ARTICLE

Clinical Research

Outcomes and clinical predictors of extracorporeal shock wave therapy in the treatment of chronic prostatitis/chronic pelvic pain syndrome: a prospective randomized double-blind placebo-controlled clinical trial

Ahmed M. Sakr[1], Amr M. Fawzi[1], Mostafa Kamel[1] and Maged M. Ali[1]✉

OBJECTIVES:: To report the one-year results of ESWT on CPPS patients and the possible clinical characteristics that may affect its efficacy.

PATIENTS & METHODS:: A prospective randomized clinical study between January 2017 and January 2021 on 155 adult patients with chronic pelvic pain syndrome. All patients were initially evaluated with a thorough history and physical examination. Baseline symptoms evaluation of each participant was assessed using NIH-CPSI score, IPSS, VAS, and IIEF-5 score. Patients were randomized into two groups: a verum treatment group and a placebo treatment group. Patients of verum group in the lithotomy position received a perineally applied ESWT treatment once a week for four weeks with 3000 impulses each. Patients of placebo group received the same therapy head of the same device with a layer of air-filled microspheres to absorb the shock waves. The previously mentioned validated scores were reassessed on regular follow-up visits at one, three, six, and 12 months after the completion of ESWT.

RESULTS:: A statistically significant improvement was noticed in the mean values of NIH-CPSI, IPSS, VAS, and IIEF-5 of the patients of verum group over the follow-up period with also statistically significant difference between both groups. At the first visit of follow-up after ESWT, 63 (82.8%) patients had ≥6 points decrease in the NIH-CPSI total score, while 13 (17.2%) patients did not. Univariate and multivariate analyses of the clinical characteristics between the responders and non-responders showed that those patients with history of psychological disorders or had higher initial NIH-CPSI score had a significantly lower response rate to ESWT ($p = 0.005$, 0.02 & $p = 0.002$, 0.004 respectively). ROC curve of NIH-CPSI score showed that a score of 32 was the cut-off point above which the response to ESWT decreased.

CONCLUSION:: ESWT is an effective treatment option for CPPS. Its efficacy remained throughout long-term follow up. High initial NIH-CPSI score and history of psychological problems are significant predictors for it.

Prostate Cancer and Prostatic Diseases; https://doi.org/10.1038/s41391-021-00464-8

INTRODUCTION

Chronic pelvic pain syndrome (CPPS) is an idiopathic disorder characterized by non-specific poorly localized pelvic pain lasting for at least three of the previous six months which causes urinary symptoms and usually affects the patient's quality of life (QoL), and even his sexual function [1, 2]. CPPS is a pertinent urologic problem affecting up to 3–10% of men of different ages in the general population and around 15% in the urologic outpatients [3]. Those patients suffer from disturbed quality of life comparable to those after a heart attack, angina pectoris, and Crohn's disease [4, 5]. The pathophysiology of CPPS combines possible psychiatric and somatic factors. It is most probably multifactorial. The most common hypothesized etiologies include former infections (via nociceptive nerve endings and receptors), alteration of local chemical environment, pelvic floor muscle dysfunction, tissue perfusion disturbances, neurobiological factors, and neurobehavioral disorders. Some women reported a similar degree of CPPS to that of men that challenges the role of the prostate in its pathogenesis [6, 7]. Many drugs were tried for treatment of CPPS either single or combination therapy. The conventional triple-A therapy including antibiotics, non-steroidal analgesics, and α-blockers was commonly used with only 50–60% response [8]. Other alternative medical approaches include 5α-reductase inhibitors, anti-depressants, corticosteroids, phytotherapy (quercetin, bee pollen, pumpkin africanum seed oil, eviprostat, terpene mixture, and serenoa repens or saw palmetto), anti-cholinergics, and muscle relaxants with disappointing results [9–11]. This made the urologists utilize complementary and alternative medicine

[1]Urology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt. ✉email: dr_magood@hotmail.com

Received: 13 May 2021 Revised: 18 September 2021 Accepted: 23 September 2021
Published online: 11 October 2021

strategies e.g nutritional supplements, bio-feedback, physiotherapy, acupuncture, traditional Chinese medicine, trigger-point massage, rectal massage, electromagnetic stimulation, hyperthermia, thermotherapy, neuromodulation, laser coagulation, balloon dilatation, and intra-prostatic injection of botulinum toxin A. However, none of these modalities has been uniformly successful [6, 12–15]. Extracorporeal shock wave therapy (ESWT) has long been used successfully in orthopedic pain syndromes, fractures, and wound healing disorders. This attracted attention toward its use in CPPS. The mechanisms through which ESWT reduces pain are interrupting the flow of nerve impulses by hyper-stimulation of nociceptors and nerve endings, revascularization of tissues enhancing their healing, and reduction in muscle tone and spasm [2, 6, 15, 16]. Many studies in the literature focused on short-term follow-up, while the long-term effect of ESWT on patients with CPPS remains unclear. In this study, we aimed to evaluate the effect of ESWT on CPPS patients over the span of a 12-months follow-up, and the possible clinical characteristics that may affect its efficacy.

