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Radiofrequency Myringotomy with the Topical Use of Mitomycin C: An Experimental Study

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Objective: To assess the use of radiofrequency myringotomy in combination with mitomycin C as an alternative myringotomy technique on rabbits.
Study Design: Experimental animal research protocol.
Setting: University of Crete, School of Medicine, Medical Experimental Education and Research Center.
Methods: Radiofrequency myringotomies were performed under general anesthesia on both ears of 20 rabbits. Mitomycin C (0.3 mg/ml) pledgets were applied in the right ears (study group) and saline pledgets in the left ears (control group). Animals were monitored using otomicroscopy weekly until myringotomy closure. Kaplan-Meier survival techniques were used to compare myringotomy patency time between the two sides.
Intervention: Radiofrequency myringotomy under general anesthesia on both ears of 20 rabbits.
Main Outcome Measure: Myringotomy patency time.
Results: The mean patency time of the study group was 5.45 weeks (95% confidence interval, 5.185–5.715 weeks). The mean patency rate for the control side was 1.60 weeks (95% confidence interval, 1.38–1.82 weeks). The Breslow (generalized Wilcoxon) test showed the study group to have significantly longer patency of radiofrequency myringotomy than the control group ($p < 0.0001$).
Conclusion: The patency period of radiofrequency myringotomy was not long enough to be proposed as an alternative to the insertion of ventilation tubes, although mitomycin C had a significant adjunct effect in prolonging the patency rate of radiofrequency myringotomy on rabbits. **Key Words:** Mitomycin C—Myringotomy—Radiofrequency—Serous otitis media—Tympanostomy.
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After failure of conservative therapy to resolve middle ear fluid in patients with serous otitis media, surgical ventilation of the tympanic cavity is indicated, as 2 or 3 weeks of continuous aeration is thought to be sufficient in treating serous otitis media (1,2). A myringotomy procedure with the placement of a ventilation tube (VT) after aspiration of middle ear fluid is the ''gold standard'' surgical method for these patients (1–5). However, persistent otorrhea, permanent perforations, atrophic scars, dislocation of the VT in the middle ear, cholesteatomas, and tympanosclerotic changes in the tympanic cavity have been associated with VT insertion (2–6).

Laser-assisted and thermal myringotomy have been proposed as alternative procedures to VT insertion (7–9). To enhance laser-assisted myringotomy patency, the associated use of topical mitomycin has been proposed, and several animal studies have yielded encouraging results. Mitomycin C (MC) is an antineoplastic agent produced by the fungus *Streptomyces caespitosus*. It has been used safely in humans since 1983, and it is widely used topically in ophthalmology to prevent laser scleral trabeculotomy closure in glaucoma patients. Even cells not actively synthesizing DNA do not proliferate after exposure (10–16). Topical 5-fluorouracil application was also used by Cakir et al. to delay radiofrequency myringotomy (RFM) closure in guinea pigs, but the patency period was not long enough to be proposed as an alternative to VT insertion (17).

The purpose of this experimental study was to assess the patency time after radiofrequency myringotomy in combination with MC in rabbits. The potential further use of this method in humans is addressed.

MATERIALS AND METHODS

The study was performed on 20 healthy female rabbits in the Medical Experimental Education and Research Center of the University of Crete. All rabbits were of similar age and weight (approximately 3,500 g). Animals were housed in the animal vivarium of the University of Crete Medical Experimental Education and Research Center. Their health was monitored by animal care technicians under veterinary supervision according to the Hellenic National Bioethic Committee guidelines. The

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research protocol was reviewed and approved by the University of Crete, School of Medicine Animal Care and Use Committee.

All procedures were performed under general anesthesia. The animals were first weighed, and then 5 mg/kg xylazine was injected intramuscularly. After 5 minutes, 35 mg/kg ketamine was injected intramuscularly. Before intervention, all ears were found to have normal tympanic membranes on otomicroscopy. After anesthesia, bilateral myringotomies of 1 to 1.5 mm diameter were performed in the anterior part of the tympanic membranes with the Ellman Surgitron (Ellman International, Inc., Oceanside, NY, U.S.A.) under the operation microscope (Zeiss microscope, with a 300-mm objective lens). The myringotomy procedure was performed in the Cut/Coag mode (fully rectified mode) of the Ellman Surgitron, with 10 power grade, by using a TEE 230 electrode (Fig. 1). Care was taken to not touch the electrode either to the external ear skin or to the promontory.

