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ORIGINAL ARTICLE

Tadalafil once daily and extracorporeal shock wave therapy in the management of patients with Peyronie's disease and erectile dysfunction: results from a prospective randomized trial

A. Palmieri, C. Imbimbo, M. Creta, P. Verze, F. Fusco and V. Mirone

Department of Urology, University Federico II of Naples, Naples, Italy

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Correspondence:
Massimiliano Creta, MD, University Federico II of Naples, Via S. Pansini, 5, 80131 Naples, Italy.
E-mail: m.creta1@gmail.com

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Summary

Extracorporeal shock wave therapy improves erectile function in patients with Peyronie's disease. However, erectile dysfunction still persists in many cases. We aimed to investigate the effects of extracorporeal shock wave therapy plus tadalafil 5 mg once daily in the management of patients with Peyronie's disease and erectile dysfunction not previously treated. One hundred patients were enrolled in a prospective, randomized, controlled study. Patients were randomly allocated to receive either extracorporeal shock wave therapy alone for 4 weeks ($n = 50$) or extracorporeal shock wave therapy plus tadalafil 5 mg once daily for 4 weeks ($n = 50$). Main outcome measures were: erectile function (evaluated through the shortened version of the International Index of Erectile Function), pain during erection (evaluated through a Visual Analog Scale), plaque size, penile curvature and quality of life (evaluated through an internal questionnaire). Follow-up evaluations were performed after 12 and 24 weeks. In both groups, at 12 weeks follow-up, mean Visual Analog Scale score, mean International Index of Erectile Function score and mean quality of life score ameliorated significantly while mean plaque size and mean curvature degree were unchanged. Intergroup analysis revealed a significantly higher mean International Index of Erectile Function score and quality of life score in patients receiving the combination. After 24 weeks, intergroup analysis revealed a significantly higher mean International Index of Erectile Function score and mean quality of life score in patients that received extracorporeal shock wave therapy plus tadalafil. In conclusion extracorporeal shock wave therapy plus tadalafil 5 mg once daily may represent a valid conservative strategy for the management of patients with Peyronie's disease and erectile dysfunction.

Introduction

Peyronie's disease (PD) is a localized disorder of the connective tissue involving the penile tunica albuginea and the surrounding areolar spaces that typically evolves in fibrotic plaques [Bivalacqua *et al.* (2000)]. Patients present with three, occasionally simultaneous, chief complaints: a palpable plaque, painful erections and a penile deformity [Palmieri *et al.* (2009)]. Moreover, PD is associated with erectile dysfunction (ED) in a percentage of patients ranging from 18 to 80% [Weidner *et al.* (1997), Levine & Latchamsetty (2002), Kadioglu *et al.* (2004), Mulhall *et al.* (2005)]. In a previous study, we demonstrated that Extracorporeal Shock Wave Therapy (ESWT) can significantly improve erectile function (EF) in patients with PD when compared to placebo [Palmieri *et al.* (2009)]. However, ED still persisted in about 50% of patients thus suggesting the need for more successful strategies [Palmieri *et al.* (2009)]. Levine L.A. demonstrated that on-demand sildenafil was an effective, safe and well tolerated first-line strategy for PD patients with ED [Levine & Latchamsetty (2002)]. Recent pre-clinical studies characterized the antifibrotic effects of chronic treatment with phosphodiesterase type 5 inhibitors

(PDE5is) in PD plaque models [Gonzalez-Cadavid & Rajfer (2009)]. Owing to its longer half-life, tadalafil was recently approved for chronic administration and this regimen was reported to be associated with improved efficacy and patients' satisfaction [Porst *et al.* (2009), McMahon (2005)]. The aim of the present study was to compare ESWT alone or in combination with once daily tadalafil 5 mg for the management of patients with PD and ED.

