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Long-term efficacy and safety of intralesional steroid injection plus oral steroid administration in preventing stricture after endoscopic submucosal dissection for esophageal epithelial neoplasms

Yuan Chu[1] · Tao Chen[1] · Hongqi Li[1] · Pinghong Zhou[1] · Yiqun Zhang[1] · Weifeng Chen[1] · Yunshi Zhong[1] · Liqing Yao[1] · Meidong Xu[1]

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Abstract

Background Endoscopic submucosal dissection (ESD) has been widely accepted as the treatment for early-stage esophageal epithelial neoplasms. However, stricture is a common complication after large-circumference ESD. This retrospective study is conducted to evaluate the efficacy and safety of intralesional steroid injection plus oral steroid administration in preventing esophageal stricture.

Methods 70 patients with a mucosal defect extending over more than two-thirds of the circumference after esophageal ESD for epithelial neoplasms were enrolled in this study. Those who received intralesional triamcinolone injection combined with oral prednisolone administration were assigned to the treatment group, while those who were treated without any prophylaxis of esophageal stricture were assigned to the control group. The primary observation result was the frequency of stricture. The secondary observation results were the number of endoscopic balloon dilation (EBD) sessions and rate of complications.

Results Compared with the control group, the frequency of stricture (14.7% 5/34 patients vs. 51.5% 19/36 patients) and number of EBD sessions (mean 0.2 vs. 3.3) were significantly lower in the treatment group. One patient suffered from perforation in the treatment group and recovered with conservative treatment. None steroid-related complications were found during a long-term follow-up.

Conclusions Intralesional steroid injection plus oral steroid administration is safe and effective in preventing stricture following esophageal ESD for esophageal epithelial neoplasms with a mucosal defect extending no less than two-thirds of the circumference in a long-term follow-up.

Keywords Esophageal neoplasms · Endoscopic submucosal dissection · Stricture · Steroid · Prevention

Endoscopic submucosal dissection (ESD) is a minimally invasive technique which has been regarded as a crucial treatment for precancerous lesion or early-stage esophageal cancer with a low risk of lymph node metastasis [1, 2]. Stricture is one of the most common post-operative complications for esophageal ESD, especially for patients with large circumferential lesions. This adverse event often leads to dysphagia that seriously influence patients' quality of life. Circumferential extension of more than three-fourths of the lumen has been widely-acknowledged as a risk factor for post-procedure stricture, as the incidence of which could be as high as 83.3–94.1% [3, 4]. Endoscopic balloon dilation (EBD) is the conventional therapy for post-procedure stricture, and has achieved remission of dysphagia among most patients [5, 6]. However, repeated procedures are needed in many cases, which inevitably lead to the increased discomfort and financial burden, as well as the increased risk of esophageal perforation. Moreover, there is still a certain number of patients suffering from refractory stricture as the

Dr. Yuan Chu and Dr. Tao Chen have contributed equally to this work.

✉ Meidong Xu
zsxumeidong@yahoo.com

[1] Endoscopy Center, and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, 180 Fenglin Rd, Shanghai 200032, China

current strategies failed to achieve sustained clinical outcome [7].

To date, there are mainly two ways of steroids interventions for the prevention of esophageal stricture after ESD, one is oral prednisolone administration and the other is local triamcinolone injection. Several studies have illustrated the usage of either way for stricture precaution after esophageal ESD, whereas with greatly varying, even divergent outcomes as well as the limited cases [8–14]. Therefore, effective countermeasures are in urgent need to solve this impending medical issue.

Based on these findings and our experience, we carried out a retrospective study to determine the long-term efficacy and safety of the prophylactic steroid injection plus oral steroid administration in preventing stricture after ESD for esophageal epithelial neoplasms among patients with mucosal defects extending no less than two-thirds of the circumference.

