COMPARATIVE EFFICACY OF COMBINED LOW-INTENSITY EXTRACORPOREAL SHOCKWAVE THERAPY AND ORAL THERAPY VS ORAL THERAPY ALONE FOR CHRONIC PELVIC PAIN SYNDROME: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective: *This study aimed to compare the efficacy of Low-Intensity Extracorporeal Shockwave Therapy (Li-ESWT) and oral therapy combination compared to sole oral therapy for reducing symptoms in CP/CPPS patients.* ***Material & Methods:*** *A systematic search was conducted from the electronic database including PubMed, Clinicaltrial.gov, and Cochrane Library, published up to July 2020 following the PRISMA guideline. We screened RCTs with the inclusion criteria and assessed the quality with the Cochrane Risk of Bias tool. The primary outcome was the National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI) and subgroup analysis for triple therapy users was conducted to improve interpretability. The analysis was performed using Review Manager 5.3.* ***Results:*** *A total of 2 RCTs consisted of 91 CP/CPPS patients were analyzed. Pooled analysis showed that compared to the oral therapy only group, combination therapy had a significant lower NIH-CPSI total score at the endpoint of the treatment (MD -7.46, 95% CI -9.85 to -5.07, p<0.001) and NIH-CPSI component pain score (MD -3.48, 95% CI -5.04 to -1.93, p<0.0001), urinary symptoms score (MD -0.96, 95% CI -1.47 to -0.45, p<0.001), and quality of life (QoL) impact score (MD -2.94; 95% CI -3.68 to -2.20, p=<0.001).* ***Conclusion:*** *This review revealed that patients undergoing combination Li-ESWT therapy have lower total NIH-CPSI scores than patients receiving oral therapy alone, this finding is consistent with each component of the score: pain, urinary symptoms, and impact on QoL.*

Keywords: *Li-ESWT, oral therapy, chronic prostatitis.*

ABSTRAK

Tujuan: *Penelitian kami bertujuan untuk mengevaluasi efikasi kombinasi Low-Intensity Extracorporeal Shockwave Therapy (Li-ESWT) dan terapi oral dibandingkan terapi oral untuk mengurangi gejala pada pasien CP/CPPS.* ***Bahan & Cara:*** *Pencarian sistematis dilakukan dari database elektronik termasuk PubMed, Clinicaltrial.gov, dan Cochrane Library, diterbitkan hingga Juli 2020 mengikuti pedoman PRISMA. Kami menyaring RCT dengan kriteria inklusi kami dan menilai kualitasnya dengan alat Cochrane Risk of Bias tool. Hasil utama adalah Indeks Gejala Prostatitis Kronis Institut Kesehatan Nasional (NIH-CPSI) dan analisis subkelompok untuk pengguna terapi tiga kali lipat dilakukan untuk meningkatkan interpretabilitas. Analisis dilakukan dengan menggunakan Review Manager 5.3* ***Hasil:*** *Sebanyak 2 RCT, terdiri dari 91 pasien CP/CPPS dianalisis. Analisis gabungan menunjukkan bahwa dibandingkan dengan kelompok terapi oral saja, terapi kombinasi memiliki skor total NIH-CPSI yang lebih rendah secara signifikan pada titik akhir pengobatan (MD -7.46, 95% CI -9.85 hingga -5.07, p<0.001) dan NIH- Skor nyeri komponen CPSI (MD -3.48, 95% CI -5.04 hingga -1.93, p<0.0001), skor keluhan miksi (MD -0.96, 95% CI -1.47 hingga -0.45, p<0.001), dan skor dampak kualitas hidup (MD -2.94; 95% CI -3.68 hingga -2.20, p=<0.001).* ***Simpulan:*** *Penelitian ini mengungkapkan bahwa pasien yang menjalani terapi kombinasi Li-ESWT memiliki skor total NIH-CPSI yang lebih rendah daripada pasien yang menerima terapi oral saja, temuan ini konsisten dengan hasil dari tiap komponen skor: nyeri, keluhan miksi, dan berdampak pada kualitas hidup.*

