 4 weeks		After 12 weeks	
	Mean difference	P Value	Mean difference	P Value
IIEF ^a 5	0.38	0.45	-0.81	.35
IPSS ^b	1.88	0.006	4.25	.0001
NIH ^c PAIN	4.25	0.0001	5.06	.0001
NIHURINE	2.25	0.0001	2.19	.001
NIHQOL ^d	3.75	0.0001	4.88	.0001
NIH Total	10.25	0.0001	12.12	.0001
Qmax	-2.22	0.004	-1.8	.04
PVR ^e	2.88	0.056	4.2	.14
VAS ^f	3.81	0.0001	3.63	.0001
	Control group			
	After 4 weeks		After 12 weeks	
	Mean difference	P Value	Mean difference	P Value
IIEF 5	0.74	0.22	-0.80	.26
IPSS	0.73	0.6	1.40	.06
NIH PAIN	2.67	0.001	3.14	.0001
NIHURINE	0.87	0.003	0.87	.0001
NIHQOL	2.4	0.0001	2.33	.0001
NIH Total	5.94	0.0001	6.34	.0001
Qmax	-0.59	0.17	0.65	.20
PVR	1.67	0.10	0.08	.92
VAS	1.73	0.0001	2.07	.0001

^aIIEF: International Index of Erectile Function, ^bIPSS: International Prostate Symptom Score, ^cNIH: National Institute of Health, ^dQOL: Quality of Life, ^ePVR: Post Void Residue, ^fVAS: Visual Analog Scale.

Table 3. Comparison of outcomes between intervention and control groups after 4 weeks

	Group	N	Mean	Std. Deviation	P Value
IIEF a 5	case	16	16.00	5.177	.45
	control	15	14.73	3.918	
IPSS b	case	16	13.81	4.679	.64
	control	15	14.67	5.473	
NIH c pain part	case	16	8.81	3.351	.02
	control	15	12.00	3.982	
NIH urination part	case	16	2.50	1.366	.01
	control	15	4.00	1.690	
NIH QOLd part	case	16	3.94	1.340	.001
	control	15	5.93	1.624	
NIH total score	case	16	15.25	4.282	.001
	control	15	21.93	5.391	
Qmax	case	16	17.044	4.8814	.54
	control	15	15.827	6.1762	
PVR e	case	16	11.8750	6.66208	.42
	control	15	14.4667	10.63597	
VAS f	case	16	2.63	1.500	.001
	control	15	4.67	1.447	

^a IIEF: International Index of Erectile Function, ^b IPSS: International Prostate Symptom Score, ^c NIH: National Institute of Health, ^d QOL: Quality of Life, ^e PVR: Post Void Residue, ^f VAS: Visual Analog Scale.

Then using random number table, the participants were randomly divided into two groups using opaque envelopes to guarantee the allocation concealment. In this protocol all patients were blind about the future procedure.

Procedure

In the intervention group, patients were treated by ESWT once a week for 4 weeks. Each time 3000 impulses, with 0.25 mJoules/mm² and 3 Hertz of frequency were delivered. After each 500 pulses, the probe position was changed. In this study, we used standard focused electromagnetic DUOLITH SD1 T-TOP by Storz Medical from Switzerland. The treatment was performed in supine position.

In the sham group, the same protocol was applied for patients but the probe was turned off.

Outcome assessment

The primary outcomes were pain reduction and improvement in urinary symptoms which were evaluated using VAS, NIHCPSI and IPSS questionnaires. The secondary outcomes included sexual performance which was assessed by IIEF5 questionnaire, objective urinary conditions (Qmax and PVR) and treatment complications.

The follow-up assessments were done 4 and 12 weeks following the first ESWT session. The follow-up study included clinical examinations and filling the questionnaires and taking a focused history of patients' complaints by the same blind person who evaluated the participants at the beginning of the study, besides measuring Qmax and PVR by uroflowmetry.

