Objective: To explore the effect of mitomycin treatment on the pediatric airway following laryngotracheal reconstruction.

Design: Randomized, double-blind, placebo-controlled trial.

Patients: Children aged 2 to 17 years with subglottic or upper tracheal stenosis undergoing laryngotracheal reconstruction at a single, tertiary care, children’s hospital.

Intervention: At the time of extubation or stent removal, the children underwent bronchoscopy and 0.4 mg/mL (2 mL of a 0.2-mg/mL solution of either mitomycin or an equal volume of isotonic sodium chloride was directly applied to the subglottic region for a single application of 2 minutes. These children then underwent interval endoscopy at 2 weeks, 6 weeks, and 3 months postoperatively for assessment of their airways.

Results: Granulation tissue was graded on a scale of 0 (none) to 4 (near-total or total occlusion). Videotapes of endoscopies were independently observed and graded by 3 pediatric otolaryngology fellows with a subsequent interobserver agreement of 91.6%. The results were then dichotomized to represent a single cohort in which further surgical intervention would be required and another separate cohort in which further surgery would not be required. At the 1-year mark, interim analysis was performed by a Data Safety and Monitoring Committee. At this time, 13 children had been randomized to the mitomycin-treated arm of the study and 11 children to the placebo-treated arm. A 2-tailed Fisher exact test revealed a value of 1.00. The Data Monitoring and Safety Committee advised that the trial should be stopped because the distributions between the 2 populations were almost identical.

Conclusion: We cannot reject the null hypothesis that a single topical dose of mitomycin exerts an equal benefit as does isotonic sodium chloride when applied to the pediatric airway after laryngotracheal reconstruction.


The issue of restenosis following pediatric laryngotracheoplasty or cricotracheal resection is a difficult and challenging problem. Many techniques including postoperative stenting and the use of the carbon dioxide laser have been employed to address this complication; however, the incidence of restenosis following these airway procedures persists at 20% to 40% depending on the initial grade of the stenosis.1 It follows that the incidence of granulation tissue following operative repair for grade 3 and 4 lesions may well be significantly higher than this quoted figure. Mitomycin is an antineoplastic antibiotic derived from Streptomyces caespitosus; it acts as an alkylating agent to inhibit DNA synthesis as well as to inhibit cell division and fibroblast proliferation. Mitomycin represents one possible nonsurgical means of reducing postoperative granulation and scar tissue formation.

Mitomycin has been used for some time by ophthalmologists to reduce scarring following surgery for glaucoma. Its efficacy and safety have been shown in numerous animal and clinical trials.2-4 At a cellular level, Khaw et al5 have shown the demonstrable effects of mitomycin on cell proliferation and cellular morphology. In the field of otolaryngology, topical administration of mitomycin has been shown to delay the closing time of maxillary antrostomies in the rabbit model.6 Specifically regarding the issue of laryngotracheal stenosis and postoperative scar formation, there have been several stud-
INTERIM ANALYSIS

The study was designed so that, at the 1-year mark, an independent Data Monitoring and Safety Committee whose members were chosen by the Children’s Hospital Medical Center statistician (J.A.B.) would review the data for adverse outcomes, as well as to identify whether there was a valid reason to end the study early.

STATISTICAL ANALYSES

Interobserver Agreement for Granulation Tissue Grading Scale

The grading system for assessment of endoluminal granulation tissue was established and the 3 pediatric otolaryngology fellows (C.J.H., B.E.J.H., and P.D.L.) who would be involved in all of the postoperative endoscopies each independently reviewed 36 videotapes of postoperative endoscopies and assigned scores to each according to the amount of granulation tissue. There was disagreement among the 3 fellows only on 3 of the 36 endoscopies for an overall interobserver agreement of 91.6%. For the 3 cases in which there was disagreement, the disparity was never greater than 1-grade difference in opinion.

Sample Size Calculations

The main outcome measure chosen for statistical evaluation was the average granulation grade at the third and fourth visits. The grades were dichotomized according to clinical relevance; it was hypothesized that patients with grades 0 through 2 would not require further open reconstructive surgery, whereas patients with grades 3 or 4 would need further surgery. The power for statistical calculations was established at 0.8%; the \( \alpha \) level was .05. We hypothesized that 70% of the patients treated with placebo and 30% of the patients treated with mitomycin would be graded as grade 3 or 4 for an overall treatment difference of 40%. Given these parameters, the sample size needed was calculated to be 23 patients per arm.

