Int. Adv. Otol. 2011; 7:(1) 1-3

ORIGINAL ARTICLE

The Poly-L-Lactide Eustachian Tube Stent: Tolerability, Safety and Resorption in a Rabbit Model

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Objective: To ascertain the tolerability and resorption of a poly-l-lactide Eustachian tube stent in a rabbit animal model.

Materials and Methods: In a prospective, controlled animal study, a poly-l-lactide stent was implanted into one Eustachian tube of ten female New Zealand white rabbits. The remaining ear of each animal served as a matched control. Serial otoscopy was performed to assess any manifestation of foreign body reaction. The rabbits were sacrificed at 24 weeks post implantation. Blinded histological sectioning was performed to determine degree of inflammatory response. The degree of stent resorption was evaluated by weight measurement of the stent prior to implantation and following extraction of the temporal bone from the cadaver.

Results: Follow-up was available for all ten animals at time of sacrifice. Of these ten animals, five developed otitis media in the test ear, and one of these four animals also developed facial cellulitis. All infections resolved with treatment relatively quickly. The stent was completely resorbed at 6 months post implantation in all test animals. None of the tympanic bullae demonstrated histologic evidence of acute or chronic inflamation.

Conclusions: The poly-l-lactide Eustachian tube stent was well tolerated by the test animals. This technology merits further evaluation for efficacy in animals.

Submitted : 15 May 2010 *Revised: 15 December 2010* *Accepted : 01 February 2011*

Introduction

Surgical insertion of pressure-equalization tubes represents the standard treatment for persistent Eustachian tube-dysfunction and serous otitis media. Possible sequelae include tympanic membrane perforation, cholesteatoma, and hearing loss[1-3]. Additionally, this treatment approach does not address the underlying etiology of the Eustachian-tube dysfunction. In furtherance of the goal to develop an approach that overcomes the aforementioned limitations of ventilation tubes, Litner et al. presented a design for a novel, resorbable, drug-eluting poly-*l*-lactide Eustachian-tube stent[4]. They reported that the stents, implanted via a transbullar approach, were well tolerated, as evidenced by the blinded histopathologic findings, in a chinchilla model. Stent resorption was minimal at six months post implantation. They concluded that a follow-up study with a larger sample size on another animal model with a larger Eustachian tube and using gas-sterilized stents is needed to further establish a safety profile.

Thus, the purpose of this study was to examine the tolerability, safety, and resorption of a gas-sterilized poly-l-lactide Eustachian-tube stent using a rabbit animal model. The rabbit was selected to be the animal model as its tympanic cavity and bullae are adequately large and the bullae are relatively accessible. Moreover, the rabbit Eustachian-tube mucosa has been noted to be similar to that of the human[5]. The rabbit animal model has been successfully utilized for the evaluation of middle-ear physiology and also has been used experimentally to evaluate the tolerability of middle ear prostheses[6-9].

Materials and Methods

The protocol of this study was evaluated and approved by the Institutional Animal Care and Use Committee at New York Medical College. All procedures and care were overseen by Department of Comparative Medicine Staff.

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Following Litner et al.[4], the stents were composed of poly-l-lactide bioabsorbable polymer and the design incorporated multiple venting of the sides.

Ten medium-sized (12-15 lbs) New Zealand white rabbits comprised the study animals. The test animals were evaluated pre-implantation for overt evidence of middle-ear disease with otoendoscopy. Each poly-l-lactide stent was sectioned legnthwise to enable its accommodation by the rabbit tympanic bullae. Pre-implantation weights were obtained on each of the cleaved stents, which then were gas sterilized for implantation.

Pilot testing had been done on cadaveric rabbits to assess the most efficient and least invasive method of bullae implantation. The results revealed that an external approach through the bullae was the most sterile and was easily accessible; hence, this approach was employed.

Implantation was performed on the left ear of each rabbit specimen. The animals were anesthetized with Ketamine (50mg/kg intramuscular) and Xylazine (10mg/kg intramuscular) along with preoperative transdermal Fentanyl (12.5 ug/ hour) for sustained analgesia. Intravenous Floxacillin (60mg/kg) was administered every other day for five days postoperatively. The soft tissue overlying the palpated bullae was incised with sharp dissection down to the bone. An electric hand drill with a #1 diamond burr was used to create an opening into the bullae. The partial stent then was inserted into the bullae and the overlying soft tissue was used to close over the defect.

