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Low-intensity extracorporeal shock wave therapy for Peyroniès disease: a systematic review and meta-analysis

Guizhong Li[1*], Xiao Xu[1] and Libo Man[1]

Abstract

Background A systematic review of the evidence was conducted to assess the efficacy of low-intensity extracorporeal shock wave therapy (LI-ESWT) for patients with Peyronie`s Disease (PD).

Methods A comprehensive search of the Cochrane Registry, PubMed and Embase databases was conducted to identify all controlled trials, including randomised controlled trials (RCTs), cohort studies and case-control studies, focusing on the efficacy of LI-ESWT in treating PD, and published before February 2023. The size of plaques, curvature deviation, visual analog scale [VAS] and International Index of Erectile Function (IIEF) were the most commonly used tool to evaluate the treatment effectiveness of LI-ESWT.

Results There were 7 studies including 475 patients from 1999 to 2023. The meta-analysis of the data revealed that LI-ESWT could considerably enhance the proportion of men experiencing a reduction in penile plaques (RD 0.27, 95% CI: 0.04–0.50, $P=0.02$), improvement in penile curvature (RD: 0.13; 95% CI, 0–0.26; $p=0.05$), alleviation of pain (RD 0.22, 95% CI: 0.01–0.42, $P=0.04$), and complete remission (RD 0.38, 95% CI 0.23–0.52, $P<0.00001$). However, there were no significant differences in improvement of sexual function (MD: 1.44; 95% CI, -3.10–5.97; $p=0.53$) between LI-ESWT and the placebo group.

Conclusions According to these studies, LI-ESWT has the potential to decrease plaque size and improve penile curvature or pain in men with PD. The publication of robust evidence from additional well-designed long-term multicenter randomized controlled trials would provide more confidence regarding use of these devices in patients with PD.

Keywords Peyronie's disease, Shock waves, Plaque, Penile deviation, Erection, Controlled trial, Meta-analysis

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Introduction

Peyronie's disease (PD) is a prevalent disease in men. It is the progressive fibrodegeneration of the tunica albuginea. The incidence rate is 22.4–25.7 per 100,000 men, with the highest incidence in men aged 50–59 year [1]. Patients typically exhibit symptoms such as penile pain, deviation, palpable plaques, and erectile dysfunction (ED) [2]. Conservative treatment is the main treatment method at present. Intralesional injections of Collagenase Clostridium histolyticum(CCH) are FDA approved as a nonsurgical treatment for men with PD. The Investigation for Maximal Peyronie's Reduction Efficacy and Safety (IMPRESS) I and II trials were instrumental in demonstrating the efficacy and safety of CCH [3]. There is lack of strong evidence to support the utilization of alternative local treatments, including calcium channel blockers, hyaluronic acid and mechanical therapies [4]. In 1980, Extracorporeal Shock Wave Therapy (ESWT) was initially utilized [5]. low-intensity extracorporeal shock wave therapy (LI-ESWT) has been used to treat conditions such as non-healing wounds [6], myocardial infarction [7], musculoskeletal disorders [8], and erectile dysfunction [9]. Several reports, which have been published since 1996, have demonstrated successful outcomes in decreasing pain and improving ED in PD patients [10, 11]. However, certain research indicates that LI-ESWT cannot improve the curvature of the penis or alleviate pain in men with PD [12–14]. The aim of this study was to to scrutinize and analyze the available information to assess and determine the effectiveness of LI-ESWT in the management of PD. In accordance with the the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) report checklist, we submit the following articles [15].

Methods

Search strategy

PubMed and Embase databases and the Cochrane Register were searched for articles on LI-ESWT and PD using keywords:"Peyronie's," "Peyronie's disease," "ESWT," "extracorporeal shockwave therapy," and "shock wave therapy." We analyzed the therapeutic effect of LI-ESWT on PD patients and the correlation between efficacy, protocol and setting parameters. Additional data were obtained by searching relevant conference abstracts, article reference lists, and contacting article authors using the methods recommended by the PRISMA guidelines [15]. The flow chart of study selection is shown in Fig. 1.

Inclusion and exclusion criteria

The inclusion criteria consisted of full articles of all controlled clinical trials that examined the impact of LI-ESWT on PD patients and were published before February 2023. Exclude all comments, case reports, animal studies, publications, literature reviews, and single arm studies.

