

ORIGINAL ARTICLE

Tolerability and Safety of a Poly-L-Lactide Eustachian Tube Stent Using a Chinchilla Animal Model

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Objective: To present the design for a novel, resorbable, drug-eluting Eustachian-tube stent and to ascertain its tolerability and resorption in a chinchilla animal model.

Materials and Methods: In a prospective, controlled animal study, a poly-l-lactide stent was implanted via a transbullar approach in one Eustachian tube (ear implanted was randomly selected) of five adult female chinchillas. The other ear served as a matched control. Otoendoscopy was performed at baseline to rule out pre-existing disease. Animals were sacrificed at varying times up to 26 weeks post implantation. Blinded histological sectioning was performed to determine degree of inflammatory response and stent resorption. All adverse events were recorded.

Results: Follow-up data were available for three animals at the time of sacrifice. The histologic findings were similar for the test and control ears. The stents did not appreciably resorb over the 6-month period of follow-up.

Conclusions: The poly-l-lactide Eustachian tube stent generally was well tolerated by the chinchillae without untoward effects. A follow-up larger sample animal study using another animal model with a larger Eustachian tube (a healthy Eustachian tube in one ear and a non-opening Eustachian tube in the other ear) is planned to further establish a safety profile, to investigate efficacy outcomes, and to follow gas-sterilized stents over time towards complete resorption.

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Tympanostomy tube or other long-term ventilation tube insertion is the prevailing procedure of choice for amelioration of persistent Eustachian tube dysfunction and serous otitis media and their consequences. The risks of tympanic membrane injury, cholesteatoma, and hearing loss have been well documented,^[1-3] and this approach fails to remedy the causal Eustachian tube pathology. Wright et al^[4] introduced the concept of trans-tympanic Eustachian tuboplasty or stenting using a Silastic[®] Eustachian tube prosthesis. Silastic[®], however, is tolerated more poorly than had been

thought previously, and appears to be deficient in tissue reactivity as compared with resorbable polymers.^[5] In addition, the Silastic[®] Eustachian tube prosthesis was easily encrusted by secretions.

We have designed a prototype of a novel resorbable polymeric Eustachian tube stent to overcome the limitations of the Silastic[®] Eustachian tube prosthesis. To minimize the problems that had affected earlier stents such as inflammatory tissue growth that can occlude the stent and mucosal incorporation, the stent material used was poly-l-lactide and the stent design

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included multiple venting of the sides. In this study, we present the design of the stent and examine, based on the histopathologic findings, the tolerability and resorption of our Eustachian tube prototype using a chinchilla animal model.

Materials and Methods

The stents utilized in this study were composed of a poly-L-lactide bioabsorbable polymer (Figure 1). The stent framework consists of two semi-rigid longitudinal arms traversing either side along its entire length. The semi-rigid construction gives the stent flexibility to negotiate the sigmoidal course of the Eustachian tube. Due to their longitudinal orientation, the arms act more as a passive conduit for aeration and drainage of secretions, and erosive forces on the Eustachian tube and adjacent ascending carotid artery are minimized.

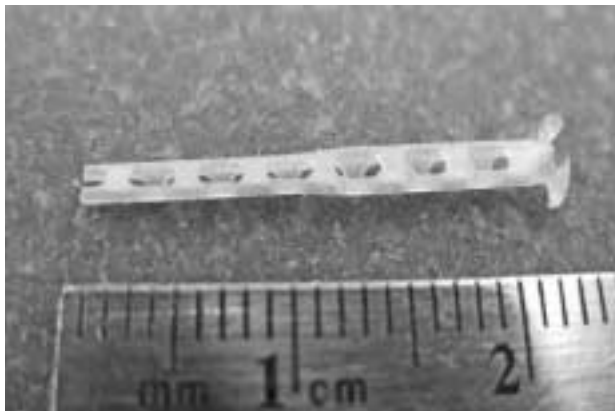


Figure 1. The stent prototype with a calibration marker (original magnification x 8). The prototype provided was not made to exact specifications.

This stent was designed for use in humans. The proximal (wider) end of the stent comprises two opposing retaining flanges placed eccentrically that secure it in the tympanic cavity, preventing migration. The flanges are oriented away from the lumen of the stent so mucociliary clearance remains unimpeded. In accordance with normal Eustachian tube dimensions, the stent is 2.0 mm in diameter over the proximal 1.0 cm of length, narrowing to 1.5 mm in diameter distal to the usual narrowing at the isthmus.