Kata Kunci: *Li-ESWT, terapi oral, prostatitis kronis.*

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INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a chronic inflammatory disease of the pelvis that often affects men. Patients with CPPS usually complain of hip pain that can be felt in the perineum, suprapubic, testes, or penis. Urinary complaints, such as lower urinary tract symptoms (LUTS) and sexual dysfunction (pain associated with ejaculation) can also be found.[1]

The prevalence of CPPS worldwide is estimated to be around 2-10%. Findings in The USA had mixed results, ranging from 5-9% of the population. The findings in Southeast Asia, which were carried out in Singapore and Malaysia, were 2.5% and 8.7%, respectively. This figure is quite large considering that this incident mostly affects the elderly male population.[2]

The National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) is an index that aims to assess the degree of CPPS severity. In addition, this index can also be used to evaluate the efficacy of therapy given by doctors to patients. The therapy that has so far been applied by doctors to patients often refers to the guidelines made by the North American NIH, as well as guidelines made by the International Consultation of Urologic Disease (ICUD)/World Health Organization (WHO).[3] However, therapeutic failure has been widely reported, so that some recommendations use combination therapy to improve the quality of life of patients.[4]

In recent years, the number of publications regarding the usefulness of Li-ESWT in the management of CPPS has increased, however, a systematic review of existing randomized clinical trials to ascertain the benefits of the method has not been published as of the writing of this study.[5]

OBJECTIVE

This study aimed to compare the efficacy of Low-Intensity Extracorporeal Shockwave Therapy (Li-ESWT) and oral therapy combination compared to sole oral therapy for reducing symptoms in CP/CPPS patients.

MATERIAL & METHODS

All authors independently searched relevant studies in PubMed, Clinicaltrial.gov, and Cochrane Library from their inception until July 2020 using. The search keywords correlated to CP/CPPS and Li-ESWT. Meanwhile, references from all retrieved papers were manually searched for further relevant articles.

This meta-analysis only included randomized controlled trial design study that compares combination therapy to pharmacological therapy only. And excluding the study with designs like case-control, cross-sectional, cohort, and non-randomized trials. The inclusion and exclusion criteria are presented in table 1.

Data were independently extracted from each study applying a standardized form by all reviewers and cross-checked. Any disagreement was resolved by a discussion between the authors. If the authors could not reach a consensus, another author was consulted to resolve the dispute and decide on a final decision.

The quality of the included RCTs was assessed by the Cochrane Risk of Bias Tool, assessing random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

The means and standard deviations were calculated using statistical algorithms described by

Table 1. Inclusion and exclusion criteria of the research.

Inclusion	Exclusion
Randomized controlled trials (RCTs)	Research review articles
Studies using Li-ESWT therapy, oral therapy (alpha-blockers, phytotherapeutic, anti-inflammatory, PDE-5 inhibitors, and/or antibiotics), combination pharmacotherapy and Li-ESWT in patients with CPPS.	Research in the form of abstract only
In the journal, provide the results of the NIH-CPSI total score as an outcome.	Using Li-ESWT with pulse size less than 3000
Li-ESWT with large size 3000	Research with male subjects aged under 18 years
Research with male subjects aged more than 18 years	Li-ESWT interventions less than once a week

Hozo et al for studies that presented continuous data as median and range values.[6] Random-effects model was used if there was evidence of heterogeneity between the studies, based on the $\chi 2$ test for heterogeneity and the I2 test. A P-value < 0.10 and an I2 value > 50%, respectively, were considered high. Otherwise, the fixed-effect model (Mantel-Haenszel) was selected. Analysis was performed using the statistical software Review Manager version 5.3.

RESULTS

The Prism results flowchart revealed 2 studies involved in this meta-analysis comparing Li-ESWT with pharmacological therapy alone. From the data presented by each - the study was then analyzed and presented in the Forest plot. Heterogeneous research data will be analyzed using a random effect model, while homogeneous data will be analyzed using a fixed effect model. The flow of this research is briefly described in the Prism Flowchart in Figure 1.

