Original Article

Low-intensity extracorporeal shock wave therapy for male chronic pelvic pain syndrome: a systematic review and meta-analysis

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Background: A systematic review of the evidence was conducted to evaluate the efficacy of low-intensity extracorporeal shock wave therapy (LI-ESWT) for patients with chronic pelvic pain syndrome (CPPS).

Methods: A comprehensive search was undertaken of the Cochrane Register, PubMed, and Embase databases for controlled trials that evaluated patients with CPPS who were treated with LI-ESWT and that were published before August 2019. The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) was the most frequently used tool to evaluate the treatment efficacy of LI-ESWT. The NIH-CPSI comprises subscales for pain [using a visual analog scale (VAS)], urinary function, and quality of life (QoL).

Results: Six studies analyzing 317 patients were published from 2009 to 2019. The overall meta-analysis of the data indicated that LI-ESWT demonstrated efficacy in the treatment of CPPS at 12 weeks [risk difference (RD): 0.46; 95% confidence interval (CI), 0.28–0.63; P<0.00001]. The studies were divided into 3 groups based on time after LI-ESWT (1, 12, and 24 weeks) and were compared in total NIH-CPSI scores, QoL, VAS scores, and urinary symptoms. The total NIH-CPSI scores, QoL, VAS scores, and urinary symptom scores improved significantly at 12 weeks after LI-ESWT (P<0.05), but not at 1 week or 24 weeks (P>0.05).

Conclusions: Based on these studies, LI-ESWT may transiently improve the total NIH-CPSI scores, QoL, pain scores, and urinary symptom scores of patients with CPPS. Future research may elucidate the mechanisms underlying the effects of LI-ESWT on CPPS. Well-designed and long-term multicenter randomized controlled trials are urgently needed to estimate the real potential and ultimate use of these devices in patients with CPPS.

Keywords: Chronic pelvic pain syndrome (CPPS); shock waves; controlled trial; meta-analysis

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Introduction

When low-intensity extracorporeal shock wave therapy (LI-ESWT) is applied to an organ, it carries an energy that can be noninvasively focused to affect a distant selected anatomical region. The shock waves interact with the targeted tissues and induce a cascade of biological reactions, resulting in the release of growth factors, which trigger tissue neovascularization and a consequent improvement in blood supply (1). LI-ESWT has been used to treat male erectile dysfunction (2), non-healing wounds (3), musculoskeletal disorders (4), and myocardial infarction (5).

Several encouraging studies have recently analyzed the efficacy of LI-ESWT for patients with chronic pelvic pain

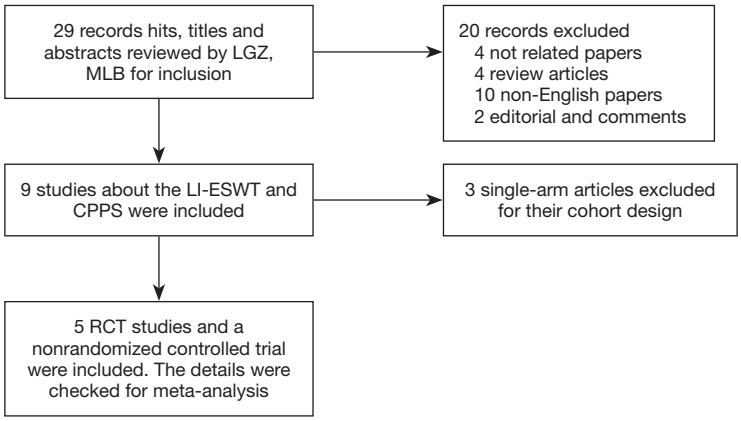

Figure 1 Flow diagram of study selection. Twenty-nine records were identified. After review, 9 studies on LI-ESWT and CPPS were included. Six studies were controlled trials and were ultimately included in the meta-analysis. LI-ESWT, low-intensity extracorporeal shock wave treatment; RCT, randomized controlled trial.

syndrome (CPPS) (6-8). However, some studies showed deterioration in total National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) scores, which includes subscales for pain, urinary function, and quality of life (QoL), at week 24 of follow-up (9-11). Our goal in this study was to examine the available data to determine the efficacy of LI-ESWT for the treatment of CPPS. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1423).

