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REVIEW

A meta-analysis of extracorporeal shock wave therapy for Peyronie's disease

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The efficiency of extracorporeal shock wave therapy (ESWT) for Peyronie's disease (PD) has been controversial for a very long time. We aimed to evaluate the efficiency of ESWT for PD and provide possible evidence on the basis of a meta-analysis of existing comparative studies. All controlled studies, including randomized controlled trials (RCTs), cohort studies and case-control studies, that focused on the efficiency of ESWT for PD, were prospectively identified through comprehensive searches of PubMed, the Cochrane Library and Embase databases. We conducted a meta-analysis of these studies. Six studies including 443 patients were selected for the meta-analysis. Pooling data of these studies showed that ESWT could significantly increase the percentage of men with lessening of penile plaques (odds ratio (OR) 2.07, 95% confidence interval (CI) 1.11–3.85, $P = 0.02$), relief of pain (OR 4.46, 95% CI 2.29–8.68, $P < 0.0001$) and complete remission of pain (OR 5.86, 95% CI 2.66–12.92, $P < 0.0001$). However, insignificant differences were found in improvement of penile curvature (OR 1.88, 95% CI 0.97–3.65, $P = 0.06$) and sexual function (OR 2.22, 95% CI 0.69–7.11, $P = 0.18$) between ESWT and placebo groups. Further, similar results were shown for sensitivity and publication bias analysis when only RCTs were included. However, sporadic complications caused by ESWT were reported, but no patient needed additional treatment aside from conservative observation. ESWT may be an effective and safe treatment for lessening of penile plaques and relieving pain for men with PD, but not for improving of penile curvature and sexual function.

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INTRODUCTION

Peyronie's disease (PD) is a relatively common disorder originating from connective tissue and characterized by progressively fibrotic plaques in the penile tunica albuginea. It is one of the most frequent causes of penile curvature, and change of penile length and diameter during erection, and is often accompanied by pain and/or ED.[1,2] Although PD has been described for over 250 years, its etiology, pathophysiology and treatment are still unidentified.

To date, dozens of therapies have been tried to treat PD, including conservative treatments (oral, intralesional, and topical treatment) and surgery.[3] Though acceptable outcomes would be obtained by intralesional treatment with collagenase, curative effects by conservative therapies have not been definite. Furthermore, although surgery is considered as one of the most effective choices for palliation of PD, it will cause iatrogenic penile shortening and ED.[4] As a topical treatment, extracorporeal shock wave therapy (ESWT) was first used to treat PD in 1989.[5] ESWT was regarded as a promising new choice, and since then, many studies have been conducted to evaluate its efficiency and safety. However, controversial results have been reported.

According to the European Association of Urology guidelines for PD, ESWT fails to improve penile curvature and plaque size, and should not be used with this intent, but it may be beneficial for penile pain.[3] However, evidence from a meta-analysis on this issue is lacking. In this study, we aimed to obtain more definitive results on the efficiency of ESWT for PD through a meta-analysis of comparative studies and a review of the literature.

MATERIALS AND METHODS

In May 2015, two reviewers independently conducted a systematic search of three databases, PubMed, Embase and the Cochrane Library, for all English literature published on or before 20 May without any restrictions. The following MeSH terms and their combinations were searched to identify relevant studies in titles and abstracts: ESW/EST/shock wave/shockwave, Peyronie's disease/Peyronie. All available randomized controlled trials (RCTs) and controlled studies (prospective or retrospective) that compared ESWT with placebo in patients with PD were included for analysis. To supplement these data, the related reference lists from identified documents were also acquired. The levels of evidence of all controlled studies were evaluated using the criteria from the Centre for Evidence-Based Medicine (Oxford, UK).

Data were extracted from the studies and compiled by two reviewers. In case of any disagreement, a consensus was reached by JY after a discussion. When multiple reports described the same population, the most comprehensive or recent one was used. However, data from conference abstracts and papers that were not extractable or the data that were not available for our analyses were disregarded. Moreover, for studies dividing patients into more than two groups, only comparisons between ESWT and placebo were extracted.