All studies selected through screening according to the PRISMA plot in Figure 1 for qualitative and quantitative analysis are presented in tabulations in Table 2. The data presented are the name of the researcher, the year the article was published, the study design, the number of patients, the intervention, the additional therapy, the Li-ESWT protocol, the control time, and the difference in the total score difference between the total NIH-CPSI Li-ESWT score and placebo. Overall, there were 91 patients from both studies. Of the therapies given, there were additional therapies that differed between the 2 studies. The alpha-blocker drugs used were Doxasozin 4 mg/day and Tamsulosin 0.4

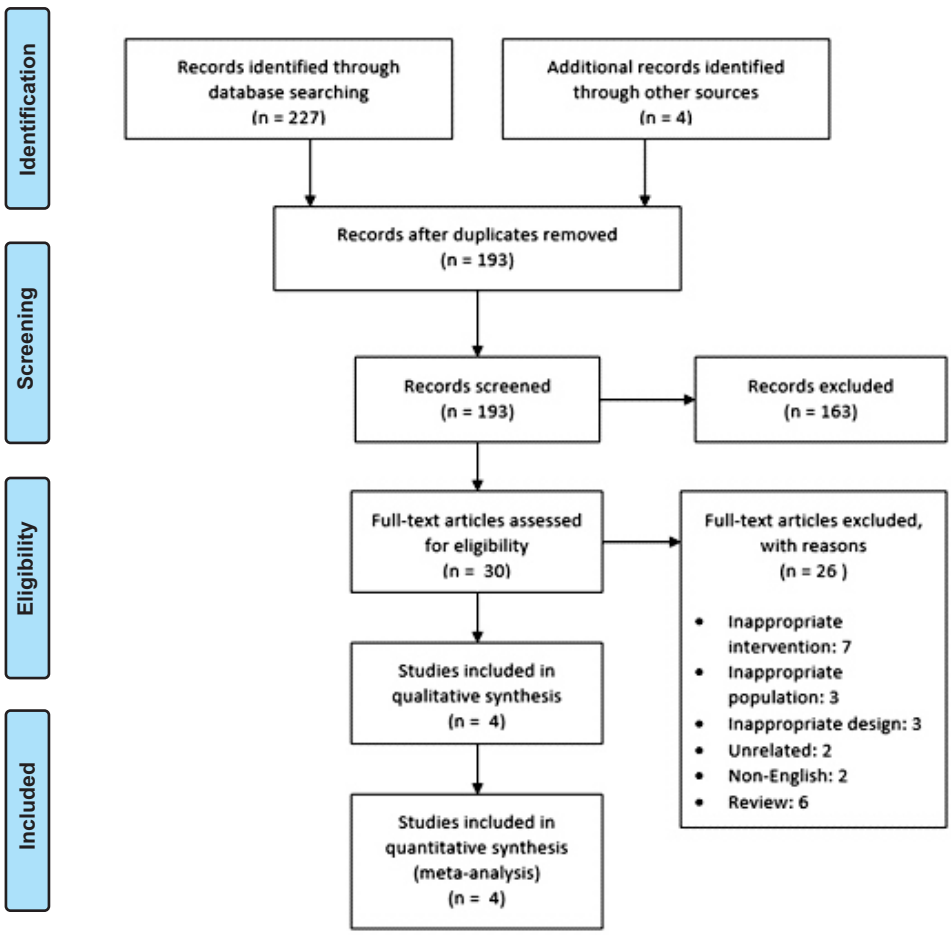

Figure 1. PRISMA flowchart.

mg/day. The anti-inflammatory drugs used were Ibuprofen 400 mg/day and Diclofenac 100 mg/day. The muscle relaxants used were Thiocolchicoside 12 mg/day and Baclofen 2x10 mg/day. In the second study, the antibiotic Ofloxacin 2x300 mg/day for 2 weeks was given to patients while in the first study both groups of patients were not given antibiotics.

This meta-analysis involved 2 studies comparing Li-ESWT with controls. The two studies involved 348 research subjects, divided by 175 as the treatment group and 173 as a control group. From the overall meta-analysis, the data is quite homogeneous based on the results from I2, so the analysis uses a fixed effect model. The components assessed in this meta-analysis were the total NIH-CPSI score, pain score, urinary complaint score, and quality of life score 12 weeks after therapy administration.

Two studies evaluated the total score of NIH-CPSI including 91 participants (46 in the combination group and 45 in oral therapy) were enrolled in the meta-analysis. Pooled data revealed that the total score of NIH-CPSI in the combination group was significantly lower than in the oral therapy group at the endpoint of the treatment (MD -7.46, 95% CI -9.85 to -5.07, $p < 0.001$). Based on our analysis, heterogeneity was not found ($I2 = 0.00\%$). among the trials and thus a fixed effects model was selected (Fig. 2).