Materials and methods

Patients

From May 2014 to July 2016, we enrolled patients with esophageal precancerous lesion or early carcinoma underwent ESD in which the lesion range was larger than one-half of the circumference and caused at least two-thirds of the circumference of the mucosal defect. The eligibility criteria were as follows: (1) no lymph node metastasis on endoscopic ultrasonagraphy (EUS) and computed tomography (CT); (2) no organ failure and non-correctable coagulopathy; (3) no poorly controlled diabetes mellitus, psychiatric disturbances, osteonecrosis of femoral head, peptic ulceration, and tuberculosis; (4) no achalasia or corrosive and mechanical injuries of the esophagus; and (5) no prior radiation therapy. Those who received endoscopic piecemeal mucosal resection (EPMR) for the lesion and post-ESD surgery were excluded. Patients who received intralesional steroid injection combined with oral administration were enrolled in the treatment group, whereas those who were treated without any prophylaxis of the esophageal stricture were enrolled in the control group. The basic demographic and clinical characteristics were collected, including age, sex, tumor location, depth of tumor invasion, maximum diameter of resected specimen and range of the esophageal circumference. The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975 and was approved by the Institutional Review Board of Zhongshan Hospital.

ESD procedure

All of the procedures were conducted by endoscopists at our center who have completed more than 100 ESD esophageal operations prior to this study. All patients were treated under general anesthesia with tracheal intubation. A high frequency generator (VIO 200D; ERBE, Tübingen, Germany) was used as the electrosurgical unit. After the tumor outlines had been delineated by iodine staining, marker dots were placed approximately 5 mm outside its margin by cautery using argon plasma coagulation (APC; ERBE) or a dual-knife (Olympus Corporation, Tokyo, Japan). Following submucosal injection of mixed solution (normal saline containing 0.4% indigo carmine and 0.025 mg/ml epinephrine), mucosal incision and submucosal dissection were performed by various knives, including a hook knife (KD-620LR; Olympus), an insulated-tip knife (KD-611L, IT2; Olympus), or a hybrid knife (ERBE). Minor bleeding was stopped using the endoscopy knives in a coagulation mode and large vessels were coagulated with a coagrasper (FD-410LR; Olympus). Carbon dioxide (CO_2) gas was used for insufflation with a CO_2 insufflator (UCR; Olympus).

Steroid injection

Immediately after ESD, a single session of intralesional steroid injections with triamcinolone acetonide (Transton; 40 mg/1 ml; Kunming Jida Pharmaceutical Co., Ltd., Kunming, China), which was diluted at 1:4 with saline to make an 8 mg/ml solution, was administered. A 25-gauge needle (Boston Scientific Corporation, Marlborough, USA) was used to inject the solution evenly into the residual submucosal tissue of the ulcer base and margins, with a 0.5–1.0 ml dose at each site (15–30 punctures). The initial injections were performed at the margins of the ulcer, and then linear injections were performed from the distal to the proximal side of the ulcer margin. To avoid perforation and potential muscle injury, injections were not performed in the area where the muscle layer was exposed during ESD. The total amount of triamcinolone acetonide varied from 80 to 120 mg depending on the lesion size.

Oral steroid administration

Oral prednisolone (SPH Sine Pharmaceutical Laboratories Co., Ltd., Shanghai, China) administration was started at a dose of 30 mg/day when oral intake was permitted (usually on the third day post-ESD), tapered gradually (30, 30, 25, 25, 20, 15, 10, and 5 mg for 7 days each) and then discontinued 8 weeks later. 10 mg/days intravenous dexamethasone

was administered when patient was fasting due to fever and chest pain.

Follow-up examinations

Esophagogastroduodenoscopy was performed whenever patients were complained about dysphagia with a score > 2, otherwise it was performed 3, 6, 12 and 24 months postoperatively to evaluate any possible stricture and recurrence. EBD was performed when patients experienced persistent dysphagia to solid food.

