

# Efficacy of Low-Intensity Extracorporeal Shock Wave Therapy on Men With Chronic Pelvic Pain Syndrome Refractory to 3-As Therapy

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## Abstract

Managing patients with chronic pelvic pain syndrome (CPPS) refractory to the traditional 3-As therapy (antibiotics, alpha-blockers, and anti-inflammatories) is a challenging task. Low-intensity extracorporeal shock wave therapy (LI-ESWT) was recently reported to be able to improve pain, urinary symptoms, and even sexual function by inducing neovascularization and anti-inflammation, reducing muscle tone, and influencing nerve impulses. This study evaluates whether combined treatment with LI-ESWT can restore clinical ability and quality of life (QoL) in patients refractory to 3-As therapy. This was an open-label, single-arm prospective study. Patients with CPPS without more than a 6-point decrease in the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) total score under the maximal dosage of 3-As therapy were enrolled. LI-ESWT treatment consisted of 3,000 shock waves administered once weekly for 4 weeks. The NIH-CPSI, visual analog scale (VAS) score, International Prostate Symptom Score (IPSS), and the five-item version of the International Index of Erectile Function (IIEF-5) were used to evaluate efficacy at 1, 4, and 12 weeks after LI-ESWT. Thirty-three patients were enrolled in this study. After LI-ESWT treatment, 27 of the 33 patients (81.82%) had a successful response to LI-ESWT, with a decrease of 3.29 and 5.97 in the VAS score and total IPSS at the 3-month follow-up. Waist circumference was the only significant predictor of a successful response to LI-ESWT. LI-ESWT can serve as a salvage therapy for patients with CPPS refractory to traditional 3-As therapy. Further studies are needed to determine an adequate therapeutic protocol and important predictors in patients with different CPPS etiologies.

## Keywords

shock wave therapy, chronic pelvic pain syndrome, 3-As therapy

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Chronic pelvic pain syndrome (CPPS), defined as non-specific, poorly localized pelvic pain without an identifiable pathology for at least 3 of the preceding 6 months, is classified as category III of prostatitis by the National Institutes of Health (NIH; Krieger, Nyberg, & Nickel, 1999). It is a common disorder in men, with the average prevalence at different ages being reported as approximately 10% (Nickel, Downey, Hunter, & Clark, 2001). Global statistics identified that the epidemiology ranges from 2.2 to 9.7%, with a mean prevalence of 8.2% (Krieger, Lee, Jeon, Cheah, & Lion, 2008). CPPS-like symptoms greatly affect urinary symptoms, quality of life (QoL), and even sexual function (Li & Kang, 2016; Walz

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et al., 2007). Although the pathophysiology of CPPS is usually multifactorial, the most common etiology is physiological disorders (Engeler et al., 2013; Magistro, Wagenlenhner, Grabe, Weidner, & Stief, 2016). By covering major physiological etiologies, directed 3-As therapy (antibiotics, alpha blockers, and anti-inflammatories), rather than monotherapy, is often used as a first-line treatment for patients with CPPS because of its convenience and good efficacy (Anothaisintawee, Attia, Nickel, Thammakraisorn, & Numthavaj, 2011; Thakkinstian, Attia, Anothaisintawee, & Nickel, 2012). Up to 46% of patients with CPPS do not respond sufficiently to the traditional 3-As therapy (Thakkinstian et al., 2012).

Traditional second-line treatments, including phytotherapy, hormone agents, neuromodulators, physical therapies, psychological treatment, or lifestyle modifications could serve as salvage therapies for patients with refractory CPPS (Herati & Moldwin, 2013; Magistro et al., 2016). Other invasive procedures, such as transcutaneous electrical nerve stimulation, intraprostatic injection, and even radical prostatectomy, have been discussed (Chopra, Satkunasivam, & Aron, 2016; Schneider, Tellenbach, Mordasini, Thalmann, & Kessler, 2013). Although these treatments are sometimes effective, they have many disadvantages, such as invasiveness, inconvenience, or side effects, and most patients may withdraw from them. Since 2009, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) demonstrated the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network to approach CPPS in a systemic manner. It described a new and novel integrated approach to define patient phenotypes, identify clinically relevant subgroups, and better understand treated natural history and pathophysiology (Clemens et al., 2014). Shoskes et al. reported that a more detailed description of clinical phenotyping with seven domains, including urinary, psychosocial, organ specific, infection, neurologic/systemic, tenderness, and sexual dysfunction (UPOINTS), is recommended to manage the poly-symptomatic presentation of patients with CPPS (Magistro et al., 2016; Shoskes, Nickel, Dolinga, & Prots, 2009). After a phenotype-directed approach, arranging a safe, convenient, and noninvasive therapy that can cover the remaining domains (such as organ specific, neurologic, sexual dysfunction, and tenderness) of UPOINTS to maximize the treatment effects in patients with refractory CPPS would be reasonable.

