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A First Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Trial Evaluating Extracorporeal Shock Wave Therapy for the Treatment of Peyronie's Disease

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Article info

Article history:
Accepted May 6, 2009
Published online ahead of print on May 18, 2009

Keywords:
Double-blind placebo-controlled study
Extracorporeal shock wave therapy
Peyronie's disease

Abstract

Background: Extracorporeal shock wave therapy (ESWT) is a conservative therapy for patients with Peyronie's disease (PD).
Objective: To investigate the effects of ESWT in patients with PD.
Design, setting, and participants: One hundred patients with a history of PD not >12 mo who had not had previous PD-related treatments were enrolled in a prospective, randomized, double-blind, placebo-controlled study. Patients were randomly allocated to either ESWT ($n = 50$) or placebo ($n = 50$). Erectile function (EF), pain during erection, plaque size, penile curvature, and quality of life (QoL) were assessed at baseline, at 12 wk, and at 24 wk follow-up.
Intervention: Four weekly treatment sessions were administered. Each ESWT session consisted of 2000 focused shock waves. For the placebo group, a non-functioning transducer was employed.
Measurements: EF was evaluated with the shortened version of the International Index of Erectile Function (IIEF-5), pain was evaluated with a visual analog scale (VAS; 0–10), plaque size was measured in cm^2, and penile curvature was measured in degrees.
Results and limitations: After 12 wk, mean VAS score, mean IIEF-5 score, and mean QoL score ameliorated significantly in patients receiving ESWT. Mean plaque size and mean curvature degree were unchanged in the ESWT group, while a slight increase was reported in the placebo group (p-value not significant vs baseline). After 24 wk, mean IIEF-5 score and mean QoL score were stable in the ESWT group, while mean VAS score was significantly lower when compared with baseline in both groups. Interestingly, after 24 wk, mean plaque size and mean curvature degree were significantly higher in the placebo group when compared with both baseline and ESWT values. The main limitations were that the QoL questionnaire was not validated, ED was not etiologically characterized, and inclusion criteria were restricted.
Conclusions: In patients with PD, ESWT leads to pain resolution and ameliorates both EF and QoL.

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0302-2838/$ – see back matter doi:10.1016/j.eururo.2009.05.012

1. Introduction

Peyronie's disease (PD) is an acquired connective tissue disorder of the penis involving the tunica albuginea of the corpus cavernosum and the adjacent areolar spaces [1]. It is characterized by the formation of inelastic fibrous plaques that alter penile anatomy [1]. PD is probably a multifactorial disease: either acute or repetitive undetected microtrauma during coitus in men with a genetic predisposition might result in delamination between the layers of the tunica albuginea, microvascular injury, and hemorrhage with local activation of inflammatory and fibrotic pathways [2,3]. The disease is more common in men aged >40 yr, with an incidence of 1–4% [4]. Clinically, PD presents as any combination of penile pain, penile curvature, and erectile dysfunction (ED) leading to detrimental psychological consequences and subsequent impairment of the quality of life (QoL) of both patients and their partners [5]. The clinical course of the disease is not homogeneous, and it is not possible to predict the individual prognosis at the beginning of the disease [2,6]. It is initially characterized by an inflammatory phase associated with painful erections, bending, or a change in plaque size. During this phase (6–18 mo), the condition may progress, stabilize, or regress. When the remodeling of the plaque becomes complete, pain tends to disappear. In 1970, Williams and Thomas reported a spontaneous resolution rate of 50% [7]. Recent observations, however, suggest that a significant percentage of patients experience disease progression [8]. A retrospective study of 97 patients with PD showed 14% to be resolving, 40% progressing, and 47% unchanging [5]. Many methods of treatment have been proposed, with unsatisfactory therapeutic success, mainly due to the limited knowledge of disease mechanisms. Since first used by Butz and Teichert in 1996, extracorporeal shock wave therapy (ESWT) has been reported to be a noninvasive, well-tolerated, therapy for PD [9,10]. ESWT, however, cannot yet be recommended as standard for PD. According to a recent exploratory meta-analysis, ESWT can exert beneficial effects on painful erections and on sexual function, but it seems to have no significant effects on plaque size or penile curvature [11]. Many of the previous studies, however, suffer from methodological bias such as the lack of controls, as the majority of patients desire therapy and refuse to serve as controls [10]. Moreover, none is double-blinded, real-versus-simulated ESWT. Only placebo-controlled studies can provide detailed information concerning efficacy, especially if the natural history is quite divergent, as in PD [5]. Our intention was to investigate the therapeutic effect of ESWT in patients with PD who had not had other related treatments.

