Article

Use of Li-ESWT, Tadalafil, and a Vacuum Device to Preserve Erectile Function in Subjects Affected by Peyronie's Disease and Undergoing Grafting Surgery

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Abstract: Background: Peyronie's disease (PD) is a little-known disease characterized by pain during erections, the presence of penile curvature, and consequent psychological disorders. In addition, concomitant erectile dysfunction may be present. The treatment of PD is adapted to the patient, especially when the penile curvature is >60°; with stabilized pathology, it is preferable to perform penile straightening approaches, such as penile plication and plaque incision, or partial excision and grafting. The most frequent side effect of straightening approaches is the onset of erectile dysfunction due to the formation of venous leakage appearing after the excision of calcific plaque. **Materials and methods**: All enrolled patients had PD, a curvature >60°, had an IIEF subdomain erectile function score >16, and refused penile prosthesis implantation concurrent with tunica albuginea grafting surgery. Subsequently, 4 weeks after surgery, all patients underwent a rehabilitation protocol that consisted of low-intensity extracorporeal shock wave therapy (Li-ESWT), the administration of 5 mg/daily of tadalafil, and the use of a vacuum device. **Results**: From January 2014 to March 2016, 15 subjects affected by PD with severe penile curvatures were enrolled in the study. At 6 months after surgery, the IIEF scores for erectile function were not statistically significantly different before and after surgery ($p > 0.05$); the other items, especially orgasmic function ($p = 0.01$), sexual desire ($p < 0.01$), intercourse satisfaction ($p = 0.01$), and overall satisfaction ($p = 0.04$), were all statistically significant. The modified EDITS questionnaire reported that 80% of patients were satisfied, that 13.3% were dissatisfied, and that 1 patient (6.6%) was dissatisfied with the surgery. Moreover, there was no statistically significant decrease in the patients' penile lengths. The aim of this study was to use a rehabilitation protocol consisting of Li-ESWT, the administration of 5 mg/daily, and the use of a vacuum device in order to preserve the erectile function of patients undergoing straightening approaches using surgical grafting. In addition, patient satisfaction following surgery was analyzed.

Keywords: Peyronie's disease; erectile dysfunction; vacuum device; Li-ESWT; tadalafil

1. Introduction

Peyronie's disease (PD) is a poorly understood, benign, wound-healing disorder characterized by the abnormal deposition of collagen and the formation of fibrous, inelastic scars in the tunica albuginea of the corpora cavernosa, which causes penile deformity and erectile dysfunction (ED) [1].

Epidemiologically, it is a rather frequent condition, with a prevalence between 3% and 9% in adult men and a peak incidence around 50 years of age. However, the disease's

prevalence is probably underestimated, due to the reluctance of many to discuss it with their urologist [2].

The disease affects the connective tissue of the tunica albuginea of the corpora cavernosa, for which the etiopathogenesis has not yet been fully clarified. The most accredited hypothesis maintains that, in genetically predisposed subjects, microvascular damage, caused by repeated penile microtraumas, may trigger a hyperergic immune response, characterized by the deposition of fibrin, which could lead to the formation of fibrous plaque responsible for the disease [3,4].

Clinically, the pathology of the disease is characterized by the symptomatological triad: painful erections, penile curvature, and erectile dysfunction [5]. The disorder is frequently associated with morphological alterations of the penis, such as shortening, narrowing, and curving [6]. Many studies have documented that, in 10–15% of men with PD, the condition resolves spontaneously over 1 year after it occurs; in 40% of patients, it stabilizes after 1 year; in approximately 45% of patients, it progresses after 1 year [7,8].

Erectile dysfunction (ED) is often linked with PD, and may be found in as high as 54% of PD sufferers [9]. Many treatment options have been used, and conservative treatments are associated with poor outcomes [10]. Often, men with PD and concomitant ED do not respond to oral therapy with PDE5-i, and therefore, straightening operations may not provide any benefit to the patient, as they are likely to continue to have inadequate rigidity for sexual intercourse [11].

