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REVIEW ARTICLE

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Efficacy of low-intensity extracorporeal shock wave therapy for the treatment of chronic prostatitis/chronic pelvic pain syndrome: A systematic review and meta-analysis

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Abstract

Aims: Low-intensity extracorporeal shock wave therapy (Li-ESWT) has been applied in urolithiasis and some chronic diseases. We performed a systematic review and meta-analysis to assess the efficacy of Li-ESWT for the treatment of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

Methods: A comprehensive search of MEDLINE, Web of Science, EMBASE, and the Cochrane Library to January 6, 2019 was performed for randomized controlled trials (RCTs) reporting on patients with CP/CPPS treated with Li-ESWT compared with the sham group. Outcomes were evaluated based on the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI). The quality assessment of included studies was performed by the Cochrane System.

Results: Six publications involving five RCTs with 280 patients were assessed in this review. NIH-CPSI total score, pain domain and quality of life (QOL) were significantly better in the Li-ESWT group than those in the control group at the endpoint ($P < 0.00001$, $P = 0.003$, and $P < 0.00001$), 4 weeks ($P < 0.00001$, $P = 0.0002$ and $P < 0.00001$) and 12 weeks ($P < 0.00001$, $P < 0.00001$, and $P = 0.0002$) after the treatment. For urinary score, significant difference existed at 12 weeks after the treatment ($P = 0.006$). At 24 weeks after treatment, there was no significant difference between the two groups in NIH-CPSI total score ($P = 0.26$), pain domain ($P = 0.32$), urinary score ($P = 0.07$), and QOL ($P = 0.29$).

Conclusions: Li-ESWT showed great efficacy for the treatment of CP/CPPS at the endpoint and during the follow-up of 4 and 12 weeks, though the efficacy of 24-week follow-up was not significantly different due to insufficient data. Generally, Li-ESWT is a promising minimal invasive method for the treatment of CP/CPPS.

KEYWORDS
chronic pelvic pain syndrome, chronic prostatitis, low-intensity extracorporeal shock wave therapy

1 | INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common discomfort in urology. The pain is special for which no certain pathological mechanism may illuminate.[1] According to national institutes of health, CP/CPPS belongs to type III prostatitis, which occurs frequently in men before the age of 50.[2] The growing prevalence rate affects about 50% of men at some point throughout their lives.[3] Additionally, its notable morbidity is comparable to that of the condition after a heart attack and angina pectoris. CP/CPPS is diagnosed by persistent pelvic pain for more than 3 months without proven infection. It causes pain and/or discomfort in the prostate, perineal, inguinal, scrotal and suprapubic regions.[4] In addition to pain, disturbance of voiding conditions and erectile dysfunction of some degree, which are called "the functional CPPS-like symptoms", can have a notable negative effect on the quality of life (QOL) which may be more severe than the pain itself.[5] Symptoms and severities of CP/CPPS are usually evaluated by the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI).[6]

Though with the vast majority of affected patients and increasing morbidity, the pathophysiology of CP/CPPS has not been clarified completely yet, which causes troublesome challenges in the diagnosis and treatment method for most doctors. Chronic nonbacterial prostatitis is the dominating etiology of CP/CPPS.[7] Related factors include inflammation, pelvic floor muscle dysfunction, neurobehavior disorder, and so on,[8] although none of them is thought to be the cause solely. Uncertain etiologies determine that no standardized or unanimous treatment is available at present.[9] Various treatment modalities including analgesics, anti-inflammatory, and antimicrobial agents, muscle relaxants, α-blockers, 5α-reductase inhibitors as monotherapy or combination therapy have been used with variable success rates.[10-12] Besides medical therapies, some available therapies that have been introduced such as acupuncture, massage in trigger-point and rectum, electromagnetic therapy, physiotherapy, thermotherapy, lifestyle interventions and so on.[10,13] However, none of these modalities have uniformly successful effects. Therefore, the new therapeutic method is needed urgently. The extracorporeal shock wave has been applied in urolithiasis as a standard method in urology successfully for a long time.[14] It can also be used for the treatment of chronic conditions such as epicondylitis, tendinitis, diabetic wounds, and planter fasciitis.[15] Recently, some studies evaluated the efficacy of Li-ESWT for pelvic pain and voiding dysfunction in patients with CP/CPPS. Zimmermann et al[16] firstly showed favorable improvements in QOL and pain after Li-ESWT compared with the baseline in 2008. Since then, several prospective trials have been performed and clarified that Li-ESWT is a feasible and promising method for improving CP/CPPS with varying degrees of success. What are the potential benefits of Li-ESWT that can offer to CP/CPPS patients? Whether this procedure worth the investment in the equipment of the hospital?

We performed a systematic review of the literature investigating the application of Li-ESWT for CP/CPPS. Our goal was to analyze the available data to determine the efficacy of Li-ESWT for CP/CPPS.

