A Critical Assessment of Extracorporeal Shock-wave Therapy for Peyronie's Disease

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Standardization of the procedure of extracorporeal shock-wave therapy (ESWT) is currently lacking. Although some positive results in terms of improvement of penile pain, penile curvature, and overall subjective symptoms have been reported, evidence-based data are lacking. ESWT seems to be well tolerated, but longer follow-up is needed to exclude possible long-term side effects. There is no clear explanation of the mechanism of action of ESWT in patients with Peyronie's disease.

Introduction

Peyronie's disease is an acquired condition characterized by formation of fibrous plaques within the tunica albuginea of the corpora cavernosa of the penis [1]. These plaques can lead to penile deformities during erection, such as curvature, shortening, or hour-glass shape, which might be associated with painful erections and a variable degree of erectile dysfunction (ED). In the most severe cases, penile bending induced by the fibrous tissue can prevent vaginal penetration. Because Peyronie's disease has been considered a rare condition with unclear natural history, epidemiologic data are inconsistent. Lindsay *et al.* [2] reported a prevalence of 388.6 cases of Peyronie's disease per 100,000 male patients in a 35-year retrospective study conducted in Rochester, Minnesota. The highest prevalence in this study was reported for the 50- to 59-year-old subgroup. However, reported epidemiologic data seem to underdiagnose the real prevalence of this disease, as indicated by biopsy studies [3]. Although many aspects of pathophysiology, diagnosis, and medical and surgical treatment of Peyronie's disease still remain under debate, recent interesting advances have been made, and the interest among investigators remains high. With regard to management, topical and systemic medical therapies have been associated with controversial results. Several surgical procedures have been developed recently, although the ideal surgical procedure, especially in the case of severe and complex curvature, has not been clearly identified. Extracorporeal shock-wave therapy (ESWT) is a noninvasive and conservative treatment that was first reported in 1998 [4] as an effective first-line therapy for Peyronie's disease. Since then, several authors have reported their clinical experiences regarding the role of ESWT in the treatment of this medical condition, with mostly controversial results because of the lack of standardization of indications for treatment and treatment protocols. Although the rationale for this treatment is not yet known, many possible mechanisms have been suggested [5]. These include direct damage to plaques induced by shock waves themselves, creating a local inflammatory response (involving changes in the free-radical milieu and in macrophage and neutrophil activity), leading to progressive plaque lysis. Furthermore, this inflammatory reaction after ESWT might indirectly affect plaque configuration through an improved vascularity with plaque reabsorption. This could lead to a progressive change in the molecular and structural characteristics of the plaque, inducing a progressive remodeling and reabsorption of the plaque itself. Furthermore, a destruction of pain receptors induced by the direct action of the shock waves has been suggested. These hypotheses have been supported by a few studies [6] regarding the use of ESWT on soft tissues. The use of extracorporeal shock waves on pigskin seems to stimulate a process of wound healing by unknown mechanisms, although no histologic changes have been noted when penile tissue subjected to shock waves has been analyzed. Furthermore, it has been hypothesized [7••] that repeated penile trauma induced by topical application of extracorporeal shock waves to plaques could induce a contralateral scarring and deformity, which could be associated with a shortening of the contralateral side of the penis, resulting in a "false"

straightening of the penis. Although many abstracts have reported the clinical benefits of ESWT in the treatment of Peyronie's disease, only a limited number of papers have been published in the peer-reviewed literature.

This review is aimed at analyzing the efficacy, tolerability, safety, and reliability of ESWT as a first-line, noninvasive treatment for Peyronie's disease. In the evaluation of the source information, we followed the guidelines recently proposed by Mulhall [8••] to decipher clinical trials in the most appropriate way. The following aspects were assessed: trial design, patient population, and endpoints used, including patient-satisfaction profiles and adverse events.

Trial Design

Most of the clinical trials using ESWT for the treatment of Peyronie's disease consist of prospective, noncontrolled studies. Hauck *et al.* [9••] published the preliminary results of a case-controlled approach, consisting of a prospectively designed trial that included 22 patients affected by Peyronie's disease who were treated with ESWT after unsuccessful oral drug therapy compared with 23 age-matched patients who had not received previous therapy but had received daily oral placebo for 6 months as a control group. The scientific significance of this case-controlled study was limited by the number of patients included who refused to serve as controls without treatment. Therefore, the same authors used a prospective design with a different technical approach [10]. Mirone *et al.* [11] reported a three-arm, noncontrolled, retrospective study, subdividing patients enrolled into three treatment groups: shock waves alone; combination of both shock waves and perilesional injections of verapamil; and injections of verapamil alone. The authors considered the patients treated by verapamil injections alone to be the control group. In all studies reported in the literature, patients were assessed before and after shock-wave administration in terms of the severity of penile curvature, pain during erection, and quality of erectile function. Unfortunately, standardized questionnaires were never used. Several authors [9••,10–12] used a pretreatment ultrasonography to assess plaque features, and, in some studies, the pre-treatment [13] and/or post-treatment [13,14•,15] penile curvature was reported only by means of patient interview results or photographs taken by the patient. The accuracy of this method in measuring the real penile curvature is highly dependent on a full erection not always reached with a nonassisted penile injection. As pointed out by Michel *et al.* [12], the evaluation of the therapeutic effect induced by ESWT on penile curvature depends strictly on the technique of objective assessment, and it has been suggested that an artificial erection seems to be the best method to evaluate the post-treatment penile curvature. The adverse events profile of this approach has been investigated by means of questions regarding presence of urethral bleeding, penile hematoma and petechiae, penile pain, and dysuria.

