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Preliminary Results of Intraoperative Mitomycin-C in the Treatment and Prevention of Glottic and Subglottic Stenosis

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Summary: Mitomycin-C is an antineoplastic antibiotic that acts as an alkylating agent by inhibiting DNA and protein synthesis. It can inhibit cell division, protein synthesis, and fibroblast proliferation. The purpose of this pilot study is to investigate intraoperative applications of topical mitomycin-C in treatment and prevention of glottic and subglottic stenosis. Eight patients with posterior glottic and/or subglottic stenosis were treated with endoscopic CO_2 laser excision followed by topical application of 0.5 cc of 0.4 mg mitomycin-C per milliliter of saline for 4 minutes at the surgical site. After mean follow-up of 15 months (10-20) all patients had clinical improvement of their airway and resolution of their preoperative symptoms. No complications were noted in this study. Although a longer follow-up and further controlled studies are needed, the use of topical mitomycin-C may prove useful in the treatment and prevention of subsequent restenosis and scar formation in the larynx and trachea. **Key Words:** Mitomycin-C—Subglottic stenosis—Laryngeal stenosis.

The management of laryngeal stenosis continues to challenge the otolaryngologist despite advances in surgical techniques and better understanding of the wound healing process. Injury to the airway mucosa is the inciting event, regardless of the etiology of stenosis. Factors contributing to the development of glottic and subglottic stenosis could be divided into congenital, traumatic, neoplastic, infectious, systemic disorders, and idiopathic.[1-3]

Methods of management have included segmental resection, expansion of the stenosed framework segment with bone or cartilage, endoscopic dilation, intralesional steroid injection, and carbon dioxide (CO_2) laser excision.[4-6]

The purpose of this report is to introduce the application of mitomycin-C in an attempt to prevent subsequent restenosis and scar formation. This prospective noncontrolled study was done to test the efficacy and safety of mitomycin-C as an adjuvant therapy in the endoscopic treatment of laryngeal stenosis.

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METHODS

Between March 1998 and January 1999, 8 patients with posterior glottic and/or subglottic stenosis were treated at New England Medical Center, Boston, Massachusetts. There were 4 males and 4 females with an average age of 44 years (range: 14-78 years; Table 1). All patients presented with exertional dyspnea interfering with routine daily activity and some degree of vocal fatigue (Table 2). Etiology of glottic and subglottic stenosis were variable (Table 3). There were 6 cases of subglottic stenosis and 2 cases of posterior glottic stenosis. A history of prolonged intubation and tracheostomy was present in patients 1-4, and two of these patients (1 and 4) were tracheotomy-dependent at the time of our evaluation.

Informed consent was obtained from all patients prior to the procedure. All patients underwent routine diagnostic laryngoscopy and bronchoscopy under general anesthesia. The lumen size and length of stenosis were measured with a rigid ventilating bronchoscope or endotracheal tube through the laryngo-

TABLE 1. *Age and Sex of Study Participants*

Patient	Age	Sex
1	48	M
2	14	M
3	56	M
4	78	M
5	33	F
6	40	F
7	45	F
8	38	F

TABLE 2. *Pre- and Postoperative Symptoms*

Patient	Preoperative Symptoms	Postoperative Symptoms
1	Dyspnea with capped tracheotomy tube	No dyspnea with tracheotomy tube capped
2	Dyspnea on exertion	Asymptomatic
3	Dyspnea on exertion	Asymptomatic
4	Dyspnea with capped tracheotomy tube	No dyspnea with tracheotomy tube capped
5	Dyspnea on exertion	Asymptomatic
6	Dyspnea on exertion	Asymptomatic
7	Dyspnea on exertion	Asymptomatic
8	Dyspnea on exertion, cough	Asymptomatic

TABLE 3. *Etiology of Subglotic and Glottic Stenosis*

Patient	Etiology	Diagnosis
1	Pneumonia, prolonged intubation	Subglottic stenosis
2	Laryngeal trauma, vocal cord avulsion	Posterior glottic stenosis
3	Intracranial hemorrhage, tracheotomy	Subglottic stenosis
4	Brain stem infarct, bilateral fold paralysis	Posterior glottic stenosis
5	Idiopathic subglottic stenosis	Subglottic stenosis
6	Idiopathic subglottic stenosis	Subglottic stenosis
7	Idiopathic subglottic stenosis	Subglottic stenosis
8	Idiopathic subglottic stenosis	Subglottic stenosis

scope (Table 4). Surgical exposure was obtained by suspension laryngoscopy using the operating microscope at 16× magnification. General intravenous anesthesia was used and ventilation was maintained through a jet technique. All patients received preoperative antibiotics and steroids. An anterior commissure laryngoscope was used for exposure of the subglottic larynx. Radial incisions of the subglottis were performed with the CO_2 laser using a microspot micromanipulator. Ventilating rigid bronchoscopes were then used for dilation of the subglottic stenotic segment. The incisions served to guide the dilating forces in a controlled manner to preserve islands of viable epithelium between each incision.[4,5]