Methods

Search strategy

We performed a systematic search of the Embase and PubMed databases and the Cochrane Register for studies on LI-ESWT and CPPS. The search terms were shock wave AND (chronic pelvic pain syndrome OR chronic prostatitis OR prostatitis OR chronic abacterial prostatitis OR noninflammatory chronic pelvic pain syndrome). We analyzed the treatment efficacy of LI-ESWT for patients with CPPS and the relationships among therapeutic efficacy, protocols, and setup parameters. Additional data were identified by searching relevant conference abstracts, scanning the reference lists of articles, and corresponding with study authors using the approach recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12). A flow diagram of the study selection is shown in *Figure 1*.

Inclusion and exclusion criteria

All controlled clinical trials that investigated the efficacy of LI-ESWT for CPPS and were published from January 2005 through to August 2019 were included. All literature reviews, editorial comments, animal studies, background publications, case reports, and single-arm studies were excluded.

Data extraction and synthesis

The abstracts were reviewed independently by the 2 authors (LM and GL) to determine inclusion eligibility following a standardized form. The study's details, assessment tools, setup parameters of the LI-ESWT machine, treatment protocols, and P values were extracted manually from each study (LM), and the data were verified (GL). Follow-up data were also extracted from these studies.

Statistical analysis

The data were analyzed using RevMan 5.3 software (Cochrane Collaboration, London, UK). Appropriate statistical analysis methods and effect sizes were used following the evaluation and different data types. The risk difference (RD) and a 95% confidence interval (CI) were calculated for discontinuous variables. The weighted mean difference (MD) and 95% CI were calculated for continuous variables. The I^2 test assessed the heterogeneity between studies. A random-effects model analyzed data

Table 1 Current studies of low-intensity extracorporeal shock wave treatment for chronic pelvic pain syndrome patients

Study	Year of publication	Device	Energy density, mJ/mm^2	No. of pulses each week	Total treatment courses, wks	Evaluation tools for CPPS	P value of NIH-CPSI after LI-ESWT	Follow-up, weeks
Zimmermann (8)	2009	SD1	0.25	3,000	4	IIEF, NIH-CPSI, VAS, IPSS	<0.001	1, 4, 12
Zeng (13)	2012	HB-ESWT 1	0.06	2,000	10	NIH-CPSI, VAS, QoL	<0.01	1, 4, 12
Vahdatpour (14)	2013	SD1	0.25	3,000	4	NIH-CPSI, VAS, QoL	<0.001	1, 2, 3, 12
Moayednia (9)	2014	SD1	0.05	3,000	4	NIH-CPSI, VAS, QoL	<0.05	16, 20,2 4
Pajovic (10)	2016	KM-2000 S	0.25	3,000	12	NIH-CPSI, VAS, QoL	<0.001	12, 24
Zhang (15)	2018	MP100	0.25	3,000	8	IIEF, NIH-CPSI, VAS, IPSS, QoL	<0.001	4, 8, 12

NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; VAS, visual analog scale; QoL, quality of life; CPPS, chronic pelvic pain syndrome.

with heterogeneity. Data without significant heterogeneity (P>0.05, I^2 ≤50%) were analyzed by a fixed-effects model. The results of the meta-analysis were presented as forest plots. The risk of bias was investigated with the Cochrane Collaboration tool. Publication bias was shown in funnel plots. The NIH-CPSI scores before and after LI-ESWT were provided in these included studies. Therefore, a meta-analysis could be performed.

