Polyglycolic acid sheet and fibrin glue for preventing esophageal stricture after endoscopic submucosal dissection: a historical control study

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A short running title

Prevention against esophageal stricture

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Abstract

Objectives: There have been several reports that steroid administration are effective at preventing strictures after ESD. However, adverse events after steroid use are of great concern. We have reported that shielding with a polyglycolic acid (PGA) sheet and fibrin glue can be useful for prevention of stricture after ESD. We conducted a retrospective analysis of efficiency of shielding with a PGA sheet and fibrin glue for prevention of esophageal stricture compared with intralesional steroid injection.

Methods: ESD was performed on a total of 489 lesions in 400 patients for superficial esophageal cancer from January 2012 to July 2016. Of these, 39 lesions were enrolled in the study group (PGA sheet and fibrin glue) and 31 lesions were enrolled in the control group. The incidence of postoperative stricture at 6 weeks and the number of sessions of endoscopic balloon dilatation (EBD) required to resolve any strictures were evaluated.

Results: The post-ESD stricture rate was 9.1% in the study group (3/33 patients), which was not significantly lower than the stricture rate of 10.3% in the historical control group (3/29 patients; p = 1.00).

The mean number of EBD was 0.057±0.24 in the study group and 1.9±5.1 in the control group, which was not significant (P = 0.95).

Conclusions: PGA sheet and fibrin glue appear to be a promising option for the prevention of esophageal stricture similar to the effect of intralesional steroid injection.

Key words: esophageal cancer, esophageal stricture, Polyglycolic acid (PGA) sheet, intralesional steroid injection, Endoscopic submucosal dissection (ESD)

Introduction

New optical imaging techniques such as narrow-band imaging endoscopy and magnified endoscopy have made it possible to detect esophageal cancer at an early stage. Endoscopic submucosal dissection (ESD) is an efficient, safe, and curative treatment for superficial esophageal cancers to achieve reliable en bloc resection rates regardless of tumor size[1]. The incidence of local recurrence is lower[2] and histological evaluation can be achieved more precisely compared with endoscopic mucosal resection. Because the esophagus is a narrow and hollow organ, esophageal stricture caused by ESD performed for widespread lesions is a major concern and sometimes results in low quality of life, including an inability to ingest food[3]. There are many reports concerning the frequency of strictures after ESD for superficial esophageal cancer, with a reported frequency of stricture ranging from 70% to 90% after creation of a semi-circumferential mucosal defect[4][5].

Recently, there have been several reports that either intralesional steroid injection[6][7] or systemic steroid administration[8] are effective at preventing strictures after ESD. In Japan, prophylactic intralesional steroid injection has become widespread because only one or a few injections are required and the techniques are easy, with an interval of systemic administration of at least 8 weeks. However, potential risks for infection[9], delayed esophageal perforation[10], and reactivation of hepatitis B[11] are associated with steroid administration. Hence, it is necessary to check the general condition carefully including infection status before steroid administration and to be vigilant for adverse events after administration. In Japan, the current situation with increasingly elderly patients being treated, adverse events after steroid use are of great concern. Therefore, safer and more effective preventive methods are desirable. We have reported that shielding with a PGA

sheet (Neoveil, Gunze Co., Kyoto, Japan) and fibrin glue (Bolheal, Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan; or Beriplast P combi-set, CSL Behring Pharma, Tokyo, Japan) can be useful for stricture prevention after ESD[12].

The PGA sheet is an absorbable suture stiffener. According to previous reports, shielding using a PGA sheet with fibrin glue has been applied in many fields of surgery and can prevent scarring and contraction after partial glossectomy[13]. We applied this method to the artificial ulcer after ESD and show that this method would prevent esophageal strictures after ESD for superficial esophageal cancer[12]. The PGA sheet is commercially available and no tissue engineering technique is needed; it can adequately cover the artificial ulcer regardless of its size. The safety level is high. We conducted a retrospective analysis of efficacy of shielding with a PGA sheet and fibrin glue for prevention of esophageal stricture compared with intralesional steroid injection which has been used extensively in Japanese clinical settings.

