Intraoperative use of mitomycin C in fibrous atresia of the external auditory canal

Saba Battelino, MD, MSc; Irena Hocevar-Boltezar, MD, PhD; Miha Zargi, MD, PhD

Abstract
The ability of mitomycin C to inhibit fibroblasts in vitro has prompted its use during standard surgical procedures as a means of preventing the development of adhesions and stenosis. We conducted a prospective study to evaluate the effectiveness of topical mitomycin C in maintaining an open external auditory canal in 6 ears of 4 patients with aural fibrotic atresia who were undergoing meatoplasty. During the procedure, we applied 1 ml of mitomycin C (0.4 mg/ml) for 4 minutes to the external auditory canal (in 1 case, mitomycin C was reapplied to an ear 1 month later). Between 3 and 14 months postoperatively, the patency of the ear canal was assessed visually and hearing was evaluated audiometrically. Adequate patency was achieved in 5 of the 6 ears (83.3%), and the air-bone gap in these 5 ears had improved to 10 dB or less. No postoperative complications or sensorineural hearing loss was observed. In this very limited number of cases, we found that the intraoperative use of mitomycin C appeared to have been helpful in preventing scarring in both congenital and secondary fibrotic atresias of the external auditory canal. These preliminary results are encouraging, and a prospective, placebo-controlled study appears to be warranted.

Introduction
Oclusions and closures of the external auditory canal are rare and difficult to manage. Either can occur as a congenital abnormality or secondary to chronic external otitis, other diseases, and trauma. The primary factors in deciding whether to operate on congenital or acquired aural atresias are the severity of the hearing impairment and the risk of cholesteatoma. Some reports of postoperative results are very encouraging. Some authors are not satisfied with classic surgical methods for treating aural atresias, and they favor instead the use of a KTP/532 laser or more extensive surgery. Numerous surgical procedures via endaural and postauricular approaches have been reported. According to some of these reports, the removal of the diseased skin from an external auditory canal was insufficient. For especially difficult cases, additional surgical procedures have been introduced in an effort to prevent abundant growth of granulation tissue and subsequent reclosure of the canal and consequent conductive hearing loss.

Mitomycin C is an antineoplastic agent produced by the fungus Streptomyces caespitosus. It inhibits DNA and RNA replication, which leads to a reduction in protein synthesis and consequent cell death. Before mitomycin C was used in clinical otology, it was tested in several animal studies as a means of preventing early closure of myringotomies. The promising results of those experiments led to its clinical use in ear surgery in humans. We conducted a study to evaluate the possibility of creating a long-term opening in the external auditory canal of patients with aural fibrous atresia, and thereby improve hearing, by administering topical mitomycin C during meatoplasty, the classic surgical procedure for this condition.

Patients and methods
Between May 1, 2003, and April 30, 2004, we treated fibrous atresia of the external auditory canal in 6 ears of 4 patients—2 men and 2 women, aged 30 to 60 years (mean: 42.3). Of this group, 2 patients had developed fibrous atresia following an episode of chronic external otitis (1 bilaterally and 1 unilaterally), 1 patient’s unilateral atresia was congenital, and 1 patient developed unilateral atresia following a severe head trauma (table 1).

After an initial clinical evaluation, we ordered computed tomography (CT) of the temporal region to exclude osse-
ous atresia of the external auditory canal and to ascertain the normal status of the middle ear cavity. CT detected no signs of osseous atresia or changes in the tympanic cavity or ossicles.

We then performed audiometry to measure air- and bone-conduction thresholds, and we used these data to calculate the air-bone gap in accordance with guidelines published by the American Academy of Otolaryngology–Head Neck Surgery (Table 2).

The pure-tone averages for air- and bone-conduction thresholds were obtained at 0.5, 1.0, 2.0, and 3.0 kHz.

All meatoplasties were undertaken via an endaural approach. At the time of surgery, all external auditory canals were dry, and no signs of necrotizing (“malignant”) external otitis were evident. The meatal skin flap was elevated and the posterior portion of the anulus tympanicus was exposed. After the tympanic membrane was visualized, the fibrous tissue was carefully excised from the external auditory canal. The tympanic membrane was covered with a thin layer of dry Gelfoam to protect it from the topical mitomycin C. Then 1 ml of mitomycin C in a concentration of 0.4 mg/ml was applied for 4 minutes to the area where the fibrous tissue had been located. Local skin flaps were used to cover the skin defects.

