Original Article

A study of the histopathology of collagen fleece (TachoSil) patching of tunica albuginea in the rat penis and a literature review of penile graft materials in experimental animals

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Background: A penile tunica defect may arise during surgery in patients with Peyronie's disease. Collagen fleece (TachoSil) has recently gained popularity in penile surgery to cover the tunica albuginea (TA) defect associated with clinical success. However, it is not known what the histological outcomes of these grafts are in the penis. We aimed to study the histopathology of the TachoSil graft in an experimental animal model for the regeneration of TA, inflammation, fibrosis, and the underlying cavernous tissue.

Methods: Six adult male Sprague Dawley rats were used. The penis was degloved through a circumferential subcoronal incision. A longitudinal 1 mm × 10 mm defect was created at the base of the lateral aspect of the penis. A TachoSil patch (Takeda, Japan) was applied to the defect. The penile skin covering was then restored. At 2 months, the rat penis was excised and examined with hematoxylin, eosin, and trichrome stains. We conducted a literature review of penile grafts in animals for comparison.

Results: Rats weighed 369.2 gm (standard deviation: 31.5). At 2 months, all rats showed normal-looking penis with complete healing, no scaring, tethering, or gross inflammatory features. Histopathology of the patch site showed fibrosis, chronic inflammation, and foreign body giant cell reaction. There was no generation of a new TA, or new vascularity. No inflammatory or pathological reaction affected the underlying corpus cavernous tissue. One rat died on the 6th postoperative day. Postmortem showed massive multiorgan hemorrhage consistent with disseminated intravascular coagulopathy (DIC). Unlike some other reported grafts, there is no TA regeneration.

Conclusions: TachoSil patching of penile TA defect forms a distinctive barrier against inflammation, protecting the underlying corpus cavernosum. However, no regeneration of the tunica defect is observed at 2 months. DIC is a potential complication of systemic absorption of TachoSil.

Keywords: Collagen fleece; experimental animal study; fibrin sealant patch; histopathology; penile tunica albuginea graft (penile TA graft)

Submitted Apr 14, 2023. Accepted for publication Jul 27, 2023. Published online Aug 15, 2023.
doi: 10.21037/tau-23-229
View this article at: https://dx.doi.org/10.21037/tau-23-229

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Introduction

A penile tunica albuginea (TA) defect may arise during penile prosthesis surgery or reconstruction of the penis in patients with Peyronie's disease (PD). Different free grafts may cover the defect in a patient with and without erectile dysfunction resulting in variable degrees of success (1-3). Of-the-shelf grafts are attractive because they are readily available and avoid donor site morbidity. These graft materials' most significant clinical outcome benchmarks are maintained erection, avoidance of recurrence curvature, and avoidance of shortening due to graft fibrosis. In experimental animals, the fate of the graft varied from degeneration, inflammation, and fibrosis, on one side of the spectrum to complete regeneration of TA-like tissue replacement on the other (*Table 1*). An alternate graft is a collagen fleece covered with thrombin and fibrinogen reported in conjunction with surgical treatment of PD (31,32). TachoSil has gained popularity for patients with good erection or who need a penile prosthesis (1,33,33-38). The use of TachoSil had distinct advantages of shelf availability, self-adhesion property, hemostatic effect, no need for suturing, shortening of the procedure time and avoidance of needle puncture of the penile prosthesis (39). The application was adapted for plaque incision or partial or complete excision with and without prosthesis implantation.

TachoSil is a fibrin sealant patch indicated as an adjunct to hemostasis during bleeding control by standard surgical technique (40). It consists of human fibrinogen and human thrombin coated onto an equine patch.

The histopathological consequences of the TachoSil patch to cover corpus cavernous tunica defects is unknown. The characteristics of resultant scar, risk of colonization, neovascularization, promotion of tunica regeneration, or changes in the corpus cavernosum tissue are unknown. However, all these factors may explain the repair outcome regarding corporal function, risk of erectile dysfunction, infection rate, and protection of the underneath penile prosthesis if present. This information may help to understand the difference in outcome between graft materials for PD in the clinical setting.