2 | MATERIALS AND METHODS

2.1 | Data sources and searches

The meta-analysis was conducted based on systematic searches of MEDLINE, Web of Science, EMBASE, and the Cochrane Library using the search terms of "extracorporeal shock wave," "chronic pelvic pain syndrome", and "chronic prostatitis" before January 6, 2019. After the removal of duplicates and the exclusion of conference abstracts, the initial selection was made based on the titles and abstracts of the articles. Papers reporting the results of randomized controlled trials (RCTs) that assessed the effects of Li-ESWT compared with the sham group were identified through the full-text review. After selection, relevant information was gathered from the articles. After the authors of this meta-analysis reached consensus, the reference lists of all identified articles and general reviews of this topic were examined manually by two independent reviewers, any disagreement was resolved by discussion, and unsolved disagreement was dealt by the third reviewer. The quality assessment of included studies in the meta-analysis was measured by the Cochrane collaboration's tool with the following six items: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, reporting bias, and other bias.

2.2 | Study selection

Inclusion and exclusion criteria were defined before the article search. Inclusion criteria included: age of over 18 years, chronic pain in the bladder, groin, genitals, lower abdomen, perineal and perianal areas without obvious abnormalities on urological examination for more than 3 months,[17] NIH-CPSI total score greater than 15 and pain domain score greater than 4, and the ability to comply with the requirements of the study. Exclusion criteria included a history of drug/narcotics abuse, chronic

urethritis, urinary stones, chronic bacterial or inflammatory prostatitis, as well as evidence of bacteria in seminal culture tests, bladder and prostate cancer, those who had been treated or were taking medications that could affect lower urinary tract function, serum prostate-specific antigen levels (PSA) in excess of 4 ng/mL,[18] history of prostate surgery or radiotherapy.

2.3 | Data abstraction

Outcomes assessed in this article were as follows: NIH-CPSI score, which included pain domain (item 1-4), urinary score (item 5-6) and QOL (item 7-9) at the termination of therapy and the follow-up period of 4, 12, and 24 weeks after the cessation of therapy.[6] Side effects during the treatment period in studies were also accessed. Besides, other results like maximum urinary flow rate (Qmax) and post void residual volume (PVR) in some studies were also recorded.

2.4 | Data synthesis and analysis

For continuous variables like NIH-CPSI score, the mean difference was used for analysis, and risk ratio for binary outcomes such as events of side effects, which were calculated by dividing the total number of specific outcomes by the total number of patients treated by each respective procedure. Both of them were determined by point estimation and 95% confidence intervals. The Cochrane χ^2-test and inconsistency (I^2) were used to assess the heterogeneity among studies. $P < 0.10$ indicated the presence of heterogeneity, and $I^2 < 50\%$ indicated that the heterogeneity was acceptable, such that a fixed-effects model was used; otherwise, a random-effects model was used. The overall effects were determined by the Z-test and $P < 0.05$ was considered statistically significant. All tests were performed using Review Manager Software (RevMan 5.3). Results are shown as forest plots by RevMan 5.3 and tables by Microsoft Office 2013.

3 | RESULTS

3.1 | Study characteristics

3.1.1 | The current studies of Li-ESWT for CP/CPPS

Our initial search yielded 1611 potential citations from MEDLINE, Web of Science, EMBASE, and the Cochrane Library, of which 1605 were excluded for reasons presented in Figure S1. The literature search and study selection process, therefore, identified five RCTs in six publications that examined a total of 280 patients who were treated with Li-ESWT (n = 140) or control (n = 140) for CP/CPPS from 2009 to 2018.[19-24] Of all the RCTs, three studies reported follow-up data collected at 12 weeks after treatment[21,23,24] and two presented 24-week results.[19,20] Table 1 provides an overview of the composite baseline characteristics (publication and year, study and follow-up date, etc). Besides, different Li-ESWT regimens (energy intensity and frequency, interval, period, etc) are also recorded. The setup parameters of Li-ESWT were different among studies. The energy flux density varied from 0.06 to 0.4 mJ/mm^2, and the number of shock wave pulses per session was between 2000 and 3000. The

