Peer Review File

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Reviewer A

This manuscript is an interesting one studying a penile graft material and its effects on the Tunica albuginea and even corpus cavernosum, however, there are some concerns about the strength of the manuscript.

Comment 1: Despite the intent to focus on Tachosil, there should be some kind of larger comparison or control group. The current separation of 6 TachoSil rates and only 1 surgicel, makes the conclusions from the study weak. Especially given the 1 surgicel rat had postoperative complications, one would think this group should be expanded to include more rats in the surgicel group.
Reply 1: The goal is to find out what happens with TachoSil. No regeneration of tunica occurs. Will this happen with surgicel is possible however surgicel is not the material to test. We might as well remove the rat with surgicel from the study. In another study we might focus on surgicel as a possible graft material. However, the clinical application of surgicel was not previously a focus of clinical application.
Changes in the text: (See reply 11, for details and changes in the text) Surgicel rat was removed from the abstract and results. The figure was adjusted to remove its histopathology. In the legend section under Figures, Fig 2, the following text was deleted "H. Shows a hematoxylin and eosin section of the Surgicel grafted rat with inflammation (white arrowheads) reaching into the corpora cavernosa (star). Black arrowhead = tunica albuginea."

Comment 2: Explanation as to how was it concluded that there was no inflammatory or pathological reaction to underlying cavernous tissue would improve this manuscript.
Reply 2: Histological examination shows no inflammatory cells or fibroblasts. The findings are based on the histopathology reading of a single fellowship certified Genito urology pathologist. (For further discussion please see reply 22).
Changes in the text: None as the methods section the text includes "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."

Comment 3: The current fusion of translational experiment methods and results with that of the systematic review is not idea. The authors should consider restructuring the methods and results section with subheadings to separate the systematic review methods/results from the experimental study's methods/results. Could alternatively list all the search criteria and results of the systematic review in the discussion portion of the paper, prior to the DIC section.

Reply 3: The authors included subheading in the methods and results sections as recommended by the reviewer.

Changes in the text:

Methods:

In page 2 line 64 the authors added "Experimental protocol:"

In page 2 line 84 the authors added "Literature review:"

Results:

In page 3 line 96 the authors added "Experimental animal study:"

In page 3 line 111 the authors added "Literature review"

Comment 4: Lines 143-145 grammatical errors.

Replay 4: the text was rephrased.

Changes to the text: *In page 4 line 141* the authors replaced "In another set of experiments however tunica vaginalis, cadaveric pericardium, and temporalis fascia grafts, and polyglycolic acid mesh did no show regeneration but rather degeneration, complete absorption, lack of vascularization, replacement by fibrous connective tissue and fibrosis of the underlying cavernous tissue." with "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."

Comment 5: Lines 176-178, would consider removing these lines as it is not appropriate to draw parallels to liver models that show Tachosil promotes regeneration given that the liver is the one organ that is especially known and studied to have innate regenerative capacity... the same cannot be said for TA.

Reply 5: The lines and the reference "50" were removed, and the sequence of references was rearranged.

Changes to the text: *In page 5 line 177* in the discussion section the following text was deleted "These findings are like those found in liver surgery experiments. It was established in the swine liver resection model that Tachosil promotes regeneration of the underlying liver cell and has less liver cell necrosis than controls or other sealant methods.[50]"

Comment 6: Given this is a systematic review, a diagram or more in depth text explanation within the manuscript should describe how many articles were initially found in the systematic review, how many were excluded as being irrelevant, without clear methodology etc., which all finally resulted in 27 articles being included.

Reply 6: The information is already present in the article. In the results section the following text reads "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 tunica albuginea grafting or shorter than the one-month follow-up, leaving 27 with adequate reporting on histopathology fate of the grafts (Table 1).[4–30]" Reviewer "C" recommended to change the method of

the review from systematic to literature review as it does not follow the Cochrane criteria for systematic review. Therefore, the authors replaced “Systematic review” with “literature review” in the whole manuscript.
Changes to the text: None.