2. Materials and methods

A prospective, randomized, double-blind, placebo-controlled clinical trial was conducted from May 2007 to September 2008 on 100 consecutive male patients affected by PD. Inclusion criteria were disease not >12 mo, patient age between 18–75 yr, only one plaque demonstrated by basal and dynamic sonography and by palpation with a maximum size of 3.75 cm^2, no previous medical or surgical therapies for PD, stable sexual relationship, presence of painful erections (score ≥5 on a visual analog scale [VAS] with a score ranging from 0–10), ED, and penis recurvatum. The last three criteria could be present as singular feature or could be variously associated. Patients were asked not to take drugs for ED or other therapies for PD during the course of the study and not to take analgesics before, during, or after painful erections. Patients with blood coagulation disorders, cardiac pacemaker, lower urinary tract infections, and vascular disorders in the path of the shock waves were excluded from the study. Our institutional ethics committee reviewed and approved the study protocol, and all patients gave informed written consent. Enrolled subjects were randomly assigned to receive either ESWT or placebo. Disease duration, presence and severity of painful erections, erectile function (EF), QoL, penile plaque size, and penile curvature degree were assessed at baseline evaluation. EF was evaluated through the shortened version of the International Index of Erectile Function (IIEF-5) questionnaire, and ED grading was determined according to Rosen et al: absent ED (score: 22–25), mild ED (score: 17–21), mild to moderate ED (score: 12–16), moderate ED (score: 8–11), and severe ED (score: 5–7) [12]. Presence and severity of painful erections were assessed through a VAS score ranging from 0–10, with 0 being no pain and 10 being severe pain. QoL was assessed by means of a structured interview that is routinely employed at our institution for patients with PD. The interview is composed of five questions, each with a score ranging from 0–5. Total QoL score is derived by summing responses to the five items and ranges from 0–25 (Table 1). Clinical evaluation of plaque position was performed on the fully stretched penis

Table 1 – Quality of life questionnaire

A. How would you describe the pain during intercourse?
0. None
1. Mild
2. Moderate
3. Strong
4. Severe
5. Unbearable

B. Does your penile curvature cause discomfort during intercourse?
0. None
1. Minimal
2. Quite severe
3. Severe
4. Very severe
5. Unbearable

C. Do you have trouble conducting a normal sexual relationship?
0. No
1. Hardly ever
2. Sometimes
3. Often
4. Almost always
5. Always

D. Do you believe that your relationships are affected by the conditions of your illness?
0. No
1. Yes, slightly affected
2. Yes, moderately affected
3. Yes, quite affected
4. Yes, very much affected
5. Yes, completely affected

E. Has anything changed in your life since developing this illness?
0. No
1. Not very much
2. Only a little
3. Quite a lot
4. Yes, unfortunately, I feel quite down
5. Yes, I have no enthusiasm for everyday life

Please cite this article in press as: Palmieri A, et al. A First Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Trial Evaluating Extracorporeal Shock Wave Therapy..., Eur Urol (2009), doi:10.1016/j.eururo.2009.05.012

Fig. 1 – Storz Duolith transducers.

during flaccidity by palpation. Plaque size assessment was conducted by color Doppler ultrasonography performed in the tumescence phase with an artificial erection induced by a standard intracavernous injection of alprostadil. The patient was in the supine position, and the exploration was performed by means of a 10-MHz linear transducer in transversal and longitudinal orientations by the same trained operator. Plaque size was determined as the product of length and width in square centimeters. The degree of penile curvature was documented using photographic pictures taken from three angles (frontal, lateral, and from above) during full artificial erection. The penile angle was measured on pictures with a goniometer by the same operator. The Storz Duolith ESWT system (Storz Medical AG, Switzerland) was used for treatment sessions, which were performed once weekly for four consecutive weeks in both groups by the same operator (Fig. 1). Two thousand impulses were applied at each ESWT session with an energy flux density of 0.25 mJ/mm^2 and an emission frequency of 4 Hz. Participants in the control group received identical placebo therapy through a modified nonfunctioning transducer provided by the manufacturing company. The outward appearance as well as setup and sound created by the shock wave device was identical in both groups so that both participants and operator were blinded to treatment allocation. Each transducer had to be recharged by the manufacturing company after 50 000 impulses. During the procedure, the probe was manually operated, and the focus of energy delivery remained static. Treatments were performed without anesthesia. Treatment complications were recorded. Follow-up evaluations were performed 12 wk and 24 wk after the final intervention session. VAS score, IIEF-5 score, QoL score, penile curvature degree, and plaque size were reassessed by the same operator. Objective outcome measures were reduction in plaque size and penile curvature. Subjective outcome measures were reduction in penile pain during erection and increase of IIEF-5 score. Additionally, treatment preference was investigated by asking patients to answer *yes*, *no*, or *don't know* to the following question: "Would you recommend this treatment to a friend?" Baseline and follow-up continuous parameters were compared statistically with the use of student *t* test. *P*-values <0.05 were considered statistically significant.

