

Introduction

Surgical treatment of Peyronie's disease (PD) is reserved for patients with significant penile deformity, difficulties in sexual intercourse and stable phase of disease for at least three months. While penile prosthesis (PP) implantation is the treatment of choice for patients with erectile dysfunction (ED) refractory to pharmacotherapy, tunical shortening or lengthening procedures can be performed in other cases ¹.

The tunical lengthening techniques are the gold standard treatment for patients with severe curvature, short penis, or complex deformities, but without ED. Although the definition of severe curvature was proposed to be greater than 60 degrees, there are no studies validating this threshold ¹. These procedures involve the concave side of the penis and consist of incision or excision of the plaque and coverage of the defect with a graft ². The significant risk of postoperative ED (up to 50%) and penile hypoesthesia (up to 52%) are the main concerns about these techniques ³⁻⁶. Although the risk for penile shortening appears lower than in tunical shortening procedures (incisional, excisional and pure plication techniques), it should be taken into account ⁵⁻⁷. Complete plaque excision may be associated with higher rates of postoperative ED due to venous leak, consequently it is rarely used ⁸.

A large variety of grafts was described for the tunical lengthening procedures, however, no one meets all criteria of an ideal graft ^{5,6}. Most published papers on grafting techniques are single-centre retrospective studies that reflect the experience of a single surgeon, besides there are only a few comparative studies available, consequently, the quality of the data in the literature is limited, and the superiority of one graft over the others has not yet been proven ^{1,9}.

Recently, a xenograft consisting of equine collagen coated with human fibrinogen and thrombin (TachoSil® - Baxter, CA, USA) has been introduced in grafting procedures for PD. This graft is gaining popularity among surgeons for its efficacy and safety, as well as for its practicality and ease of use which favours the reduction of operative time ^{1,9-15}.

The aim of the present study was to describe the results of a multicentre prospective registry on PD patients undergoing plaque incision or excision and grafting with collagen fleece TachoSil®, in order to evaluate the efficacy and safety of this procedure.

Materials and Methods

Study design

We designed a prospective non-controlled multicentre study in which PD patients referred to ten Spanish tertiary centres from May 2016 to March 2018 were recruited. The institutional review board approval was obtained.

Patient enrollment

Patients with stable PD for at least 3 months, difficulties in sexual intercourse, normal erectile function (IIEF-5 \geq 22 points ¹⁶) with or without pharmacological treatment were included in the study. Any type of penile curvature $> 45^\circ$, no adequate penile length, or complex deformities (hourglass, hinge) were other inclusion criteria. Patients with impaired erectile function (IIEF-5 $<$ 22 points) who refused penile prosthesis implantation were also enrolled.

Previous penile surgery affecting corpora cavernosa, active infectious diseases, and suspected penile tumour were exclusion criteria.

All patients were informed about the characteristics of the study and provided their written informed consent to participate.

Patient assessment: variables and measurement methods

Each patient enrolled underwent medical, surgical, and sexual history as well as an accurate physical examination. The variables assessed at baseline were: sociodemographic data, duration of disease (from onset and stabilization), penile curvature (direction and angle), plaque size, 5-item version of the International Index of Erectile Function (IIEF-5) ¹⁶, Peyronie's Disease Questionnaire (PDQ) ¹⁷, and Erection Hardness Score (EHS) ¹⁸. Penile curvature was evaluated with Kelami method (self-photographs of the penis at maximum erection, from above, laterally and frontally) ¹⁹. Stretched penile length was assessed using a tape measure, from the base (pubo-penile junction) to the tip of the glans (meatus) on the dorsal aspect of the penis. The study of penile plaques was performed with ultrasonography. IIEF-5, EHS, and PDQ were self-administrated to patients.

The perioperative data recorded were type of surgery, type of anaesthesia, operative time, need of additional tunical shortening procedures, penile curvature correction (intraoperative), penile shortening (intraoperative), bandage time, and complications. A curvature assessment was performed with intracavernous saline injection (Gittes test) ²⁰ at the beginning of the surgery and repeated at the end (inducing a partial erection) to evaluate the curvature correction and penile shortening with a goniometer and a rigid ruler, respectively. The residual penile curvature was considered not significant when it was less than 10 degrees.

After 3 and 6 months from surgery, PDQ, IIEF-5, EHS, and subjective patient outcomes (using not validated questionnaires), were assessed.