Results

This review included 6 studies involving 317 patients who were treated with different medical devices in different countries. Details of the studies are presented in *Table 1*. Patient inclusion criteria were based on the NIH classification (8-10,13-15). Some of the studies required the total scores and pain scores to meet specified requirements (10,13,15). Most of the studies emphasized a medical history of more than 3 months, and only the study by Zhang *et al.* failed to include a history of more than 3 months (15). Zeng *et al.*'s study included patients for whom drug treatments were ineffective (13). The studies by Zhang *et al.* (15) and Pajovic *et al.* (10) used the drug treatment group as the control group, while the other studies used a sham control (8,9,13,14). Four studies introduced evaluation criteria for treatment efficacy (8,10,13,15). Pajovic *et al.* (10) and Zhang *et al.* (15) used the primary endpoint of QoL score ≤2 at the treatment endpoint, and the secondary endpoints were a greater than 50% reduction in pain scores and total NIH-CPSI scores. In the study by Zeng *et al.* (13), responders were defined as men who experienced a decrease of 6 or more points in the total NIH-CPSI score (perceptible improvement) compared to baseline, or a 12 point decrease (clinically significant improvement), which reflected a 50% decrease in the total NIH-CPSI score compared to baseline. Zimmermann *et al.* (8) considered a decrease of 5 or more points in the total NIH-CPSI score as the criterion for treatment efficacy. Zimmermann *et al.* (8), Moayednia *et al.* (9), Vahadpour *et al.* (14), and Zhang *et al.* (15) employed the Duolith® SD1 and MP100 devices (Storz Medical, Tägerwilen, Switzerland), Zeng *et al.* (13) used the HB-ESWT 1® device (Haibin Medical Equipment Co. Ltd., Beijing, China), and Pajovic *et al.* (10) used the Lubisone KM-2000 S device (K1 Med Co., Ltd., Seoul, Korea). The device used in the study by Zhang *et al.* (15) was a shock wave unit with a radial shock wave source, but the devices used in the other 5 studies had a focus shock wave source (8-10,13,14). The setup parameters of LI-ESWT differed among the studies. The energy flux density (EFD) in most studies was 0.25 mJ/mm^2, while only 2 studies had lower EFDs of 0.05 and 0.06 mJ/mm^2 (9,13). In most of the studies, each treatment consisted of 3,000 shock wave pulses, while only 1 study administered fewer shock wave pulses (2,000) (13). The treatment course ranged

from 4 to 12 weeks (8-10,13,14). Each study's endpoint was the longest follow-up time, namely, 12 (8,13-15) or 24 weeks (9,10) after LI-ESWT.

The quality of the studies and the risk of bias were assessed by the Cochrane Collaboration tool (shown in *Figures 2,3*). Only 1 of the 6 studies did not use a randomization method (14). The randomized controlled trials (RCTs) reported that the patients were assigned randomly into the LI-ESWT or control groups but did not further describe the randomization process (8-10,14). Only Zeng *et al.* mentioned the closed-envelope method. Most of the studies did not describe how the doctors were blinded to participants' allocation (9,10,13-15). Blinding of the physician would be difficult to maintain since the LI-ESWT output energy would need to be reduced to zero for patients in the control group receiving sham treatment. Only Zimmermann *et al.* (8) described the process of ensuring double-blinding. As shown in *Figure 3*, 66.7% of the studies had an unclear risk of bias in randomization, and only 16.7% of the studies had good blinding for both patients and doctors.

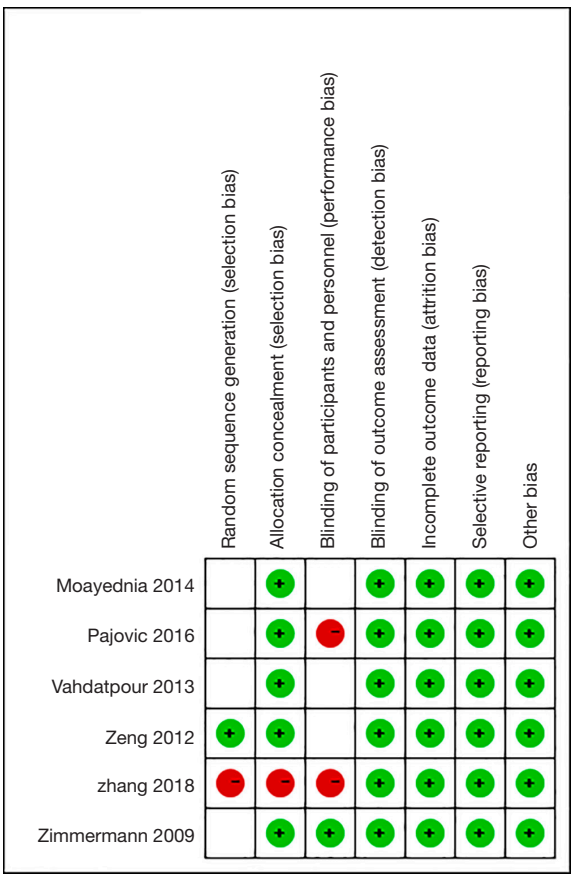

Figure 2 Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

At 12 weeks after treatment, the data indicated that LI-ESWT was effective for the treatment of CPPS (RD: 0.46; 95% CI, 0.28–0.63; P<0.00001) according to the overall meta-analysis (shown in *Figure 4*). Additionally, a subgroup analysis was conducted in this study. The total NIH-CPSI scores at 1 and 12 weeks after LI-ESWT were significantly decreased (MD: −4.46; 95% CI, −6.67–−2.25; P<0.00001, shown in *Figure 5*; and MD: −5.00; 95% CI, −7.24–−2.75; P<0.0001, shown in *Figure 6*, respectively). However, the total NIH-CPSI scores at 24 weeks after treatment were not significantly decreased (MD: −4.59, 95% CI, −12.63–3.46; P=0.26, shown in *Figure 7*).