The primary observation result was the frequency of stricture after ESD in both groups. The secondary observation results were the number of EBD sessions required to resolve any stricture, complication rate and hospital stays. Stricture was defined as dysphagia to certain solids (dysphagia score 2) or an inability to pass a ≥ 9.8 mm diameter conventional endoscope (GIF-H260; Olympus). Refractory stricture was defined as the requirement for more than three sessions of EBD to resolve the stricture. Dysphagia was evaluated using the Mellow–Pinkas score as follows [15]: 0, able to eat a normal diet; 1, unable to swallow certain solids; 2, able to swallow semi-solid food; 3, able to swallow liquids only; and 4, unable to swallow liquids. Complications mainly included perforation and procedure-related bleeding. Perforation was diagnosed as any visible connective tissue observed during or after the ESD and EBD procedure. Procedure-related bleeding after ESD and EBD was defined as bleeding that required transfusion and/or surgical intervention or bleeding that caused the hemoglobin level to decrease by 2 g/dl.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 19 (IBM SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the means ± standard deviation. Statistical comparison was conducted using the Student's t test for parametric data, and the χ^2 test, Fisher's exact test or Mann–Whitney U test as appropriate for nonparametric data, respectively, with significance assumed at $P < 0.05$.

Results

Patients

There were 90 patients with tumor extending over at least half of the circumferential esophagus being expected to undergo esophageal ESD. Of these, two patients were excluded due to severe diabetes ($n = 1$) and achalasia ($n = 1$), leaving 88 patients eligible before ESD. During the procedure, there were 13 patients excluded due to receiving EPMR. During the follow-up, there were two patients in the treatment group and three patients in the control group being excluded respectively because of receiving esophagectomy. Ultimately, there were 34 patients in the treatment group and 36 patients in the control group that were included (Fig. 1). These patients all had a mucosal defect involving at least two-thirds of the circumference. There was no significant difference in terms of background characteristics between these two groups (Table 1). 91.4% (64/70) of patients have received the en bloc resection with tumor-free lateral and basal margins (R0 resection). If not, as well as with submucosal invaded lesions, radiotherapy was conducted due to the high risks of surgery or unwillingness of patients to receive surgery.

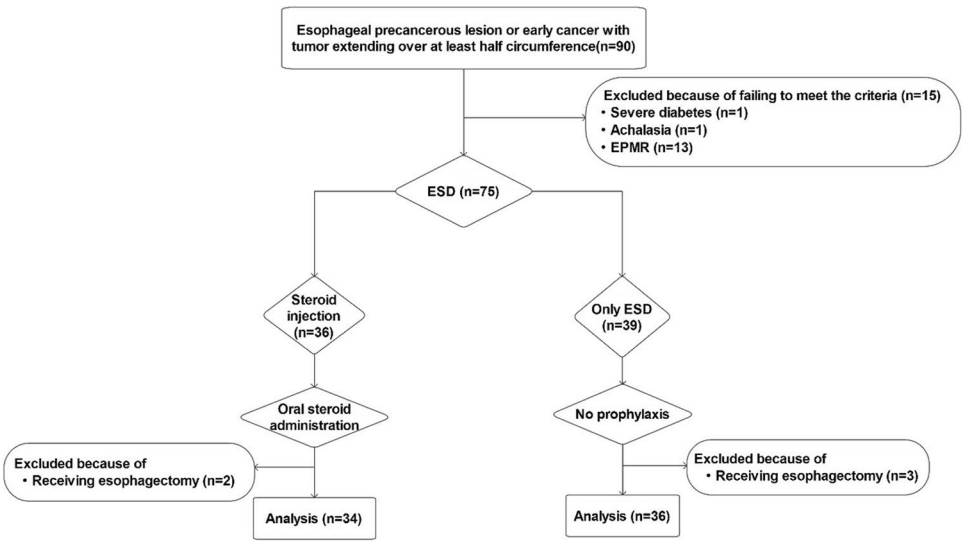

Fig. 1 Flow chart showing recruitment and exclusion of patients for two groups in this retrospective study

Table 1 Background characteristics of two groups

	Treatment group $n=34$	Control group $n=36$	P value
Age, years (mean ± SD, range)	63.7 ± 8.0 (46–80)	64.9 ± 7.2 (47–80)	0.53
Sex			0.86
Male	22	24	
Female	12	12	
Tumor location, *n*			0.38
Cervical esophagus	1	0	
Upper thoracic esophagus	7	5	
Mid-thoracic esophagus	18	21	
Lower thoracic esophagus	8	10	
Esophageal circumference involved, *n*			0.48
2/3–3/4	9	7	
3/4–1	25	29	
Maximum diameter of the resected specimen, mm, mean ± SD (range)	43.3 ± 11.0 (25–80)	40.4 ± 11.1 (26–65)	0.07
Depth of tumor invasion			0.25
M1	9	17	
M2	13	8	
M3	8	6	
SM1	3	3	
SM2/3	1	2	
Rate of R0 resection, *n* (%)	31 (91.2)	33 (91.7)	1.00
Follow-up period, month (mean ± SD, range)	29.4 ± 9.2 (16–41)	27.0 ± 4.8 (19–41)	0.168