Reviewer B

Comment 7: I enjoyed reading the this paper and review of literature. I would have liked if you had a series of time-points to see if histology changes in time.
Reply 7: The reviewer put forward a significant improvement point to this manuscript. The authors will consider this modification of the experiments in further studies on Tachosil grafts. This same point was raised by reviewer “E” below. The authors found several experiments of graft the rat penis with outcome measure at 2 months. In a larger animal, the rabbit had complete regeneration of the tunica albuginea at 3 months in several reports. The authors believe that the complete absence of regeneration and new vascularization at 2 months will probably not convert to complete generation at 3 months. Further time points however will certainly show any additional long term adverse effects such as fibrosis and is worth including in further studies. (Please see reply 23.)
Changes to the text: None

Reviewer C

I was thrilled when I got the TAU editor's request to review your article, since I myself have a lot of questions using Tachosil as a patch in the TA, However I must say, I am a little disappointed with your work.

Comment 8: Abstract: The results section is confusing, the reader need to make an effort to understand that the histopathological fibrosis, does not corelates with a fibrous layer.
Reply 8: The “no fibrous tissue” was deleted. The paragraph was rewritten for clarity.
Changes to the text: *In page 1, line 20*, the authors replaced following text “There was no generation of a new TA, no new vascularity, or distinct fibrous layer development. Any inflammatory or pathological reaction did not affect the underlying corpus cavernous tissue.” with “There was no generation of a new TA, or new vascularity. No inflammatory or pathological reaction affected the underlying corpus cavernous tissue.” *In the result section page 3, line 101*, the authors replaced the text “Histopathologic examination of the site of the Tachosil patches showed fibrosis, chronic inflammation, and foreign body giant cell reaction in all rats (Fig.2 A-G). There was no generation of a new tunica albuginea, no new vascularity or distinct fibrous layer development. Any inflammatory or pathological reaction did not affect the underlying corpus cavernous tissue.” with “Histopathologic examination of the site of the Tachosil patches showed fibrosis, chronic inflammation, and foreign body giant cell reaction in all rats (Fig.2 A-G). There was no generation of a new tunica albuginea, or new vascularity. No

inflammatory or pathological reaction affected the underlying corpus cavernous tissue."

Comment 9: Methods:

1- Explain why the TA defect was 1x10mm and why longitudinal and not circumferential.

Reply 9: *Longitudinal not circumferential:* The defect was not made circumferential because that would require dissection of the neurovascular bundle dorsally or the corpus spongiosum ventrally to get a large graft area. The dissection would have increased the complexity of the surgery and increased the chance of complications not related to the grafting itself.

Dimensions of the defect: The length of the adult rat penis is 40 mm of which 1/3 of the length is the glans and the circumference is 9 mm corresponding to a 3 mm diameter [1]. Subtracting the dorsal and ventral circumference length occupied by the neurovascular bundle and urethra leaves approximately 3 mm circumference for each tunica albuginea on either side of the penis. The choice of the width at 1 mm was based on the available width of the lateral tunica albuginea comprising 1/3 of the lateral circumference. Furthermore, wider excision would have required longer duration of observation. The 10 mm longitudinal excision was considered relatively appropriate. The graft size, however, in our experiments is large enough (5x15 mm) to cover the lateral side of the tunica. Other studies used a defect in the rat of 2x10 [2]; 5x2mm [3]; 2x4mm [4–7] I shaped incision covered by 3x10 mm graft [8], elliptical incision covered by 3x7 mm graft [9]. There is similarity between our graft site defect with others. However, we felt that a narrow graft defect will permit more rapid regeneration of the tunica to be observed which did not materialize in our experiments.

Changes to the text: None.

Comment 10:

2- What this defect size means to the total area of the rat penis? (10%, 15%, 20 %?) *

Reply 10: The approximate one side tunica area from the dorsal neurovascular bundle to the ventral corpus spongiosum is 3 x 20 mm = 60mm2. The defect was 10 mm2. The ratio of the defect to the area of the grafted side is approximately 10/60 = 16%.

Change to the text: None.

Comment 11:

3- Why you use Surgicel only in one rat? This does not add any substantial information to your study or help to make it more interesting, since you can't compare the groups. ** I suggest remove this from your study.

Reply 11: the authors agree with the reviewer and the surgicel rat was removed form text and figure.

Changes to the text:

In the abstract methods section, page 1, line 12, the authors replaced "Seven" with "Six".