The longitudinal arms are stabilized by arched fibers staggered at 2-mm intervals over the superior and inferior surfaces. The most distal 3 to 5 mm of the stent lacks these structural supporting fibers to permit the distal end to partially collapse during normal Eustachian tube closure or in the setting of significant nasopharyngeal positive pressure, thus acting as a type of anti-reflux valve to diminish ascending infection and noise or pressure-induced trauma. The stents were provided in non-sterile preparation by PPD Meditech (Waterville, Quebec, Canada).

Five purpose-bred adult female Chinchillas (*C. laniger* species) weighing 400 to 500 g were studied.

The study protocol was approved by the Institutional Animal Care and Use Committee of the College's Department of Comparative Medicine. Because of the unknown effect of gas sterilization upon longevity and chemical structure, we did not sterilize the stents; they were provided clean to the principal investigator (JAL), who performed all surgical procedures.

After a period of acclimation, baseline otoendoscopy was performed in all animals under light sedation (ketamine 15mg/kg intramuscular) to rule out pre-existing middle ear disease. These images were analyzed blindly by study authors (JAL and CJL) to assess tympanic membrane integrity and middle ear status. Post baseline otoendoscopy, the Eustachian tube was bilaterally surgically accessed via a myringotomy incision and then using a transbullar incision under general anesthesia (ketamine 35mg/kg and xylazine 5mg/kg intramuscular). A stent (uncoated) was implanted in one ear (random selection of ear) while the opposing untreated ear remained as a matched control. The stent was sectioned lengthwise and its length was trimmed at the distal end to fit it into the Eustachian tube. The stent was implanted partially in the Eustachian tube and partially in the tympanic bulla (Figure 2) as the Eustachian tube was too small to accommodate the entire stent (only the distal end could be trimmed). All animals were treated peri-operatively with systemic chloramphenicol (40mg/kg). Otological antibiotics (Cortisporin otic suspension, Monarch Pharmaceuticals, Bristol, TN)

were administered to any ears developing otorrhea. One animal, at each of 10, 18, and 26 weeks following implantation, was randomly pre-selected for necropsy. The stent was removed from the middle ear bulla by a postauricular incision. The temporal bones were sectioned and histologically evaluated blindly by a head and neck pathologist (SAM) to qualitatively assess cellular composition, degree of host inflammatory response, and extent of stent degradation.

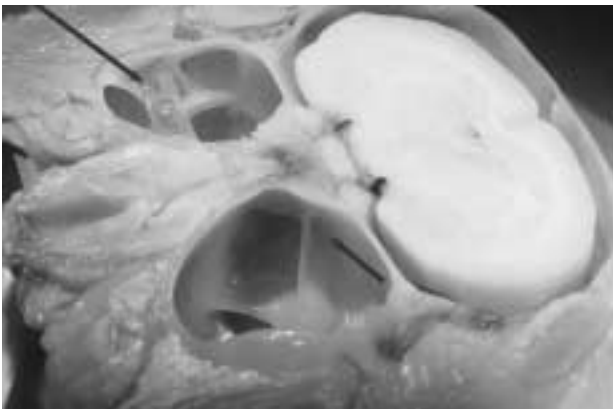


Figure 2. Gross coronal section of an implanted Chinchilla temporal bone through the labyrinthine portion of the bulla. The long arrow depicts the position of the stent within the bulla of the right Eustachian tube; note the slight amount of mucus in the stent. The short arrow depicts the tympanic orifice of the left Eustachian tube adjacent to the anterior bony cochlear strut.

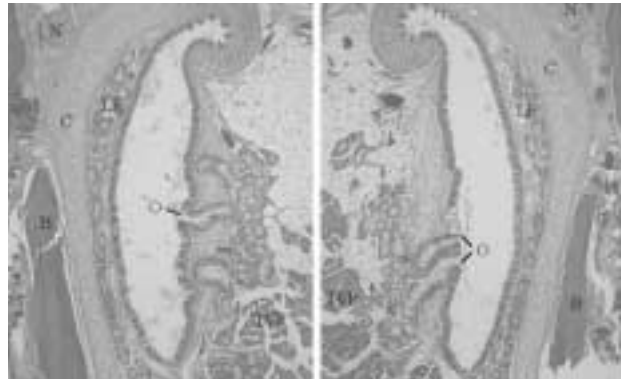
Results

Two animals died intra-operatively due to respiratory arrest associated with anesthetic complications; one died prior to any incision and one died just after the initial incision. Thus, study data were available for three animals. One animal developed transient otorrhea almost immediately post-operatively in the implanted ear; the otorrhea resolved post treatment.