The right ears were classified as the study group and a Gelfoam (Upjohn Co., Kalamazoo, MI, U.S.A.) sponge (methylcellulose) soaked with MC 0.3 mg/ml was applied and held in contact with the myringotomy site for 10 minutes. At the same time, a Gelfoam sponge soaked in saline solution was applied to the left myringotomy site (control side). Cotrimoxazole (48 mg/kg administered subcutaneously two times per day) was given for 5 days to reduce the chance of middle ear infection.

Postoperative follow-up included ear examination with the operative microscope on a weekly basis until the tympanostomy was closed. Patency time (defined as the time within which the myringotomy heals) and postoperative complications were assessed in every group. Data were recorded in a database and statistically compared. Kaplan-Meier survival techniques were used to compare myringotomy patency time between study and control sides. SSPS 13.0 software (SPSS, Inc., Chicago, IL, U.S.A.) was used for statistical analysis. The Breslow (generalized Wilcoxon) test was chosen to assess significance between study and control sides.

RESULTS

The mean patency time of the study side (RFM and MC) was 5.45 weeks (95% confidence interval, 5.185–5.715 weeks). The mean patency rate for the control side (treated with saline) was 1.60 weeks (95% confidence interval, 1.38–1.82 weeks). The Breslow (generalized Wilcoxon) test showed the study group (RFM and MC) to have significantly longer patency of the RFM than the control group ($p < 0.0001$) (Fig. 2). Otorrhea occurred in one ear of the control group and one ear of the study group but was spontaneously resolved by the second and third weeks respectively. No permanent perforations, tympanosclerotic plaques, or atrophic scar formation occurred.

DISCUSSION

Myringotomy with VT placement is the most common surgical procedure performed on children, with an estimated 2 million tubes inserted per year in the United States. The indications and efficacy of VTs have been

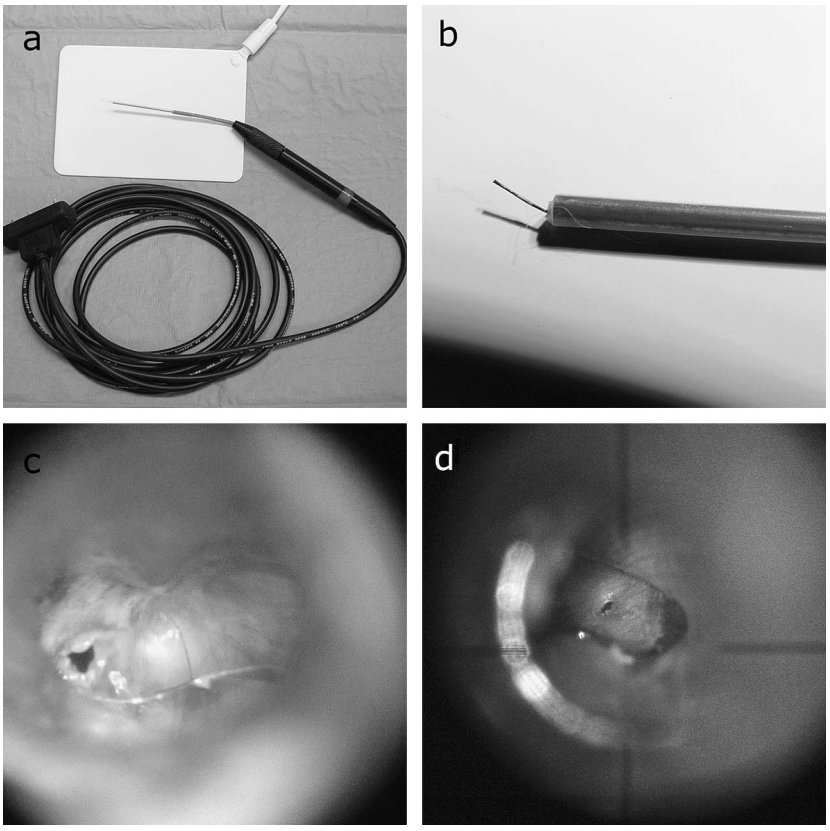

FIG. 1. (*a*) The TEE 230 electrode for the Ellman Surgitron. (*b*) The tip of the TEE 230 electrode. (*c* and *d*) Radiofrequency myringotomies.

