Prevention of esophageal strictures after endoscopic submucosal dissection with the injection of botulinum toxin type A

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Background and Aims: The use of endoscopic submucosal dissection (ESD) for management of widespread superficial esophageal squamous carcinoma is closely associated with esophageal stenosis. We investigated the efficacy and feasibility of endoscopic injection of botulinum toxin type A (BTX-A) for preventing esophageal strictures after ESD for superficial esophageal squamous carcinoma.

Methods: Sixty-seven patients with superficial esophageal squamous cell carcinomas with mucosal defects that exceeded one half of the circumference of the esophagus after ESD treatment were enrolled and randomly divided into 2 groups (group A, n = 33; group B, n = 34). Patients in group A (BTX-A group) were immediately injected with BTX-A after ESD, whereas patients in group B (control group) received ESD only. Endoscopy was performed when patients reported dysphagia symptoms and at 12 weeks post-ESD in patients without symptoms. Patients who experienced post-ESD esophageal strictures in both groups received bougie dilation.

Results: The number of patients who experienced esophageal strictures in group A (per protocol analysis, 6.1%, 2/33; intention to treat analysis, 11.4%, 4/35) was significantly less than that seen in group B (per protocol analysis, 32.4%, 11/34; intention to treat analysis, 37.8%, 14/37) ($P < .05$). Moreover, the number of bougie dilation procedures was significantly lower in group A (mean, 1.5; range, 0-2) than in group B (mean, 2.8; range, 0-5) ($P < .05$).

Conclusions: Endoscopic injection of BTX-A was effective in preventing post-ESD esophageal strictures and decreasing the times of bougie dilation procedures. (Clinical trial registration number: ChiCTR-TRC-12003188.) (Gastrointest Endosc 2016;84:606-13.)

Developments in endoscopic techniques for the treatment of superficial esophageal squamous cell neoplasia have gained widespread acceptance and provided patients with a minimally invasive alternative to open surgery.[1,2] However, the residual mucosal defect after endoscopic submucosal dissection (ESD) may cause acute inflammation, deep ulcers, local submucosal fibrous connective tissue proliferation, collagen deposition, esophageal wall fibrosis, and esophageal stricture formation.[3] The incidence of esophageal strictures after endoscopic resection resulting in large near-circumferential or circumferential esophageal mucosal defects has been reported to be 88% to 100%.[4-9] Although endoscopic balloon dilation is effective for the treatment of benign strictures, it must be performed repeatedly until dysphagia resolves. Repeated dilation not only increases the risk of perforation and bleeding but also reduces the patient's quality of life. Yamaguchi et al[9,10] reported that the oral administration of prednisolone can prevent esophageal stricture after ESD, but corticosteroids can cause adverse effects, including immune suppression, optical damage, psychiatric disturbances, diabetes, peptic ulceration, and osteoporosis. In addition, frequent corticosteroid use renders elderly patients more susceptible to infection.

Abbreviations: BTX-A, botulinum toxin type A; EORTC, European Organisation for Research and Treatment of Cancer; ESD, endoscopic submucosal dissection.

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Therefore, it is important to develop new methods for the prevention and treatment of esophageal stenosis. Gassner et al[11] concluded for the first time that a single injection of botulinum toxin type A (BTX-A) improved the cosmetic appearance of cutaneous scars, which inspired scholars to pay attention to the role of BTX-A in the inhibiting scar formation. Some studies[12,13] reported that BTX-A was used to decrease the fibrosis of a surgical wound and prevent widening of facial scars. In our early animal experimental studies, we observed that endoscopic injection of BTX-A could reduce the symptoms, extent of stricture, and corresponding histopathologic changes of benign esophageal strictures caused by electrocautery in rabbits. BTX-A could also down-regulate the expression of both transforming growth factor-β1 mRNA and transforming growth factor-β1 protein in the esophageal scar tissues, leading to less deposition of both type I and type III collagen in the tissues.