In the abstract methods section, page 1, line 14, the authors replaced "A TachoSil patch (Takeda, Japan) was applied to the defect in six rats and Surgicel (Ethicon) in one."

with “A TachoSil patch (Takeda, Japan) was applied to the defect.”
In the abstract results section, page 1, line 18, the authors replaced “Results: Rats weighed 390 gm (SD 33.8). At two months, all rats with TachoSil showed normal-looking penis …” with “Results: Rats weighed 369.2 gm (SD 31.5). At two months, all rats showed normal-looking penis …”
In the abstract results section, page 1, line 24, the authors deleted “The seventh rat with a Surgicel patch had a postoperative hematoma, and at two months, large pockets of pus were seen at the penis. Histopathology showed chronic inflammation and fibrosis extending into the corpus cavernosum.”
In the methods section, page 2, line 65, the authors replaced “Seven Sprague Dawley adult male rats were used.” with “Six Sprague Dawley adult male rats were used.”
In the methods section, page 2, line 73, the authors deleted “One rat received a Surgicel (Ethicon) patch.”
In the results section, page 3, line 97, the authors replaced “At the time of surgery, the rats’ weight was 390 gm (SD 33.8). Five rats with TachoSil showed at gross examination a normal-looking penis...” with “At the time of surgery, the rats’ weight was 369.2 gm (SD 31.5). Five rats showed at gross examination a normal-looking penis…”
In the results section, page 3, line 105, the authors replaced “One rat of the Tachosil group died on the 6th postoperative day.” with “One rat died on the 6th postoperative day.”.
In the results section, page 3, line 109, the authors deleted “The seventh rat with a Surgicel patch showed immediate hematoma of the penis controlled by compression. After two months, during harvesting of the penis, large pockets of pus were seen spreading from the site of the patch to surrounding structures. Histopathology showed chronic inflammation and fibrosis extending into the corpus cavernosum with scattered hemosiderin deposition (Fig. 2 H).”
In the legend section, *page 11, Fig 2,* the authors deleted the following text “H. Shows a hematoxylin and eosin section of the Surgicel grafted rat with inflammation (white arrowheads) reaching into the corpora cavernosa (star). Black arrowhead = tunica albuginea.”
In figure 2 the authors removed the histology section labeled 2H.

Comment 12:
4. Your review does not meet the Cochrane criteria for systematic reviews. I recommend you change it to literature review.
Reply 12: The systematic review was changed to literature review.
Changes in the text: *In page 1, line 2,* the authors changed the title “A study of the histopathology of collagen fleece (TachoSil) patching of tunica albuginea in the rat penis and a systematic review of penile graft materials in experimental animals.” which was replaced with “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.”
In the manuscript, page 1, line 16; page 2, line 84; page 2, line 85; page 3, line 111;

page 3, line 112; page 3, line 127; and page 4, line 136, "systematic review" was replaced by "literature review."

Comment 13: * Morgado's study Reference 46 shows that the size of the grafting has direct correlation to post op ED development, i.e., smaller grafts = Less post op ED
Reply 13: The authors added text to reflect this finding.
Changes in the text: *In the dissuasion section, page 5, line 182,* the authors added "The development of ED is directly proportional to the size of the graft.[47]" The reference number was changed to 47 because of the insertion of one reference as suggested by reviewer "D".

Comment 14: ** El-Assmy study Reference 23 already have shown the Surgicel was replaced by TA regeneration in rabbit penis.
Reply 14: The authors reported in the discussion "Seventeen articles reported complete or similar tissue regeneration of tunica albuginea. 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." These findings were also reported in Table 1.
Changes in the text: None.

Comment 15: Results: Line 101 - 2" Histopathology examination if the site of tachosil showed fibrosis, chronic inflammation and foreign body giant cell reaction ... no generation (* here the word regeneration of TA) of new TA, no new vascularity or distinct fibrous layer ..." Although no fibrosis layer was not formed, what that means in the penile rat physical exam? Could you fill an induration where the patch was placed comparing to the normal TA tissue on the rat's penis?
Reply 15: Gross examination at the time of harvest did not show any induration. The authors reflected that by adding text.
Changes in the text: *In the result section, page 3, line 99,* the authors added. "No induration could be felt upon palpation of the graft site of the rat penis."

Comment 16: On line 199: American FDA is redundancy since there is only FDA in the USA, remove the word "american".
Reply 16: Removed.
Changes in the text: *In page 5, line 199,* the authors deleted "American."