3. Results

3.1. Baseline patient characteristics and treatment complications

Baseline data relative to the whole study population are reported in Table 2. Differences in pretreatment characteristics between ESWT and placebo groups were not statistically significant. No major complications were observed in patients receiving ESWT, and all patients tolerated the treatment well. Only four patients in the ESWT group and two in the placebo group complained of bruising over the treatment site. None of the patients needed analgesics administration during the treatment.

3.2. Follow-up assessments

In both groups, all patients completed the treatment protocol and were available for follow-up examinations.

Table 2 – Baseline data

	Placebo group ($n = 50$)	ESWT group ($n = 50$)	*p*-value
Age (yr), mean (range)	55.2 (30–70)	54 (24–76)	ns
Disease duration (mo), mean (range), median	8.62 (5–12), 9	8.74 (5–12), 9	ns
Patients with painful erections, *n* (%)	43 (95.55)	42 (93.33)	
VAS score, mean (range)	5.51 (1–9)	5.19 (1–9)	ns
VAS score ≥5, *n* (%)	33 (78.57)	35 (81.39)	
IIEF-5 score, mean (range)	14.16 (5–24)	14 (5–25)	ns
Plaque position, *n* (%)			–
Dorsal	35 (70)	32 (64)	
Lateral	5 (10)	7 (14)	
Ventral	4 (8)	7 (14)	
Septum	6 (12)	4 (8)	
Plaque size (cm^2), mean (range)	1.41 (0.49–3.75)	1.53 (0.25–3.50)	ns
Patients with penis recurvatum, *n* (%)	44 (88)	44 (88)	
Penile curvature, degree, mean (range), median	29.45 (15–45), 32	28.88 (15–40), 30	ns
Penile deformity, *n* (%)			
Dorsal curvature	38 (86.36)	35 (79.54)	
Ventral curvature	1 (2.27)	3 (6.81)	
Lateral curvature	5 (11.36)	6 (13.63)	
Hourglass deformity	0 (0)	0 (0)	
QoL score, mean (range)	17.52 (13–23)	16.6 (10–21)	ns

ESWT = extracorporeal shock-wave therapy; VAS = visual analog scale; IIEF-5 = International Index of Erectile Function, short form; ns = not significant; QoL = quality of life.

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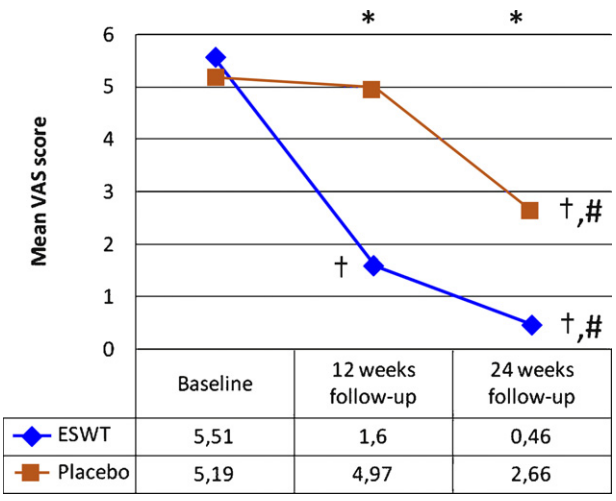

Fig. 2 – Mean visual analog scale (VAS) scores as estimated by patients complaining of pain during erection in extracorporeal shock wave therapy (ESWT) ($n = 43$) and placebo ($n = 42$) groups at both baseline and at follow-up evaluations.
† $p < 0.001$ versus baseline.
 # $p < 0.001$ versus 12-wk follow-up.
*** Between-group difference statistically significant ($p < 0.001$).**