Low-intensity extracorporeal shock wave therapy (LI-ESWT), a noninvasive therapy, has been applied recently in the treatment of CPPS (Marszalek, Berger, & Madersbacher, 2009) because it can induce neovascularization and anti-inflammation, nerve impulse interruption, reduce passive muscle tone, influence neuroplasticity of the pain memory, and is well applied in musculoskeletal

disorders, peripheral neuropathy, and inflammatory diseases (Hausner & Nogradi, 2013; Mani-Babu, Morrissey, Waugh, Screen, & Barton, 2015; Mariotto, Prati, Cavalieri, Amelio, & Marlinghuas, 2009; Schmitz, Csaszar, Milz, Schieker, & Maffulli, 2015). Zimmermann et al. demonstrated that extracorporeal shock waves at a low-energy density could enhance improvement of pain, urination, erectile function, and QoL (Zimmermann, Cumanas, Miclea, & Janetschek, 2009). Although most of the published results identified that LI-ESWT can be a useful treatment for patients with CPPS, particularly those who are still responders to 3-As therapy (Marszalek et al., 2009; Pajovic, Radojevic, Dimitrovski, & Vukovic, 2016; Zimmermann et al., 2009), few studies have evaluated the role of LI-ESWT in patients with refractory CPPS who were nonresponders to 3-As therapy. The aim of the current study is to evaluate whether a combined phenotype-directed approach and LI-ESWT can improve clinical symptoms and QoL in Taiwanese patients refractory to 3-As therapy.

## Materials and Methods

This was an open-label, single-arm prospective study. Patients who were unable to achieve clinical improvement after receiving full dosages of the 3-As therapy between January 2016 and December 2016 were enrolled from Kaohsiung Municipal Ta-Tung Hospital and Hsiao-Kang Hospital, in southwestern Taiwan. Eligible subjects were more than 18 years old and in a stable mental status. All patients had received at least a 6-week trial of 3-As therapy, including fluoroquinolone (500 mg once daily), alpha-blocker (recommend dose once daily), and acetaminophen/nonsteroidal anti-inflammatory drug (NSAID; recommend dose twice or three times daily). These patients did not have more than a 6-point decrease in the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) total score after taking the full course and maximal dosage of the 3-As therapy for at least 3 of the preceding 6 months (Thakkinstian et al., 2012). If unrecognized hypogonadism with serum total testosterone levels <350 ng/dL was noted during initial screening, a testosterone replacement therapy (TRT) trial of at least 3 months was performed first to restore testosterone levels to a normal range (Aversa, Francomano, & Lenzi, 2015; Wang et al., 2009). If prostate-specific antigen (PSA) levels >4 ng/mL were noted during initial screening, prostate biopsy was performed first to exclude potential malignancy. Before the LI-ESWT treatment period, all patients received phenotype-directed approach by a urologist. Subjects were excluded if they had significant coagulopathy, perineal anatomical abnormalities, neurological abnormalities, unstable psychiatric disorders, uncorrected hormone abnormalities, clinically significant medical diseases, and history of extensive pelvic surgery or irradiation. Subjects

with unstable psychosocial problems were excluded, and specialist counseling was performed simultaneously, unless their condition had improved. Only those subjects who still failed to respond to 3-As therapy after their clinical phenotypes were reevaluated and corrected were enrolled. The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital. Each participant provided signed informed consent.

### Initial Screening

All participants were assessed using a structured questionnaire to collect their demographic information and detailed medical, surgical, psychiatric, and sexual history. The well-known risk factors for CPPS, including genitourinary tract infection, pelvic organ surgery/trauma, psychological disorder, diabetes, hypertension, hyperlipidemia, cardiovascular disease, peripheral or central neuropathy, sleep disorder, hypogonadism, cigarette smoking, alcohol drinking, betel nut chewing, sexual activity, and exercise habits were completely reviewed (Gallo, 2014; Pontari & Ruggieri, 2004; Zhang, Sutcliffe, Giovannucci, Willett, & Platz, 2015). The subjects were classified as alcohol drinkers, cigarette smokers, or betel nut chewers if they had consumed any alcoholic beverage  $\geq 1$  time per week, had smoked  $\geq 10$  cigarettes per week, or had chewed  $\geq 10$  betel nuts per week for at least 6 months. Current users were those who were still using any of these substances within 1 year before the interview (Liu, Lee, Tsai, Cheng, & Wu, 2015; Zhang et al., 2015). The subjects were classified as those who had regular sexual activity or exercise habits if they had sexual activity at least two times per week or exercised 30 to 60 min per day, 2 to 3 times per week, respectively, for at least the past 6 months (Gallo, 2014; Kwak, Um, Son, & Kim, 2008). In addition to a detailed physical examination, 20-mL blood samples were drawn from all participants between 8:00 and 11:00 AM after overnight fasting  $> 8$  hr, for analyses of serum glucose, lipid panels, routine biochemical profiles, PSA, and total testosterone levels. Baseline evaluation of each participant was assessed using detailed questionnaires, including NIH-CPSI score, visual analog scale (VAS) score, International Prostate Symptom Score (IPSS), five-item version of the International Index of Erectile Function (IIEF-5), erection hardness score (EHS), and self-reported intravaginal ejaculation latency time (IELT).

### Treatment Protocol

All participants underwent LI-ESWT (Duolith SD1 T-TOP, Storz, Switzerland) once weekly for 4 weeks in an outpatient setting without local or systemic anesthesia. At

each treatment session, LI-ESWT was applied on the perineum at six different anatomical sites (500 shocks per site with a total of 3,000 shocks) with an energy setting of  $0.25 \text{ mJ/mm}^2$  at a frequency of 240 shocks/min. Because the penetration depth of LI-ESWT is adequate for covering the pelvic organs, the application site at the perineum differed for achievement of maximal treatment. During the LI-ESWT treatment period, patients added or remained on their regular medicine dosing schedules, including alpha-blockers and anti-inflammatories, in subjects with special domains. Because all patients had received full-dose antibiotics before enrolling into this study, antibiotics were not used. Dose tapering of the anti-inflammatories and alpha-blockers was allowed and dependent on the clinical condition.