SD standard deviation

Table 2 Clinical outcomes of two groups after endoscopic submucosal dissection for epithelial esophageal neoplasms

	Treatment group $n=34$	Control group $n=36$	P value
Frequency of stricture, *n* (%)	5 (14.7)	19 (52.8)	0.001
Frequency of refractory stricture, *n* (%)	0 (0)	11 (30.6)	< 0.001
Dysphagia score			0.001
0	24	15	
1	4	4	
2	4	4	
3	0	4	
4	0	9	
Number of EBDs, *n*, mean ± SD (range)	0.2 ± 0.6 (0–3)	3.3 ± 5.4 (0–23)	< 0.001
Perforation, *n* (%)	1 (2.9)	0 (0)	0.49
Bleeding, *n* (%)	0 (0)	1 (2.8)	1.00
Hospital stays after ESD, days, mean ± SD (range)	3.9 ± 3.7 (1–23)	4.1 ± 1.6 (1–7)	0.73

EBD endoscopic balloon dilation, *SD* standard deviation

Clinical evaluation

As shown in Table 2, the post-ESD frequency of stricture was 14.7% in the treatment group (5/34), which was significantly lower than that of 52.8% in the control group (19/36; $P=0.001$). Additionally, there was no refractory stricture happened in the treatment group while there were 30.6% of patients suffered from refractory stricture (11/36) in the control group ($P<0.001$). Moreover, the dysphagia score was significantly different between the groups (score 0/1/2/3/4: 24/4/4/0/0 vs. 15/4/4/4/9; $P=0.001$) and the number of EBD sessions was significantly lower in the treatment group (mean = 0.2, range 0–3) than that in the control group (mean = 3.3, range 0–23; $P=0.001$). Nevertheless, both