Finding the ideal treatment for PD has been a major challenge for us, and a gold standard technique has yet to be developed. This reflects the fact that the presentation of PD varies widely among patients in terms of the degree of deformity, penile shortening, and residual erectile function.

Surgery is the most effective treatment for PD, but it should be offered only when the acute, inflammatory phase has settled, when the condition is completely stable, if the curvature impedes adequate penetrative intercourse, or if there is associated ED that fails to respond to medical treatment [12].

Surgical grafting techniques include plaque incision and partial excision and are suggested for patients with adequate preoperative erectile function, a simple curvature of more than 70°, or a complex or hourglass deformity or when the presumed loss of length caused by the plication is more than 20% of the total erect length. Conversely, patients experiencing poor quality erections are better treated with penile prosthesis implantation [13,14].

Additionally, patients with mild ED, complex anatomical deformities, and/or a short penis are best served by penile prosthesis implantation, as the risk of worsening erectile function after graft surgery is significant [14].

The aim of this study is to demonstrate how to preserve erectile function after albugineal grafting in patients with PD, with severe but stable curvature, and who refused the concomitant penile prosthesis implantation, by using a rehabilitation protocol.

The second objective of the study is to analyze patient satisfaction after surgery and the rehabilitation protocol.

2. Materials and Methods

This was a retrospective study. All patients signed an informed consent form explaining the nature of the study and the possibility of treatment failure. Before surgery, all patients were counseled regarding all of the potential complications: onset of ED, penile shortening, curvature recurrence, loss of glans sensation, and infection. The study was conducted in accordance with the Privacy Act and the principles of the Declaration of Helsinki.

The exclusion criteria were subjects who were not capable of completing a questionnaire; with a history of psychiatric disorders, alcohol and/or substance abuse, difficulties in verbal and/or written communication, or cognitive deterioration; who had undergone pelvic surgery within the previous 12 months; with neurological diseases; with diabetes;

who had taken PDE5i regularly within the previous 6 months; with NYHA IV; or with active phase PD.

The inclusion criteria were subjects with PD (after 6 months from the onset of symptomatology with absence of pain during erections), with severe curvature (>60°) and an IIEF subdomain erectile function score >16, and who had refused penile prosthesis implantation concurrent with tunica albuginea grafting surgery.

The medical and psychosexual histories of all patients were evaluated at baseline to detect comorbidities.

In order to enroll patients with good erectile function, all subjects, after being administered 10 mcg of Alprostadil, underwent a preoperative assessment of the quality of their erections with a dynamic color Doppler ultrasound scan. In addition, the IIEF 15 questionnaire was administered to assess the following domains: erectile function (items 1–5 and 15), orgasmic function (items 9–10), sexual desire (items 11–12), intercourse satisfaction (items 6–8), and overall satisfaction (questions 13–14) [15].

All patients were given the following questions: questionnaire SEP question 2 ("Were you able to insert your penis into your partner's vagina?"), SEP question 3 ("Did your erection last long enough for you to have successful intercourse?"), and SEP question 5 ("Were you satisfied overall with this sexual experience?") [16].

All patients with an IIEF subdomain erectile function score of less than 16 and a peak systolic velocity (PSV) in both cavernous arteries (left and right) of less than 35 cm/s were excluded from this study.

All recruited patients were examined 6 months after surgery. The degree of post-operative erectile function was evaluated with the IIEF questionnaire. All patients were given the modified EDITS questionnaire, consisting of the following questions: general satisfaction, general confidence, loss of post-operative sensitivity, post-operative penis length, and post-operative loss of penis length [17].