### Outcome Measures of LI-ESWT

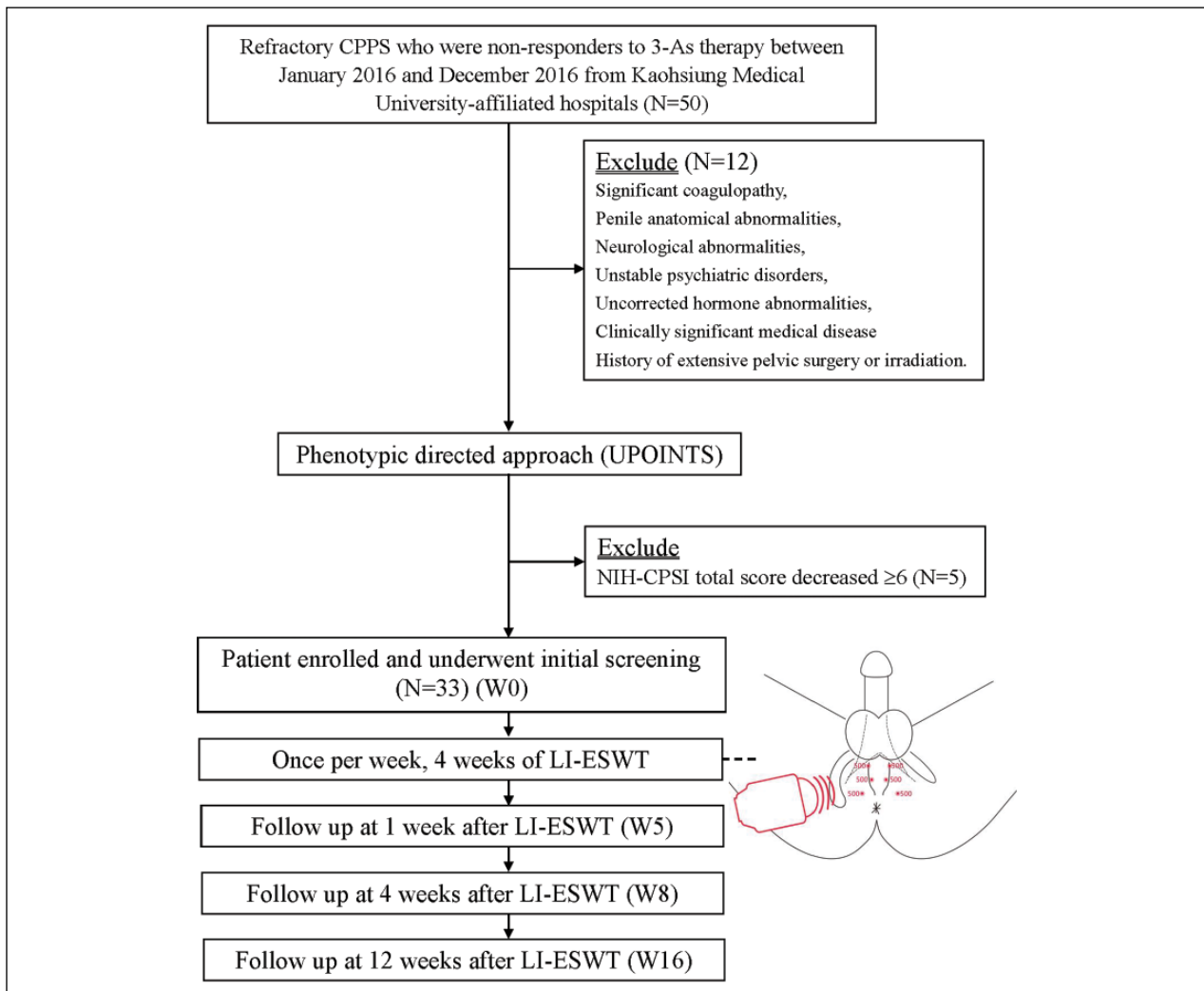
Clinical symptoms of the participants were reassessed using NIH-CPSI score, VAS score, IIEF-5, and IPSS at 1, 4, and 12 weeks after a complete course of LI-ESWT. The main outcome measure for efficacy of LI-ESWT was the NIH-CPSI total score. Treatment success was defined as a 6-point decrease or greater in the NIH-CPSI total score, which provided a valid outcome measure for response to therapy (Litwin, 2002). During treatment, any adverse effect associated with LI-ESWT was recorded. The protocol and its application are depicted in Figure 1.

### Statistical Analysis

Quantitative data were represented as means  $\pm$  standard deviations (*SD*), and categorical data were represented as numbers (*n*) and percentages. To quantify the difference between subjects with and without response to LI-ESWT, categorized variables were compared using the chi-square test and Fisher's exact test, whereas continuous variables were compared using the Student's *t*-test. For all statistical analyses,  $p < .05$  was considered statistically significant. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

### Results

A total of 33 patients with a mean age of  $46.55 \pm 13.15$  years and waist circumference of  $86.12 \pm 7.49$  cm were enrolled. The mean history of CPPS was 43.14 months (range: 6–360 months), with 17 patients (51.5%) CPPS IIIa and 16 patients (48.5%) CPPS IIIb. Because patients could have more than one comorbidity, all comorbidities are reported in Table 1. More than half of the patients had been diagnosed with sleep disorder (63.6%) and a history of genitourinary tract infection (60.6%). The prevalence of current smoking and regular exercise was 39.4 and



**Figure 1.** Flow chart of sample selection and treatment protocol.

45.5%, respectively. The mean serum PSA was  $1.59 \pm 1.57$  ng/mL. Of the 33 patients, 2 (6.1%) had serum PSA levels  $>4$  ng/mL. With regard to medical treatment with an insufficient response before LI-ESWT, our patients failed to respond to a maximal dosage of antibiotics, anti-inflammatory drugs, and alpha-blockers, in a mean trial of 3.76, 9.59, and 23.7 months, respectively (Table 1).

