ORIGINAL ARTICLE

Efficacy of prednisone for prevention of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma

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Abstract

Background: Our objective was to investigate the efficacy and safety of oral prednisone for the prevention of esophageal stricture formation after endoscopic submucosal dissection (ESD) in an optimal administration program.

Methods: Patients who underwent circumferential or semi-circumferential (more than three quarters but not a complete circular) ESD for esophageal squamous cell carcinoma were eligible for this study. Oral prednisolone was administered to the study group at a dose of 30 mg/day on the third day post-ESD, and then tapered gradually (30, 25, 20, 15, 10, and 5 mg for 14 days). Serial esophagoscopy with iodine staining was performed to assess stenosis and tumor recurrence at one, three, six, and 12 months after ESD. Endoscopic balloon dilatation was performed whenever patients experienced persistent dysphagia to solids. Data were statistically analyzed.

Results: Twenty-three patients (15 men, mean age 66.6 years) were enrolled in the study. Post-procedural esophageal stricture was significantly lower in the study group (23.1%) compared to the control (80%) ($P < 0.05$). A significantly higher number of endoscopic balloon dilatation sessions were performed ($P < 0.05$) in the control (13.5) than in the study group (0.69). There were no adverse events related to oral prednisolone or the procedure itself and no treatment-related mortality was observed during the 12 month follow-up.

Conclusions: Our study suggested an optimal administration program of oral prednisone therapy and demonstrated that it is safe and effective for the prevention of esophageal stricture in patients after complete or semi-circular ESD for esophageal squamous cell carcinoma.

Introduction

Endoscopic submucosal dissection (ESD) is widely performed to remove superficial esophageal squamous cell carcinomas (ESCC), even when they cover large areas in an almost circumferential pattern.[1–3] However, a substantial risk of procedure-related complications has been reported, including potentially life-threatening perforation and post-procedural stenosis.[4] Multivariate analysis has demonstrated that a mucosal defect of more than three-quarters of the circumference is a reliable predictor of stricture.[3,5] The resultant dysphagia substantially decreases patient quality of life and usually requires multiple sessions of risky endoscopic balloon dilatation (EBD).[6]

Although preventive EBD has been the treatment of choice to prevent stricture, stricture is a frequent complication even after several EBD sessions.[7] Recently, corticosteroids have been used to prevent post-ESD stricture, and have shown excellent results.[8–11] Hashimoto *et al.* reported that intralesional injection of triamcinolone reduced the

incidence of stricture and the number of required EBD sessions.[8] However, we consider triamcinolone injections to be time-consuming, and are accompanied with risks of perforation and infection after local injection in a naked esophageal muscle. Prophylactic oral prednisolone for the prevention of post-ESD stricture is preferable. A number of studies concluded that systemic steroid administration also may be more effective than endoscopic injection, suggesting that oral prednisolone may offer a useful prevention option.[12,13] However, none of the previous studies performed defined the optimal dose, duration, and form of administration of steroids for preventing stricture in Chinese patients.

In this study, we examined the efficacy and safety of an optimal administration program of oral prednisolone for the prevention of benign esophageal stricture after ESD for superficial ESCC involving more than three quarters of the circumference of the lumen.

Methods

Patients

A total of 23 patients with superficial ESCC who underwent circumferential or semi-circumferential (more than three quarters but not a complete circular) ESD from January 2009 to January 2015, at our Digestive Endoscopy Center at Nanfang Hospital, Southern Medical University, Guangzhou, China, were enrolled in this study. Written informed consent was obtained from each patient before conducting the procedure. The institute's ethics committee on human research approved the study protocol. The study group comprised 13 patients who received oral prednisolone (patients treated since November 2011), and the control group comprised 10 patients who did not receive oral prednisolone (patients treated before November 2011). Magnification endoscopy with narrow-band imaging was performed to estimate tumor depth and chromoendoscopy with iodine staining to clearly delineate the tumor margins. Patients identified with lesions confined to the mucosa underwent ESD after computed tomography (CT) scanning showed no lymph node or distant metastatic lesions. Patients with lesions deeper than the mucosa or metastatic lesions in any location were excluded from this study because of the high likelihood that additional therapy would be required.

Endoscopic submucosal dissection (ESD) procedure

Endoscopic submucosal dissection was performed with patients under general anesthesia. Carbon dioxide insufflation was used throughout the procedure to mitigate mediastinal emphysema in case of perforation. The ESD procedure was performed using a single-channel upper endoscope with a transparent cap (GIF-H260Z; Olympus, Tokyo, Japan). Circumferential markings were made on the proximal and distal sides of the normal-appearing mucosa at least 5 mm from the lesions using a flush knife (DK2618JN; Fujifilm Medical, Tokyo, Japan) or a hook knife (KD-620LR; Olympus Medical, Tokyo, Japan). A 0.4% sodium hyaluronic acid solution was injected into the submucosal layer to lift the surrounding mucosa. Mucosal incision and submucosal dissection were then performed using a flush or hook knife (Fig 1). In order to control bleeding during ESD or to prevent possible bleeding from visible larger vessels, hemostatic forceps (Coagrasper; Olympus) were used in the soft coagulation mode at 80 W. Experienced endoscopy physicians conducted the procedure.

