ORIGINAL ARTICLE

The Role of Mitomycin in the Prevention and Treatment of Scar Formation in the Pediatric Aerodigestive Tract

Friend or Foe?

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Objective: To evaluate the role of mitomycin in the prevention and treatment of scar formation in the pediatric aerodigestive tract.

Design: Prospective study; institutional review board–approved clinical trial.

Setting: Tertiary care pediatric medical center.

Patients: Fifteen patients; choanal atresia in 5 patients, airway stenosis in 8 patients, hypopharyngeal stenosis in 1 patient, and esophageal stenosis in 1 patient.

Outcome: The efficacy and safety of mitomycin in the prevention of scar formation.

Intervention: All patients underwent surgical repair of the stenotic area, followed by topical application of mitomycin (1 mL of 0.4 mg/mL) for 4 minutes.

Results: Ten patients (67%) showed major improvement, 4 patients (27%) showed minor improvement, and 1 patient (7%) showed no improvement.

Conclusion: Topical application of mitomycin can play an effective role in the prevention and treatment of scar formation in the aerodigestive tract.

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SCAR FORMATION and restenosis continue to be the main cause of failure in surgical management of the choana, oropharynx, esophagus, and laryngotracheal complex. Mucosal injury appears to be the inciting event, causing fibroblast proliferation and collagen formation, which are key steps in the initiation of scar formation. Modulation of wound healing and minimization of scar formation can be effective in increasing the success rate of surgery in these areas of the aerodigestive tract.

In the past decade, there has been a surge of interest in using pharmacological agents for altering wound healing to prevent scar formation.[1-3] Mitomycin has gained wide acceptance in the field of ophthalmology as an agent to reduce scar formation and restenosis in conditions such as glaucoma, dacryocystorhinostomy, and pterygium surgery.[4,5]

Favorable clinical responses to the topical application of mitomycin in reducing scar formation in the larynx and trachea have been described in previous reports.[6,7] In 1998, an institutional review board–approved prospective clinical study was undertaken at Children's Hospital Boston to evaluate the safety and efficacy of the topical application of mitomycin in the prevention and treatment of scar formation in the pediatric aerodigestive tract. Three patients in this study were described earlier[7] and are herein reviewed again with a longer follow-up.

RESULTS

CHOANAL ATRESIA

Five patients presented with unilateral mixed bony membranous choanal atresia (4 on the left side and 1 on the right) (mean age, 3.4 years; range, 2-5 years). Two had undergone failed surgical repair before enrollment in the study: patient 2 had 2 prior endoscopic transnasal approaches and patient 3 had 1. Ten procedures were performed on the 5 patients (mean, 2 per patient). Patients 1, 2, and 3 had 2 procedures each, patient 4 had 1, and patient 5 had 3. The method of repair (transnasal vs transpalatal, with or without stenting) was at the discretion of the primary surgeon.

Patients 1, 2, 4, and 5 underwent endoscopic transnasal repair with topical

PATIENTS AND METHODS

Fifteen patients were enrolled in an institutional review board–approved clinical trial at Children's Hospital Boston between July 1, 1998, and December 30, 2000. Five patients presented with choanal atresia, and 10 patients presented with stenosis in other areas of the aerodigestive tract (3 glottic, 4 subglottic, 1 trachea, 1 hypopharynx, and 1 esophagus). Informed consent was obtained from all patients or their parents. All patients received topical application of mitomycin at the completion of surgical repair of the stenotic area. A 10-mm neurosurgical cottonoid sponge was soaked with mitomycin (1 mL of 0.4 mg/mL) and applied to the area of repair for 4 minutes. Thereafter, the area was irrigated with 30 mL of isotonic sodium chloride solution and suctioned thoroughly.

application of mitomycin (**Figure 1**). Patient 3, who also had a history of CHARGE syndrome and history of a failed transnasal approach, underwent transpalatal repair with application of mitomycin. Stents were used in patients 1, 2, 3, and 5 for a mean duration of 4.3 weeks (range, 2-6 weeks). These patients underwent a second procedure for stent removal and nasal endoscopy under general anesthesia. All 4 patients showed patent choanae without scar tissue or need for dilation. Patient 5 presented with minimal scarring 1 month after the second look, which required dilation once. Patient 4, who had transnasal repair without stenting, underwent nasopharyngoscopy in the office, which revealed a patent choana without scar tissue formation. The mean follow-up for the 5 patients was 20 months (range, 11-32 months).