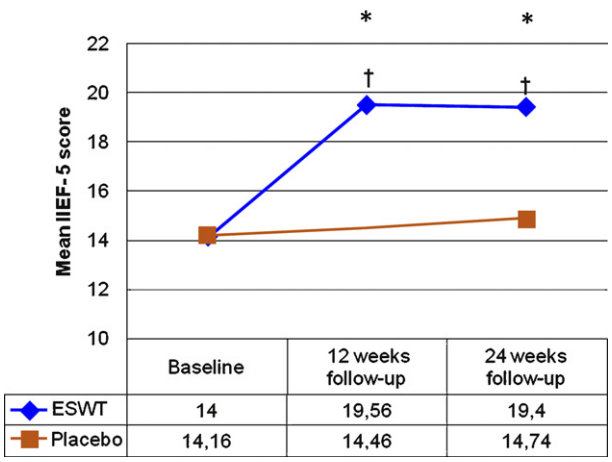

Fig. 3 – Mean International Index of Erectile Function (IIEF-5) scores in patients belonging to the extracorporeal shock wave therapy (ESWT) and placebo groups at baseline and at follow-up evaluations.
† $p < 0.001$ versus baseline.
*** Between-group difference statistically significant ($p < 0.001$).**

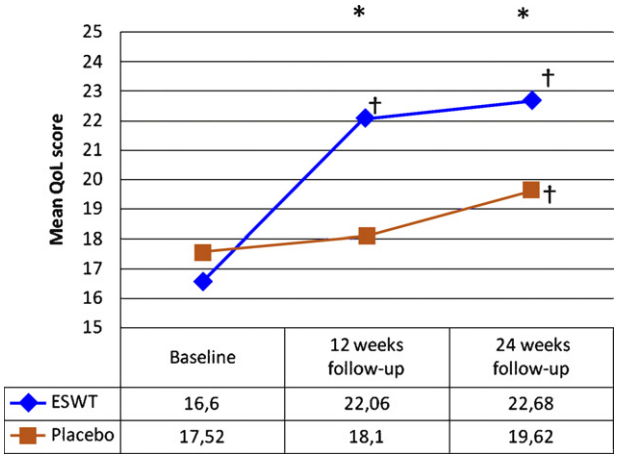

Fig. 4 – Mean quality of life (QoL) scores in patients belonging to the extracorporeal shock wave therapy (ESWT) and placebo groups at baseline and at follow-up evaluations.
† $p < 0.001$ versus baseline.
*** Between-group difference statistically significant ($p < 0.001$).**

3.2.1. *12-wk follow-up assessment*

At 12-wk follow-up, out of 43 patients with preexistent painful erections assigned to the ESWT group, 23 (53.48%) reported pain disappearance and 13 (30.23%) reported pain reduction; pain remained stable in 4 patients (9.30%) and worsened in 3 patients (6.97%). In the placebo group, 3 (7.14%) patients with preexistent painful erections reported pain disappearance, 15 (35.71%) reported pain reduction, 14 (33.33%) reported pain stability, and 10 (23.80%) reported pain worsening. Mean VAS score was significantly lower when compared with baseline values in the ESWT group, while no statistically significant differences were found in the placebo group (Fig. 2). A significant difference in terms of mean IIEF-5 score was also reported in the ESWT group when compared with baseline values, while no significant differences were found in the placebo group (Fig. 3, Table 3). Similarly, mean QoL score was significantly higher when compared with baseline only in the ESWT group (Fig. 4). Intergroup analysis revealed significant differences in terms of mean VAS score, IIEF-5 score, and QoL score. Mean plaque size and mean curvature degree decreased in the ESWT group and increased in the placebo group (Figs. 5 and 6). In both cases, no statistically significant differences were found versus baseline values or after intergroup analysis.