Patients and methods

After local ethics committee approval number 3616 and informed consent from all patients was obtained, we conducted this prospective randomized clinical study between January 2017 and January 2021 on 155 adult patients with chronic pelvic pain syndrome / chronic prostatitis type III (chronic non-bacterial prostatitis) according to National Institutes of Health (NIH) classification with perineal or pelvic pain or discomfort of at least 3 months and negative semen and urine cultures for bacteria. Patients with prostate cancer or other prostatic pathologies (via serum prostate-specific antigen, digital rectal examination, and trans-rectal ultrasound) were excluded. Other exclusion criteria included uncontrolled coagulopathy, perineal anatomical abnormalities, neurological abnormalities, or previous extensive pelvic injuries. All patients were initially evaluated with a thorough history and physical examination including medical, surgical, psychological, and sexual aspects. Comorbidities and risk factors for CPPS were reviewed well. Routine laboratory investigations (Blood picture, bleeding profile, kidney & liver function tests, urinalysis & culture, four-glass test, and semen culture and sensitivity) were done. Baseline evaluation for symptoms of each participant was assessed using validated questionnaires including National Institute of Health-developed Chronic Prostatitis Symptoms Index (NIH-CPSI) score, International Prostate Symptom Score (IPSS), Visual Analog Scale (VAS), and Five item version of International Index of Erectile Function (IIEF-5) Score. Patients were randomized by closed envelop method into two groups: a verum treatment group and a placebo treatment group.

Treatment protocol

The patients were randomized by closed envelop method into two groups. Group A (verum treatment group) and group B

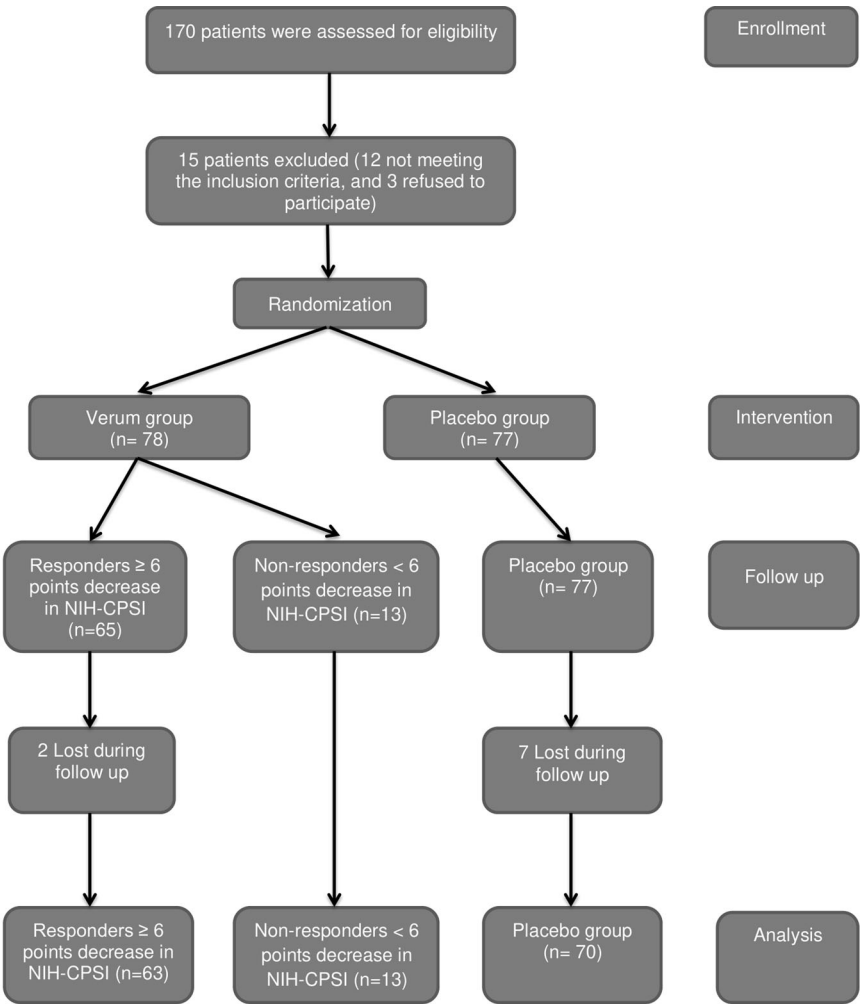

Fig. 1 Consolidated Standards of Reporting Trial (CONSORT) flow diagram of the patients through the study.