GLOTTIC STENOSIS

Three patients presented with glottic stenosis (mean age, 7 years; range, 5-10 years). Patients 6 and 8 presented with posterior glottic stenosis. Patient 6 was born at 31 weeks' gestation and had a history of prolonged intubation and bilateral vocal cord paralysis. She had originally undergone laryngotracheal reconstruction (LTR) for subglottic stenosis and left arytenoidopexy for vocal cord paralysis. This patient was tracheostomy dependent and did not tolerate capping of the tracheostomy tube. Patient 8 had a history of prolonged intubation because of prematurity and had undergone LTR. He represented with posterior glottic stenosis, causing shortness of breath at rest. Patient 7 presented with shortness of breath and vocal fatigue and was diagnosed as having an anterior glottic web (**Figure 2**).

All 3 patients underwent microlaryngoscopy and bronchoscopy. Patients 6 and 8 had moderate scarring at the level of the left arytenoid and interarytenoid areas. Both underwent suspension microlaryngoscopy and partial excision of the scarred area using a carbon dioxide laser, followed by application of mitomycin. Because of the degree and location of stenosis, it was not possible to completely excise the scarred areas. They have shown improvement of the airway on follow-up endoscopy. Patient 6 continues to be tracheostomy dependent, although she is tolerating capping of the tracheostomy tube. Patient 8 has mild shortness of breath on exertion.

Patient 7 had a 60% anterior glottic web of 4-mm thickness. A carbon dioxide laser was used for excision of the web, followed by application of mitomycin (Figure 2). Follow-up evaluation revealed a much improved glottic inlet, with only a 10% persistence of scar in the anterior commissure. At 9 months' follow-up, there is complete resolution of her preoperative symptoms.

SUBGLOTTIC STENOSIS

Patients 9, 10, 11, and 12 presented with shortness of breath and stridor due to subglottic stenosis (mean age, 7 years; range, 1-15 years). All had a history of prolonged intubation. Patients 10, 11, and 12 had a history of LTR for subglottic stenosis. All patients underwent suspension microlaryngoscopy and bronchoscopy. The airway size and length of stenosis were measured with a ventilating bronchoscope or an endotracheal tube through a laryngoscope. The preoperative subglottic stenoses were circumferential in all 4 patients and ranged from 50% to 80% (mean, 66%), with a thickness of 4 to 8 mm (mean, 6 mm). A carbon dioxide laser was used to excise the subglottic stenosis via radial incision and dilation, followed by topical application of mitomycin (**Figure 3**).[8] All patients underwent a subsequent airway endoscopy at 6 weeks and 4 months (within 3 weeks), which showed a postoperative stenosis that ranged from 20% to 60% (mean, 32%), with a thickness of 3 to 8 mm (mean, 5.5 mm).

Patients 10 and 12 had history of prolonged intubation and had undergone LTR. Both presented with restenosis and were tracheostomy dependent before our evaluation. Although both have shown improvement of their airways on follow-up endoscopy, they remain tracheostomy dependent. Patient 11, with a history of prolonged intubation and subglottic stenosis, underwent LTR and presented with restenosis of the subglottic area. He had previously undergone 3 bronchoscopy and dilation procedures without any improvement. He underwent carbon dioxide laser excision of the stenotic area and mitomycin application. He responded well and at 12 months' follow-up is asymptomatic. Patient 9 presented with a 50% subglottic stenosis of 5-mm thickness. He responded well to carbon dioxide laser excision and mitomycin application. Subsequently, he underwent multiple procedures because of congenital cardiac anomalies and required a prolonged course of intubation because of cardiac and pulmonary conditions. He is now tracheostomy dependent due to recurrence of subglottic stenosis.