The length of postoperative follow-up ranged from 3 to 14 months (mean: 7.2). The external auditory canal was examined microscopically at each follow-up visit. Postoperative audiometry was performed at each patient’s final follow-up visit.

Results

Postoperatively, the external auditory canal remained open in 5 of the 6 ears (83.3%). In the 5 ears, visualization of the tympanic membrane was good without the need for special procedures, such as cleaning the external ear canal with instruments. In 1 of these 5 ears, granulation tissue developed near the tympanic membrane 1 month postoperatively, and mitomycin C was applied for a second time.

The 1 ear that was not successfully treated had remained open for 2 months; there was no air-bone gap. One month later, the patient returned with a complaint of recurrent hearing loss. Otomicroscopic examination revealed that the tympanic membrane was again covered with granulation tissue.

The mean postoperative air-bone gap had closed to 10 dB or less in the 5 successfully opened ears and to within 30 dB in the other ear (Table 3). Bone-conduction thresholds did not change postoperatively in any of the 6 ears.

Discussion

A recurrence of adhesions and stenoses following treatment of fibrous atresias of the external auditory canal is common despite proper surgical technique.\(^3\) Several surgical and adjunctive treatments have been introduced to minimize recurrence.\(^1,8,11,12,26\) One of these adjunctive treatments is topical mitomycin C.

Mitomycin C was isolated by Wakaki et al in the 1950s from Streptomyces caesipitosus.\(^27\) In 1967, Oboshi et al described both its antimicrobial properties and its suppressive effects on tumor growth.\(^28\)

Ophthalmology. Mitomycin C was used clinically in ophthalmology as a means of preventing recurrent pterygium, as reported by Murakami et al in 1967.\(^29\) After its initial use in ophthalmology, Lee et al described its suppressive effects on human fibroblastic inhibition.\(^30\) Cruz reported good results with mitomycin C in preventing postoperative adhesions in strabismus.\(^15\) Schmidt-Erfurth et al reported that mitomycin C was useful in maintaining filter function in sclerostomy.\(^31\)

Rhinolaryngology. Following the publication of two promising experimental studies—one on rat sinus mucosal healing by Ingrams et al in 1998 and another on dog larynges by Eliashar et al in 1999—mitomycin C was successfully used on humans. In 2000, Rahbar et al reported the effectiveness of topically applied mitomycin C in 8 patients with posterior glottic and subglottic stenosis.\(^33\) The next year, Holland and McGuirt reported the successful use of mitomycin C in the surgical management of bony choanal atresia; they proposed that its use might preclude the need for surgical stenting.\(^34\)

Otology. The use of mitomycin C in patients with

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age/sex</th>
<th>Cause of fibrous atresia</th>
<th>Ears (n)</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30/F</td>
<td>Chronic external otitis</td>
<td>2</td>
<td>Left 14, right 3</td>
</tr>
<tr>
<td>2</td>
<td>60/M</td>
<td>Congenital abnormality</td>
<td>2</td>
<td>Left 10, right 3</td>
</tr>
<tr>
<td>3</td>
<td>47/F</td>
<td>Chronic external otitis</td>
<td>1</td>
<td>Left 8</td>
</tr>
<tr>
<td>4</td>
<td>32/M</td>
<td>Trauma injury</td>
<td>1</td>
<td>Right 5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Preoperative pure-tone thresholds (dB)</th>
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<tbody>
<tr>
<td>Pt.</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td></td>
</tr>
<tr>
<td>2</td>
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<tr>
<td></td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>4</td>
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Ménière's disease was first described by Yazawa et al. in 1999. They used intraoperative topical mitomycin C in 14 patients with Ménière's disease who were undergoing endolymphatic sac mastoid shunt surgery. Patients were followed for more than 6 months. None of these patients experienced vertigo, although some did complain of slight dizziness.

In 2002, Huang reported the outcomes of 103 patients with Ménière's disease who had been treated with endolymphatic sac surgery and topical mitomycin C. This group was compared with a control group of 109 patients with Ménière's disease who underwent the same surgery without the drug. The mitomycin C group experienced a significantly greater improvement in hearing and no recurrences.

During the past few years, several reports of the effects of mitomycin C on the tympanic membrane and skin have appeared. The maintenance of myringotomy patency was reported in rat tympanic membranes by Yucel in 2000. Similar results in guinea pigs were soon reported by Estrem and Vanleeuwen. Estrem and Baker, Jassir et al., and O'Reilly et al. Mitomycin C has also been found to delay the healing of surgical wounds in rat skin.