Statistical analysis was performed using the McNemar Chi-Square test to compare paired categorical variables; the paired T-test for continuous parametric variables; and the Wilcoxon and Kruskal–Wallis tests for quantitative variables and for mean and median values, respectively. All calculations were performed using IBM-SPSS® version 22.0 (IBM Corp., Armonk, NY, USA, 2013). We considered $p < 0.05$ to be statistically significant.

The penis was degloved using a circumferential subcoronal incision, and an artificial erection was induced to assess the degree of deformity and the point of maximal curvature. After an accurate dissection of Buck's fascia, the albuginea was marked with a dermographic pen in order to calculate the angle of curvature, and then, an incomplete circumferential double Y incision of the tunica albuginea was carried out at the point of maximal curvature. The incision in the tunica albuginea was made distally to the urethra, which was not mobilized (dorsal, dorsolateral, and lateral curvatures); for ventral curvatures, the urethra was dissected from the corpora cavernosa, and an incomplete circumferential incision was performed. Once the incision was performed, we measured the defect. The tunical defect was covered with a graft of porcine derma (Permacol-Convidien®) of 0.5 mm thickness, using a continuous 4-0 polydioxanone® suture. The procedure was completed with the closure of Buck's and Dartos' fasciae and the skin with a 5-0 polyglactin® suture. An elastocompressive bandage was applied and left on for 3 days. A vesical catheter was used for 24 h.

Patients were discharged from the hospital 1 or 2 days post-operatively with a compressive bandage that was to be left on for 1 week.

Patients were checked every day for the first 10 days after being discharged in order to avoid any early complications. Sexual activity was prohibited for 6 weeks after surgery.

At 4 weeks after surgery, all patients started a rehabilitation protocol that aimed to preserve their erectile function. This protocol consisted of a combination of vacuum erectile device therapy, low-intensity shock-wave therapy (Li—ESWT), and daily administration of 5 mg of tadalafil.

Vacuum therapy was carried out for 10 min/twice a day for 12 weeks in order to prevent penile shortening due to the scarring process. Once daily for 12 weeks, 5 mg of tadalafil was administered.

Simultaneously, patients underwent 12 weekly sessions of Li-ESWT. During each session, 3000 shocks at 0.09 mJ/mm^2 were given, with 750 shocks on each anatomical area (right and left corpus cavernosum, and right and left crus).

3. Results

From January 2014 to March 2016, 15 subjects affected by PD and with severe penile curvature were enrolled in the study.

The demographic and clinical data are shown in Table 1. The average age of the patients was 58 (40–75) years old.

Table 1. Demographic and clinical data.

Parameters	Value
male age median (range)	58 (40–75)
Degree of curvature median (range)	71 (60–75)
Curvature type	
Dorsal (n)	8
Lateral (n)	3
Dorsolateral (n)	3
Ventral (n)	1
Pre-operative penis length in the flaccid state	10 (5–15)
Pre-operative penis length in the erect state	14 (10–21)

Five patients (33.3%) had grade 1 hypertension, and two patients (13.3%) had dyslipidemia after monotherapy treatment with statins. None of the patients missed the 6-month follow-up.

The results of the IIEF questionnaire submitted to the patients pre-operatively and 6 months after surgery are listed in Table 2. In particular, there was no statistically significant difference between erectile function before and after surgery ($p > 0.05$); the other items, especially orgasmic function ($p = 0.01$), sexual desire ($p < 0.01$), intercourse satisfaction ($p = 0.01$), and overall satisfaction ($p = 0.04$), were all statistically significant.

Table 2. Pre-operative and post-operative IIEF scores, * $p < 0.05$.

	Pre-Operative	Post-Operative	p
Erectile function, median(range)	21 (17–27)	23 (17–30)	0.08
Orgasmic function, median (range)	3.5 (0–6)	6 (2–10)	0.01 *
Sexual desire, median (range)	4 (2–5)	6 (1–10)	0.002 *
Intercourse satisfaction, median (range)	5 (0–9)	9 (2–15)	0.01 *
Overall satisfaction, median (range)	5 (2–7)	6 (3–10)	0.04 *

All patients were administered the modified EDITS questionnaire (Table 3); 80% of patients were satisfied, 13.3% were dissatisfied, and 1 patient (6.6%) was dissatisfied with the surgery.

