World J Urol
DOI 10.1007/s00345-016-1834-2

INVITED REVIEW

Extracorporeal shock wave therapy (ESWT) in urology: a systematic review of outcome in Peyronie's disease, erectile dysfunction and chronic pelvic pain

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Received: 7 March 2016 / Accepted: 12 April 2016

Abstract
Purpose The objective was to evaluate high-level evidence studies of extracorporeal shock wave therapy (ESWT) for urological disorders.
Methods We included randomized controlled trials reporting outcomes of ESWT in urology. Literature search on trials published in English using EMBASE, Medline and PubMed was carried out. The systematic review was performed according to PRISMA guidelines.
Results We identified 10 trials on 3 urological indications. Two of 3 trials on Peyronie's disease (PD) involving 238 patients reported improvement in pain; however, no clinical significant changes in penile deviation and plaque size were observed. Four studies on erectile dysfunction (ED) including 337 participants were included. Using International Index of Erectile Function (IIEF-EF) and erectile hardness scale (EHS) data suggested a significant positive effect of ESWT in phosphodiesterase-5 inhibitor (PDE-5i) responders in 2 of 4 trials and 3 of 4 trials, respectively. Three studies on chronic pelvic pain (CPP) engaging 200 men reported positive changes in National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI). There was considerable heterogeneity between trials both with regard to treatment techniques and outcome measures, making it difficult to compare results.
Conclusions ESWT may resolve pain in PD patients, while evidence for reducing curvature and plaques size is poor. Effects of ESWT on IIEF in ED patients are inconsistent; however, data on EHS does imply that the treatment potentially may recover natural erection in PDE-5i responders. ESWT seems to be able to resolve pain in CPP patients in the short term. In all three disease entities, long-term outcome data are still warranted.

Keywords Extracorporeal shock wave therapy · Urology · Systematic review · Peyronie's disease · Erectile dysfunction · Chronic pelvic pain

Introduction

Extracorporeal shock wave treatment (ESWT) was introduced in medicine about 40 years ago [1]. A plausible explanation of the mechanism of how shock waves (SW) affect living organisms remains unknown. Despite several theories addressing the effect of lithotripters [2], these cannot be directly applied to understand the effect of SW on soft tissues. Contrary to lithotripsy, which has a destructive impact on a urinary stone, a regenerative potential of SW on several organs has been suggested. The *mechanotransduction theory* explains the process, how mechanical stimulation is perceived in living cells [3, 4] by synthesis of nitric oxide (NO) and increase in vascular endothelial growth factor (VEGF), thereby creating a potential for treatment of several conditions such as bone non-unions [5, 6], chronic wounds [7, 8], ischemic hearth disease [9, 10] and nephropathy [11].

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Published online: 23 April 2016

The aim of this review was to identify urological disorders that may be treated with ESWT from an evidence-based perspective.

Methods

Protocol registration Our review was registered at PROSPERO database March 10, 2015, registration number CRD42015015665.

Eligibility criteria Randomized, controlled single- or double-blinded studies reporting outcome of treatment with SW for urological disorders were included in the analysis. Manuscripts regarding urinary stone therapy were excluded, since it is an established indication [12]. Articles in English published to the search date were considered. The systematic review was performed according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [13].

Information sources Authors performed systematic literature review of English language literature search on December 22, 2014 using EMBASE, Medline and PubMed databases. Additional search was performed at November 9, 2015. We searched for articles in PubMed with MeSH terms (Ultrasonic Therapy OR shockwave therapy OR ESWT OR extracorporeal shock wave therapy) AND (Male Urogenital Diseases OR Female Urogenital Disease).

In collaboration with a librarian from the University of Southern Denmark, the first author performed the search. No additional sources were identified utilizing references cited in the primarily selected articles and previous review articles on the topic. Records were screened for titles and abstracts by one reviewer (GF). Two independent authors (GF and ST) were involved in full text study selection and data extraction. For this purpose, a data extraction sheet was developed. Discrepancies were resolved by open discussion. We contacted one author for further information, but the author did not reply.

Data items Data extracted from each article included:

1. Number and characteristics of participants (stage of disease and method of diagnosis), inclusion and exclusion criteria.
2. Intervention (type of ESWT device, treatment protocol).
3. Outcome measures.