(placebo treatment group. All patients of the verum treatment group in the lithotomy position received a perineally applied ESWT treatment once a week for four weeks with 3000 impulses each, with maximum total energy flow density of 0.25 mJ/mm^2, and maximum frequency of 4 Hz [2]. The device used for the study was an electromagnetic shock wave unit (Duolith SD1, T-TOP, Storz, Tägerwilen, Switzerland) with a focus zone penetration depth of 35–65 mm to deliver the shock waves to the prostate and pelvic floor easily. The position of the transducer was changed every 500 impulses at six different anatomical sites to scan virtually the entire prostatic and pelvic floor region. The procedure was performed without local or systemic anesthesia in an outpatient clinic. The treatment in the placebo group was performed with the same therapy head of the same device with a layer of air-filled microspheres to absorb the shock waves. The settings were identical to the verum treatment with the same output pressure. Both the patient and the performer/follow-up observer were not aware of placebo or verum assignment. All the patients of both groups did not receive any type of medical therapy during the period of treatment or follow-up.

Follow up and outcome measurements

Clinical outcomes were reassessed on regular follow-up visits at one, three, six, and 12 months after the completion of four sessions of ESWT. Each visit consisted of reassessing the validated questionnaires of NIH-CPSI score (evaluating severity of pain and urinary symptoms and the impact on quality of life), IPSS (evaluating urinary symptoms), VAS (evaluating the pain either disease-related or treatment-related), and IIEF-5 score (evaluating erectile and sexual symptoms). A six-point or more decrease in the NIH-CPSI total score was defined as the minimal clinically important difference (MCID) of the questionnaire and successful response to the treatment protocol [2]. MCID of IPSS score is three points decrease in the total score [17]. Three cm decrease in VAS score was considered clinically meaningful difference [18], while MCID of IIEF-5 is four points [19]. Any

Table 1. Subject baseline and demographic data.

	Verum group	Placebo group	*p* value
Continuous data, mean ± SD (range)			
Age (years)	42.8 ± 11.5 (20–65)	45.2 ± 12.4 (24–66)	0.87[a]
BMI (Kg/m^2)	25.6 ± 2.9 (18.2–34.6)	24.9 ± 2.7 (17.2–35.1)	0.95[a]
Period of complaint (months)	53.1 ± 32.6 (6–300)	50.7 ± 34.3 (6–270)	0.72[a]
Laboratory findings:			
-PSA (ng/mL)	3.7 ± 1.9 (0.5–8.2)	3.4 ± 1.8 (0.5–7.9)	0.76[a]
-Total testosterone (ng/dL)	615.4 ± 132.7 (293–935)	591.6 ± 129.7 (299–915)	0.65[a]
-Fasting blood glucose (mg/dL)	107.2 ± 13.6 (82–194)	105.7 ± 13.8 (87–189)	0.09[a]
Symptomatology & QoL:			
-NIH-CPSI	29.52 ± 5.96 (19–38)	28.92 ± 5.69 (18–38)	0.47[a]
-IPSS	15.45 ± 4.86 (10–20)	15.74 ± 4.98 (10–20)	0.46[a]
-VAS	5.75 ± 1.28 (3–8)	5.58 ± 1.31 (3–8)	0.09[a]
-IIEF-5	16.97 ± 1.65 (12–23)	17.12 ± 1.55 (12–24)	0.21[a]
Categorical data, *N* (%)			
CPPS category:			
-CPPS IIIa	41 (53.9)	40 (58.2)	0.71[b]
-CPPS IIIb	35 (46.1)	30 (42.8)	0.13[b]
Associated comorbidities:			
-Diabetes mellitus	7 (9.2)	7 (10)	0.88[b]
-Hypertension	18 (23.6)	15 (21.4)	0.06[b]
-Cardiovascular disease	4 (5.2)	5 (7.2)	0.81[b]
-Hyperlipidemia	20 (26.3)	21 (30)	0.66[b]
-Urinary tract infection	35 (46.1)	30 (42.8)	0.08[b]
-Pelvic trauma	5 (6.5)	6 (8.5)	0.23[b]
-Sleep disorder	34 (44.7)	32 (45.7)	0.77[b]
-Psychological disorder	19 (25)	20 (28.5)	0.54[b]
Lifestyle & special habits:			
-Regular exercise habits	19 (25)	18 (25.7)	0.98[b]
-Regular sexual activity	54 (71.1)	57 (81.4)	0.74[b]
-Smoking	41 (53.9)	44 (62.8)	0.55[b]
-Alcohol drinking	3 (3.9)	3 (4.2)	0.17[b]