In this experiment, we are looking for a histological evaluation of the fate of TachoSil graft application to the TA and its effect on the underlying corpora cavernosa. We present this article in accordance with the ARRIVE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-229/rc).

Highlight box

Key findings

- TachoSil patching of penile tunica albuginea (TA) defect forms a distinctive barrier against inflammation, protecting the underlying corpus cavernosum (CC). However, no regeneration of the tunica defect is observed at 2 months in experiments in rats.

What is known and what is new?

- TachoSil patch is used in patients to bridge gaps in TA during surgery for Peyronie's disease with or without penile prosthesis implantation. However, the histopathological changes in the defect and the underlying CC are unknown.
- Unlike other reported materials, a complete regeneration of TA is not seen. However, TachoSil protects the underlying CC from inflammation.

What is the implication, and what should change now?

- Using TachoSil to cover gaps in TA during penile surgery has the advantage of protecting the underlying CC. However, a better understanding of the mechanism TachoSil sustains erection without a penile prosthesis is needed.

Methods

Experimental protocol

Six Sprague Dawley adult male rats were used. The experiments and animal care were conducted in the Comparative Medicine Department of our institution. The house veterinarian and veterinarian assistants carried out anesthesia and perioperative care. Rats were allowed free access to water and food perioperatively. All procedures were carried out under general inhalation anesthesia with isoflurane. Cefazolin 100 mg/kg/i.m. was injected at induction. Under sterile conditions and operative microscope magnification up to ×20, the penis was degloved through a circumferential subcoronal incision. A 1 mm × 10 mm defect was created at the base of the lateral aspect of the penis. A TachoSil patch (Takeda, Japan) was fashioned 5 mm × 15 mm, applied dry to the defect, and trimmed. Pressure on the patch was applied for three minutes. The penile skin covering was restored and fixed with interrupted 5–6 zero absorbable sutures. Postoperatively, for analgesia, 2 mg/kg of Carprofen was administered subcutaneously every 24 hours for 5 days. The rats were inspected daily for general condition and wound appearance.

At 2 months under general inhalation anesthesia, the rat penis was excised. Euthanasia was carried out with an overdose of inhalation anesthesia and chest opening to

Table 1 Experimental animal studies showing the outcome of grafting of TA defect using different materials

Study	Graft	Setting	Animal	Duration	Histology of graft	Erection	Cavernosography
Leungwattanakij (4), 2003	Cadaveric pericardium	Cadaveric pericardium *vs.* vein	Rat	4 months	Penile fibrosis is significantly higher with pericardium than with vein or control	NA	NA
Leungwattanakij (5), 2003	Cadaveric pericardium	Cadaveric pericardium *vs.* dermis, vein, or Gore-Tex	Rat	6 months	Minimal fibrosis for all grafts but moderate to severe with Gore-Tex	No difference of nerve induced erection among groups	NA
Leungwattanakij (6), 2000	Cadaveric pericardium	Graft *vs.* control	Rat	4 months	Fibrosis under graft, no graft replacement with normal TA	Comparable to controls	NA
Stefanovic (7), 1994	Fascia	Temporoparietal fascia; vascularized *vs.* non-vascularized graft	Rat	3 months	Secondary degeneration in all non-vascularized and one-third of vascularized graft	Strait erections	NA
Hafez (8), 2004	Fibrin glue	Cover a 5 mm × 15 mm tunica defect	Rabbit	12 weeks	Complete regeneration of TA	Straight pharmacologic-induced erection	No narrowing or venous leakage
Eberli (9), 2007	Matrix	Acellular bladder matrix grafts	Rabbit	3 months	Biomechanically compatible tunica substitution	maintenance of normal intracavernous pressure	normal anatomy
Joo (10), 2006	Matrix	Acellular porcine bladder matrix *vs.* normal controls	Rabbit	6 months	No significant histological differences between the implanted tunica and the normal control tunica	NA	NA
Shokeir (11), 2004	Matrix	TA acellular matrix; cover a 30 mm × 10 mm tunica defect	Dog	6 months	Regeneration of tunica histologically similar to normal tunica	Straight, rigid pharmacologic-induced erection	Patent corpora cavernosa
Wefer (12), 2002	Matrix	Acellular matrix; penile reconstruction	Rabbit	6 months	No difference between natural and regenerated tunica	Papaverine erection in 15/18 animals, 11/18 rigid and straight	Four penile deviations
Ferretti (13), 2012	Polyglycolic acid	Scaffold *vs.* scaffold seeded with autologous fibroblast *vs.* autograft *vs.* sham	Rat	4 months	Seeded TA displayed higher collagen density and preserved but small sinusoidal spaces; outer layer longitudinal reorganization and external collagen bundles have the same spatial orientation as the original	Significantly less than controls	NA
Bazeed (14), 1983	Polyglycolic acid	Mesh	Dog	6 months	Replacement by fibrous connective tissue	NA	No curvature of the penis, bulging, or obstruction
Blumenfrucht (15), 1983	Polytetrafluoroethylene	Replacement of segmentally excised TA	Dog	–	None had an inflammatory reaction	–	–