Surgical details

All patients underwent plaque incision and grafting (PIG) or partial/complete plaque excision and grafting (PEG). Collagen fleece TachoSil[®] was the graft used in all patients. There were no restrictions on the type of anaesthesia. A subcoronal approach was of choice, performing circumcision in all uncircumcised patients. After degloving and insulation of neurovascular bundle, plaque incision or excision was performed. TachoSil[®] graft, moistened with saline solution, was placed over the albuginea defect without the need to suture it because of its self-adhesive properties. None of the patients received the implantation of a penile prosthesis. The size of the graft, the Buck's fascia closure, the execution of additional tunical shortening procedures, and the type of bandage were at the discretion of the surgeon. In each centre, all surgeries were performed by a single surgeon. Postoperative penile rehabilitation protocol was at the discretion of the surgeon.

Statistics

The categorical variables were described as frequencies and percentages, while for the quantitative variables mean and standard deviation (SD) were used as a measure of central tendency and statistical dispersion, respectively. The Student's t-test, paired t-test and chi-squared test were used to analyze the data. P-value threshold was set at 0.05. IBM SPSS Statistics[®] (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) was used for the statistical analyses.

Results

A total of 52 patients, with a mean (SD) age of 54.5 (5.9) years, were enrolled in the study. The minimum and maximum number of patients recruited from each centre was 1 and 12, respectively. The mean (SD) time from the stabilization of PD was 11.7 (10.1) months, while the mean (SD) preoperative penile curvature was 72.8 (17.0) degrees, being the dorsal bending the most frequent (78.8%). The mean (SD) preoperative IIEF-5, EHS, and PDQ-Overall score were 19.5 (5.4), 3.4 (0.7), and 28.5 (10.5) points, respectively. The complete baseline characteristics of patients are summarized in *Table 1*.

The preferred surgical technique was the PIG (80.8%), followed by PEG with partial plaque excision (13.4%), and PEG with complete plaque excision (5.8%). The most common anaesthesia used during surgery was the spinal (51.9%). The mean (SD) operative time was 101.1 (32.1) minutes. Only 2 patients (3.8%) required additional tunical shortening procedures. Complete curvature correction (residual curvature < 10 degrees) was achieved in 92.3% of patients, and no significant penile shortening was recorded in 80.8% of subjects. No cases of

reduction in penile length greater than 2 cm were recorded. The perioperative data are reported in *Table 2*.

The patients evaluated in follow-up visits were 47 (90.4%) and 42 (80.8%) at 3 and 6 months from surgery, respectively; the mean (SD) follow-up time was 5.2 (1.7) months. A statistically significant improvement of PDQ-Overall score was recorded at 3 months (14.4 ± 13.7 ; $p < 0.001$) and confirmed at 6 months (11.1 ± 10.4 ; $p < 0.001$). No statistically significant difference ($p > 0.05$) in IIEF-5 and EHS was found at 3 months (18.7 ± 5.8 and 3.2 ± 0.9 , respectively) nor at 6 months (19.3 ± 5.6 and 3.2 ± 0.9 , respectively). However, IIEF-5 and EHS worsened significantly at 6 months from surgery in 7 (16.7%) and 8 (19%) patients, respectively. Besides, 6 patients (14.3%) started medical therapy for ED after surgery due to the worsening of erectile function. The complete results of validated questionnaires are shown in *Table 3*.

Six months after surgery, 88.0% of patients reported completely or almost completely correction of penile curvature, while 64.3% of patients reported subjective penile shortening present but less than 2 cm. A great improvement of clinical condition with the intervention was declared by 66.7% of subjects, 78.5% of men were very or somewhat satisfied with intervention, and 88.0% of patients would recommend the same treatment. The subjective patient outcomes are summarized in *Table 4*.

Swelling (23.1%) and ecchymosis/hematoma (17.3%) were the most common perioperative complications. These minor adverse events were treated with conservative measures. Two cases (3.8%) of wound infection treated with oral antibiotics were recorded. At the end of follow-up, only 3 patients (5.8%) needed reoperation due to ED or residual penile curvature. At 6 months from surgery, 61.9% of patients had normal penile sensitivity, 35.7% reported mild hypoesthesia, and only 1 patient (2.4%) complained of penile pain.

Discussion

Several types of grafts can be used to close the tunical defect after incision or excision of plaque in PD patients. Each graft available has pros and cons, and none has all the characteristics of an ideal graft, nor has it proved superior to the other^{5,6}. Depending on the origin, they can be classified into four types: autografts, allografts, xenografts, and synthetic grafts¹.