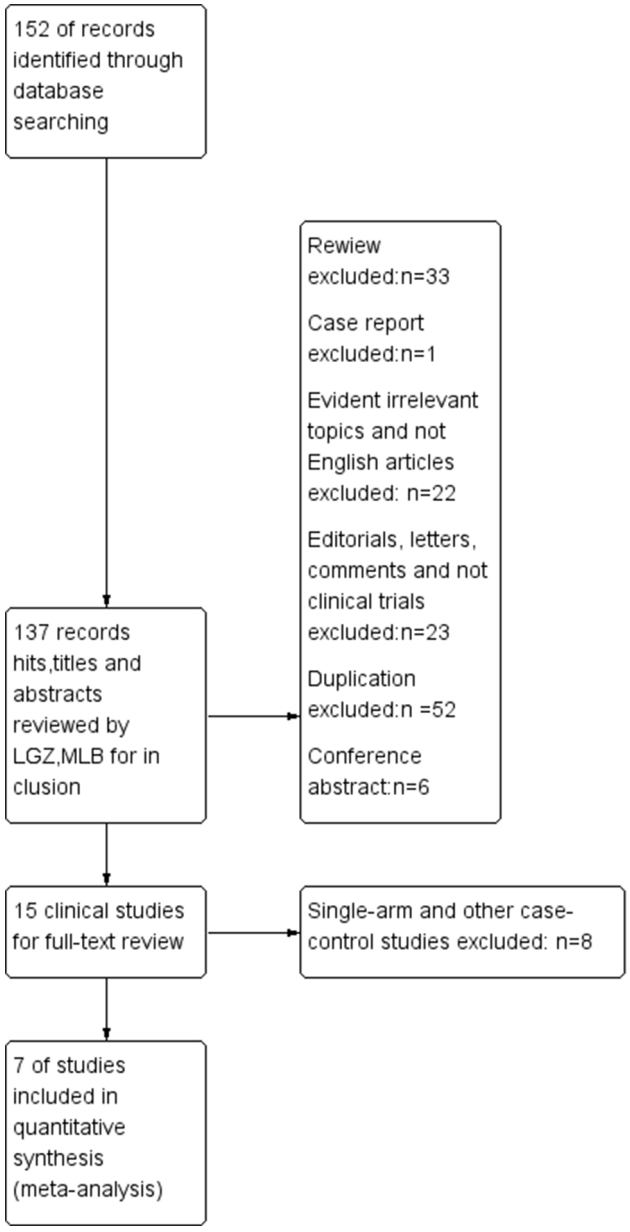

Fig. 1 Flow diagram of study selection. 152 records were identified. After review, 7 controlled trials on LI-ESWT and PD were included in the meta-analysis. LI-ESWT = low-intensity extracorporeal shock wave treatment; RCT = randomized controlled trial

Data extraction and synthesis

Three authors conducted an independent review of the articles to determine eligibility according to a standardized form, with discrepancies resolved by consensus or consultation with a third researcher. Manually extracting the study details, penile deviation angle, setup parameters of the LI-ESWT machine, treatment protocols, erectile function assessment and pain scale were extracted

from each study, and the data were verified by two authors. Follow-up data were also obtained from these studies. Outcomes data revealed alterations in penile deviation angle, plaque size, erectile function score, and pain degree. The primary outcomes were plaque reduction and improvement in penile curvature.The secondary outcomes included pain reduction and complete relief, as well as improvement in sexual function.

Statistical analysis

RevMan 5.3 software (Cochrane Collaboration, London, UK) was used for statistical analysis. Continuous variables were analyzed using the weighted mean difference (MD) and 95% CI. The risk difference (RD) and a 95% confidence interval (CI) were calculated for discontinuous variables. The I^2 test assessed the heterogeneity in effect size among studies. A fixed-effects model analyzed data without significant heterogeneity ($p>0.05$, $I^2 \leq 50\%$). Data with heterogeneity were analyzed by a random-effects model. The forest plots were used to present the results of the meta-analysis. Funnel plots indicate publication bias. The Cochrane Collaboration tool was used to assess the quality of the studies and the risk of bias (shown in Figs. 2 and 3). Of the 7 studies [10–14, 16–17], only 3 did not utilize a randomization method [10, 12, 13]. Most of the studies mentioned the closed-envelope method or computer generated sequence. Only Palmier A et al. did not describe how the doctors were blinded to participants' allocation [11]. Blinding of the physician would be difficult to maintain because the LI-ESWT output energy would need to be reduced to zero or be prevented the delivery of shockwaves using a different stand-off for the shockwave device for patients in the control group receiving sham treatment. Only Palmier A et al. [11] did not describe the process of ensuring double-blinding. As shown in Figs. 3, 62.5% of the studies displayed a distinctly low risk of bias in randomization,