Table 1 (*continued*)

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Study	Graft	Setting	Animal	Duration	Histology of graft	Erection	Cavernosography
Gundogdu (16), 2021	Silk fibroin scaffold	Silk fibroin scaffold, SIS, TV *vs.* nonsurgical controls	Rabbit	3 months	Fibroin scaffold, SIS: neo tissue similar to control TA; SIS and TV: the corpus cavernosum showed significant fibrosis and loss of smooth muscle cells	TV and fibroin scaffold: 80% of animals had a full pharmacologic erection; SIS: only 40%	No leak in all grafted.
Ma (17), 2012	SIS	SIS *vs.* SIS seeded with stem cells	Rat	8 weeks	Mild fibrosis around the graft and the elastic fibers of the graft were orientated in two layers similar to the adjacent TA	Seeded grafts were comparable to controls	NA
Leungwattanakij (18), 2006	SIS	Penile enhancement	Rat	2 months	Replaced with circularly oriented elastic fibers with minimal fibrosis under the graft	NA	NA
El-Assmy (19), 2004	SIS	SIS *vs.* TV flap	Rabbit	12 weeks	Replaced by normal TA-like tissue	Straight, rigid pharmacologic-induced erection	Intact veno-occlusive mechanism
Hafez (20), 2004	SIS	SIS 1 layer *vs.* 4-layer graft	Rabbit	12 weeks	One layer of SIS graft was entirely replaced by tissue similar to normal TA with no inflammatory infiltrate; 4-layer graft showed dense fibrosis, chronic inflammation, and focal calcification	NA	NA
Kropp (21), 2002	SIS	SIS graft *vs.* autologous tunica graft	Rat	6 months	Complete integration and histological similarity to autologous tunica graft	No graft ballooning or expansion was noted with pharmacologically induced erection	NA
Monga (22), 2002	SIS	SIS *vs.* sham	Rabbit	45 days	Minimal inflammation, and no cavernous smooth muscle loss or fibrosis underneath the graft	Preservation of pharmacologic erection	NA
El-Assmy (23), 2007	Surgicel	Cover a 15 mm × 5 mm tunica defect	Rabbit	3 months	Complete replacement of the defect by regenerated tunica, absorption of the Surgicel	Straight and rigid erection	straight erection with patent corpora and no evidence of narrowing or a venous leak
Sansalone (24), 2017	TA	Allotransplantation	Rat	6 months	Biointegration with surrounding TA	NA	NA
Ferretti (25), 2014	TA	Autograft *vs.* allograft	Rat	12 weeks	Penile curvature 25 degrees, decreased elastin fiber length, intense scarring and cartilage formation, chronic inflammation, and localized osteogenesis	Erection maintained below 12 weeks	NA

Table 1 (*continued*)

induce pneumothorax. The excised penis was fixed in 10% formalin and sent to the anatomical pathology lab. Tissue cross sections of the penis were stained with hematoxylin, eosin, and trichrome. The pathologist evaluated the tissue sections for fibrosis, inflammation, new vascularity, graft resorption, and new tissue regeneration.