Xenografts are obtained from tissues of animals of different species, including bovine pericardium, porcine small intestinal submucosa (SIS), bovine and porcine dermis, and equine collagen (TachoSil®). Xenografts have become popular in recent years, because of ready availability in various sizes, good traction resistance, no need to take tissues from the patient's

body resulting in reduced morbidity compared to allografts, and lower risk of infection and greater tolerability compared to synthetic grafts ^{5,6}.

Collagen fleece TachoSil[®] is simple to use, indeed it is not necessary to adapt it to the shape of the tunical defect (it is sufficient to overlap the graft on the edges of the defect) and, having self-adhesive properties, it is not necessary to suture it after the application, these advantages result in reduced operative times ⁹. Another possible advantage over other xenografts is the presumed reduced risk of postoperative hematoma due to its hemostatic properties ^{14,15}. Two recent comparative studies between SIS and collagen fleece showed shorter operative time, lower cost and less risk of penile shortening with TachoSil[®] ^{12,13}. It is important to note that the intraoperative assessment of the residual penile curvature at maximum erection with intracavernous saline injection is not possible with TachoSil[®] for the risk of detachment of the graft. However, a partial erection could be safely induced for curvature evaluation ⁵.

To the best of our knowledge, this is the first multicentre study on PD patients undergoing grafting with TachoSil[®] without concomitant placement of PP. As such, it is the first paper to analyze the outcomes achieved by multiple surgeons with this technique. Furthermore, unlike several other studies ^{10,12-14}, it does not focus on a single surgical procedure but evaluates the use of collagen fleece with both PEG and PIG. To date, there is only another multicentre study available in the literature on grafting procedures with TachoSil[®] in PD patients, however, this focuses specifically on patients treated with PIG and inflatable PP placement for concomitant ED ²¹.

We analyzed the outcomes of 52 PD patients who underwent grafting with collagen fleece after plaque incision or partial/complete plaque excision. We found a complete curvature correction in 92.3% of patients, and no significant penile shortening in 80.8% of subjects. The development of ecchymosis/hematoma was recorded in 17.3% of patients. No statistically significant difference in IIEF-5 and EHS was found at 3 months (18.7 ± 5.8 and 3.2 ± 0.9 , respectively) nor 6 months (19.3 ± 5.6 and 3.2 ± 0.9 , respectively), however, 6 months after surgery 16.7% and 19% of subjects worsened significantly their IIEF-5 and EHS, respectively. Mild penile hypoesthesia was reported in 35.7% of patients at 6 months of follow-up.

According to available studies, the grafting procedures with collagen fleece are successful in 93.1% of cases, and they are associated with 10.6% of de novo ED and 10.9% of penile shortening, resulting among the most effective and safest grafting techniques. However, this synthesis of the data was performed from different non-comparable studies ¹. The largest series currently available on grafting procedures with collagen fleece TachoSil[®] in PD patients was published by Hatzichristodoulou et al in 2017. The authors described the outcomes of 319 PD

patients underwent partial plaque excision and grafting with collagen fleece. The penile curvature was dorsal in 78.1% of subjects and dorsolateral in 21.9%. Mean curvature angle was 73.5 (45-110) degrees dorsal and 23.2 (15-40) degrees lateral. Mean operative time was 79.8 (50-130) minutes. A complete correction of penile curvature was achieved in 93.7% of patients, and mean penile length before and after surgery was 13.8 (6-21) and 14.9 (8-22) cm, respectively. The mean follow-up was 47.2 (12-100) months. The erectile function worsened in 15.7% of cases, and the glans sensibility was preserved in 94.0% of patients²². It is important to emphasize that these data were published only in a congressional abstract; besides, the study likely reflects a monocentric experience and focuses only on PEG. A recently published comparative study between Tachosil[®] and small intestinal submucosa (SIS) graft in PD patients showed that postoperative penile shortening occurred less often in the Tachosil[®] group (5 vs. 28%, $p = 0.007$) and operative time was significantly shorter when TachoSil[®] was used (80 vs. 104 min, $p < 0.001$). Median IIEF-5 score improvement was higher in the SIS group (+4.5 vs. +1 points, $p = 0.002$), however, no statistically significant difference was found in the percentage of patients with worsening erectile function (7% and 5% in the SIS and TachoSil[®] group respectively, $p = 1.000$). Reduction of penile sensitivity was the main long-term complication with low rates after both procedures (9% and 7% in the SIS and TachoSil[®] group respectively, $p = 0.100$)¹².