SD Standard deviation, *BMI* Body mass index, *CPPS* Chronic pelvic pain syndrome, *PSA* Prostatic specific antigen, *QoL* Quality of life, *NIH-CPSI* National Institute of Health-developed Chronic Prostatitis Symptoms Index score, *IPSS* International Prostate Symptom Score, *VAS* Visual Analog Scale, *IIEF-5* Five item version of International Index of Erectile Function Score.
[a]Independent *t*-test.
[b]Chi-square test.

Table 2. Parameters of clinical changes after therapy.

	At one month			At three months			At six months			At 12 months		
	Verum group Mean (SD)	Placebo group Mean (SD)	[b]*p* value	Verum group Mean (SD)	Placebo group Mean (SD)	[b]*p* value	Verum group Mean (SD)	Placebo group Mean (SD)	[b]*p* value	Verum group Mean (SD)	Placebo group Mean (SD)	[b]*p* value
NIH-CPSI	18.77 (4.87)	28.92 (5.69)	≤0.01	15.34 (4.54)	28.92 (5.69)	≤0.01	16.27 (4.91)	28.92 (5.69)	≤0.01	16.88 (5.12)	30.15 (5.74)	≤0.01
Baseline difference	10.75 (1.09)	0.00 (0.00)		14.18 (1.42)	0.00 (0.00)		113.25 (1.05)	0.00 (0.00)		12.64 (0.84)	−1.23 (0.05)	
[a]*p* value	≤0.001	0.99		≤0.001	0.99		≤0.001	0.99		≤0.001	0.22	
IPSS	11.54 (3.92)	15.74 (4.98)	≤0.01	9.88 (3.74)	15.74 (4.98)	≤0.01	19.91 (3.78)	15.74 (4.98)	≤0.01	9.59 (3.69)	16.23 (3.92)	≤0.01
Baseline difference	3.91 (0.94)	0.00 (0.00)		15.57 (1.12)	0.00 (0.00)		15.54 (1.08)	0.00 (0.00)		5.86 (1.17)	−0.49 (1.06)	
[a]*p* value	0.022	0.98		≤0.001	0.98		1≤0.001	0.98		≤0.001	0.41	
VAS	3.21 (0.92)	5.58 (1.31)	≤0.01	12.78 (1.1)	5.58 (1.31)	≤0.01	2.88 (0.89)	5.58 (1.31)	≤0.01	2.41 (1.08)	5.99 (1.47)	≤0.01
Baseline difference	2.54 (0.26)	0.00 (0.00)		12.97 (0.18)	0.00 (0.00)		2.87 (0.39)	0.00 (0.00)		3.34 (0.2)	−0.41 (0.16)	
[a]*p* value	0.033	0.86		10.012	0.86		0.021	0.86		≤0.001	0.35	
IIEF-5	20.01 (1.98)	17.12 (1.55)	≤0.01	19.89 (1.91)	17.12 (1.55)	≤0.01	19.91 (1.97)	17.12 (1.55)	≤0.01	20.21 (1.88)	16.65 (1.33)	≤0.01
Baseline difference	−3.04 (0.67)	0.00 (0.00)		−2.92 (0.74)	0.00 (0.00)		−2.94 (0.68)	0.00 (0.00)		−3.24 (0.77)	0.47 (0.22)	
[a]*p* value	≤0.001	0.63		≤0.001	0.63		≤0.001	0.63		≤0.001	0.17	

NIH-CPSI National Institute of Health-developed Chronic Prostatitis Symptoms Index score, *IPSS* International Prostate Symptom Score, *VAS* Visual Analog Scale, *IIEF-5* Five-item version of International Index of Erectile Function Score.

[a]Paired *t*-test for comparison in the same group with difference from the baseline.

[b]Independent *t*-test for comparison between both groups.

Table 3. Comparison of baseline criteria between responders and non-responders of the verum group.

