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A Randomized Controlled Trial of Adjuvant Mitomycin-C in Endoscopic Surgery for Laryngotracheal Stenosis

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Objectives/Hypothesis: Topical mitomycin-C (MMC) application is a commonly accepted adjuvant therapy in the surgical treatment for laryngotracheal stenosis (LTS). However, the efficacy of MMC has not been examined in a prospective, randomized clinical trial in humans. We aimed to examine the efficacy of MMC in the treatment of LTS patients as compared to a placebo-controlled group.

Study Design: Prospective, randomized, double-blind, placebo-controlled clinical trial.

Methods: Fifteen patients with LTS were enrolled in a 24-month trial and randomized into one of two groups: 1) endoscopic surgical treatment with topical application of MMC or 2) endoscopic surgical treatment with topical application of saline. Postoperatively, patients were evaluated at standardized intervals with a symptom questionnaire and spirometry. Subsequent surgery was performed as needed based on relapse of stenosis on exam and patient-reported symptom severity.

Results: The average interval between surgical treatments was 17.9 months in the placebo group and 17.4 months in the MMC group (P = .95). There was no difference in magnitude of peak inspiratory flow (PIF) improvement between groups. The average magnitude of PIF change was 1.3 L/sec and 1.1 L/sec for the placebo and MMC groups, respectively (P = .64). Similarly, there was no difference in magnitude of symptom improvement or duration of symptom improvement between the two groups.

Conclusions: This prospective, randomized. double-blind. placebo-controlled trial suggests that the use of MMC as a topical adjuvant therapy has no additional benefit in the endoscopic surgical management of LTS. Further study is needed.

Key Words: Laryngotracheal stenosis, subglottic stenosis, tracheal stenosis, airway stenosis, mitomycin, dilation.

Level of Evidence: 1b

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INTRODUCTION

Obstruction of the upper airway caused by laryngotracheal stenosis (LTS) often results in severe morbidity and even mortality. LTS in the current era is most commonly caused by mechanical trauma from prolonged intubation or tracheotomy.[1,2] Other etiologies include respiratory infections, external trauma, or inflammatory rheumatological disease such as granulomatosis with polyangiitis. In many patients, no specific etiology is found, and they are diagnosed with idiopathic LTS.[1,2]

Treatment of LTS continues to present a challenge, and a wide array of surgical techniques have been employed.[1] Despite careful patient selection and multiple endoscopic and/or open reconstructive procedures, patients often experience restenosis as a result of the abnormal wound-healing process that initially instigated the airway obstruction.[3–5] The high rate of stenosis relapse has therefore motivated researchers to find new methods to modulate and control the wound-healing process of the airway. Although other adjuvant treatments such as steroids and antibiotics have been investigated in LTS,[6,7] much attention in recent years has turned to the use of topical mitomycin-C (MMC).

Discovered in 1956, MMC is an antimicrobial agent that has antimetabolite and antiproliferative properties.[8] It is produced by *Streptomyces caespitosus* and acts as an alkylating agent to inhibit DNA synthesis.[9] As a topical application, MMC has been shown to inhibit fibroblast proliferation in wound-healing processes.[10] The first clinical use of topical MMC occurred in 1963 by ophthalmologists to reduce scar tissue formation in pterygium surgery with remarkable results.[11] The use of MMC in the treatment of airway stenosis was first reported in 1998[12] and is now routinely used in the endoscopic management of LTS with the intent to prevent scar reformation. However, despite numerous animal and human studies,[13–18] the benefit of MMC in LTS patients remains questionable.

With two exceptions, published clinical studies of MMC in LTS have been retrospective case series or cohort studies. Most report positive outcomes, supporting the use of MMC as an adjuvant treatment.[15–20] Yet, in a prospective, randomized control trial of MMC in pediatric patients after open laryngotracheal reconstruction, outcomes were

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identical between the group who received MMC and the saline placebo group.[21] The second exception is a randomized, prospective, double-blind, placebo-controlled trial that examined the efficacy of two topical applications of MMC given 3 to 6 weeks apart compared to a single topical application in endoscopic treatment of LTS.[22] Although the results suggest that two applications reduced the restenosis rate for 2 to 3 years, relapse rates at 5 years were the same between the two groups. A recent literature review on the use of topical MMC as an adjunctive in airway surgery concluded that "heterogeneity within the clinic studies, the lack of controlled data, and the lack of significance in the pooled animal data suggest that the utility of MMC is still undetermined."[23]

With the overarching goal to improve LTS treatment, we conducted a prospective, randomized, double-blinded, placebo-controlled study to assess the efficacy of MMC as an adjuvant therapy in the treatment of LTS. The primary outcome measure were the interval to repeat surgical intervention. Secondary outcome measures were the change in patient reported symptom scores, duration of symptom improvement, and peak inspiratory flow measurements.

