ORIGINAL RESEARCH—PEYRONIE'S DISEASE

Extracorporeal Shock Wave Therapy in Peyronie's Disease: Results of a Placebo-Controlled, Prospective, Randomized, Single-Blind Study

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ABSTRACT

Introduction. Extracorporeal shock wave therapy (ESWT) for treatment of Peyronie's disease (PD) is controversial.
Aim. To study the efficacy of ESWT by a placebo-controlled, randomized trial.
Methods. Patients with PD (n = 102) were randomly assigned (n = 51) to each group (ESWT or placebo). All patients were given 6 weekly treatments. Patients in the ESWT-group received 2,000 shock waves per session, using the Piezoson 100 lithotripter (Richard Wolf, Knittlingen, Germany). Patients in the placebo-group were treated with interposition of a plastic membrane, which prevented any transmission of shock waves.
Main Outcome Measures. Primary end point was decrease of pain between baseline and after 4 weeks follow-up. Secondary end points were changes in deviation, plaque size, and sexual function. Pain was assessed by a visual analog scale. Deviation was measured by a goniometer after artificial erection using Alprostadil (Viridal®, Schwarz Pharma, Monheim, Germany). Plaque size was measured with a ruler and sexual function assessed by a scale regarding the ability to perform sexual intercourse.
Results. Overall, only 45 patients experienced pain at baseline. In the subgroup analysis of these patients, pain decreased in 17/20 (85.0%) patients in the ESWT group and 12/25 (48.0%) patients in the placebo group ($P = 0.013$, relative risk [RR] = 0.29, 95% confidence interval: 0.09–0.87). Penile deviation was not reduced by ESWT ($P = 0.66$) but worsened in 20/50 (40%) and 12/49 (24.5%) patients of the ESWT and placebo-group, respectively ($P = 0.133$). Plaque size reduction was not different between the two groups ($P = 0.33$). Additional, plaque size increased in five patients (10.9%) of the ESWT group only. An improvement in sexual function could not be verified ($P = 0.126$, RR = 0.46).
Conclusions. Despite some potential benefit of ESWT in regard to pain reduction, it should be emphasized that pain usually resolves spontaneously with time. Given this and the fact that deviation may worsen with ESWT, this treatment cannot be recommended. **Hatzichristodoulou G, Meisner C, Gschwend JE, Stenzl A, and Lahme S. Extracorporeal shock wave therapy in Peyronie's disease: Results of a placebo-controlled, prospective, randomized, single-blind study. J Sex Med 2013;10:2815–2821.**

Key Words. Extracorporeal Shock Wave Therapy; Peyronie's Disease; Placebo-Controlled Study; Randomized Clinical Trial

Abbreviations

PD, Peyronie's disease; ESWT, extracorporeal shock wave therapy; ED, erectile dysfunction; IIEF, International Index of Erectile Function.

Introduction

Peyronie's disease (PD) affects the penile tunica albuginea, leading to palpable plaques. Main symptoms of PD are penile deviation, pain, and occasionally erectile dysfunction (ED). Deviation may lead to inability for sexual intercourse [1–4].

Because of lack of pathophysiological knowledge, there is no causal therapy for PD [5,6]. Several nonsurgical treatment options have been investigated in the last decade, but no one therapy can relieve all symptoms associated with PD [1,3,7–13]. Surgery is the gold-standard to correct deviation [3,8,14–18].

Since Bellorofonte et al. described extracorporeal shock wave therapy (ESWT) for PD, it has been widely used [19]. Positive results have been reported regarding pain reduction, whereas reduction of deviation has been infrequently observed [20–24]. However, most studies were not randomized, and the protocols were not standardized. To date, only two studies have been published with a placebo-controlled trial showing minimal, if any, benefit of ESWT in regard to penile deviation [25,26].

We performed a placebo-controlled, prospective study to assess the efficacy of ESWT in PD using a standardized protocol.

Patients and Methods

From July 2002 to May 2004, patients with PD were included in this placebo-controlled, prospective, randomized, single-blind study at the Department of Urology, University of Tübingen, Germany. Inclusion criteria comprised previous unsuccessful oral medical therapy, patient age ≥18 years, and plaques and/or pain at erection and/or deviation. The last three criteria could be present individually or in combination. Inclusion criteria were also disease duration ≥12 months and additionally unchanged symptoms (deviation, pain, and plaques) for ≥3 months. Oral medical therapy was defined unsuccessful when there was no improvement in pain or deviation. Exclusion criteria were prior penile surgery and ED not responding to phoshodiesterase-type-5 inhibitors or intracavernous injections.