3.2.2. *24-wk follow-up assessment*

After 24 wk, mean VAS score further decreased and was significantly lower when compared with baseline and with 12-wk values in both groups (Fig. 2). According to intergroup analysis, mean VAS score was significantly

Table 3 – Number of patients with absent, mild, mild to moderate, moderate, and severe erectile dysfunction (ED) in the extracorporeal shock-wave therapy (ESWT) and placebo groups at baseline and at follow-up examinations

ED severity	ESWT group ($n = 50$)			Placebo group ($n = 50$)		
	Baseline	12-wk follow-up	24-wk follow-up	Baseline	12-wk follow-up	24-wk follow-up
Absent	4	25	27	3	0	1
Mild	5	13	11	11	15	13
Mild to moderate	34	2	3	22	26	26
Moderate	4	9	8	11	6	8
Severe	3	1	1	3	3	2

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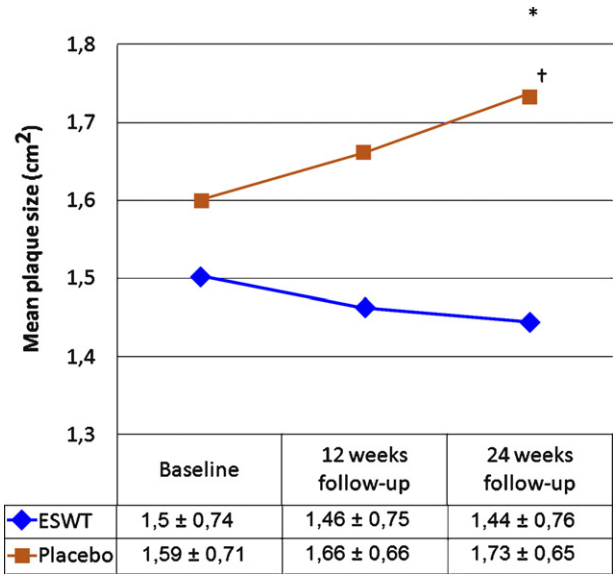

Fig. 5 – Plaque size in patients belonging to the extracorporeal shock wave therapy (ESWT) and placebo groups at baseline and at follow-up evaluations (mean values plus or minus standard deviation).
† $p < 0.05$ versus baseline.
*** Between-group difference statistically significant ($p < 0.05$).**

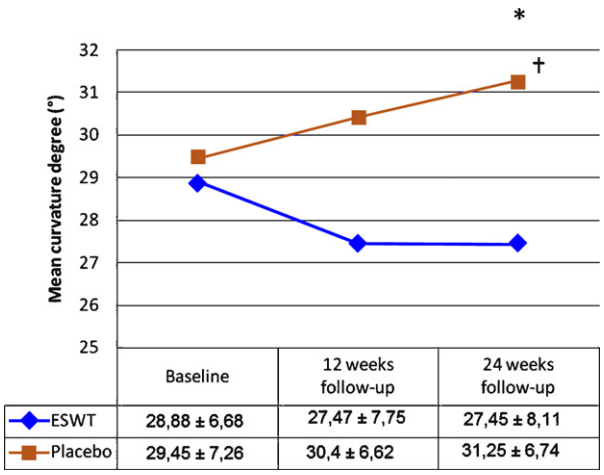

Fig. 6 – Curvature degree in patients with penis recurvatum ($n = 44$ in both the extracorporeal shock wave therapy [ESWT] and placebo groups) at baseline and at follow-up evaluations (mean values plus or minus standard deviation).
† $p < 0.05$ versus baseline.
*** Between-group difference statistically significant ($p < 0.05$).**

lower in the ESWT group. Mean IIEF-5 score remained stable in the ESWT group, while a slight increase was noted in the placebo group, although statistical analysis revealed no significant difference versus baseline values (Fig. 3, Table 3). Between-group differences remained statistically significant. Mean QoL score increased in both groups, and significant differences were found versus baseline values (Fig. 4). Mean QoL score, therefore, was higher in the ESWT group (between-group difference was significant). Mean plaque size and mean curvature degree further increased in the placebo group, and significant differences were found versus baseline values (Figs. 5 and 6). In the ESWT group, both values decreased but no significant differences versus baseline were found. Intergroup analysis revealed significant differences in terms of mean plaque size and mean penile curvature degree. The number of patients answering *yes*, *no*, and *don't know* to the question, "Would you recommend this treatment to a friend?" were 35, 5, and 10, respectively, in the ESWT group and 9, 29, and 12, respectively, in the placebo group.