MATERIALS AND METHODS

Approval from the institutional review board was obtained. Patients were recruited from the University of California–San Francisco Voice and Swallowing Center, and the study was active from August 1, 2012 until February 1, 2018. Patient inclusion criteria included age greater than 18 years and disease amenable to treatment with endoscopic CO_2 laser radial incision and balloon dilation. Exclusion criteria included pregnant women, patients with glottic and supraglottic stenosis, and patients with cartilaginous involvement.

Eligible patients underwent a full clinical evaluation including history, physical exam, computed tomography (CT) scan, videolaryngoscopy, clinical chronic obstructive pulmonary disease questionnaire (CCQ), and pulmonary function testing. Patients were randomized into one of two groups: 1) endoscopic surgical treatment with topical application of MMC or 2) endoscopic surgical treatment with topical saline. Randomization was achieved using a Web-based application. Both patients and physicians were blinded to treatment group assignments during the entire study period. Postoperatively, patients were evaluated at standardized intervals with CCQs and pulmonary function tests (PFT). Subsequent surgery was performed as needed based on relapse of stenosis on exam as well as symptom severity. Group assignments remained constant through subsequent surgeries. Additional details as well as a schematic representation of the study are provided in Figure 1. The study duration for each subject was 24 months.

Surgical treatment for both treatment groups was standardized. The technique for endoscopic microsubglottoscopy with CO_2 laser radial incisions and balloon dilation has been well described.[24] After dilation, cottonoids soaked in either 0.4 mg/mL MMC or normal saline were then applied to the incisions for 3 minutes. Kenalog-40 (triamcinolone acetonide) was injected into the stenotic region.

Collected study measurements included demographic information, medical history, interval to repeat surgery, CCQ scores,[25] and PFT measurements. Data were then stored on an electronic database and analyzed using Excel (Microsoft, Redmond, WA) and RStudio (RStudio, Boston, MA) software. The Student t test and Fisher exact test were used to determine statistical significance for univariate analyses. Regression analysis including calculation of P values was performed in RStudio. A P value <.05 was considered a significant association.

The target sample size for this study was 44 patients to provide 90% power. This study reports the results from the first 15 patients.

RESULTS

Patient Demographics

Nine subjects were randomized to the placebo group and six subjects to the MMC group. Two additional patients initially consented to take part in the study were subsequently excluded. One patient was excluded based on CT study results showing cartilaginous stenosis and the other patient chose to withdraw and receive MMC during surgery. Between the two groups, there were no statistically significant differences in age, gender, age of onset, etiology, site of disease, history of prior LTS surgeries, number of LTS surgeries, or prior treatment with MMC or Kenalog (Table I). Nine subjects out of 15 had undergone previous endoscopic LTS treatment. Total number of surgeries performed during the study period was 17 in the placebo group and 12 surgeries in the MMC group. Three subjects did not have complete 24-month follow-up. One patient in the MMC group withdrew after 9 months and two surgeries. She was concerned that she was in the placebo group and decided to withdraw and opt for MMC. An additional patient in each group was lost to follow-up after 1 year with only one surgery each.

Outcome Measures

Surgical interval. There were no significant differences between average time interval between surgeries in the MMC and placebo groups. The average interval for each patient was 17.9 months in the placebo group and 17.4 months in the MMC group (P = .95). There were six surgeries in the placebo group and two surgeries in the MMC group that did not have a subsequent surgery, and therefore, a surgical interval could not be calculated.

Because many of the patients had undergone surgery prior to study enrollment, we additionally obtained relevant retrospective data. In particular, the interval duration between surgeries for those patients treated with MMC prior to enrollment and who were then randomized to the placebo group was of particular interest. Three patients qualified for this subgroup analysis. There was no obvious pattern difference in surgical interval for patients who were treated with MMC prior to the study and who were then randomized to the placebo group during the study (Fig. 2).