Various lithotriptors and schemes of extra-wave application have been used, although their clinical significance in reducing penile symptoms and plaque size are still under debate [16]. Some groups used the Storz Minilith SL1 (Storz Medical AG, Kreuzlingen, Switzerland) [9••,10–12,14•,17••,18–20,21•,22], whereas others used the Siemens Multiline (Siemens Medical Solutions, Erlangen, Germany) [13,15]. The Wolf Piezolith 2500 [23], the Dornier EPOS ULTRA devices [16,22], and the EDAP LT-02 (Techno Medical Systems, Vaulx en Veline, France), with a special device to fix and localize the plaque [24], have also been reported. A general agreement regarding the dose of shock wave energy to be used has not been reached yet. The most used dose of shock waves has been 3000, with a range of 1000 to 4000 and an emission frequency of generally 120 shocks/min per session. This dose application has been repeated generally for three sessions (range, 1–10) and was eventually readministered in additional sessions if any modification in penile plaque and/or subjective symptoms were recorded. Recently, a direct comparison of clinical effects of ESWT on penile symptoms was performed based on different degree of energy used in 10 different sessions: patients were randomized to receive high (energy density 0.6 mJ/mm^2), medium (0.28 mJ/mm^2), or low energy (0.08 mJ/mm^2) shock waves [16]. Furthermore, Manikandan *et al.* [14•] used a randomization regarding the timing of sessions distribution to eventually record any clinical differences between two groups of patients who were randomly divided into two different energy application schedules: three sessions of ESWT at 4-week intervals and three sessions on consecutive days. Based on the various trial designs developed for ESWT, the absence of a standard protocol regarding patient selection, modalities of shock-wave application, and pre- and post-treatment patient evaluation contributes to making this kind of treatment for Peyronie's disease investigational and not actually fully applicable in everyday clinical practice.

Patient Populations

Patient selection varied significantly among the studies performed, causing a major difficulty in comparing results obtained. In many studies [4,10,13,18], symptomatic patients (*eg*, patients with penile curvature and/or pain during erection), regardless of the presence or absence of palpable plaques and possible previous treatments, were treated with ESWT. Often, there was no mention of previously administered oral drug therapy, with the exception of the study by Hauck *et al.* [9••], who reported the previous unsuccessful treatment with potassium p-aminobenzoate and vitamin E in patients treated with ESWT. In other studies [9••,24,25], only patients who had previously failed to respond to oral drug therapy received ESWT, leading to a selection of patients with more severe penile deformities and with a more stable disease. In contrast, a prospective study by Lebret *et al.* [15] was designed to

assess the results obtained by ESWT only in patients with recently developed (*ie*, less than 6 mo) palpable penile plaques. This is in contrast with another study [17••], in which only patients affected by Peyronie's disease for more than 1 year and who were deemed to be in the stable phase of the disease were recruited and underwent pretreatment penile ultrasonography. In addition, in the study by Mirone *et al.* [11], only patients affected by incompletely calcified plaque, as determined by ultrasound evaluation, and with a disease duration of less than 12 months were considered to be suitable for ESWT treatment. It is clear that these differences in patient selection make the comparative evaluation of results very difficult.

Trial Endpoints

Because many patients affected by Peyronie's disease complain of penile curvature, the primary endpoint in an ESWT study should probably be the reduction of penile angulation and the subsequent ability to resume sexual intercourse. Furthermore, because of the subjective discomfort created by painful erections in patients with Peyronie's disease, evaluating the impact of ESWT on penile pain is essential, although it is difficult to estimate the real effect of ESWT on this symptom, because most of these patients experience resolution of their pain during the first year of the disease process [26]. The first report by Butz and Teichert [4] regarding the use of ESWT in the treatment of Peyronie's disease defined this kind of treatment as an effective and safe first-line, noninvasive therapy. After the application of 3000 shock waves per treatment session (with a range of 1 to 7 sessions), the improvement in penile curvature was reported by 35% of the patients enrolled, and sexual intercourse was resumed by 55% of patients affected by ED before treatment. Eighty-three percent of the patients who complained of painful erections reported a marked reduction of pain after therapy.

