International Journal of Pediatric Otorhinolaryngology 101 (2017) 20–24

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: http://www.ijporlonline.com/

"On-command" dissolvable tympanostomy tube in the chinchilla model: A proof of concept☆

Joshua P. Wiedermann [a, *], Johnny P. Mai [a], Matthieu Dumont [b], Audrey Jenkins [c], Kevin Cleary [b], Brian K. Reilly [d]

[a] The Department of Surgery, Division of Otolaryngology-Head and Neck Surgery, The George Washington University Hospital, Washington, DC, USA
[b] The Sheikh Zayed Center for Pediatric Surgical Innovation, Washington, DC, USA
[c] MedStar Health Research Institute, Washington, DC, USA
[d] The Department of Surgery, Division of Otolaryngology-Head and Neck Surgery, The Children's National Medical Center, Washington, DC, USA

ARTICLE INFO

Article history:
Received 27 May 2017
Received in revised form
12 July 2017
Accepted 16 July 2017
Available online 18 July 2017

Keywords:
Tympanostomy tube
Tympanic membrane
On-command
Chinchilla
Bioabsorbable
Hydrogen peroxide

ABSTRACT

Objectives: To prove the concept that a dissolvable "on-command" tympanostomy tube placed into the tympanic membrane of a chinchilla can dissolve when a benign solution is applied and result in a well healed tympanic membrane without histologic evidence of injury.
Study design: Prospective Randomized Single-Subject Controlled Trial.
Methods: Prototype tympanostomy tubes were fabricated from poly(butyl methacrylate-*co*-(2-dimethylaminoethyl) methacrylate-*co*- methyl methacrylate) (PBM). "*In vitro*" dissolution studies were performed with applications of the benign chemical, hydrogen peroxide (HP). PBM tubes were placed into ten chinchilla tympanic membranes matched with standard plastic tubes placed into the contralateral side. All 20 tubes were exposed to HP for 21 days with serial endoscopic examinations. *In vitro* PBM tubes were weighed before and after interventions and compared to control tubes. *In vivo* photo documentation was used to show progression of dissolution and histologic slides were obtained to show the effect of the PBM on surrounding tissues.
Results: Compared to control tubes, all those exposed to hydrogen peroxide had a statistically significant reduction in weight ($p < 0.01$). After placement into the tympanic membrane of chinchillas, all PBM tubes dissolved within 21 days of hydrogen peroxide treatment leaving behind histologically normal, intact tympanic membranes.
Conclusion: Our PBM tubes dissolve "on-command" in a chinchilla model when exposed to treatment with a benign chemical. Dissolvable "on-command" tympanostomy tubes may reduce significant complications related to pediatric tympanostomy tube use.

1. Introduction

In the United States, illness related to otitis media results in at least 16 million office visits. In fact, otitis media is the second most common pathology in the pediatric population, surpassed only by upper respiratory tract infections [1]. At least 5 billion dollars are spent annually on the care of otitis media and its sequelae [2]. Moreover, otitis media can have significant consequences: prolonged middle ear effusion can cause significant hearing loss leading to developmental delay [3–5].

Due to its common presentation and serious sequelae, otitis media is the driving force behind the insertion of tympanostomy tubes, the most common surgical procedure performed by otolaryngologists. At least one million tympanostomy tubes are placed annually [6]. While the procedure is quick, simple and often resolves hearing loss caused by middle ear effusion, complications can occur when a tube stays in the ear too long or fails to extrude. Those complications can require additional surgical procedures under general anesthesia.

In particular, although tube shapes and materials are engineered to remain in place for 9–16 months, the actual duration is variable

☆ **Podium presentation** at American Society of Pediatric Otolaryngology (ASPO) annual meeting May 20–22, 2016. Chicago, IL.

* Corresponding author. 1107 Edgevale Rd, Silver Spring, MD 20910, USA.
E-mail addresses: josh.wiedermann@gmail.com (J.P. Wiedermann), johnny.pv.mai@gmail.com (J.P. Mai), dumontchemistry@gmail.com (M. Dumont), Audrey.Jenkins@medstar.net (A. Jenkins), KCleary@childrensnational.org (K. Cleary), BReilly@childrensnational.org (B.K. Reilly).

http://dx.doi.org/10.1016/j.ijporl.2017.07.017
0165-5876/

[7]. Additionally, the theory of biofilm formation and persistent otorrhea may necessitate removal of the tube [8]. Bhattacharyya, in 2006, found that roughly 3.8% of tubes need to be removed surgically [9]. Paradise noted that up to 2% of naturally extruded tubes and 13% of surgically extracted tubes resulted in persistent tympanic membrane perforation [10]. Extrapolating from these studies, up to 6% (60,000) of patients with tubes placed will require one additional surgical procedure and 0.5% (5000) will require at least two additional surgical procedures every year.

Attempts have been made to explore degradable tympanostomy tubes with mixed results [9,13,14]. We previously presented our first stage in the development of a dissolvable "on-command" tympanostomy tube. In that first stage, we successfully demonstrated our polymer's resistance to degradation when implanted in rat dermis and its ability to completely dissolve "on-command" when exposed to alcohol [15].