Pulmonary function tests. Although complete spirometric measurements were obtained, and previous studies have shown that specific ratios based on spirometric data may be useful, there is no evidence to support using these ratios to assess severity of laryngotracheal stenosis.[26] Clinically, the authors use peak inspiratory flow (PIF) as an easily obtained and consistent assessment of upper airway obstruction. Previously published work has described the utility of using PIF to monitor airway status in patients with subglottis stenosis.[27] In this

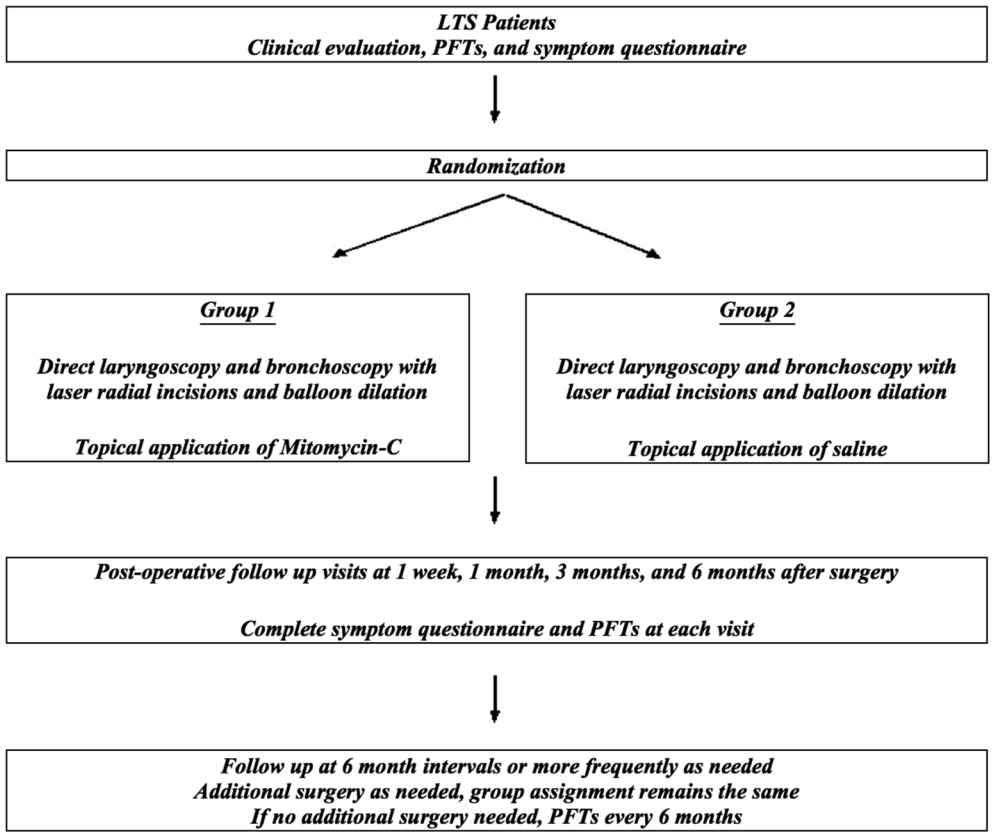

Fig. 1. Schematic diagram of the study. LTS = laryngotracheal stenosis; PFTs = pulmonary function tests.

study, PIF improved following surgery in both groups; in most cases it continued to improve beyond the first post-operative visit (Fig. 3). Time to maximum improvement in PIF was 2.6 months and 2.0 months for the placebo and MMC groups, respectively (P = .61).

There was no difference in magnitude of PIF improvement between groups. The average magnitude of PIF change was 1.3 L/s and 1.1 L/s for the placebo and MMC groups, respectively (P = .64). The percent PIF

TABLE I.
Patient Demographics.