Changes in clinical symptoms at the 1-week, 1-month, and 3-month follow-up after 4 weeks of LI-ESWT are reported in Table 2. The mean value of the NIH-CPSI total score decreased from  $28.03 \pm 6.18$  to  $18.97 \pm 8.35$  and  $15.06 \pm 7.67$ , with a difference of 9.06 and 12.97 ( $p < .001$ ) at the 1-month and 3-month follow-up period, respectively. Of 33 patients, 27 (81.82%) had a successful response (6-point decrease or greater in the NIH-CPSI total score) to LI-ESWT, with a decrease of 3.29 and 5.97 in VAS score and total IPSS, respectively, at the 3-month follow-up period. The mean value of the IIEF-5 also

increased from  $17.52 \pm 4.71$  to  $19.42 \pm 4.12$  points, with a difference of 1.9 ( $p = .002$ ) at the 3-month follow-up. No difference was identified in IELT after LI-ESWT ( $p = .177$ ). The improvement of pain, urination, and erectile function could be noted at 1-week follow-up and persistent at the 1-month and 3-month follow-up (Figure 2). No adverse effect associated with LI-ESWT, such as hematuria, hemospermia, perineal pain, or ecchymosis, was seen in any of the patients.

Clinical characteristics and laboratory data of subjects with and without a response to LI-ESWT at the 3-month follow-up period revealed no significant difference in age, body mass index (BMI), CPPS period and category, common comorbidities, lifestyle, current cigarette smoking and alcohol drinking, or laboratory data (Table 3). However, subjects with higher waist circumference at baseline had a significantly low response rate to LI-ESWT ( $p = .022$ ).

**Table 1.** Baseline Characteristics of Study Population (N = 33).

Parameter	N (%)	Mean ( $\pm$ SD)	Range
Age (years)		46.55 (13.15)	(23–72)
BMI (kg/m <sup>2</sup> )		24.34 (2.79)	(18.72–32.22)
Waistline (cm)		86.12 (7.49)	(73–107)
CPPS period (months)		43.14 (62.82)	(6–360)
	CPPS category		
CPPS IIIa	17 (51.5)		
CPPS IIIb	16 (48.5)		
	Comorbidities and lifestyle		
Genitourinary tract infection	20 (60.60)		
Pelvic organ surgery or trauma	6 (18.20)		
Psychological disorder	4 (12.10)		
Diabetes mellitus	2 (6.10)		
Hypertension	6 (18.20)		
Hyperlipidemia	9 (27.30)		
Cardiovascular disease	2 (6.10)		
Peripheral or central neuropathy	4 (12.10)		
Sleep disorder	21 (63.60)		
Hypogonadism	6 (18.20)		
Current smoking	13 (39.40)		
Current alcohol drinking	12 (36.40)		
Current betel nut chewing	3 (9.10)		
Regular sexual activity	24 (72.70)		
Regular exercise habits	15 (45.50)		
	Laboratory data		
Total testosterone (ng/dL)		521.02 (170.45)	(220.80–863.30)
Prostate-specific antigen (ng/mL)		1.59 (1.57)	(0.3–7.1)
Creatinine (mg/dL)		0.92 (0.15)	(0.6–1.2)
Alanine aminotransferase (mg/dL)		25.97 (9.09)	(15–56)
Fasting sugar (mg/dL)		102.18 (24.07)	(78–214)
Triglycerides (mg/dL)		120.12 (47.08)	(53–539)
Total cholesterol (mg/dL)		178.03 (35.34)	(97–264)
High-density lipoprotein (mg/dL)		45.56 (13.65)	(30.8–107.0)
Low-density lipoprotein (mg/dL)		107.07 (26.89)	(36.10–168.00)
	History of medicine		
Antibiotics(months)		3.76 (3.35)	(2–15)
Anti-inflammatory		9.59 (9.05)	(2–45)
Alpha-blocker		23.7 (44.08)	(2–240)

Note. CPPS = chronic pelvic pain syndrome; SD = standard deviation.

## Discussion

All patients had undergone at least a 6-week trial of 3-As therapy, received adequate education by a urologist about the optimization of their 3-As use, and their clinical phenotypes of UPOINTS were reevaluated and corrected before enrolling in this study. Therefore, the current study population represented true nonresponders to 3-As therapy, which is a significant challenge to manage in clinical practice. In this study, 75.8% of patients with refractory CPPS who failed to respond to traditional 3-As therapy could achieve a clinical significant improvement after 4

weeks of LI-ESWT treatment; even more subjects (81.8%) were able to maintain the therapeutic efficacy at the 3-month follow-up. The current results are compatible with those of previous studies (Table 4). In addition, none of the patients reported any adverse effect associated with LI-ESWT.

