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Efficacy of oral steroid gel in preventing esophageal stricture after extensive endoscopic submucosal dissection: a randomized controlled trial

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Abstract

Background and aims Esophageal stricture is a distressing issue for patients with early esophageal cancer following extensive endoscopic submucosal dissection (ESD), and the current steroid-based approaches are unsatisfactory for stricture prophylaxis. We evaluated the efficacy of oral hydrocortisone sodium succinate and aluminum phosphate gel (OHA) for stricture prophylaxis after extensive ESD.

Methods Patients undergoing > 3/4 circumferential ESD were randomized to either the endoscopic loco-regional triamcinolone acetonide injection (ETI) plus oral prednisone group or the OHA group. The primary endpoint was incidence of esophageal stricture, and the secondary endpoints included adverse events (AEs) and endoscopic balloon dilations (EBDs).

Results The incidence of esophageal stricture in OHA group (per-protocol analysis, 9.4%, 3/32; intention-to-treat analysis, 12.1%, 4/33) was significantly less than that of control group (per-protocol analysis, 35.5%, 11/31, $P=0.013$; intention-to-treat analysis, 39.4%, 13/33, $P=0.011$). Two sessions of EBD were necessary to release all strictures in the OHA group, while the similar EBDs (median 2, range 1–4) for 11 of the control. Operation-related AEs included infection (control vs. OHA group = 9.7% vs. 31.3%, $P=0.034$), operation-related hypokalemia (19.4% vs. 31.3%, $P=0.278$), perforation (3.2% vs. 3.1%), post-ESD hemorrhage (6.5% vs. 0%), and cardiac arrhythmia (0% vs. 6.3%). Steroid-related AEs included steroid-related hypokalemia (16.1% vs. 25%) and bone fracture (3.2% vs. 0%). Multivariate logistic regression analysis demonstrated that OHA was an independent protective factor for stricture (OR 0.079; 95%CI 0.011, 0.544; $P=0.01$) and mucosal defect > 11/12 circumference was an independent risk factor (OR 49.91; 95%CI 6.7, 371.83; $P<0.001$).

Conclusions OHA showed significantly better efficacy in preventing esophageal stricture after > 3/4 circumferential ESD compared to ETI plus oral prednisone.

Keywords Early esophageal cancer · Esophageal stricture · Endoscopic submucosal dissection · Steroid

Endoscopic submucosal dissection (ESD) is now widely used for treating early esophageal cancer [1–3]. Its main complications are hemorrhage, perforation, esophageal stricture, etc. For patients with mucosal defect > 3/4 esophageal circumference, post-ESD stricture is the most important complication affecting patients' quality of life as it leads to dysphagia, vomiting, and the need for endoscopic balloon dilations (EBDs) [4–6].

Dilation with balloon or bougie is the main treatment for post-ESD stricture [7–9]. In addition to operational discomfort, multiple dilations carry risks of esophageal perforation and hemorrhage [10]. Approximately 30 sessions of EBDs are needed to completely relieve stricture following complete circumferential ESD [11]. The application of esophageal self-expandable stents is limited by adverse events (AEs) and post-removal restenosis. Although absorbable stents avoid the risks associated with stent removal, unsatisfactory efficacy and self-dislocation remain considerable issues [12–15].

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Regarding pharmacological treatment, steroid-based approaches have become the mainstream treatment for stricture prophylaxis. Since the two preventive methods of oral steroid and local injection of triamcinolone acetonide were demonstrated in 2011 [16, 17], many studies have examined their efficacy, as well as that of their variants and combinations. These studies have demonstrated that the stricture rate was approximately 29.4% (range from 0 to 50%) among patients with > 3/4 circumferential defects [18–21]. Abe et al. [22] reviewed 21 original relevant articles and concluded that oral and local-injection/administered steroids were the first-line treatment options for stricture prophylaxis. Kadota [21] found that for patients with > 7/8 circumferential ESD, the endoscopic loco-regional triamcinolone injection (ETI) was unsatisfactory, while ETI together with oral steroid was also ineffective for complete circumferential ESD. Therefore, novel approaches are necessary for stricture prophylaxis after extensive ESD.

Hydrocortisone cream for external use in dermatology is absorbed through the skin and to a greater extent in lesions, which may be consistent with the absorption through the esophageal mucosa. Moreover, viscous aluminum phosphate gel continuously provides a local physical barrier and increased hydrocortisone to lesions. We invented oral hydrocortisone sodium succinate and aluminum phosphate gel (OHA) and hypothesized that the aluminum phosphate gel could help to maintain higher local steroid concentration in lesions, suppressing inflammation and preventing stricture formation. Preliminary experiment had shown its superiority, especially in complete circumferential ESD [23]. In this study, we tested the hypothesis that the novel prophylactic method, OHA gel would reduce esophageal stricture incidence after > 3/4 circumferential ESD.

Materials and methods

Study design and participants

The study was registered at https://clinicaltrials.gov/ (NCT03165344), and was a randomized, controlled, open-label, single-center trial of OHA gel in patients with early esophageal cancer undergoing > 3/4 circumferential ESD. Authors who were responsible for data analysis and evaluation of esophageal stricture were blind to group allocation. Primary aims were to determine the efficacy and safety of OHA gel in preventing esophageal stricture after > 3/4 circumferential ESD.

