Airway Complications from Topical Mitomycin C

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OBJECTIVE: Topical application of mitomycin C appears to be a useful adjunct in reducing cicatricial scarring of the airways. Human and animal studies have demonstrated the efficacy and safety of mitomycin C topically in the treatment of airway stenosis at concentrations ranging from 0.4 mg/mL to 10 mg/mL. Although no reports of mitomycin C toxicity have been reported in the otolaryngology literature, the ophthalmologic literature has documented serious, vision-threatening complications resulting from the use of topical mitomycin C. The purpose of this study is to report complications related to mitomycin C use in the treatment of glottic and subglottic stenosis. Risk factors associated with these complications are identified.

STUDY DESIGN AND SETTING: A retrospective chart review of all patients treated by the senior author for laryngotracheal stenosis with endoscopic CO2 laser incisions/dilation and adjuvant topical mitomycin C was performed to determine the incidence of complications. Variables studied included patient age and gender, location and severity of stenosis, medical comorbidities, length of procedure, postoperative instrumentation of the airway, and mitomycin C concentration.

RESULTS: Eighty-five cases of adjuvant topical mitomycin C use after CO2 laser endoscopic treatment and dilation for upper airway stenosis were identified in a total of 44 patients. Complications that were believed to be caused by the local toxicity of mitomycin C occurred in 4 cases out of 85 (or 4.7%), manifested by accumulation of fibrinous debris at the operative site, resulting in partial airway obstruction and the need for emergent airway intervention.

CONCLUSIONS: Caution should be exercised when topical mitomycin C is used in the treatment of airway stenosis.

EBM RATING: B-3

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Laryngotracheal stenosis (LTS) represents a challenge to all otolaryngologists who treat this condition. Endoscopic laser treatment of LTS, although widely used as a treatment modality for the past 20 years, is associated with an unacceptably high rate of repeat stenosis. Since 1998, a great deal of attention has been focused on the use of topical mitomycin C as an adjuvant to reduce re-stenosis after endoscopic laser management of LTS.

Mitomycin C is an antibiotic isolated from the broth of Streptomyces caesipitosus, which is thought to act as an alkylating agent able to inhibit DNA synthesis. It has also been shown to inhibit fibroblast proliferation and activity, which can reduce scar formation. Mitomycin C has been used in ophthalmology as an adjunct to glaucoma surgery and to prevent recurrence after pterygium removal.1-3 Numerous randomized, prospective animal studies4-6 have shown convincing results from the use of mitomycin C in the prevention of glottic and subglottic stenosis in the postoperative period. Human studies have also demonstrated the efficacy and safety of mitomycin C topically (0.4 mg/mL) in the treatment of airway stenosis.7-9 Although no reports of mitomycin C toxicity have been reported in the otolaryngology literature, the ophthalmologic literature has documented serious, vision-threatening complications. These include severe secondary glaucoma, corneal edema and perforation, corectopia, iritis, sudden onset mature cataract, scleral calcification, incapacitating photophobia, and pain.3

The purpose of this study is to report complications related to mitomycin C use in the endoscopic treatment of glottic and subglottic stenosis.

METHODS AND MATERIALS

The University of Texas Health Science Center San Antonio Institutional Review Board approved this study. A...
A retrospective chart review of all patients treated by the senior author for supraglottic, glottic, and subglottic/tracheal stenosis was performed to determine incidence of complications. The study included all patients with airway stenosis treated between October 1999 and August 2004 at the University of Texas Health Science Center in San Antonio who underwent direct microlaryngoscopy with CO2 laser treatment of stenosis and topical application of topical mitomycin C. Two concentrations of mitomycin C were used: (1) a standard preparation of 0.4 mg/mL, referred to as “low” concentration, and (2) a “supersaturated” 1% formulation of 10 mg/mL, referred to as “high” concentration. Application time for the mitomycin C varied slightly, but in most cases was 4 minutes (range, 3-5 minutes). No rinsing of the operative site was performed after mitomycin C application. A total of 85 endoscopic laser procedures with topical application of mitomycin C were identified in 44 patients with LTS. A standard protocol was used in the treatment of the patients, including preoperative and postoperative acid-suppressive medications (proton pump inhibitors in most patients), perioperative antibiotic prophylaxis, laser radial incisions with a setting of 4 to 6 watts superpulse, and rigid dilation (in adult patients only) before topical mitomycin C application. The size of the airway at the end of the case was recorded; all patients were asymptomatic in the immediate postoperative period, with no stridor or airway symptoms, and were discharged from outpatient surgery in good condition. A detailed chart review of these procedures was carried out. Clinical and demographic data were collected for all 85 surgical procedures and included the patient’s age, sex, date and length of procedure, length of mitomycin C topical application, concentration of mitomycin C, location and severity of stenosis, medical comorbidities, postoperative instrumentation of the airway, and any evidence of complications associated with the case.