The studies were divided into 3 groups based on time after LI-ESWT (1, 12, and 24 weeks), and the visual analog scale (VAS) scores were compared. According to the meta-analysis, the patients' VAS scores improved significantly at 12 weeks after LI-ESWT (MD: −3.16; 95% CI, −5.03–−1.30; P=0.0009), but did not improve significantly at 1 and

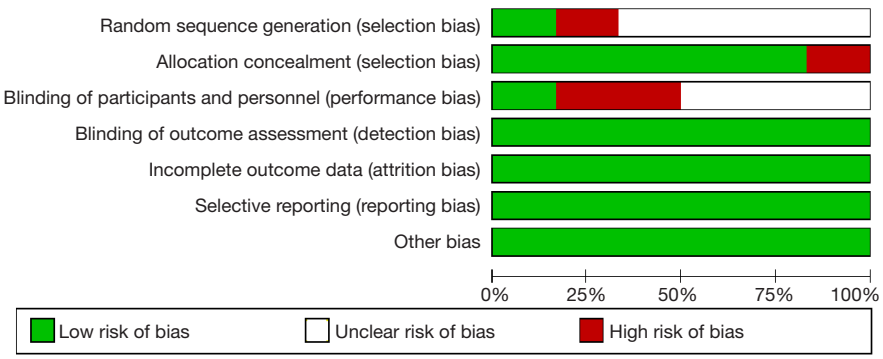

Figure 3 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

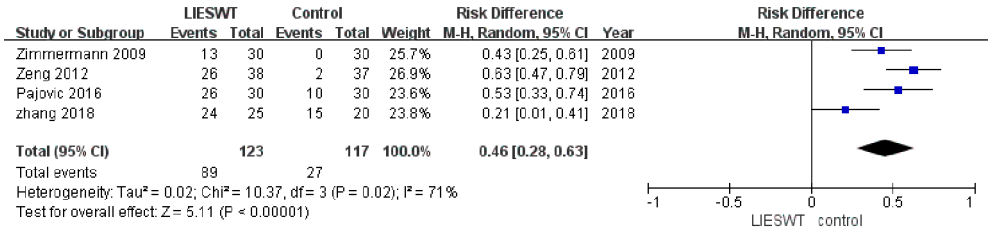

Figure 4 Forest plot of the total effectiveness rates of LI-ESWT for CPPS compared to controls. LI-ESWT, low-intensity extracorporeal shock wave treatment.

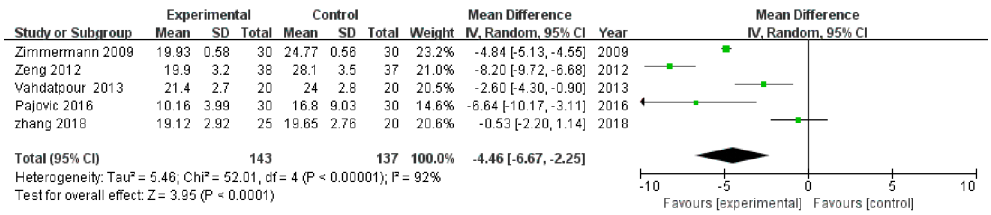

Figure 5 Forest plot of the total NIH-CPSI scores of patients with CPPS treated with LI-ESWT compared to controls at 1 week after treatment. LI-ESWT, low-intensity extracorporeal shock wave treatment.

