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Topical Mitomycin C application in the treatment of refractory benign esophageal strictures in adults and comprehensive literature review

Michael J. Bartel[a], Kristina Seeger[b], Kayin Jeffers[b], Donnesha Clayton[b], Michael B. Wallace[a], Massimo Raimondo[a], Timothy A. Woodward[a,*]

[a] Gastroentrology and Hepatology, Mayo Clinic, Jacksonville, FL, USA
[b] General Internal Medicine, Mayo Clinic, Jacksonville, FL, USA

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ABSTRACT

Background: Recurrent complex esophageal strictures remain difficult to manage.
Aims: To determine the efficacy of topical Mitomycin C application for recurrent benign esophageal strictures.
Methods: All patients who underwent balloon dilation followed by topical Mitomycin C application for recurrent benign esophageal strictures were included. Primary outcome was number of dilations and change of dysphagia score.
Results: Nine patients with anastomotic (3), radiation-induced (3), caustic (2), and combined anastomotic and radiation-induced (1) strictures were included. Strictures had a mean length of 13.75 mm, diameter of 8.0 mm, and were dilated 10.7 times over a median of 8 months (1.5 dilations per month). Following Mitomycin C application, the need for further dilation decreased to 0.39 dilations per month over a median of 10 months; however, dysphagia scores improved not significantly from 3.2 to 2.6 (mean).
Conclusion: In this pilot study, topical Mitomycin C in conjunction with dilation decreased the frequency of esophageal dilations for recurrent benign esophageal strictures.

1. Introduction

Treatment of dysphagia secondary to esophageal stricture is a mainstay of a gastroenterological practice. Benign strictures are usually the sequelae of peptic injury, radiation, caustic agent ingestion, surgical anastomoses, or endoscopic mucosal resection [1]. Complex recurrent or refractory strictures are a subgroup of benign strictures, recurrent or refractory to standard course of dilations. They are fibrotic, cicatricial strictures, defined by length (>2 cm) and/or diameter (severely narrowed lumen) and angulation [2–4].

Mitomycin C has been successfully used as an antifibrotic agent in ophthalmologic and pulmonary literature [5,6]. Along these lines, Mitomycin C has been utilized for complex esophageal strictures, as demonstrated recently in a double-blinded, randomized, placebo-controlled trial for treatment naïve caustic strictures in pediatric patients [7].

The purpose of this study was to assess whether the addition of topical Mitomycin C for recurrent benign complex esophageal strictures in conjunction with dilation and/or other complex therapeutics (needle-knife incision; stent) resulted in measurable improvement in clinical outcomes. In addition, a comprehensive review of the literature on the use of Mitomycin C for benign esophageal strictures was performed.

2. Methods

Patients with recurrent complex benign esophageal strictures, as defined by American Society for Gastrointestinal Endoscopy guidelines, were the population in this study (Table 1) [8]. All patients had previously undergone at least five esophageal dilations, as well as the following, individually or in combination: steroid injection, needle-knife incision, and/or stent placement. Patient recruitment was additionally based on expert endoscopist discretion, including only subjects with suspected high likelihood of early recurrent benign stricture formation. All other strictures were excluded, including benign strictures longer than 5 cm, multiple concurrent strictures, and malignant strictures.

The institutional review board of Mayo Clinic approved this study. A retrospective chart review of all patients treated with Mitomycin C was undertaken. Subjects first underwent esophageal

* Corresponding author at: Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224-1865, USA. Tel.: +1 904 953 6982; fax: +1 904 953 7366.
E-mail address: Woodward.timothy@mayo.edu (T.A. Woodward).

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Table 1
Baseline characteristics Baseline characteristics of patients with benign recurrent esophageal strictures who underwent topical Mitomycin C application.