Because multiple physiological disorders account for major etiologies in most patients with CPPS, 3-As therapy, which covers several domains of UPOINTS, has been widely accepted as a first-line treatment for CPPS (Anothaisintawee et al., 2011; Engeler et al., 2013; Magistro et al., 2016; Thakkinstian et al., 2012). However,

**Table 2.** Change of Clinical Symptoms After LI-ESWT ( $n = 33$ ).

Parameter	Baseline		After LI-ESWT				<i>p</i> value		
	W0		W5	W8	W16				
NIH-CPSI, Mean ( $\pm$ SD)	-		-		-				
Total score	28.03	(6.18)	18.48	(6.97)	18.97	(8.35)	15.06	(7.67)	<.001
Pain subscales	12.85	(3.17)	7	(3.67)	7.79	(4.72)	5.64	(4.21)	<.001
Urinary subscales	5.85	(2.40)	4.55	(2.55)	3.94	(2.37)	3.67	(2.30)	<.001
QoL subscales	9.33	(2.10)	6.94	(2.59)	7.24	(2.81)	5.76	(2.65)	<.001
CPSI decline $\geq 6$ , <i>n</i> (%)	NA		25	(75.80)	25	(75.80)	27	(81.82)	
VAS, mean ( $\pm$ SD)	5.56	(1.64)	2.79	(1.98)	3.18	(2.40)	2.27	(2.18)	<.001
IPSS, mean ( $\pm$ SD)									
Total score	14.97	(8.88)	11.55	(7.19)	9.79	(7.52)	9	(6.59)	<.001
Irritative score	6.82	(3.17)	5.33	(2.71)	4.55	(2.99)	4.15	(2.86)	<.001
Obstructive score	8.15	(6.11)	6.21	(5.08)	5.24	(4.94)	4.85	(3.99)	<.001
IIEF-5, mean ( $\pm$ SD)	17.52	(4.71)	19.03	(4.22)	18.97	(4.47)	19.42	(4.12)	.002
EHS, mean ( $\pm$ SD)	3.18	(0.92)	3.45	(0.79)	3.45	(0.71)	3.48	(0.71)	.047
IELT (min), mean ( $\pm$ SD)	4.39	(2.84)	4.53	(2.87)	3.89	(2.64)	4.09	(2.85)	.177
Medication tapering, <i>n</i> (%)	NA		24	(72.70)	28	(84.80)	29	(87.90)	
Current painkiller use, <i>n</i> (%)	NA		23	(69.70)	18	(54.50)	12	(36.40)	

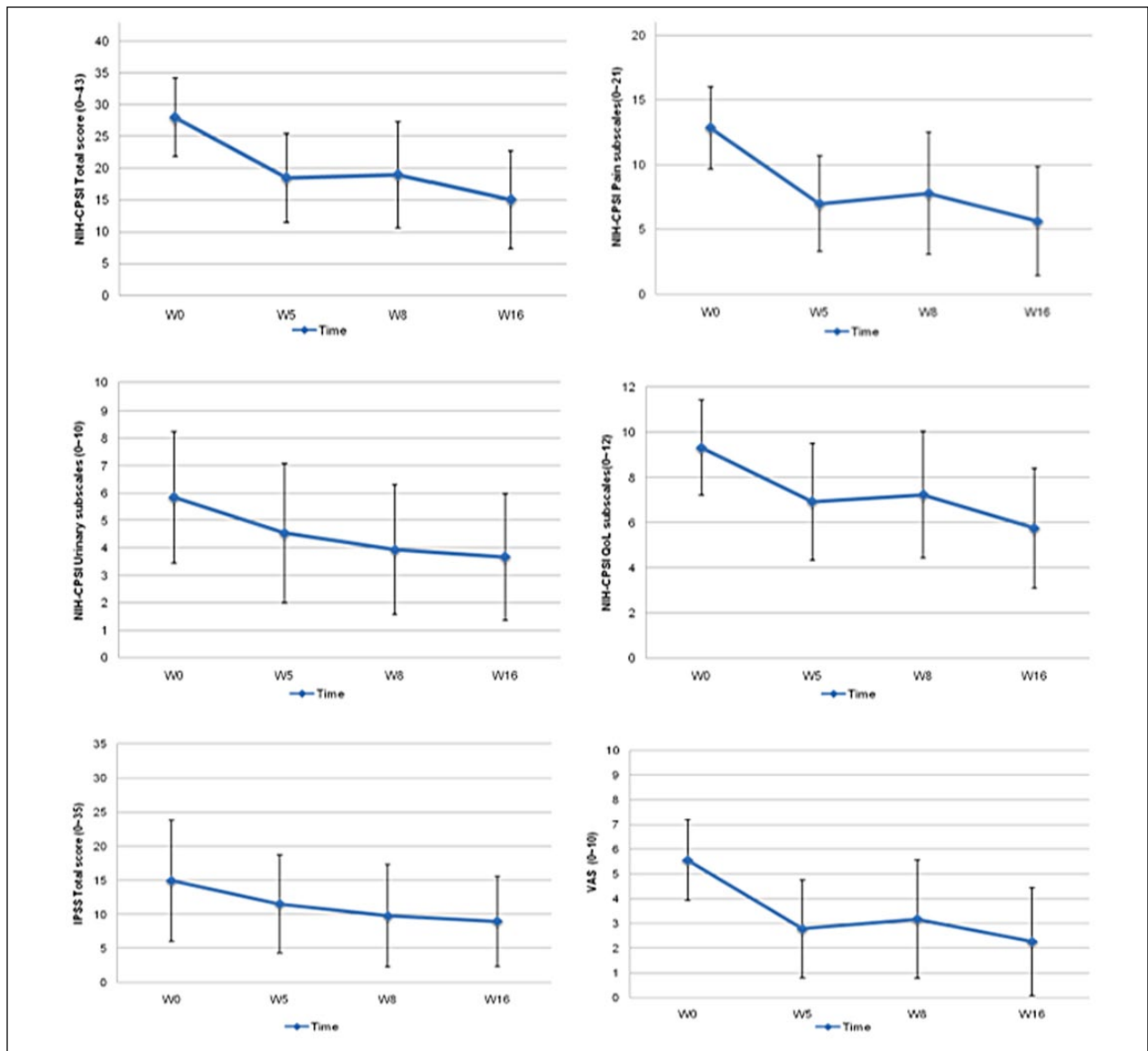
Note. EHS = erection hardness score; IELT = intravaginal ejaculation latency time; IIEF-5 = five-item version of the International Index of Erectile Function; IPSS = International Prostate Symptom Score; LI-ESWT = low-intensity extracorporeal shockwave therapy; NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index, QoL = quality of life; SD = standard deviation; VAS = visual analog scale; W = week.