All the meta-analyses were performed using Review Manager 5.2 (Cochrane Collaboration, Oxford, UK). The primary outcomes were lessening of plaques and improvement of penile curvature. The secondary outcomes were relief and complete remission of pain, and improvement of sexual function. Statistical heterogeneity

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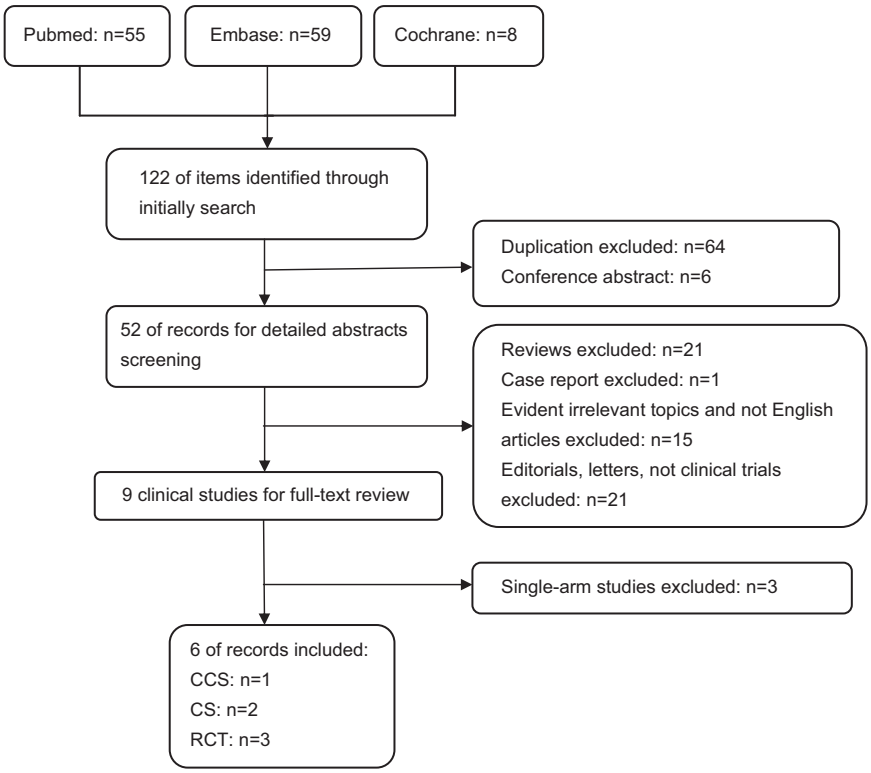

Figure 1. Data flow chart of meta-analysis. CCS, case-control study; CS, cohort study; RCT, randomized controlled study.

between trials was evaluated using the I^2- and χ^2-tests with significance set at *P*-values of < 0.05. I^2 values of 25, 50 and 75% corresponded to low, medium and high levels of heterogeneity, respectively.

Meta-analysis was performed using the fixed-effects method or the random-effects method if significant heterogeneity was observed. The odds ratio (OR) was used to describe results for dichotomous variables. During data extraction, we found few quantitative data available for pooled analysis. Therefore, only dichotomous data were pooled after thorough consideration. All results are reported with 95% confidence intervals (CIs).

RESULTS

In total, 122 items were initially retrieved from three databases, and six comparative studies including 443 men were finally identified[6–11] (Figure 1). Two were case-control studies (level of evidence: 3b),[7,8] one was cohort study (level of evidence: 2b)[6] and three were RCTs (level of evidence: 1b).[9–11] Four were prospective and two were retrospective studies.[7,8]

A blind method was used in the three RCTs; one study was single-blind[11] and the other two were double-blind.[9,10] Most patients were treated without anesthesia or sedation. In addition, one study reported comparisons among three groups, but we extracted only the comparison between ESWT and simple drug therapy.[6] Detailed information and characteristics of each study are summarized in Table 1.

