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Endoscopic Bougie Dilation Combined with Bleomycin Injection is Effective for Benign Esophageal Anastomotic Stricture

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Bleomycin; Endoscopic dilation; Esophageal anastomotic stricture; Efficacy; Safety

Key Messages: We first demonstrated that bleomycin injection combined with endoscopic bougie dilation for benign esophageal anastomotic stricture might improve re-stricture-free survival the re-stricture-free period for benign postoperative esophageal anastomic stricture compared with single dilation.

Citation:

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Abbreviations:

MMC: Mitomycin C; TCA: Triamcinolone; EBD: Endoscopic bougie dilation

1. Abstract

1.1. Background/Aim: The longstanding effect of the existing treatments have been limited for managing benign postoperative esophageal anastomotic stricture. This study was conducted to explore the safety and efficacy of endoscopic dilation combined with bleomycin for the treatment of benign anastomotic esophageal stricture.

1.2. Patients and Methods: Sixty patients with benign postoperative esophageal anastomotic stricture, received from June of 2015 to June of 2019 in First People's Hospital of Foshan, were retrospectively studied. Thirty patients underwent bleomycin injection combined with endoscopic dilation (bleomycin group) and thirty patients received single endoscopic dilation (control group). The successful rate, numbers of dilation required to resolve esophageal stricture, dilation-related cost, complications and restructure-free survival were compared.

1.3. Results: All of the 60 patients successfully finished the procedure and achieve endoscopic and clinical remission. The short-term successful rate and complications showed no difference between bleomycin group and control group (P>0.05). However, the one-year re-stricture rate was significantly lower in bleomycin group (23.3% vs 100%, P<0.01), and the restricture-free survival was significantly better in bleomycin group than that in control group (72% vs 0, P<0.01). Moreover, the median numbers of dilation required to resolve esophageal stricture (1[1-2] vs 3[3-4], P<0.01), and dilation-related cost ($827.32 [712.48-1424.97] vs $2297.71 [2005.15-2727.70], P<0.01) were all significantly lower in bleomycin group than that in control group.

1.4. Conclusions: Endoscopic bougie dilation combined with bleomycin injection may safely improve the restricture-free survival for benign postoperative esophageal anastomotic stricture, without causing severe complications.

2. Introduction

Esophageal anastomotic strictures happen in approximately 40% of patients with esophagectomy followed by gastric construction [1-3]. Those patients will suffer dysphagia even aphagia, which will severely affect their quality of life. The treatments for benign esophageal stricture involve surgical operation and endoscopic procedure. Surgical operations often lead to extensive injury and higher incidence of re-narrowing, which can only be applied to those not able to receive endoscopic treatment [4]. Endoscopic approaches include endoscopic balloon or bougie dilation, endoscopic stent placement and inci-

sional therapy, etc. However, these existing approaches have limited long-term effect and high complications so as not to be broadly taken into application [5-7].

Post-operative stenosis is the result of interlaced collagen, therefore, some study has treated esophageal strictures by suppressing inflammation with topical application of steroid combining endoscopic dilation. However, the efficacy and safety of this approach remains unknown [8, 9]. Mitomycin C (MMC) has recently been introduced as an alternative to steroid, which has shown some efficacy in limited studies [10, 11]. However, it is hard to achieve such drugs in China. Hence, we have found a similar drug bleomycin. Bleomycin has been commonly applied into carcinomas of the head and neck including esophageal carcinoma as an antineoplastic agent. On the other hand, bleomycin can inhibit fibroblast proliferation and decreases fibroblastic collagen synthesis, and it has been proven to be safe and effective in treating chronic inflammatory lesions and hypertrophic scars [12]. Liu et al has successfully treated rectal anastomotic stricture using intra-lesional injecting bleomycin with endoscopic balloon dilation [13]. We therefore conducted this retrospective study to compare the efficacy and safety of Endoscopic Bougie Dilation (EBD) combined with intra-lesional bleomycin injection to single endoscopic bougie dilation.

3. Materials and Methods

3.1. Ethical Considerations

The present trial was performed at First People's Hospital of Foshan. This study was approved by the Ethics Committee of First People's Hospital of Foshan and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All included patients have signed their consents on the endoscopic operation and having their images and other related clinal information published. All authors had access to the study data, and reviewed and approved the final manuscript.