TRACHEAL STENOSIS

Patient 13, with a history of prolonged intubation because of prematurity (26 weeks' gestation) had a 99% subglottic stenosis, for which she underwent LTR. She presented with stridor and shortness of breath. Microlaryngoscopy and bronchoscopy revealed a 70% tra-

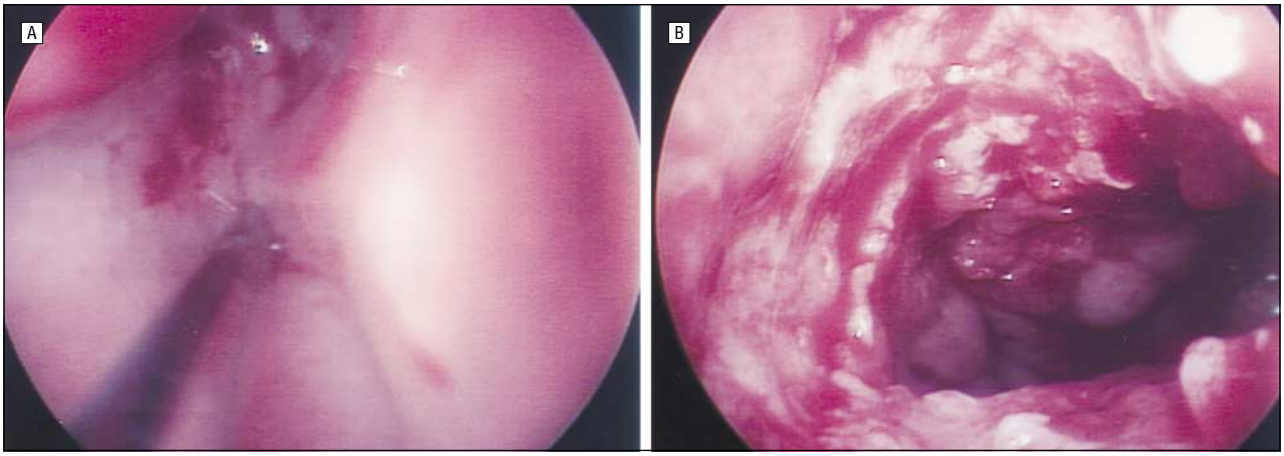

Figure 1. A, Choanal atresia. B, Endoscopic repair.

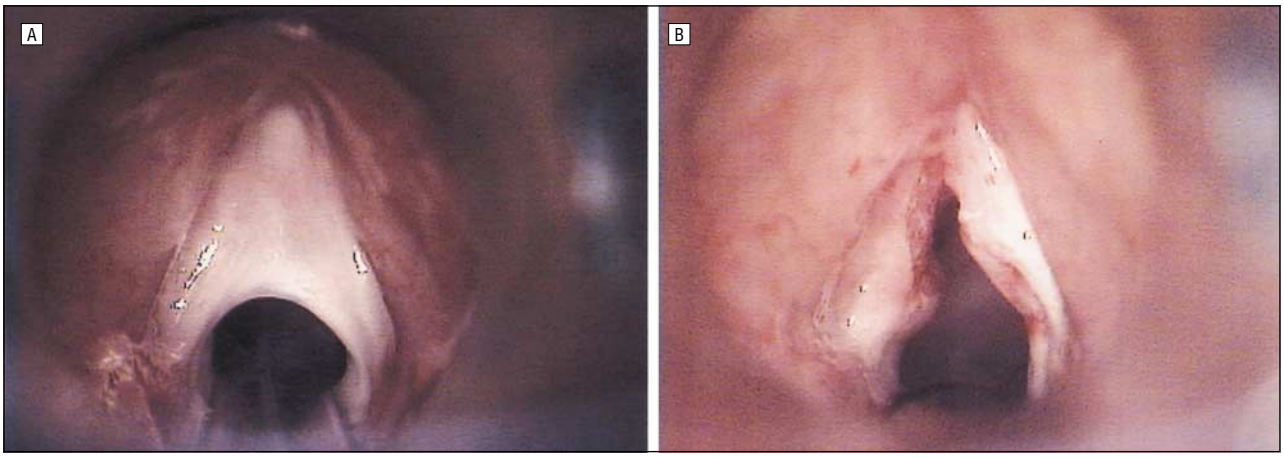

Figure 2. A, Glottic web. B, Laser excision.

cheal circumferential stenosis of 4-mm thickness. She underwent suspension microlaryngoscopy, and a carbon dioxide laser was used for radial excision and dilation of the stenotic area, followed by application of mitomycin. Follow-up endoscopy revealed a much improved airway, with a 10% circumferential narrowing of the trachea. At 23 months' follow-up, she has remained asymptomatic without any shortness of breath, with or without exertion.