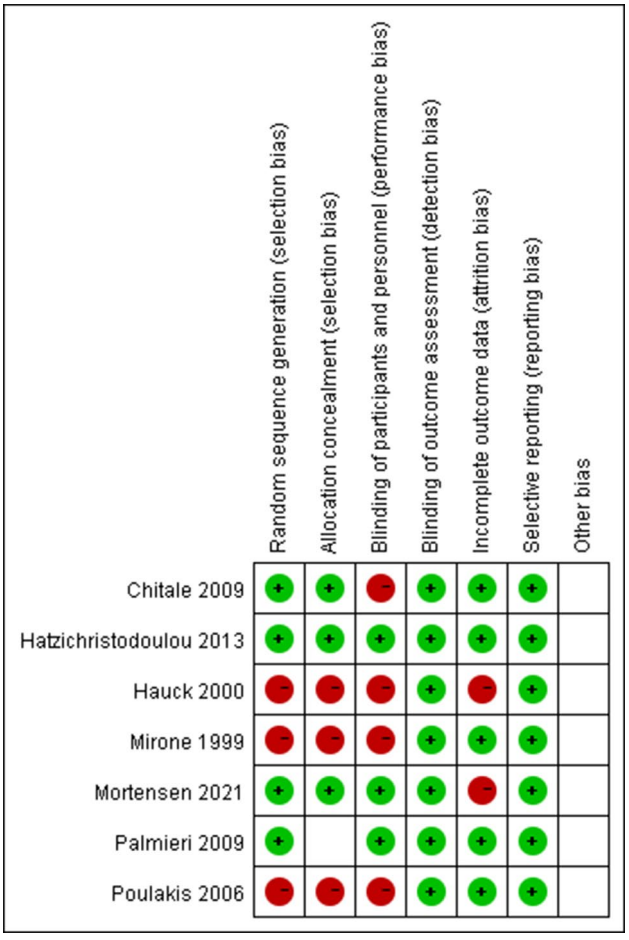

Fig. 2 Risk of bias summary: review authors' judgments about each risk of bias item for each included study

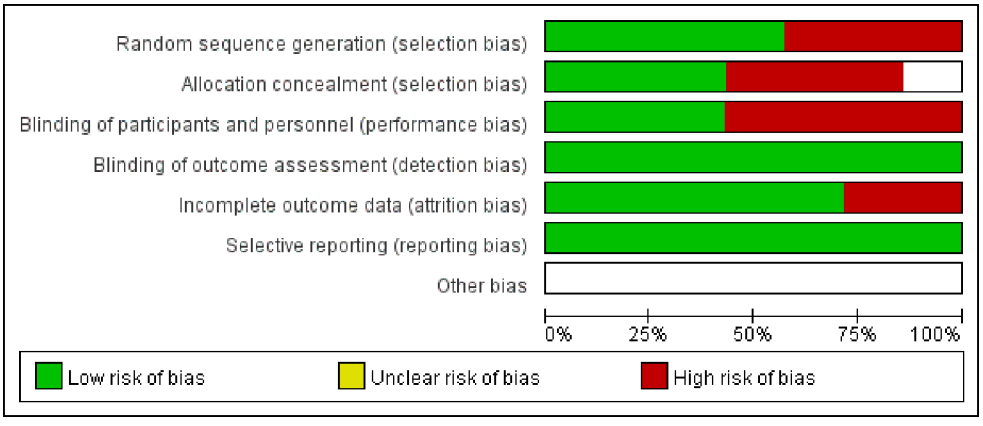

Fig. 3 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

while 50% of the studies had effective blinding in both patient and doctor.

Results

The review comprised of seven studies involving 475 patients who received treatment with diverse medical devices across various countries. Details of the studies are shown in Table 1. Two were case-control studies [12, 13], One was cohort study [10] and four were RCTs [11, 14, 16–17]. One were retrospective [13] and six were prospective studies [10–12, 14, 16–17]. In the five RCTs, a blind method was utilized; two study was single-blind [16, 18] and the other two were double-blind [11, 14]. The majority of patients received treatment without the use of anesthesia or sedation. Furthermore, one study reported comparisons among three groups, however, we extracted only the comparison between LI-ESWT and simple drug therapy [10]. In the study of Mortensen J et al., both study groups were provided with a vacuum pump at baseline / inclusion date and directed to complete manipulation exercises daily for 10–15 min the next 6 months [17].

The criteria for patient inclusion were established on the basis of different specific requirements [10–14, 16–17]. Some studies emphasized a duration of symptoms history of over 3 months [13, 16–17]. Some studies reported a medical history of up to 12 months

Table 1 Current studies of low-intensity extracorporeal shock wave treatment for Peyronie`s Disease patients