3.2. Study Population

This was a retrospective study of patients with a dysphagia symptom score of ≥2 after esophagectomy with an endoscopy-confirmed benign anastomotic stricture admitted to First People's Hospital of Foshan between June of 2015 to June of 2019. Dysphagia was graded using Atkinson grades 0 to 4 (grade 0: no dysphagia, grade 1: dysphagia with solid food, grade 2: dysphagia to semisolid food, grade 3: dysphagia to liquids, grade 4: aphagia) [14]. The inclusion criteria were dysphagia scores of 2 to 4, no history of dilation, no residual tumor, narrow anastomosis without entry for endoscopes and with the stricture length of <3 cm. The exclusion criteria were the presence of malignant lesions, abscess or fistula around the anastomosis, with severe comorbidity or coagulation disorders.

3.3. Procedure

The patients lied down in the left lateral position with intravenous anesthesia using protocol (0.02 mg/kg). The esophageal diameter before expansion was recorded (standard with opened biopsy forceps). First, we used the small-caliber gastroscope to cross the stricture segment and enter the gastric cavity to advance the guidewire. Then we inserted the Savary-gilliard bougie dilator (Wilson-Cook SGD-100-1) slowly into the esophagus along the guide wire for endoscopic dilatation. The diameter of the probe was started from 7 mm and gradually increased to 12~15 mm, and each dilation was maintained for 1 to 2 minutes. If there were no complications such as severe bleeding or mucosal tears, the dilatation process would be continued. The stenosis diameter would be measured again. The diameter of the targeted esophageal dilation should be ≥12 mm. After confirming that no perforation or massive hemorrhage happened, patients immediately received 4-quadrant injections of bleomycin (15 USP unit/10ml) in the bleomycin group in the muscular layer of anastomotic stenosis. A successful injection was indicated by the sense of resistance in the procedure of injection and the absence of liquid leakage. Endoscopic manipulation details were shown (Figure 1).

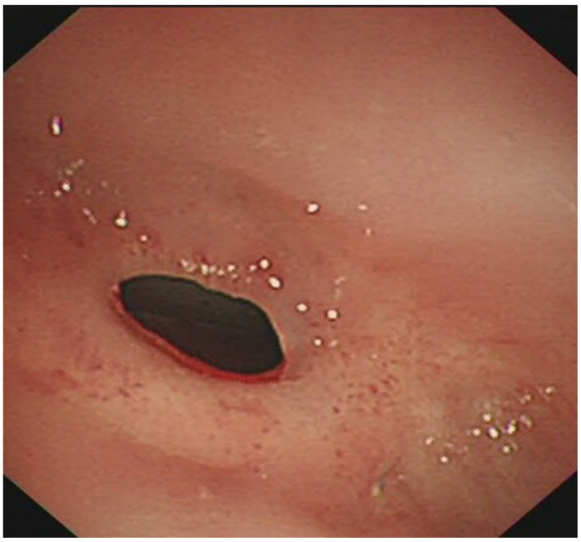

Figure 1A: The procedure of endoscopic bugie dilation followed by intramucosal injection. A. Anastomotic stricture. Endoscopic imgae of a benign esophageal anastomotic stenosis after esophagectomy.

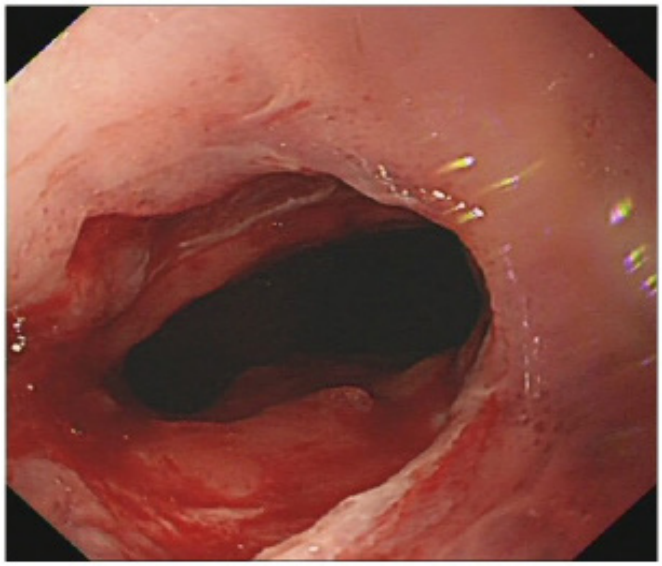

Figure 1B: Initial endoscopic bugie dilation. The diameter of the probe was gradually increased, and each dilation was maintained for 1 to 2 minutes. The diameter of the targeted esophageal dilation should be ≥12 mm.