Comment 17: One of the goals of the surgeries using graft is to restore erection, the lack of evaluation of the erectile function in the studied subjects, weaks your article.
Reply 17: The authors admitted this shortcoming in the weakness of the article comment. However, the author's report on the histological fate of the Tachosil in the graft area has not been previously reported. The authors think that the findings are essential in the case of using Tachosil to bridge tunica defects when a penile prosthesis is implanted. The effect on erection in this situation is irrelevant. Of our literature review, out of 27 experimental studies, eight focused on the histological and morphological changes with no reporting on erection (Table 1). However, as the

reviewer correctly stated, the evaluation of erection is important when considering Tachosil grafting in Peyronie's disease surgical correction without prosthesis implantation. This information will shed some more basic science background to the clinical application where minimal or no ED was reported. The authors plan to study erection in another experiment involving larger animals where pharmacological erection will be assessed. Unfortunately, the authors do not have the facility for nerve-stimulated erection and sensitive erectile pressure recording in the rat experimental animal model.
Changes in the text: None.

Comment 18: In the discussion (lines 157 - 170) you wrote that the EHS decreases about 1 point in patients who had Tachosil patches, this changes the patient ED from Hard enough for penetration to not hard enough to penetration. Since you did not evaluate the rat erectile function an evaluation if there is a difference in the tension force that needs to by apply to rupture the normal rat's TA to the one that was replaced by the Tachosil would strength your data. (if possible I suggest you add this information)
Reply 18: The authors did not experiment on the tension rupture relation in this study.
Changes in the text: None.

Comment 19: As final comments: In practical terms, what the physician wants to understand is the results when extrapolated to Humans will be useful. 1- Your article misses important assessment as subjective physical exam tactile sensation, even with no histopathological fibrous layer the examiner, therefore the patient would feel a "fibrotic area" where the patch was inserted (to decrease the bias, you could ask someone who did not know here the patch was place to perform the PE); 2- Did the tachosil affected the rats erection/capacity to have intercourse?
Reply 19: These points were answered for comments 15 (induration) and 17 (erection). Gross examination of the penis at harvest did not indicate the presence of an induration at the site of the graft. This corresponds with the lack of fibrous plaque formation. Erection was not evaluated either by observing rat copulation changes or by measuring intracavernous pressure response to nerve or pharmacological stimulation.
Changes in the text: please see reply 15 and 17.

Comment 20: Your article has an excellent idea and hypothesis, the fact that you were able to show that there is no TA regeneration after Tachosil it's an important achievement. I suggest you perform a major re-writing changing the focus of the article to describe the histological aspects.
Reply 20: The authors thank the reviewer for acknowledging the importance of histological evaluation of Tachosil in penile surgery as it is increasingly reported in the clinical arena with no histopathology reports available. The authors focus in the article is histopathology and comparison with reported literature. No assessment of other parameters was included.
Changes in the text: None.

Reviewer D

Comment 21: PD is still a surgical disease. The surgical plaque management has not yet found an answer as to which is the best heterologous or autologous patch in terms of adaptability to the defect created in the tunica albuginea. The authors explored the histopathological response to tachosil application in penile albuginea, in animal setting. The results corroborated the applicability of the patch already observed in clinical practice. In this regard, please also insert the bibliographic entry relating to the use of the Tachosil patch also in the complications of plaque surgery.
Fabiani A., Fioretti F., Filosa A., Servi L., Mammana G. Patch bulging after plaque incision and grafting procedure for Peyronie's disease. Surgical repair with a collagen fleece. doi:10.4081/aiua.2015.2.173.
No major revisions required.
Reply 21: The authors added the finding from the aforementioned article in the discussion section and updated the reference list accordingly by inserting the reference [10] at the manuscript reference list number (46).
Changes in the text: *In the discussion section, page 4, line 131,* the authors added "Furthermore, TachoSil was used to repair failed grafting of Peyronie's disease.[46]"
In page 4, line 153, the authors replaced the reference numbers "1,46,47' with "1,47,48".
In the discussion section, page 4, line 166, the authors replaced the text "One factor which may have contributed to the support of the cavernous pressure is the tensile power of TachoSil demonstrated in other surgical applications." with "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 page 4, line 170, the reference number 48 was changed to 49.
In page 4, line 173, the reference number 49 was changed to 50.
In page 5, line 182, the reference numbers 44,46,47,53–57 were change to 44,47,48,53–57.