Procedure-related bleeding after ESD was defined as bleeding that required transfusion or surgical intervention or bleeding that caused the hemoglobin level to decrease by 2 g/dL.[14] Procedure-related perforation was diagnosed endoscopically or by the presence of free air on a plain chest radiograph or chest CT.[15]

Post-ESD management to prevent stricture

In the study group, patients with superficial ESCC who underwent circumferential or semi-circumferential ESD were administered a systemic steroid. Oral prednisolone was administered at a dose of 30 mg/day on the third day after ESD, and then tapered gradually (30, 25, 20, 15, 10, and 5 mg for 14 days). EBD was applied whenever patients experienced persistent dysphagia to solids. Patients in the control group only received EBD after ESD when required.

Serial esophagoscopy with iodine staining was performed to assess for stenosis and tumor recurrence at one, three, six, and 12 months after ESD. Post-ESD stricture was defined when patients complained of dysphagia or when a standard endoscope (GIF-Q240; Olympus Medical Systems, Tokyo, Japan) could not be passed through the scar induced by ESD. In such cases, EBD was performed using an esophageal balloon dilation catheter (CRE Fixed Wire 15/16.5/18 mm, Boston Scientific Corporation, Boston, MA, USA), and dilation was repeated as necessary until the symptom was resolved.

Surveillance esophagoscopy was terminated if the patient remained free from stricture during the 12-month follow-up period and negative results were obtained on the last endoscopic examination.

Statistical analysis

All data were analyzed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Independent *t*-tests and

Figure 1 (**a**) A discolored area in the middle thoracic esophagus. (**b**) The tumor was removed en bloc. (**c**) A mucosal defect of more than three quarters of the circumference after endoscopic submucosal dissection. (**d**) No stricture was found during the 12-month follow-up.
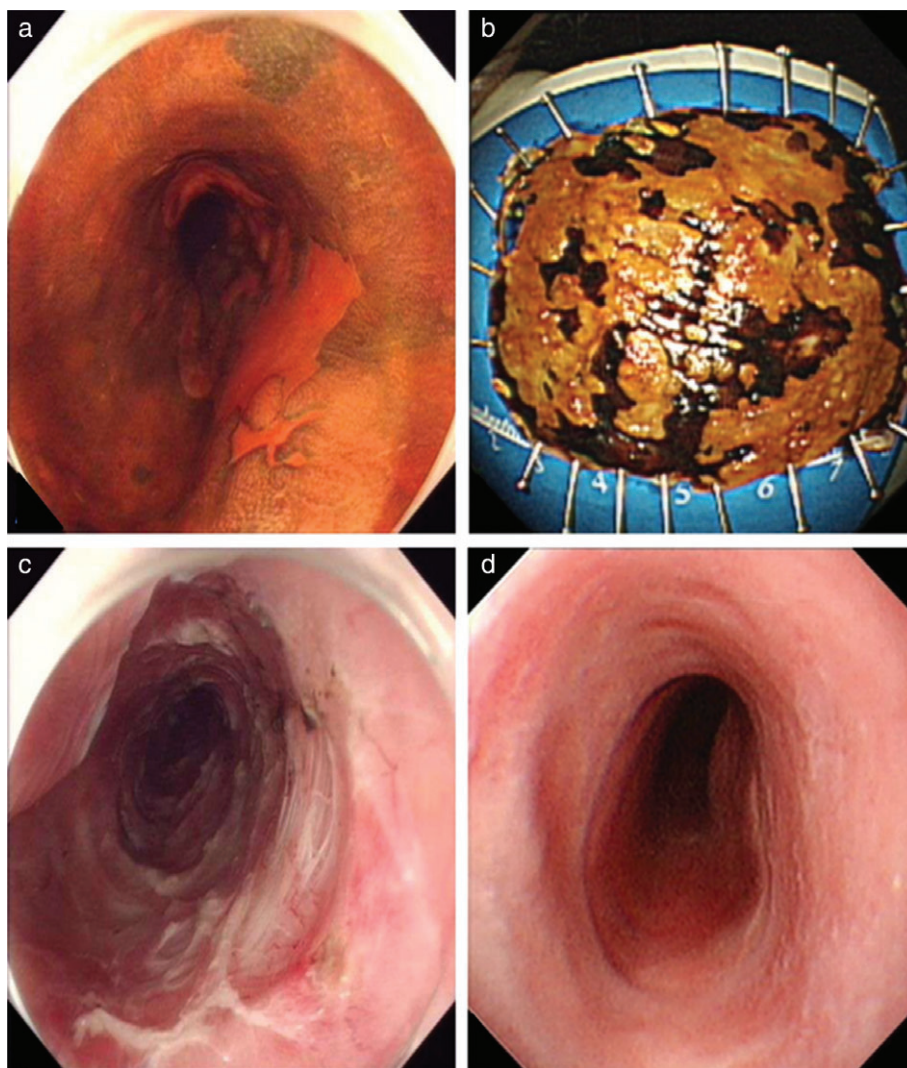
chi-square analysis were used to compare the basic data and treatment outcomes between the groups. When the expected frequency in more than 20% of the frames of R × C contingency table was <5 or the expected frequency in any frame was <1, a Fisher's exact test was used to analyzed data. $P < 0.05$ in a two-sided hypothesis test was considered statistically significant.