Risk of bias Pair of reviewers (GF and ST) working independently assessed adequacy of inclusion process, randomization and blinding. Studies in which risk of bias was present received mark b; otherwise, mark a was given (Table 1).

Results

Study selection We reviewed 11 publications, selected from 12,638 initially identified records, which met the inclusion criteria and were eligible for further analysis (Fig. 1). Clinical trials on three urological indications were identified, including Peyronie's disease (PD), erectile dysfunction (ED) and chronic pelvic pain (CPP). Results are presented separately for each disease entity.

Peyronie's disease (PD)

PD is of unknown origin. Prevalence of PD was recently reported between 3.8 [14] and 8 % [15]. Incidence increases with age. The main apparent finding is fibrous plaques that may cause penile deviation, narrowing and distal instability. It may be associated with pain and/or sexual dysfunction. Most common deviation is a dorsal curvature followed by ventral and lateral [15]. Observational studies reveal that only in cases with lack of a compacted calcified plaque, there is a potential for the deviation to diminish; in other cases, it may even progress [16]. Pain is reported to be a self-limiting symptom in almost all cases [16, 17].

Characteristics of studies of ESWT for PD Three [18–20] of 15 [21–33] studies on treatment of PD with ESWT were selected according to inclusion criteria. Studies included 238 patients. Hatzichristodoulou et al. [18] and Chitale et al. [19] included men in stable disease phase, while in the study of Palmieri et al. [20], all cases with symptoms present for a period shorter than 12 months were eligible. Thus, in the latter study, patients in the acute phase of disease also may have been included. Patients in the Hatzichristodoulou et al. [18] trial all had been treated pharmacologically without effect prior to inclusion, while the other two studies applied ESWT as first-line treatment [19]. A Piezoson 100 (Wolf GmbH, Knittlingen, Germany) and a Duolith® device (Storz Medical, Tägerwilen, Switzerland) were used for treatment in two studies, respectively [18, 20], while the third study did not inform about the device used [19]. Study protocol of Hatzichristodoulou et al. [18] was based on a previous

Table 1 Quality assessment

References	Selection of study population	Randomization process reported	Blinding of the patient	Blinding of the healthcare provider	Blinding of the assessor	Outcome measurements	Feasibility study	Risk of bias
[18]	+	+	+	−	?	Penile deviation, plaque size, VAS, sexual function	−	b
[19]	+	+	+	−	+	Penile deviation, plaque size, VAS, IIEF	−	b
[20]	?	?	+	+	+	Penile deviation, plaque size, VAS, IIEF, QoL	−	b
[38]	+	+	+	+	?	IIEF, EHS, hemodynamics	+	b
[39]	?	+	+	+	?	EHS, IIEF	+	b
[40]	+	?	+	+	?	IIEF, EHS	+	b
[41]	+	+	+	?	?	IIEF	+	b
[50]	+	?	+	−	?	NIH-CPSI	−	b
[51]	+	?	+	+	?	IPPS, NHI-CPSI, IIEF-EF, VAS	+	b
[52]	+	?	+	?	?	NIH-CPSI	−	b

VAS visual analog scale, *IIEF-EF* International Index of Erectile Function—Erectile Function Domain, *QoL* quality of life, *EHS* erection hardness scale, *NIH-CPSI* National Institutes of Health Chronic Prostatitis Symptom Index, *IPSS* International Prostate Symptom Score

pilot series while in the studies of Chitale et al. [19] and Palmieri et al. [20] no rational explanation for treatment settings was given. Follow-up period varied from 4 weeks [18] to 6 months [19].

Results of individual studies on PD Overall results of the three included PD studies are presented in Table 2. Hatzichristodoulou et al. [18] showed no statistically significant beneficial effects on sexual function (non-standardized questionnaire) and plaque size. Furthermore, authors were concerned for an increase in penile deviation in the treated group, due to the fact that plaque size increased in five individuals in the ESWT group only. A positive effect on pain using a VAS scale was reported. Chitale et al. [19] did not observe any positive changes in pain, International Index of Erectile Function (IIEF) and curvature after therapy. On the contrary, mean dorsal and lateral angle deterioration was observed in the ESWT group compared to a moderate improvement in the sham group (20). Palmieri et al. [20] found at 12 weeks post-treatment that mean pain VAS score, IIEF and mean quality of life score (QoL) were significantly improved in the active-treated group. At 24 weeks, mean plaque size and curvature were significantly higher in the sham-treated group when compared to both baseline and ESWT values.