Lessening of plaques

The size of penile plaques was measured using ultrasonography. Three studies including a total of 225 patients reported the results of penile plaques.[6,10,11] The pooled data of these studies revealed a significant lessening of plaque size in the ESWT group compared with the control group (OR 2.07, 95% CI 1.11–3.85, $P = 0.02$). The percentages of patients who experienced a lessening of plaques were 39.8% (33 of 83) in the ESWT group compared with 30.3% (43 of 142) in the control group (Figure 2).

Improvement of penile curvature

Penis deformity was assessed based on photographs before and after treatment. Data describing improvement of penile curvature were pooled from three studies including 198 men,[6,7,11] and revealed that 44% (37 of 84) of patients in the ESWT group experienced a significant improvement of penile curvature compared with 42.1% (48 of 114) of patients in the control group. However, the difference between groups was insignificant (OR 1.88, 95% CI 0.97–3.65, $P = 0.06$) (Figure 3).

Relief and complete remission of pain

The degree of pain was evaluated by a self-scored visual analog scale that ranged from 0 (no pain) to 10 (strong pain). Compared with the control group, in which 51.6% (66 of 128) and 18.8% (12 of 64) of patients experienced relief and complete remission of pain, respectively, the ESWT group presented significantly higher rates with 82.1% (69 of 84) experiencing pain relief (OR 4.46, 95% CI 2.29–8.68, $P < 0.0001$)[6,9,11] (Figure 4a) and 61% (61 of 100) experiencing complete remission (OR 5.86, 95% CI 2.66–12.92, $P < 0.0001$)[7–9] (Figure 4b).

Improvement of sexual function

All publications evaluated in our study reported results regarding sexual function improvement based on self-reported questionnaires. In total, 296 patients with PD had complained of varying degrees of ED, and 39.9% (55 of 138) of patients in the ESWT group had a recovery compared with 29.7% in the control group. However, the difference was not significant (OR 2.22, 95% CI 0.69–7.11, $P = 0.18$) (Figure 5).

Table 1. Basic information and characteristics of studies for meta-analysis

Author	*Year*	*Design*	*Level of evidence*	*Patients*		*Age matched*	*Therapy for control group*	*System for ESWT*	*Energy and frequency*	*Sessions and duration*	*Whether patients received unsuccessful medical therapy*	*Follow-up*
				ESWT	*Control*							
Mirone *et al.*[6]	1999	CS	2b	21	73	N	Verapamil (perilesional or intralesional injection)	Minilith SL1 lithotripter (Storz Medical AG, Kreuzlingen, Switzerland)	NM	Three times a week and 20 min each time for 6 months	NM	0
Hauck *et al.*[7]	2000	CCS	3b	20	23	Y	Oral placebo drug	'Storz Minilith SL1' lithotripter	0.35 mJ mm^{-2} and 2 Hz	Two sessions within 3 days and repeated after 3 months	'Y' for ESWT group and 'N' for control group	An average of 8.5 months for ESWT group and exactly 6 months of control group
Poulakis *et al.*[8]	2006	CCS	3b	53	15	Y	No treatment	Piezoson 100 lithotripter (Richard Wolf, Knittlingen, Germany)	0.07 mJ–0.17 mJ mm^{-2}	A minimum of three sessions, and most of the patients received five sessions at weekly intervals	'Y' for 40% patients in ESWT group and 'N' for control group	1, 3 and 6 months
Palmieri *et al.*[9]	2009	RCT	1b	50	50	N	Sham treatment	Storz Duolith ESWT system (Storz Medical AG)	0.25 mJ mm^{-2} and 4 Hz	12 min once weekly for 4 consecutive weeks	N	12 and 24 weeks
Chitale *et al.*[10]	2009	RCT	1b	16	20	N	Sham treatment	NM	3000 shock waves at level 25 (38 MPa)	Once weekly for 6 weeks	N	6 months
Hatzichristodoulou *et al.*[11]	2013	RCT	1b	51	51	N	Sham treatment	Piezoson 100 lithotripter (Richard Wolf)	0.29 mJ mm^{-2} and 3 Hz	Six times at weekly intervals	Y	4 weeks (4-26 weeks)

Abbreviations: CCS, case-control study; CS, cohort study; ESWT, extracorporeal shock wave therapy; N, no; NM, not mentioned; RCT, randomized controlled study; Y, yes.