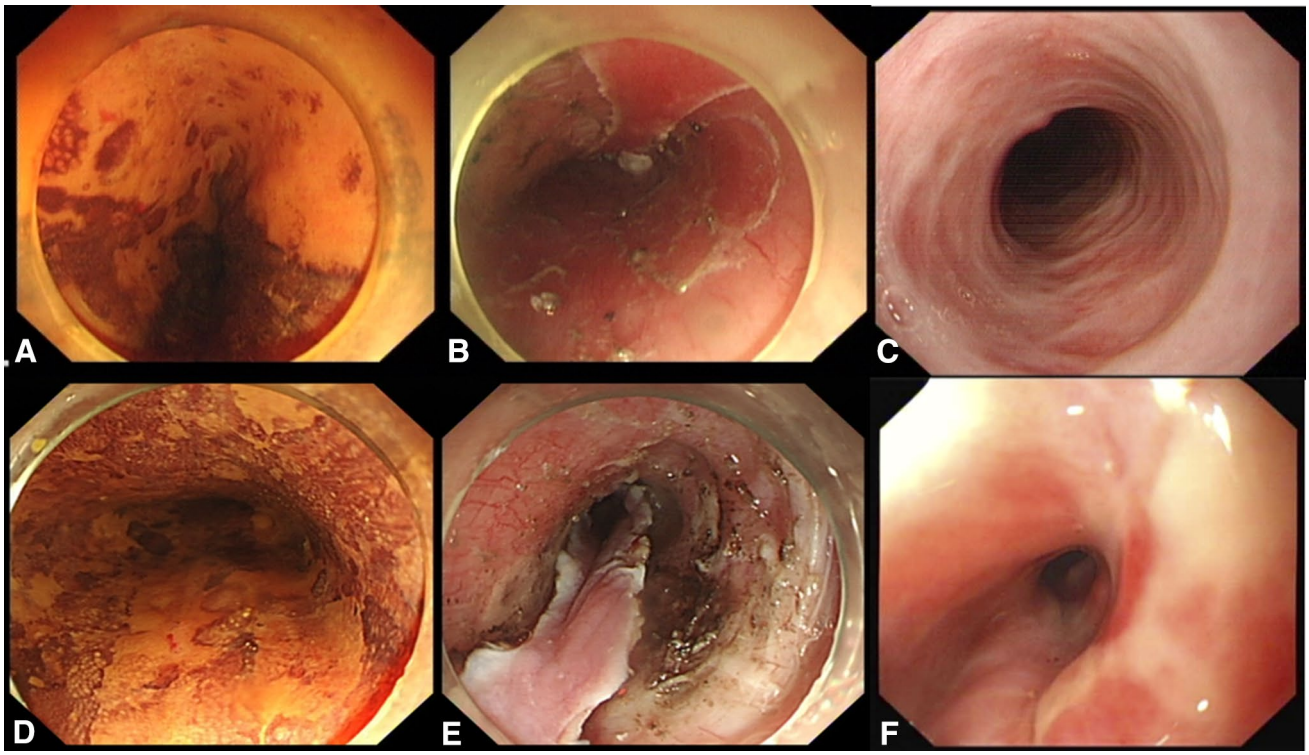

Fig. 2 Endoscopic views of the esophagus in a typical non-stricture case in the treatment group and control group. **A** Chromoendoscopy with iodine staining revealed an unstained area extending over three-quarters of the circumference of the middle-thoracic esophagus; **B** an artificial ulcer resulting in a mucosal defect affecting near-whole circumference created by ESD; **C** no evidence of stricture under esophagogastroduodenoscopy after single triamcinolone injection combined with oral prednisone administration for consecutive 12 weeks (3 months after ESD); **D** chromoendoscopy with iodine staining revealed an unstained area extending over three-quarters of the circumference of the middle-thoracic esophagus; **E** an artificial ulcer resulting in a mucosal defect affecting about four-fifths of circumference created by ESD; **F** severe stricture under esophagogastroduodenoscopy (1 month after ESD)

Table 3 Subgroup analysis of patient with mucosal defects affecting whole or near-whole circumference (> 90% circumference)

	Treatment group $n=11$	Control group $n=18$	*P* value
Frequency of stricture, *n* (%)	2 (18.2)	15 (83.3)	0.001
Frequency of refractory stricture, *n* (%)	0 (0)	10 (55.6)	0.003
Dysphagia score			< 0.001
0	8	3	
1	1	1	
2	2	1	
3	0	4	
4	0	9	
EBDs, *n*, (mean ± SD, range)	0.4 ± 1.0 (0–3)	6.1 ± 6.5 (0–23)	0.001
Hospital stays after ESD, days, (mean ± SD, range)	3.6 ± 1.5 (2–7)	4.4 ± 2.0 (1–7)	0.29

EBD endoscopic balloon dilation, *SD* standard deviation

groups had similar post-ESD hospital stays (mean = 3.9, range 1–23 vs. mean = 4.1, range 1–7, $P = 0.73$). Representative cases in two groups are shown in Fig. 2.

As demonstrated in Table 3, in addition, regarding to the subgroup of patients with whole or near-whole (larger than 90% of circumference) circumferential defects, the post-ESD stricture rate was significantly higher in the control group (83.3%, 15/18) than that in the treatment group (18.2%, 2/11; $P = 0.001$). Besides, no patients suffered from refractory stricture after EBD in the treatment group, whereas 55.6% of patients suffered from refractory stricture in the control group (10/18; $P = 0.003$). The number of EBD sessions was

significantly lower in the treatment group (mean = 0.4, range 0–3) than that in the control group (mean = 6.1, range 0–23; $P = 0.001$).