Study	Year of publication	Design	Patients		Therapy for control group	Energy (mJ/mm^2)	Frequency (Hz)	Sessions and duration	System for ESWT	Follow-up
			ESWT	Control						
Mirone et al. [10]	1999	CS	21	73	Verapamil (perilesional or intralesional injection)	NA	NA	Three times a week and 20 min each time for 6 months	Minilith™ SL1 lithotripter (Storz Medical AG, Kreuzlingen, Switzerland)	0
Hauck et al. [12]	2000	CCS	20	23	Oral placebo drug	0.35 mJ/mm^2	2	Two sessions within 3 days and repeated after 3 month	'Storz Minilith™ SL1'lithotripter	An average of 8.5 months for ESWT group and exactly 6 months of control group
Poulakis et al. [13]	2006	CCS	53	15	No treatment	0.07–0.17	NA	A minimum of three sessions, and most of the patients received five sessions at weekly interval	Piezoson™ 100 lithotripter (Richard Wolf, Knittlingen, Germany)	1, 3 and 6 months
Palmieri et al. [11]	2009	RCT	50	50	Sham treatment	0.25	4	12 min once weekly for 4 consecutive weeks	Storz Duolith® ESWT system (Storz Medical AG, Switzerland)	12 and 24 week
Chitale et al. [14]	2009	RCT	16	20	Sham treatment	3000 shock waves at level 25	NA	Once weekly for 6 weeks	NM	6 months
Hatzichristodoulou et al. [16]	2013	RCT	51	51	Sham treatment	0.29	3	Six times at weekly	Piezoson™ 100 lithotripter (Richard Wolf)	4 weeks (4–26 weeks
Mortensen et al. [17]	2021	RCT	16	16	Sham treatment	2000 shock waves at 0.5 mJ/mm^2	3	Five times at weekly	Storz Duolith® SD1 (Storz Medical AG, Switzerland)	1,3,6 months

CS: Cohort study; CCS: Case-controlstudy; RCT: Randomized controlled trial; NA: Not available

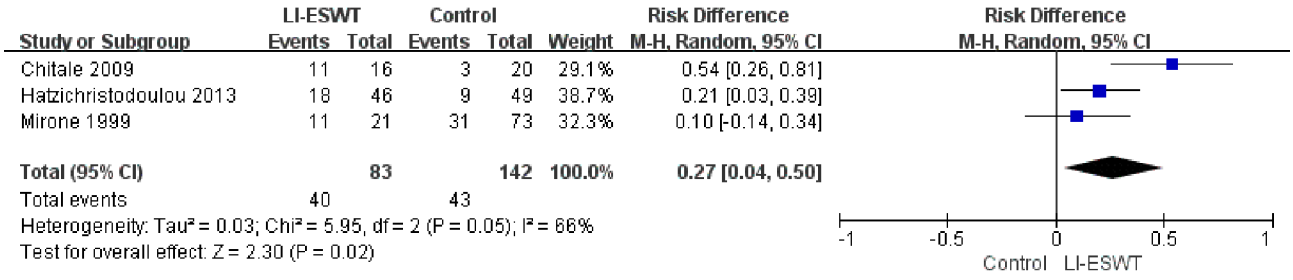

Fig. 4 Forest plot and meta-analysis of lessening of plaque

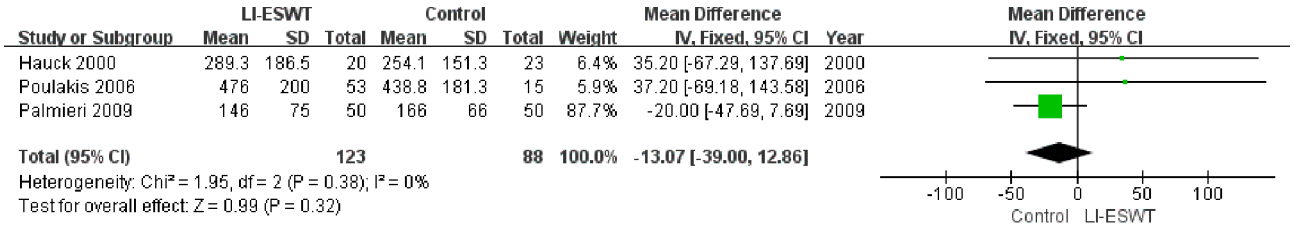

Fig. 5 Forest Plot and pooled data about effect of LI-ESWT on plaque size reduction (in mm^2) vs. placebo

[10–13, 16–17]. In other studies, patients were included for whom drug treatments were ineffective [12, 13, 16]. The studies by Mirone V et al. [10] and Hauck EW et al. [12] used the drug treatment group as the control group, while the other studies used a sham control [11, 13, 14, 16–17]. Three studies have introduced evaluation criteria for assessing the efficacy of treatment [12, 14, 16]. Two studies utilized the primary endpoint of pain reduction at the treatment endpoint, with the secondary endpoints being changes in penile curvature and sexual function [16]. According to the study by hauck EW et al. [12], a successful outcome of therapy was only deemed successful if the deviation angle showed a reduction of more than 30% from its pre-therapy state. However, the primary outcome measures were the difference in the angle of deformity, and the difference in IIEF score before and after treatment; the secondary outcome measures were the difference in VAS before and after treatment and the difference in the response to the GAQ in the study of Chitale et al. [14]. Mirone V et al. and hauk EW et al. employed the Minilith™ SL1 system devices (Storz Medical, Tägerwilen, Switzerland). Palmieri A et al. employed the Storz Duolith® LI-ESWT system (Storz Medical AG, Switzerland) [10]. Mortensen J et al. empoy the Duolith® SD1 devices (Storz Medical, Tägerwilen, Switzerland) [18]. Poulakis V et al. [13], Hatzichristodoulou G et al. [16] used the Piezoson™ 100 lithotripter (Richard Wolf, Knittlingen, Germany). The setup parameters of LI-ESWT varied in different studies. The energy flux density (EFD) in most studies was 0.25–0.29 mJ/mm^2, while only one studies had lower EFDs of 0.07 mJ/mm^2 -0.17 mJ/mm^2 [11–14, 16–17]. The course of treatment was 4–6 weeks [10–14, 16–17].