Materials and methods

From February 2009 to December 2009 we conducted a prospective, randomized, controlled clinical study on 100 consecutive male patients affected by PD and ED. Patients with the following characteristics were included into the study protocol: disease not >12 months, age between 18 and 75 years, a single penile plaque demonstrated by basal and dynamic sonography and by palpation, plaque maximum size of 3.75 cm^2, monogamous sexual relationship with a female partner, presence of ED, presence of painful erections [score ≥5 on a visual analog scale (VAS) with a score ranging from 0 to 10], and penis recurvatum <30° (the last two criteria could be present as singular feature or could be associated). Subjects were excluded from enrolment for any of the following symptoms: lower urinary tract infections, vascular disorders in the path of the shock waves, disorders of blood coagulation, cardiac pacemaker, premature ejaculation, hypogonadism, history of radical prostatectomy or other pelvic surgery with subsequent ED, clinically significant hepatobiliary or renal disease, diabetes mellitus, lipid disorders, smoking habit, cardiovascular diseases, current nitrate use, alcohol abuse, recent significant central nervous system injuries and previous medical or surgical therapies for PD or ED. All patients gave their informed written consent. Subjects were randomly assigned to receive either ESWT or ESWT plus tadalafil 5 mg once daily for 4 weeks. Patients randomized to receive tadalafil were presented with oral as well as written instructions regarding the use and potential side effects of the drug. EF, presence and severity of painful erections, penile plaque size, penile curvature degree and quality of life (QoL) were assessed at baseline and follow-up evaluations by the same operator. EF was evaluated through the shortened version of the International Index of Erectile Function (IIEF-5) questionnaire, and ED was graded according to Rosen *et al.* (1999). Severity of painful erections was assessed by means of a VAS score ranging from 0 to 10, with 0 being no pain and 10 being severe pain. QoL was assessed by means of a structured interview composed of five questions, each with a score ranging from 0 to 5 [Palmieri *et al.* (2009)]. Plaque position was evaluated by palpation and plaque size was assessed by ultrasonography in the tumescence phase during an artificial erection induced by a standard injection of alprostadil. The size of the plaque was measured as the product of length and width in square centimetres. The degree of penile curvature was determined with a goniometer using photographic pictures during full artificial erection. The Storz Duolith system (Storz Medical AG, Lohstampfestrasse, Switzerland) was used for ESWT. Treatments were administered once weekly for four consecutive weeks in both groups by the same operator. On each ESWT session, two thousand impulses were applied. The energy flux density was 0.25 mJ/mm^2 and an emission frequency was 4 Hz. The probe was manually operated, and the focus of energy delivery remained static. Treatments were performed without anaesthesia. Treatment complications and side effects were recorded. Patients were asked not to take other therapies for ED and PD during the 4 weeks treatment period as well as during the 24 weeks follow-up period. Moreover, they were asked not to take analgesics before, during, or after painful erections during the same periods. Follow-up evaluations were performed 12 weeks and 24 weeks after the final intervention session. 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?''. Statistical analysis of the mean values of continuous variables was performed using the Student's *t*-test and analysis of the significance of the categorical variables was performed using the chi-square and the Fisher tests. A $p < 0.05$ was considered to indicate statistical significance.

Results

Patients characteristics at inclusion are reported in Table 1. Not statistically significant differences emerged between the two groups at baseline. All patients completed the study protocol. All of them tolerated treatments well and reported no major complications. Moreover, they did not require analgesics during the treatments. Treatment-emerged adverse events are reported in Table 2. No discontinuations ascribable to adverse events were reported. All patients were available for follow-up examinations and declared to have adhered to the request to avoid other therapies for ED and PD during the 4 weeks treatment period and the 24 weeks follow-up period. Moreover, they did not take analgesics before, during, or after painful erections during the same periods.

12-weeks follow-up assessment

Twelve weeks after the final intervention session, mean curvature degree and mean plaque size decreased in both

Table 1 Basic pre-treatment data

	ESWT (n = 50)	ESWT + tadalafil (n = 50)	p value
Age, years (mean, range)	54 (29–71)	55.5 (32–75)	NS
Disease duration, months (mean, range)	9 (7–12)	8.76 (6–12)	NS
Patients with painful erections (n, %)	40 (80)	37 (74)	NS
VAS score (mean, range)	5.22 (2–9)	4.91 (2–9)	
VAS score ≥5 (n, %)	31 (62)	29 (58)	
IIEF-5 score (mean, range)	12.58 (5–20)	11.56 (5–20)	NS
Plaque position (n, %)			
Dorsal	30 (60)	36 (72)	
Lateral	7 (14)	8 (16)	
Ventral	2 (4)	4 (8)	
Septum	11 (22)	2 (4)	
Plaque size, cm^2 (mean, range)	1.58 (0.44–3.10)	1.57 (0.64–2.90)	NS
Patients with penis recurvatum, (n, %)	40 (80)	41 (82)	NS
Penile curvature, degree (mean, range)	21.73 (10–29)	22.34 (13–28)	
QoL score, (mean, range)	17.46 (12–23)	17.5 (12–23)	NS

NS, not significant between-group differences.