Statistical analysis

The mean and standard deviation of the body weight of rats was reported. The endpoint was preset at 2 months. No other analysis was performed on the histopathology images.

Literature review

A literature review of PubMed citations was conducted using the search terms combining TA with either graft, rat, rabbit, or dog. The search was limited to the English language literature but not the publication date. The search syntax was as follows: Search: ((((((tunica albuginea) AND (("rat"[All Fields]) OR (rats))) OR ((tunica albuginea) AND (("rabbit"[All Fields]) OR ("rabbits"[All Fields])))) OR ((tunica albuginea) AND (("dog"[All Fields]) OR ("dogs"[All Fields])))) OR ((("graft"[All Fields]) AND (TUNICA ALBUGINEA)) AND (("dog"[All Fields]) OR ("dogs"[All Fields])))) OR ((("graft"[All Fields]) AND (TUNICA ALBUGINEA)) AND (("rat"[All Fields]) OR (rats)))) OR ((("graft"[All Fields]) AND (TUNICA ALBUGINEA)) AND (("rabbit"[All Fields]) OR ("rabbits"[All Fields]))).

Ethical statement

A protocol was prepared before the study without registration. Experiments were performed under a project license (No. 2210008) granted by the Animal Use and Care Committee of King Faisal Specialist Hospital and Research Center Office of Research Affairs, in accordance with the Guide for the Care and Use of Laboratory Animals, 8th edition.

Results

Experimental animal study

At the time of surgery, the rats' weight was 369.2 gm (standard deviation: 31.5). Five rats showed at gross examination a normal-looking penis at 2 months with complete healing, no scaring, tethering, or gross inflammatory

Table 1 (*continued*)

Study	Graft	Setting	Animal	Duration	Histology of graft	Erection	Cavernosography
Seyam (26), 2007	TA	Autologous crura TA	Baboon	12 months	Graft was indistinguishable from the adjacent tunica with no fibrosis	No change in pressure	Venous leak in 2/8, angulation of penis in 4/8 animals
Bagbanci (27), 2015	TV	TV or rectus muscle fascia; penile enhancement	Rat	2 months	Complete resorption due to lack of vascularization	NA	NA
Hafez (28), 2001	TV	Compare TV graft *vs.* TV flap	Rabbit	12 weeks	Contracted by a mean of 42%, fibrosis	NA	NA
Brannigan (29), 1998	Vein	Dorsal vein *vs.* silicon *vs.* skin	Dog	3 months	Reformation of tunica, moderate fibrosis, loss of typical venous architecture	Comparable to preoperative pressures	NA
Brock (30), 1993	Vein	Femoral vein *vs.* control	Rat	6 months	A return of near normal tunica structure with areas of mild fibrosis	Comparable to controls	NA

TA, tunica albuginea; NA, not available; SIS, small intestinal submucosa; TV, tunica vaginalis.

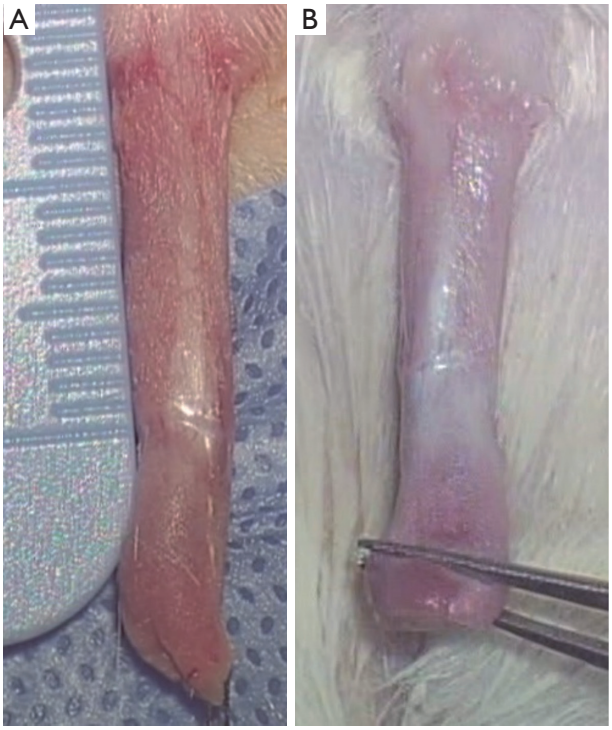

Figure 1 Rat penis gross appearance, (A) before and (B) after 2 months post-TachoSil patch.