RESULTS

Eighty-five cases of adjuvant topical mitomycin C use after laser laryngoscopic treatment and dilation for upper airway stenosis were identified in a total of 44 patients. Twenty patients were male (45%), and 24 were female (55%). Mean age was 44.8 years (range, 2-80 years). Twenty-five patients (57%) underwent a single procedure, 7 patients (16%) had 2 procedures, 6 patients (13.5%) underwent 3 procedures, and 6 patients (13.5%) underwent 4 or more surgeries (Table 1). Twenty-six patients were diagnosed with subglottic or tracheal stenosis, 8 with posterior glottic stenosis, 5 with combined glottic and subglottic, and 2 with supraglottic stenosis. The 4 additional patients (numbers of patients add to more than 44 because some patients had stenosis at more than one site) had topical mitomycin C application secondary to granulation tissue formation (2), secondary to anterior glottic web (1), and for prevention of web formation (1) (Table 2). Airway diameter and length of stenosis were not consistently documented but averaged 3.5 mm in maximal airway dimension and were less than 2 cm in length in all cases.

In 71 cases out of 85, a standard concentration mitomycin C was used, 0.4 mg/mL. Supersaturated concentration mitomycin C (10 mg/mL) was used in 14 of 85 cases (Table 3). Complications due to local toxicity of mitomycin C occurred in 4 of 85 cases (4.7%) and in all instances were manifested by accumulation of fibrinous debris at the operative site, resulting in partial airway obstruction and the need for emergent airway intervention. The complication rate associated with standard (low) concentration of mitomycin C was 2.8% (2/71). In cases where supersaturated (high) concentration mitomycin C was employed, the complication rate was 14% (2/14) (Table 3). Higher-concentration mitomycin C was not associated with a statistically significant increase in the rate of airway complications ($P = .27$) when compared with the lower-concentration preparation. This may be due to the small number of patients in the high-dose mitomycin C treatment group.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Number of endoscopic airway procedures performed on each patient</th>
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<tbody>
<tr>
<td>No. of procedures</td>
<td>No. of patients</td>
</tr>
<tr>
<td>1</td>
<td>25 (57%)</td>
</tr>
<tr>
<td>2</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>3</td>
<td>6 (13.5%)</td>
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<tr>
<td>4 or more</td>
<td>6 (13.5%)</td>
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<th>Table 2</th>
<th>Location of stenosis</th>
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<tbody>
<tr>
<td>Stenosis location</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Subglottic/tracheal</td>
<td>26</td>
</tr>
<tr>
<td>Posterior glottic</td>
<td>8</td>
</tr>
<tr>
<td>Combined glottic/subglottic</td>
<td>5</td>
</tr>
<tr>
<td>Supraglottic</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous*</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Some patients had more than 1 site of stenosis.
*2 for suprastomal granulation tissue, 1 for anterior glottic web, and 1 for prophylactic prevention of anterior glottic web.