The study protocol was performed in accordance with the Declaration of Helsinki and approved by the Ethics

Table 4. Comparison of outcomes between intervention and control groups after 12 weeks.

	Group	N	Mean	Std. Deviation	P Value
IIEF ^a 5	case	16	17.19	2.713	.34
	control	15	16.27	3.327	
IPSS ^b	case	16	11.44	3.669	.93
	control	15	14.00	4.536	
NIH ^c PAIN part	case	16	8.00	3.899	.01
	control	15	11.53	3.980	
NIH Urination part	case	16	2.56	1.094	.003
	control	15	4.00	1.363	
NIH QOL ^d part	case	16	2.81	1.047	.0001
	control	15	6.00	1.309	
NIH Total score	case	16	13.38	4.703	.0001
	control	15	21.53	4.533	
Qmax	case	10	14.600	3.8038	.40
	control	12	16.333	5.4249	
PVR ^e	case	10	14.5000	4.30116	.80
	control	12	13.5000	11.63459	
VAS ^f	case	16	2.81	1.167	.004
	control	15	4.33	1.543	

^a IIEF: International Index of Erectile Function, ^b IPSS: International Prostate Symptom Score, ^c NIH: National Institute of Health, ^d QOL: Quality of Life, ^e PVR: Post Void Residue, ^f VAS: Visual Analog Scale.

Committee of Shahid Beheshti University of Medical Sciences and it is registered on IRCT database with the following code: IRCT2017082635911N1. The informed consent was obtained after all patients were informed of the treatment methods and also about publishing the data without disclosure of their names. It must be mentioned that there was no deviations from the study protocol in all phases of the project.

Statistical Analysis

The data were analyzed by SPSS (version 23). The biostatistician was blind about treatment groups. Statistical analyses such as chi-square, paired t-test and independent t-test were used. *P* value less than 0.05 implied statistical significance.

RESULTS

Thirty-one male patients were randomly assigned to the intervention group ($n=16$) and control group ($n=15$). The CONSORT flow diagram is shown in **Figure 1**. The mean age of the patients in the intervention and sham groups were 44.3 ± 13.8 and 43.07 ± 11.7 years, respectively. The demographic data were summarized in **Table 1**. At baseline, the mean scores of IIEF5, VAS, IPSS and NIH-CPSI were not statistically different in the two groups. The mean scores of objective parameters including Qmax (14.825 ± 6.77 versus 15.23 ± 7.06 , $p = .87$) and PVR (14.75 ± 9.83 versus 16.13 ± 11.84 , $p = .72$) were also similar in both groups.

With respect to within-group data analysis, VAS score, total NIH-CPSI and all subdomains were significantly improved in both groups. The difference became statistically significant 4 and 12 weeks after treatment. (**Table 2**). IPSS and Qmax were significantly improved in the intervention group ($P < .006$) but insignificantly improved in the sham group, 4 and 12 weeks after treatment. In addition, IIEF5 scores and PVR were not improved in either group at any follow-up time points. Regarding between-group analysis, the scores of NIH-CPSI subdomains including pain, urinary symptoms and QOL became significantly different in the two groups at week 4. Total NIH-CPSI and VAS scores at this follow-up time point were also significantly different in favor of the intervention group (**Table 3**).

After 12 weeks, the difference between the two groups was also noted and the mean \pm SD NIH-CPSI total scores including pain, urinary symptoms and QOL subdomains were 13.38 ± 4.70 in the intervention group and 21.53 ± 4.53 in the sham group ($P = .0001$). VAS score was different in the two groups and the mean was 2.81 ± 1.16 versus 4.33 ± 1.54 in the intervention and control group, respectively ($P = .004$). But the mean scores of Qmax (14.6 ± 3.80 versus 16.33 ± 5.42 , $P = .40$) and PVR (14.5 ± 4.30 cc versus 13.50 ± 11.63 cc, $P = .80$) were not significantly different. Also, the mean of IIEF5 (17.19 ± 2.71 versus 16.27 ± 3.32 , $P = .34$) and IPSS (11.44 ± 3.66 versus 14 ± 4.53 , $P = .93$) were not different in the two populations (**Table 4**).