The eligibility criteria were as follows: (1) early esophaealg cancer limited to the mucosal layer, (2) eligible for ESD and expected mucosal defect involving > 3/4 circumference, (3) ≥ 18 years old, and (4) no lymph node metastasis on endoscopic ultrasonography and computed tomography. The exclusion criteria were as follows: (1) ineligibility for ESD, (2) occurrence of perforation requiring conversion to surgery, (3) history of chemo-radiotherapy or surgery for esophageal cancer, or (4) contraindications for ESD, anesthesia, and long-term steroid use (e.g., organ failure, non-correctable coagulopathy, and uncontrolled diabetes mellitus).

This trial was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Peking University Third Hospital Medical Science Research Ethics (M2016171). Written informed consent was obtained from all patients.

Sample size

Based on previous studies and a preliminary experiment, we estimated that 5.3% patients from the OHA group would develop esophageal stricture [23], compared to 29.4% from the ETI plus oral prednisone group [16, 18–21]. We determined that 54 patients (27 per group) would provide a power of 80% to detect a difference between the two groups based on a one-sided α level of 0.05 (PASS 11, NCSS LLC, Kaysville, UT, USA). The sample size was determined to be 66, with an allowance of approximately 20% for drop out.

Randomization

A statistician from the Clinical Epidemiology Research Centre of Peking University Third Hospital created the randomization sequence. The 1:1 randomization sequence was generated using blocks of four. The allocation was prepared in individual sealed opaque envelopes, and patients were randomly assigned to the control group (ETI + oral prednisone) or the OHA group.

Data collection

The collected demographic and clinical characteristics included age, sex, lesion location (upper, middle, and lower thoracic esophagus, cardiac esophagus), invasive depth (dysplasia-M1-M2, M3-SM1, SM2), vertical margin residue, mucosal defect percentage (%), circumference of mucosal defect (3/4 to 5/6, 5/6 to 11/12, 11/12 to 1, 1), longitudinal length, en bloc resection, AEs (e.g., infection, hypokalemia, perforation, hemorrhage, bone fracture, and so on), delay of oral steroid application and delayed days, dysphagia occurrence time, stricture incidence, number of sessions of EBDs, and follow-up time. If patients demonstrated infection after ESD and oral steroid application was delayed for several days, "delayed days of steroid application" were recorded.

ESD procedure

All ESDs were performed with patients under general anesthesia and tracheal intubation and were completed by an experienced chief physician from our center. Lesions were stained with iodine, and marker dots were placed 5 mm outside the margin. After submucosal injection of 0.005% adrenaline, glycerol fructose, and methylene blue solution, lesion dissection was completed by mucosal incision and submucosal dissection using IT-NANO knives (KD-612U; Olympus Corporation, Tokyo, Japan) and Dual knives (Olympus Corporation, Tokyo, Japan), followed by hemostasis. The mucosal defect percentage was measured based on the intraoperative photography when the esophageal lumen was spread to its maximum width using full insufflation (Fig. 1D). The mucosal defect percentage was calculated as follows: $100\% \times (360^\circ - \alpha)/360^\circ$, where angle α is the peripheral angle occupied by the residual esophageal mucosa where the circumferential mucosal defect is the greatest.