In a study published by Lebret *et al.* [13], a mean of 1.6 sessions, 3000 shock waves each, were applied to 54 patients using the Siemens Multiline device, under radioscopic guidance, after the injection of a contrast agent into the plaque. Encouraging results were seen at the 1- and 3-month follow-up dates. A mean reduction of 31 degrees in penile curvature was noted in almost 54% of patients, and the penile bend was never worse after treatment. However, the straightening effect of ESWT was assessed by photographs taken by the patients, and not by an injection-assisted penile erection. In addition, 25% of patients who were also affected by ED (according to the pre- and post-treatment filing of the International Index of Erectile Function (IIEF) [27]) showed a significant increase in erectile capacity, although, for the overall population, the benefit on erection was not statistically significant. Furthermore, 91% of patients who complained of penile pain during erection noted a marked improvement, which was assessed by the administration of visual analog pain scale immediately following the procedure. Because of the early recovery of painless erections, the authors suggested an immediate, direct, therapeutic effect of ESWT on penile pain.

Timing of ESWT application does not seem to influence the results in terms of improvement of penile symptoms. Manikandan *et al.* [14•] used a minimum of three sessions of ESWT on 42 patients who were divided into two groups: one group received ESWT sessions at a time interval of 4 weeks, and the other group received treatments on consecutive days. The mean follow-up was 5.9 months (range, 2–18 mo). The results showed no statistically significant differences between the two groups. Overall, 14% of patients reported an almost complete straightening of the penis and disappearance of pain; 50% had significant improvement, described as a clearly visible change of the penile angulation and disappearance of pain; 17% reported slight improvement; and 19% had no improvement at all. The post-treatment curvature evaluation was based on photographs taken by the patients, which, as mentioned previously, limits the reliability of results. Pain was reduced in 85% of the patients. Although a slight improvement in erectile function was reported, the lack of a valid questionnaire makes the assessment of this parameter difficult.

Another study performed by Lebret *et al.* [15] was designed to evaluate the results obtained with ESWT (3000 impacts in one session) on plaques present for less than 6 months. A marked reduction of penile pain was reported by 73% of patients, whereas 31% reported reduction of penile curvature during erection. Unfortunately, this decrease in penile bending could be demonstrated objectively (by tracing or photographs) in only 11% of the patients. Thirty-seven percent of the patients suffering from ED before treatment reported an improvement in the quality of erections. When patients affected by Peyronie's disease for more than 1 year were considered, 20 of 28 men (71%) reported an improvement in erectile function assessed by means of IIEF after a mean of 3.9 (range, 3–5) treatments of ESWT with a maximum of 3000 shock waves administered per plaque. Fifteen patients (53%) reported a decrease in the curvature of the penis, whereas 13 of 16 (81%) patients reported a marked decrease in penile pain during erection.

Hauck *et al.* [9••] reported the first results of a case-controlled study assessing 22 patients who were treated with ESWT after previous unsuccessful oral drug therapy (potassium p-aminobenzoate and vitamin E) and 23 age-matched patients without previous therapy who received daily oral placebo for 6 months. The ESWT treatment consisted of two sessions of 2000 high energetic shock waves administered with a 3-day interval using the Storz Minilith SL1 device; patients who reported some improvement received an additional session of ESWT after 3 months. After a mean follow-up of 8.5 and 6 months in the ESWT and in the placebo group, respectively, the plaque disappeared at physical examination in 10% of patients treated with ESWT and in 13% of

the control-group patients. Interestingly, in one of the 12 patients with a documented calcified plaque (8.3%), the calcification was no longer visible by ultrasound at the end of the observation period. No statistically significant improvement in penile deviation between the pre- and post-treatment periods were found in the ESWT group or the placebo group. In addition, no significant effect on pain during penile flaccidity and erection and on erectile function in either the ESWT or the case-controlled group was reported in this study. A general subjective improvement was reported by 65% and 52% of the patients in the ESWT and in the control group, respectively. In this study, a complete disappearance of the plaque was found in 10% of the patients, comparable with the 9.1% rate reported by Gianneo *et al.* [19], whereas in a very small group of patients treated with ESWT and previous unsuccessful oral therapy, plaques disappeared in 25% of the cases [24]. Interestingly, plaque disappearance was reported also in patients who did not receive any specific therapy for Peyronie's disease [28]. This raises the question whether these changes could be due to an actual therapeutic effect of ESWT or to the natural clinical evolution of the disease itself. Furthermore, Hauck *et al.* [9••] reported for the first time an objective change of plaque size in the ESWT and in the control-group patients. A slight increase of the mean plaque area (from 182.9 to 205.6 mm^2) was found before and after ESWT, whereas a moderate decrease in the mean plaque area was found in the control group. This finding was different from previous reports [12,18,28], which had evidenced a decrease in plaque size in 20%, 54%, and 28% of the patients who underwent ESWT, although details of the reduction of the plaque area were not given. Complete disappearance of calcified plaques was never reported in the literature; of note, Baumann and Tauber [23] demonstrated a decrease in the size of penile calcifications in four cases and an increase in four other cases in a group of 17 men.