Outcome Analysis

Using the dichotomized, binomial variables as described earlier, a 2-tailed Fisher exact test analysis was chosen for analysis. If there was a statistically significant difference between the 2 populations, a Mantel-Haenszel test for trend was chosen to shed more light on this difference between the populations.

PATIENTS, MATERIALS, AND METHODS

INCLUSION AND EXCLUSION CRITERIA

All children younger than 18 years who had grades 3 and 4 Myer-Cotton stage laryngotracheal stenosis when undergoing either laryngotracheoplasty or cricotracheal resection with postoperative stenting were enrolled in the study during the period of the study (September 1, 1999, to September 1, 2000). Male and female patients and all minorities were equally enrolled. The sole criterion was the severity of laryngotracheal stenosis and that the type of surgery require some form of postoperative stenting whether that be from a suprastomal stent, a T-tube, or an endotracheal tube. Patients who have had previous endolaryngeal topical application of mitomycin were excluded from this study.

PROTOCOL

The parents or primary caregivers of patients enrolled in the study were each informed of the study and were enrolled after signing an institutional review board–approved informed consent (IRB 99-7-16). When the stent was removed (any form of stent), all children received an intravenous dose of 0.5 mg/kg of dexamethasone acetate (Decadron); this dose was repeated at postoperative days 2 and 4 for all patients. Patients then received either a single topical application of 0.4 mg/mL of either mitomycin for 2 minutes or isotonic sodium chloride. The surgeon was blinded to the type of topical medication applied; the solution consisted of 1 of the 2 agents (mitomycin or control) that were prepared and numbered in advance and then chosen according to a random number generation list provided by the pharmacy.

The postoperative follow-up consisted of the routine follow-up for children operated on at Children’s Hospital Medical Center, Cincinnati, Ohio. The children underwent interval laryngoscopy and bronchoscopy at 2 weeks, 6 weeks, and 3 months after the stents were removed. At each interval evaluation, the amount of granulation tissue and the airway diameter were recorded. The following 0-to-4-point scoring system was used for rating the amount of granulation tissue: 0, none; 1, single focus of granulation tissue; 2, multiple small foci, polyps; 3, moderate polypoid tissue; and 4, near-total or total occlusion with granulation tissue. The airway diameter was graded according to the Myer-Cotton grading system.13
This study represents the next step in the investigation of mitomycin and its effect on the airway. Whereas there have been single-arm human clinical studies, the only randomized controlled studies to date have involved animals. By establishing a randomized, double-blind, placebo-controlled study, we hope to be able to shed light on the human paradigm of mitomycin as it affects the airway.

### RESULTS

Over the first year of the study, 24 patients were enrolled. Their diagnoses consisted of posterior glottic, subglottic, or upper tracheal stenosis. Twenty-two of the 24 had acquired an abnormal condition; 2 children had congenital subglottic stenosis. Eighteen of the 24 patients underwent single-stage laryngotracheal reconstruction or cricotracheal resection. All 18 patients received endotracheal tubess as interim stents. The remaining 6 patients had an assortment of stents placed that consisted of either an above stoma stent (or, in 1 case, a glottic keel). The demographics for all 24 patients are given in the Table.

At the 1-year mark, the Data Monitoring and Safety Committee reviewed the data for all 24 patients. The dichotomous results, using the Fisher 2-tailed exact test, for patients receiving either mitomycin or placebo were as follows: (1) those with an average granulation grade of 3 or 4 and mitomycin treated, 3 patients; placebo treated, 1 patient; (2) those with an average granulation grade of 0 through 2 and mitomycin treated, 11 patients; placebo treated, 10 patients. A Fisher 2-tailed exact test was performed and calculated as 1.00. The Data Monitoring and Safety Committee advised that the trial should be stopped because the distributions between the 2 patient populations were almost identical.