Results

As shown in Table 1, 23 patients (15 men, 8 women; mean age 66.6 years; range 52–76) with a tumor extending over three quarters of the esophageal circumference who underwent ESD between January 2009 and January 2015 were enrolled in this study. There were no significant differences in background parameters including gender, age, tumor location, depth of tumor invasion, ESD procedure duration or resection size between the groups. All lesions were

resected en bloc and removed with tumor-free vertical and lateral margins (R0: curative resection = 100%).

As shown in Table 2, after ESD, all patients had a mucosal defect involving at least three quarters of the circumference. There were two complete circular ESD cases in each group. There were no significant differences between the groups in size or extent of mucosa defect after ESD. Postprocedural esophageal stricture was significantly lower in the study group (23.1%, 3/13) than in the control (80%, 8/10) ($P < 0.05$). During the 12 weeks of systemic prednisone treatment, three patients (23.1%) in the study group experienced post-procedural esophageal stricture accompanied by dysphagia at four, six, and seven weeks. These three patients only required three sessions of EBD. The remaining 10 patients were free from stricture at the end of follow-up, and none required additional EBD. The number of EBD sessions was significantly higher ($P < 0.05$) in the control (13.5) compared to the study group (0.69).

Table 1 Clinicopathological characteristics of patients

Characteristic	Study group ($n = 13$)	Control group ($n = 10$)	P†
Gender (male/female)	8/5	7/3	0.689
Age (year, mean ± SD)	65 ± 5.958	67.8 ± 6.63	0.299
Tumor location	—	—	0.892
Upper-thoracic esophagus	0/10 (0)	1/10 (10%)	—
Mid-thoracic esophagus	10/13 (76.9%)	6/10 (60%)	—
Low-thoracic esophagus	3/13 (23%)	3/10 (30%)	—
Depth of tumor invasion	—	—	0.532
M1‡	7/13 (53.8%)	6/10 (60%)	—
M2§	6/13 (46.1%)	4/10 (40%)	—
Resection size (mm, mean [range])	54.6 (35–100)	58.5 (30–90)	0.624
ESD procedure (time, min, mean [range])	135 (105–246)	147.1 (86–225)	0.524

†For comparison between study and control groups; ‡M1, tumor limited to the epithelium; §M2, tumor invaded the lamina propria. ESD, endoscopic submucosal dissection; SD, standard deviation.

Table 2 Treatment outcomes of each group

	Study group	Control group	P†
No. analyzed	13	10	
Defect size after ESD (mm, mean [range])	59.2 (35–110)	64.7 (32–98)	0.532
Extent of defect after ESD	—	—	0.736
3/4	10/13 (76.9%)	7/10 (70%)	—
4/5	1/13 (7.6%)	1/10 (10%)	—
Circumferential	2/13 (15%)	2/10 (20%)	—
Stricture (no., %)	23.1 (3/13)	80 (8/10)	0.007
Total EBD session (mean [range])	0.69 (0–3)	13.5 (0–28)	0.004
Adverse events related to prednisolone	0	0	—
Complications related to ESD/EBD	0	0	—
Average follow-up (months)	12	12	—
Local recurrence	0	0	—
Metastatic tumors	0	0	—
Treatment-related mortality	0	0	—

†For comparison between study and control groups. ESD, endoscopic submucosal dissection; EBD, endoscopic balloon dilation.

Although minor bleeding during ESD occurred in most cases, hemostasis was achieved during all procedures. No procedure-related perforation or other complications related to EBD occurred in either group. There were no adverse events related to oral prednisolone. No patients showed local recurrence or metastatic tumors, and all patients were alive during the follow-up period.