features (*Figure 1*). No induration could be felt upon palpation of the graft site of the rat penis. However, upon excision, two rats had subcutaneous pockets of pus. Histopathologic examination of the site of the TachoSil patches showed fibrosis, chronic inflammation, and foreign body giant cell reaction in all rats (*Figure 2*). There was no generation of a new TA, or new vascularity. No inflammatory or pathological reaction affected the underlying corpus cavernous tissue.

One rat died on the 6th postoperative day. Postmortem showed massive gastrointestinal bleeding, intraperitoneal hemorrhage, and punctate hemorrhages of the parenchyma of both suprarenal glands, both kidneys, and the liver (*Figure 3*). A clinical diagnosis of disseminated intravascular coagulopathy (DIC) was made. Histopathology of the penis, however, did not show micro thrombosis.

Literature review

The literature review search retrieved 259 articles. A review of the abstracts and selected full-text articles resulted in eliminating irrelevant articles or articles with no clear methodology or conclusion on TA grafting or shorter than the one-month follow-up, leaving 27 with adequate reporting on histopathology fate of the grafts (*Table 1*). Seventeen articles reported complete or similar tissue regeneration of TA. Six of these grafts were SIS, four acellular matrices, two veins, two auto or allografts, one fibrin glue, one Surgicel, and one polyglycolic acid scaffold. The other four articles reported degeneration of the graft area associated with tunica vaginalis, cadaveric pericardium, temporalis fascia, and polyglycolic acid mesh. Three papers described no inflammation and no or minimal fibrosis of the cavernous tissue, while two articles reported moderate to severe fibrosis.

Discussion

Experimental animal and clinical studies indicated that various graft materials for penile surgery have different advantages. The ideal graft for PD surgery has yet to be discovered. Multiple literature reviews reported that these grafts are comparable regarding clinical outcomes; however, the heterogeneity of the series published makes it difficult to conclude (1-3,41-43). Nevertheless, TachoSil stands out as an operative time saver compared to others (3,36,37,44,45). Due to its ready availability, sutureless application, and hemostatic effect, TachoSil gained popularity in PD surgery. Furthermore, TachoSil was used to repair failed grafting of Peyronie's disease (46).

Regeneration of TA

Unlike other grafts that were tested in the experimental animal, the fate of the TachoSil graft for the penile TA defect is not known. The literature review of other graft materials yields varied results extending from complete regeneration of the TA on one end of the spectrum to complete degeneration and fibrosis at the other (*Table 1*). SIS, vein, and TA acellular matrix grafts were the most commonly reported grafts replaced with identical or nearly identical TA with minimal impact on the underlying cavernous tissue (8-13,16-21,23,29,30). In another set of experiments, however, tunica vaginalis, cadaveric pericardium, temporalis fascia grafts, and polyglycolic acid mesh did not show regeneration. These studies, however, reported degeneration, complete absorption, lack of vascularization, replacement by fibrous connective tissue, and fibrosis of the underlying cavernous tissue (6,7,14,27). In our experiment, there is no evidence of regeneration of the TA or neovascularity commonly reported.