Characteristic	MMC, n = 6	Placebo, n = 9	*P* Value
Age, yr	48.0 ± 8.3	57.1 ± 12.4	.11
Gender			.14
Male	2 (33%)	0 (0%)	
Female	4 (66%)	9 (100%)	
Age of onset, yr	44.2 ± 9.2	52.2 ± 13.5	.19
Etiology			.99
Idiopathic	5 (83%)	6 (66%)	
GPA	1 (17%)	2 (22%)	
Postintubation	0 (0%)	1 (11%)	
Site			.66
Subglottis	5 (83%)	8 (88%)	
Trachea	0 (0%)	1 (11%)	
Subglottis and trachea	1 (17%)	0 (0%)	
Prior LTS surgery	5 (83%)	4 (44%)	.29
Average prior LTS surgeries	4.0 ± 4.9	1.1 ± 1.5	.21
Prior treatment with MMC	4 (66%)	3 (33%)	.31
Prior treatment with Kenalog	4 (66%)	2 (22%)	.14

GPA = granulomatosis with polyangiitis; LTS = laryngotracheal stenosis; MMC = mitomycin C.

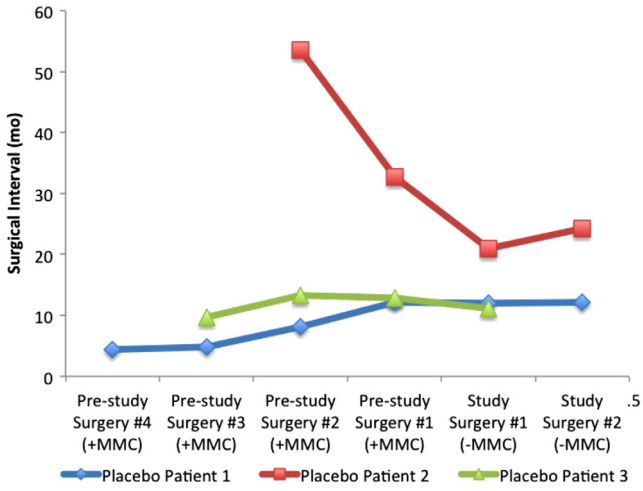

Fig. 2. Cross-over patients: MMC to no MMC. Patients who were treated with MMC prior to the study and were randomized to the placebo group showed no clear change in surgical interval. MMC = mitomycin C. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

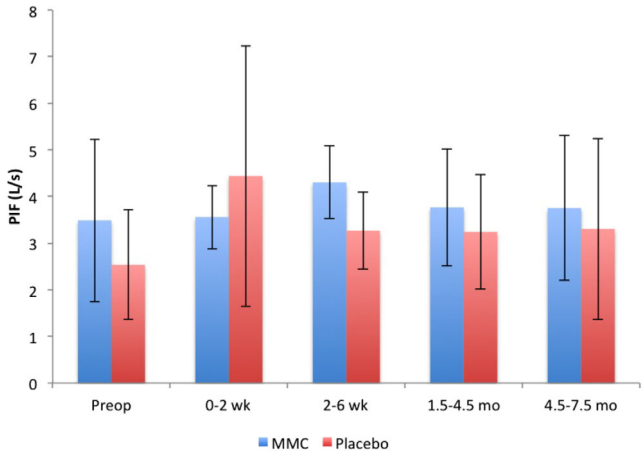

Fig. 3. Average PIF progression. PIF improved over multiple weeks following surgery in both groups. MMC = mitomycin C; PIF = peak inspiratory flow. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

change from preoperative values was 64% in the placebo group and 40% in the MMC group (P = .23).

CCQ scores. CCQ scores improved following surgery in both groups and continued to improve beyond the first postoperative visit (Fig. 4). Time to maximum symptom improvement in CCQ score was 2.2 months and 3.1 months for the placebo and MMC groups, respectively (P = .56).

There was no difference in magnitude of symptom improvement or duration of symptom improvement between the two groups. The average magnitude of symptom improvement was 2.4 and 2.2 for the placebo and MMC groups, respectively (P = .73). The percent improvement in CCQ score was 73% in the placebo group and 69% in the MMC group (P = .53). Time to symptom progression was 4.1 months and 6.0 months for the placebo and MMC groups, respectively (P = .52). A CCQ of 1 is equivalent to hardly ever having symptoms or being very