Table 3. Modified EDITS questionnaire.

General Satisfaction (Question 1)	Satisfied	12 (80%)
	Little Satisfied	2 (13.3%)
	Not Satisfied	1 (6.6%)
General Confidence (Question 2)	Confident	14 (93.3%)
	Unsure of himself	1 (6.6%)
	Not at all sure of himself	0 (0%)
Post-Operative Loss of Sensitivity (Question 8)	Loss of sensitivity	0 (0%)
	Minimum loss of sensitivity	1 (6.6%)
	No loss of sensitivity	14 (93.3%)
Post-Operative Penis Length (Question 9)	Satisfied	13 (86.6%)
	Little satisfied	1 (6.6%)
Post-Operative Loss of Penis Length (Question 10)	Yes	1 (6.6%)
	No	14 (93.3%)

In total, 14 patients (93.3%) reported good overall confidence, while one patient (6.6%) complained of low self-confidence. Subsequently, 6 months after surgery, 14 patients reported no loss of glans sensitivity and 6.6% of patients reported minimal loss of sensitivity.

One patient enrolled was not satisfied with their post-operative penis length, 6.6% of patients were also dissatisfied, and 86.6% were satisfied with their penile lengths.

Finally, 93.3% of patients did not complain about post-operative losses of penile length. Table 4 shows the results of SEP2, SEP3, and SEP5.

Table 4. SEP questionnaire, N: number.

Total Patient N°15	N° of Patients Who Answered "Yes" to SEP2	N° of Patients Who Answered "Yes" to SEP3	N° of Patients Who Answered "Yes" to SEP5
Before surgery	2 (13.3%)	12 (80%)	3 (20%)
After surgery	13 (86.6%)	14 (93.3%)	13 (80%)
Change	11 (73.3%)	2 (13.3%)	10 (66.6%)

Further, 6 months after surgery, the length of patients' penises was measured in the flaccid state and following drug-induced erection. Both in the flaccid ($p > 0.05$) and in the erect state ($p > 0.05$), there was no statistically significant change compared with before surgery (Table 5).

Table 5. Penile length before and after surgery.

	Before Surgery	**After Surgery**	*p* **Value**
Flaccid state (cm)	10 (5–15)	9 (5–15)	0.64
Erect state (cm)	14 (10–21)	17 (12–22)	0.06

Post-operative complications included a loss of glans sensitivity in two patients (13.3%), and one patient (6.6%) had a fever < 39 °C after 7 days of surgery and was treated with antipyretics. Moreover, in 20% of patients, a residual dorsal curvature < 20° that did not prevent penetrative intercourse was recorded.

4. Discussion

The ideal treatment for Peyronie's disease still does not exist. In fact, there is no surgical procedure that achieves patient satisfaction, the complete straightening of the penis, a lack of post-operative ED and ease of execution by surgeons. In addition, surgeons

must perform the procedure only on patients who have a longstanding stable disease, and they must inform patients of possible post-operative complications and recurrence of the disease over time. Venous leakage, and subsequent partial or complete excision of calcific plaque may be associated with a high risk of post-operative ED.

The surgical technique used in this study is suggested for patients with penile curvature (>60°) that causes obvious limitations in sexual intercourse. With regard to materials that can be used for grafting, there are several possibilities: autologous grafts, such as buccal mucosa or saphenous veins; allogeneic grafts and heterologous grafts, such as bovine pericardium or freeze-dried porcine dermis; or synthetic grafts with dacron or Gore Tex [18]. In this study, we preferred to use allogeneic grafts because autologous grafts are more susceptible to infection, pain, lymphedema, and scarring [19].