Lessening of plaques

The size of penis plaque was measured by ultrasonography. Three studies, including 225 patients, reported the results of penile plaque [10, 14, 16]. The combined results of these studies demonstrated a significant increase in the proportion of patients with reduced plaque size in the LI-ESWT group compared to the control group (RD 0.27, 95% CI: 0.04–0.50, P=0.02) (Fig. 4). Compared to the control group, the plaque size reduction used as a quantitative evaluation index in the LI-ESWT group was not significantly improved (MD: -13.07, 95% CI:-39–12.86, P=0.32). (Fig. 5) [11–13].

Improvement of penile curvature

The penis deformity was measured based on the photos before and after treatment.The assessment of penile curvature was reported in 2 styles. The meta-analysis showed that the percentages of patients with penile curvature experienced a significant improvement after undergoing LI-ESWT (RD: 0.13; 95% CI, 0–0.26; p=0.05) (Fig. 6) (10,12,16). According to the meta-analysis, LI-ESWT did not significantly improve the of penile deviation angle in degrees among the treatment groups (MD: -2.14; 95% CI, -7.16–2.87; p=0. 4) (Fig. 7)(11–14,16–17).

Relief and complete remission of pain

The pain degree was assessed using a self-scored visual analog scale, which ranged from 0 (no pain) to 10 (severe pain). The LI-ESWT group had a significantly higher

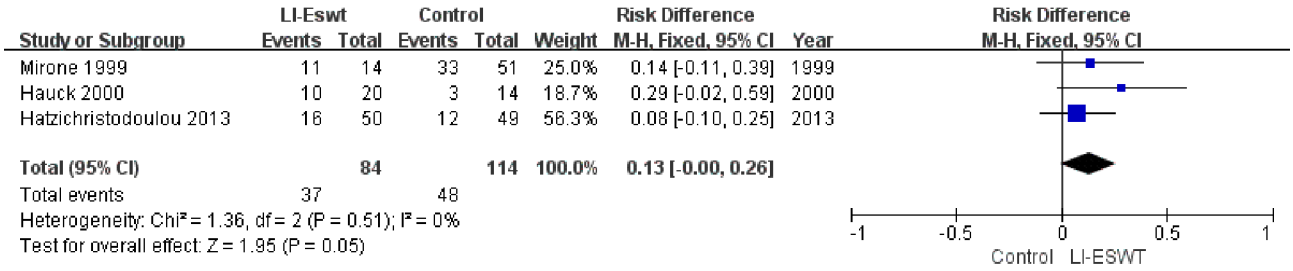

Fig. 6 Forest plot and meta-analysis of improvement of penile curvature

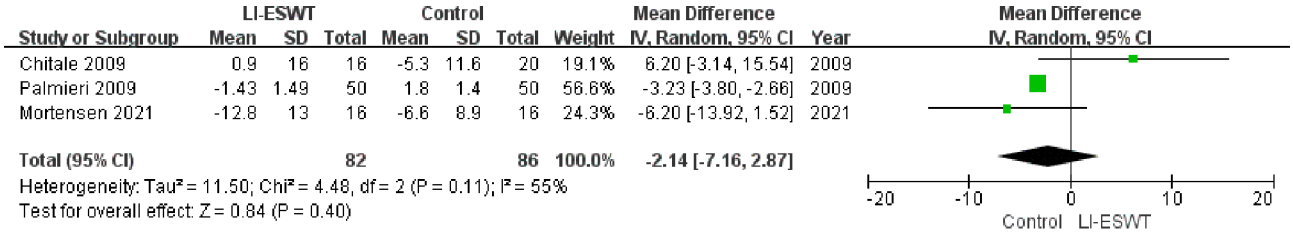

Fig. 7 Forest Plot and pooled data about effect of LI-ESWT on penile deviation angle (in degrees) vs. control