up to 46% of patients with CPPS are still refractory to the adequate trial and maximum dosage of 3-As therapy in clinical practice, particularly among difficult-to-treat subpopulations (e.g., patients with prolonged symptoms and multifocal pain points; Thakkinstian et al., 2012). Lifestyle modification, physiotherapy, trigger point massage, rectal massage, thermotherapy, reevaluating UPOINTS, switching to another type of 3-As medicine, and alternative medical approaches (such as phytotherapy, pentosan polysulfate, antidepressants, steroids, 5 $\alpha$ -reductase inhibitors, anticholinergics, antispasmodics, and traditional Chinese medicine) are the common strategies adopted for nonresponders to 3-As therapy. Other invasive procedures, such as transcutaneous electrical nerve stimulation, electromagnetic treatment, acupuncture, balloon dilatation, laser coagulation, neuromodulation, intraprostatic injection, and even radical prostatectomy, were discussed (Chopra et al., 2016; El-Enen et al., 2015; Herati & Moldwin, 2013; Magistro et al., 2016; Marszalek et al., 2009; Schneider et al., 2013). However, their efficacy is usually unsatisfactory and none of these procedures has entered clinical practice on a broader scale.

LI-ESWT, a noninvasive treatment that can reduce passive muscle tone, influence neuroplasticity and, most importantly, induce neovascularization and anti-inflammation, has become a novel, alternative treatment for CPPS (Hausner & Nogradi, 2013; Mani-Babu et al., 2015; Mariotto et al., 2009; Schmitz et al., 2015). The hypothesis on the appropriate energy from LI-ESWT that could induce shear stress and intracellular microtrauma,

and then stimulate endothelial nitric oxide synthase (eNOS) and release of vascular endothelial growth factors (VEGF) and proliferating cell nuclear antigen (PCNA), resulting in angiogenesis, has been proved in several animal studies (Wang et al., 2003; Goertz, Von der Lohe, Lauer, Khosrawipour, & Ring, 2014; Tepeköylü, Wang, Kozaryn, Albrecht-Schgoer, & Theurl, 2013). Another possible mechanism through which LI-ESWT can improve CPPS may be mediated by anti-inflammatory action. Mariotto et al. reported that LI-ESWT could induce downregulation of NF- $\kappa$ B and NF- $\kappa$ B-dependent inflammatory genes, resulting in beneficial action on tissue inflammation (Mariotto et al., 2009). LI-ESWT could also recruit endogenous mesenchymal stem cells to promote angiogenesis, tissue repair, and nerve generation in a rat model of pelvic neurovascular injuries (Li et al., 2016). Based on the gate control theory, LI-ESWT could stimulate high-frequency nerve impulses on the nociceptors, which then block the nerve impulse, by alleviating pain (Wess, 2008). The dose-effect relationship in ESWT should be of concern (Zhang, Yan, Wang, Tang, & Chai, 2014), and the optimal parameters of ESWT for CPPS are not yet determined.

Although LI-ESWT has been used in urology for treating Peyronie's disease and erectile dysfunction (Fojecki, Tiessen, & Ooster, 2017), Zimmermann et al. first reported the experience of using LI-ESWT in the treatment of CPPS in 2008 (Zimmermann, Cumanas, Hoeltl, Janetschek, & Stenzl, 2008). In recent years, limited



**Figure 2.** The improvement of pain, urination, and erectile function during 1-week, 1-month, and 3-month follow-up.

studies on LI-ESWT have reported positive results in the improvement of CPPS. The current study reviewed studies since 2008 in Table 4 (Al Edwan, Muheilan, & Atta, 2017; Moayednia, Haghani, Khosrawi, Yousefi, & Vahdatpour, 2014; Pajovic et al., 2016; Vahdatpour, Alizadeh, Moayednia, Emadi, & Khorami, 2013; Zeng, Liang, & Ye, 2012; Zimmermann et al., 2008; Zimmermann et al., 2009). Most of them had limited patient numbers or were not randomized controlled trials. The long-term effect of LI-ESWT is still equivocal (Al Edwan et al., 2017; Moayednia et al., 2014), and only one study prior to the current study had evaluated the role of LI-ESWT in the treatment of patients with CPPS who were nonresponders to traditional 3-As therapy (Al Edwan et al.,

2017). Because different generators and protocols of LI-ESWT were used in previous studies, the current results can only be compared with the other four studies that used the same device. Further studies are still needed to define an adequate therapeutic protocol, including location of the applied probe, energy density, and number of pulses and sessions, and to determine important predictors of successful response to LI-ESWT in patients with CPPS.