ID	Age [years]	Gender	Stricture etiology	Details of stricture etiology	Number of dilations	Duration of follow up prior index procedure [months]	Prior steroid injection	Prior stent	Stricture length [mm]	Stricture diameter [mm]	Stricture location Ab incisors [cm]
1	76	M	Anastomotic	Esophagectomy, gastric conduit reconstruction for esophageal cancer	16	4	+	+	20	6	20
2	64	F	Radiation	60 Gy external beam radiation for thyroid cancer	8	8	+	+	10	7	15
3	55	F	Radiation	60 Gy external beam radiation for left lung adenocarcinoma	8	5	+		30	12	24
4	73	M	Anastomotic, radiation	Esophagectomy, gastric conduit reconstruction for esophageal cancer followed by 50.4 Gy external beam radiation	6	12	+		10	6	20
5	65	F	Anastomotic	Esophagectomy, gastric conduit reconstruction for gastrointestinal stromal tumor	12	12			10	8	22
6	60	F	Caustic	Lye ingestion	14	9	+	+	10	8	20
7	80	M	Anastomotic	Esophagectomy, gastric conduit reconstruction for esophageal cancer	9	7	+	+	10	9	38
8	64	F	Caustic	Lye ingestion	15	8			10	8	21
9	79	F	Radiation	66 Gy external beam radiation following laryngectomy of squamous cell carcinoma	8	9					15

balloon dilation utilizing the CRE™ Wire-guided through-the-scope Balloon Dilator (Boston Scientific, Natick, MA), and if warranted, needle-knife incision (MicroKnife XL Needleknife, Boston Scientific, Natick, MA). Subsequently, cap-assisted upper endoscopy was performed and Mitomycin C [0.4 mg/mL; dose as determined by previous studies (Table 2 [5,7,9–28]), total volume of 4 ml] soaked cotton pledgets or 3–4 mm wide strips of sterile gauze were topically applied by rubbing for a total of three minutes per quadrant (Video 1) [10,29]. All procedures were performed between May 2012 and December 2014 by one endoscopist (TW).

Primary outcome was the number of dilations following topical Mitomycin C application and change in the periodic dilation index (PDI), defined as number of dilations divided by months of follow-up, was measured [30]. Dysphagia score was recorded prior to Mitomycin C application and at the last follow-up (0 = no dysphagia, 1 = tolerate some solid food, 2 = tolerate semisolid food, 3 = tolerate liquids only, 4 = complete dysphagia) [31]. Adverse events were defined as all procedure-related complications leading to hospital admission following dilation with Mitomycin C application, including immediate and delayed (within 48 h post-procedure) complications.

Subsequent esophagogastroduodenoscopies following index procedure were performed in a time interval between 2 weeks and 3 months, which was based on expert endoscopist discretion. In this context, decision for any repeat dilation and consideration of adjuvant therapy was performed for recurrent dysphagia affecting patient's quality of life.

The difference between PDI and dysphagia score was compared with Wilcoxon signed rank test. The significance level for all tests was two-sided, at 5%. All data were analyzed using JMP Pro software (version 9.0.1; SAS, Cary, NC).

Lastly, we performed a literature review on Mitomycin C application for treatment of esophageal strictures. A computer-assisted search was performed utilizing PUBMED on all English language published articles up to February 2016. The following keywords were used: "esophageal OR esophagus AND Mitomycin" and "stricture AND Mitomycin". A manual search of the cross-references of identified studies and relevant reviews were used for completion of the literature search.

3. Results

Nine patients (mean age 68.4 years, 67% female) with symptomatic dysphagia were included in the study. Three patients had anastomotic strictures, three had radiation-induced strictures, two had caustic-induced strictures, and one had a combined anastomotic and radiation-induced stricture (Table 1). The strictures had a mean length of 13.75 mm (standard deviation [SD] 7.4) and luminal diameter of 8.0 mm (SD 1.9).

Patients underwent a mean of 10.7 dilations (SD 3.6) over a median of 8 months (SD 2.7) prior to study inclusion. Seven patients had previous steroid injections, four patients underwent stent placements, and three patients had previous incisional therapy. At the time of study inclusion, the subjects had a median dysphagia score of 3 (range 1–4; Tables 1 and 3).

The mean PDI decreased from 1.53 (SD 1) to 0.39 (SD 0.3) ($p = 0.01$) following Mitomycin C application in conjunction with dilation, whereas the mean dysphagia score deceased from 3.2 to 2.6 (not significant) at last follow-up (Table 3 and Fig. 1). Six patients underwent additional Mitomycin C applications (median 1.5, range 1–6) during follow-up (median 10 months). Temporary esophageal stents were placed in three patients, and four patients had incisional therapy with needle-knife. Two patients eventually required an esophagectomy.