The study was approved by the ethics committee of the University of Tübingen (protocol number 50/2002). Patients were informed in detail about the study, and written informed consent was obtained. Patients were randomly assigned to the ESWT or placebo group by a computer-generated sequence. Only the attending doctor was informed of the affiliation of patients within the groups (GH).

Plaque localization and size, pain, deviation, and sexual function were assessed at baseline and follow-up examination. Plaque localization was performed by palpation and sonography using a 7.5-MHz linear transducer. Plaque size, determined as product of length and width in mm^2, was measured with a ruler. Patients with >2 plaques or with one big scar that showed irregularities within it, making measurement not feasible, were not measured and excluded from the analysis regarding plaque size. Penile pain was assessed by a visual analog scale (VAS) ranging from 0 (no pain) to 10 (strong pain). Deviation angles were measured by a goniometer after artificial erection using Alprostadil (Viridal®, Schwarz Pharma, Monheim, Germany). Sexual function was assessed by a self-made scale regarding the ability to perform sexual intercourse ("impossible," "hindered," and "possible without restrictions").

ESWT was performed with the Piezoson 100 lithotripter (Richard Wolf, Knittlingen, Germany). The frames for the penis and transducer were fixed by special holding devices provided by the manufacturer (Figure 1). The placebo group was treated with interposition of a plastic membrane in the transducer, which prevented any transmission of shock waves (Figure 2). Otherwise, the setting, including the generator noise, was equal in both groups. No one patient had undergone ESWT before the study; therefore, no patient was aware of how this treatment felt like. Moreover, as the patients were treated

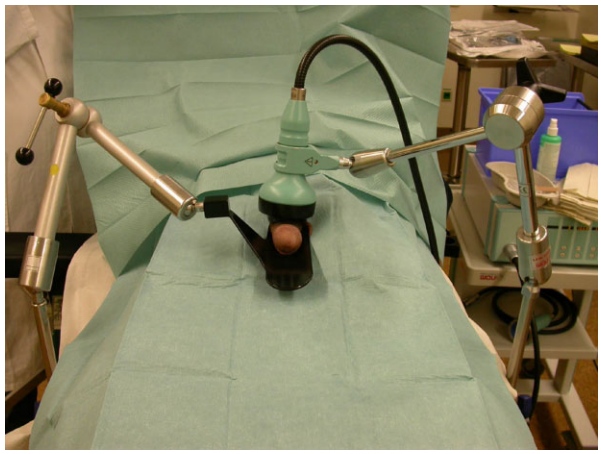

Figure 1 Setting during extracorporeal shock wave therapy. Fixation of frames for penis and transducer by special holding devices

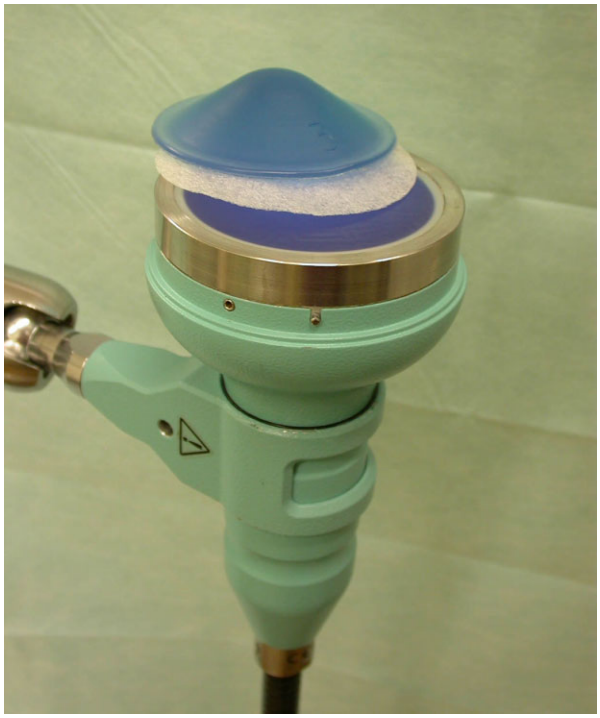

Figure 2 Transducer for placebo group. Interposition of plastic membrane, thus preventing any transmission of shock waves

independently from each other, a comparison between patients was not possible. All patients were treated six times at weekly intervals, comprising 2,000 shock waves per session with constant energy flow density of 0.29 mJ/mm^2 and emission frequency of 3 Hz. This treatment schedule was designed considering previous studies, as there was no standardized treatment protocol available for ESWT in PD [19,24]. The shock wave generator implemented in our study can also be used for treatment of orthopaedic diseases such as pseudarthrosis and tendinopathy, or even for the treatment of salivary stones.