Two studies including 91 participants (46 in the combination group and 45 in the oral therapy only) estimated the NIH-CPSI pain score 12 weeks after the treatment. According to our analysis, heterogeneity was not found among the trials and thus, a fixed effects model was chosen. Pooled analysis showed that there was a significant lower in the combination group compared to the oral therapy only group (MD -3.48, 95% CI -5.04 to -1.93, $p < 0.0001$).

Compared to the oral therapy only group a significant lower was observed in NIH-CPSI urinary score (MD -0.96, 95% CI -1.47 to -0.45, $p < 0.001$) in combination group. There was an indication of homogeneity ($I2 = 39\%$), thus a fixed effect model was chosen.

Table 2. Research subject's characteristic.

Study	Year	Design	Patients	Intervention	Additional therapy	Li-ESWT protocol	Follow Up	Total Score difference
Pajovic et al.	2016	Monocentri RCT Type IIIB CPPS Placebo Control	60	Focused Li ESWT KM 2000 S	Alpha -blocker Anti-inflammation Muscle relaxant	1x/week 12 weeks therapy 3000 pulses, 3Hz	12th weeks	6.64 (40% reduction)
Rayegani et al.	2020	Monocentric RCT Type IIIB CPPS Placebo control	31	Focused Li ESWT Duolith SD1	Alpha -blocker Anti-inflammation Muscle relaxant Antibiotic	1x/week 4 weeks therapy 3000 pulses, 3Hz	12th weeks	8.15 (38% reduction)

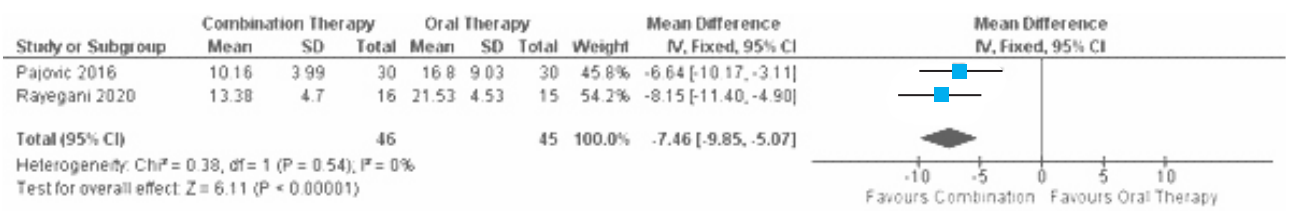

Figure 2. Forest plot of NIH-CPSI Total Score after 12 weeks.

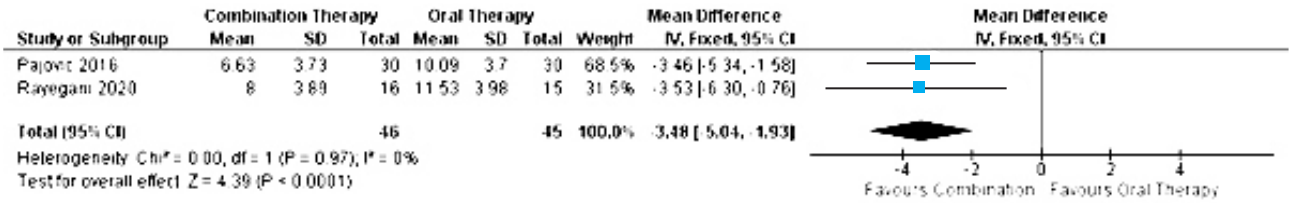

Figure 3. Forest plot of NIH-CPSI Pain Score after 12 weeks.