TABLE 1 Overview of baseline characteristics and Li-ESWT regimens of studies

Reference	Sample size	Study dates	Follow-up week	Age	Pain domain	Urinary score	Quality of life	NIH-CPSI	Parameters
Zimmermann[24]	30/30	N/A	12	42.0/43.0	5.33/5.73[a]	N/A	N/A	23.20/25.07	3000impulses 0.25 mJ/mm^2,3 Hz
Xiaoyong[23]	40/40	2009.8-2011.5	12	48.7/46.3	15.6/14.7	4.4/4.7	10.5/9.9	30.5/29.3	2000impulses 0.06mJ/mm^2 ,2 Hz
Vahdatpour[22] + Moayednia[19]	20/20	2011.10-2012.10	24	35.4/37.0	13.8/13.6	4.6/5.2	8.1/8.3	26.5/27.1	3000impulses 0.25-0.4 mJ/mm^2, 3 Hz
Pajovic[20]	30/30	2013.9-2015.2	24	39.4/39.4	15.9/14.5	5.03/5.76	9.96/9.1	31.06/29.3	3000impuls[b]es 0.25 mJ/mm^2,3 Hz
Salama[21]	20/20	2015.12-2017.11	8	37.6/35.1	12.0/12.8	5.8/5.1	8.35/8.15	26.15/26	3000impulses 3 Hz

Abbreviations: Li-ESWT, low-intensity extracorporeal shock wave therapy; N/A, not available; NIH-CPSI, the National Institutes of Health Chronic Prostatitis Symptom Index

[a]The pain domain was evaluated using the visual analog scale, which is different from other studies.

[b]The energy density was gradually increased until it reached the maximum possible tolerable pain level reported by the patient.

treatment course of most studies was not longer than 4 week, and one study had a longer treatment course of 12 weeks.

3.1.2 | The quality evaluation of the studies and analysis for the risk of bias

The results of quality and risk of bias assessment of included studies in the meta-analysis by the Cochrane Collaboration's tool are shown in Figure S2. The RCTs reported the condition of randomization, allocation, and blindness between Li-ESWT and control groups in some degree. Two studies[23,24] described the process of blindness to participants. Li-ESWT output energy needed to be turned off for patients received the sham therapy in the control group.

3.2 | Quantitative data synthesis

3.2.1 | NIH-CPSI total score

The NIH-CPSI total score data between Li-ESWT and control groups were acquired from five trials.[19-24] Of them, five[20-24] reported at the endpoint and 12 weeks, four[21-24] at 4 weeks and two at 24 weeks.[19,20] Figure 1 shows the results. Except for the results of 24 weeks after the treatment, NIH-CPSI total scores were significantly higher in the control group than those in the Li-ESWT group at the endpoint (−5.47 [−7.47, −3.47], $P < 0.00001$), 4 (−8.74 [−11.78, −5.70], $P < 0.00001$) and 12 weeks (−8.90, [−12.28,−5.53], $P < 0.00001$) after the treatment, which meant Li-ESWT had better effects on CP/CPPS within 12 weeks as a whole. In regard to 24 weeks after the treatment, NIH-CPSI total score was not significantly