	Patients with ≥6 points decrease in NIH-CPSI ($n = 63$)	Patients with <6 points decrease in NIH-CPSI ($n = 13$)	Uni-variate Analysis	Multi-variate Analysis[c] HR (95% CI) p value
Continuous data, (Mean ± SD)				
Age (years)	44.4 ± 13.1	45.2 ± 12.7	0.95[a]	NS
BMI (Kg/m2)	26.2 ± 2.4	25.8 ± 2.7	0.81[a]	NS
Period of complaint (months)	57.8 ± 37.6	61.2 ± 32.4	0.88[a]	NS
Laboratory findings:				
-PSA (ng/mL)	3.1 ± 1.2	4.2 ± 1.4	0.12[a]	NS
-T. testosterone (ng/dL)	633.4 ± 142.7	675.4 ± 139.4	0.23[a]	NS
-FBG (mg/dL)	105.5 ± 13.4	108.1 ± 13.6	0.78[a]	NS
Symptomatology & QoL:				
-NIH-CPSI	25.5 ± 4.9	31.2 ± 5.6	0.02[a]	2.4 (1.3–11.8) 0.004
-IPSS	15.2 ± 3.8	14.9 ± 4.1	0.91[a]	NS
-VAS	5.5 ± 1.8	6.2 ± 1.2	0.09[a]	NS
-IIEF-5	16.7 ± 1.5	16.1 ± 1.8	0.45[a]	NS
Categorical data, No (%)				
CPPS category:				
-CPPS IIIa	34 (53.9)	7 (53.8)	0.99[b]	NS
-CPPS IIIb	29 (46.1)	6 (46.2)	0.99[b]	NS
Associated comorbidities:				
-Diabetes mellitus	6 (9.5)	1 (7.6)	0.74b	NS
-Hypertension	15 (23.8)	3 (23.1)	0.89[b]	NS
-CVD	3 (4.7)	1 (7.6)	0.09[b]	NS
-Hyperlipidemia	16 (25.3)	4 (30.7)	0.12[b]	NS
-Urinary tract infection	30 (47.6)	5 (38.4)	0.13[b]	NS
-Pelvic trauma	4 (6.3)	1 (7.6)	0.64[b]	NS
-Sleep disorder	28 (44.4)	6 (46.1)	0.67[b]	NS
-Psychological disorder	9 (14.2)	10 (76.9)	0.005[b]	3.5 (1.5–14.2) 0.002
Lifestyle & special habits:				
-Regular exercise habits	15 (23.8)	4 (30.7)	0.87[b]	NS
-Regular sexual activity	46 (73.1)	8 (61.5)	0.09[b]	NS
-Smoking	33 (52.9)	8 (61.5)	0.07[b]	NS
-Alcohol drinking	2 (3.2)	1 (7.6)	0.08[b]	NS

HR Hazard ratio, *CI* Confidence interval, *SD* Standard deviation, *BMI* Body mass index, *QoL* Quality of life, *FBG* Fasting blood glucose, *CPPS* Chronic pelvic pain syndrome, *PSA* Prostatic specific antigen, *NIH-CPSI* National Institute of Health-developed Chronic Prostatitis Symptoms Index score, *IPSS* International Prostate Symptom Score, *VAS* Visual Analog Scale, *IIEF-5* Five item version of International Index of Erectile Function Score, *CVD* Cardio-vascular disease.
[a]Independent *t*-test.
[b]Chi-square test.
[c]Cox proportional hazard test.

adverse event associated with ESWT or the need of any adjuvant therapy was recorded.

Endpoints

The primary endpoint of the study for all patients was the completion of 12 months period of follow up.

Statistical analysis

The sample size was calculated providing that the effect size is 0.5 with error protection of 0.05 and 80% power of the study. After adding 10% for possible dropout or loss during follow-up, the sample size was at least 70 patients in each group. According to the type of data, quantitative continuous data were represented by mean ± SD, while categorical data were represented by number (absolute frequency) and percentage (relative frequency). Differences between both groups and also between the responders and non-responders were tested by independent *t*-test when quantitative and by chi-square test when categorical. Paired analysis by paired t-test was used for comparison between pre-ESWT and post-ESWT results. Multivariate analysis was done by cox proportional hazard test. A p value <0.05 was considered statistically significant for all analyses. Data were analyzed using SPSS version 20.

RESULTS

One hundred and seventy patients of CPPS were tested for eligibility for the study inclusion criteria, 155 patients fulfilled inclusion and exclusion criteria and agreed to participate. The patients were randomized into two groups. A verum treatment group included 78 patients with two of them lost during follow-up period. A placebo treatment group included 77 patients with seven of them lost during the follow-up period. So, the final analysis was performed for 146 patients who completed the study