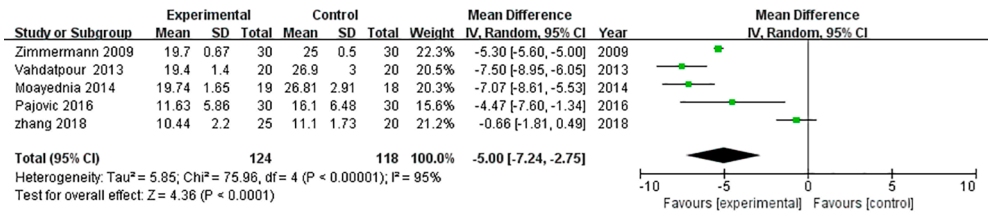

Figure 6 Forest plot of the total NIH-CPSI scores of patients with CPPS treated with LI-ESWT compared to controls at 12 weeks after treatment. LI-ESWT, low-intensity extracorporeal shock wave treatment.

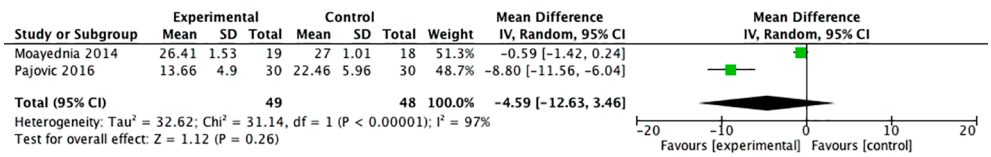

Figure 7 Forest plot of the total NIH-CPSI scores of patients with CPPS treated with LI-ESWT compared to controls at 24 weeks after treatment. LI-ESWT, low-intensity extracorporeal shock wave treatment.

24 weeks (MD: −1.18; 95% CI, −2.55–0.20; P=0.09; and MD: −3.39; 95% CI, −10.10–3.32; P=0.32, respectively).

The urinary symptom scores were not significantly improved at 1 and 24 weeks after treatment (MD: −0.24, 95% CI, −1.17–0.69; P=0.61; and MD: −1.02; 95% CI, −2.01–0.05; P=0.06, respectively), but were significantly improved at 12 weeks after treatment (MD: −1.29; 95% CI, −1.95–−0.64; P=0.0001).

Furthermore, the QoL scores were significantly improved at 12 weeks after treatment (MD: −1.31; 95% CI, −2.33–−0.30; P=0.01), but not at 1 or 24 weeks after treatment (MD: −1.08, 95% CI, −2.57–0.41; P=0.15; and

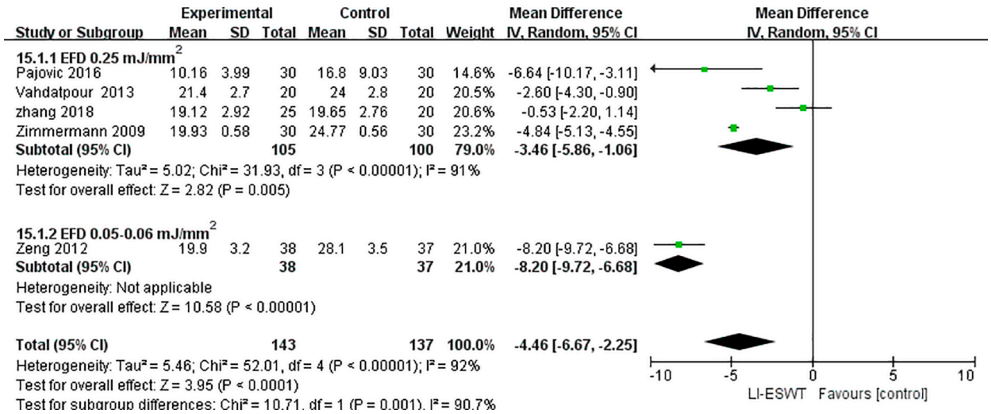

Figure 8 Forest plot of the improvements in the total NIH-CPSI scores of patients with CPPS treated with LI-ESWT at EFD 0.25 mJ/mm^2 compared to those treated with EFD 0.05–0.06 mJ/mm^2. LI-ESWT, low-intensity extracorporeal shock wave treatment.

MD: -1.78; 95% CI, −5.08–1.52; P=0.29, respectively).

Different LI-ESWT setup parameters, such as EFDs, resulted in differences in reported efficacy. The studies were divided into 2 groups according to EFD. The total NIH-CPSI scores using the EFDs 0.06 and 0.25 mJ/mm^2 were significantly decreased (MD: −8.20; 95% CI, −9.72–−6.68; P<0.00001; and MD: −3.46; 95% CI, −5.86–−1.06; P=0.005, shown in *Figure 8*, respectively).