Materials and Methods

Study group

ESD for superficial esophageal cancer was performed on a total of 489 lesions from January 2012 to July 2016 (Figure 1). Of these, 39 patients were enrolled in the study after they had provided written informed consent. Inclusion criteria were a preoperative assessment that the tumor depth was limited to the lamina propria layer and the assumption that the lesion would be more than half but less than the whole circumference of the mucosal defect after ESD. Exclusion criteria were a history of esophagectomy or radiation therapy, a lesion determined on endoscopy to be located near a scar left after

previous endoscopic resection, a lesion that was located at the cervical or abdominal esophagus, uncontrolled diabetes mellitus, whole circumferential mucosal defect, and current steroid hormone use.

Historical control group

Among the total lesions seen during the study period, intralesional steroid injection was made in 75 lesions. It was thought to be necessary by the operator. Among them, 47 lesions met the following exclusion criteria and excluded in this study. A total of 31 lesions were retrospectively extracted. The exclusion criteria for the control group were the same as for the study group. This study was approved by the institutional review board.

ESD procedure

ESD was performed as reported previously. An EG450-RD5 scope (Fujifilm Medical Co., Ltd., Tokyo Japan) and a dual knife (Olympus Optical Co., Ltd., Tokyo, Japan) were used for ESD. Glycerol with small amounts of indigocarmine and epinephrine was used for injection, and a VIO300 high-frequency generator (Erbe, Tübingen, Germany) was used for radiofrequency ablation. The extent of the lesion was identified by spraying iodine, and dots were marked around the lesion. The lesion was lifted by injecting glycerol into the submucosal layer at the posterior end of the lesion, and submucosal dissection was performed. Next, the same procedure was performed on the anterior end of the lesion. Submucosal dissection was performed sequentially in the posterior direction and the lesion was resected en bloc. Exteriorized small vessels were treated by a hemostatic procedure, and a submucosal injection was given if necessary during submucosal dissection.

Delivery and affixation of the PGA sheet

The method of affixing the PGA sheet has varied over time. In the first period from January 2012 to December 2013, PGA sheets were cut into patches measuring 15 × 7 mm. First, a small amount of fibrinogen was sprayed onto the artificial ulcer, and the PGA sheet patches were placed over the ulcer without overlapping. Fibrinogen and thrombin were then sprayed onto the PGA sheet patches. In the second period from January 2014 to October 2014, PGA sheets were cut into patches measuring 40 × 40 mm. Each patch was then grasped with endoscopic forceps and wrapped around the endoscope, which was then inserted orally to the site of the post-ESD defect. The PGA sheet was anchored to the anal end of the post-ESD mucosal defect using endoscopic clips. The sheet was then deployed so as to cover the entire circumference of the esophagus using several clips. Fibrin glue was instilled along the entire length of the sheet, firmly fixing it to the post-ESD mucosal defect. In the third period from December 2014 to date, PGA sheets were cut into patches measuring 15-20 × 7-10 mm. Each patch was doused with one drop of fibrinogen and then placed over the artificial ulcer. Fibrinogen and thrombin were then sprayed onto the patches (Figure 2).

Steroid injection into submucosal layer of artificial ulcer

Basically, a single session of intralesional steroid injections was undertaken immediately after ESD. When muscle damage was observed during the ESD procedure, steroid was injected several days later. Triamcinolone acetonide (Kenacort; 40mg/1 mL; Bristol-Meyers Squibb Co., Tokyo, Japan) was diluted with saline. A 25-gauge needle was used to inject the solution evenly into the residual submucosal tissue of the ulcer bed in 0.5 mL increments. The initial injections were given at the margins of the ulcer

followed by linear injections given from the distal to the proximal side of the ulcer margin (Figure 3). Additional injections were administered if it was thought to be necessary.