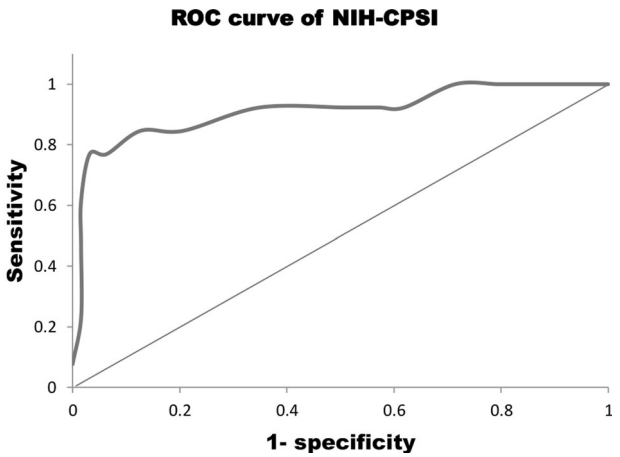

Fig. 2 ROC curve of NIH-CPSI. NIH-CPSI National Institute of Health-developed Chronic Prostatitis Symptoms Index score, ROC curve Receiver Operating Characteristic curve.

and follow up period. The flow of patients in the study is shown in the Consolidated Standards of Reporting Trials (CONSORT) chart (Fig. 1). The mean age of the verum and placebo groups was 42.81 ± 11.15 and 45.2 ± 12.4 years old respectively. The rest of patients' demographics and baseline criteria were shown in (Table 1). A statistically significant improvement was noticed in the mean values of NIH-CPSI, IPSS, VAS, and IIEF-5 of the verum group patients from the baseline criteria over the follow-up period (Table 2). Also, there was a statistically significant difference between both groups regarding the mean values of NIH-CPSI, IPSS, VAS, and IIEF-5 throughout the period of follow-up (Table 2). The protocol of therapy was tolerable without appearance of side effects e.g ecchymosis, hematuria, or hematospermia during follow-up. At the first visit of follow-up 1 month after ESWT, 63 (82.8%) patients of the verum group had ≥6 points decrease in the NIH-CPSI total score, while 13 (17.2%) patients did not. All the 63 patients who showed well response to ESWT from the verum group at the 1month follow-up could maintain their response throughout follow-up period. Univariate and multivariate analyses of the clinical characteristics and baseline data between the responders and non-responders of patients showed that those patients with history of psychological disorders (e.g depression, anxiety, dysthymia, bipolar affective disorder, somatoform disorders, and post-traumatic stress disease) or had higher initial NIH-CPSI total score had a significantly lower response rate to ESWT ($p = 0.005$, 0.02 & $p = 0.002$, 0.004 respectively) (Table 3). Receiver Operating Characteristic (ROC) curve of NIH-CPSI total score showed that a score of 32 was the cut-off point with the highest sensitivity and specificity above which the response to ESWT decreased (Fig. 2).

DISCUSSION

Diseases that have unclear etiology with multiple theories usually have no consensus on their ideal satisfactory treatment [5]. CPPS is one of these diseases with many proposed mechanisms of pathogenesis including recurrent previous infection, pelvic floor hypertonicity, local chemical environment disturbance, perfusion disturbances, and neuro-psychiatric components. Moreover, the obviously prolonged and insufficiently treated acute pain reflects a negative learning process for the patient that may lead to neuroplastic changes in the central nervous system (CNS) with establishment of the belief of incurable chronic pain [2, 20]. ESWT is a non-invasive treatment protocol for CPPS with many suggested mechanisms of action such as nociceptors hyperstimulation, passive muscle tone reduction, nitric oxide synthesis induction, an increase of local microvascularisation, and interruption of nerve impulses [21]. Mechano-transduction is the process of transformation of the shock waves into biochemical signals that stimulate high-frequent nerve impulses on the nociceptors thus blocking nerve impulses of pain alleviating it [21, 22]. Another action of the shock waves is generating micro-bubbles that pop and generate micro-jets and intracellular micro-trauma that stimulate endothelial nitric oxide synthase enzyme thus releasing vascular endothelial growth factors and proliferating cell nuclear antigen initiating angiogenesis [23]. The anti-inflammatory effect of ESWT may prevent tissue inflammation and stimulates endogenous mesenchymal stem cells that help tissue repair and nerve generation [24, 25]. In fact, the two leading studies of Zimmerman et al. in 2008 and 2009 were the cresset for many urologists about the use of ESWT in CPPS. By reviewing the literature we found that the maximum period of follow-up for the results of ESWT was one year. This may be because it is ethically questionable to leave the patients of placebo group without treatment for a long time. In our study, we found that 82.8% of the patients of the verum group achieved ≥6 points decrease in NIH-CPSI and all of them could maintain their response throughout the follow-up period. This result was comparable or mostly better than the results of other studies either using ESWT or other modalities of treatment for CPPS [2, 5, 6, 8, 9, 13, 14, 22, 26–28]. The other parameters of QoL e.g IPSS, IIEF-5, and VAS also improved significantly after ESWT and remained for the period of follow-up. Some studies tried to detect clinical and psychological predictors of CPPS to different modalities of treatment [29, 30]. In our study, we tried to prospectively examine a wide range of clinical characteristics as predictors of treatment response. We found that high initial NIH-CPSI total score and history of psych-social problems were the only significant predictors for ESWT response. Some studies mentioned body waist as a predictor for treatment response, others mentioned NIH-CPSI as a predictor especially question 4. Most of studies emphasized on psychologic problems as influencing factor for different modalities of treatment for CPPS including ESWT. Many studies showed associations of CPPS with rates of depression, anxiety, increased presence of dissociation, pain, and physical and/or sexual abuse [31–34]. These data raised the attention to a possible chain reaction in which psychological trauma could participate in the etiology of CPP which may also act as risk factors for the increase in experiences of pain, especially of somatic origin. We also, for the first time, determined NIH-CPSI total score of 32 as a cut-off point above which the response to ESWT declined.