Surgical exposure was also obtained in a similar fashion in two cases of posterior glottic stenosis. Surgical incision of the stenotic area was performed using the CO_2 laser at a power setting of 6 watts and time frequency of 0.3 seconds in a super-pulsed mode (0.25-mm spot size).

Following the completion of the incisions, a 10-mm neurosugical cottonoid sponge was soaked with 0.5 cc of 0.4 mL mitomycin-C per mL of normal saline, and topically applied to the surgical site for 4 minutes. Thereafter, the area was irrigated with 30 cc of normal saline solution. All patients were observed postoperatively for possible complications. Patients were examined twice during the first month after the surgery and then every 3 months. Success was defined as improvement of preoperative symptoms and size of the airway.

RESULTS

All patients underwent excision of the stenotic segment with the CO_2 laser and patients with subglottic stenosis had additional bronchoscopic dilation after radial incisions were performed. All patients received topical applications of mitomycin-C. A total of 12 operations were performed. Four patients including two with posterior glottic stenosis required a second procedure. (Table 5). Follow-up ranged from 10 to 20 months (mean: 15 months), one patient was lost to follow-up. No complications were noted.

Symptoms

All patients had improvement of their preoperative symptoms of dyspnea on exertion and vocal fatigue. Two patients with tracheotomy have not been decannulated due to their general medical condition. Patient 1 has had major improvement after surgery and will undergo decannulation in the near future. Patient 4, who presented with posterior glottic stenosis, underwent a left posterior cordotomy in his first procedure and a left arytenoidectomy in his second procedure. Currently he presents no dyspnea with a capped tracheotomy. Patients 5 and 8 with stenotic segments greater than 1 cm in vertical length have responded favorably to endoscopic treatment despite their higher risk for failure, and have no dyspnea on exertion.

Stenosis

All patients with posterior glottic and subglottic stenosis showed improvement of their airways. Rigid

TABLE 4. *Pre- and Postoperative Stenosis*

Patient	Preoperative Stenosis	Postoperative Stenosis	Length of the Stenosis
1	95%	40%	4 mm
2	70%	30%	- δ
3	70%	30%	5 mm
4	90%	50%	- δ
5	80%	20%	1.5 cm
6	80%	20%	4 mm
7	70%	LTFU	1 cm
8	50%	20%	1.2 cm

Abbreviations: LTFU, posterior glottic stenosis—lost to follow-up.

TABLE 5. *Length of Follow-up*

Patient	Number of Procedures	Follow-up
1	2	12
2	2	14
3	1	20
4	2	10
5	2	15
6	1	13
7	1	Lost to follow-up
8	1	19

bronchoscopes and endotracheal tubes were used for measurement of length and degree of stenosis under general anesthesia, or still photographs taken using a 70° rigid telescope under topical anesthesia. Two patients with posterior glottic stenosis had circumferencial narrowing of 70% and 90%. Postoperative evaluation showed improvement of their airway and stenosis of 30% and 50%, respectively, an average increase of about 50% in the circumferencial area of the glottis. Six patients were treated for subglottic stenosis; one was lost to follow-up. Five patients had preoperative subglottic stenosis of 50-95% (mean 75%), compared to postoperative stenosis of 20-40% (mean 26%). This shows a 35% average improvement of subglottic stenosis, even though two of these patients had preoperative length of stenosis of greater than 1 cm.

Postoperative length of subglottic stenosis did not show any significant change from preoperative measurement ranging from 4 mm to 15 mm (mean: 9 mm) (see Table 4).

DISCUSSION

Treatment of glottic and subglottic stenosis remains a therapeutic challenge. Different approaches have been proposed, and no single surgical technique has proven satisfactory for all cases.

Endoscopic management of glottic and subglottic stenosis has a 40-60% success rate in properly selected cases.[7] Stenotic lesions larger than 1 cm in vertical length with circumferential scarring, and loss of cartilage have been associated with a poor prognosis when treated endoscopically.[7] A major cause of failure is the re-formation of the scar following its excision. Modulation of the wound healing response to prevent excessive scar formation can play a major role in increasing the success and reducing the need for further surgery.