Table 2 Treatment-emerged adverse events

	ESWT (n = 50) n (%)	ESWT + tadalafil (n = 50) n (%)	p
Bruising over the treatment site	6 (12)	8 (16)	NS
Dyspepsia	1 (2)	2 (4)	NS
Headache	1 (2)	2 (4)	NS
Back pain	1 (2)	2 (4)	NS
Upper abdominal pain	0 (0)	1 (2)	NS
Myalgia	0 (0)	1 (2)	NS
Flushing	0 (0)	1 (2)	NS

groups. However, not statistically significant differences emerged with respect to baseline values and from intergroup analysis (Figs 1 & 2). Mean VAS score improved significantly in both groups without significant intergroup differences (Fig. 3). Mean IIEF-5 score improved significantly in both groups (Fig. 4). Intergroup analysis revealed a significantly higher mean IIEF-5 score in patients treated with ESWT + tadalafil. Moreover, the number of patients with normal EF was significantly higher in the ESWT + tadalafil group (16 vs. 5, $p < 0.05$). Mean QoL score increased significantly in both groups (Fig. 5). Intergroup analysis revealed a significantly higher mean QoL score in patients treated with ESWT + tadalafil.

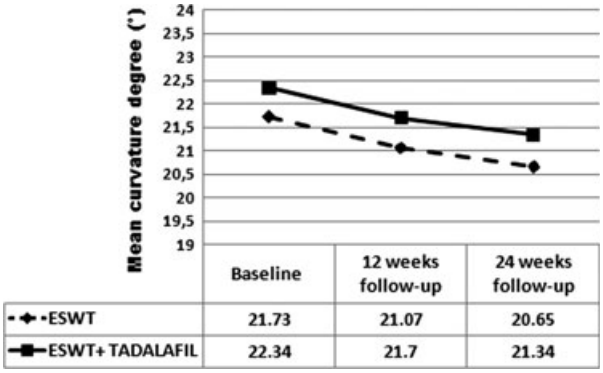


Figure 1 Curvature degree in patients with penis recurvatum in the extracorporeal shock wave therapy (ESWT) (n = 40) and ESWT + tadalafil (n = 41) groups at baseline and at follow-up evaluations.

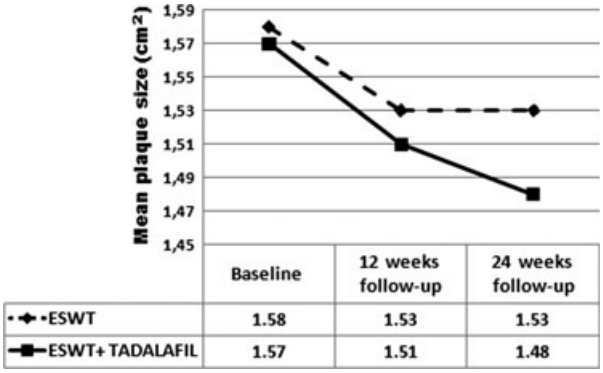
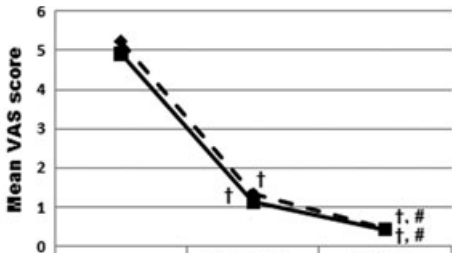


Figure 2 Mean plaque size in patients belonging to the extracorporeal shock wave therapy (ESWT) and ESWT + tadalafil groups at baseline and at follow-up evaluations.

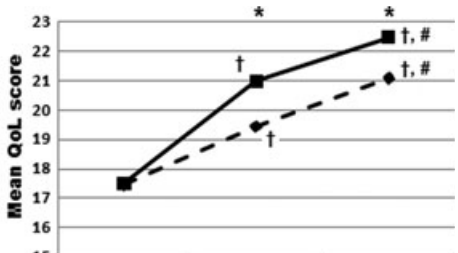
24-weeks follow-up assessment

Twenty-four weeks after the final intervention session mean curvature degree further decreased in both groups without statistically significant differences with respect to 12-weeks values. Intergroup analysis did not reveale significant differences, too (Fig. 1). Mean plaque size remained stable in the ESWT group while a further, slight decrease was evident in the ESWT + tadalafil group (Fig. 2). However, statistical analysis did not revealed significant differences when comparing mean plaque size values recorded at 24 weeks with that recorded in the same group at 12 weeks. Intergroup analysis did not reveale significant differences, too (Fig. 2). Mean VAS score further improved significantly in both groups without significant intergroup differences (Fig. 3). Mean IIEF-5 score further improved significantly in the ESWT plus tadalafil group (Fig. 4). Intergroup analysis revealed a significantly higher mean IIEF-5 score in patients treated with ESWT + tadalafil and the number of patients with normal EF