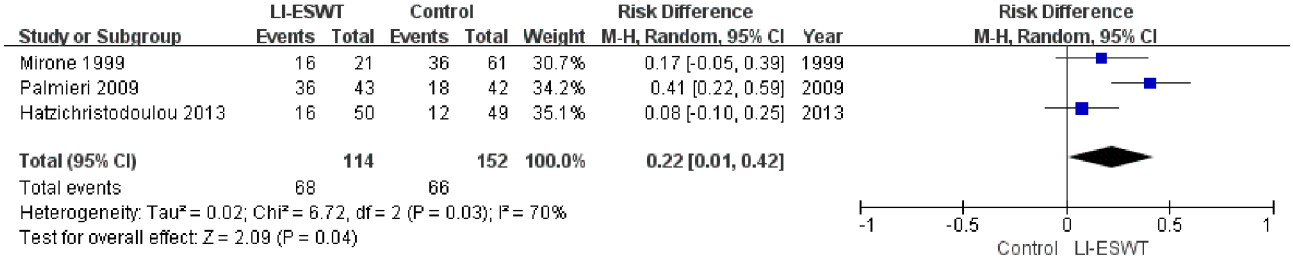

Fig. 8 Forest plot and meta-analysis of relief remission of pain

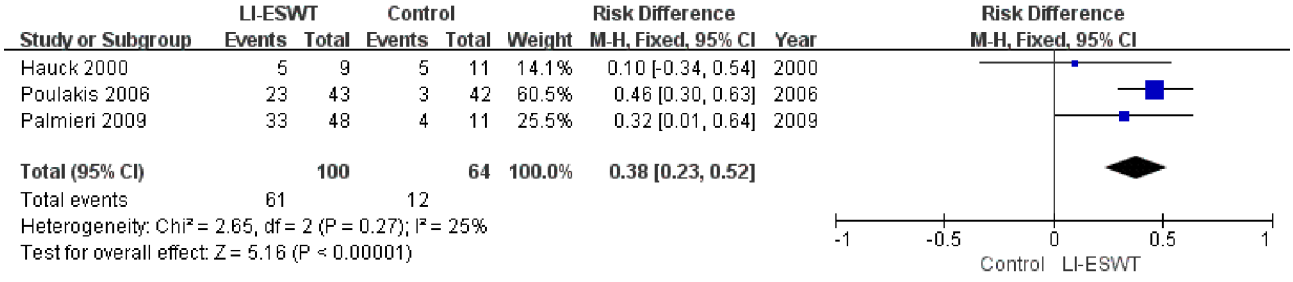

Fig. 9 Forest plot and meta-analysis of completely remission of pain

rate of pain relief (RD 0.22, 95% CI: 0.01 −0.42, *P*=0.04) (Fig. 8) [10, 11, 16] and that of complete remission (RD 0.38, 95% CI 0.23–0.52, *P*<0.00001) compared to the control group (Fig. 9) [11–13].

Improvement of sexual function

In our study, all publications examined reported on the improvement of sexual function based on self-reported questionnaires.The meta-analysis revealed that there was no significant increase in the IIEF of patients in the LI-ESWT group compared to the control group (MD: 1.44; 95% CI, -3.10–5.97; *p*=0.53) (Fig. 10)(13,14). The improvement of sexual function in patients did not exhibit a significant difference between the LI-ESWT group and the control group (RD 0.16, 95% CI -0.06–0.39, *P*=0.15) (Fig. 11) [10–14, 16].