In this study, we aim to prove the concept; namely, that tubes formulated from our specific polymer can dissolve "on-command" with a standard application of hydrogen peroxide not only *in vitro*, but also when placed into the tympanic membrane of a chinchilla. If the tympanostomy tube can successfully dissolve "on-command," its use in the pediatric population could reduce additional surgical procedures for patients who require tympanostomy tube placement.

2. Methods

2.1. In vitro study

Engineering of the poly(butyl methacrylate-*co*-(2-dimethylaminoethyl) methacrylate-*co*- methyl methacrylate) (PBM) tubes and their biomechanical properties were discussed in detail in our previous publication [15]. In order to observe their dissolution when exposed to hydrogen peroxide, twelve tympanostomy tubes created from PBM by our bio-engineering department were placed into 12 circular clear plastic sheets to simulate a tympanic membrane. Before placement, the tubes were measured on a precision balance and values were rounded up to the nearest tenth of a milligram. Two tubes were used as negative controls (no treatment and three daily treatments of 5 min of saline (5 m TID)) and two tubes were used as positive controls (continuous 3% hydrogen peroxide (HP)). The remaining tubes were paired and divided into the HP treatment groups of: one minute twice a day treatment (1 m BID), one minute three times a day treatment (1 m TID), 5 min twice a day treatment (5 m BID) and 5 min three times a day treatment (5 m TID). In each instance when a liquid was used, 2 mL would be placed directly on the tube. Following the designated time period of treatment, the remaining fluid would be decanted from contact with the tubes. This regimen was maintained for 7 days. The entire experiment was completed in an incubator at 37°C to simulate BID or TID treatments in a chinchilla. Following the 7-day experiment, remaining fluid was decanted and dried and the residual tubes were weighed and recorded. A one-way ANOVA was completed comparing the controls to each of the other 4 treatment groups. Statistical significance was set for a P-value less than 0.05. Post-hoc analysis were performed for inter-group comparisons.

2.2. In vivo study (Fig. 1)

Ten chinchillas (*Chinchilla lanigera*) were purchased from Moulton Chinchilla Ranch (Rochester, MN). Following quarantine, each chinchilla and each of their ears were randomized. Under 3–5% isoflurane general anesthesia, administered by our institution's veterinarian, either a PBM or control (Reuter Bobbin: Medtronic, Minneapolis Minnesota) tympanostomy tube was endoscopically placed into the tympanic membrane using standard surgical technique. A Storz 2.7 mm rigid endoscope was used (Karl Storz, Tuttlingen, German). Placement was confirmed with photo documentation. All procedures, photodocumentation, and data analysis was performed by the lead author.

At the completion of the procedure, each chinchilla had one PBM tube and one control tube. One chinchilla (#7) expired due to complications from general anesthesia and a new chinchilla was added to the experimental group (#11). Chinchilla #7 was removed from statistical analysis.

For the following 7 days, the chinchillas were given daily treatments of ofloxacin otic topical solution to help avoid infection. The chinchillas were again given general anesthesia and their experimental sites were photo documented at the end of week one. Their first dose of HP was given during this time. Over the next week, the veterinarian staff applied HP to each ear once a day using an eye dropper to directly place HP into the external auditory canal.

At the end of week two, the chinchillas were given general anesthesia and their experimental sites were photo documented. During the third week, HP dosing was increased to BID. This continued until the termination of the experiment. At the end of weeks 3 and 4, the chinchillas were given general anesthesia and their sites photo documented. The experiment ended at the completion of the 4th week. Throughout the course of the study, the chinchillas were monitored for signs of distress, such as head pressing, ataxia, isolation, weight loss and poor hygiene.

Following standard euthanasia protocol by the veterinarian staff, the heads were immediately fixed in 10% formalin for at least 24 h and their temporal bones were sectioned, processed, and paraffin-embedded. Slides were cut at 4 μm thick and stained using standard H&E protocols.

3. Results

3.1. In vitro study

The PBM tubes subjected to air and saline experienced no degradation. The tube exposed to continuous HP had a complete dissolution. Compared to negative control tubes, all those exposed to hydrogen peroxide had a statistically significant reduction in weight ($p = 0.0002–0.0130$) (Fig. 2). Of the HP experimental groups, 1 m BID and 5 m BID tubes experienced 41% ($p = 0.013$) and 57% ($P = 0.0009$) reductions in weight respectively when compared to controls. 1 m TID HP tubes had a 90% ($p = 0.0002$) reduction in weight and were left with small fragments. Those tubes exposed to 5 m TID of HP were left with no discernable material to weigh following the 7 day experiment.

3.2. In vivo study

Through the course of the study, the observational logs did not reveal any signs of distress in any of the chinchilla subjects. As mentioned in the Methods section, chinchilla #7 expired following the initial general anesthesia and the data was removed from analysis. Initial placement of the control tubes was confirmed with photo documentation and at the termination of the study. No control tubes were extruded in the 28 days.

Following a week of daily ofloxacin treatment, all tubes were confirmed in place with photo documentation. The structural integrity of the PBM tubes appeared intact (Fig. 3) and patency was confirmed when HP was applied resulting in air bubbles from the middle ear. After 7 days of daily HP applications, initial degradation of the PBM tubes could be appreciated (Fig. 4). The frequency of HP applications increased to twice a day during the 3rd week of the experiment and following 7 days of this, near complete dissolution