### COMMENT

In designing this randomized, double-blind, placebo-controlled trial, the goal was to establish a working paradigm where the potential confounding factors would be evenly distributed between the 2 populations. Focusing on pediatric airway reconstructions in which a stent was involved seemed to be a reasonable model because there was a definable starting point for each case when the stent was removed. The initial diagnoses were fairly uniform as were the surgical reconstructive procedures. The Table illustrates how the various procedures and choice of stents were distributed evenly between the mitomycin-treated and control groups.

The decision of an outcome parameter to be observed and monitored for statistical analysis was made with the knowledge that many of the possibilities would be directly influenced by the initial pathologic condition, the type of surgery, or the type of graft chosen. For this reason, we decided not to use operation-specific or overall extubation or decannulation rates as an outcome measure. We also decided that although there was a semiquantitative means of assessing the size of the airway, still this end point was influenced more by the surgical procedure than by the use or avoidance of mito-

| Demographics of 24 Pediatric Patients Who Received Mitomycin or Placebo Treatment After Laryngotracheal Reconstruction* |
|---|---|---|
| Treatment Group | Mitomycin (n = 11) | Placebo (n = 13) |
| Variable | | |
| Sex | Male | 6 | 9 |
| | Female | 5 | 4 |
| Age, mean, y | 3.6 | 4.7 |
| Type of stenosis | Subglottic | 11 | 9 |
| | Upper tracheal | 1 | 4 |
| Type of reconstruction | Laryngotracheal | 10 | 11 |
| | Cricotracheal | 2 | 2 |
| Type of stent | Endotracheal tube | 10 | 8 |
| | Other | 2 | 4 |
| Duration for type of indwelling stent, mean, d | Endotracheal tube | 6.4 | 5.6 |
| | Other | 28 | 42 |

*Data are given as the number of patients unless otherwise indicated.

Symptoms and on an increase in the size of the airway. Again, this is a single-arm study in which the effects of mitomycin are difficult to quantify; moreover, the outcome measurement of airway size is qualitative and difficult to assess critically.

Eliashar et al determined the role of mitomycin on laryngotracheal stenosis in the dog model by intravenously injuring the canine larynx or trachea and then administering topical mitomycin, 0.2 mg/mL. They found that over a 21-day postoperative period, a single dose of mitomycin significantly reduced the amount of laryngotracheal stenosis. A second administration of mitomycin was of no additional benefit.

Three randomized controlled studies examining the effects of mitomycin on the airway have been undertaken previously in animal models. Correa et al used a canine model in which they created radial incisions to the subglottic region and treated these incisions with either a 1% solution of mitomycin with a single application for 5 minutes or with a control where no application was administered. They were able to confirm statistically that dogs treated with mitomycin exhibited a larger airway with decreased collagen and scar formation. Spector et al also used a canine model and created laser incisions to the glottis of 16 dogs. Compared with controls, a single application of 1% mitomycin for an application of 3 minutes significantly reduced the amount of postoperative granulation tissue. However, Coppit et al used a pig model and examined the effect of mitomycin compared with a control after single-stage laryngotracheal reconstruction and stenting. They administered 0.5 mg/mL of mitomycin over 2 minutes for a total of 2 applications of mitomycin per animal. They found that there was no statistically significant difference in the amount of inflammatory tissue between the mitomycin-treated and the control pigs.
mitomycin treatment. Short of histopathologic analysis, the development of postoperative granulation tissue relative to the application of either mitomycin or placebo seemed a reasonable outcome parameter as previously cited work has focused on the effect of mitomycin on this development. The creation and validation of a grading scale facilitated statistical analysis.

About the administration of mitomycin itself, the dosage, length of application time, and amount of applications were each chosen by reviewing the literature for established benchmarks. Mitomycin has been applied to the human and animal airway in dosages of 0.1 to 10 mg/mL. In the human clinical model, previous literature has documented dosages from 0.1 to 0.4 mg/mL. We chose a dosage of 0.2 mg/mL as it was the dosage that had been used in the only previously reported on application following laryngotraheal reconstruction.

The duration of topical application has also varied in the literature from 1 to 5 minutes. Most of the citations referenced used an application time of 2 to 3 minutes; we chose a 2-minute application time to be a conservative but effective time frame.

Neither dosage nor application time has been studied in any form of titration study, therefore the choices were made by comparing different studies. The number of applications of mitomycin for maximum effectiveness has been investigated, at least in a preliminary fashion, by Eliashar et al. As they found that a second application of mitomycin yielded no more results than a single application, we decided to limit the number of applications to 1.