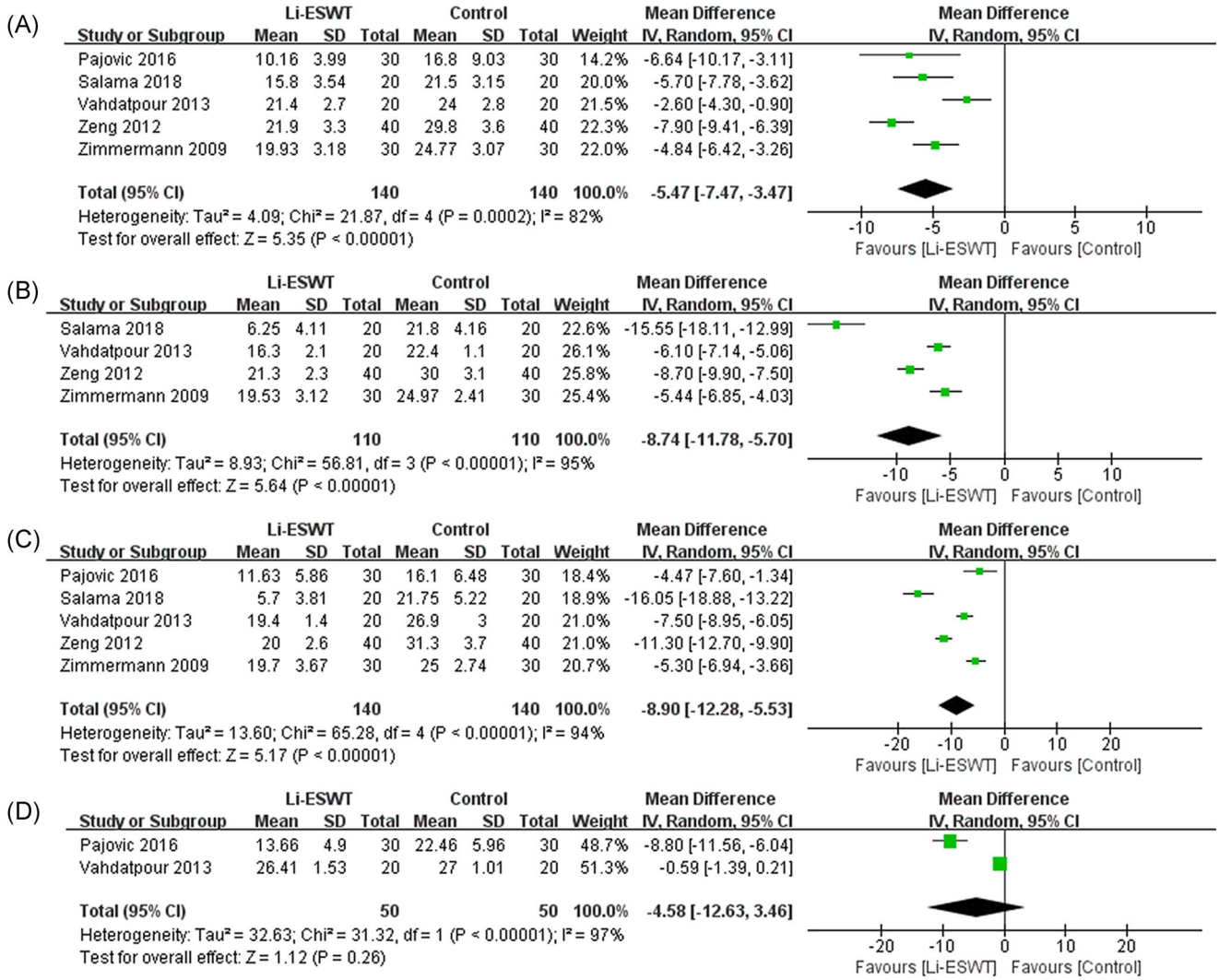

FIGURE 1 Forest plots of NIH-CPSI total score after the treatment. A, At the endpoint; B, at 4 weeks; C, at 12 weeks; D, at 24 weeks. CI, confidence interval; Li-ESWT, low-intensity extracorporeal shock wave therapy; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; QOL, quality of life

different between Li-ESWT and control groups (− 4.58 [− 12.63, 3.46], $P = 0.26$).

Since NIH-CPSI total score consists of pain domain, urinary, and QOL, to analyze in detail, we conducted quantitative analysis for three subdomains below.

Pain domain

Figure 2 shows results of pain domain acquired from four trials.[19-23] Of them, four[20-23] reported them at the endpoint and 12 weeks, three[21-23] at 4 weeks and two[19,20] at 24 weeks. Similar to NIH-CPSI total score, pain domain was significantly in favor of Li-ESWT group at the endpoint (− 2.84 [− 4.73, − 0.95], $P = 0.003$), 4 (− 4.75 [− 7.29, − 2.21], $P = 0.0002$) and 12 weeks (− 5.60, [− 7.16, − 4.03], $P < 0.00001$) after the treatment. As for 24 weeks after the treatment, there were no significant differences between Li-ESWT and control groups (−3.39 [− 10.10, 3.32], $P = 0.32$).

Urinary score

Figure 3 demonstrates the results of the urinary score, which were acquired four trials.[19-23] Of them, four[20-23] reported data at the endpoint and 12 weeks, three[21-23] at 4 weeks and two[19,20] at 24 weeks. Li-ESWT group showed better results of urinary score significantly at 12 weeks after the treatment (− 1.36, [− 2.33, − 0.38], $P = 0.006$). However at the endpoint, 4 and 24 weeks of follow-up, significant differences didn't exist between Li-ESWT and control groups (− 0.32 [− 0.66, 0.02], $P = 0.06$, − 1.42 [− 3.10, 0.26], $P = 0.10$ and − 1.01 [− 2.09, 0.07], $P = 0.07$, respectively).

QOL

Four trials[20-23] reported QOL at the endpoint and 12 weeks after the treatment, three[21-23] at 4 weeks and two[19,20] at 24 weeks. The data are shown in Figure 4. Similar to NIH-CPSI total score and pain domain, better results were noted in Li-ESWT group at the endpoint (− 2.35 [− 3.29, − 1.42], $P < 0.00001$), 4 (− 3.92 [− 5.63,