Erectile dysfunction (ED)

ED is defined as the persistent inability to obtain and maintain an erection sufficient to permit satisfactory sexual performance. ED may affect physical and psychosocial health and may have a significant impact on the quality of life of sufferers and their partners [34]. About 30–65 % men over the age of 40 complain of ED [35]. ED is recognized as an indicator of endothelial dysfunction and may precede a coronary incidence by 1–3 year. Therefore, it is recommended that men complaining on acquired ED should undergo standard screening for vascular risk factors with assessment of lipid profiles and fasten glucose levels [36, 37].

Characteristics of studies of ESWT for ED Four [38–41] of 8 [42–44] trials showing results of ESWT on ED were included. Studies involved 337 patients with vascular erectile dysfunction. Vardi et al. [38], Olsen et al. [39] and Srini et al. [40] only included responders to phosphodiesterase-5 inhibitors (PDE-5i), while this was not an obligatory

Fig. 1 Study selection process

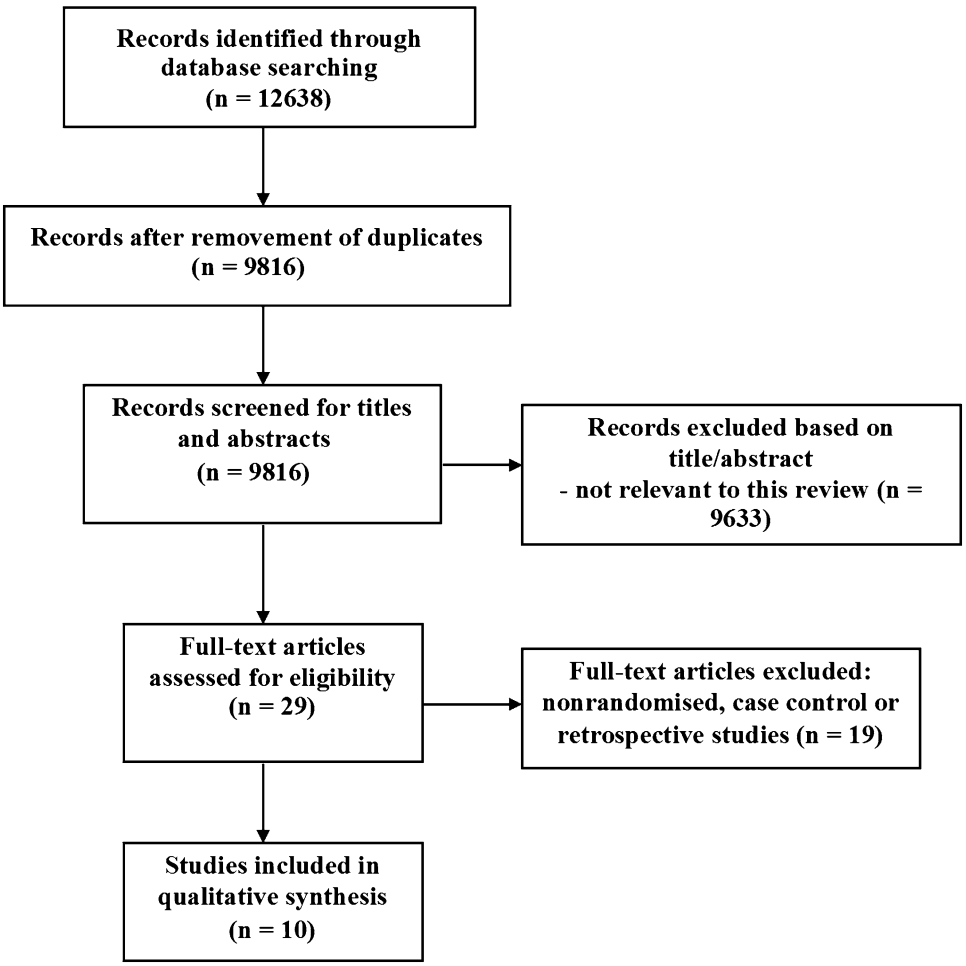

Table 2 Summary of basic characteristics and results—Peyronie's disease studies

References	Year	Number of patients	Treatment protocol	Changes in plaque size	Changes in penile deviation	Pain (VAS)	Changes in erectile function
[18]	2013	102	6 weekly sessions 2000 SW, *Efd* 0.29 mJ/mm^2, 3 Hz	No effect	No effect	85 versus 48 %	No effect (nonstandard questionnaire)
[19]	2010	36	6 weekly sessions 3000 SW, level 25 (38 Mpa)	No effect	No effect	95 % CI (−1 to 1.5)	IIEF 95 % CI (−1.6 to 2.5)
[20]	2009	100	4 weekly sessions 2000 SW, E*fd* 0.25 mJ/mm^2, 4 Hz	−0.06* versus 1.40 cm^2	−1.43°* versus 1.85°	−3.90* versus −0.22	IIEF 5.56* versus 0.30

Results shown as mean change, percentage of responders or *CI* confidence interval: active versus sham treatment

SW shock wave, *Efd* energy flux density, *VAS* visual analog scale, *IIEF* International Index of Erectile Function

* Statistically significant difference

criterion in the Yee et al. [41] study. Men should have discontinued treatment with PDE-5i 4 weeks before ESWT in two studies [38, 40]; Yee et al. [41] required a 2-week washout period, while Olsen et al. [39] did not apply any restriction prior to therapy. IIEF and erectile hardness scale (EHS) were used to assess treatment outcome. Additionally, Vardi et al. [38] examined penile hemodynamics as an objective measurement of erectile function.