Biweekly, through week 24 postoperatively, the test animals underwent otoendoscopy to assess any untoward reactions. Ototopical antibiotics (Cortisporin otic suspension, Monarch Pharmaceuticals, Bristol, TN) were administered for ten days to any ear developing otorrhea. Local and systemic infections were treated with intramuscular injections of Floxacillin for 10 days.

At six months post implantation, each animal was euthanized and the respective temporal bones were sectioned and analyzed. Each skull was preserved in formalin and explored for the presence of remnant stent material. Thereafter, the specimens were decalcified in a dilute nitric acid solution and dissected. Bilateral temporal bones were removed from each cadaver and further decalcified in 10% EDTA (ethylenediaminetetraacetic acid). Once decalcified, the specimens were sectioned, embedded in paraffin and prepared with H&E stain (hematoxylin and eosin)**.** A blinded senior head and neck pathologist evaluated the H&E stained slides for evidence of foreign body reaction or acute or chronic inflammation.

Results

Table 1 shows the time sequence for the occurrence and resolution of sequelae for the five animals who suffered sequelae. As can be seen from this table, the onset of the sequelae was early (within two weeks) for two of the animals, and late (between 3-12 weeks) for three of the animals. The two animals with early onset sequelae developed purulent otitis media with tympanic-membrane perforation; the infection resolved after treatment with ototopical medications and the perforation healed spontaneously. One of the three animals with late sequelae had otitis media with facial cellulitis that was treated effectively with intramuscular Floxacillin.

Table 1. Postoperative sequelae.

Week	Animal 2	Animal 3	Animal 5	Animal 8	Animal 9
1-2	Purulent otitis media with tympanic-membrane perforation	None	None	Purulent otitis media with tympanic-membrane perforation	None
3-4	Purulent otitis media with tympanic-membrane perforation	None	None	Resolved	Otitis media with facial cellulitis
5-6	Resolved	None	Otitis media	None	Resolved
7-8	None	None	None	None	None
9-10	None	Otitis media	Resolved	None	None
11-12	None	Otitis media	None	None	None
13-14	None	Resolved	None	None	None
15-24	None	None	None	None	None

All of the test animals survived the 6-month observation period. The aforementioned infections were effectively treated and no further incidences were noted. Following sacrifice of the animals, exploration of the middle ear/bullae revealed the absence of any remnants of the Eustachian-tube stent in all animals.

The H&E stains revealed the absence of any inflammatory response in the experimental ears of the animals after the 6-month incubation period. Incidentally, a cholesteatoma was noted histologically in the control ear of one of the animals.

Discussion

The purpose of this study was to examine the tolerability and safety of a gas-sterilized poly-l-lactide Eustachian-tube stent using a rabbit animal model. In contrast with the Litner et al.[4] study on chinchillas, all the test rabbits survived. The clinical and pathologic findings revealed that the stents were well tolerated in the rabbit animal model and the infections that occurred in some animals resolved relatively quickly. At 6 months post implantation, the stents were completely resorbed in all rabbits, in contrast with the minimal resorption in the smaller chinchilla. Thus, resorption was improved in the larger than smaller animals, which bodes well for future studies in humans as complete resorption eliminates any need for stent removal after a specified treatment period.

As safety and tolerability now have been demonstrated based on two animal models—chinchilla and rabbits—future animal research should evaluate the efficacy of the poly-l-lactide stent for treatment of laboratory induced otitis media whereby one ear is stented and the other ear serves as a matched control. If favorable findings occur, then the study should be repeated using bilateral poly-l-lactide stents—with surfactant in one ear and without surfactant in the contralateral ear. Based on these and our previous4 findings, we have demonstrated tolerability and safety of the stent in two laboratory animal models (chinchilla and now the rabbit). As the poly-l-lactide stent is considered an invasive medical device, pre-clinical animal testing with the device is required, and the data from animal studies need to demonstrate efficacy as well as safety and tolerability before the device can be tested on humans. Some medical device regulatory agencies such as the Food and Drug Administration in the U.S. recommend additional testing of stents that are drug eluting.

Conclusion

In this study, the tolerability, safety, and resorption of poly-l-lactide Eustachian tube stent implantation was established in a rabbit animal model, thereby extending the safety profile to include rabbits as well as chinchillas. The stents were generally well tolerated in this sample of 10 rabbits and postoperative infections resolved relatively quickly with treatment. The stents appeared to engender no inflammatory host responses and were completely resorbed at six months. The success of this study on rabbits is compelling and warrants further follow-up studies on the efficacy of the poly-l-lactide stent, first without surfactant and then with surfactant in animals prior to conducting human studies.

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