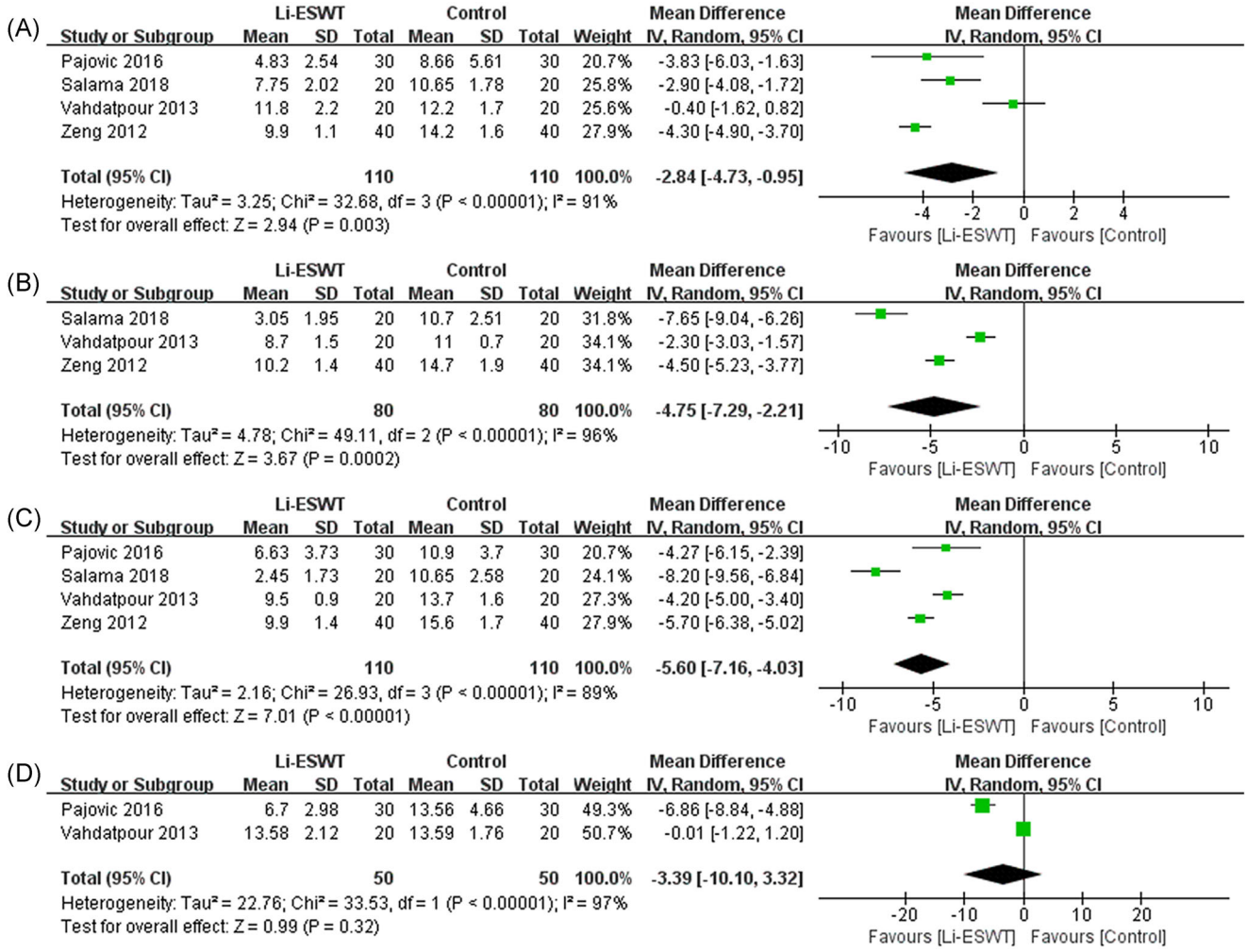

FIGURE 2 Forest plots of pain domain after the treatment. A, At the endpoint; B, at 4 weeks; C, at 12 weeks; D, at 24 weeks. CI, confidence interval; Li-ESWT, low-intensity extracorporeal shock wave therapy; QOL, quality of life