HYPOPHARYNGEAL STENOSIS

Patient 14 presented with hypopharyngeal stenosis. Her history was significant for necrotizing fasciitis of the hypopharynx following a routine tonsillectomy and adenoidectomy for obstructive sleep disorder at age 2 at another institution. She was tracheostomy dependent and required a gastrostomy tube for nutritional support. Following decannulation, she presented with moderate obstructive sleep disorder due to worsening of the pharyngeal stenosis, documented by a sleep study. She underwent carbon dioxide laser excision of the pharyngeal scar and topical application of mitomycin. A postoperative sleep study has shown resolution of the preoperative obstructive sleep disorder. At 19 months' follow-up, she is doing well, with improvement of her preoperative symptoms of snoring, restlessness of sleep, and apnea.

ESOPHAGEAL STENOSIS

Patient 15 presented with esophageal stenosis. His history was significant for stage III rhabdomyosarcoma of the neck and base of the skull, treated with chemotherapy and radiation. He presented with inability to swallow and recurrent aspiration. Microlaryngoscopy and esophagoscopy revealed a 99% stenosis of the esophagus below the cricopharyngeal level, with a 10-mm extension to the cervical esophagus. He underwent routine dilation without any success. Subsequently, he underwent dilation and application of mitomycin (**Figure 4**). He is doing well and is tolerating liquids without difficulty. A postoperative modified barium swallow showed normal swallowing of liquids, without aspiration.

ANALYSIS

For further analysis of our results, we used a grading classification to describe the degree of clinical response to our protocol: "major," "minor," or "none." We defined success as: (1) clinical improvement on follow-up endoscopy and (2) resolution of preoperative symptoms. If both were present, the response was described as major; partial improvement, minor; and no improvement, none. Analysis of our data (**Tables 1**, **2**, and **3**)