Discussion

This systematic review and meta-analysis of 6 studies involving 317 male patients revealed significant improvements in total NIH-CPSI scores, QoL, pain scores, and urinary symptom scores in the LI-ESWT group compared to the control group at 12 weeks after treatment.

Some deterioration of total NIH-CPSI scores, pain scores, QoL, and urinary symptom scores was observed at 24 weeks of follow-up compared with 1 week. As described in the study by Fojiecki *et al.*, LI-ESWT is likely to relieve pain in CPPS patients in the short term (16,17). One potential explanation could be the mechanism of LI-ESWT. Mechanotransduction (18), microcavitation (19), and thermodynamic effects lead to the energy transfer of LI-ESWT. LI-ESWT applies a mechanical force on cell membranes and contents. LI-ESWT can regulate cellular signal transduction and affects the transcription and modification of intracellular proteins (20). LI-ESWT shock waves are transformed into biochemical signals through the process of mechanotransduction, which may hyperstimulate nociceptors and interrupt the former pain memory nerve impulses to achieve 'reprogramming', thereby alleviating pain (21). Furthermore, cavitation bubbles are generated and popped, producing secondary energy waves called microjets that lead to additional mechanical forces, which increases local microvascularity (8), reduces pain, and helps heal tissue (22). This mechanism may explain the short-term nature of shock waves' effects, as pain sensations can be prevented relatively transiently without persistent modulation of sensitivity at the treatment area.

The longer-term effect of LI-ESWT may involve other mechanisms. A possible cause of CPPS is immunogenic inflammation, which activates prostate afferent nerves and induces inflammation, prostate pain, and referred pain (23). LI-ESWT may trigger an anti-inflammatory response related to the mechanism of mechanotherapy, inducing different biological reactions and immunomodulation pathways. LI-ESWT suppresses the production of proinflammatory cytokines (IL-1α, IL-4, IL-6, etc.), chemokines (CCL2, CCL12, etc.), and matrix metalloproteinases (MMPs) (23). LI-ESWT is administered at different time points, and energies exert different effects on inflammatory processes (24). Moreover, long-term effects of LI-ESWT are considered to be mediated by multiple overlapping and crosstalking signaling pathways, for example, protein synthesis/secretion, structural reorganization, proliferation, and vitality (25). Specific cellular processes and molecules modulated by LI-ESWT include extracellular signal-regulated kinase (ERK) (26), focal adhesion kinase (FAK) (27), ATP/P2X7 (28), Wnt (28), protein kinase R-like endoplasmic reticulum kinase/activated transcription factor (PERK/ATF) (29), vascular

endothelial growth factor (VEGF), and brain-derived neurotrophic factor (BDNF) (30).

BDNF promotes the survival of neurons and stimulates the growth and differentiation of new neurons. LI-ESWT has been shown to improve the expression of BDNF at a level that was maintained until 26 days after nerve injury (31). This prolonged expression may likely sustain neurotrophic healing beyond what can be expected naturally and without intervention. The LI-ESWT-mediated BDNF activation mechanism was studied in RT4-D6P2T Schwann cells and was revealed to be related to the activation of PERK/ATF4 (31). The p75 gene and p-ERK1/2 were considered as Schwann cell activation-related markers and were upregulated after LI-ESWT (32). The PERK inhibitor GSK265615753 decreased LI-ESWT-mediated eIF2α phosphorylation and downstream target gene ATF4 expression. Accordingly, the expression of BDNF was also significantly reduced in this context (31).

Other studies have revealed that LI-ESWT induces mesenchymal stem cells to express VEGF, and VEGF then upregulates the PI3K/AKT/mTOR pathway, thus inducing autophagy. Autophagy and apoptosis assays have shown that LI-ESWT activates autophagy and effectively decreases apoptosis. Some studies applied LI-ESWT to the injured spinal cords of rats. In the LI-ESWT group, CD31 and alpha-smooth muscle actin expression increased, and TUNEL-positive cells were reduced in the injured spinal cords (33). VEGF expression also significantly improved in the NeuN-, GFAP, and Olig2-labeled cells. These studies suggest that the neuroprotective effects of VEGF induced by LI-ESWT may decrease axonal damage and cell apoptosis and promote locomotor and sensory functions after spinal cord injury.