Adverse events

In the treatment group, one patient experienced dyspnea 3 days after ESD. Pneumothorax and mediastinal emphysema were confirmed by chest CT scan and delayed perforation of the post-ESD ulcer bed was confirmed by esophagogastroduodenoscopy. This patient was treated with fasting, antibiotics and chest tube insertion, and discontinued oral steroid administration. After 2 weeks, the perforation healed, which was confirmed by endoscopic examination, and this patient started eating and steroid administration. In the control group, one patient had procedure-related bleeding 1 day after ESD, and received endoscopic hemostasis, which successfully controlled the bleeding. During a long-term follow-up, there were no complications related to EBD itself or adverse events related to oral steroid administration. No local recurrence, metastatic tumors, or treatment-related mortalities were found.

Discussion

Esophageal ESD was accompanied by a potential risk of complications, and post-procedure stricture is a common one for patients with large circumferential lesions. This adverse event often leads to dysphagia that inevitably decreases patients' quality of life. In this scenario, it is of great importance to manage this complication properly. Current treatments, including EBD and stent placement, are not always successful in dealing with stricture, thus repeated procedures are often necessary. Preventive countermeasures are demanded to meet this impending medical issue. Steroid is a drug which can inhibit fibrosis and inflammation by reducing collagen systhesis as well as fibroblast proliferation, and promoting fibroblast degeneration and inhibition of growth, thus has a potential effect of preventing postoperative esophageal stricture [16, 17]. The application of steroid in post-ESD stricture prevention has been firstly introduced by Hashimoto and his team [8]. According to Hashimoto et al., after multiple sessions of intralesional triamcinolone injection, a remarkable reduction of stricture rate (19%) was observed compared with that in control group (75%). However, these repeated injections are obviously not time- and cost-efficient. In another study regarding locoregional triamcinolone injection in a single session after ESD, 10% stricture rate was exhibited by Hanaoka et al. [11]. This result is encouraging whereas intralesional steroid injection was not always that effective. In a study where patients were endoscopically injected with triamcinolone acetonide immediately after ESD procedure, the frequency of stricture was as high as 62.5% (10/16) in treatment group, which has no significant difference with that in control group (87.5%, 14/16) [14]. In our early clinical practice, we didn't get promising results after only injecting triamcinolone acetonide either. According to a case report, two patients with esophageal benign strictures that didn't react to local steroid injection were healed by systemic methylprednisolone administration [18]. Meanwhile, Yamaguchi et al. [10] reported the usefulness of oral prednisolone in the prevention of post-ESD stricture, with a promising result that the stricture rate was only 5.3% (1/19). It seems that the systemic steroid administration is superior over local injection in stricture precaution. However, in their study, the definition of stricture was different from us (the frequency of post-procedure esophageal stricture was assessed 3 months after treatment ended), which may lead to a lower probability of stricture. Nevertheless, there were still evidences proving that the oral steroid administration alone was not satisfactory in preventing post-ESD stricture in patients with whole circumferential defect [12]. Therefore, in our study, we take advantage of both methods and applied the combination of intralesional and systemic steroid, which resulted in a decreased stricture rate of 14.7% (5/34) compared with that in control group (52.8%, 19/36). In addition, another potential advantage of combined steroid strategy is that it can help prevent refractory stricture (the requirement for more than three sessions of EBD to resolve the stricture). In Hanaoka et al.'s study, 18.9% (24/127) patients were found to suffer from refractory stricture, while no patients were found in our study [19]. Although the number of cases in our research is relatively small, we think combined strategy can decrease the severity of stricture if it happens. More studies are needed to prove the efficacy of steroid in preventing refractory stricture.

In our study, a mucosal defect of no less than two-thirds of esophageal circumference, including whole circumference was defined as the inclusion criteria, which seemed to be quite divergent with previously established risk factor of three-quarters [3]. It's necessary to take preventive measures among patients with mucosal defects of no less than two-thirds of the circumference as the frequency of stricture was high in accordance with previous studies. Ono et al. and our team have revealed respectively that there was still 23.5% (4/17) and 27.6% (8/29) of patients who had lesions extending to between one-half and three-quarters of the circumference, which usually cause at least two-thirds of the circumference of the mucosal defect, inevitably suffered from stricture if preventive measurements were not conducted [3, 4]. Moreover, some studies tended to exclude patients with a defect extending over the whole circumference because according to the previous researches, this kind of defect would definitely develop extremely severe stricture