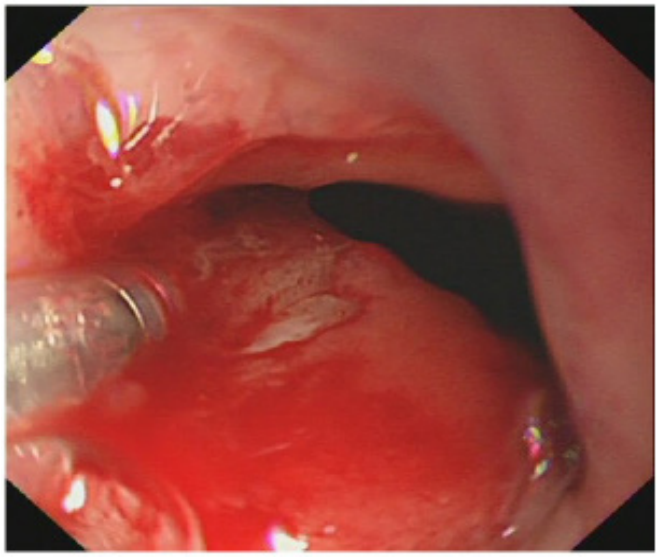

Figure 1C: Injection with bleomycin into the laceration. After confirming that no perforation or massive hemorrhage happened, patients received 4-quadrant injections of bleomycin (15 USP unit/10ml) in the bleomycin group in the muscular layer of anastomotic stenosis.

3.4. Endpoints

The primary endpoint was restricture-free survival. Stricture was defined as with a dysphagia symptom score of ≥2 and inability of passing an endoscopy with diameter of ≥9.2 mm. Restricture-free survival was defined as the days from inclusion to either with dysphagia score of ≥2, with inability to pass a standard endoscope through the stenosis lesion, dilation for any reason, or death from disease. The secondary endpoints were the remission rate, the one-year re-stricture rate, numbers of dilation required to resolve esophageal stricture, dilation-related cost and complications especially pulmonary fibrosis. If dysphagia and other symptoms disappeared, and gastroscopy could pass through the anastomotic stoma smoothly after treatment, the patient had achieved remission.

3.5. Post-Operation Management and Follow-Up

Patients were required to fast for 24 hours after the endoscopic dilation and injection, receiving parenteral nutrition and acid suppression therapy. If the patient had no fever, chest pain, abdominal pain or subcutaneous emphysema, he could gradually take liquid food and transit to a normal diet. All the patients would be followed up in the 1st, 3rd, 6th and 12th months following the procedure. Phone calls could be used for patients who could not come to hospital for follow-up. Medical imaging or endoscopy should be performed if symptoms recurred or other related complications appeared. Chest X-ray would be taken before the procedure and 12 months after the procedure. Recurrence was confirmed if anastomotic stenosis was present and malignancy was excluded. In this study, we retrospectively studied the results in the computerized patient record system.

4. Statistical Analysis

Continuous variables were compared using t test or Mann-Whitney U test in the condition of conforming to normal distribution or not, while categorical data were compared using the Pearson $\chi 2$ test or Fisher's exact test as appropriate. Restricture-free survival was estimated using Kaplan–Meier method. A p value of <0.05 was considered as statistical significant. Statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA).

5. Results

During the period from June of 2015 to June of 2019, 30 patients with benign esophageal anastomotic structure receiving bleomycin injection and 30 patients receiving single EBD were retrospectively studied. All patients underwent esophagectomy with hand-sewn anastomosis without esophageal substitute.

The patients` baseline characteristics were shown in (Table 1). There existed no difference in the patients` characteristics between bleomycin group and control group. The time to develop stricture after esophagectomy, dysphagia score and stricture diameter were all similar in the two groups (p>0.05).

All of the 60 patients successfully finished the endoscopic procedure. As shown in (Table 2), dysphagia and esophageal stricture resolved in the patients of both groups after the endoscopic procedure with passable endoscopy in the esophageal tube (P>0.05). The complication rate between the two groups showed no significant difference (P>0.05). No severe complications, such as pulmonary fibrosis, perforation, hemorrhage or infection related to endoscopic procedure, happened. During the one-year follow-up, the re-stricture rate (23.3% vs 100%, P<0.01), median numbers of dilation required to resolve esophageal stricture (1[1-2] vs 3[3-4], P<0.01), and dilation-related cost ($827.32 [712.48-1424.97] vs $2297.71 [2005.15-2727.70], P<0.01) were all significantly lower in bleomycin group than those in control group. The results of Kaplan–Meier analysis demonstrated that the one-year re-stricture-free survival was significantly better in blemycin group (11.12±0.41 vs 3.87±0.21 months, P<0.01, (Figure 2).