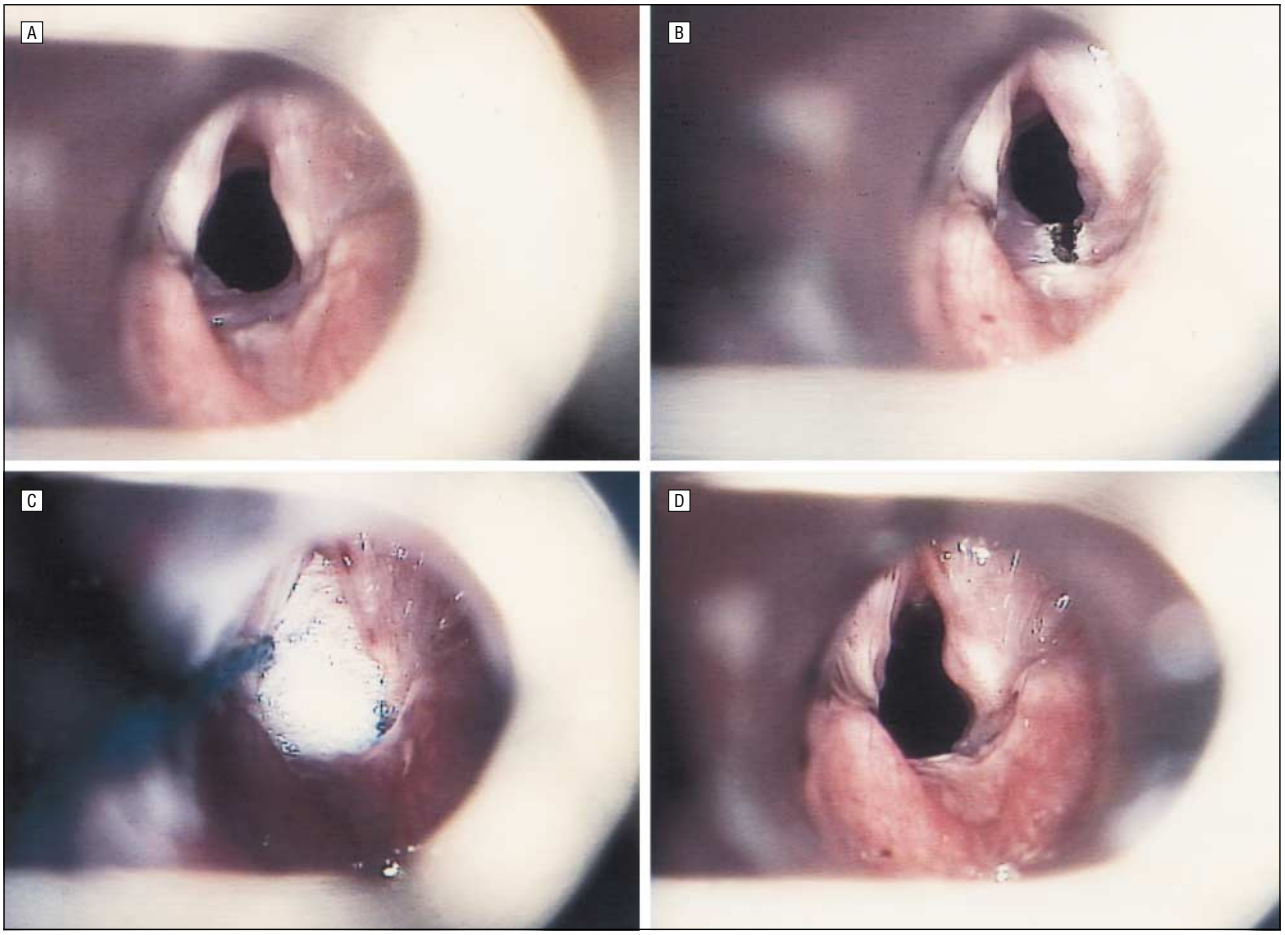

Figure 3. A, Subglottic stenosis. B, Laser excision. C, Topical application of mitomycin. D, After surgery.

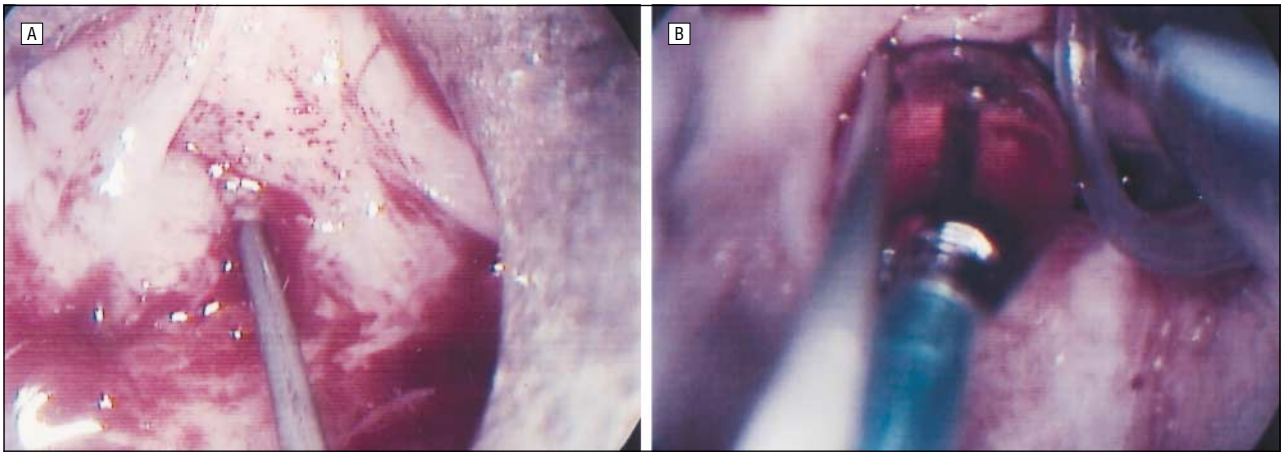

Figure 4. A, Near-total esophageal stenosis. B, Retrograde dilation using a balloon dilator.

shows that 10 patients (67%) had major improvement; 4 patients (27%), minor improvement; and 1 patient (7%), no improvement.