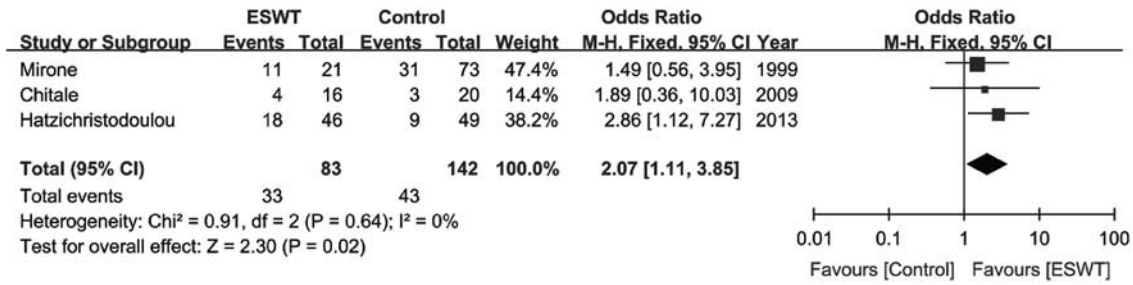

Figure 2. Forest plot and meta-analysis of lessening of plaque. CI, confidence interval; ESWT, extracorporeal shock wave therapy.

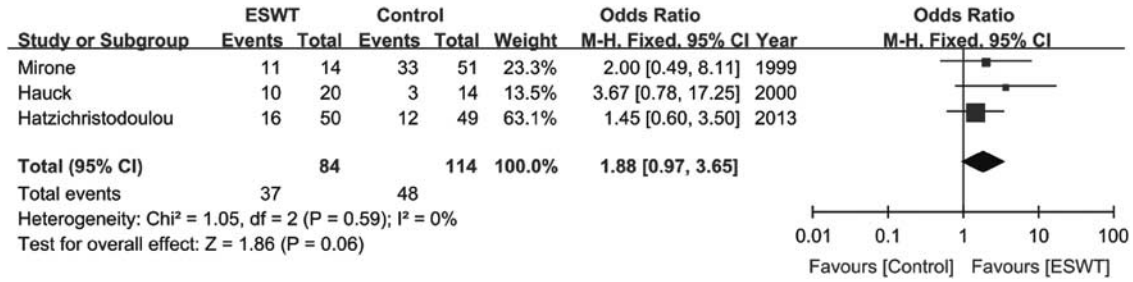

Figure 3. Forest plot and meta-analysis of improvement of penile curvature. CI, confidence interval; ESWT, extracorporeal shock wave therapy.