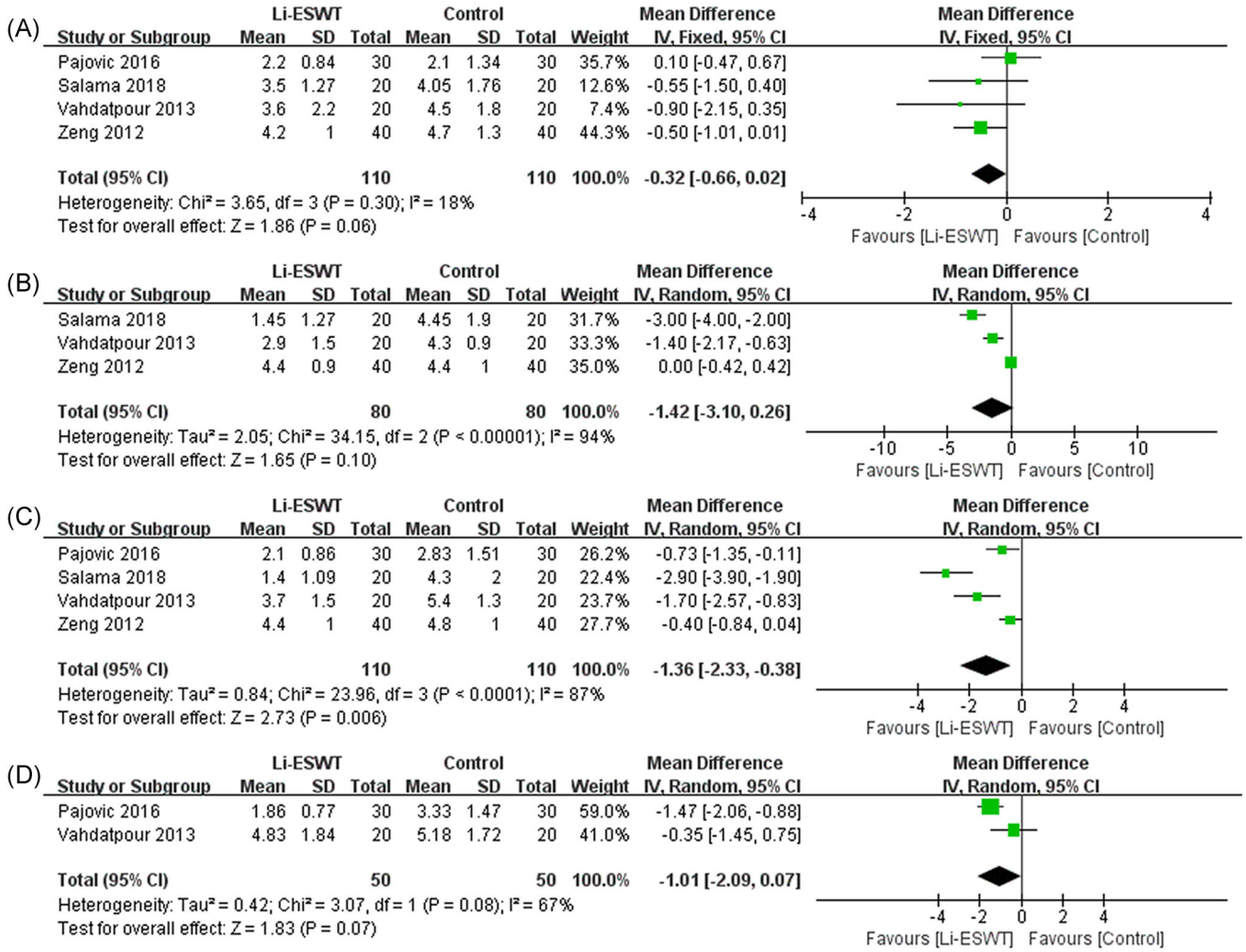

FIGURE 3 Forest plots of the urinary score after the treatment. A, At the endpoint; B, at 4 weeks; C, at 12 weeks; D, at 24 weeks. CI, confidence interval; Li-ESWT, low-intensity extracorporeal shock wave therapy; QOL, quality of life

-2.21], $P < 0.00001$) and 12 weeks (-3.21 [-4.90, -1.52], $P = 0.0002$) after the treatment. And there were no significant differences between Li-ESWT and control groups at 24 weeks (-1.78 [-5.08, 1.52], $P = 0.29$).

4 | DISCUSSION

Li-ESWT has been used as a therapy for patients in urology for a long time, especially in lithotripsy.[14] Encouraging results for Li-ESWT in male erectile dysfunction have been reported for almost 10 years.[25,26] Besides, pain in Peyronie's disease can also be resolved by Li-ESWT.[27] Reports and trials about CP/CPPS have increased in recent years substantially, which implies that Li-ESWT as a therapeutic method for CP/CPPS has been adopted by both physicians and patients gradually. This meta-analysis of RCTs demonstrated a significant improvement in the NIH-CPSI score of patients with CP/CPPS undergoing Li-ESWT compared with sham therapy. This favorable result suggests that Li-ESWT benefits patients with CP/CPPS.

The pathophysiology of CP/CPPS is not elucidated completely. Possible mechanisms include pelvic floor hyperactivity, pain by means of nociceptors due to infection, neurologic disorders and local chemical alterations.[28,29] In the meantime, the mechanism of action that leads to improvement in patients of CP/CPPS treated with Li-ESWT has not been fully explained. Different from extracorporeal shock wave lithotripsy applied in urolithiasis, which is characterized by high energy density and powerful energy density and used for corporal stone fragmentation together with tissue injury sometimes, Li-ESWT shows particular biological effects with low energy density. In general, Li-ESWT mediates transformation from mechanical signals into biochemical signals and particular alterations in living cells and tissues. Shock waves produce extracellular cavitations as