therefore with a relative contraindication for ESD [11]. Takahashi et al. [14] has reported all ten cases of patients involving the whole esophageal circumference who experienced stricture, even if five patients received local injection of triamcinolone. Similarly result was achieved by Kataoka el al [13] as two patients with complete circular ESD have both suffered from post-operative stricture with no exception. However, in the same study, with oral prednisolone administration post-operatively for 3 weeks, only one out of three patients with whole circumference defect has still withstood stricture, which was relieved after twice EBD. Accordingly, in our study, after treated with the combined steroids, the stricture rate of patients with a whole or near-whole circumference defect was only 18.2% (2/11), which is significantly lower than that in control group (83.3%, 15/18). Most importantly, there was no refractory stenosis happened. Surprisingly, in another study of 12 patients with whole circumferential defect, same steroid combination therapy as ours was performed whereas turned out to fail to protect 11 patients from post-operative stricture [19]. This discrepancy may probably be due to the different dose of orally-taken prednisolone as in this study.

Intra-operative injection is certainly related to a variety of complications including bleeding and perforation. If minor bleeding occurred during injection, there was no need for extra measurements. In our study, one patient was found with perforation 3 days after ESD when she complained of dyspnea. During ESD, there was a muscular laceration. Although metal clips were applied to close the defect, and injections were not performed in the surrounding area, delayed perforation still occurred. ESD procedure, not the injection, should be regarded as the cause of perforation. A case of delayed perforation after triamcinolone injection has been reported by Yamashina et al. [20]. The onset of delayed perforation was probably due to tissue damage caused by the injection into the muscularis propria. Moreover, the EBD procedure before injection may also contribute to the vulnerability of esophageal wall. Of note, direct puncture of the muscularis propria should be avoided. Meanwhile, systemic steroids are related to adverse events, including immunosuppression, psychiatric disturbances, peptic ulceration, diabetes mellitus, fracture, etc. [21]. In our protocol, the cumulative dose of oral steroids was 1120 mg, which was similar to that of other studies, and no patients complained of adverse events related to oral prednisolone [10, 12]. Although this moderate dose of prednisolone was rarely accompanied by severe adverse events, a study found that even short durations of steroid use were associated with increased risks of adverse events [22, 23]. Some of them can be prevented by taking extra drugs, for instance, taking PPI or caltrate to avoid peptic ulceration or fracture. Therefore, the route, timing, and dose for preventive purposes of steroid after esophageal ESD are still controversial and needed to be standardized by further studies.

In addition to steroid, other anti-inflammation or anti-fibrosis drugs, such as mitomycin C, botulinum toxin type A and tranilast have been proved to prevent post-ESD stricture effectively in recent years [24–27]. Additionally, there are studies about the efficacy and safety of biodegradable poly-L-lactic acid stents, epithelial-cell sheets from the oral mucosa or amniotic membrane grafts in preventing stenosis [28–31]. However, only limited cases were included in these studies, and problems of cost-effectiveness and technical difficulties cannot be ignored.

There were several limitations in our study. First, the study was a single-center retrospective analysis and possible bias could not be eliminated. Second, the sample size of the study was relatively small, and future studies with larger sample sizes are needed. Third, the adverse events of oral steroid administration should be monitored more closely by different ways. Fourth, in this retrospective study, patients in the control group didn't receive any prophylaxis after ESD because in our early practice, we were not sure about the efficacy and safety of steroid in stricture prevention, and the result of intralesional steroid alone was not satisfactory.

In conclusion, our study proves that intralesional steroid injection plus oral steroid administration is significantly efficient in preventing esophageal stricture after ESD without an increased incidence of complications among patients whose mucosal defect is larger than two-thirds of circumference in the long-term period.

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Compliance with ethical standards

Disclosure Yuan Chu, Tao Chen, Hongqi Li, Pinghong Zhou, Yiqun Zhang, Weifeng Chen, Yunshi Zhong, Liqing Yao, Meidong Xu have no conflicts of interest or financial ties to disclose.

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