Our results, compared to previous studies, confirm the high success rate of grafting procedures with TachoSil[®] (92.3% of complete curvature correction) and the low percentage of penile shortening (19.2%). It is fundamental to underline that these outcomes were completely different when entrusted to the subjective perception of the patient (88.0% and 83.3%, respectively); however, 78.5% of patients were very or somewhat satisfied with intervention, and 88.0% patients would have recommended the same treatment.

Postoperative ecchymosis/hematoma were recorded in 17.3% of cases, therefore, our results cannot confirm the hypothesized advantages deriving from the haemostatic properties of TachoSil[®]. This complication was not associated with the increased frequency of other adverse events or reoperations. The grouping of simple ecchymoses and hematomas into a single category of complications could explain the high percentage recorded. The incidence of this adverse event could be influenced by the different Buck's fascia closure and type of bandage among surgeons. We recorded a high incidence of penile hypoesthesia (35.7%); however, this was always a mild symptom, and patients reported an improvement in the overall clinical condition in 97.6% of cases. Although no statistically significant difference in IIEF-5 and EHS was found at 3 months nor 6 months, 16.7% and 19% of subjects worsened their IIEF-5 and

EHS significantly and needed new treatments for ED. The data regarding the erectile function could be affected by the inclusion in the study of patients with IIEF-5 < 22 who refused the concomitant implantation of a PP. In this regard, we found that patients with lower preoperative IIEF-5 (< 17 points) were less satisfied with the intervention (42.9% vs. 87.5%; $p = 0.045$) and would have recommended the same intervention with less probability (57.1% vs. 93.8%; $p = 0.067$).

In 3 patients (5.8%), due to ossification and size of the plaque, a complete excision was performed. Overall, worse outcomes were observed in these cases. Although a not statistically significant difference in reduction of IIEF-5 (-3.5 vs. -1.1; $p = 0.201$) and satisfaction related to the intervention (33.3% vs. 79.5%; $p = 0.136$) were found, a significantly higher probability of reoperation (66.6% vs. 5.3%; $p = 0.021$) and lower probability of recommending the same type of intervention (33.3% vs. 90%; $p = 0.035$) were recorded. Therefore, the recommendation to perform a complete plaque excision only in case of concomitant implantation of PP appears confirmed.

At the end of the study, all surgeons involved agreed on the ease of use of TachoSil® and reported a subjective perception of shorter operative times, confirming the main advantages of collagen fleece reported by previous studies.^{9,12}

Our results should be read and interpreted considering the limitations of the study. The main limitations of our research are the short follow-up time and the relatively small sample size. Another relevant issue is the inclusion in the study also of PD patients with ED who refused the implantation of penile prosthesis. Other weaknesses are the non-negligible percentage of patients lost to follow-up, the use of not validated questionnaires to evaluate the subjective patient outcomes, and the lack of objective measurements of penile curvature and length during follow-up. The absence of comparison with other grafts constitutes a further limitation. However, this lack of a control group should not be considered a substantial weakness since there is no gold standard graft for the tunical lengthening procedures and the use of placebo is not ethically possible.

Conclusions

Grafting with collagen fleece TachoSil® after plaque incision or partial excision in PD patients is an effective and safe procedure. Among the main advantages of this technique there are ease of use of the graft and reduced operative time. PIG and PEG remain technically challenging surgery with a significant risk of ED and loss of penile sensitivity regardless of graft used, therefore should be performed only by experienced and high-volume surgeons. Further large

multicentre prospective randomized comparative study on collagen fleece TachoSil® as graft for tunical lengthening procedures in PD patients are needed to confirm our encouraging results.

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The authors declare that there is no conflict of interest.