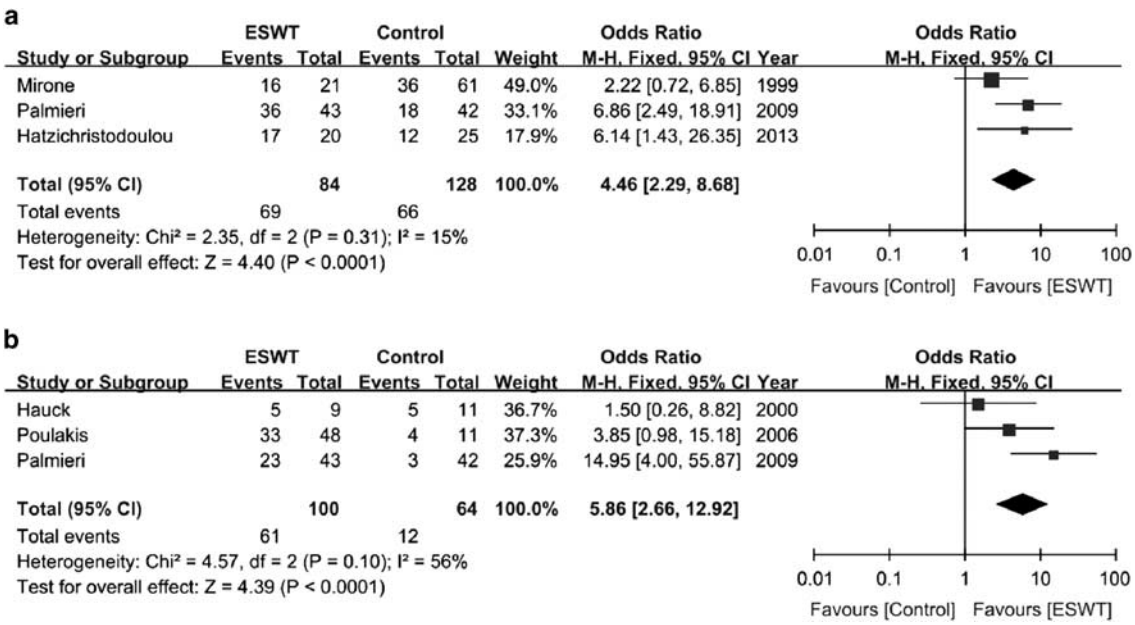

Figure 4. Forest plot and meta-analysis of relief (**a**) and completely remission (**b**) of pain. CI, confidence interval; ESWT, extracorporeal shock wave therapy.

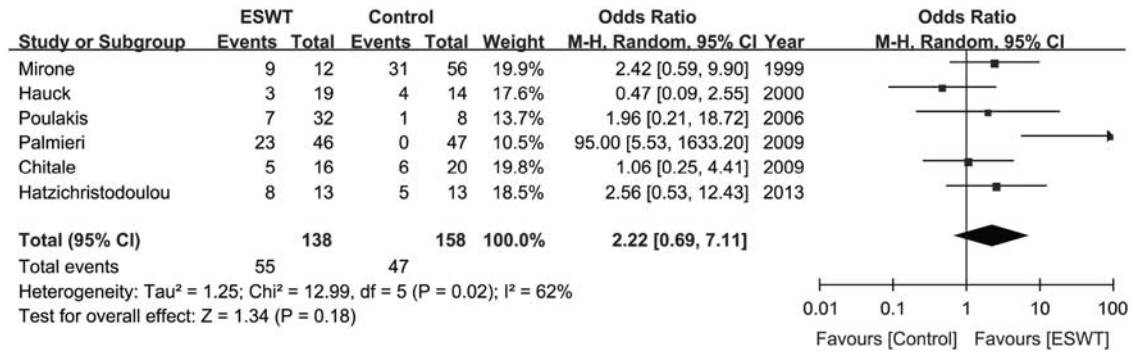

Figure 5. Forest plot and meta-analysis of improvement of sexual function. CI, confidence interval; ESWT, extracorporeal shock wave therapy.

Sensitivity analysis and publication bias

To avoid the bias caused by low-quality studies, only three high-quality RCTs were retained for sensitivity analysis. The meta-analysis of RCTs showed similar results for all parameters (lessening of plaques: OR 2.59, 95% CI 1.15–5.85, $P = 0.02$; relief of pain: OR 6.61, 95% CI 2.87–15.19, $P < 0.00001$; complete remission of pain: OR 14.95, 95% CI 4.00–55.87, $P < 0.0001$). However, more inconspicuous differences could be found when focusing on improvement of penile curvature (OR 1.45, 95% CI 0.60–3.50, $P = 0.41$) and sexual function (OR 4.82, 95% CI 0.45–51.71, $P = 0.19$). Publication bias was excluded using funnel plots.