Reviewer E

I read this article with interest.
The Authors want to evaluate the histopathology of collagen fleece (TachoSil) patching of tunica albuginea in the rat penis and submit a systematic review of penile graft materials in experimental animals.
This article can be very interesting since a penile tunica defect may arise during surgery in patients with Peyronie's disease.
Despite this topic is poorly covered in the current literature I think that the paper is not suitable for publication due to several reasons mainly related to a high number of weak points.

Comment 22: Althought population of rats studied is too small in number (7) and for this reason we cannot know if the results are statistically significant. Furthermore a control group of rats was not designed.

Reply 22: The evaluable animals were actually 5 with the Tachosil graft. Definitely, increasing the number of animals will provide more significant findings. However, histopathological findings in five consistently similar rats reflect what is happening at the graft site. Some image analysis reports can yield objective histopathological data; however, the authors did not use any. The findings are based on the histopathology reading of a single fellowship certified Genito urology pathologist. There was no numerical data in the project to analyze with statistics.

Comment 23: The median follow-up time was only 2 months with after surgery wich is inadequate, as it does not allow to correctly evaluate the final results and establish whether the outcomes are definitive.

Reply 23: The authors agree with the reviewer that a more extended follow-up over two months may show additional histopathological changes. However, the authors believe that the two-month results indicate the major histological changes that occur, and a significant event such as new tunica regeneration or do novo damage to the corpus cavernosum is less likely. The authors gave considerable thought to the time of tissue harvesting based on the literature and similar small animal studies. Significantly, the follow-up duration in an animal must correspond to an approximate period in the human life span. The rat's lifespan is 3.5 years, with an accelerated growth and maturity pattern compared to humans [11]. Six months in adult rat life is equivalent to 18 years in human life, and in experiments, one day in rat life is equivalent to 30 days in human life [11]. In several studies in our table 1, 2 months were used as an endpoint histological study in rat penis grafting [8,12,13]. Even at one month, a study showed that bio integration has occurred [7]. In the table, larger animals were assessed at longer experimental observation. The rabbit penile grafts were commonly evaluated at three months [14–20]. One study assessed at 45 days [21]. Some of these studies showed complete regeneration of the tunica albuginea at three months. The authors have chosen two months for histological evaluation as in the rat we postulated that the regenerative process of the tunica will be visible. Our experiment showed none. We were surprised as in several experiments with rabbits at three months there was complete regeneration of the tunica albuginea or replacement with tissue similar to it bridging the defect site. More extended observation would probably show more changes. However, we do not feel that the generative process will start after two months from a point where none existed. Longer observation will likely show more fibrosis, a point to consider in further experimentation. In the absence of regeneration of tunica, various time points of assessment of corporal fibrosis and damage to the cavernous tissue will also be relevant. Although we did not see significant changes at two months, further evaluation at increasing time points will shed more robust conclusions on the effect on the cavernous tissue.

Comment 24: It is difficult to compare SIS with TachoSil stating that was associated with less recurrence of curvature and less shortening of the penis.

For how the study is designed it is not possible to evaluate erection performance over time after the application of TachoSil.

The evaluation of the main outcomes (tissue sections for fibrosis, inflammation, new vascularity, graft resorption, and new tissue regeneration) can be different if the follow up had been longer.
It is difficult to compare SIS withTachoSil stating that was associated with less recurrence of curvature and less shortening of the penis.
Reply 24: The SIS information is quoted from the literature, reference 44 in the manuscript [Rosenhammer B, et al. 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 Jul;31(4):256-262.]. The concerns raised by the reviewer on the evaluation of erection and the duration of the experiment were addressed in replies 17 and 23. The primary outcome, as the reviewer stated, is histopathology. To our knowledge, no similar reports are available, though the clinical application has started since 2013. The information is relevant to the surgery of Peyronie's disease with penile prosthesis implantation. The evaluation of erection is an important addition to such an experiment and will address the use of Tachosil in the non-prosthetic surgical treatment of Peyronie's disease. However, the authors' focus in this report is on histology, and in another set of experiments, the erection will be assessed. The study did not compare SIS with Tachosil. The statement in the discussion is derived from the review of experimental animal literature.

References of the rebuttal letter:

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3. Ferretti L, Giuliani M, Bessède T, Qiu X, Zhang H, Alsaid B, et al. Tissue engineering for penile surgery: comparative study of noncellular and cell-seeded synthetic grafts for tunica albuginea replacement. J Sex Med. 2012 Feb;9(2):625–31.

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