Olsen et al. [39] used a Duolith® SD1 (Storz Medical, Tägerwilen, Switzerland), while the others used the Omnispec® ED1000 device (Medispec, Germantown, MD, USA). Effectiveness of both treatment settings was tested in pilot series [39, 44]. Patients were assessed 4 weeks after last treatment in the Vardi et al. [38] and Yee et al. [41] trials, compared to up to 24 weeks in the study of Olsen et al. [39], and up to 1 year in the study of Srini et al. [40].

Results of individual studies on ED Overall results are presented in Table 3. Vardi et al. [38] and Srini et al. [40] showed a clinical significant effect of ESWT on IIEF and EHS. In the Vardi et al. [38] trial, there were 19 of 28 men (68 %) in the treated group who were initially unable to achieve erections hard enough for penetration (EHS 2 or less), who were able to achieve erections sufficiently firm for penetration (EHS 3 or greater) after ESWT, compared to none in the sham group. Physiologically penile hemodynamics significantly improved in the treated group but not in the sham group [38]. In the Srini et al. [40] study, 71 % of the treated men achieved an EHS of 3 or greater. Olsen et al. [39] reported positive effect in the EHS scale, but no significant improvement in IIEF score. The overall results of Yee et al. [41] were negative both with regard to IIEF and EHS. They did, however, report a significant positive effect in patients with severe ED. Dropout rates were 40 [40], 10 [38, 39] and 20 % [41], in the four studies, respectively.

Chronic pelvic pain (CPP)

CPP is defined as persistent or recurrent pain localized in pelvic structures of either men or women without underlying pathology or infection [45]. Symptoms may be accompanied by voiding disturbances and have negative impact on sexual performance [46] and overall QoL [47]. The underlying pathology of CPP is unknown, and treatment so far has been symptomatic. According to epidemiological studies, between 2 and 12 % of men complain of CPP [48]. Our review revealed that ESWT was applied only in men with CPP corresponding to type III chronic pelvic pain syndrome (CPPS).