Statistical analysis is based on the intention-to-treat population and includes all randomized patients. As pain reduction was observed more often than reduction of penile deviation in previous studies, we defined pain reduction as the primary end point of our study. This was defined as negative difference in VAS between baseline and follow-up. Secondary end points were changes in deviation, plaque size, and sexual function. Statistical analysis for primary end point and sexual function were performed using Fisher's exact test. Relative risk (RR), including 95% confidence interval, was estimated to describe effect sizes of ESWT in comparison with placebo for pain reduction. The Wilcoxon test was applied for analysis of changes in deviation and plaque size. The level of significance was 5% (P value < 0.05). Assuming that nearly 100% of patients in the study group have pain, and that 35% of patients in the placebo group will experience pain reduction, a sample size of 49 per group was determined for a Fisher's exact test, with a power of 80% and a two-sided significance level of 5%, to show an improvement in the proportion of patients with pain reduction in the ESWT group of 30–65%. Analyses were performed with SAS 9.1.3 (SAS Institute, Cary, NC, USA).

Results

From July 2002 to May 2004, n = 102 patients were included in this study. Fifty-one patients were randomized into each group (ESWT or placebo). All patients were treated six times at weekly intervals and completed the protocol. Follow-up occurred after median of 4 weeks (range 4–26 weeks). All patients had prior medical therapy (ESWT group: 32 patients [62.7%] potassium paraaminobenzoate [Potaba®, 12 g daily], 19 patients [37.3%] vitamin E [600 mg daily]; placebo group: 30 patients [58.9%] Potaba, 21 patients [41.1%] vitamin E). There was no significant difference in patient age and time of follow-up between the groups. A detailed overview of patients' characteristics and results is given in Tables 1 and 2.

Penile Pain

Overall, only 45 patients experienced pain at baseline. In the subgroup analysis of these patients, pain decreased in 17/20 patients (85.0%) in the ESWT group and 12/25 patients (48.0%) in the

Table 1 Patients' baseline characteristics

	ESWT group	Placebo group	P value
Patients (n)	51	51	
Mean patient age with range (years)	53.8 (25–72)	55.2 (30–72)	0.527
Median follow-up with range (weeks)	5 (4–26)	4 (4–9)	0.06
Penile pain	20/51 (39.2%)	25/51 (49.0%)	0.425
Penile deviation	50/51 (98.0%)	49/51 (96.1%)	>0.99
Penile plaques	51/51 (100%)	51/51 (100%)	
Measurable penile plaques before therapy	46/51 (90.2%)	49/51 (96.1%)	0.44

ESWT = extracorporeal shock wave therapy; n = number of patients

Table 2 Study results

	ESWT group	Placebo group	*P* value
Penile pain after therapy			
Reduced	17/20 (85.0%)	12/25 (48.0%)	0.013
Unchanged	3/20 (15.0%)	12/25 (48.0%)	
Increased	0/20 (0%)	1/25 (4.0%)	
Mean VAS pain score with range in patients with pain at baseline			
Before therapy	4 (1–7)	4 (1–8)	
After therapy	1.5 (1–7)	3 (1–8)	
Deviation angle after therapy			
Reduced	16/50 (32.0%)	12/49 (24.5%)	0.66
Unchanged	14/50 (28.0%)	25/49 (51.0%)	
Increased	20/50 (40.0%)	12/49 (24.5%)	0.133
Mean deviation angle (degrees)			
Before therapy	44	43	
After therapy	35	38	
Plaque size after therapy			
Reduced	18/46 (39.1%)	9/49 (18.4%)	0.33
Unchanged	23/46 (50.0%)	40/49 (81.6%)	
Increased	5/46 (10.9%)	0/49 (0%)	0.98
Sexual intercourse possible			
Before therapy	38/51 (74.5%)	38/51 (74.5%)	
After therapy	45/51 (88.2%)	38/51 (74.5%)	0.126
Improvement of SI after therapy in patients incapable of SI before therapy	8/13 (61.5%)	5/13 (38.5%)	0.43
Deterioration of SI after therapy in patients capable of SI before therapy	1/38 (6.2%)	5/38 (13.2%)	0.20

ESWT = extracorporeal shock wave therapy; SI = sexual intercourse; VAS = visual analog scale

placebo group ($P = 0.013$, RR = 0.29, 95% confidence interval 0.09–0.87). Pain worsened in 1/25 patients (4.0%) of the placebo group only.