There were only 18% ($n = 4$) and 13% ($n = 2$) loss to follow-up in intervention and control groups respectively, yet all the questionnaires were filled by interview on phone and only uroflowmetry was not performed.

In this study, four patients in the intervention group experienced minor complications that included transient hematuria and hematospermia which were not statistically and clinically noteworthy.

DISCUSSION

Our study showed that ESWT and drug therapy could improve urinary symptoms, pain and QOL of patients with CPPS.

Numerous studies in other fields of medicine such as cardiology and orthopedics have shown that ESWT is effective and has no significant side effects.^(17,21) This issue was confirmed in the present study. Furthermore, ESWT is effective to alleviate pain and help heal tissue. This can be explained by local muscle relaxation and ESWT-induced neovascularization.^(22,23)

A randomized double-blind study of ESWT in patients with CPPS performed by Zimmermann et al.⁽¹⁹⁾ showed that all outcome parameters improved significantly in the treatment group at month 3 (IPSS: 25% decrease; IIEF: 5.3% increase; NIH-CPSI: 17% decrease; VAS: 50% decrease), with no improvement in the sham-treatment group. This study was the first study to recommend level 1 evidence for ESWT in patients with CPPS.⁽¹⁹⁾

In the study of 80 CPPS patients,⁽²⁴⁾ there was a significant improvement in pain, QOL and total NIH-CPSI scores in the ESWT group compared to the sham group. In our study, an improvement in symptoms was observed in both intervention and sham groups that can be in line with the sham effect and also the medications used in both groups. However, the difference became significant at weeks 4 and 12 after treatment for VAS and NIH-CPSI total and subdomain scores in favor of ESWT. Yet IPSS was not significantly different in each follow-up time.

In most studies^(23,25,26), identical to the present research, focused ESWT was used, with the exception of only one study.⁽²⁷⁾ In this randomized controlled study, a radial shock wave device was used in CPPS patients and the outcomes were compared with the second group in which pharmacological treatment was administered. A significant improvement of pain and QOL was reported in the first group.

In the present study, Qmax and PVR were not significantly different in the two groups in each follow-up time, while the study conducted by Pajovic et al.⁽²⁵⁾ showed statistically significant improvement in both PVR and Qmax after receiving a combination of triple drug therapy and ESWT, which could be due to the longer duration of treatment (12 sessions of ESWT, once-weekly)

Although, in this study, the mean score of IIEF at the baseline was similar to some previous studies, there were no significant changes in our follow-up study, contrary to the findings of above-mentioned studies.^(19,28,29)

The average of follow-up in most studies was 12 weeks after ESWT^(19,24,26,27) but some studies extended their follow-up ranging from 24 weeks to one year.^(25,29,30) Moayednia et al.⁽³⁰⁾ showed that at week 24 of follow-up, the mean scores of pain, urinary symptoms, QOL and total NIH-CPSI score were not statistically different from baseline in the ESWT group. While in another study,⁽²⁹⁾ the efficacy of shock wave was proven for one year after treatment. It seems that further studies are needed to determine its long-term efficacy.

Although our data looks very promising, some limiting factors in our study need to be considered: the study period of only 3 months is short, therefore, the durability of this approach is unknown.

The lack of side-effects specific to ESWT make it possible to repeat the ESWT cycle at any time. In the future, it might be possible to significantly extend the treatment sessions possibly to achieve a long-lasting treatment effect.

CONCLUSIONS

ESWT is an outpatient and easy procedure that in combination with pharmacotherapy could improve treatment outcomes in patients with CP/CPPS.

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CONFLICT OF INTEREST

It should be mentioned that the authors had no conflict of interest during this mission.

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