Follow-up after ESD

Patients in the study group (PGA sheet) were fasted for 2 days after ESD to maintain attachment of the PGA sheet, and oral feeding was resumed at least 48 hours after ESD. Endoscopic examination was performed at 1, 4, and 6 weeks after ESD and the prevalence of esophageal stricture was evaluated at 6 weeks. For patients in the control group, oral feeding was resumed the next day after ESD if no severe muscle damage was confirmed during ESD or no fever was observed. Endoscopic examination was performed at 1 and 6 weeks and the prevalence of esophageal stricture was evaluated at 6 weeks. No proton pump inhibitors were administered to any of the patients.

Evaluation parameters

The primary endpoint of this study was the incidence of postoperative stricture at 6 weeks after esophageal ESD. The secondary endpoints were the number of sessions of endoscopic balloon dilatation (EBD) required to resolve any strictures and the rate of adverse events including post-procedure bleeding, perforation, and pneumonia.

Definition of esophageal stricture

Postoperative stricture was defined as the presence of a stenosis of the esophageal lumen that had progressed to the point where a 9.8-mm diameter upper gastrointestinal endoscope (GIF H260; Olympus Co.) could not be passed through it. The day of

stricture occurrence was defined as the day when the stricture was endoscopically confirmed. In addition to the scheduled endoscopies, endoscopy was also performed if the patient began to experience symptoms of dysphagia in swallowing of solid food.

Statistical analysis

Continuous variables were compared using the Mann–Whitney *U* test and categorical variables were compared using the $\chi 2$ test or Fisher's exact test as appropriate. A P value of < 0.05 was considered indicative of statistical significance. All statistical analyses were performed using STATA software (ver. 11, StataCorp LP, Texas, USA).

Results

The clinicopathological characteristics of the study participants are shown in Table 1. Both groups were similar with respect to gender, age, location, endoscopic appearance, histology, tumor invasion depth, tumor size, longitudinal length of ESD ulcer, and the degree of circumferential mucosal defect. The cause of complementary surgery was a tumor of M3 or deeper in all cases and, in addition, positive lymphovascular involvement in 6 cases. No statistical difference was noted between the groups in the number of patients who required additional surgery.

These results are shown in Table 2. The post-ESD stricture rate was 9.1% in the study group (3/33 patients; 95% confidence interval [CI] 0.11-7.06), and was not significantly lower than the stricture rate of 10.3% in the historical control group (3/29 patients; 95% CI 0.14-9.36: p = 1.00). Among 6 patients with stricture, 2 complained of dysphagia, specifically with certain solid foods.

We performed subgroup analysis to clarify the relationship between stricture

development and the extent of ESD (Table 3). In the study group, esophageal stricture developed only when the mucosal defect accounted for >75% of the circumference of the esophagus. In the control group, esophageal strictures developed in 2 cases with a mucosal defect of ≤75% of the circumference and in 1 case with a defect of >75%. No significant difference was noted in the subgroup analysis.

The median number of EBD sessions was 0 in both groups and the mean number of EBD was 0.057±0.24 in the study group and 1.9±5.1 in the control group, which was not significant ($p = 0.95$). Post-ESD bleeding was observed in 1 patient in the study group as an adverse event, in which hemostasis was achieved by endoscopically. No blood transfusion was needed. There was no adverse event during ESD and after shielding with PGA sheet, intralesional injection, and EBD.

In reviewing the patient who developed esophageal stricture after shielding with PGA sheet (Figure 4), it was observed that most of the PGA sheet had detached from the artificial ulcer by 1 week after ESD. Table 4 shows the correlation between the occurrence of the post-ESD stricture and the detachment rate of the PGA sheet in 1 week. There is a significant difference between them ($p=0.021$). In 1 patient in the control group, EBD was required 10 times because of steroid injected 1 week later due to muscle damage during ESD. In the others, EBD was required once or twice. Table 5 shows the correlation between the occurrence of the post-ESD stricture and the interval from ESD to intralesional injection.