However, it is important to point out that patients 6, 10, and 12 were tracheostomy dependent before our evaluation. All 3 have had a complicated medical and surgical history of their airways. Although all 3 have shown improvement on subsequent endoscopy, we have not been able to decannulate them. Patient 6 is now tolerating capping of the tracheostomy tube.

Further analysis of our results reveals that we were able to excise the areas of stenosis and obtain major clinical improvement in 9 patients (patients 1, 2, 3, 4, 5, 7, 11, 13, and 14). In patients 6, 8, 10, and 12, in whom total excision was not possible because of the degree or location of stenosis (subglottic or posterior glottic stenosis), partial excision and dilation were not as effective and resulted in minor improvement. Simple dilation without excision of the area of stenosis showed major improvement only in patient 15, who had esophageal stenosis.

Table 1. Characteristics of Patients With Choanal Atresia

Patient No./ Sex/Age, y	Type of Stenosis	Previous Surgery	Surgery Plus Mitomycin	Duration of Stents, wk	No. of Surgeries	Follow-up, mo	Complications
1/M/4	Atresia, left	None	Transnasal	2	2	32	None
2/F/2	Atresia, left	2 Transnasal with stenting	Transnasal	6	2	22	None
3/F/5	Atresia, left	1 Transnasal with stenting	Transpalatal	6	2	22	None
4/M/2	Atresia, left	None	Transnasal	None	1	13	None
5/F/4	Atresia, right	None	Transnasal	3	3	11	Minimal scar

Table 2. Characteristics of Patients With Glottic, Subglottic, Tracheal, Hypopharyngeal, and Esophageal Stenosis*

Patient No./ Sex/Age, y	Location of Stenosis	Tracheostomy Dependent	Initial		Follow-up		Follow-up, mo
			Stenosis, %	Thickness, mm	Stenosis, %	Thickness, mm	
6/F/6	Glottic, posterior	Yes	NA	NA	NA	NA	25
7/F/5	Glottic web	No	60	4	20	4	21
8/M/10	Glottic, posterior	No	NA	NA	NA	NA	9
9/M/1	Subglottic	No	50	5	20	5	23
10/M/15	Subglottic	Yes	80	7	60	6	15
11/M/7	Subglottic	No	75	4	20	3	12
12/M/5	Subglottic	Yes	60	8	30	8	11
13/F/5	Trachea	No	70	4	10	3	23
14/F/6	Hypopharynx	No	NA	NA	NA	NA	19
15/M/8	Esophagus	No	99	10	80	10	6

*NA indicates not available.

COMMENT

Treatment of aerodigestive stenosis in the pediatric population remains one of the most difficult challenges in the area of pediatric otolaryngology. In the past decade, there has been a surge of interest in using pharmacological agents or different surgical approaches to reduce the degree of scar formation and increase the success rate of these surgeries.

An understanding of the basic steps of scar formation is essential in the modulation of wound healing. Inciting events, such as mucosal injury (intubation, trauma, and surgery), cause release of plasma proteins, blood cells, and platelets, which react with tissue factors to form a fibrin-fibronectin clot.[9] This serves as a matrix for the migration of capillaries, fibroblasts, and inflammatory cells. Fibroblasts synthesize collagen, glycosaminoglycans, and fibronectin to form granulation tissue. Over time, there is collagen maturation, capillary resorption, and myofibroblast contraction, causing scar formation.[9] Different agents have been used to affect wound healing at different stages. One of the most commonly used agents is corticosteroid, which can cause inhibition of the inflammatory response and fibroblast proliferation. Agents such as penicillamine and beta-aminoproprionitrile have also been tried with some success owing to their ability to inhibit cross-linking of collagen, therefore reducing scar formation.[10] In the past decade, mitomycin has gained wide attention in the prevention of scar formation because of its potent inhibition of fibroblast proliferation.