Limitations of the study include the relatively small number of patients which could be increased in future studies. Another limitation is that there is no consensus about the appropriate dose of shock waves therapy or technique of energy delivery. We tried to overcome this problem by using the technique previously described in other urologic or non-urologic studies.

CONCLUSION

ESWT is an effective treatment option for patients with CPPS. Its efficacy remained throughout long-term follow-up. High initial NIH-CPSI total score and history of psych-social problems are significant predictors for its response.

REFERENCES

1. Doiron RC, Shoskes DA, Nickel JC. Male CP/CPPS: where do we stand? World J Urol. 2019;37:1015–22.
2. Zimmermann R, Cumpanas A, Hoeltl L, Janetschek G, Stenzl A, Miclea F, et al. Extracorporeal shock-wave therapy for treating chronic pelvic pain syndrome: a feasibility study and the first clinical results. BJU Int. 2008;102:976–80.

3. Nickel JC, Downey J, Hunter D, Clark J. Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. J Urol. 2001;165:842–5.
4. Collins MM, Pontari MA, O'Leary MP, Calhoun EA, Santanna J, Landis JR, et al. Quality of life is impaired in men with chronic prostatitis: the chronic prostatitis collaborative research network. Gen Intern Med J. 2001;16:656–62.
5. Ghazi MA, Muheilan MM, Omar N, Atta M. Long term efficacy of extracorporeal shock wave therapy [ESWT] for treatment of refractory chronic abacterial prostatitis. Ann Med Surg. 2017;14:12–17.
6. Zimmermann R, Cumpanas A, Miclea F, Janetschek G. Extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome in males: a randomized, double-blind, placebo-controlled study. Eur Urol. 2009;56:418–24.
7. Marszalek M, Wehrberger C, Temml C, Ponholzer A, Berger I, Madersbacher S. Chronic pelvic pain and lower urinary tract symptoms in both sexes: analysis of 2749 participants of an urban health screening project. Eur Urol. 2009;55:499–508.
8. Thakkinstian A, Attia J, Anothaisintawee T, Nickel JC. α-Blockers, antibiotics and anti-inflammatories have a role in the management of chronic prostatitis/chronic pelvic pain syndrome. BJU Int. 2012;110:1014–22.
9. Bates SM, Hill VA, Anderson JB, Chapple CR, Spence R, Ryan C, et al. A prospective, randomized, double-blind trial to evaluate the role of a short reducing course of oral corticosteroid therapy in the treatment of chronic prostatitis/chronic pelvic pain syndrome. BJU Int. 2007;99:355–9.
10. Dhar NB, Shoskes DA. New therapies in chronic prostatitis. Curr Urol Rep. 2007;8:313–8.
11. Hu M, Wazir J, Ullah R, Wang W, Cui X, Tang M, et al. Phytotherapy and physical therapy in the management of chronic prostatitis-chronic pelvic pain syndrome. Int Urol Neph. 2019;51:1081–8.
12. Capodice JL, Bemis DL, Buttyan R, Kaplan SA, Katz AE. Complementary and alternative medicine for chronic prostatitis/chronic pelvic pain syndrome. Evid Based Complement Altern Med. 2005;2:495–501.
13. Giubilei G, Mondaini N, Minervini A, Saieva C, Lapini A, Serni S, et al. Physical activity of men with chronic prostatitis/chronic pelvic pain syndrome not satisfied with conventional treatments – could it represent a valid option? The physical activity and male pelvic pain trial: a double blind, randomized trial. J Urol. 2007;177:159–65.
14. Nickel JC, Sorensen R. Transurethral microwave thermotherapy for nonbacterial prostatitis: a randomized double blind sham controlled study using new prostatitis specific assessment questionnaires. J Urol. 1996;155:1950–5.
15. 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.
16. Wess OJ. A neural model for chronic pain and pain relief by extracorporeal shock wave treatment. Urol Res. 2008;36:327–34.