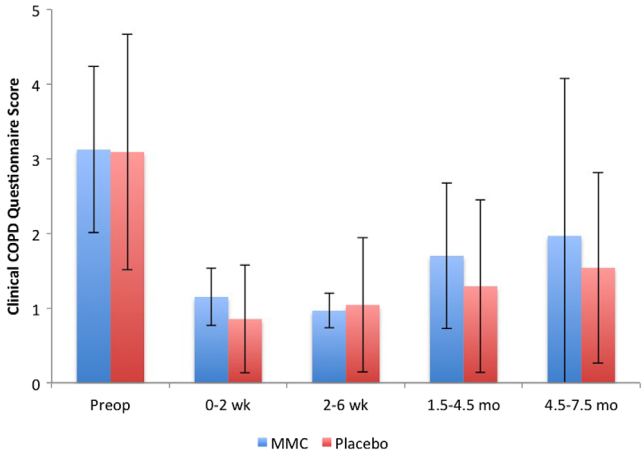

Fig. 4. Average symptom progression. Clinical COPD questionnaire score improved over multiple weeks following surgery in both groups. COPD = chronic obstructive pulmonary disease; MMC = mitomycin C. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

slightly limited.[28] Therefore, time to symptom progression was defined as the time for symptoms to worsen beyond a CCQ score of 1 or time to the subsequent operation if the CCQ score never exceeded 1. Four placebo and three MMC procedures did not meet either of these criteria for symptom progression and were excluded for insufficient follow-up.

CCQ score and PIF were weakly associated with an R^2 value of 0.145 (P = .0003). R^2 values relating patients' PIF and CCQ score varied from 0.06 to 0.99 with an average of 0.48.

DISCUSSION

Laryngotracheal stenosis is a challenging, frequently relapsing disorder that can result in symptomatic and even life-threatening airway restriction. Successful management of LTS has been a primary goal of otolaryngologists throughout the modern medical era. Therefore, much effort has been placed into developing surgical techniques and adjuvant therapies to better treat LTS. The use of topical MMC as an adjuvant treatment in surgical treatment of LTS has become commonly accepted practice. The majority of the published literature regarding MMC and airway surgery suggests that the use of topical MMC improves outcomes. However, the vast majority of the publications have been retrospective case-series studies. To our knowledge, this is the first prospective, double-blinded, placebo-controlled clinical trial designed to study the efficacy of MMC as an adjuvant treatment in endoscopic surgical treatment of LTS.

In our preliminary group of 15 subjects, nine were randomized to the placebo group, with the remaining six subjects enrolled in the MMC group. Surgical treatments were identical with the exception that placebo patients underwent topical saline treatment instead of topical MMC treatment. Nine patients had undergone previous endoscopic surgery prior to enrollment. The subjects predominantly had idiopathic LTS (11 of 15 subjects, 5/6 in the MMC group, 6/9 in the placebo group).

The primary outcome measurement was the duration between surgeries. There was no significant difference between average time intervals between surgeries in the MMC and placebo groups. The average interval for each patient was 17.9 months in the placebo group and 17.4 months in the MMC group (P = .95). PIF measurements and CCQ scores were used as secondary outcome measurements. In our study, PIF improved following surgery in both groups. There was no statistical difference in magnitude of PIF improvement between groups, and there was also no statistical difference in time to maximum improvement between the groups (P = .64 and P = .61, respectively).

Three patients were included in a subgroup analysis as a pseudo-crossover study. These patients had endoscopic surgical treatment for LTS including topical MMC prior to study enrollment, but were then randomized to the placebo group. All three subjects had idiopathic LTS. There was no clear difference in surgical interval for these patients prior to study enrollment and afterward (Fig. 2). For patient 1, prior to study enrollment, surgery intervals appeared to be quite stable around every 10 months for

four consecutive procedures. After enrollment, the patient did not require any additional surgery for the entire 24-month study period. Patient 3 had surgery intervals of 5 to 10 months for five consecutive procedures at the time of enrollment, followed by a surgery interval of about 10 months after enrollment. Patient 2 had the most variation in surgery interval with the smallest interval of 20 months at the time of enrollment. After enrollment, the surgery interval increased somewhat.

The results of this study do not support the hypothesis that adjuvant topical MMC improves surgical outcomes for LTS treatment. Although this result is not in alignment with most of the published retrospective literature, it does support previously published controlled animal trials and prospective human studies. In a 2003 prospective, randomized, controlled canine study by Eliashar et al., no difference was found between the MMC group and the control group in the change in percent stenosis (P = .83).[13] Additional studies published by Shvidler et al. and Roh et al. describing their prospective randomized studies in ferrets and rabbits, respectively, reported similar results.[14,20] There was no significant difference in cross-sectional area between control and MMC-treated groups.