In the current study, most patients had concomitant alpha-blocker and anti-inflammatory drug use during and after LI-ESWT. After 12 weeks of LI-ESWT treatment, up to 72.7% of patients could taper 3-As medication and only 36.4% of patients still needed painkillers. The

**Table 3.** Comparison of Clinical Characteristics and Laboratory Data Between Subjects With and Without Response to LI-ESWT.

Parameter	Subjects without response (N = 6)	Subjects with response (N = 27)	p value
Age (years), mean ( $\pm$ SD)	42.67 (16.12)	47.41 (12.58)	.433
BMI ( $\text{kg}/\text{m}^2$ ), mean ( $\pm$ SD)	25.85 (3.97)	24.00 (2.44)	.147
Waistline (cm), mean ( $\pm$ SD)	92.33 (10.30)	84.74 (6.13)	.022
CPSS period (months), mean ( $\pm$ SD)	31.67 (26.65)	45.69 (68.43)	.629
CPSS category, n (%)			
CPSS IIIa	4 (66.70)	13 (48.10)	.656
CPSS IIIb	2 (33.30)	14 (51.90)	
Comorbidities, n (%)			
Genitourinary tract infection	4 (66.70)	16 (59.30)	>.999
Pelvic organ surgery or trauma	2 (33.30)	4 (14.80)	.295
Psychological disorder	1 (16.70)	3 (11.10)	>.999
Diabetes mellitus	1 (16.70)	1 (3.70)	.335
Hypertension	1 (16.70)	5 (18.50)	>.999
Hyperlipidemia	2 (33.30)	7 (25.90)	>.999
Cardiovascular disease	1 (16.70)	1 (3.70)	.335
Peripheral or central neuropathy	0 (0.00)	4 (14.80)	NA
Hypogonadism	2 (33.30)	4 (14.80)	.295
Current smoking	2 (33.30)	11 (40.70)	>.999
Current alcohol drinking	1 (16.70)	11 (40.70)	.379
Current betel nut chewing	1 (16.70)	2 (7.40)	.464
Sleep disorder	5 (83.30)	16 (59.30)	.379
No regular exercise	3 (50.00)	15 (55.60)	>.999
No regular sex	2 (33.30)	7 (25.90)	>.999
Number of comorbidities, mean ( $\pm$ SD)	5.33 (2.94)	4.04 (2.17)	.224
History of medicine (months), mean ( $\pm$ SD)			
Antibiotics	2.67 (1.72)	4 (3.59)	.387
Anti-inflammatory	8.33 (4.92)	9.87 (9.77)	.173
Alpha-blocker	18.83 (23.60)	24.78 (47.72)	.77
Laboratory data, mean ( $\pm$ SD)			
Total testosterone (ng/dL)	493.4 (173.99)	527.15 (172.39)	.668
Prostate-specific antigen (ng/mL)	2.53 (2.57)	1.38 (1.24)	.106
Initial clinical severity, mean ( $\pm$ SD)			
NIH-CPSI			
Total score	24.33 (7.45)	28.85 (5.70)	.106
Pain subscales	11.83 (4.07)	13.07 (2.99)	.395
Urinary subscales	4.33 (2.81)	6.19 (2.22)	.087
QoL subscales	8.17 (3.43)	9.59 (1.67)	.135
VAS	5.00 (2.68)	5.70 (1.35)	.350
IPSS			
Total score	11.67 (9.03)	15.70 (8.74)	.316
Irritative score	6.00 (6.51)	8.63 (6.04)	.348
Obstructive score	5.67 (2.88)	7.07 (3.22)	.333
IIEF-5	18.33 (4.13)	17.33 (4.88)	.645
EHS	3.17 (0.98)	3.19 (0.92)	.965

Note. BMI = body mass index; CPSS = chronic pelvic pain syndrome; EHS = erection hardness score; IIEF-5: five-item version of the International Index of Erectile Function; IPSS = International Prostate Symptom Score; LI-ESWT = low-intensity extracorporeal shockwave therapy; NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index, QoL = quality of life; SD = standard deviation; VAS = visual analog scale.



