Exosome-Induced Genitourinary Regeneration in a Rabbit Model of Mesh Exposure: A Proposal

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Abstract

Importance: Surgical implantation of polypropylene mesh is a widely accepted and durable treatment for women experiencing stress urinary incontinence and pelvic organ prolapse; however, these surgeries carry a 1-11% risk of mesh exposure in the vagina, bladder, or urethra. Treatment often requires surgical mesh excision. In pilot studies using a porcine model, I have shown that exosome injections (**purified exosome product; PEP**) incite tissue regeneration and resolve vaginal mesh exposures.

Objectives: (1) replicate the pilot studies in a rabbit model of vaginal mesh exposure, evaluate (2) rates of bladder mesh exposure resolution following PEP injection versus sham and (3) the efficacy of PEP as a preventative therapy for mesh exposures.

Methods: 45 New Zealand white rabbits will be randomly divided into 3 groups:

1. Vaginal mesh exposure: Created via sacrohysteropexy technique, injected with PEP or sham at 2 weeks
2. Bladder mesh exposure: Created via intentional cystotomy with a mesh sling, injected with PEP or sham at 2 weeks
3. Mesh exposure prevention: A high-risk for mesh exposure model will be used and treated with PEP or sham at the time of implantation

Results: Forthcoming

Conclusions: This novel study will build upon the prior evidence utilizing an exosome regenerative platform for vaginal mesh exposures. The proposed study will utilize a larger sample size and evaluate the breadth of application to inform clinical translation.

Purified Exosome Product

What are exosomes?

Transporter vesicles that carry mRNA, antioxidants, signaling proteins

They activate host paracrine/autocrine pathways and mesenchymal precursors

Purified Exosome Product (PEP)

GMP grade, produced by RION LLC

Harvested from pooled human plasma

Shelf stable

Reconstituted in sterile water + bovine collagen

Figure 1: Preliminary Study Methods

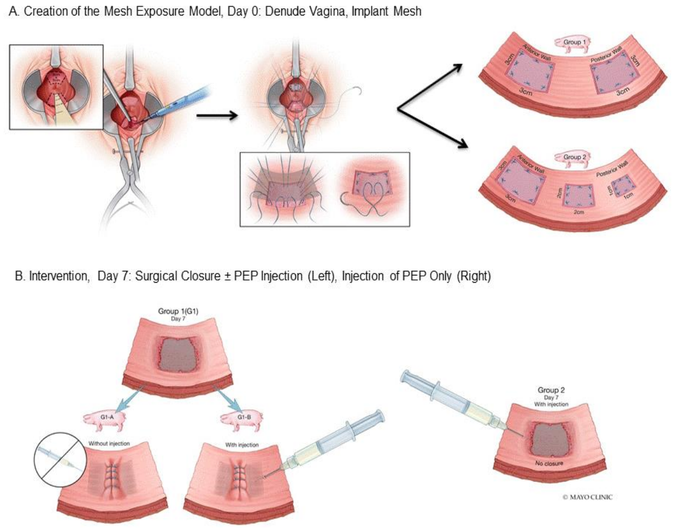
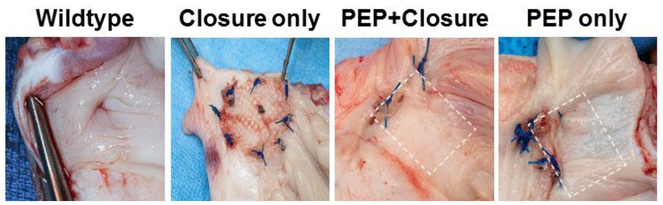
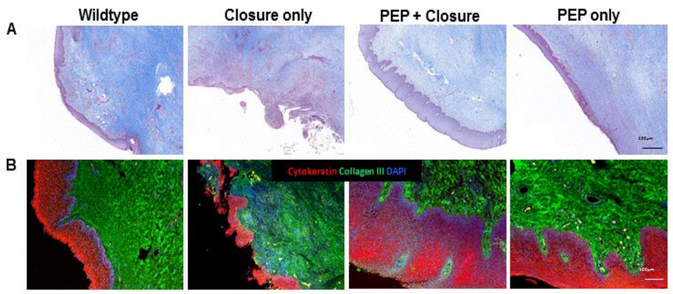


Figure 2: Preliminary Study Results



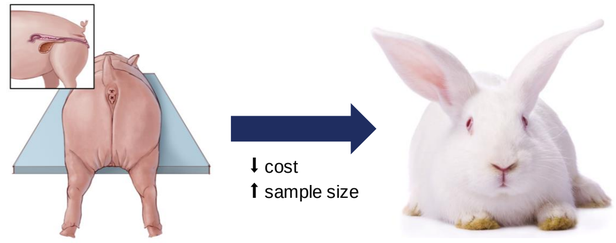
Vaginal healing 4 weeks after intervention. Note: white dotted areas represent the areas of underlying mesh. Wildtype (left) is an un-instrumented animal of equivalent age/weight.



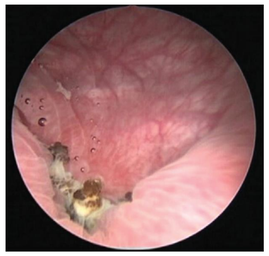
Masson's Trichrome, 4X: Representative tissue sections by group **(A)**.

Epithelium: **Cytokeratin** is a marker for epithelium; **Collagen III**; **DAPI** is a nuclear marker. Epithelial thickness is noted to be thin/fragmented in the closure only group, and higher in the PEP-treated groups (**B**).

AIM 1 – Vaginal Mesh, Rabbit Model



AIM 2 – Bladder Mesh Exposures

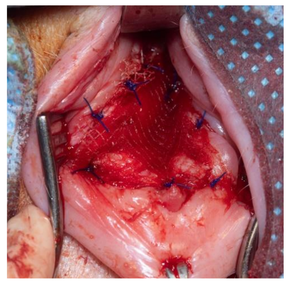


Cystoscopic view of bladder mesh exposure

Injection with PEP or sham

Does PEP injection aid in bladder mucosa regeneration and mesh exposure resolution?

AIM 3 – Mesh Exposure Prevention



Implanted polypropylene mesh

Injection with PEP or sham *at the time of implantation*

Does PEP injection *prevent* mesh exposure?

Outcomes

- For AIM 1 & 2: Sacrifice and tissue analysis at 6 weeks
- For AIM 3: A vaginal exam under anesthesia will be performed at 6 weeks & 12 weeks to assess for presence of mesh exposure
- Following intervention, all animals will be dosed with 2'-Deoxy-5-ethynyluridine (EdU) to track cellular proliferation
- Mesh exposure resolution:
  - Yes/No for complete exposure resolution *or*
  - surface area resolution for incomplete resolution Fig 3
- H&E and Masson's trichrome stains
- IHC will be used to quantify:
  - epithelial thickness
  - capillary density
  - macrophage ratio
  - cellular proliferation/regenerating proportions (EdU)

Figure 3: Measuring surface area with ImageJ software

Significance

Use of PEP as non-surgical management of mesh exposure

- Decrease healthcare costs
- Avoid repeat surgery/associated risks
- Prevent resection of mesh/return of symptoms
- Remove stigma surrounding use of mesh

- Future Directions: The authors plan to initiate a Phase I Clinical Trial

References

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