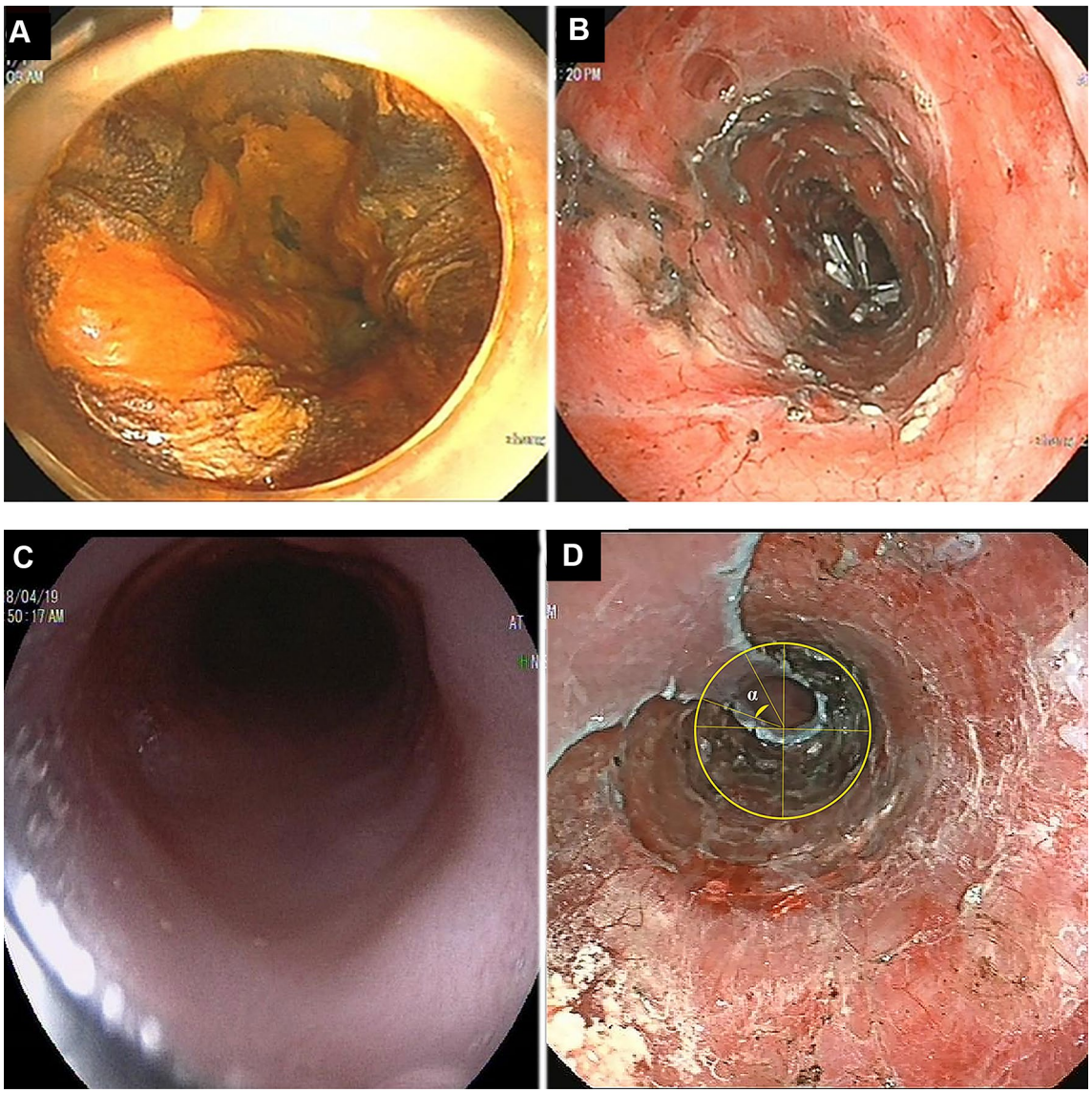

Fig. 1 Endoscopic views of the esophagus of a case from the OHA group. **A** Esophageal cancer extends to almost the entire circumference. **B** The entire circumferential mucosal defect after ESD. **C** Follow-up endoscopy 3 months after ESD showed no esophageal stricture after complete circumferential ESD. **D** Schematic diagram demonstrating the measurement of the degree of the mucosal defect (mucosal defect percentage = $100\% \times (360^\circ - \alpha)/360^\circ$), where angle α is the peripheral angle occupied by the narrowest residual esophageal mucosa. *ESD* endoscopic submucosal dissection, *OHA* oral mixture of hydrocortisone sodium succinate and aluminum phosphate gel

Steroid regimens

In the control group, immediately after ESD, patients received a single session of loco-regional injection of 80 mg triamcinolone acetonide which was diluted with saline to 4 mL and injected into 8–10 points in the residual submucosal tissue of the ulcer bed using a 25-gage, 4-mm needle. Oral prednisone was started at 24 h after ESDs and tapered over 8 weeks (Fig. 2A) if no AEs, e.g., infection or perforation, occurred within 24 h of ESD. Accidental injection of steroid into the muscularis propria was avoided, as it may cause delayed perforation and muscularis propria necrosis.

For the OHA group, after exclusion of infection and perforation within 24 h of ESD, OHA was initiated and tapered over the following 8 weeks (Fig. 2B). One unit of OHA comprised 50/25/12.5 mg hydrocortisone sodium succinate and 20 g aluminum phosphate gel. The patients were instructed to fast for 2 h before taking OHA, lay flat for 1 h, roll sideways several times, and continue fasting for another 2 h. The OHA gel was produced by dissolving one vial of hydrocortisone sodium succinate (each vial contained 50 mg hydrocortisone) with 2 ml saline and mixing with 20 g aluminum phosphate gel in a 50 ml cup. When preparing a unit containing 25 mg hydrocortisone, 1 ml was extracted from the 2 ml hydrocortisone sodium succinate solution to be mixed with the 20 g aluminum phosphate gel. Similarly, 0.5 ml was extracted for the 12.5 mg preparation.

Following ESDs, all participants fasted for 3 days, followed by liquid food for 2 days, and semisolid food for 1 day. Within 72 h of ESD, the mixture of 20 g aluminum phosphate gel and 1000 units of thrombin dissolved by 10 ml saline was swallowed four times daily by all participants. The participants of the OHA group had 50 mg hydrocortisone sodium succinate added to the above mixture when no infection and perforation occurred within 24 h of ESD. Proton pump inhibitors (PPIs) were administered for 3 months. Patients encountering esophageal stricture and undergoing EBD were also followed by one session of OHA regimen. Patients received calcium and vitamin D supplement to prevent osteoporosis and fracture.