A recent randomized controlled animal study describes the role of MMC and triamcinolone acetonide in rabbits with subglottic injury.[29] The rabbits were divided into control, MMC only, steroid only, and MMC with steroid groups. Rabbits in the control and MMC only groups were noted to have more respiratory distress than those treated with triamcinolone acetonide. Histopathological changes were studied and they found that MMC did not alter the wound healing process, whereas steroid application significantly altered wound healing in the subglottis.

The use of triamcinolone acetonide may account for the difference between this study and the previous retrospective studies supporting the use of MMC. The aforementioned prospective, randomized, double-blind, placebo-controlled clinical trial examining one application of MMC versus two MMC applications given 3 to 6 weeks apart found that median interval to relapse was 3.8 years in the two-application group as opposed to 2.4 years in the single-application group.[22] Relapse rates at 5 years were the same. Steroid injection was not part of their surgical procedure. Because patients in this study received steroid injection as part of the standard endoscopic surgical procedure, it is possible that the beneficial effect of the triamcinolone acetonide outweighed any smaller effect that MMC might have had.

In this study, 11 of 15 subjects had idiopathic LTS. Given that the literature describes iatrogenic causes of LTS to be most common, one might speculate that this disproportionate percentage of subjects with idiopathic etiology may have affected our results. Previously published reports supporting the efficacy of topical MMC use including Perepelitsyn and Shapshay,[15] as well as Simpson and James,[17] do not differentiate idiopathic LTS from iatrogenic LTS. In the afore-referenced Hseu et al. study,[2] only 33% of subjects had idiopathic LTS, compared to 25% iatrogenic and 45% autoimmune etiologies. Despite this disparity in subject etiologies, their study also reported that the use of MMC did not result in longer intervals between surgeries. Given that there is recent focus on idiopathic LTS as an inflammatory disorder, including our three granulomatosis with polyangiitis patients, 14/15 subjects in this study could be considered as having an inflammatory etiology, possibly accounting for a better response to triamcinolone acetonide treatment.

The results of this study suggest that MMC is not efficacious as an adjuvant therapy in the endoscopic surgical treatment of LTS. Eliminating the use of MMC results in cost savings as well as risk reduction. In a study published in 2003, the incremental cost of MMC application was estimated to be $455, including an estimated additional 10 minutes of surgical time.[30] Additionally, MMC application is not without risk. In a retrospective case-series from Hueman and Simpson, complications believed to be caused by local toxicity of MMC occurred in 4 cases out of 85 (4.7%).[31] Although uncommon, airway obstruction caused by fibrinous debris as a result of MMC can be a life-threatening and clinically significant complication.

Obstacles in performing prospective randomized studies in surgical fields have been well documented.[32] We aimed to minimize systemic error by having the patients randomized by a third party using a Web-based application, maintaining concealment of the allocation throughout the study duration, and blinding both the patient and the surgeons. We performed a sample-size calculation in an attempt to minimize random error. The main limitation of this study as reported is the small number of subjects. It is conceivable that the sample size is too small to detect a difference between the two groups. The target sample size was 44 patients. However, although our clinical volume made the target sample size feasible, patients were mostly unwilling to be randomized. After the description of the research protocol, many patients opted to get the MMC, although there were a few patients that opted for no MMC. Recruitment of subjects is unfortunately a difficult challenge in surgical trials. After over 5 years of study enrollment, the decision was made to analyze the preliminary data. A multicentered trial would be helpful to recruit additional patients and further evaluate the efficacy of MMC.

Since the study first opened for enrollment in 2012, clinical practice has continued to evolve. Serial in-office intralesional steroid injections have been described as an option to improve airway stenosis and reduce the surgical burden in LTS patients.[33] The multicentered study published by the North American Airway Collective group reports that *Mycobacterium* species are uniquely associated with idiopathic subglottic stenosis, possibly providing a new target for treatment.[34] These contemporary studies may lead to future therapeutic directions that render the issue of MMC efficacy less relevant.

CONCLUSION

This prospective, randomized, double-blinded, placebo-controlled trial does not support the use of MMC as an adjuvant topical application in the endoscopic surgical management of patients with LTS. There was no statistically significant difference in duration between surgeries in the MMC and placebo groups. Future studies are necessary to

further expand our understanding of LTS pathogenesis and subsequent development of therapeutic interventions.

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