Discussion

Post-ESD stricture formation remains a challenging complication in the treatment of superficial ESCC, especially in China.[2] Worldwide, esophageal stricture mostly occurs after semi-circumferential or circumferential ESD at a rate of 88–100%.[4] Esophageal strictures can cause dysphagia and result in decreased quality of life or complications, such as aspiration pneumonia.[3] We assessed the efficacy and safety of oral prednisone administration for the prevention of stricture after esophageal circumference or semi-circumference ESD.

Although EBD is usually indicated for benign stricture caused by ESD, the effect of EBD is sometimes only temporary, thus stricture can reappear,[16,17] and its efficacy might be affected by the length and diameter of the strictures occurring before EBD is performed.[18–20] Mucosal defects of greater than three quarters of the total circumference area after ESD are accompanied with a high risk of developing stricture. Ezoe et al. reported that even when preventive EBD was performed in patients who had undergone circumference ESD, 60% of patients still developed stricture, thus the number of EBD sessions required tended to be greater.[7] Our results indicated an 80% incidence of stricture in patients who underwent extensive ESD without system steroid administration. These patients required multiple EBD sessions. At present, there are no guidelines or well-established methods to prevent stricture after ESD.

Recently, several authors have described the usefulness of intralesional steroid injection and temporary stent insertion to prevent post-ESD stenosis. Hashimoto et al. reported on the application of intralesional steroid

injection to prevent stricture after esophageal ESD.[8] Triamcinolone was injected into post-ESD ulceration three, seven, and 10 days after ESD. The 19% stricture rate achieved was satisfactory, but three additional endoscopic procedures were required, causing additional cost and patient inconvenience. In a prospective study, Hanaoka *et al.* showed promising results with a single session of intralesional steroid injection immediately after ESD to prevent post-ESD stricture.[9] However, all patients in Hanaoka *et al.*'s study had semi-circumferential, not circumferential mucosal defects, which may not have a relatively high risk of stricture. Furthermore, the potential risk of delayed perforation and pleural effusion or mediastinitis are complicated with local therapy.[21]

Recently, Morikawa *et al.* described a case series in which persistent esophageal stricture was fully managed by systemic steroid administration. They concluded that this approach might deliver the steroid into the fibrotic tissue of the stenosis more effectively than an endoscopic injection.[12]

Similarly, Yamaguchi *et al.* performed a retrospective study of the efficacy of prophylactic oral prednisolone for the prevention of post-ESD stricture.[10] They concluded that post-ESD esophageal strictures were persistent even if treated with multiple EBD sessions, but oral prednisolone may offer a useful prevention option. However, none of these previous studies defined the optimal dose, duration, and form of administration of steroids for preventing stricture.

Based on the results of previous studies, we initiated a new oral prednisolone administration program. Our results showed that the ratio of stricture was 23.1% versus 80% in the study and control groups, respectively, and could be easily resolved with a few sessions of EBD (mean 0.69). Oral prednisone produced a marked effect in preventing esophageal stricture formation after ESD, leading to success in controlling dysphagia. EBD is the preferred mode to treat esophageal stricture, irrespective of etiology.[6] Another striking observation of our study is that administering oral prednisone can reduce the number of EBD sessions required. Our data showed that significantly fewer EBD sessions were required in the study group (0.69) compared to the control (11.8; $P < 0.05$). No procedure-related perforation or other complications related to EBD occurred.

Use of prednisolone can lead to adverse effects, including immune suppression, infection, optical damage, psychiatric disturbance, diabetes, peptic ulceration, and osteoporosis, which could represent severe clinical problems.[13] In our study, oral prednisolone was administered at a dose of 30 mg/day on the third day after ESD, then tapered gradually and discontinued. In clinical practice, for diverse autoimmune disorders, such as inflammatory bowel, collagen, and neurological diseases, moderate doses (30–40 mg/day) of prednisolone have been effectively applied in the short term and were rarely accompanied by severe adverse events. A larger sample is required to determine the appropriate dose of prednisone for controlling and preventing esophageal stricture after ESD. In our study, there were no adverse events related to oral prednisolone, no treatment-related mortality occurred, and none of the patients showed local recurrence or metastatic tumors during the 12 month follow-up. Therefore, we suggest that our results indicate the optimal dose, duration, and form of administration of steroids for preventing stricture after ESD.

Our study was limited in that we only enrolled patients from a single endoscopic center and the study was a non-randomized controlled study. Further investigation using a larger sample and multiple centers is required.

In conclusion, an optimal oral prednisolone administration program is effective and safe for preventing post-ESD stricture and reducing the number of EBD sessions required after complete or semi-circular ESD.

Acknowledgment

Disclosure

No authors report any conflict of interest.

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