Endpoints

The primary endpoint was the incidence of esophageal stricture at 3 months after ESD. Esophageal stricture was defined as the impossibility of passing a standard 9.2-mm endoscopy through the lumen [14, 24]. The secondary endpoints included AEs (e.g., infection, hypokalemia, perforation, hemorrhage, bone fracture, etc.) and the number of EBD. AEs were grouped by their relation with operation and steroid. Patients undergoing ESD operation with general anesthesia may develop complications such as infection, perforation, hemorrhage, cardiac arrhythmia, and so on. After steroid regimens started, some systemic AEs may also occur. Those patients who reported infection symptoms (such as fever, cough, and trembling), positive signs, and supportive laboratory and radiologic evidence (such as elevated white blood cells and procalcitonin, and typical radiologic image of respiratory infection) within 24 h after ESD, were diagnosed as post-ESD infection. Once infections occurred, antibiotics were applied and steroid regimens were launched 48 h or 72 h after the patient's temperature returned to normal. Hypokalemia was defined as blood potassium < 3.5 mmol/L, which was classified into operation- or steroid-related hypokalemia based on the occurrence time. Oral steroid treatment started after correcting the hypokalemia. Perforation was diagnosed by corresponding symptoms, signs, and CT scan. Treatment-related

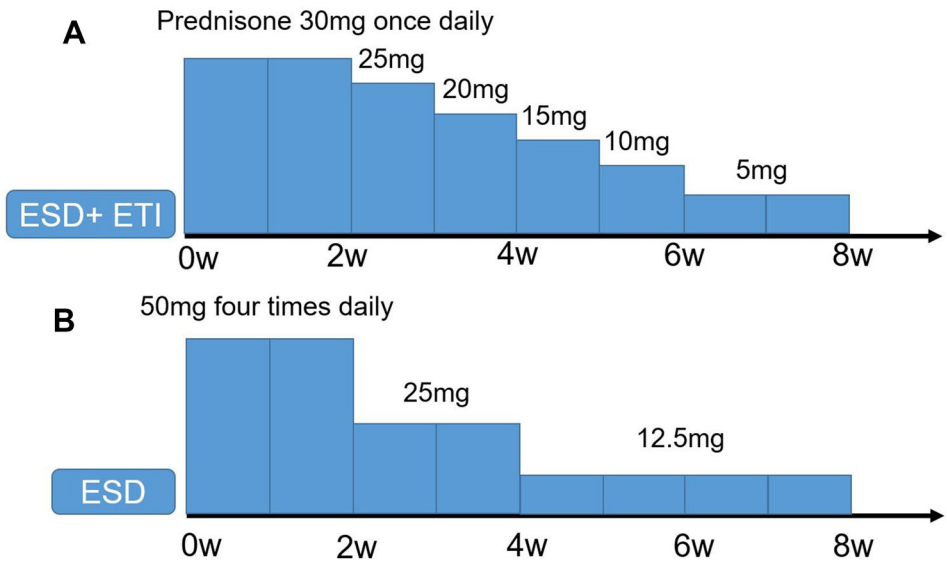

Fig. 2 Both groups received tapered oral steroid for 8 weeks. **A** Control group (ETI plus oral prednisone group): injection of 80 mg triamcinolone acetonide followed by 8 weeks of oral prednisone. **B** Treatment group (OHA group): one unit of OHA gel = 20 g aluminum phosphate gel + 50/25/12.5 mg hydrocortisone sodium succinate dissolved by 2/1/0.5 ml saline. *ESD* endoscopic submucosal dissection, *ETI* endoscopic loco-regional triamcinolone injection, *OHA* oral mixture of hydrocortisone sodium succinate and aluminum phosphate gel

hemorrhage was diagnosed by hematemesis, melena, and hemoglobin decline > 2 g/dL.

Follow-up

Follow-ups lasted at least 3 months, all of which ended in December 2019. Since the majority of esophageal strictures after ESD occur within 4 weeks, a 3-month follow-up was considered to be sufficient and has been shown to rarely lead to underestimation [16, 25]. We conducted a telephone follow-up with every participant and their families every 2 weeks in order to improve medical compliance. All participants received outpatient follow-up 1 month after ESD, and endoscopy followed at 3 months to evaluate the esophageal lumen and local residual tumor or recurrence. If suspicious lesions were observed, biopsy and lesion resection followed. Two specially trained doctors questioned patients about dysphagia or other symptoms. After 6 and 12 months, patients underwent other endoscopies, and patients who encountered dysphagia associated with semisolid foods (Mellow-Pinkas score ≥ 2) also received endoscopies. Patients with definite esophageal strictures underwent several sessions of EBD followed by the OHA regimen until completely relieved.

Statistical analysis

Continuous variables, presented as mean ± SD, were tested for normal distribution using the Kolmogorov–Smirnov test and were compared by Student's *t* test (normal distribution), or as median (range) and analyzed using the Mann–Whitney U test (skewed distribution). Categorical variables were analyzed using the Pearson chi-square test or the Fisher's exact test. Independent predictive variables were determined with univariate and multivariate logistic regression analysis by the method of Forward LR after initial screening by chi-square test. A two-sided p value < 0.05 was considered statistically significant. Intention-to-treat analysis and per-protocol analyses were performed. All analyses were conducted using SPSS 19.0 (IBM, Armonk, NY, USA).