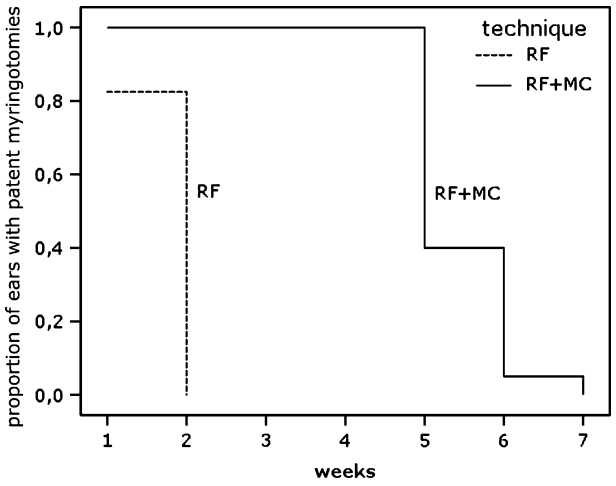

FIG. 2. Kaplan-Meier analysis shows the proportion of ears with patent myringotomies as a function of study week ($p < 0.0001$).

well-established (2,3,12,18). Unfortunately, VT placement carries with it a risk for long-term complications including persistent otorrhea, permanent perforations, atrophic scars, dislocation of the VT in the middle ear, cholesteatomas, and tympanosclerotic changes in the tympanic membrane (2–6). Some of these complications are not rare: purulent otorrhea may occur in up to 40.4% of cases, and Goode estimated the persistent perforation rate at 11.5%, after T-tube insertion (2,3,12,18). Myringotomy alone is considered inadequate, as it heals within 1 to 2 days, which is usually too short to offer a therapeutic effect (2–6). Laser-assisted and thermal myringotomy have been proposed to prolong myringotomy patency time (7–9). The advantage of laser or thermal myringotomy compared with VT insertion is the low complication rate. Nevertheless, debate exists regarding their efficacy (5,7,10,11). Laser myringotomy has an intermediate duration, of about 3 weeks, and may be advisable in selected cases; however, when longer patency time rates are required, VT insertion has to be considered, with all the attendant risks and complications (7,18).

The radiofrequency energy is an alternative technology. The tissue heats in response to the radiofrequency current passing through it and tissue damage occurs as heat is allowed to accumulate in it. The electrosurgical circuit includes the radiofrequency generator, active electrode, grounding pad, and the patient. It produces five distinct waveforms: fully filtered, fully rectified, partially rectified, fulguration, and bipolar. Each of these modes uses a combination of frequency, power, waveform, electrode size, and time of application to produce the required tissue damage (19–22). To our knowledge (MEDLINE search in April 2005), there is only one study regarding the subject of radiofrequency use in performing myringotomies. Cakir et al. performed RFMs on guinea pigs using the Ellman Surgitron unit in the cut (fully filtered) mode (4–5 power grade), and an A3 electrode, while 5-fluorouracil was applied to half of them to prolong myringotomy patency time. In their study, all RFMs (without 5-fluorouracil application) healed within the first week (17). We used the Ellman Surgitron unit in the filter Cut/Coag (fully rectified) mode, with 10 power grade, and a TEE 230 electrode. The fully filtered mode gives off the least lateral heat and the partially rectified gives off the most, with the fully rectified mode (50% Cut, 50% Coag) in between. Moreover, accumulation of lateral heat depends on the power intensity (22). In our control group, 13 of 20 RFMs (65%) closed within the second week (mean patency time, 1.60 weeks). We believe this difference may be attributable to different settings and interspecies variation among animals (rabbit versus guinea pig). Further studies may demonstrate the association between radiofrequency settings and RFM patency time.