Discussion

Of all post-ESD complications, esophageal stricture is the most critical and various measures, especially steroid-based treatment, have been developed to prevent its

occurrence. A systematic review by Barret et al. classified these preventive measures as being a protective, regenerative, anti-proliferative, or mechanical approach[14]. Our method of shielding the ESD site with a PGA sheet and fibrin glue[12] was classified as a protective approach, while a regenerative approach was represented by autologous cell sheets as described by Ohki et al.[15]. In addition, steroid-based treatment was reported to be an anti-proliferative approach. To date, only a few studies have used the PGA sheet. In a recent study of concurrent use of a PGA sheet and steroid, Sakaguchi et al. reported that the occurrence of stricture was 11.1% (1/9) after extensive non-circumferential resection[16]. Tissue-engineered cell sheet transplantation reported by Ohki et al. is attractive, but this is expensive and time-consuming and has not reached the point of practical application at any institution. In contrast, many studies analyzed steroid-based preventive measures against stricture, enabling Wang et al. to perform a meta-analysis, revealing that intralesional steroid injection reduced the incidence of esophageal stricture more effectively than oral steroids[17].

Therefore, we used steroid injection as a historical control group in this study. In Japan, local steroid injection is performed frequently because of its convenience, making the procedure a standard treatment. In addition, because it is currently well-known that stricture occurs with high frequency after extensive resection, it is difficult as well as unethical to have a no-treatment group as control. Taking these into consideration, we retrospectively performed a comparative study of post-ESD patients treated with either PGA sheet or steroid injection. Figure 1 showed the stricture rate was 3.1% in the subjects with no preventative treatment. The risk developing the post-ESD stricture was judged to be low by the operator because the degree of mucosal defects in those all subjects was equal or less than third quarter of the circumference. Therefore, the subjects with no

preventative treatment was not targeted in this analysis.

No significant intergroup difference was observed in the incidence of stricture, which was the primary endpoint of this study. The occurrence of stricture among patients who were treated with PGA sheet was 9.1%, a demonstrably favorable outcome. Despite the increased number of patients in this study, the incidence was almost identical to the incidence we reported previously. Early detachment of the PGA sheet might have been the cause of stricture among these patients. At the 1-week follow-up examination, we found that the PGA sheet had detached from the artificial ulcer, and the area was covered by a white membranous film similar to those found in patients who had not undergone treatment, suggesting that the PGA sheet had detached prematurely after ESD. Therefore, elucidating how to prevent early detachment of the PGA sheet is key to improving the utility of this procedure. From this perspective, techniques used to affix the PGA sheet to the surgical site have changed over time. Early on, the sheet was cut into small patches and then affixed with fibrin glue. Then, after the report by Ono et al. [18], clips were used to immobilize a relatively large PGA sheet. Presently, the PGA strips are soaked with a drop of fibrinogen before being applied onto the ulcer floor. The outcome of the third method is not yet definitive, however, there has been no case of detachment within the first week. The mechanism underlying the prevention of the esophageal stricture when using the PGA sheet has yet to be clarified. However, endoscopic observation of all the cases revealed morphological differences in the ulcer surface between the areas with and without the PGA sheet. Areas that were covered by the PGA sheet appeared reddish, fairly vascular, and showed no white coating on the surface. In contrast, areas without the PGA sheet were covered with a white coating. We speculate that the PGA sheet plays an important role in inhibiting localized inflammation by protecting against exogenous

stimulation and subsequent organization of the granulation tissue, thereby resulting in less cicatrization. Taking this into consideration, it is important that the PGA sheet should be fixed firmly and longer. We also found that the rate of detachment in the first week after ESD was 55.6% (5/9) in the case of clipping the PGA sheet, while it was 20.8% (5/24) without clipping. In terms of the detachment of the PGA sheet, we would recommend using fibrinogen only.

In this study, regarding intralesional steroid injection, the rate of stricture was 10.3%. In previous studies, the rate was 19% in 21 patients[6], 10% in 30 patients[7], and 51% in 35 patients[19], all showing similar outcomes. Although the dose, site, and frequency of intralesional steroid injection varied among the studies (Table 6), as in the present study, similar results among the studies suggest the significance of intralesional steroid injection. While Hanaoka et al. observed the side effects of steroid injection, such as submucosal tear and bleeding, in 7% of the patients, no side effects were observed in the studies conducted by Hashimoto et al. and Funakawa et al. A study conducted in pigs reported the formation of abscess in the esophageal musculature after injection of Kenacort[20]. This and another study reporting the occurrence of delayed perforation[10] might be affected by the technical aspects of ESD, so intralesional steroid injection should be administered with caution. In contrast, although the PGA sheet has been used in various surgical procedures, no side effects have been reported to date. Similarly, we observed no side effects in this study, suggesting that the PGA sheet is highly advantageous in terms of safety.