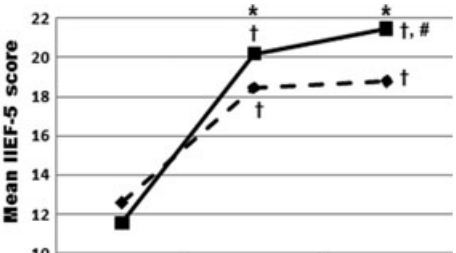
	Baseline	12 weeks follow-up	24 weeks follow-up
ESWT	5.22	1.35	0.45
ESWT+ TADALAFIL	4.91	1.13	0.43

Figure 3 Mean visual analog scale (VAS) scores as estimated by patients complaining of pain during erection in extracorporeal shock wave therapy (ESWT) (n = 40) and ESWT + tadalafil (n = 37) groups at both baseline and at follow-up evaluations. †p < 0.05 vs. baseline. #p < 0.05 vs. 12- weeks follow-up.



	Baseline	12 weeks follow-up	24 weeks follow-up
ESWT	17.46	19.46	21.08
ESWT+ TADALAFIL	17.5	20.98	22.48

Figure 5 Mean quality of life (QoL) scores in patients belonging to the extracorporeal shock wave therapy (ESWT) and ESWT + tadalafil groups at baseline and at follow-up evaluations. †p < 0.05 vs. baseline. #p < 0.05 vs. 12- weeks follow-up. *Between-group difference statistically significant (p < 0.05).



	Baseline	12 weeks follow-up	24 weeks follow-up
ESWT	12.58	18.48	18.78
ESWT+ TADALAFIL	11.56	20.18	21.48

Figure 4 Mean International Index of Erectile Function (IIEF-5) scores in patients belonging to the extracorporeal shock wave therapy (ESWT) and ESWT + tadalafil groups at baseline and at follow-up evaluations. †p < 0.05 vs. baseline. #p < 0.05 vs. 12-weeks follow-up. *Between-group difference statistically significant (p < 0.05).

was significantly higher in the ESWT + tadalafil group (25 vs. 14, p < 0.05). Mean QoL score further increased significantly in both groups (Fig. 5). Intergroup analysis revealed a significantly higher mean QoL score in patients treated with ESWT + tadalafil. There was no worsening of PD symptoms in both arms. The number of patients answering 'yes', 'no', 'and don't know' to the question, 'Would you recommend this treatment to a friend?' were 40, 5 and 5, respectively, in the ESWT + tadalafil group and 31, 9 and 10, respectively, in the ESWT group.

Discussion

To date, an aetiological therapy for patients with PD is not available. The natural course of the disease is unpredictable and it is characterized by percentages of curvature improvement, stability and worsening of 12, 40 and 48%, respectively [Mulhall *et al.* (2006), Hauck *et al.* (2004b)]. About 32% of untreated patients complain of some degree of ED, with a mean IIEF-5 score of 19.2 [Mulhall *et al.* (2006)]. Other reports have suggested that the prevalence of ED to some degree in PD patients may be up to 80% [Weidner *et al.* (1997)]. Surgical correction is the standard treatment in patients with severe curvature and when the disease is in a stable stage. For many years, penile prosthesis implantation has been considered the strategy of choice for PD patients with ED [Mulhall *et al.* (2005)]. However, not all men with combined ED and PD require penile prosthetic surgery, and a conservative therapy is frequently advocated [Mulhall *et al.* (2005)]. Moreover, non-invasive strategies are indicated in early painful and progressive stages of the disease with the intent to control symptoms and stabilize the disease [Dohle (2006), Hauck *et al.* (2006)]. Unfortunately, there is no conservative strategy that can relieve all symptoms in all affected patients [Hauck *et al.* (2006)]. To our knowledge, we performed the first clinical study evaluating the role of a combination strategy consisting of ESWT and a chronic PDE5i in the management of PD patients with ED. Although direct therapeutic mechanisms of ESWT on PD plaque have been hypothesized, results from the present study as well as from other clinical studies, failed to demonstrate a significant reduction of plaque size and curvature degree after this treatment strategy [Claro *et al.* (2004), Wild *et al.* (2000), Mirone *et al.* (2002), Palmieri *et al.* (2009)]. However, a potential stabilizing effect on the spontaneous progression of the disease has been reported [Palmieri *et al.* (2009)]. Recently, pre-clinical evidences showed that overexpression of profibrotic factors is a key event in PD plaque pathogenesis