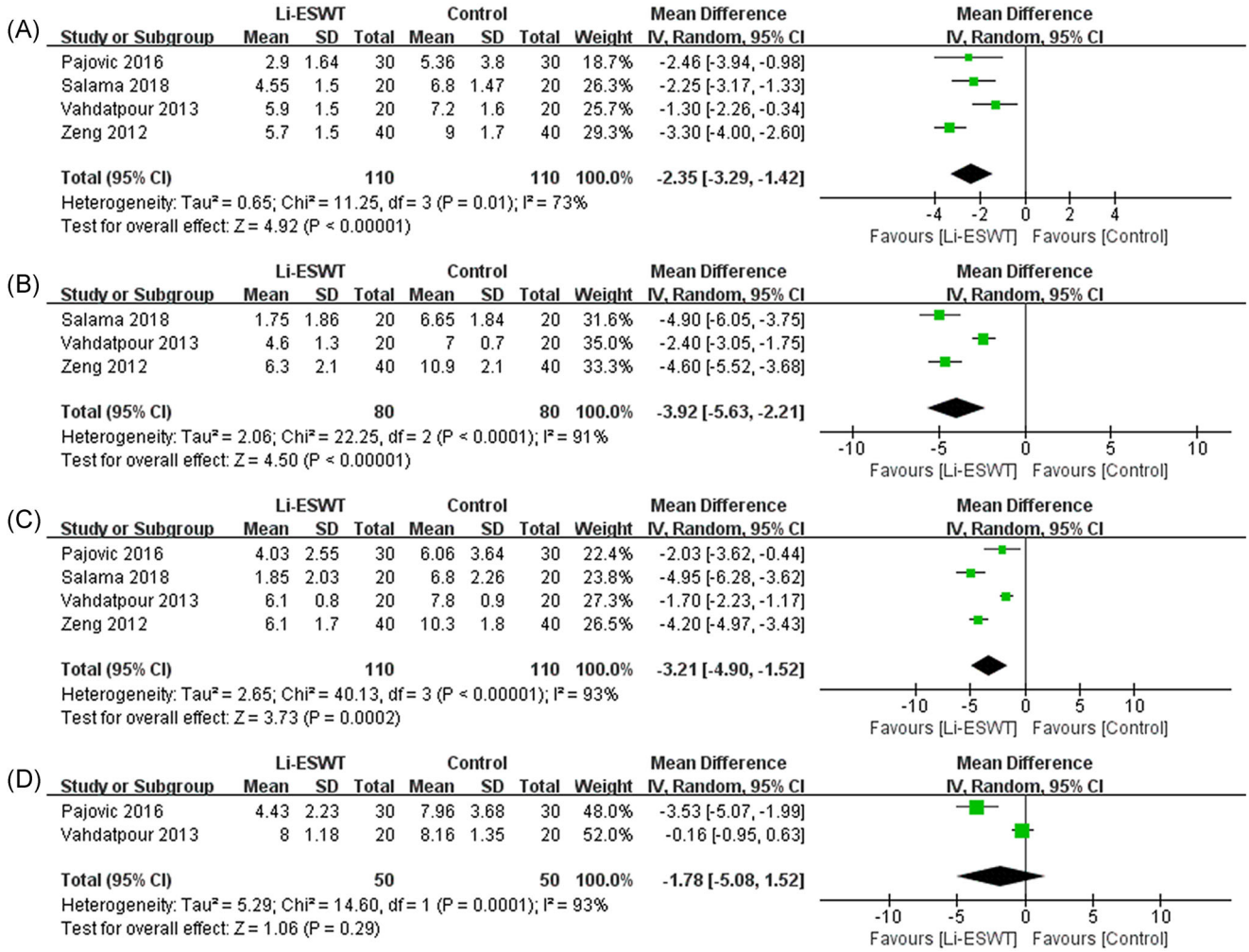

FIGURE 4 Forest plots of QOL after the treatment. A, At the endpoint; B, at 4 weeks; C, at 12 weeks; D, at 24 weeks. CI, confidence interval; Li-ESWT, low-intensity extracorporeal shock wave therapy; QOL, quality of life

mechanical stimuli when passing through tissues. The result is the damage of cell membrane nerves by cavitation and the transmission of pain signals.[30] Mariotto et al[31] reported shock waves to induce nitric oxide (NO) synthesis, which is one of the mechanisms of the effectiveness of shock waves for inflammatory reaction, since NO is mediated in neuromuscular junction formation such as synaptic plasticity and neurotransmission in the peripheral nervous system. Besides, interrupting the flow of nerve impulses by stimulation of nociceptive receptors and reduction in muscle tone are the potential mechanisms.[3]

NIH-CPSI scores are usually for the assessments of symptoms and severities for CP/CPPS with pain domain, urinary score and QOL.[6] In this review, we analyzed NIH-CPSI total score with three subdomains at the endpoint, 4, 12 and 24 weeks after the treatment. Similar results were shown in pain domain, QOL and total score, in which Li-ESWT was significantly better at the endpoint, 4 and 12 weeks after the treatment. In this review, we found that in some studies,[21,23] patients in the control group also reported a significant decrease in all domains of the NIH-CPSI as compared to the baseline ($P < 0.05$); however, patients in the Li-ESWT group decreased more significantly than those in the control group. Additionally, significant effects in the control group didn't last long, and these effects vanished in late-term of follow-up, which indicates that psychological factors play important roles in patients with CP/CPPS. One trial[24] reported the condition in the control group remained unchanged or worse. It may be explained by the natural process of the disease in the long term.