Another potential explanation for the effect of short term of LI-EWST in this article is that only 2 of the 6 studies performed a long-term follow-up at 24 weeks. In the study by Pajovic *et al*. (10), the treatment effects of LI-ESWT + triple therapy (α-blocker, anti-inflammatory agent, and muscle relaxant) were compared with those of triple therapy alone to evaluate the long-term efficacy of LI-ESWT for CPPS (24 weeks). Combination therapy might have been the main reason for the positive long-term effects. A randomized controlled study by Moaydenia *et al*. (9) indicated that the NIH-CPSI scores, QoL, urinary symptom scores, and pain domain scores gradually deteriorated from week 16 to week 24. The scores recorded at week 24 were close to those at baseline, implying a questionable long-term effect of LI-ESWT on CPPS. However, the total treatment course in the study by Moaydenia *et al*. was 4 weeks, whereas the total treatment course in the study by Pajovic *et al*. was 12 weeks. The effect of LI-ESWT should also correspond to the dose applied (34). In a single-arm study, treatment efficacy was determined over a longer treatment course, such as 6 and 12 months, after applying a protocol of 2,500 pulses once a week for 1 month (11). The long-term effect of LI-ESWT on CPPS is controversial due to different mechanisms, small sample sizes, different protocols, and different treatment courses. In the future, more long-term, multicenter, large RCTs should be performed to determine the efficacy of LI-ESWT for CPPS.

This systematic review and meta-analysis were the first to examine the efficacy of LI-ESWT for the treatment of CPPS. However, our study had some limitations. The sample sizes in most trials were small. The largest sample size in our meta-analysis only included 80 male patients (10). No blinding of personnel occurred in most of the RCTs (9,13,14).

Regarding patient demographics, few studies described the selection criteria and previous treatment strategies. The short-term follow-up of the included studies is also an important limitation. For most studies, follow-up was limited to approximately 12 weeks. Therefore, the robustness of this approach remains unknown, and long-term data are needed. The 6 studies in this meta-analysis included 5 RCTs and a nonrandomized controlled trial. No placebo response was observed in the sham-treated arm, which is unusual. Previously treated men were also included in some trials (10,13). If any bias occurred, it would substantially affect the interpretation of the results of this meta-analysis.

Additionally, our study had a very high level of heterogeneity (I^2 =71%). The potential reasons for this heterogeneity might be subject selection and the therapeutic regimen. Pajovic *et al*. (10) used 3,000 treatment shocks over 12 weeks, and Zeng *et al*. (13) applied 2,000 treatment shocks over 10 weeks, whereas other studies administered 3,000 treatment shocks over 4 weeks. Also, Pajovic *et al*. (10) and Zhang *et al*. (15) used the drug therapy group as the control group to reveal the effect of LI-ESWT.

Different setup parameters and different treatment protocols of LI-ESWT have a substantial influence on therapeutic efficacy. The clinical outcome of LI-ESWT is closely related to the energy delivered to the target unit area or EFD. The EFDs used in the included studies varied from 0.05 to 0.25 mJ/mm^2. Based on this review,

we could not determine the best EFD for CPPS therapy. Most of the included studies used an EFD of 0.25 mJ/mm^2, which Zimmermann *et al.* first reported in 2009 (8). Most subsequent studies adopted this EFD and presented encouraging results. Additional studies and a longer duration of treatment are needed to establish whether therapeutic efficacy is positively correlated with energy density.

Future LI-ESWT research should rely on basic science and clinical studies. Extensive basic research is necessary to understand the mechanism of action of LI-ESWT. Several devices with a radial or focus shock wave source, such as electrohydraulic, electromagnetic, and piezoelectric generators, are available on the market, and each type of device employs a different treatment protocol. Further studies are needed to evaluate the different devices and protocols. Well-designed and long-term multicenter RCTs are urgently needed to estimate the real potential and ultimate use of these devices in patients with CPPS.

Conclusions

In this meta-analysis on the efficacy of LI-ESWT for CPPS, total NIH-CPSI scores, QoL, pain scores, and urinary symptom scores transiently improved in the LI-ESWT group compared with the control group. Future research may elucidate the mechanisms underlying the effect of LI-ESWT on CPPS. Well-designed and long-term multicenter RCTs are urgently needed to estimate the real potential and ultimate use of these devices before LI-ESWT is widely applied as a treatment for CPPS.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tau-20-1423

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-20-1423). Dr. GI and Dr. LM report grants from Beijing Municipal Science & Technology Commission, during the conduct of the study.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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