<table>
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<th>Table 3</th>
<th>Concentration of mitomycin C related to complications</th>
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<tr>
<td>Concentration of mitomycin C</td>
<td>No. of cases</td>
</tr>
<tr>
<td>0.4 mg/mL (low)</td>
<td>71</td>
</tr>
<tr>
<td>10 mg/mL (high)</td>
<td>14</td>
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</table>
In the 4 patients in whom complications occurred, 3 patients reported shortness of breath beginning 48 to 72 hours after their surgery. These symptoms progressed rapidly in the 2 pediatric patients, both of whom had been treated with high-concentration (1%) mitomycin C. One of the patients, a 6-year-old boy with aggressive recurrent respiratory papillomatosis and iatrogenic posterior glottic stenosis, was treated with laser removal of papilloma and scar division/dilation. He developed progressive biphasic stridor on postoperative day 2 and was urgently taken to the operating room for management. He was found to have large fronds of tenacious fibrinous exudate at the surgical site, which were noted to prolapse into the airway during inspiration (Figs 1 and 2). These were removed with a cup forceps and sent for histopathologic analysis, revealing fibrinoid membrane with neutrophils and keratin debris. In the other pediatric patient, an 8-year-old boy with severe glottic stenosis and recurrent respiratory papillomatosis, a similar procedure was performed, and again dyspnea developed within 48 to 72 hours after surgery. The patient experienced a respiratory arrest on postoperative day 5 and was intubated by EMS and transferred to an intensive care unit. The patient expired 10 days later. Autopsy demonstrated acute and chronic inflammatory reaction in the larynx, with fibrillar material present at the luminal surface. It should be noted that in both of these pediatric patients, cidofovir injection (75 mg total) was used in combination with the mitomycin C. Each patient had undergone combined low-concentration mitomycin plus cidofovir treatment on 4 separate occasions previously, without any untoward events. Only when the concentration of mitomycin C was increased to a 1% (high-concentration) solution with the fifth treatment did complications arise.

In the 2 adult patients with airway complications, the lower concentration of mitomycin C was used. One patient, a 28-year-old woman on dialysis for end-stage renal disease, was treated with endoscopic laser radial incision and topical low-concentration mitomycin C. She was intubated with a 5.0 endotracheal tube for 2 hours after her otolaryngologic procedure, to allow for obstetrical management of an intrauterine fetal demise. Forty-eight to 72 hours postoperatively, she developed a dry cough and progressive dyspnea and was evaluated in our outpatient clinic. Fiberoptic laryngoscopy showed glottic/subglottic edema and shaggy fibrinous debris in the infraglottic region. The patient was admitted to the ICU and given racemic epinephrine and systemic corticosteroids, resulting in improvement in her symptoms. She was discharged the next day on a prednisone taper but had recrudescence of her symptoms within 24 hours, and was urgently taken to the operating room on postoperative day 7. Partially obstructing fibrinous exudate accumulation was noted in the subglottis and removed easily with cup forceps. The patient had an uneventful postoperative course thereafter and had a well-healed, patent airway at her 3-month-follow-up visit. She did not require additional treatments and remains asymptomatic 2 years after her initial treatment.

The other adult patient, a 43-year-old man with posterior glottic stenosis, was treated with CO2 laser posterior cordotomy, medial arytenoidectomy, and topical low-concentration mitomycin C. He complained of cough and “congestion” immediately after surgery, but no dyspnea. On postoperative day 16, he presented to the emergency room with a 2-day history of shortness of breath and required urgent intubation for hypercapnic respiratory failure secondary to airway obstruction. This resulted in a prolonged MICU stay, followed by a tracheostomy on postoperative day 20. He underwent urgent intubation performed with fiberoptic assistance by a pulmonary attending physician who commented on severe edema and white, thick secretions and material in the subglottic region. The patient was discharged in stable condition on postoperative day 27. He subsequently underwent a successful revision CO2 laser treatment with mitomycin C application. The tracheostomy was left in place until after the patient had healed from the revision surgery. He was decanulated 6 months later and has no airway-related complaints.
DISCUSSION

Before this study, serious complications from topical application of mitomycin C had not been reported in the otolaryngology literature. In contrast, the ophthalmology literature is replete with descriptions of toxic local reactions due to topical mitomycin C application. Rubinfeld et al reported a series of 10 patients who experienced serious, vision-threatening complications associated with the use of topical mitomycin C after pterygium surgery, including secondary glaucoma, iritis, and corneal perforation. The authors suggest that mitomycin C-induced inhibition of fibroblast and vascular endothelial stem cells could have led to these complications.