4. Discussion

Despite preclinical investigations identifying potential pathophysiological mechanisms, PD remains a therapeutic dilemma, as no causal therapy is available [13,14]. Surgical correction is the standard treatment in patients with severe curvature and when the disease is in a stable stage. Surgical therapy, however, has some potential disadvantages such as reduction in penile length and de novo ED, so most patients require a conservative approach [6]. Among minimally invasive therapies, ESWT has been increasingly employed for treating symptomatic plaques in patients with PD, with controversial results reported by clinical studies [15]. The unpredictable natural course of the disease is one of the reasons that it is so difficult to assess the efficacy of a conservative treatment modality, and the absence of a control group limits the ability to interpret data [6]. A further limitation of previous studies is inaccuracy due to subjective assessments of outcome measures [6]. To improve scientific evidence concerning the effects of ESWT in patients with PD, we performed the first prospective, randomized, double-blind, placebo-controlled study in a cohort of patients with no history of previous related treatments. Twelve weeks after the final intervention session, statistically significant intergroup differences emerged concerning mean VAS score and mean IIEF-5 score as a consequence of significantly higher scores compared with baseline reported by patients receiving ESWT treatment. Concerning the effects of ESWT on painful erections, results from the present study are in accordance with published data demonstrating an immediate marked analgesic effect with anticipation of pain resolution in a percentage of patients ranging from 40% to 100% [15–19]. Direct disturbance of pain receptors and hyperstimulation analgesia have been proposed as possible underlying mechanisms [20]. In the placebo group, pain diminished later, in accordance with data provided by studies evaluating the natural history of the disease [8]. ED is an important concern in patients affected by PD. In a study by Mulhall et al, the percentage of untreated patients complaining of some degree of ED was 32% with a mean IIEF-5 score of 19.2 that had not changed significantly after a mean follow-up of 14.5 mo [8]. Mean IIEF-5 scores we reported at baseline evaluation in both groups were comparable to those reported by Mulhall et al [8]. Moreover, similar to Mulhall et al, mean IIEF-5 score did not change significantly in patients receiving no treatment [8]. Causes responsible for increased ED prevalence in patients with PD are both psychogenic and organic in nature. Penile pain and

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deformity, flail penis, lack of tumescence due to cavernosal fibrosis, and penile vascular (arterial and/or venous) disease are the main organic factors [16,21]. PD affects QoL of both patients and partners, causing psychological distress [22].The anxiety associated with the disease and the apprehension about intercourse because of pain are responsible for performance anxiety, thus contributing to EF impairment [23]. According to data in the literature, the percentage of patients showing an improvement of sexual function after ESWT ranges from 12% to 80% [11]. Studies evaluating EF by means of the validated IIEF questionnaire report improvements of EF in patients with PD treated with ESWT ranging from 25% to 96% [19,23,24]. Lebret et al emphasized the real and immediate beneficial effects to the patient's sex life from ESWT due to the therapeutic effect on pain [23]. In our opinion, the precocious resolution of painful erections is of critical relevance in improving patients' sexual health and, consequently, QoL. In contrast, the slow reduction of pain observed during the natural course of the disease, as well as in patients from our study treated with placebo, is potentially responsible for the establishment of psychological vicious circles that can persist even after the spontaneous resolution of pain. Possible therapeutic mechanisms of ESWT on PD plaque have been hypothesized, that is, direct plaque damage and heat-induced increased vascularity of the area, leading to the induction of an inflammatory reaction with lysis of the plaque, calcification resorption, and removal by macrophages [25,26]. In a previous study, we demonstrated a decreased packing and clumping of collagen fibers within the plaque of patients with PD treated with ESWT [3]. Subjectively, patients often perceive the plaque as being smoother or softened after ESWT [15,23]. The percentage of patients showing plaque-size improvement after ESWT ranges from 10% to 68%, while a decrease in mean penile curvature degree has been reported by 0–79% of treated patients [8,10,11,27]. Data on a significant curvature decrease, however, were only reported in two series [23,28]. The natural course of the disease is associated with percentages of 12%, 40%, and 48% of curvature improvement, stability, and worsening, respectively [8,10]. Our results underline the progressive nature of PD in untreated patients, characterized by a slow increase of both plaque size and penile curvature. ESWT can interfere with the spontaneous progression of the disease through a stabilizing effect and shares the possible advantage of avoiding the need for surgery. Such an effect, even if not clinically significant, could be pathogenetically relevant.

Results from the present study are in accordance with data that emerged from the meta-analysis conducted by Hauck et al [11]. Moreover, our results confirm that ESWT is safe and well tolerated and has the further advantage that it can be performed in an outpatient setting without anesthesia. Most patients are satisfied and would recommend treatment to a friend. Data in the literature show the percentage of patients reporting a positive opinion toward ESWT ranging from 44% to 78% [23]. Study limitations were the lack of etiological ED characterization, the use of a nonvalidated QoL questionnaire, and the evaluation of ESWT in a selected subgroup of patients who, according to our experience, may better respond to ESWT. The latter was a voluntary bias. Consequently, our results cannot be extended to all PD patients.