Table 1: Patients` baseline characteristics

	Bleomycin group	Placebo group	P value
Age (Mean ± SD)	52.92±7.61	56.07±8.75	0.17
Sex (male/female)	23/7	25/5	0.47
Dysphagia score (Mean ± SD)	3.40±0.50	3.30±0.49	0.73
Stricture diameter (mm, Mean ± SD)	5.52±0.65	5.33±0.80	0.69
Time to stenosis after surgery, (days, Mean ± SD)	60.18±2.51	63.67±3.65	0.75

Table 2: The comparison of efficacy and safety between the two groups.

	Bleomycin group	Placebo group	P value
Stricture diameter (mm, Mean ± SD)	13.68±1.14	13.47±1.13	0.76
Complication, n(%)	3(10%)	2(6.7%)	0.83
One-year restricture rate, n(%)	7(23.3%)	30(100%)	P<0.01

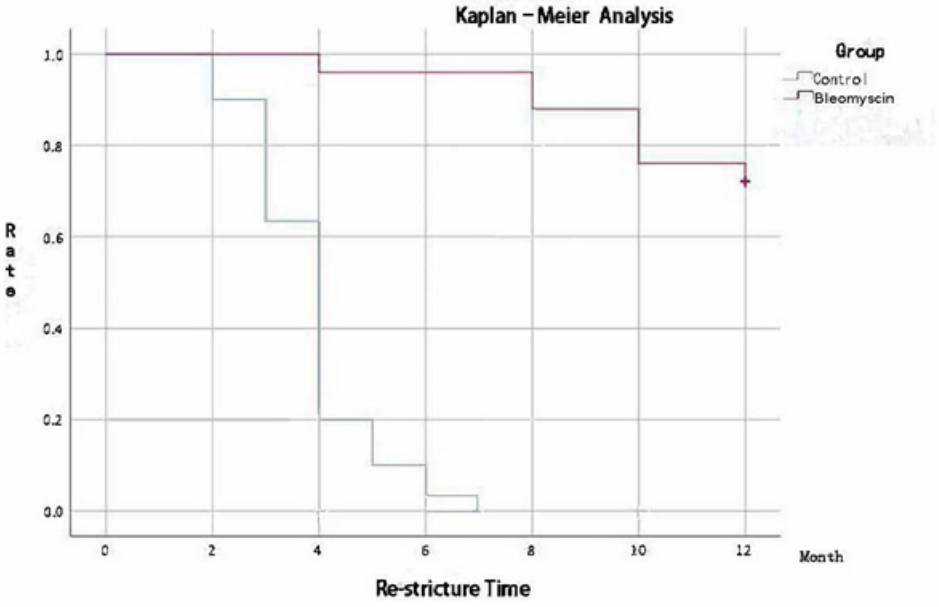

Figure 2: Restricture-free survival analysis of the two groups estimated using Kaplan–Meier method. The one-year re-stricture-free survival was significantly better in blemycin group than that in control group(72% vs 0,P<0.01)

6. Discussion

The present retrospective study suggests that endoscopic bugie dilation combined with intramucosal injection of bleomycin may prolong the stricture-free survival compared to single bugie dilation. In the one-year follow-up, only 23.3% of the patients receiving bleomycin injection had recurrence of esophageal stricture, while all of the patients receiving single EBD replase with dysphagia-related stricture. Bleomycin group required less dilation (1[1-2] vs 3[3-4], P<0.01) and lower cost ($827.32 [712.48-1424.97] vs $2297.71 [2005.15-2727.70], P<0.01). In addition, the one-year re-stricture-free survival in bleomycin group was significantly better than that in control group(72% vs 0%, P<0.01). Moreover, no severe complication was noticed in the one-year follow-up after the endoscopic procedure.

The treatment of benign esophageal anastomotic stricture remains a difficult clinical practice. The risk factors of post-operative esophageal stricture include stapler anastomosis, anastomosis leakage, radiotherapy, etc [3, 15]. The first-line treatment of esophageal anastomotic strictures is endoscopic dilation, but the dilation causes mucosa laceration which will gradually heal with over-fibration so as to cause restrictures and repeated dilations [5, 16, 17]. Endoscopic dilators can be categorized into mechanical bougie or balloon dilations. Although the two dilators have similar safety and efficacy for treating esophageal stricture [18], they act in different patterns. Bougie dilators dilate a stenotic segment with a longitudinal and radial force, while balloon dilators only use a radial force. Bougie dilators is suggested to be used for simple stenosis and for stenosis of the proximal esophagus, especially anastomotic stenosis [4]. Nevertheless, endoscopic dilation often results in repeated dilation and higher complication incidence.