Results

Patients

During the study, 66 patients were included in the intention-to-treat analysis. Three patients were excluded because they received additional radiotherapy, or surgical treatment for positive vertical margin residue. Post-ESD histopathology confirmed that 4.8% (3/63) invaded the middle layer of the submucosa; it was unclear whether the vertical margins were free of tumor residue. They chose to continue oral steroid administration and refused further surgery or chemo-radiotherapy. Afterwards, no evidence of recurrence or metastasis was observed by several endoscopies and CT scans after 8, 15, and 24-months follow-ups, respectively. Consequently, 63 patients (the control vs. OHA group = 31 vs. 32) were included in the per-protocol analysis (Fig. 3). In Table 1, there was no significant difference between two groups regarding demographic and basic clinical characteristics except delayed application of steroid (the control vs. OHA group = 16.1% [5/31] vs. 40.6% [13/32], $P = 0.031$). The delay time was similar in both groups (4.6 vs. 4.9 days, $P = 0.779$).

Outcomes

As shown in Table 2, the stricture incidence of the OHA group (per-protocol analysis, 9.4%, 3/32; intention-to-treat analysis, 12.1%, 4/33) was significantly less than that of the control (per-protocol analysis, 35.5%, 11/31, $P = 0.013$; intention-to-treat analysis, 39.4%, 13/33, $P = 0.011$). Dysphagia of 3 patients from the OHA group was completely relieved after a median 2 (range, 2–2) sessions of EBD, and 11 from the control required a median of 2 (range, 1–4)

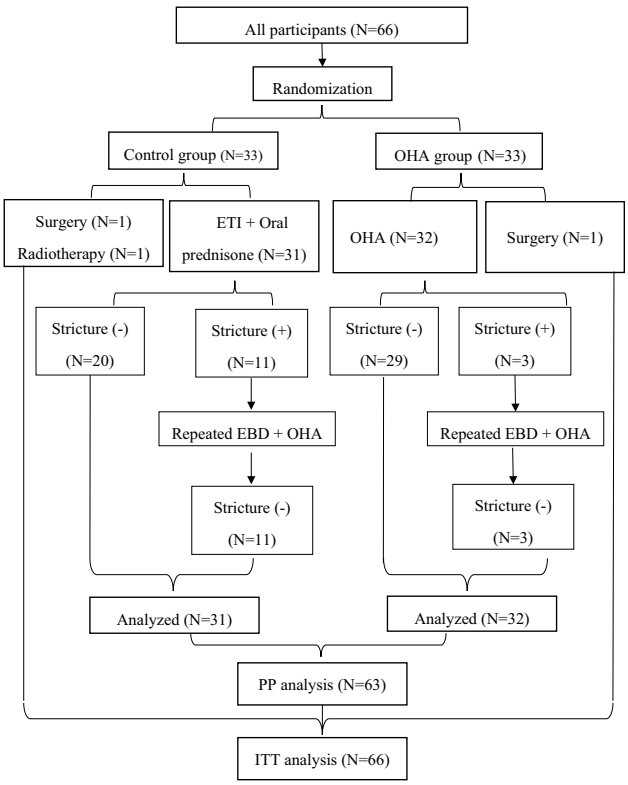

Fig. 3 CONSORT 2010 Flow Diagram. Details on participants' enrollment, randomization, allocation, and follow-up and analysis are presented. *EBD* endoscopic balloon dilation; *ETI* endoscopic loco-regional triamcinolone injection; *ITT* intention-to-treat; *OHA* oral hydrocortisone succinate sodium and aluminum phosphate gel; *PP* per-protocol

Table 1 Demographic and basic clinical characteristics of patients

Characteristics	Total $N=63$	Control $n=31$	OHA $n=32$	P value
Age, years (median [range])	65 (41–85)	63 (48–84)	67 (41–85)	0.113
Sex, *n* (%)				0.252
Male	49 (77.8)	26 (83.9)	23 (71.9)	
Female	14 (22.2)	5 (16.1)	9 (28.1)	
Lesion location extent, *n* (%)				
Upper thoracic esophagus	10 (15.9)	7 (22.6)	3 (9.4)	0.276†
Middle thoracic esophagus	44 (69.8)	21 (67.7)	23 (71.9)	0.721
Lower thoracic esophagus	34 (54.0)	14 (45.2)	20 (62.5)	0.167
Cardiac esophagus	5 (7.9)	1 (3.2)	4 (12.5)	0.371†
Invasion depth				0.772‡
≤M2	40 (63.5)	20 (64.5)	20 (62.5)	
M3, SM1	20 (31.7)	9 (29)	11 (34.4)	
SM2/3	3 (4.8)	2 (6.5)	1 (3.1)	
Vertical margin residue, *n* (%)	3 (4.8)	2 (6.5)	1 (3.1)	0.978†
Circumferential percentage of mucosal defect (%), mean ± SD	88.2 ± 7.7	88.8 ± 7.6	87.7 ± 7.8	0.584
Circumference of mucosal defect				1.000‡
3/4 to 5/6	19 (30.2)	9 (29)	10 (31.3)	
5/6 to 11/12	23 (36.5)	11 (35.5)	12 (37.5)	
11/12 to 1	9 (14.3)	5 (16.1)	4 (12.5)	
1	12 (19.0)	6 (19.4)	6 (18.8)	
Longitudinal length, cm (mean ± SD)	7.6 ± 2.6	7.6 ± 2.6	7.5 ± 2.6	0.979
En bloc resection, *n* (%)	58 (92.1)	28 (90.3)	30 (93.8)	0.970†
Delayed application of steroid				0.031
Yes	18 (28.6)	5 (16.1)	13 (40.6)	
No	45 (71.4)	26 (83.9)	19 (59.4)	
Delayed days of steroid application, mean ± SD	4.8 ± 2.1	4.6 ± 2.5	4.9 ± 2.0	0.779
Dysphagia occurrence time, week (median [range])	4 (2–12)	4 (2–12)	8 (4–8)	0.291
Follow-up, month (mean ± SD)	15.5 ± 6.7	15.5 ± 7	15.6 ± 6.5	0.919