Given the negative findings documented by this study, the choices made about dosage, application time, and number of applications all must be regarded as possible factors that, if altered, may well have changed the study’s outcome. We chose conservatively in our decisions as to these values, in part because this was an area of research in which previous titration studies had not been performed; we were concerned with the possibilities of potential adverse effects and morbidities from the application of mitomycin. No adverse effects were seen for any of the patients who were treated with mitomycin. Moreover, the vast majority of patients who received mitomycin treatment exhibited granulation with grades of 0 through 2. This would suggest that a single application of mitomycin at the defined dose, when applied for 2 minutes, is effective in inhibiting the development of granulation tissue. The problem that confounded statistical analysis was not the results seen in the mitomycin-treated group, rather it was those seen in the control population. Ten of the 11 children treated with placebo exhibited postoperative granulation that was graded as 0, 1, or 2. This suggests that although a significant proportion of children may develop granulation tissue subsequent to airway reconstruction and stent placement, this granulation tissue may not be exuberant enough to allow for this form of comparative study. All patients in the study received a course of corticosteroids and this may have produced an overall decrease in granulation tissue formation. The decision was made to offer corticosteroid treatment for all because corticosteroids are given in an anecdotal fashion according to the appearance of the airway. It appeared that it would be more reasonable and ethical to give a short course of corticosteroids to all rather than withholding it from those who might need it.

The decision to stop the study before the appropriate sample size was obtained was not made lightly. The use of an independent Data Monitoring and Safety Committee to review the data at appropriate intervals is a well-established mechanism for ensuring that no untoward adverse effects are occurring. Interval analysis also allows for heavily positive findings to be discovered in a timely fashion; such early findings would spur the argument that it would be unethical to continue a study and continue to give some population a placebo. Similarly, if the interval findings show identical or near-identical outcomes where the distributions are approximated to a level that it is believed that statistically significant differences cannot be achieved, the argument is raised that it may be unethical to allow for the possibility of untoward adverse effects when the outcome of the study is already known. One of the critical points that frames this decision is a firm knowledge of the nature of the assumptions that were made to make projections and to calculate sample size initially. In the case of this study design, we projected that there would be a 40% difference in the incidence of significant granulation tissue formation postoperatively between the 2 populations studied. Examining the data shows that the difference in the incidence of significant granulation tissue formation between the 2 groupings is statistically negligible and this is perhaps the critical reason why the study’s conclusions would not have deviated from the interval projections if the calculated sample size had been achieved.

After a close review of the data, it becomes clear that although the dose, application time, number of applications, as well as a host of other factors may play a role in the outcomes of studies such as this, still the central deficit that future studies will need to address is to define a model where the granulation tissue seen within the control population is at a level high enough so that comparisons can be made when a given therapy significantly alters the equation and diminishes the amount of granulation tissue. It may be that future studies in which corticosteroids are not administered to each patient would allow for an adequate control population and would illuminate treatment differences specific to mitomycin.

No significant difference in granulation tissue formation was noted in the only 1 of the 3 randomized trials involving animals in which the effect of mitomycin after stent placement was examined. Models that have illustrated the greatest benefit of mitomycin regarding the airway have consisted of models in which radial incisions are made with the carbon dioxide laser, mitomycin is topically applied, and the airway is then examined prospectively. To answer the question of whether mitomycin affects granulation tissue and scar tissue formation in the airway, perhaps another model would be to look at procedures in which discrete laser incisions are made (eg, arytenoidectomies, cordotomies, or treatment of more minor subglottic stenosis). A consistent grading system for measuring outcome parameters would need to be tailored to this study design, and the
number of patients required might well necessitate a multi-institutional effort; however, such a study holds the potential for enough of a difference between the treated and control populations to be apparent such that meaningful conclusions could be drawn. Until such a study is performed, the sole conclusion we can draw from the findings of our study is that we can reject the null hypothesis established to frame our study that a single topical 0.2-mg/mL dose of mitomycin exerts an equal benefit to a dose of isotonic sodium chloride when applied to the pediatric airway after laryngotracheal reconstruction.

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