by leading to myofibroblast accumulation and excessive deposition of collagen [Gonzalez-Cadavid & Rajfer (2010)]. Endogenous antifibrotic mechanisms consisting of the expression of inducible nitric oxide have been also demonstrated [Gonzalez-Cadavid & Rajfer (2009)]. The increase in nitric oxide levels by long-term administration of PDE5is, may be effective in reversing the fibrosis of PD [Gonzalez-Cadavid & Rajfer (2009),Valente *et al.* (2003)]. Long-term oral treatment with vardenafil was demonstrated to slow and reverse the early stages of an experimental PD-like plaque in the rat, and might have the potential to ameliorate a more advanced plaque [Ferrini *et al.* (2006)]. Moreover, it has been proposed that partial erections may facilitate penile trauma, a key factor in PD pathogenesis [Kadioglu *et al.* (2004)]. As a consequence, the improvement of penile erections may counteract this causative mechanism. Results from the present study demonstrated no significant disease progression in terms of plaque size and curvature degree in both groups. Despite pre-clinical evidences, patients receiving daily tadalafil in combination with ESWT did not report significant differences in terms of mean curvature degree when compared to patients receiving ESWT alone. A slight decrease of mean plaque size was evident in patients receiving the combination strategy but it was not clinical neither statistically significant. In accordance with published data, ESWT allowed a rapid resolution of painful erections [Palmieri *et al.* (2009)]. Tadalafil did not provide any adjunctive effect on pain. The aetiology of ED in PD patients includes penile deformity, painful erections, flail penis ascribable to circumferential plaque and impaired local vascular function (arterial, venous, or both) [Pryor (1988)]. Anxiety associated with the disease and painful erections are responsible for performance anxiety, thus contributing to EF impairment [Palmieri *et al.* (2009), Levine & Latchamsetty (2002),Valente *et al.* (2003)]. Comorbidities which may affect the penile vascular system may also influence the erectile status [Kadioglu *et al.* (2004)]. PD and ED affect QoL of both patients and partners causing psychological distress [Rosen *et al.* (2008)]. ESWT has been reported to improve EF in 25 – 96% of patients with PD [Palmieri *et al.* (2009), Hauck *et al.* (2004a,b)]. The precocious resolution of painful erections may represent an explanation for the improvement of EF and, consequently, QoL as it counteracts the establishment of psychological vicious circles that may persist even after the slow spontaneous pain resolution [Palmieri *et al.* (2009), Lebret *et al.* (2002)]. In a previous experiment, we demonstrated that ESWT can significantly improve EF and QoL in PD patients. However, EF improvement was sub-optimal as ED still persisted in about half of the patients [Palmieri *et al.* (2009)]. Sildenafil has been demonstrated to represent a safe and efficacious strategy in PD patients with ED [Levine & Latchamsetty (2002)]. In accordance with our previous study, EF and QoL significantly improved after ESWT [Palmieri *et al.* (2009)]. However, ED still persisted, although improved, in 68% and in 50% of patients treated with only ESWT at 12 weeks and 24 weeks follow-up, respectively. If compared to patients receiving only ESWT, those treated with ESWT plus tadalafil reported a significantly higher mean IIEF-5 score at both 12 weeks and 24 weeks follow-up. The difference in terms of mean IIEF-5 scores between the two groups at 12 and 24 weeks was only 1.7 and 2.7, respectively. However, the number of patients with persistent ED was significantly lower among those receiving the combination therapy. QoL score was significantly higher in patients receiving the combination therapy maybe ascribable to the reported effect on EF. Moreover, the number of patients preferring the combination therapy was higher than those preferring ESWT alone. The significant additional improvement of EF in patients receiving the combination therapy demonstrates the efficacy of tadalafil administered once daily at low dose in this specific ED population.

Local complications were similar in both groups while systemic complications were higher in patients receiving ESWT plus tadalafil. However, systemic complications were similar to those reported in previous studies on tadalafil 5 mg once daily [Claro *et al.* (2004),Donatucci *et al.* (2008)].

The main limits of the present study include: lack of aetiological ED characterization, use of a non-validated QoL questionnaire. Moreover, as patients were enrolled according to highly selective inclusion and exclusion criteria, our results cannot be extended to all PD patients with ED.

In conclusion, these initial results suggest that the combination of ESWT and tadalafil 5 mg once daily may represent a valid strategy for the conservative management of selected PD patients complaining of ED as it significantly improves EF and QoL when compared to ESWT alone. The potential protective effect of ESWT on plaque progression was confirmed in both groups. However, ESWT neither alone, nor in combination with tadalafil 5 mg once daily was able to significantly improve plaque size and curvature degree in our subset of patients. Further studies are advocated to confirm the effects of ESWT plus PDE5is on EF in PD patients and to better investigate their effects on PD plaque physiology and clinical behaviour.

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