OHA oral mixture of hydrocortisone sodium succinate and aluminum phosphate gel, *M2* tumor invades laminar propria, *M3* tumor involves muscularis mucosa, *SM1* tumor invades < 200 μm from the muscularis mucosa, *SM2/3* tumor invades ≥ 200 μm from the muscularis mucosa, *SD* Standard deviation

†Correction for continuity, ‡Fisher's exact test. Other variables were tested by Pearson Chi-square test, Student's *t* test, and Mann–Whitney U test

EBDs. All strictures were followed by the OHA regimen to prevent restenosis. The characteristics of patients with stricture are summarized in Table 3.

In Table 2, AEs were grouped according to relation with operation and steroid. Operation-related AEs included infection (control vs. OHA group = 9.7% vs. 31.3%, $P=0.034$), operation-related hypokalemia (19.4% vs. 31.3%, $P=0.278$), perforation (3.2% vs. 3.1%), post-ESD hemorrhage (6.5% vs. 0%), and cardiac arrhythmia (0% vs. 6.3%). Steroid-related AEs included steroid-related hypokalemia (16.1% vs. 25%) and bone fracture (3.2% vs. 0%).

In total, 7 cases of severe AEs were reported. One patient from the control group encountered esophageal perforation after minor injury of the annular muscle during ESD. Although titanium clips were used in time, subcutaneous and mediastinal emphysema occurred within post-ESD 24 h. Another one from OHA group also suffered from transient atrial fibrillation in addition to perforation. Both patients fully recovered after gastrointestinal decompression and conservative treatments. One patient of the control group complained of tarry stools and was flustered and weak on the 10th day after ESD. She was diagnosed with gastrointestinal major hemorrhage and quickly controlled by conservative treatment of fasting, PPIs, blood transfusion, and discontinued administration of oral steroids. Another patient of the control group had minor hemorrhage on the 2nd day and was cured after similar treatments. A 76-year-old female of the control group countering stricture suffered from two instances of spine vertebral compression fractures before and after the fourth EBD. A male of OHA group suffered a short burst of ventricular tachycardia and frequent premature ventricular contractions during postoperative

Table 2 Primary and secondary endpoint results

	Total $n=63$	Control $n=31$	OHA $n=32$	P value
Stricture, *n* (%), PP analysis	14 (22.2)	11 (35.5)	3 (9.4)	0.013
Stricture, *n* (%), ITT analysis	17 (25.8)	13 (39.4)	4 (12.1)	0.011
Operation-related AE, *n* (%)				
Infection	13 (20.6)	3 (9.7)	10 (31.3)	0.034
Operation-related hypokalemia	16 (25.4)	6 (19.4)	10 (31.3)	0.278
Perforation	2 (3.2)	1 (3.2)	1 (3.1)	1.000[†]
Post-ESD hemorrhage	2 (3.2)	2 (6.5)	0	0.238[†]
Cardiac arrhythmia	2 (3.2)	0	2 (6.3)	0.492[†]
Steroid-related AE, *n* (%)				
Steroid-related hypokalemia	13 (20.6)	5 (16.1)	8 (25)	0.384
Bone fracture	1 (1.6)	1 (3.2)	0	0.492[†]
Number of EBD (median [range])	2 (1–4)	2 (1–4)	2 (2–2)	1.000

OHA oral mixture of hydrocortisone sodium succinate and aluminum phosphate gel, *PP analysis* Per-Protocol analysis, *ITT analysis* Intention-To-Treat analysis, *AE* adverse event, *ESD* endoscopic submucosal dissection, *EBD* endoscopic balloon dilation

[†]Fisher's exact test. Other variables were tested by Pearson Chi-square test and Mann–Whitney U test

Table 3 Characteristics of patients with esophageal stricture post-ESD

No.	Sex & age	Circumferential extent	Distance from incisors (cm)	Preventing method	Delayed days of steroid	Dysphagia occurrence time (weeks)	Time of EBD	SAEs
1	M/63	11/12–1	25–33	ETI + oral	0	12	1	No
2	M/62	11/12–1	19–30	ETI + oral	7	4	3	Bleeding
3	M/52	1	19–26	ETI + oral	0	3	1	Perforation
4	M/72	1	30–40	ETI + oral	0	12	1	No
5	F/76	11/12–1	18–26	ETI + oral	0	3	4	Fracture
6	M/63	11/12–1	29–34	ETI + oral	0	4	1	No
7	M/61	1	18–24	ETI + oral	0	5	3	No
8	M/48	1	24–35	ETI + oral	0	2	3	No
9	M/65	1	15–22	ETI + oral	4	4	2	No
10	F/60	5/6–11/12	20–24	ETI + oral	0	3	3	No
11	M/70	5/6–11/12	29–35	ETI + oral	0	4	1	No
12	M/41	1	30–42	OHA	3	4	2	No
13	F/63	1	23–30	OHA	7	8	2	No
14	F/67	1	19–27	OHA	0	8	2	No

EBD endoscopic balloon dilation, *SAEs* severe adverse events, *ETI* endoscopic loco-regional triamcinolone injection, *OHA* oral hydrocortisone sodium succinate and aluminum phosphate gel

anesthesia recovery; this stopped after intravenous injection of lidocaine.