5. Conclusions

In the present study, significant differences emerged between baseline mean VAS score, mean IIEF-5 score and mean QoL score and posttreatment values in patients with PD receiving ESWT. Although no significant differences in terms of mean plaque size and preexisting mean penile curvature degree were evident in patients receiving ESWT, the worsening of such values in the placebo group may suggest a potential protective effect of ESWT on disease progression.

Author contributions: Massimiliano Creta had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Palmieri, Imbimbo, Mirone.
Acquisition of data: Palmieri, Verze, Fusco.
Analysis and interpretation of data: Mangiapia, Fusco, Creta.
Drafting of the manuscript: Palmieri, Creta, Verze.
Critical revision of the manuscript for important intellectual content: Mirone, Longo, Mangiapia.
Statistical analysis: Longo, Verze, Creta.
Obtaining funding: None.
Administrative, technical, or material support: Mirone, Imbimbo, Longo.
Supervision: Imbimbo, Fusco, Mangiapia.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

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Editorial Comment on: A First Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Trial Evaluating Extracorporeal Shock Wave Therapy for the Treatment of Peyronie's Disease

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Peyronie's disease (PD) is a common complaint for which conservative management has been widely accepted. Prevalence is between 1–9% of the adult male population. The disease presents as any combination of penile pain, penile angulation, erectile dysfunction, and, in most cases, palpable plaques. Pain and angulation are mainly related to the erect state. Etiology remains unclear, and natural history is thought to comprise two phases: acute and established. During the initial acute phase (6–18 mo), the condition may progress, stabilize, or regress. Surgery is considered when PD patients do not respond to conservative or medical therapy for approximately 1 yr and cannot perform satisfactory sexual activity.

Among the conservative treatment modalities, extracorporeal shock wave therapy (ESWT) has been proposed and tested, with frequents reports in the literature. As a result of an exploratory meta-analysis, one could read that "ESWT in Peyronie's disease at least seems to be effective in regard to penile pain and sexual function compared to natural history"; that "the effect on plaque size and curvature remains questionable"; that "ESWT is not an evidence based therapy at present"; or that "a controlled (preferably pairwise matched), single blind, multicenter study with careful, detailed documentation of disease symptoms before intervention and of outcomes is required to evaluate the real effect of ESWT" [1].

Hauck et al [2] consider >20 original papers and 2 review articles on ESWT for PD and show that the majority of uncontrolled studies describe positive effects on nearly all symptoms associated with PD. Studies with exact documentation of the symptoms before and after the intervention, however, do not reveal significant effects on penile curvature and plaque size [3].

The paper under comment is the first prospective, randomized, double-blind, placebo-controlled trial on the effect of ESWT on PD [4]. At the short-term follow-up (12 wk), the evidence-based conclusion of this paper coincides with the data from both the meta-analysis and

Please cite this article in press as: Palmieri A, et al. A First Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Trial Evaluating Extracorporeal Shock Wave Therapy. . ., Eur Urol (2009), doi:10.1016/j.eururo.2009.05.013

the critical analysis: ESWT improves subjective PD parameters but fails to affect objective features such as penile angulation and plaque size. After 24 wk, however, mean plaque size and mean curvature degree were significantly higher in the placebo group when compared to both baseline and ESWT values; this information is new. Statistical significance should not be confused with clinical significance: Improvements in plaque size and curvature are quite discrete in this study and, thus, are considered to be a clinical benefit of ESWT.

Unfortunately, the study has some limitations, which the authors recognize. Limitations include use of an unvalidated quality-of-life questionnaire, lack of an etiologic characterization of erectile dysfunction, and restricted inclusion criteria.

The authors must be congratulated for undertaking this sound study to clarify the role of ESWT in PD. Other points still need to be addressed: Should ESWT be used for established or acute PD? Does the outcome improve over time? How many sessions are needed? What should the frequency of sessions be? How much energy is delivered? These questions remain—in fact, some studies look at some of them [5,6]—but robust, well-designed trials that provide evidence-based data, such as this one [4], are lacking.

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DOI: 10.1016/j.eururo.2009.05.013

DOI of original article: 10.1016/j.eururo.2009.05.012