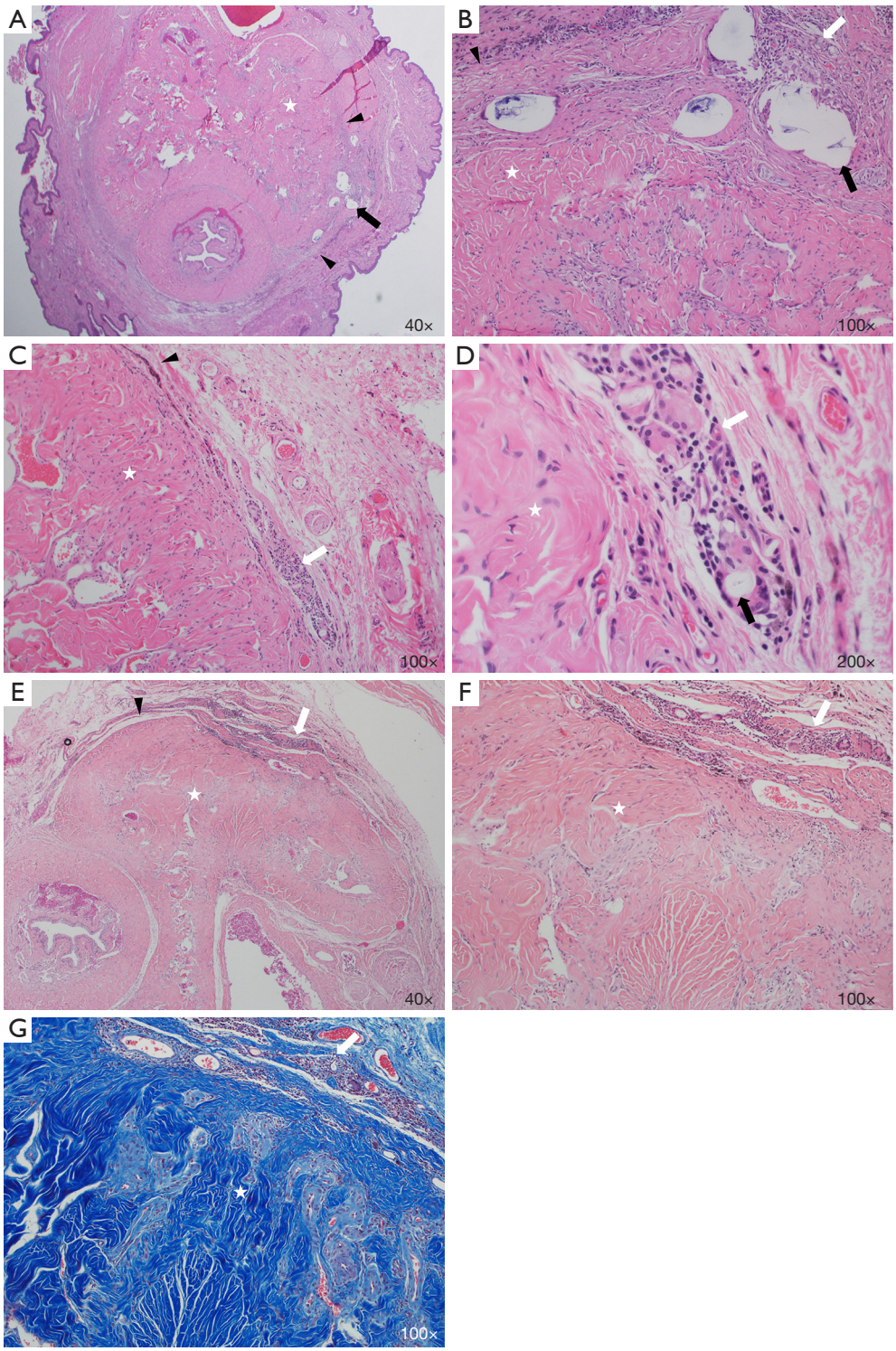

Figure 2 Histopathology of rat penis at the graft site after 2 months. Sections (A-F) show hematoxylin and eosin staining. There are remnants of the TachoSil (black arrows) inciting a chronic inflammation with foreign body giant cells (white arrows). However, the corpus cavernosum (stars) is sealed off from the inflammation and shows an intact structure. No regeneration of the TA (black arrowheads) bridges the graft area. Section (G) shows a trichrome stain intact corpus cavernosum (star) underneath the chronic inflammation induced by TachoSil (white arrow). TA, tunica albuginea.