Because the fibroblast population and collagen formation is increased during inflammation and the healing process, inhibiting this process should be useful in preventing scar formation.[8] Pharmacological inhibition of collagen formation has been tried with agents such an aminopropionitrile (APA) and 5-fluorouracil in the past.[8,9]

Mitomycin is an antineoplastic antibiotic produced by *Streptomyces caespitosus*. It is also referred to as mitomycin-C to differentiate it from mitomycin-A and -B, which under certain conditions are also produced. Mitomycin's mechanism of antineoplastic activity is similar to that of the alkylating agents. Its enzymatic reduction within the susceptible cells is necessary for its antineoplastic activity. It causes cross-linking of DNA and in high concentration can inhibit RNA and protein synthesis.

Mitomycin-C acts as an antiproliferative agent that would inhibit fibroblastic activity and scarring. It has been successfully used as an adjunct in glaucoma surgery, dacryocystorhinostomy, optic nerve sheath fenestration, and pterygium recurrence.[10-12]

In this study we have found that mitomycin-C can be beneficial as an adjuvant for endoscopic CO_2 laser excision of glottic and subglottic stenosis. All our patients had improved of their airway and resolution of their symptoms.

We recognize that it is difficult or impossible to attribute any potential differences in scarring to mitomycin-C treatment since these results are compared with data from historical controls. For example, any differences could be explained by changes in surgical techniques and postoperative care over time, in addition to the use of mitomycin. Despite these limitations, our preliminary data support that mitomycin-C can play a major role in modulation of wound healing and decreasing scar formation. This decreases the need for further surgery and increases the success rate of endoscopic procedures for glottic and subglottic stenosis. Mitomycin-C may prove to be useful as well to prevent scarring after high-risk microsurgery of the vocal folds, such as sulcus vocalis and microflap excision of dysplasia.

CONCLUSION

Treatment of laryngeal stenosis remains one of the most difficult challenges in the area of laryngology. We recognize that a randomized controlled clinical trial provides the best design for evaluating the use of mitomycin-C therapy. However, this pilot study reveals promising results on the efficacy and safety of mitomycin-C as an adjunct modality for the CO_2 laser endoscopic management of selected cases.

REFERENCES

1. Courey MS. Airway obstruction: the problem and its causes. *Otolaryngol Clin North Am.* 1995;28:673-684.
2. Gayner EB, Danoff SJ. The role of gentle ventilation in prevention of subglottic stenosis in the newborn. *Otolaryngol Head Neck Surg.* 1993;109:701-706.
3. Lano CF Jr, Duncavage JA, Reinisch L, et al. Laryngotracheal reconstruction in the adult: a ten-year experience. *Ann Otol Rhinol Laryngol.* 1998;107:92-97.
4. Shapshay SM, Beamis JF Jr, Hybels RL, Bohigian RK. Endoscopic treatment of subglottic and tracheal stenosis by radial laser incision and dilation. *Ann Otol Rhinol Laryngol.* 1987;96:661-664.
5. Streitz JM Jr, Shapshay SM. Airway injury after tracheotomy and endotracheal intubation. *Surg Clin North Am.* 1991;71:1211-1230.
6. Grillo HC, Mark EJ, Mathisen DJ, Wain JC. Idiopathic laryngotracheal stenosis and its management. *Ann Thorac Surg.* 1993;56:80-87.
7. Simpson GT, Strong MS, Healy GB, Shapshay SM, Vaughan WC. Predictive factors for success or failure in the endoscopic management of laryngeal and tracheal stenosis. *Ann Otol Rhinol Laryngol.* 1982;91:384-388.
8. Doolin EJ, Strande LF, Tsuno K, Santos MC. Pharmacologic inhibition of collagen in an experimental model of subglottic stenosis. *Ann Otol Rhinol Laryngol.* 1998;107:275-279.
9. Ingrams DR, Sukin SW, Ashton P, et al. Does Slow-release 5 flurouracil and Triamcinolone reduce subglottic stenosis. *Otolaryngol Head Neck Surg.* 1998;118:174-177.
10. Palmer SS. Mitomycin as adjunct chemotherapy with trabeculectomy. *Ophthalmology.* 1991;98:317-321.
11. Bergstrom TJ, et al. The effects of subconjunctival mitomycin C on glaucoma filtration surgery in rabbits. *Arch Ophthalmol.* 1991;109:1725-1730.
12. Kao SCS, Liao CL, Tseng JH, Chen MS, Hou PK. Dacryocystorhinostomy with intraoperative mitomycin. *Ophthalmology.* 1997;104:86-91.