Penile Deviation

Overall, penile deviation was present in 99 patients (97.1%). Deviation increased in 20/50 (40.0%) and 12/49 (24.5%) patients of the ESWT and placebo group, respectively ($P = 0.13$). Deviation was reduced in 16/50 patients (32.0%) of the ESWT group and 12/49 patients (24.5%) of the placebo group ($P = 0.66$).

Plaque Size

All patients showed plaques. Multiple plaques (>2 plaques) were found in five and two patients of the ESWT and placebo group, respectively. Exact measurement of plaque size in those patients was not feasible; therefore, they were not included in this analysis. Plaque size decreased in 18 patients (39.1%) and 9 patients (18.4%) of the ESWT and placebo group, respectively ($P = 0.33$). Increase of plaque size was found in five patients (10.9%) of the ESWT group only ($P = 0.98$).

Sexual Function

Sexual function was assessed by a three-step scale regarding the ability to perform satisfying sexual intercourse, including the characteristics "impossible," "hindered," and "possible without restrictions." For statistical analysis, characteristics "hindered" and "possible without restrictions" were combined. Before therapy, 38/51 (74.5%) patients in each group were able to fulfill coitus. After therapy, 45 patients in the ESWT group and 38 patients in the placebo group had successful intercourse (RR = 0.46, 95% confidence interval 0.19–1.12, $P = 0.126$). Regarding only patients unable for intercourse before treatment, there was an improvement in 8/13 (61.5%) and 5/13 patients (38.5%) of the ESWT and placebo group, respectively ($P = 0.43$).

Complications

All patients tolerated the therapy well without anaesthesia. Overall, 612 treatment sessions were performed (306 in each group). Local petechial bleeding was observed in 247/306 sessions (80.7%) and small ecchymosis in 15/306 sessions (4.9%) of the ESWT group but resolved spontaneously in all cases. We did not observe urethral bleeding as reported in literature [20–22]. No side effects occurred in the placebo group.

Discussion

ESWT for PD has been used widely in the past. However, most studies investigating ESWT were conducted without standardized protocols, with different outcome measures and without placebo

controls [20–24], thus making interpretation and recommendations difficult. We performed a placebo-controlled study to assess the efficacy of ESWT in PD using a standardized protocol.

Penile Pain

Penile pain was not an absolute inclusion criterion in our study; consequently, only 45 patients had pain before treatment. A significant reduction of pain in the ESWT group compared with the placebo group was only seen in the subgroup of patients with pain at baseline. Comparing our results with the two previous published placebo-controlled studies, only Palmieri et al. found a significant pain reduction [25]. In contrast, Chitale et al. failed to report a significant pain reduction in the ESWT group compared to the placebo group [26].

Pain seems to resolve faster with ESWT than during the natural disease course [22,23,25]. However, in this context, the question arises whether pain should be treated because most patients will experience spontaneous improvement with time. According to the natural history of PD, 89% of patients will be pain-free after a mean of 18 months without any treatment. Pain usually occurs only during the acute phase, which lasts approximately 12–18 months [2]. This fact is also displayed in our study where only 45/102 (44.1%) patients experienced pain before treatment compared with penile deviation that was present in nearly all patients (99/102 [97.1%] patients). Despite the significant pain reduction in the ESWT group in our study, it should be mentioned that 48% of patients in the placebo group also experienced pain reduction, which is most likely attributed to the spontaneous improvement during the disease course. The potential benefit of ESWT in regard to pain reduction overstates the value of this treatment, as it does require at least six treatment sessions and consequently six visits to the treatment facility, which are associated with costs to the patient and health-care system. Pain can be treated more effectively with anti-inflammatory medications, pain medications, or intralesional injections [9–11,27]. However, patients whose pain is significantly effecting their lives (i.e., requiring frequent pain medications or preventing intercourse) would be reasonable candidates for ESWT based on this therapy as long as they are counseled that the treatment is for pain only (especially if they have failed a few months of anti-inflammatory medications). In conclusion, pain reduction should not be the primary treatment goal of ESWT as pain is not the predominant symptom of patients with PD and because pain resolves spontaneously in nearly all patients with time.