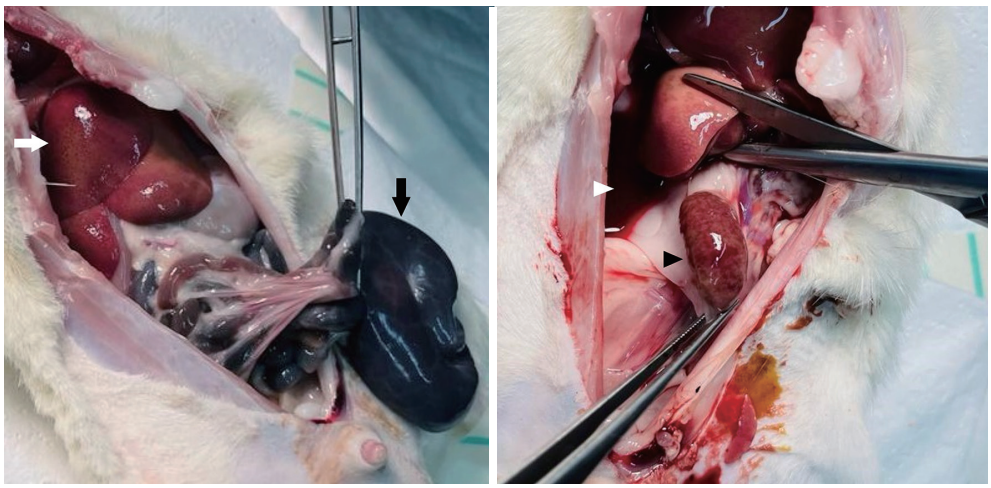

Figure 3 Postmortem on the 6th postoperative day of TachoSil patching showed intraperitoneal hemorrhage (white arrowhead), hepatic (white arrow), and renal (black arrowhead) punctate hemorrhages and bowel hemorrhage (black arrow).

Tissue reaction

After 2 months, TachoSil grafts almost resorb, leaving granulation tissue and chronic inflammatory cells. No fibrous sheet bridging the TA defect was seen. There was no development of fibrosis. Clinically, when compared to SIS, TachoSil was associated with less recurrence of curvature and less shortening of the penis (44). These differences might be related to the tendency of SIS to contract even with techniques to mitigate penile shortening (1,47,48).

How TachoSil sustains penile rigidity?

Early experience with TachoSil patching and plaque incision or excision in patients with an erection hardness score of a mean of 3.4 showed that the score decreased significantly to 2.6 (31). In subsequent larger and multicenter clinical studies, the TachoSil patch, even with a relatively large size, was associated with nearly ~ 16% *de novo* erectile dysfunction (36,37). The reported mean longitudinal length of TA defect is 21.9 mm (range, 5–40) for plaque excision (38). After patching, the only support to the graft is from the reapproximated buck's fascia. Early postoperative assessment of erection was not reported; however, longer follow-up results from the same author indicated that 84.3% of patients had unchanged or improved erection (36). This figure is comparable to or even better than all other graft applications for patients with PD and absent erectile dysfunction.

One factor which may have contributed to the support of the cavernous pressure is the tensile power of TachoSil demonstrated in other surgical applications (46,49,50). In the dog, a 1 cm longitudinal incision in the external iliac artery, non-sutured and patched for 5 minutes with TachoSil similar graft (Tachotop, Hormonchemie, Munich, Germany) could stand pressure up to 260 mmHg (49). At four weeks, resorption of the patch occurred and was replaced by mature granulation tissue and cell-depleted collagen tissue. Subsequently, TachoSil is used to bolster the high-pressure cardiovascular structures during surgery, such as the cardiac ventricles and aorta (50).