Characteristics of studies of ESWT for CPP Four [49–52] of 6 [53, 54] papers describing three trials on this topic were included. Moaydenia et al. [49] reported long-term follow-up data of the patients involved in the study of Vahdatpour et al. [50]. Two hundred patients, examined for non-bacterial prostatitis with negative urine and sperm culture, were included in these studies. Zimmermann et al. [51] and Vahadpour et al. [50] used the Duolith® SD1 device (Storz Medical, Tägerwilen, Switzerland); Zeng et al. [52] used the HB-ESWT 1® device (Haibin Medical

Table 3 Summary of basic characteristics and results—erectile dysfunction studies

References	Year	No. of patients	Protocol	IIEF	No patients EHS increased ≥3	Hemodynamics
[38]	2012	67	6 sessions 1500 SW, *Efd* 0.09 mJ/mm^2, 2 Hz in 3 weeks repeated after 3 weeks break	6.7* versus 3.0	19/28 versus 0/?	Maximal post-ischemic penile blood flow 8.2 versus 0.1 ml per min per dl
[39]	2014	112	5 weekly sessions 3000 SW, *Efd* 0.15 mJ/mm^2, 5 Hz	Increased >5 points 19/51* versus 19/54	29/51 versus 5/54	–
[40]	2015	135	The same as [38]	12.5 versus 1.4*	54/60 versus not specified	–
[41]	2014	70	The same as [38]	5.3 ± 5.5 versus 3.8 ± 3.6	No effect	–

Results shown as mean difference or number of patients: active versus sham treatment

SW shock wave, *Efd* energy flux density, *IIEF-EF* International Index of Erectile Function—Erectile Function domain, *EHS* erection hardness scale

* Statistically significant difference

Table 4 Summary of basic characteristics and results—chronic pelvic pain studies

References	Year	No patients	Protocol	NIH-CPSI mean score	VAS	IPSS	IIEF-EF
[50]	2009	40	4 weekly sessions 3000 SW, *Efd* 0.25 mJ/mm^2 (increased 0.05 mJ/mm^2 each week), 3 Hz	19.4 ± 1.4 versus 26.9 ± 3.0*	–	–	–
[51]	2012	60	4 weekly sessions Efd 0.25 mJ/mm^2, 3 Hz	19.70 ± 0.67* versus 25.00 ± 0.50	3.13 ± 0.28 versus 6.13 ± 0.26*	12.53 ± 0.31 versus 17.03 ± 0.55*	20.17 ± 0.32 versus 16.83 ± 0.59*
[52]	2013	80	10 sessions of 2000 SW in 2 weeks, *Efd* 0.06 mJ/mm^2 to max tolerated, 2 Hz	20 versus 30*	–	–	–

Results shown as mean difference: active versus sham treatment

SW shock wave, *Efd* energy flux density, *NIH-CPSI* National Institutes of Health Chronic Prostatitis Symptom Index, *VAS* visual analog scale, *IPSS* International Prostate Symptom Score, *IIEF-EF* International Index of Erectile Function—Erectile Function domain

* Statistically significant difference

Equipment Co. Ltd., Beijing, China). Treatment protocol of the Zimmermann et al. [51] trial was primarily tested in a feasibility study [53]. Follow-up ranged from 12 [51, 52] to 24 weeks [50].

Results of individual studies on CPP Overall results are presented in Table 4. Vahdatpour et al. [50] reported positive effects on NIH-CPSI score, QoL and pain 12 weeks after treatment. This effect vanished at the 6-month follow-up performed in the study of Moaydenia et al. [49]. Zimmermann et al. [51] and Zeng et al. [52] showed a statistical significant difference between the groups in NIH-CPSI in favor of ESWT. Furthermore, Zimmermann et al. [51] found improvement in voiding symptoms, pain and erectile function.

In all series of ESWT, regardless of the disease treated, there were no serious adverse effects reported.

Discussion

Randomized controlled trials have tested outcome in three urological disease entities: PD, ED and CPP.

None of the trials were without risk of bias (Table 1). Although only randomized trials were included in this review, sequence generation was only reported adequately in half of the included studies [18, 19, 38, 39, 41], while in the others the randomization process was unclear [20, 40, 50–52]. Also, allocation concealment was inadequately reported in all but 2 trials (21, 22), thereby introducing selection bias [55]. In three trials [18, 19, 50], the design was single-blinded, which may have affected outcome measure. The remaining trials were designed as double-blinded [20, 38–41, 52]. Blinding was sought by using a SW absorbing material in the sham groups in most trials. However, in two studies [41, 52], there was adjustment of the energy level during treatment, and it was not described who was responsible for that, and how it was blinded for the investigator and the patient, thereby questioning the double-blinded design.