Penile Deviation

In our study, no benefit with respect to penile deviation could be shown. Decreases in deviation in literature vary between 21% and 74%, but if we examine the actual change in deviation, it is in the 4–7° range [22,23,25]. Hauck et al. found a significant reduction in the subgroup of patients with deviation of 31–60° before ESWT [22]. Mean deviation decreased from 45.7° to 38.5° in this group, thus questioning its clinical benefit. Like this, Palmieri et al. noted a significant reduction in deviation between the ESWT and placebo group (31° vs. 27°, respectively) [25]. However, again, this difference is only 4° and therefore not clinically meaningful. It should be emphasized that in our study deviation worsened in 40% of patients in the ESWT group. This alone should be an indication to not suggest ESWT as possible treatment option for PD.

Surgery will remain gold-standard for correction of deviation [1]. In any case, PD is inhomogeneous with variable disease courses and constellation of symptoms; therefore, therapeutic regimens should be devised for each patient individually [1,2,9].

Plaque Size

According to the meta-analysis by Hauck et al., decrease in plaque size varies from 0% to 68% after ESWT [23]. Like in our study, in most of these studies, decrease in plaque size was not significant [23,28]. In this regard, it should be noted that accurate measurement of plaque size is virtually impossible with any imaging or mechanical modality. Moreover, results regarding plaques are difficult to interpret because plaque size reduction is not really a treatment goal, as penile deviation is the most bothersome symptom [1,29]. However, increasing plaques may have negative impact on erectile tissue leading to ED. Additional, it seems that plaque size may correlate with the extent of deviation.

Palmieri et al. assumed that ESWT may have a protective effect on disease progression by stabilizing deviation and plaques [25]. They observed that deviation and plaque size increased in the placebo group only. However, results in literature regarding this aspect are controversial [22,23].

Hauck et al. reported that deviation worsened in 10% of patients after ESWT [22]. In our study, deviation increased in 40% in the ESWT group compared with 24.5% in the placebo group. Moreover, plaque size increased in five patients (10.9%) of the ESWT group only. In fact, those patients also showed an increased deviation after ESWT, showing that increase in plaque size correlates with worsening of deviation. Overall, our findings do not support the hypothesis of Palmieri.

Sexual Function

Unfortunately, we did not use the International Index of Erectile Function (IIEF) questionnaire because when we designed the study in 2002, it was not as commonly used as it is today. Moreover, there was no validated questionnaire for PD available [1,9]. Therefore, we applied a self-made questionnaire like in previous studies [22,24]. Like in our study, most of the studies in literature did not show a positive effect of ESWT in regard to sexual function [22–24,28]. Even when the IIEF questionnaire was applied there was no benefit after ESWT [28]. This again shows that ESWT has minimal, if any, benefit for patients with PD.

Limitations

Limitations of our study include the nonvalidated questionnaire for assessment of sexual function, previous medical therapy that may have influence on the outcome of ESWT and the single-blind study design, which may lead to bias. Follow-up period in the ESWT group was longer, assuming spontaneous pain reduction. However, time of follow-up was not significant between the two groups. Data from standardized long-term follow-up are needed to confirm the results of our study. Another limitation is the treatment schedule, as this was designed considering previous studies because of lack of standardized treatment protocols. In this regard, worsening of penile deviation in the ESWT group might be due to an intense energy flow density resulting in tissue damage.

The present study is the third placebo-controlled study investigating ESWT as potential treatment modality for PD [25,26]. All three studies have not shown a marked benefit in terms of reduction of penile deviation, which is the most important symptom of the disease and should be the primary treatment goal. Pain reduction was reported in two studies, but given the fact that pain resolves spontaneously with time, the use of ESWT is not justified. Moreover, as shown in our study, penile deviation can worsen in a considerable amount of patients with ESWT. Overall, this treatment cannot be recommended for patients with PD.

Recently, low-intensity ESWT has been investigated for treatment of ED [30]. This is a newly developed treatment modality for patients suffering from ED, which is currently under investigation. However, further studies are needed to assess the possible role of ESWT for this indication.

Conclusions

Any treatment modality for PD should primarily focus on reduction of penile deviation as this is the most important and bothersome symptom in affected patients and can lead to inability for sexual intercourse. ESWT is not indicated for correction of deviation. Despite some potential benefit of ESWT in regard to pain reduction, it should be emphasized that pain usually resolves spontaneously with time. Given this and the fact that penile deviation may worsen with ESWT, this treatment cannot be recommended for patients with PD.

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