References

- 1 Salonia A, Bettocchi C, Carvalho J, *et al.* EAU Guidelines on Sexual and Reproductive Health. In: European Association of Urology Guidelines. Arnhem, Netherlands, 2020.
- 2 Hatzichristodoulou G, Tsambarlis P, Kübler H, Levine LA. Peyronie's graft surgery-tips and tricks from the masters in andrologic surgery. *Transl Androl Urol* 2017; **6**: 645–56.
- 3 Carson CC, Levine LA. Outcomes of surgical treatment of Peyronie's disease. *BJU Int* 2014; **113**: 704–13.
- 4 Terrier JE, Tal R, Nelson CJ, Mulhall JP. Penile Sensory Changes After Plaque Incision and Grafting Surgery for Peyronie's Disease. *J Sex Med* 2018; **15**: 1491–7.
- 5 Garcia-Gomez B, Ralph D, Levine L, *et al.* Grafts for Peyronie's disease: a comprehensive review. *Andrology* 2018; **6**: 117–26.
- 6 Rice PG, Somani BK, Rees RW. Twenty Years of Plaque Incision and Grafting for Peyronie's Disease: A Review of Literature. *Sex Med* 2019; **7**: 115–28.
- 7 Langston JP, Carson CC. Peyronie Disease: Plication or Grafting. *Urol Clin North Am* 2011; **38**: 207–16.
- 8 Dalkin B, Carter M. Venogenic Impotence Following Dermal Graft Repair for Peyronie's Disease. *J Urol* 1991; **146**: 849–51.
- 9 Hatzichristodoulou G. Evolution of the surgical sealing patch TachoSil® in Peyronie's disease reconstructive surgery: technique and contemporary literature review. *World J Urol* 2020; **38**: 315–21.
- 10 Lahme S, Götz T, Bichler KH. Collagen fleece for defect coverage following plaque excision in patients with Peyronie's disease. *Eur Urol* 2002; **41**: 401–5.
- 11 Horstmann M, Kwol M, Amend B, Hennenlotter J, Stenzl A. A self-reported long-term follow-up of patients operated with either shortening techniques or a TachoSil grafting procedure. *Asian J Androl* 2011; **13**: 326–31.
- 12 Rosenhammer B, Sayedahmed K, Fritsche HM, Burger M, Kübler H, Hatzichristodoulou G. Long-term outcome after grafting with small intestinal

- submucosa and collagen fleece in patients with Peyronie's disease: a matched pair analysis. *Int J Impot Res* 2019; **31**: 256–62.
- 13 Falcone M, Preto M, Ceruti C, *et al.* A Comparative Study Between 2 Different Grafts Used as Patches After Plaque Incision and Inflatable Penile Prosthesis Implantation for End-Stage Peyronie's Disease. *J Sex Med* 2018; **15**: 848–52.
 - 14 Hatzichristodoulou G, Gschwend JE, Lahme S. Surgical therapy of Peyronie's disease by partial plaque excision and grafting with collagen fleece: Feasibility study of a new technique. *Int J Impot Res* 2013; **25**: 183–7.
 - 15 Hatzichristodoulou G, Fiechtner S, Gschwend JE, Lahme S. 033 Surgical Therapy of Peyronie's Disease by Partial Plaque Excision and Sealing of Tunical Defect With Collagen Fleece: The Sealing Technique. *J Sex Med* 2017; **14**: S15–6.
 - 16 Rosen R, Cappellari J, Smith M, Lipsky J, Peña B. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999; **11**: 319–26.
 - 17 Hellstrom WJG, Feldman R, Rosen RC, Smith T, Kaufman G, Tursi J. Bother and distress associated with peyronie's disease: Validation of the peyronie's disease questionnaire. *J Urol* 2013; **190**: 627–34.
 - 18 Mulhall JP, Goldstein I, Bushmakin AG, Cappelleri JC, Hvidsten K. Validation of the erection hardness score. *J Sex Med* 2007; **4**: 1626–34.
 - 19 Kelâmi A. Classification of congenital and acquired penile deviation. *Urol Int* 1983; **38**: 229-33.
 - 20 Gittes RF, McLaughlin AP. Injection technique to induce penile erection. *Urology* 1974; **4**: 473–4.
 - 21 Hatzichristodoulou G, Yang DY, Ring JD, Hebert KJ, Ziegelman MJ, Köhler TS. Multicenter Experience Using Collagen Fleece for Plaque Incision With Grafting to Correct Residual Curvature at the Time of Inflatable Penile Prosthesis Placement in Patients With Peyronie's Disease. *J Sex Med* 2020; : 1–7.
 - 22 Hatzichristodoulou G, Fiechtner S, Gschwend J, Kübler H, Lahme S. Suture-free sealing of tunical defect with collagen fleece after partial plaque excision in Peyronie's disease: Long-term outcomes of the sealing technique. *Eur Urol Suppl* 2017; **16**: e2152.