Cakir et al. applied 5-fluorouracil in half of the RFMs to prolong myringotomy healing. However, 5-fluorouracil application did not prolong patency time enough to be proposed as an alternative to the VT insertion technique, as all cases healed within a 2- to 3-week period (17). Topical MC application has also been used to enhance laser-assisted myringotomy patency, and several animal studies have been encouraging. In cultured rabbit fibroblasts, MC was proved to be approximately 100 times more potent than 5-fluorouracil in inhibiting mitosis (23). MC is an aminoglycoside produced by the fungus *Streptomyces caespitosus*. It has been safely used in humans as an antineoplastic agent since 1983. It is widely used locally in ophthalmology to prevent laser scleral trabeculotomy closure in glaucoma patients. MC selectively inhibits DNA replication, mitosis, and protein synthesis and is active against all cells regardless of the cell cycle phase they are in. Even cells not actively synthesizing DNA will not proliferate after exposure (10–16). Estrem and Batra used topical MC in rats to delay tympanic membrane healing. In their study, the application of MC (2 mg/ml) for 10 minutes on myringotomies performed with potassium-titanyl-phosphate laser significantly increased the myringotomy closure time. Moreover, they noticed that increased exposure beyond a single 10-minute application of MC did not statistically prolong the patency rate (10). Those results were confirmed experimentally by other colleagues (11–15). Preapplication of MC before laser myringotomy was also found to be effective in prolonging the patency of laser myringotomies in rats (16). In our study with MC application on RFMs, a mean patency time of 5.45 weeks (95% confidence interval, 5.185–5.715 weeks) was achieved. Thus, we believe that RFM in combination with MC can be proposed as an alternative technique.

Jassir et al. demonstrated that there is a dose-response relationship of topically applied MC for the prevention of laser myringotomy closure. They concluded that doses of MC higher than 0.4 mg/ml do not appear to prolong patency and are associated with greater otorrhea, suggesting middle ear toxicity, whereas no otorrhea occurred in concentrations of less than 0.2 mg/ml (15). In our study, MC was used at a concentration of 0.3 mg/ml. Otorrhea

occurred in one ear of the control group and one ear of the study group and was spontaneously resolved by the second and third weeks, respectively.

Another issue of interest is that MC as an aminoglycoside antibiotic may potentially exert ototoxic effects. Jassir et al. demonstrated no differences in control ears on distortion-product otoacoustic emissions audiography, suggesting no influence on cochlear functions (12). In addition, no residual hearing loss was observed in cases involving MC preapplication in children undergoing laser myringotomy. Moreover, there are no reports of MC-related ototoxicity when used as a systemic chemotherapeutic agent. It should also be mentioned that MC is a carcinogen, although the quantity used for myringotomy is tiny compared with that used in chemotherapy (18).

In conclusion we believe that RFM may be an alternative myringotomy technique. It is a safe, low-cost, and easy-to-use technology, and no special training is required. In our study, we were able to perform bloodless myringotomy in a safe and controlled fashion. This is believed to be an advantage of RFM over the classic surgical myringotomy, as there is an increased myringotomy patency period. Thus, it can be recommended in performing myringotomy instead of surgical myringotomy. Further studies will demonstrate the association between radiofrequency settings and RFM patency time. MC application to RFMs prolongs myringotomy patency time enough to be proposed as an alternative to the VT insertion technique. Moreover, we believe that the patency times achieved in our study are comparable to MC application in laser myringotomies. In our department, there is currently an experimental study in progress, comparing RFM with carbon dioxide laser myringotomy and the MC effect to the above techniques.