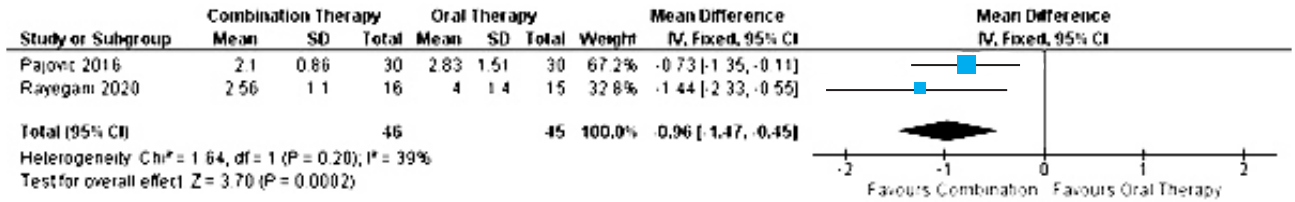

Figure 4. Forest plot of NIH-CPSI Urinary Score after 12 weeks.

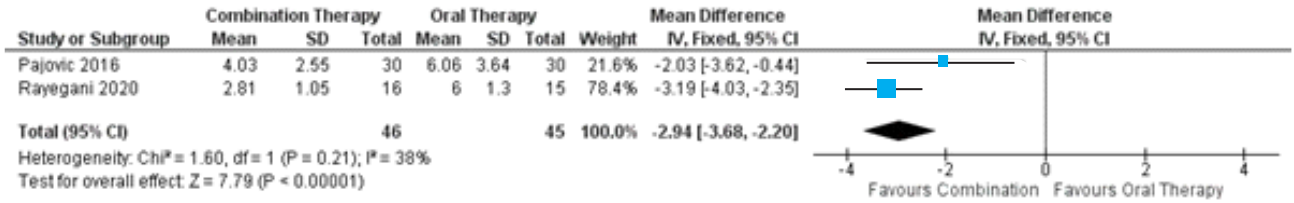

Figure 5. Forest plot of NIH-CPSI QOL Impact Score after 12 weeks.

The significant difference was found in term of NIH-CPSI QoL impact 12 weeks after the treatment given (MD -2.94; 95% CI -3.68 to -2.20, p=<0.001), the combination group had lower score compared to oral therapy only group. Based on our analysis, homogeneity was found among the trials (I2 = 38%), and thus a fixed effects model was selected.

DISCUSSION

CP/CPPS is a chronic pelvic pain condition that can cause pain persistently without a clear etiology or clear clinical pathology.[7] The pathophysiology of CP/CPPS is not fully known, some popular hypotheses include pelvic floor hyperactivity, infection-related pain at nociceptors, neurological disorders, and changes in local biochemical reactions.[8-9] The most common treatment alternatives are pharmacotherapy, such as α-receptor blockers, gram-negative antibiotics, analgesics like non-steroidal anti-inflammatory drugs (NSAIDs), and 5α-receptor reductase inhibitors used either as a monotherapy or in combination with other therapies.[10] However, it has been shown that monotherapy alone cannot reach the expected clinical spectrum, even some suggesting that success rates can only be achieved with a combination of three different therapies.[11]

Extracorporeal Shockwave Therapy (ESWT) has long been used as standard therapy for urological patients, especially in lithotripsy.[10] Since a decade ago, it has been proven previously that Li-ESWT can alleviate erection complaints.[12] It has also shown promising results for other diseases such as pain in the field of orthopedics.[13] The study of Li-ESWT in CP/CPPS has improved significantly in recent years, indicating that Li-ESWT is increasingly accepted by patients and physicians as a treatment tool for CP/CPPS.

Meanwhile, the mechanism of how it can lead to improvement has not been fully explained by Li-ESWT. Several proposed mechanisms are aimed at disrupting the movement of nerve impulses by hyperstimulation of nociceptors, re-vascularization of tissues, and loss of muscle tone.[14] Compared with lithotripsy in urolithiasis, which is characterized by high and strong energy to break body stones, Li-ESWT for CP/CPPS has a unique biological effect even though it uses low energy.[15]

In addition, Li-ESWT mediates the conversion in cells and tissues from mechanical stimuli to complex biochemical signals and changes. As the waves travel through the tissue, they cause extracellular cavitation as well as mechanical stimulation. The result is damage to nerve cell membranes and transmission of pain signals disruption. Mariotto et al. reported that the wave can induce the synthesis of nitric oxide (NO), which is one of the wave effectiveness mechanisms for inflammatory reactions.[16] Because NO plays an important role in the formation of neuromuscular junctions such as synaptic plasticity and nerve transmission in the peripheral nervous system.