Mitomycin is an antibiotic produced by *Streptomyces caespitosus*. It was first isolated by Wakaki and associates in 1958.[11] It has antineoplastic and antiproliferative properties. Mitomycin's antineoplastic activity is similar to that of the alkylating agents, causing single-band breakage and cross-linking of DNA at the adenosine and guanine molecules, therefore inhibiting RNA and protein synthesis. As an antiproliferative agent, it can inhibit fibroblast proliferation and decrease scar formation.

Table 3. Analysis of Results

Location of Stenosis	Patient No.	Improvement		
		Major	Minor	None
Choana	1	x		
	2	x		
	3	x		
	4	x		
	5	x		
Glottic	6		x	
	7	x		
	8		x	
Subglottic	9			x
	10		x	
	11	x		
	12		x	
Trachea	13	x		
Hypopharynx	14	x		
Esophagus	15	x		

In 1963, Kunitomo and Mori[12] presented the first clinical application of mitomycin for the treatment of pterygium. Mitomycin's antiproliferative properties on fibroblasts have been shown in vivo and in vitro.[13,14] Since the 1980s, mitomycin has gained wide acceptance as an antiscarring agent in the field of ophthalmology and has been successfully used as an adjunct treatment in glaucoma surgery, dacryocystorhinostomy, and optic nerve sheath fenestration.[4,15,16] Ward and April[17] have shown

that mitomycin can be effective in the reduction of tracheal cicatrix and granulation tissue. Correa[18] and Eliashar[19] and their colleagues have shown the efficacy of mitomycin in the prevention of subglottic stenosis in a canine model. Rahbar and colleagues[6,7] reported the first clinical use of topical application of mitomycin as an adjuvant treatment to endoscopic carbon dioxide laser management of laryngeal and tracheal stenosis in the pediatric and adult populations.

The exact mechanism by which mitomycin exerts an antifibroblast activity is unknown. Studies[4-7,17] have shown beneficial results using different concentrations of mitomycin and durations of exposure. To our knowledge, there are no data indicating what concentration, duration, or frequency of application of mitomycin is more efficacious. In this study, we used mitomycin as an adjuvant treatment in the surgical management of 15 patients with stenosis in different areas of the aerodigestive tract. The dosage (1 mL of 0.4 mg/mL) and duration of exposure (4 minutes) were chosen based on previous reports[6,7] that ensured efficacy and safety, in conformity with the guidelines of the institutional review board committee at our institution. There are certain limitations to our study, including the lack of a control group, small number of patients in each group, different primary surgeons, and use or lack of use of stenting in the choana. However, this study, along with previous reports,[6,7] confirms that topical application of mitomycin can be effective in the treatment and prevention of scar formation in the aerodigestive tract.

When considering use of mitomycin as an antiscarring agent, it is essential to recognize its limited effect on fibroblast activity. It is clear that fibroblasts are key players in the scarring process. Fibroblasts not only undergo proliferation during wound healing but also cause extracellular matrix production, migration, and contraction. Occleston and colleagues[20] have shown that a single exposure to mitomycin can arrest growth and proliferation of fibroblasts. However, they note that fibroblasts appear to continue to express growth factors, form extracellular matrix molecules, and migrate. This could explain why there is some scar formation and restenosis, despite topical application of mitomycin. Also, it is imperative to consider the long-term safety of mitomycin. There have been reports in the ophthalmology literature of complications, such as secondary glaucoma, corneal perforation, secondary cataract, and infection.[21,22] A possible higher rate of postoperative infection is attributed to weakness of the wound-healing phase. Although there have not been any complications seen in our patient population at a mean follow-up of 18 months, the risk-benefit ratio must be considered with respect to possible long-term complications.

It appears that mitomycin will be an increasingly important component of the therapeutic armamentarium in different areas of otolaryngology. Future work should be directed toward gaining a better understanding of its mechanism of action and long-term safety.

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