**Table 4.** Literature Review of Studies About LI-ESWT in Patients With Chronic Pelvic Pain Syndrome.

Authors	Study		Setup and protocol of LI-ESWT					Combined 3-As therapy				Outcomes				
	Study design	Generator	Patient number	Follow-up (weeks after ESWT)	Energy (mj/mm <sup>2</sup> )	No. of pulses each treatment	Frequency (shocks/min)	No. of treatments each week	No. of Treatment courses (weeks)	Neoadjuvant therapy before LI-ESWT		Concomitant therapy during LI-ESWT		Adjuvant therapy after LI-ESWT		
										LI-ESWT	NIH-CPSI	LI-ESWT	NIH-CPSI	LI-ESWT	VAS	LI-ESWT
Zimmermann et al., 2008	Cohort study	Minilith SLI	14	1, 4, 12	0.11	2000	180	3	2	NA	No	No	No	-2.7(12wk)	-3.1(12wk)	NA
Zimmermann et al., 2008	Cohort study	Duolith SDI	20	1, 4, 12	0.25	3000	180	1	4	NA	No	No	No	-8.6(1wk)	-2.4(1wk)	-4.1(1wk)
														-8.9(4wk)	-2.8(4wk)	-3.8(4wk)
														-5.5(12wk)	-2.0(12wk)	0.0(12wk)
Zimmermann et al., 2009	RCT	Duolith SDI	30	1, 4, 12	0.25	3000	180	1	4	NA	No	No	No	-16.7(1wk)	-33.3(1wk)	-15.6(1wk)
														-16.7(4wk)	-50(4wk)	-18.8(4wk)
														-16.7(12wk)	-50(12wk)	-25(12wk)
Zeng et al, 2012	RCT	HB-ESWT-01	8	4, 12	0.06-MTD	2000	120	5	2	Yes	No	No	No	CPSI <sub>↓</sub> ≥6: 21.1% (4wk) 23.7% (12wk)	NA	NA
Vahdatpour et al, 2013	RCT	Duolith SDI	40	1, 2, 3, 12 after first session	0.25-0.4 mm <sup>2</sup> was added in each week),	3000	180	1	4	NA	No	No	No	-5.1(1wk)	-2.0(1wk) <sup>a</sup>	-1.0(1wk) <sup>b</sup>
														-10.2(3wk)	-5.1(3wk) <sup>b</sup>	-1.7(3wk) <sup>b</sup>
														-7.1(12wk)	-4.3(12wk) <sup>a</sup>	-0.9(12wk)*
Moayednia et al, 2014	RCT	Duolith SDI	19	16, 20, 24	0.25	3000	180	1	4	NA	NA	NA	NA	-4.47(16wk)	-2.66(16wk)	-0.71(16wk)
														-1.06(20wk)	-1.24(20wk)	-0.39(20wk)
														+0.38(24wk)	+0.53(24wk)	+0.12(24wk)
Pajovic et al, 2016	RCT	KM-2000 S	30	12, 24	0.25	3000	180	1	12	No	Yes	NA	NA	-19.4(12wk)	-9.3(12wk) <sup>a</sup>	-2.9(12wk) <sup>b</sup>
														-17.4(24wk)	-9.2(24wk) <sup>a</sup>	-3.2(24wk) <sup>a</sup>
Al Edwan et al, 2017	Cohort study	E-S.W.T Roland, pagani, Italy	41	2, 24, 48	0.25	2500	180	1	4	Yes	No	NA	NA	-9.2(2wk)	-4.1(2wk)	-5.9(2wk)
														-8.8(24wk)	-3.5(24wk)	-6.6(24wk)
														-8.2(48wk)	-3.2(48wk)	-6.6(48wk)
Our study	Cohort study	Duolith SDI	33	1, 4, 12	0.25	3000	240	1	4	Yes	Yes	Yes	Dose taping	-9.06(4wk)	-2.38(4wk)	-5.18(4wk)
														-12.97(12wk)	-3.29(12wk)	-5.97(12wk)
														CPSI <sub>↓</sub> ≥6: 75.8% (4wk) 81.8% (12wk)		

Note. IPSS = International Prostate Symptom Score; LI-ESWT = low-intensity extracorporeal shock wave therapy; MTD = maximum tolerated dose; NA = not available; NIH-CPSI = National Institutes of Health-Chronic Prostatitis Symptom Index; RCT = randomized controlled trial; VAS = Visual Analogue Scale.

<sup>a</sup>In NIH-CPSI pain domain. <sup>b</sup>In NIH-CPSI urinary domain.

efficacy was maintained even better at the 3-month follow-up. The good efficacy of LI-ESWT in refractory CPPS may be because the therapy can cover the remaining domains of UPOINTS (such as organ specific, neurologic/systemic, tenderness, and even sexual dysfunction) to maximize the treatment effects. 3-As therapy only covers parts of UPOINTS, such as the domains of urinary and organ-specific function, infection, whereas LI-ESWT can play a part in other domains, thereby complementing the positive effect from a different perspective. In addition, no statistically significant difference in age, BMI, CPPS period and category, comorbidities, and personal habits was reported in the current study when responders were compared with nonresponders to LI-ESWT. Waist circumference was the only significant predictor identified for successful response to LI-ESWT in the current study. Patients who were nonresponders to LI-ESWT at the 3-month follow-up had a larger waist circumference ( $p = .022$ ). In an in vitro study, the energy of LI-ESWT was reported to slowly decay or attenuate in fat tissue because it could not accumulate adequate energy in the target (Liang, Zheng, Yan, Wan, & Wen, 2010). In contrast, Rogowski et al. reported that waist circumference appears to exert the most influence upon the presence and intensity of the inflammatory markers and micro-inflammatory response (Rogowski et al., 2010). Thus, larger waist circumference, as the primary contributor of the inflammatory state and energy decay, might be a negative predictive factor for LI-ESWT in patients with CPPS.

The current study has several limitations. First, it was a single-arm prospective study, which lacks control or comparison to other types of therapy. Second, the patient number was limited; hence, comparison of the efficacy of LI-ESWT for different etiologies of CPPS is difficult. Third, the follow-up period was only 3 months; hence, the long-term efficacy of LI-ESWT could not be evaluated.

## Conclusions

LI-ESWT can serve as a salvage therapy in patients with CPPS who fail to respond to traditional 3-As therapy. At the 3-month follow-up, 81.8% of refractory patients with CPPS achieved a clinically significant improvement. Waist circumference was identified to be the only significant predictor of successful response to LI-ESWT. Further large and long-term studies are needed to compare the efficacy of different generators of LI-ESWT and to determine an adequate therapeutic protocol and important predictors in patients with different CPPS etiologies.

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