The histologic findings after temporal bone sectioning were similar for test and control ears. Representative photomicrographs for the test and control ears are depicted (Figures. 3A and 3B, respectively). Normal cellular architecture was retained at the transitional zone and over the entire lengths of the Eustachian tubes. The lamina propria layer was not loaded with

polymorphoneucleocytes in the test ear, consistent with the absence of infection although a slight inflammatory response was present. Thus, the cellular composition of the test and control ears were qualitatively similar and the stented ears did not manifest any evidence of significant inflammatory cell infiltration.

The stents did not appreciably resorb during the follow-up period in any of the animals. A photo of the stent at six months after implantation juxtaposed with an unused stent for animal #3 is shown (Figure 4).



Figures 3A and 3B. Cross-sectional views of the pharyngeal portion of the Eustachian tubes in test (Figure 3A) and control (Figure 3B) ears (Animal #2). Shown are cartilage [C], bone [B], lamina propria [LP], nerve [N], openings of tubal glands [O], and tensor veli palatini muscle [TVP]. The stent was not preserved during sectioning. (hematoxylin-eosin, original magnification x60).

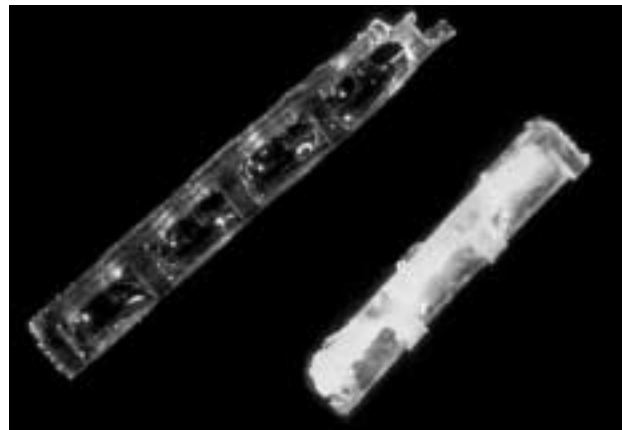


Figure 4. Unused segment of stent prototype adjacent to stent removed from the bulla after 6 months. The stent is partially coated by secretions but is unoccluded. Resorption appears negligible at this stage.

Discussion

Our poly-l-lactide stents generally were well tolerated by the animals in our study, as demonstrated by the

histopathologic findings. Although the poly-l-lactide stent directly targets the pathologic Eustachian tube, the surgical procedure for stent insertion is more complex than that for tympanostomy tube insertion. The deaths of two of the animals were unrelated to placement or effect of the stent. We attribute the development of transient post-operative otorrhea by one animal to possible pre-existing or intra-operative contamination of the implant, or, perhaps, to partial obstruction of the chinchilla's small Eustachian tube; the luminal height was only 1.0 (0.2 mm on average in the tympanic portion, and perhaps was too small to accommodate the bulk of the trimmed stent and remain optimally functioning^[6].

Favorable mechanical properties of poly-l-lactide material in upper airway use have been reported^[5]. The stent design (initiated by JAL) retains qualities that are desirable in the Eustachian tube. Considerations that influenced design included (a) ease of stent deployment, (b) need for stent retrieval, (c) stent longevity, and (d) prevention of adverse indwelling effects (e.g., erosion or perforation of surrounding tissues, stent migration or extrusion, luminal occlusion, ascending infection, and induction of symptoms such as autophony).

In our animals, on gross pathology, the segment of stent wedged in the bulla was partially layered with bullar secretions because of its location. Nonetheless, the lumen remained unoccluded at six months post implantation. The stents also did not develop significant fibrous ingrowth and were easily removed. We hypothesize that the use of stent coatings will prevent the development of stent encrustation over time.

The stent should degrade at a programmed rate over an 18-24 month period; this period, slightly less than the mean time for long-tem T-tube spontaneous extrusion,^[7] would facilitate resolution of tubal dysfunction without the risk factors associated with tympanostomy tubes.

Conclusion

The tolerability and resorption of a novel, resorbable Eustachian tube poly-l-lactide stent was examined in the chinchilla animal model. The stents appeared to engender only a mild inflammatory host response and were minimally resorbed at six months. A follow-up larger sample animal study using another animal model with a larger Eustachian tube (a healthy Eustachian tube in one ear and a non-opening Eustachian tube in the other ear) is planned to further establish a safety profile, to investigate efficacy outcomes, and to follow gas-sterilized stents over time towards complete resorption.

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