No EBD-related complications were observed, and no local recurrence or metastasis was observed during follow-up.

Risk factors for stricture

Primary analysis of the association between stricture and categorical variables showed that several variables may be related to stricture, i.e., tumors involving the upper thoracic esophagus or not involving the lower thoracic esophagus, and the circumference of the mucosal defect (Table 4). Multivariate logistic regression analysis demonstrated that OHA was an independent protective factor for stricture (OR 0.079; 95%CI 0.011, 0.544; $P=0.01$) and mucosal defect > 11/12 circumference was an independent risk factors (OR 49.91; 95%CI 6.7, 37.183; $P<0.001$) (Table 5).

Table 4 Univariate predictors of esophageal stricture formation following extensive ESD

Characteristics	Stricture, *n* (%)		Total stricture, *n* (%)	*P*
	Control *n* = 31	OHA *n* = 32		
Sex				0.492†
Male	9 (34.6)	1 (4.3)	10 (20.4)	
Female	2 (40)	2 (22.2)	4 (28.6)	
Lesion location extent				
Upper thoracic esophagus	6 (85.7)	1 (33.3)	7 (70)	0.001†
Middle thoracic esophagus	5 (23.8)	3 (13)	8 (18.2)	0.324†
Lower thoracic esophagus	2 (14.3)	1 (5)	3 (8.8)	0.007†
Cardiac esophagus	0	1 (25)	1 (20.0)	1.000†
Invasion depth				0.670†
≤ M2	7 (35)	1 (5)	8 (20)	
M3, SM1	3 (33.3)	2 (18.2)	5 (25)	
SM2/3	1 (50)	0	1 (33.3)	
Vertical margin residue	1 (50)	0	1 (33.3)	0.536†
Circumference of mucosal defect				< 0.001†
3/4 to 5/6	0	0	0 (0)	
5/6 to 11/12	2 (18.2)	0	2 (8.7)	
11/12 to 1	4 (80)	0	4 (44.4)	
1	5 (83.3)	3 (50)	8 (66.7)	
En bloc resection, *n* (%)				1.000†
Yes	10 (35.7)	3 (10)	13 (22.4)	
No	1 (33.3)	0	1 (20)	
Delayed application of steroid				1.000†
Yes	2 (40)	2 (15.4)	4 (22.2)	
No	9 (34.6)	1 (5.3)	10 (22.2)	

ESD endoscopic submucosal dissection, *OHA* oral mixture of hydrocortisone sodium succinate and aluminum phosphate gel, *M2* tumor invades laminar propria, *M3* tumor involves muscularis mucosa, *NA* not applicable, *SM1* tumor invades < 200 μm from the muscularis mucosa, *SM2/3* tumor invades ≥ 200 μm from the muscularis mucosa

†Fisher's exact test. Other variables were tested by Pearson Chi-square test

Table 5 Logistic regression analysis between high-risk variables and esophageal stricture

	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P*	OR	95%CI	*P*
Lesion location extent						
Upper thoracic esophagus	15.33	3.19, 73.62	0.001	–	–	–
Lower thoracic esophagus	0.16	0.039, 0.64	0.010	–	–	–
Circumferential extent of mucosal defect						
3/4 to 11/12	1.00	–	–	1.00	–	–
> 11/12	26.67	5.06, 140.59	< 0.001	49.91	6.70, 371.83	< 0.001
Prophylactic methods						
ETI + oral prednisone	1.00	–	–	1.00	–	–
OHA	0.19	0.046, 0.761	0.019	0.079	0.011, 0.544	0.01

The entry method was forward LR

OR odds ratio, *CI* confidence interval, *ETI* endoscopic loco-regional triamcinolone injection, *OHA* oral hydrocortisone sodium succinate and aluminum phosphate gel

Discussion

This is the first randomized controlled trial to test the protective effect of OHA among patients undergoing > 3/4 circumferential ESD against esophageal stricture. This study demonstrated significantly better efficacy and similar safety of OHA in preventing esophageal stricture compared to ETI plus oral prednisone. OHA also showed benefits in preventing esophageal restenosis and need less EBDs for releasing strictures compared with previous studies [7, 11, 19, 21].

Although ESD has been the mainstream treatment for early esophageal cancer, post-ESD stricture afflicts 83.3–94.1% of patients with > 3/4 circumferential ESD [4, 6]. After formation of the mucosal defect, fibroblasts produce collagen fibers which deposit in the granulation tissue, resulting in scar and stricture. Animal experiments and observations of humans found that the majority of esophageal strictures were evident 2–4 weeks after ESD [6, 26–28]. Steroids could inhibit the local inflammatory response and the maturation of granulation tissue, replace spindle-shaped myofibroblasts with stellate SMA-positive stromal cells arranged haphazardly, and also delay ulcer re-epithelialization for approximately 2 weeks, which was related to the delay and disappearance of strictures [29].