Mitomycin C is an alkylating antibiotic derived from Streptomyces caesiptosus and has been demonstrated to inhibit mitosis in a variety of cell lines, including fibroblasts. Quantitative studies have demonstrated that mitomycin C-induced inhibition of fibroblast proliferation becomes irreversible at higher doses or after longer treatment times. Additional evidence also indicates that fibroblast death may result from higher levels of mitomycin C exposure. On the basis of our clinical and histologic observations in this study, we believe the accumulation of fibrinous exudate at the wound site is related to complete fibroblast inhibition or cytotoxicity at the wound site. Surgical manipulation of the airway results in injury to endothelium and basement membranes, which causes increased vascular permeability resulting in protein leakage (including fibrinogen, which polymerizes to fibrin). The end result of this process is fibrinous exudation. Intraoperatively, this fibrinous exudate is seen in Fig 1 and Fig 2 as a yellow-white or pale tan, stringy exudation. Intraoperatively, this fibrinous exudate is seen in the lumen of tubular organs. This is an acute process, which can form in a matter of seconds. Histologically, these exudates are composed of threadlike eosinophilic meshwork that can form masses of solid amorphous material. Fibrin provides the support for the eventual ingrowth of fibroblasts and new capillaries. The transformation of the fibrinous exudate into well-vascularized connective tissue is known as organization of the exudates, which leads to scar-tissue formation. Fibrin can be dissolved by enzymatic fibrinolysis or phagocytosis by macrophages. The irreversible fibroblast inhibition that can be seen with high-dose mitomycin C (1%) appears to put the patient at a significantly increased risk of airway complications, possibly due to the lack of fibrinolysis activity. Consultation with our clinical pathologist revealed it is also possible that these exudates are caused by direct toxic effects on the mucosa with marked exudation, similar to what is seen with diphtheria toxin. Perhaps there is some effect on vascular channels or endothelial cells, resulting in leaky vessels and greater transudation.

Mitomycin C topical application has been used at dosages ranging from 0.2 mg/mL to as high as 10 mg/mL in the treatment of LTS. Exposure times also range from 2 to 5 minutes. In general, clinical studies have used a concentration of 0.4 mg applied for 4 minutes, but there does not appear to be a consensus opinion. Initially, we used a concentration of 0.4 mg/mL for 4 minutes in all cases. We eventually discovered that certain patients with recalcitrant LTS did not appear to have any benefit from the addition of mitomycin C to their endoscopic treatments. In this small subset of patients, we began using supersaturated mitomycin C (10 mg/mL, or 1%), reasoning that the enhanced fibroblast inhibition might be more effective in these patients. After our initial experience with airway complications in 2 pediatric patients treated with 1% mitomycin, we have become considerably more cautious with the use of this preparation. Current protocol requires a tracheostomy in place below the level of stenosis if 1% mitomycin is to be employed. Since the institution of this policy, we have not experienced any further complications from the higher concentration of mitomycin C. Our clinical impression is that 1% mitomycin C is significantly more efficacious than low-dose (0.4 mg/mL) mitomycin C in preventing cicatricial scar formation in the airway. For this reason, we continue to use 1% mitomycin C in select cases.

The dangers of topical mitomycin C application in the airway are not limited to the higher-concentration mitomycin C patients, as 2 adult patients developed airway complications with the use of lower-dose (0.4 mg/mL) preparation. It is unclear what factors predisposed these patients to develop complications. In 1 patient, an endotracheal tube was placed for 2 hours at the end of the case. Normally the patients are awakened with mask ventilation, in an effort to avoid postprocedure instrumentation of the surgical site. It is possible that pressure from the tube led to increased edema at the operative site or enhanced the topical distribution of the mitomycin C. It is also possible that the presence of end-stage renal disease in this patient impaired mitomycin C clearance. The other patient treated with low-dose mitomycin C developed complications much later, 14 days postoperatively. No potential risk factors could be identified in this patient. This case differs from the other 3 cases clinically in that the airway complication occurred much later postoperatively. Although we cannot prove that mitomycin C was the cause, the histologic and clinical findings were identical to the other 3 cases.

CONCLUSION

This is the first report in the otolaryngology literature describing potentially life-threatening airway complications associated with the use of topical mitomycin C in endoscopic management of LTS. Four of 85 cases (4.7%) presented with partial airway obstruction and the need for emergent airway intervention postoperatively. Airway obstruction was caused by the characteristic accumulation of obstructing fibrinous exudate at the operative site in all cases. This pathologic response may be caused by mitomycin C inhibition of fibroblast-mediated enzymatic activity,
an important pathway in the breakdown of postsurgical inflammatory fibrinous exudate. Caution should be exercised when topical mitomycin C is used in the treatment of airway stenosis, especially when higher concentrations of mitomycin C (e.g., 10 mg/mL) are used. Further study is needed to determine if risk factors can be identified that may predispose certain patients to develop airway complications when exposed to topical mitomycin C in the laryngotracheal region.

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**REFERENCES**