Different from pain domain, QOL, and total score, urinary score only showed a significant difference at 12 weeks after the treatment. Actually, the pain has more impact on QOL than urinary symptoms. Turner et al[32] reported that a worse QOL was associated with greater pain and urinary symptoms, and the former was more associated with worse QOL than the latter. Also, Tripp et al[33] reported that both pain and urinary symptoms

were predictors of QOL, with the former representing the stronger effect. These reflect to a large extent that pain relief could alleviate the overall symptoms and improve the potential for effective treatment. Concerned with a urinary score, voiding conditions are obviously impaired by CP/CPPS. The interpretation of the urinary score is limited since it reflects only subjective changes. IPSS has the same defect, which was measured in one trial.[24] Based on these, we could not conclude the effect of Li-ESWT for voiding conditions. It is necessary to objectify these results by uroflowmetry and urodynamic evaluation. Pajovic et al[20] evaluated objective outcomes of voiding conditions with PVR and Qmax. Statistically significant differences existed in PVR between Li-ESWT and control groups at the endpoint (26.3 vs 28.3; $P < 0.05$) and 24 weeks (32.03 vs 35.21; $P < 0.05$), and Qmax at the endpoint (15.55 vs 13.05; $P < 0.05$). We concluded objective evaluation for voiding conditions should be considered in clinical research in the future.

The results of the 24-week follow-up term were analyzed in our article. None of the items above was significantly different between these groups, which challenged the persistence of the therapeutic effect of Li-ESWT. Since only two[19,20] involved trials reported 24-week follow-up results, we couldn't draw conclusions without more sufficient data. Therefore, more comprehensive research with long-term follow-up is needed to approve our findings.

Besides NIH-CPSI scores, we also collected results of sexual function and side effects. Zimmermann et al[24] reported sexual function by The International Index of Erectile Function (IIEF). The significant improvement of the IIEF was noted in the Li-ESWT group compared with that in the control group at the endpoint, 4 and 12 weeks after the treatment. It could be explained by the fact that the improvement in QOL makes a favorable difference in sexual function, which is reduced notably in patients with CP/CPPS.[34] What's more, the local application of shock waves has significant effects on erectile function.[35] In regard to side effects, though all the trials recorded them during the treatment period, only one trial[20] reported side effects (1.22 [0.59, 2.51]), in which dizziness, gastrointestinal complaint, and postural hypotension were noted and no anesthetic deemed necessary. These further confirm the safety of Li-ESWT for CP/CPPS.

As reported in many studies, the effect of Li-ESWT is taken for dose dependence, which means the energy of shock wave influences the final results markedly.[36] In involved trials, the energy density and impulses of shock waves were empirical, which were determined to refer to applications of previous clinical studies. The effectiveness of different therapeutic regimens should be assessed further to decide optimum regimens for Li-ESWT.

In addition, several limitations must be noted in this meta-analysis. Of all the trials involved in this article, most of them had small samples, and the largest study included in our meta-analysis enrolled only 80 patients.[23] More sufficient data were needed for analysis further. Though we tried to analyze long-term follow-up data, it failed. Most follow-ups were limited to 12 weeks. Two of the RCTs reported 24-week follow-up data, which were involved in quantitative analysis. Though all of the trials involved in this meta-analysis were RCTs, there were still some deficiencies. Some of them did not clarify the details of blindness. Besides, Li-ESWT regimens were different among studies. The energy density varied from 0.06 to 0.4 mJ/mm^2. Different therapeutic schedules include once or twice a week and last for different weeks. These caused great heterogeneity, for which a random-effects model was used to analyze these data. In the future, we could make a subgroup analysis with sufficient data to decide the optimum treatment regimens.

5 | CONCLUSIONS

Li-ESWT showed great efficacy for the treatment of CP/CPPS during the follow-up of endpoint, 4 and 12 weeks, as well as significantly better pain domain and QOL, though the efficacy of 24-week follow-up was not significantly different due to insufficient data. Li-ESWT is likely to result in a decrease in prostatitis symptoms and may not be associated with a greater incidence of an adverse event. Generally, Li-ESWT is a promising minimal invasive method for the treatment of CP/CPPS.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

XL, JL, PY, and YZ conceptualized the study. Methodology of the study was given by XG, DM, and RL. Formal analysis was done by PY, XG, ZL, and SW. Investigation was performed by PY, XG, and TW; PY and XL wrote the manuscript while review, editing, and revision was done by PY and XL. JL supervised the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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