Prior to the study described in this article, only 3 reports of mitomycin C's effects on the tympanic membrane and on scar tissue formation in humans have appeared in the literature. In 2003, Kriukov et al. reported good results with mitomycin C in preventing scar formation in tympanic cavities during surgery on patients with suppurative otitis media. The same year, however, Banthia and Selesnick reported that mitomycin C was not effective in preventing the formation of recurrent granulation tissue following canaloplasty in 6 patients. Likewise, in 2004, D'eredita reported that mitomycin C was no more effective than placebo during diode laser myringotomy in both ears in 15 children.

In the latter study, mitomycin C was applied to the right ear of each patient and saline to the left ear. After 3 to 4 months of follow-up, no difference in the duration of patency was observed between the 2 groups.

Despite its rarity, fibrous atresia of the external auditory canal has been well described by Declau et al., Slattery and Saadat, Goodman and Middleton, McKennan and Chole, and Smouha et al. Good meatoplasty results can be obtained in cases where chronic external otitis primarily affects the cartilaginous part of the external auditory canal. In these cases, an M meatoplasty is usually sufficient. In 2002, Cremers reviewed surgical outcomes in 12 series of patients with acquired aural atresia and reported promising results. Surgical results are not always as good in other types of aural atresia.

In the patient in our study who had congenital fibrous atresia, previous surgery had been unsuccessful in both ears. In an effort to improve surgical outcomes, investigators have tested various strategies. In 1997, Kriukov et al. recommended the use of the KTP/532 laser. In 2001, Haapaniemi et al. recommend radical meatoplasty.

Important complications can occur during surgery that is limited to the external auditory canal. In a series of 22 operations on 20 patients with exostosis of the external auditory canal, Reber and Mudry described 2 cases of tympanic membrane perforation, 2 cases of exposure of the temporomandibular joint, and 2 cases of soft-tissue stenosis. In all 6 of our cases, we used the endaural approach recommended by Tos and Balle.

Dosing. In previously published studies, the concentration of mitomycin C solution varied from 0.2 to 4.0 mg/ml and the duration of administration ranged from 2 to 10 minutes. Kriukov et al. used 0.2 mg/ml to prevent recurrent scarring of the tympanic cavity. In his study of diode laser myringotomy, D'eredita used a concentration of 0.4 mg/ml. Holland and McGuirt reported good results in treating choanal atresia with a 3-minute application of 0.4 mg/ml. For the prevention of glottic and subglottic stenosis, Rahbar et al. used 0.4 mg/ml for 4 minutes. Banthia and Selesnick used 0.5 mg/ml for 5 minutes for preventing scar formation in the postaural surgical canal.

During endolymphatic sac surgery, Huang used 1 mg/ml for 5 minutes. Jassir et al. described a dose-response curve with doses up to 0.4 mg/ml for 10 minutes in prolonging myringotomy patency; according to that study, a higher dose (2.0 mg/ml) did not appear to prolong patency but was associated with an increase in otorrhea and possible ototoxicity. In our study, 1 ml of 0.4 mg/ml of mitomycin C in saline for 4 minutes yielded satisfactory results.

Follow-up. Our study of 6 ears with a follow-up of 3 to 14 months is similar to protocols described by Goodman and Middleton, McKennan and Chole, and Cremers. The only treatment failure in our study occurred 2 months postoperatively, and it is therefore likely that our reported success rate (83.3%) is final.

Complications. In 1999, Yazawa et al. published their experience with mitomycin C during endolymphatic sac surgery, and they reported no hearing impairment or dizziness among 14 patients who had been followed for more than 6 months. In 2001, Jassir et al. reported that they had performed otomicroscopic examinations and measured otoacoustic emissions in 20 guinea pigs after

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**Table 3. Number of ears in various pre- and postoperative ranges of mean air-bone gaps**

<table>
<thead>
<tr>
<th>Preop (n ears)</th>
<th>0 to 10 dB</th>
<th>11 to 20 dB</th>
<th>21 to 30 dB</th>
<th>31 to 40 dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postop (n ears)</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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administering mitomycin C for myringotomy patency, and they detected no ototoxicity. 38 Cankaya et al performed light and electron microscopic studies of the inner ears of 30 guinea pigs after applying topical mitomycin C to their tympanic cavities; again, no toxic effects on the inner ear were observed. 44 Likewise, we detected no damage to the inner ear as determined by pure-tone audimetry.

In conclusion, our study of a limited number of ears showed that a conservative surgical approach combined with topical application of mitomycin C can be a safe and successful method of treating fibrous atresia of the external auditory canal.

Acknowledgment

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References