Different technology of SW generation was used in different studies. Since there is a lack of methods to monitor device output, it seems essential to perform optimal dose-finding studies (feasibility studies) similar to pharmaceutical trials. This will help in choosing the most effective treatment protocol, thereby helping not to undermine the potential benefit of the treatment. This was done in only three of the ten included studies [38, 39, 51], although in two additional trials [40, 41] a protocol similar to a previous feasibility validated protocol [38] was used.

For PD the evidence of ESWT reducing plaque size and correcting deviation seems very weak. In two of the three trials, there were no differences in these parameters between active- and sham-treated groups [18, 19]. One trial showed a statistically significant mean difference of curvature of three degrees and a mean plaque size difference of 0.2 cm^2 in favor of the active-treated group [20]. Although these differences may seem very modest from a clinical point of view, they did translate into statistically significant improvements in erectile function and QoL [20]. This may be due to the fact that men included in this trial all

had painful erections, and since in two of three trials, it was shown that ESWT did reduce pain score significantly [18, 20]. Thus, current evidence does not unequivocally support ESWT for treatment of penile deviation or for minimizing plaque size in PD patients; however, ESWT may be applied to resolve pain in selected patients. Data on long-term outcome of ESWT in PD are still lacking.

Effect of ESWT for ED was in all trials evaluated with the IIEF questionnaire, comparing sexual performance after treatment with the preceding 4 weeks. A minimum of 4 weeks washout period, thus, may be essential prior to inclusion in an ESWT trial for patients receiving PDE-5i, since shorter washout periods may make it difficult for the patients to properly assess treatment outcome. This was applied only in the Vardi et al. [38] and the Srini et al. [40] trials. Overall, the data on ESWT for ED seem to be inconclusive. Two of four trials reported no improvement in the IIEF domain [39, 41], and a third trial reporting improvement [40] was undermined by a dropout rate of 40 %. All three trials that strictly included PDE-5i responders showed a positive outcome of ESWT using the EHS [38–40], suggesting that ESWT potentially may recover natural erection in this group. On the other hand, in the Yee et al. [41] trial, a positive outcome as evaluated by the IIEF was restricted to the group of men with severe ED, which normally would be considered poor responders of PDE-5i. Anyhow, the combined EHS data seem to provide the strongest evidence for a positive effect of ESWT in the treatment of ED. Although EHS is considered a valuable tool for simple clinical assessment, it is generally recognized as statistically problematic for pre-post and two-group study designs, as highlighted by Vardi et al. [38]. Future trials may consider including specific psychometric measures of sexual quality of life such as the sexual quality of life questionnaire (SQOL-M) [56], in order to systematically capture impact of intervention on sexual heath. Follow-up ranged between 4 and 24 weeks in the three studies with lowest dropout rates (10–20 %) [38, 39], and up to 12 months in the study with a 40 % dropout rate [40]. Thus, valid long-term outcome data are still needed, before ESWT can be recommended as standard treatment for ED.

ESWT seems to be a well-documented therapy for CPP in the short term [50–52]; however, its long-term efficacy is poor [49]. Since ESWT has no or minimal side effects, the treatment may be repeated in this group of patients with a symptom complex that are poorly handled by other therapeutic measures. Trials evaluating therapeutic protocols for repeated ESWT in CPP are warranted.

Conclusions

ESWT may resolve pain in PD patients, while the evidence for reducing curvature and plaques size is poor. Data on ESWT for ED are inconclusive. Effects of ESWT on IIEF are inconsistent; however, data on EHS do imply that the treatment potentially may recover natural erection in PDE-5i responders. ESWT seems to be able to resolve pain in CPP patients in the short term.

In all three diseases entities, PD, ED and CPP, long-term outcome data are still warranted, and prior to conducting trials on ESWT, dose-finding studies should be performed.

Author contribution G. Fojecki and S. Tiessen contributed to data collection, data analysis and manuscript writing. P. J. Osther helped with data analysis, manuscript writing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

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