Surgical grafting involving the total excision of plaque was practiced, which resulted in onlays of large grafts. For patients with high rates of ED, the use of a technique involving a double Y incision made in the area of maximum curvature allowed the tunic to be expanded, thereby not only correcting the curvature and shaft caliber but also minimizing the underlying exposure of the cavernous tissue. This subsequently reduced potential fibrosis of the cavernosal tissue and interrupted the delicate veno-occlusive mechanism, which, for these grafting procedures, is considered the most likely contributor to post-operative ED [20]. In accordance with our results, Sansalone et al. conducted a multicenter clinical trial that included 157 patients with complex penile curvatures and stable PD without erectile dysfunction. They used a graft of bovine pericardium. The authors performed a double Y-incision at the point of maximum curvature and used a grafting veneer. At follow-up after 20 months, 88% of patients had a completely straight penis and 97% reported complete satisfaction with the surgical results [21].

Another study by Otero et al. included 43 patients with stable PD. Calcific plaque was excised from all patients, and the defect was closed with a bovine pericardium graft. At follow-up after approximately 14 months, complete penile straightening was observed in 80% of patients, and 75% of patients reported satisfactory sexual intercourse. They also reported minimal losses of glans sensitivity (5%) [22].

In this study, we used a rehabilitative protocol to prevent both decreases in penis length and de novo onset of erectile dysfunction. In particular, the use of daily PDE5 inhibitors promotes endothelial function. The endothelium is an organ that synthesizes substances that act in a paracrine and endocrine manner on vascular tone. Foresta et al. demonstrated that the use of tadalafil in patients with endothelial damage promoted the mobilization of endothelial progenitor cells and restored endothelial function [23].

The vacuum device, which works by generating negative pressure, is able to increase blood flow to the penis and to relax the sinusoids. Increased blood flow within the corpora cavernosa aids in the oxygenation of the organ and may be helpful in preventing fibrosis formation within the tissues [24]. The use of Li-ESWT also assists in the regeneration of the endothelial tissues of damaged corpora cavernosa. In fact, stress caused by shock waves promotes the production of angiogenetic factors, such as increased nitric oxide (NO) production, through increased endothelial (eNOS) and neuronal (nNOS) NO synthase activity [25]. In their review, Sokolakis et al. summarized that Li-ESWT may partially reverse fibromuscular pathologic changes in the smooth muscle of corpora cavernosa and may restore the elasticity of the erectile tissue. Moreover, with the reduction in cavernosal fibrosis and restoration of smooth muscle content, stem cell activation and improved blood flow often occur. Additionally, Li-ESWT might trigger the endoplasmic reticulum stress response and might enhance Schwann-cell-mediated nitrergic-nerve repair after injury, although Li-ESWT also seems to stimulate fibroblasts and collagen production [26]. In a meta-analysis published in 2017 by Lu et al. in which 14 studies that collectively included 833 patients were analyzed, it was demonstrated that Li-ESWT could significantly improve the IIEF and EHS scores of ED patients [27]. Dong et al. in a meta-analysis published in 2019, revealed that men treated with Li-ESWT showed significant improvements in pooled mean IIEF–EF scores from baseline to follow-up compared with sham therapy [28]. In

patients who refuse penile prosthesis implantation, it is critical that, after the correction of PD deformities, they should be administered low doses of a PDE5 inhibitor and undergo Li-ESWT treatment in order to enhance blood flow and to nourish the graft; furthermore, penile massage with vacuum therapy should be performed to reduce the loss of penile length and to guide the straight healing of the penis. The limitations of our study are as follows: the lack of an adequate control group and the small sample size.

5. Conclusions

The administration of 5 mg of tadalafil, and the use of Li-ESWT and a vacuum device may assist in maintaining erectile function in subjects undergoing tunica albuginea grafting surgery for penile curvatures and who refuse penile prosthesis implantation.

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