REFERENCES

1. Bluestone CD. Role of surgery for otitis media in the era of resistant bacteria. *Pediatr Infect Dis J* 1998;17:1090–8.
2. Mandel EM, Rockette HE, Bluestone CD, Paradise JL, Nozza RJ. Efficacy of myringotomy with and without tympanostomy tubes for chronic otitis media with effusion. *Pediatr Infect Dis J* 1992; 11:270–7.
3. Goode RL. Long-term middle ear ventilation with T tubes: the perforation problem. *Otolaryngol Head Neck Surg* 1996;115:500–1.
4. Prokopakis EP, Hajiioannou JK, Velegrakis GA, Christodoulou PN, Scordalakis C, Helidonis ES. The role of laser assisted tympanostomy (LAT) in treating allergic children with chronic serous otitis media. *Int J Pediatr Otorhinolaryngol* 2002;62:207–14.
5. Prokopakis EP, Lachanas VA, Christodoulou PN, Bizakis JG, Karatzanis AD, Velegrakis GA. Implications of laser assisted tympanostomy in adults. *Otol Neurotol* 2005;26:361–3.
6. Prokopakis EP, Lachanas VA, Christodoulou PN, Velegrakis GA, Helidonis ES. Laser assisted tympanostomy in pediatric patients with serous otitis media. *Otolaryngol Head Neck Surg* 2005 (in press).
7. Söderberg O, Hellström S, Stenfors LE. Myringotomy made by CO2 laser: an alternative to the ventilation tube? *Acta Otolaryngol* 1984;97:335–41.
8. Silverstein H, Kuhn J, Choo D, Krespi YP, Rosenberg SI, Rowan PT. Laser-assisted tympanostomy. *Laryngoscope* 1996;106:1067–74.
9. Lau P, Shelton C, Goode RL. Heat myringotomy. *Laryngoscope* 1985;95:38–42.
10. Estrem SA, Batra PS. Preventing myringotomy closure with topical mitomycin C in rats. *Otolaryngol Head Neck Surg* 1999; 120:794–8.
11. Estrem SA, VanLeeuwen RN. Use of mitomycin C for maintaining myringotomy patency. *Otolaryngol Head Neck Surg* 2000;122:8–10.
12. Jassir D, Buchman CA, Gomez-Marin O. Safety and efficacy of topical mitomycin C in myringotomy patency. *Otolaryngol Head Neck Surg* 2001;124:368–73.
13. O'Reilly RC, Goldman SA, Widner SA, Cass SP. Creating a stable tympanic membrane perforation using mitomycin C. *Otolaryngol Head Neck Surg* 2001;124:40–5.
14. Yucel OT. Topical use of mitomycin C in laser myringotomy: an experimental study in rats. *Int J Pediatr Otorhinolaryngol* 2000; 54:93–6.
15. Jassir D, Odabasi O, Gomez-Marin O, Buchman CA. Dose-response relationship of topically applied mitomycin C for the prevention of laser myringotomy closure. *Otolaryngol Head Neck Surg* 2003;129:471–4.
16. Estrem SA, Baker TJ. Preapplication of mitomycin C for enhanced patency of myringotomy. *Otolaryngol Head Neck Surg* 2000;122: 346–8.
17. Cakir BO, Dadas B, Basak T, et al. Effect of topical 5-fluorouracil on closure time of myringotomies created by a radiofrequency surgical unit in guinea pigs. *Otol Neurotol* 2002;23:146–51.
18. D'Eredita R. Contact diode laser myringotomy and mitomycin C in children. *Otolaryngol Head Neck Surg* 2004;130:742–6.
19. Plant RL. Radiofrequency treatment of tonsillar hypertrophy. *Laryngoscope* 2002;112:20–2.
20. Maddern BR. Electrosurgery for tonsillectomy. *Laryngoscope* 2002;112:11–3.
21. Shehata EM, Ragab SM, Behiry AB, Erfan FH, Gamea AM. Telescopic-assisted radiofrequency adenoidectomy: a prospective randomized controlled trial. *Laryngoscope* 2005;115:162–6.
22. Aferzon M, Millman B. Excision of rhinophyma with high-frequency electrosurgery. *Dermatol Surg* 2002;28:735–8.
23. Yamamoto T, Varani J, Soong HK, Lichter PR. Effects of 5-fluorouracil and mitomycin C on cultured rabbit subconjunctival fibroblasts. *Ophthalmology* 1990;97:1204–10.