17. Ferdinando F, Gianluca D'Anzeo, Carsten H, Andrea R, Hartwig B, et al. Predictors of individual response to placebo or tadalafil 5 mg among men with lower urinary tract symptoms secondary to benign prostatic hyperplasia: an integrated clinical data mining analysis. PLoS One 2015;10:e0135484.
18. Jacques Simon L, Elisabeth H, Ian G, George A. Clinically important change in the visual analog scale after adequate pain control. Acad Emerg Med. 2003;10:1128–30.
19. Raymond CR, Kerstin RA, Xiao NI, Andre BA. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol. 2011;60:1010–6.
20. Pontari MA, Ruggieri MR. Mechanisms in prostatitis/chronic pelvic pain syndrome. J Urol. 2004;172:839–45.
21. Shiao-Jin G, Jiun-Hung G, I-Ting C, Hui-Tzu L, Yung-Chin L, Yung-Shun J, et al. Efficacy of low-intensity extracorporeal shock wave therapy on men with chronic pelvic pain syndrome refractory to 3-As Therapy. Am J Men Heal. 2017;12:441–52.
22. Shiao-Jin G, Chia-Chu L, Yung-Shun J, Ching-Chia L, Chia-Chun T. The 12-month follow-up of the low-intensity extrcorporeal shockwave therapy in the treatment of patients with chronic pelvic pain syndrome refractory to 3-As medications. J Aging Male. 2019:23:1–9.
23. Wang CJ, Wang FS, Yang KD, Weng LH, Hsu CC, Huang CS, et al. Shock wave therapy induces neovascularization at the tendon-bone junction. a study in rabbits. J Ortho Res. 2003;21:984–9.
24. Mariotto S, de Prati AC, Cavalieri E, Amelio E, Marlinghaus E, Suzuki H. Extracorporeal shock wave therapy in inflammatory diseases: molecular mechanism that triggers anti-inflammatory action. Cur. Med Chem. 2009;16:2366–72.
25. Li HJ, Kang DY. Prevalence of sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome: a meta-analysis. World J Urol. 2016;34:1009–17.
26. Al Edwan GM, Muheilan MM, Atta ON. Long term efficacy of extracorporeal shock wave therapy [ESWT] for treatment of refractory chronic abacterial prostatitis. Ann Med Surg. 2017;14:12–17.
27. El-Enen MA, Abou-Farha M, El-Abd A, El-Tatawy H, Tawfik A, El-Abd S, et al. Intraprostatic injection of botulinum toxin-A in patients with refractory chronic pelvic pain syndrome: The transurethral vs. transrectal approach. Arab J Urol. 2015;13:94–99.
28. Zeng XY, Liang C, Ye ZQ. 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.
29. Tripp DA, Nickel JC, Landis JR, Yan LW, Knauss JS. 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.
30. Naliboff BD, Stephens AJ, Lai HH, Griffith JW, Clemens JQ, Lutgendorf S, et al. Clinical and psychosocial predictors of urologic chronic pelvic pain symptom change over one year: a prospective study from the MAPP research network. J Urol. 2017;198:848–57.
31. Kang Sup K, Yong Sun C, Woong Jin B, Hyuk Jin C, U-Syn HA, Sung-Hoo Hong, et al. Efficacy of Low-intensity extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome IIIb: a prospective-randomized, double-blind, placebo-controlled study. World J Men Health. 2021;4:1–8. Jul2021
32. Ioannis M, Dimitrios K, Filimon Z, Paraskevi K, Agrippina F, Evangelos P, et al. Evaluation of a low-intensity shockwave therapy for chronic prostatitis type IIIb/chronic pelvic pain syndrome: a double-blind randomized sham-controlled clinical trial. Prost Can Prost Dis. 2021;24:370–9.
33. Ana Carolina F, Omero Benedito P, José de Souza C, Jaime Eduardo C, Flávia de Lima O. Associations between chronic pelvic pain and psychiatric disorders and symptoms. Arch Clin Psychiatr 2015;42:25–30.
34. Flávia de Lima O, Ana Carolina F, Mariana F, André LMoreno, Omero Polli-Neto. Chronic pelvic pain, psychiatric disorders and early emotional traumas: Results of a cross sectional case-control study. World J Psychiatr 2016;6:339–44.

AUTHOR CONTRIBUTIONS

AMS: Project development. AMF: Manuscript writing. MK: Data collection. MMA: Manuscript writing, data collection, data analysis, and revision.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Maged M. Ali.