In the near decades, some studies have demonstrated some advantages in combining endoscopic dilation and intra-lesional injection of steroid [9, 19-22]. Noboru et al have conducted a RCT of 65 patients with anastomotic strictures, finding that endoscopic injection of triamcinolone combined with dilation reduced times of repeated dilation and improved the re-stenosis survival compared with sham injection. However, the results of another multicenter, double-blind trial of 60 patients have shown that corticosteroid injections did not decrease the frequency of repeated dilations or prolong the dysphagia-free period in patients with benign anastomotic esophagogastric stricture [23]. Moreover, this study has reported an increased risk of candida-related esophagitis in the remaining esophagus after injecting steroid [23]. Therefore, it remains unclear whether combining intramucosal injection of steroid can safely treat benign esophageal anastomotic stricture.

As an alternative to steroid injection, mitomycin C (MMC) has recently been introduced. MMC is an antineoplastic agent inhibiting the proliferation of fibroblast and decreasing the synthesis of fibroblastic collagens. Most studies applying MMC injection to esophageal strictures are case reports with a limited number of patients and mostly in pediatrics [10, 11, 24], although they have demonstrated some efficacy and safety with limited complications. Furthermore, MMC is not readily available in some nation like China. Therefore, we have used another anti-neoplastic agent bleomycin as an alternative, which has been topically used in treating esophagus carcinoma and dermatologic diseases with limited complications. Natsugoe et al have successfully used topical injection of 30 mg bleomycin adsorbed on silica particles to prolong the survival of patients with esophageal carcinoma, and only fever was reported in some patients [25]. Bleomycin has been shown to be effective and superior to MMC in treating keloids and hypertrophic scars [26-27]. Payapvipapong et al have demonstrated that intralesional injection of bleomycin (1 mg/mL) had equal effectiveness as triamcinolone (TCA) in the treatment of keloids and hypertrophic scars, and that no significant systemic absorption and skin atrophy was observed [28]. Naeini et al has reported that intralesional injection of bleomycin (1.5 U/ml, ≤2 ml/cm2, ≤10 U per session) was safe and superior to cytotherapy combined with TCA injection in treating keloids and hypertrophic scars (88.3% vs 67.3%, p=0.001) [29]. Xu et al have found that combining intralesional bleomycin injection (15 USP unit into 10 ml per session, at 4 locations) and endoscopic dilation could effectively treat rectal anastomotic stenosis and prolong the stricture-free time (8.0±1.5 vs 5.1±1.0 months, P=0.01), and only fever was reported in one patient in bleomycin group [13, 30]. Cutaneous toxicity of bleomycin has been reported to occur at total doses of between 200 and 300 U, and pulmonary fibrosis occur at doses > 400 U [31-32]. In dermatology, the dosage of local injection of bleomycin has been usually at 9U [33], and the maximum dosage has been reported to be 15U per session [29-30, 34]. Considering the safety and effectiveness of topical usage of bleomycin in dermatology and rectal anastomotic stricture, we firstly applied bleomycin injection (1.5U/ml, 15U per session) combined with endoscopic dilation to benign esophageal anastomotic stricture.

A major strength of this study is that it is the first study, to our knowledge, comparing the effect of bleomycin injection combined with endoscopic dilation and single dilation for benign esophageal anastomotic stricture. In addition, the patients included have been observed for one year, a considerably long period.

The present study also has some limitations. Firstly, the sample size is relatively small and has not been estimated appropriately. However, the incidence of stricture formation is lower than 10% among patients undergoing esophagectomy, and thus it will be difficult to conduct a study with a large sample size. Secondly, this study has focused on patients without prior endoscopic treatment but not on those with refractory benign esophageal anastomotic stricture, which deserves further study. Thirdly, this is a retrospective controlled study but not prospective randomized controlled study.

Other new approaches of benign esophageal anastomotic stricture have been developed in recent years. Stent placement has shown lim-

ited effectiveness and safety, and its adverse events such as migration or hemorrhage should be considered [35]. Another approach is endoscopic incisional therapy, which needs especially high technique for endoscopist and will easily lead to perforation and severe bleeding. However, a prospective randomized trial, including 62 patients with no previously-treated esophageal anastomotic strictures, showed no difference between incisional therapy and dilation [36]. In addition, a retrospective study, including 50 patients with refractory esophageal anastomotic strictures, found that incisional therapy provided shorter duration of dysphagia relief compared with stent placement [37]. Therefore, we believe that endoscopic dilation followed by bleomycin injection will be a promising effective method for the treatment of benign esophageal strictures.

7. Conclusions

The present study demonstrates that combining intralesional injection of bleomycin immediately after endoscopic bougie dilation decrease the need to repeated dilation and improve the stricture-free survival for patients with benign esophageal anastomotic stricture.

8. Funding

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