In addition, disrupting the flow of nerve impulses by stimulating nociceptive receptors and reducing muscle tone is also a potential mechanism for the use of Li-ESWT in CP/CPPS.[8-9] Even though the brands of Li-ESWT device used in the two analyzed studies were different, Duolith SD1 T-TOP made by Storz Medical from Switzerland and Lubisone KM-2000 S from South Korea, the impulse settings used was the same, which was 3000 with a total energy of 0.25 mJoule/mm^2 and a frequency of 3 Hz. The same specifications from the two different brands will provide a similar therapeutic effect.[17]

The results assessed in the current study were the NIH-CPSI score and the domains that included pain, urinary complaints, and effects on quality of life. This scoring system is commonly used to assess the symptoms and severity of CP/CPPS.[18] Data from pooled RCTs showed significant improvement of the total NIH-CPSI score 12 weeks after the combination treatment (MD -7.46, 95% CI -9.85 to -5.07, $p < 0.001$). These findings showed positive results of the combined Li-ESWT therapy. Similar results were found in another study, showing improvement in the combination Li-ESWT and oral therapy groups. These results are consistent with the study conducted by Salama & Abouelnaga.[19]

The combination group had a smaller score than the oral therapy group, which showed treatment success and symptom improvement. However, there is one study that stated that there is worsening in the control group over time. This is in accordance with the chronic course of the disease.[20]

One study reported that pain and urinary complaints were predictors of quality of life, where the pain had a stronger effect on the quality of life than urinary complaints. It is a consideration that the main therapeutic goal is pain relief which is an effective method for CP/CPPS.[21] In the present study, the use of combination therapy reduced pain complaints significantly in patients undergoing combination therapy compared to the oral therapy group alone (MD -3.48, 95% CI -5.04 to -1.93, $p < 0.001$). Regarding urinary complaints, the combination group had significantly fewer complaints than the oral therapy group (MD -0.96, 95% CI -1.47 to -0.45, $p < 0.001$). CP/CPPS patients with urolithiasis also complained of urinary symptoms. However, the interpretation of the urinary score is limited because it is subjective, similar to IPSS.[20]

Based on these findings, we could not determine whether Li-ESWT therapy is suitable for urinary complaints. It is necessary to carry out further examinations focusing on urinary conditions which can be done using uroflowmetry or urodynamic evaluation. Pajovic et. al evaluated voiding condition objectively using PVR and Qmax, resulting in a significant PVR difference between Li-ESWT and control group 12 weeks after therapy (26.3 vs 28.3; $P < 0.05$) and 24 weeks after therapy (32.03 vs 35.21; $P < 0.05$), and Q-max results in 12 weeks after therapy (15.55 vs 13.05; $P < 0.05$).[17] Thus, these results are in line with the research of Tripp et al. who claimed that pain and urinary symptoms were in line with the quality of life. This study also found significant results (MD -2.94; 95% CI -3.68 to -2.20, $p = < 0.001$).[21]

Regarding adverse events, although there were many incidents in the ongoing study, only one study reported minor eye blur, GI complaints, and postural hypotension. These findings support the safety of Li-ESWT for CP/CPPS therapy.[17] Previous studies have shown the effect of using Li-ESWT is highly dose-dependent, which suggested that wave energy has a strong effect on the outcome. Energy density and wave strength were quantitatively calculated prior to implementation in clinical studies. The efficiency of the therapeutic regimen needs further research to assess optimal results for Li-ESWT.[22]

In this study, we performed a subgroup analysis to evaluate the effect of Li-ESWT in patients who had been given triple therapy which is a recommendation from the European Association of Urology (EAU).[11] This study has several limitations, one of which was that the number of clinical research samples used is small. This is due to the limited number of randomized clinical trials comparing Li-ESWT therapy as combination therapy for CPPS with monotherapy. The second limitation is the duration of the study for only 12 weeks. Longer studies can be used to evaluate the long-term effects

of therapy and to look for possible side effects. In this study, the Li-ESWT therapy regimen varies between studies due to the administration of different antibiotics and anti-inflammatory agents.

CONCLUSION

This review revealed that patients undergoing combination Li-ESWT therapy have lower total NIH-CPSI scores than patients receiving oral therapy alone, this finding is consistent with each component of the score: pain, urinary symptoms, and impact on QoL.

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