DISCUSSION

Up to now, little has been known about PD. It is reported that up to 8.9% of the general population has experienced this condition.[12] Furthermore, the prevalence can increase to 20.3% in diabetic patients with ED.[13] Patients with PD often present with three chief complaints: palpable plaque, painful erection and penile curvature. In addition, 18–80% of patients with PD can experience ED.[14]

However, the generation of plaque is obscure. Multiple hypotheses have been put forward, including trauma during intercourse with aberrant healing, genetic predisposition, autoimmune disorder and overexpression of proinflammatory cytokines.[15,16] As the plaque is inelastic compared with normal tunica albuginea, a penile curvature and pain can occur during erection and intercourse. The combination of psychogenic and somatic factors leads to ED and further influences the quality of life of men as well as their partners.

The mechanism of ESWT's effect in PD is unclear, although satisfactory results were obtained from a lot of studies. Two hypotheses have been speculated. First, ESWT may directly damage and remodel penile plaque. Second, local circulation may be increased in consequence of generating heat caused by ESWT, which can result in an inflammatory reaction followed by increased macrophage activity, leading to plaque lysis and resorption.[3]

In our study, significant improvements could be found in the ESWT group for plaque lessening, pain relief and complete remission of pain, whereas effectiveness for penile curvature recovery and sexual function improvement was not obvious. Although the final results may be influenced by low-quality studies, similar results were also found from further analysis based on only RCTs. More interestingly, all RCTs were carried out more recently, which made the results regarding sensitivity analysis more credible.

According to the natural history of PD, most patients will experience disease progression or stabilization, but pain symptoms can be completely resolved with time in 89% men.[3,17] To overcome the interference from pain relief, studies with a comparative or matched design may provide more accurate results. Therefore, our study could avoid this limitation. Furthermore, the effectiveness of ESWT in decreasing erectile pain has also been described by Husain *et al*.[18] Conversely, a large percentage of patients (47%) had an improvement of penile curvature. Furthermore, in a small-scale single-arm study, five patients with PD followed up after unsuccessful medical therapy were recruited for ESWT, and all five patients had achieved softening of plaque and complete pain remission.[19] Moreover, promising results were demonstrated in the trial of Manikandan *et al*.,[20] but a little improvement in erectile function was reported.

In the trial of Hauck *et al*.[21] including 96 patients, significant curative effects could not be found regarding plaque size, penile curvature or sexual function, although possible efficacy in pain relief was shown. In addition, Strebel *et al*.[22] did not recommend ESWT as a primary treatment for PD as they found limited advantages in their study. In addition, a consensus was seemingly reached based on three double-blind RCTs that low-intensity ESWT may improve sexual function.[23–25] However, a combination of ESWT and oral tadalafil used for patients with PD, with accompanying ED, led to satisfactory outcomes in improving sexual function.[14] In a previously exploratory meta-analysis of clinical trials, penile pain and sexual function seemed to be effectively treated by ESWT.[26] However, sexual function improvement was not observed in our pooled data, and evidence from our analysis may be considered more dependable as no RCT was included in the previous meta-analysis.

As a conservative choice for patients with PD, the risks of complications caused by ESWT should be taken into consideration, mainly penile bruising and urethral bleeding. Fortunately, although reported in sporadic studies, these complications were very slight, and no one needed further treatment except for observation. Indeed, the energy used in these trials was relatively low. Furthermore, some reported complications were not caused by shock waves, but by other affiliated procedures, such as catheter insertion.[7] Although higher energy can lead to better results in rats,[27] physicians must be strictly cautioned about using ESWT with higher energy in patients pursuing more effective results. Above all, despite that no severe complications occurred, the safety of ESWT should be confirmed in future studies.

Importantly, several limitations should be considered in our study. First, although our results were pooled from six comparative studies, half of these publications were considered low-quality. However, influences caused by these low-quality publications could be excluded by sensitivity analysis in some degree. Furthermore, outcomes included for analysis were sporadically described by continuous variables, which made a more comprehensive analysis difficult. Regrettably, this limitation could not be avoided in the present study.

CONCLUSION

Results from our meta-analysis revealed that ESWT may be an effective and relatively safe choice for patients with PD with penile plaque and painful erection. However, the efficacy of ESWT could be very limited in patients with penile curvature and ED. More high-quality double-blind RCTs are required to overcome the limitations in current studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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