A preliminary aim of this study was to determine the relationship between the extent of the esophageal mucosal defect after ESD and the risk of stricture formation. Specifically, we determined the risk of strictures in superficial esophageal carcinoma patients with mucosal defects more than one half of the circumference of the esophagus after ESD treatment. Our prospective study's primary aim was to investigate the efficacy and feasibility of the endoscopic injection of BTX-A for the prevention of esophageal strictures after ESD for superficial esophageal squamous carcinoma.

METHODS

Study patients

We enrolled 72 patients with superficial esophageal carcinoma who underwent ESD at the Chinese PLA General Hospital from June 2012 to February 2015. All enrolled patients had mucosal defects that exceeded half of the circumference of the esophagus after ESD treatment. Eligibility criteria were (1) the absence of lymph node metastases confirmed by CT, (2) a maximal tumor length < 7 cm, (3) no evidence of organ failure, and (4) the patient's signed informed consent. We excluded patients who had other GI tumors or associated conditions such as renal, cardiac, or respiratory failure; brain dysfunction; diabetes; esophageal cancer after radiotherapy; or multiple esophageal cancers. All patients or their relatives provided consent after being informed of the risks and benefits of ESD and stent placement. This study was approved by the institutional review board of the ethics committee of PLA General Hospital, and all authors had access to the study data and reviewed and approved the final manuscript. (Clinical trial registration number: ChiCTR-TRC-12003188.)

Study design and procedures

After the ESD procedure, the mucosal defect was classified based on the extent of the area affected: 1 was defined as one half to two thirds of the esophageal circumference, 2 as two thirds to three fourths of the esophageal circumference, 3 as three fourths to the full esophageal circumference, and 4 as full circumferential mucosal defect). Patients were categorized into 1 of these 4 groups. Patients were then randomized into 1 of 2 groups (groups A and B) using a computer-generated randomization table. Patients in group A (BTX-A group, n = 36) were injected with BTX-A immediately after ESD, whereas patients in group B (control group, n = 36) received ESD only, without BTX-A injection. In patients in group B with a complete circumferential mucosal defect, a fully covered esophageal stent was placed immediately after ESD. However, for patients in group A with a complete circumferential mucosal defect, the stent was placed immediately after the endoscopic injection of BTX-A. The esophageal stent was removed 8 weeks post-ESD in both groups.

BTX-A injection

A single session of BTX-A (Lanzhou Institute of Biological Products, Lanzhou, China) injections was undertaken immediately after ESD. A total of 100 units of BTX-A was diluted with 5 mL of saline solution (20 units/mL). The BTX-A solution was injected in .5-mL increments into 10 separate points equally spaced along the circumference of the defect with a 25-gauge, 4-mm needle (TOP Corporation, Tokyo, Japan). The injections were placed deeply at the level of the muscularis propria along the junction of the defect and the normal tissue (Fig. 1). However, in patients with full circumferential mucosal defects, BTX-A was injected superficially into the base of the cautery ulcer. All patients in group A were injected with 100 units of BTX-A, regardless of the lesion size.

Follow-up and endpoints

Dysphagia was evaluated using the Mellow-Pinkas score as follows[14]: 0 = no dysphagia, 1 = dysphagia to normal solids, 2 = dysphagia to soft solids, 3 = dysphagia to solids and liquids, and 4 = complete dysphagia, even to saliva. Stricture was defined as a <9.8-mm opening that did not allow the passage of a standard endoscope (GIF H260; Olympus Medical Systems, Tokyo, Japan) through the stenotic area.

Hospital outpatient follow-up was arranged at 6 and 12 weeks post-ESD, and telephone follow-up was conducted by a senior nurse every week post-ESD. Repeat endoscopy was performed to assess possible recurrence or relapse at 6 weeks after operation. The dysphagia grading scores and Quality of Life Questionnaire (European Organisation for Research and Treatment of Cancer [EORTC] QLQ-OES18) scores were recorded at 12 weeks post-ESD. However, endoscopy was performed on demand in patients with a dysphagia score > 2. Patients with or without dysphagia were also evaluated for possible strictures 12 weeks after ESD. Patients experiencing post-ESD esophageal strictures in both groups were treated with bougie dilation using Savary-Gilliard