The preventive efficacy of current steroid-based approaches is unsatisfactory, especially for patients undergoing complete circumferential ESD [16, 21, 30]. Only ETI plus oral prednisone for 18 weeks showed a stricture incidence of 36.4% (4/11) for patients after complete circumferential ESD vs. 82% (9/11) for ETI plus oral prednisone for 8-weeks, and 6.2 vs. 19.4 sessions of EBDs were required, respectively [31]. In this study, the control group had a 35.5% stricture rate and reported poor efficacy for complete circumferential ESD (stricture rate 83.3% [5/6]). The reason why stricture incidence of the control group was higher than previous studies (35.5% vs. 29.4%) was that esophageal lesions in the current study were larger than that in previous studies, both in terms of circumference and longitudinal length [18–21]. However, for 5 patients with stricture after complete circumferential ESD, only a median of 2 (1, 1, 2, 3, and 3, respectively) sessions of EBDs were required to completely relieve dysphagia symptom. Our previous study had reported the efficiency of OHA gel at preventing restenosis after EBD of benign esophageal stricture [32]. Consequently, the reduction of required EBDs may attribute to the OHA gel following each EBD.

In OHA group, 0% (0/26) in patients with non-complete circumferential ESD and 50% (3/6) in patients with complete circumferential ESD reported stricture, which was slightly higher than ETI plus oral prednisone for 18 weeks [31]. The dysphagia was relieved after only two sessions of EBD. OHA is a mixture of aluminum phosphate gel and hydrocortisone sodium succinate; the former is a neutral buffer, and the main component aluminum phosphate can form a strong ion buffer system in an acidic environment. The structure of its auxiliary components, agar and pectin, mimics natural mucus to act as a barrier and adheres to the whole ulcer bed for an extended duration. Aluminum phosphate gel could also resist attacks from non-acid reflux. Hydrocortisone cream applied for dermatoses indicated that topical hydrocortisone can be absorbed from normal intact skin and more from broken lesions. Consequently, while protecting the local artificial ulcer from repeated physicochemical stimulation, OHA creates a local microenvironment rich in hydrocortisone that inhibits the local inflammatory response, reduces the production and deposition of collagen fibers, disrupts the originally arranged myofibroblasts, and replaces them with disorderly stromal cells, and ultimately avoids esophageal stricture secondary to the rapid formation of local scars. Furthermore, hydrocortisone can also be absorbed from the digestive tract and affect the wound again through the circulation system in a manner similar to oral prednisone.

This study also found no strictures when the mucosal defect did not exceed 90% circumference, regardless of the prophylactic methods. OHA gel promoted the optimal cut-off value of the mucosal defect percentage for stricture from the 90.6% of ETI plus oral prednisone to 97.9%.

In this study, hypokalemia and infection were the two most common AEs related with ESD operations. The only AEs were related with post-ESD steroid regimens: hypokalemia (control vs. OHA group = 16.1% vs. 25%) and bone fracture (3.2% vs. 0%). Hypokalemia was closely related to the relatively higher mineralocorticoid activity of hydrocortisone, in addition to longer fasting because of infection occurrence after ESD. Even though OHA group reported significantly higher infection prevalence compared with the control, most of them were cured soon after antibiotics treatment. Only 2 patients in each group reported the procalcitonin (PCT) values greater than 0.5 ng/ml. In OHA group, only 4 patients were definitely diagnosed as lung infection, and the remaining 6 patients had symptoms of infection and supportive blood test results. However, the evidences of urinary tract, respiratory tract, and digestive tract infections were insufficient. We thought that their symptoms may be caused by the inflammatory reaction of esophageal post-ESD lesions. The lower infection incidence of the control group could attribute to the anti-inflammation effect of local–regional injection of triamcinolone acetonide. Overall, due to infection, perforation, and other factors, 40.6% (13/32) patients of the OHA group delayed OHA application by 4.9 ± 2.0 days, while 16.1% (5/31) of the control group delayed by 4.6 ± 2.5 days. 3–7 days was the key period for

collagen deposition and fibrosis [33, 34]. Early application of steroids after ESD was more helpful to prevent inflammation and stricture. The fact that OHA group encountered significantly more delayed steroid application provided further evidence of the efficacy of OHA. In terms of severe AEs, the control group reported slightly more than OHA group. During the follow-up, there were no new or uncontrolled cases of hypertension and diabetes, peptic ulcers, severe infection, etc.

The current study has some limitations. First, despite a power of 0.825 showing that the sample size was sufficient, the sample was still small and from a single center, which limits the generalizability of the results. Studies of larger sample sizes across multiple centers are needed to define the optimal dose, duration, and type of drugs. A sub-analysis could have been performed for other findings if there were more patients.

In conclusion, OHA showed significantly better efficacy than ETI plus oral prednisone (stricture rate 9.4% vs. 35.5%, optimal cut-off value 97.9% vs. 90.6%). The circumferential extents of the mucosal defect and prophylactic methods were independently associated with esophageal stricture.

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Author contributions YZ and XY completed the work of follow-up, carried out the initial analysis, and prepared the first draft of manuscript. YH and HC critically reviewed and revised the manuscript. DN, YW, YZ, WY and KL conducted the research and collected the data.

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Compliance with ethical standards

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