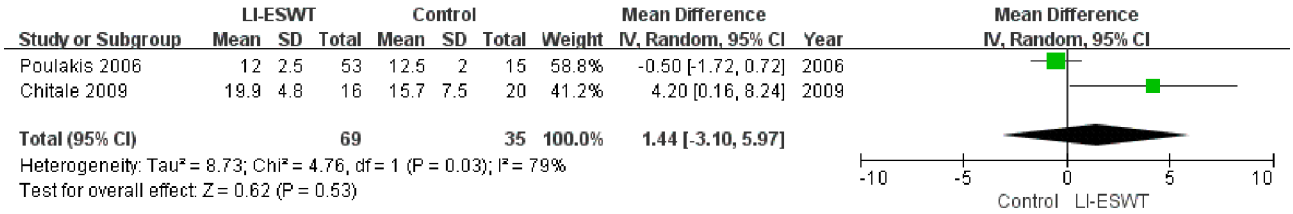

Fig. 10 Forest plot and meta-analysis of improvement of sexual function in IIEF5

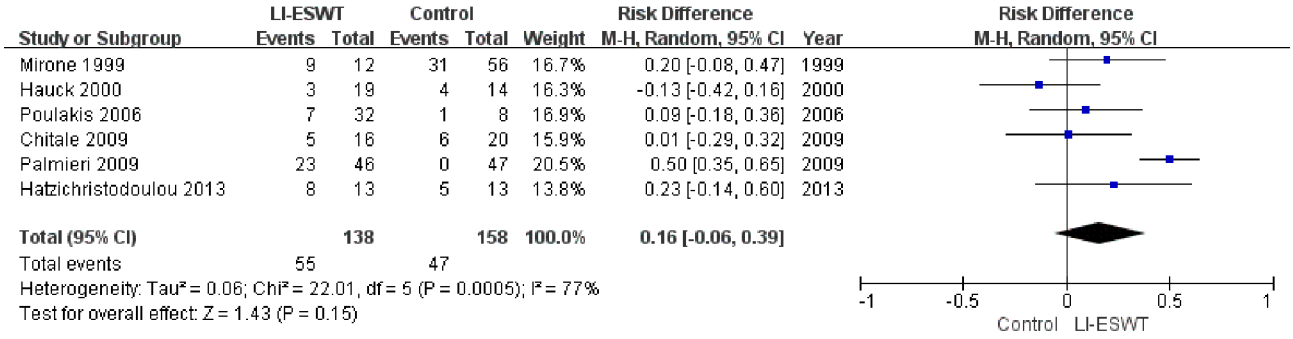

Fig. 11 Forest plot and meta-analysis of improvement of sexual function

Discussion

This systematic review and meta-analysis of 7 studies involving 475 male patients revealed significant improvements in the percentage of men with lessening of penile plaques, penile curvature, relief of pain and complete remission.

Although satisfactory results were obtained from numerous studies, the mechanism of LI-ESWT's effect in PD remains unclear. Numerous studies have demonstrated that LI-ESWs can induce cell proliferation, angiogenesis, and facilitate tissue regeneration [18]. LI-ESW stimulates the focal adhesion kinase, extracellular-signal-regulated kinase, PERK, ATP/P2×7, and Wnt signaling pathways, leading to cell proliferation, endothelial and smooth muscle restoration [19]. It is hypothesized that LI-ESWT may play a significant role in plaque remodelling and direct damage, leading to consecutive resorption of calcification and softer plaque, ultimately resulting in further correction and/or resolution of penile curvature [20]. Second, Research indicates that LI-ESWT enhances the expression of multiple angiogenesis-related factors, such as VEGF, IL-8, stromal cell-derived factor 1, eNOS, CXC motif chemokine 4, and basic fibroblast growth factor. Additionally, it improves tissue perfusion in both clinical trials and animal models(19, 21–22). LI-ESWT enhances penile hemodynamics in patients with PD, and the local circulation may be increased due to the generation of heat caused by this treatment, which can trigger an inflammatory reaction and subsequently enhance macrophage activity, resulting in plaque lysis and resorption [23]. LI-ESWT has the potential to trigger anti-inflammatory responses through the mechanism of mechanotherapy, while also inducing diverse biological responses and immune regulatory pathways. LI-ESWT has the ability to inhibit the production of pro-inflammatory cytokines (such as IL-1α, IL-4, IL-6, etc.), chemokines (like CCL2, CCL12, etc.), and matrix metalloproteinases (MMPs) by stopping their production [18]. LI-ESWT is administered at different time points, and energy has different effects on the inflammatory process [24].

Although we stress that our study is not the first systematic review and meta-analysis to cover the use of LI-ESWT in PD, we believe our study has significant strengths and limitations. In a previous meta-analysis of clinical trials, it was found that LI-ESWT was effective in treating penile pain and sexual dysfunction [20]. However, one important flaw in their analysis, as admitted by the authors, is the heterogeneity of study populations and methods across intervention trials and control groups [20]. According to a meta-analysis published by Fojecki GL et al., two out of three studies on PD reported significant improvement in pain, yet no clinically significant changes were observed in penile deviation and plaque size, however, a meta-analysis was not conducted [25]. The meta-analysis conducted by Gao L et al. concluded that LI-ESWT improved pain, curvature, and plaque size, however, it did not show a statistically significant improvement in erectile function. Nevertheless, the meta-analysis encompassed a limited number of low-quality publications, diverse shockwave generators, varied protocols, and diverse inclusion and exclusion

criteria. While acute side effects were reported, no studies have explored the long-term effects or consequences. The longest follow-up period was 6.5 months [26].

To summarize, the meta-analysis mentioned above included only three randomized placebo-controlled clinical trials. Only one meta-analysis was conducted, which included comparative (nonrandomized) studies along with three randomized controlled trials. Due to the missed majority of required data, a meta-analysis cannot be completed. Bakr AM et al. therefore analyzed the available data and estimated the missing data whenever feasible [27]. They propose that LI-ESWT does not enhance the curvature of the penis or pain in men with PD. However, their study also has limitations. RCTs utilize various metrics to indicate the same outcome.The data that were missed were imputed to satisfy the meta-analysis requirements. Furthermore, there exists a significant amount of data that remains unestimateable [27].