Another contributing factor to the preservation of erection is the intact underlying cavernous smooth muscle. Our experiment showed that TachoSil protects the underlying corpus cavernous from superficial inflammation by forming a barrier. There is no evidence of fibrosis or necrosis as well. Furthermore, the effect on erection compared to other graft materials may not be related to the tensile strength of the graft but rather the incision or excision of TA during surgery. Autologous TA grafts are associated with 11–18% ED, implicating that the damage of the underlying layer at the TA cavernous tissue junction is a significant contributing factor (26,51,52). Clinical reports of grafts that are replaced by a TA-like tissue still were associated with 4.5–56.5% *de novo* ED (44,47,48,53-57). The development of ED is directly proportional to the size of the graft (47).

The tensile strength of TachoSil is also important in patients undergoing penile prosthesis implantation.

Grafting materials including TachoSil in association with penile prosthesis did not show significant differences in the outcomes (3). To our knowledge, there is no report of aneurysmal dilation at the site of TachoSil patch in those patients.

DIC

One of our rats developed DIC on the sixth postoperative day and expired. Reviewing the literature for the association of TachoSil and DIC or thrombosis did not provide similar reports in PubMed. TachoSil is impregnated with thrombin. However, a search of DIC and thrombin identified some studies and case reports (58-67). The thrombovascular event like DVT/PE could be related to two mechanisms. One is the direct activation of the hemostatic agent to the coagulation mechanism as a dose-dependent phenomenon. The other is an immune-mediated mechanism associated with bovine-driven thrombin use in humans. As TachoSil contains human-derived thrombin, an immune reaction of the rat may have mediated the DIC in our experiment.

In the prescription details of TachoSil approved by the FDA, there is a warning of thrombosis if the TachoSil gets into systemic circulation. FDA safety reports DIC in a six-month-old female patient in association with the TachoSil arm of hemostasis in a liver resection trial (68). On the 12th day, the patient developed DIC and mycobacterium septicemia, and on the 13th-day portal vein thrombosis. After protracted surgical morbidity, the patient died. The reviewer concluded that there is no evidence that these events are related to the TachoSil application. However, there is a concern, though theoretical, of perturbation of the coagulation system, and routine laboratory vigilance is needed.

Fortunately, there are no clinical reports of thrombosis associated with TachoSil applications in PD surgery. The surgeon, however, should be vigilant as the cavernous tissue exposed is vascular tissue with direct drainage into the systemic venous system. The problem might be more significant in patients with healthy cavernous tissue and a large TA defect created during surgery when venous drainage is unimpeded. A factor that may have lessened the risk of thrombin reaching the systemic circulation in patients is the avoidance of artificial erection by infusing saline in the corpora not to dislodge the un-sutured TachoSil patch. Although saline infusion at this test is usually applied with a tourniquet at the base of the penis, the release of the tourniquet will immediately lead to cavernous drainage into the systemic veins.

The strength of our study is that it is the first to demonstrate the histopathology of the TachoSil patch applied to the penile TA defect. In addition, the results help to understand the outcomes of TachoSil applications in PD surgery and how it compares to other grafting materials.

The weakness of this study is that it lacks control animals, a short follow-up time, and a lack of evaluation of erection.

Conclusions

TachoSil grafting of the TA protects the underlying cavernous tissue from inflammation, fibrosis, and necrosis. However, there is no regeneration of TA-like tissue bridging the created defect. TachoSil almost resorbs by 2 months of grafting, leaving a chronic inflammation with foreign body giant cells in place. Fatal DIC developed in one of our rats. Although clinically not proven, laboratory vigilance toward developing DIC is advised.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-229/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-229/dss

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-229/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-229/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Experiments were performed under a project license (No. 2210008) granted by the Animal Use and Care Committee of King Faisal

Specialist Hospital and Research Center Office of Research Affairs, in accordance with the Guide for the Care and Use of Laboratory Animals, 8th edition.

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Cite this article as: Seyam RM, Mandourah HM, Kattan MS, Al-Hussain T, Altaweel WM, Kattan SA. A study of the histopathology of collagen fleece (TachoSil) patching of tunica albuginea in the rat penis and a literature review of penile graft materials in experimental animals. Transl Androl Urol 2023;12(8):1238-1249. doi: 10.21037/tau-23-229