Recently, Hauck *et al.* [10] studied 96 men affected by Peyronie's disease, with and without calcified plaques and during the active and stable phases of the disease. The standardized diagnostic evaluation consisted of pre- and post-treatment measurement of plaque size, documentation of penile curvature using photographs taken by the patients or during an intracavernous injection test, and general assessment questions regarding penile pain and sexual function. After one session of 4000 shock waves with an emission frequency of 120 shocks per minute, repeated after 3 months, penile pain ceased or decreased in 76% of the patients enrolled. Plaque size, penile curvature, and sexual function were not significantly changed by ESWT in these patients. However, the subanalysis aimed to evaluate various degrees of pretreatment curvatures revealed that ESWT improved penile angulation significantly in the patients affected by a 31- to 60-degree penile curvature.

The association of ESWT combined with perilesional injections of verapamil has also been reported. A comparison of clinical efficacy, safety, and tolerability among the administration of ESWT alone (three sessions per week for 20 min); the combination of ESWT plus a cycle of 12 perilesional injections of verapamil (10 mg) every 2 weeks for 6 months; and verapamil alone was performed [11]. In this study, patients with completely calcified plaques, as determined by ultrasound evaluation, were excluded, and all patients complained of penile symptoms for less than 12 months. Ultrasonographically determined volume reduction of the plaques, pain alleviation, and subjective improvement in intercourse were greater in the patients who received the combination of ESWT and verapamil injections, although without a statistically significant difference from the other two groups. The authors suggested a possible synergism between mechanical and biochemical effects of ESWT and verapamil injections that must be confirmed. In this study, the modality of penile curvature measurement before and after treatment was not clarified, and the lack of use of validated questionnaires might render the interpretation of the results more difficult. Interestingly, Colombo *et al.* [20,21•], based on an experience of 90 patients treated, noted a reduction in pain, a decrease in penile curvature, and a subjective improvement of symptoms in 94%, 43%, and 76% of the patients treated with ESWT, respectively. The protocol used provided at least three weekly treatment sessions for each patient, with an emission frequency of 120 shock waves per minute. In this series, 73% of patients with calcified plaques reported improvement after a significantly larger number of treatments. These findings suggest that although fibrotic plaques seem to rapidly regress after a limited number of ESWT sessions, calcified plaques seem to require more intensive treatment, including more ESWT sessions. In addition, the increase in the energy applied to the plaque seems to be associated with a more favorable outcome after treatment [16]. Other series reported similar percentages of response after ESWT [22,25].

Adverse Events Profile

Side effects of ESWT for the treatment of Peyronie's disease include buttock petechiae, penile hematoma due to bleeding at the point of entry of the shock waves, urethral bleeding, pain during treatment, bruising over the treatment site, and dysuria. Side effects do not seem to represent a real issue during or after ESWT. This treatment seems to be well tolerated, and no major complications have been reported in published studies. The most common side effect consisted of penile bruising (occurring in 2% to 90% of the patients). Penile petechiae and skin hematoma localized along the path of the waves tend to disappear after conservative treatment and affect patients only for a few minutes after therapy [11,18]. Severe pain requiring local penile block has been reported [14•]. Local penile anesthesia before therapy has also been described [25]. Urethral bleeding has been reported in 1% [19,21•], 5.7% [5], 7% [10], 21% [9••], and 30% [12] of patients. A high rate of urethral bleeding might have been correlated with the insertion of a urethral catheter in some of the trials

mentioned [9••]. A longer follow-up is needed to verify that this symptom anticipates further urethral damage, including urethral strictures over time.

Conclusions

Although recent studies suggest the clinical efficacy and safety of ESWT in the treatment of Peyronie's disease, its real application in clinical practice remains under debate because there is a lack of clearly visible evidence-based findings. The mechanisms by which ESWT exerts its clinical effects remain unknown, and many variables, such as timing and modality of application, seem to play critical roles in the treatment of this condition. Although ESWT has been shown to be well tolerated by patients, the absence of controlled data and the short duration of the available follow-up do not allow the exclusion of potential risks and long-term side effects. Additional studies are needed to assess how ESWT is able to interfere with the natural history of Peyronie's disease, the pathologic and biochemical mechanisms of which are not yet completely understood.

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