Our meta-analysis presently comprises the outcomes of the most trials. Shalom J's [28] study is the first to report on the long-term results of LI-ESWT for Peyronie's disease, with a mean follow-up of approaching 4 years. Despite the greatest criticism towards this and other LI-ESWT studies being the absence of a control group, their longitudinal data suggest that LI-ESWT has a positive impact on Peyronie's disease, such as a reduction in angulation.The study by Sokolakis I et al. demonstrated that LI-ESWT is a safe and effective treatment option for pain management in both the short- and long term. No significant differences were observed between the two groups in terms of improving penile curvature or sexual function [29].

This systematic review and meta-analysis aimed to investigate the effectiveness of LI-ESWT in treating PD. Nevertheless, our study encountered certain limitations. There is controversy over whether LI-ESWT can reduce plaque size in PD. Some studies hold a negative view [11–13, 16]. Different studies use different measurement methods, including subjective and objective methods, to obtain different conclusions. Shimpi et al.uses both scoring method and ultrasound detection to show that LI-ESWT can reduce plaques [30]. This meta-analysis also shows that shock wave therapy can increase the percentage of men with lessing of penile plaques used as a qualitative evaluation index, which is consistent with the meta-analysis of Gao L et al. [26] and Bakr AM [27]. However, if plaque size is evaluated using objective measurable indicators, there is no significant improvement in plaque size reduction in the LI-ESWT group compared to the control group, indicating that plaque size is notoriously difficult to assess and its impact on peyronie's outcomes is difficult to interpret. The same situation also exists in the utilization of the degree of curvature as a different subjective and objective therapeutic evaluation indicator. Therefore, it also indicates the need for unified and accurate efficacy evaluation indicators in the future.

Most trials had small sample sizes.In our meta-analysis, the largest sample size only consisted of 102 male patients [16]. Regarding patient demographics, several studies have described the selection criteria and previous treatment strategies. Another important limitation of the included studies is their short-term follow-up. Follow-up was typically limited to approximately 6 months for most studies. Therefore, the robustness of this approach remains unknown, and more long-term data are required. In this meta-analysis, the 7 studies comprised 4 randomized controlled trials and 3 non-randomized controlled trials.In the event of any bias, the outcome of this meta-analysis would be significantly impacted.

Furthermore, our study exhibited a remarkably high level of heterogeneity (I^2=55-79%). One possible explanation for this heterogeneity could be the selection of subjects and the subsequent therapeutic regimen. In most studies, the energy flux density (EFD) ranged from 0.25 to 0.29 mJ/mm^2, while only one study had EFDs as low as 0.07 mJ/mm^2 -0.17 mJ/mm^2 [13]. The treatment course lasted for either 4 or 6 weeks. Furthermore, Mirone V et al. [10] and Hauck et al. [12] employed the drug therapy group as the control group to uncover the impact of LI-ESWT. Additionally, it should be noted that PD has a natural onset process, and pain typically subsides as it transitions from the active phase to the stable phase. This to some extent affects the conclusions of research with pain as the endpoint, especially the lack of control group studies.

Extracorporeal shock wave therapy (ESWT) has also been employed for urological indications since the mid-1990s. The conventional shock wave lithotriptors utilize higher energy densities (0.5–0.9 mJ/mm^2) for treatment. The energy range examined in this review is 0.07–0.5 mJ/mm^2, which is not highly accurate and should be categorized as medium to low energy. However, the principal objective of this study is to differentiate it from high energy [31].

In the future, research on LI-ESWT should be based on both basic and clinical science. To comprehend the mechanism of LI-ESWT, extensive fundamental research is required.Several types of equipment are available on the market, each equipped with focused shock sources, including electrohydraulic, electromagnetic, and piezoelectric generators. Different types of equipment require distinct treatment plans. More research is required to assess various devices. There is an urgent demand for well-designed, long-term, multicenter randomized controlled trials to assess the true potential and ultimate usage of such devices in Peyronie`s disease patients.

Conclusion

In this meta-analysis regarding the effectiveness of LI-ESWT in treating PD, it was observed that the percentage of men experiencing lessening of penile plaques, penile curvature, pain relief, and complete remission was higher in the LI-ESWT group than in the control group. Future studies may provide insights into the potential mechanism of action of LI-EWST. Before LI-ESWT can be widely used in the treatment of PD, it is imperative to conduct well-designed long-term multicenter randomized controlled trials to accurately assess the actual potential and ultimate use of these devices using the objective and accurate efficacy evaluation indicators.

Abbreviations

LI-ESWT	Low-intensity extracorporeal shock wave therapy
PD	Peyronie`s Disease
PDQ	Peyronie`s Disease Questionnaire
VAS	Visual analog scale
IIEF	International Index of Erectile Function
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trials
RD	Risk difference
95% CI	95% Confidence interval
MD	Mean difference

Author contributions

(I) Conception and design: All authors; (II) Administrative support: Libo MAN; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Guizhong LI and Xiao XU; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethical approval

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.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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