This study has several limitations. First, this was a retrospective single-institution study with a small number of patients, not a prospective randomized study. Additionally, in both groups, the methods used for the attachment of PGA sheet and the dosing of

Kenacort were not consistent. To address these problems, we plan to perform a randomized multi-institutional study with a large number of patients in the future. Third, the timing for evaluation was set in 6 weeks. We recognize that strictures may occur beyond the follow-up period of 6 weeks used in the present study. Future studies with longer follow-up durations are warranted to address this issue.

Along with technological advances in ESD, many studies are currently investigating preventive measures against esophageal stricture. Because esophageal cancer has little risk of lymph node metastasis in patients who were indicated to be treated by ESD, it is important not to jeopardize post-treatment quality of life among these patients as much as possible. Once stricture occurs, the patients need to undergo EBD, which comes with a risk of pneumothorax and mediastinitis due to muscle tear during dilation[21]. In addition, repeated EBD is costly and psychologically burdensome to patients. However, this burden was largely partly overcome in previous studies using intralesional steroid injection. In addition, Kenacort is relatively inexpensive and requires few injections, reducing the number of endoscopic examinations to check the stricture. Furthermore, the PGA sheet can prevent adverse events, such as delayed perforation, commonly attributable to techniques used in intralesional steroid injection. Another merit of the PGA sheet is that it can be used safely in patients for whom steroids are contraindicated, such as those with dormant Mycobacterium Tuberculosis[22]. Based on the findings of this study, the present method using a PGA sheet and fibrin glue is thought to be a promising option, and as effective as intralesional steroid injection, in preventing esophageal stricture.

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Legends

Table 1: Clinicopathological characteristics of study participants

Table 2: Stricture formation and endoscopic balloon dilation

Table 3: Subgroup analysis of the relationship between stricture development and the extent of ESD

Table 4: The correlation between the occurrence of the post-ESD stricture and the detachment rate of the PGA sheet in 1 week

Table 5: The correlation between the occurrence of the post-ESD stricture and the interval from ESD to intralesional injection

Table 6: Some dedicated statements to injection variables in the literature

Fig. 1: Flow diagram of the participants

Fig. 2: Delivery and affixation of the PGA sheet

a: PGA sheet delivered onto the artificial ulcer using endoscopic forceps

b: Fibrin glue sprayed after shielding with PGA sheet

Fig. 3: Representative case of successful treatment observed in the study group.

a: Semicircular mucosal defect seen immediately after ESD

b: Shielding with PGA sheet and fibrin glue

c: No stricture found 3 months after ESD

Fig. 4: Esophageal stricture observed after shielding with PGA sheet and fibrin glue.

a: Artificial ulcer shielded with PGA sheet and fibrin glue immediately after ESD in the first case.

b: PGA sheet mostly detached at 1 week in the first case.

c: Esophageal stricture seen at 4 weeks in the first case

Table 1: Clinicopathological characteristics of study participants

	PGA sheet (n=39)	Injection of steroid (n=31)	P value
Age, mean±SD, years	68.7±9.0	67.1±8.4	0.46
Sex			
Male	30	25	0.78
Female	9	6	
Tumor location			
Upper	5	6	0.54
Middle	23	14	
Lower	11	11	
Macroscopic type			
Elevated	8	4	0.53
Flat/ depressed	31	27	
Length of tumor, mean±SD, mm	39.4±10.2	39.4±15.5	0.20
Mucosal defect			
1/2 ≦ <3/4	10	11	0.37
3/4 ≦ < entire circumference	29	20	
Longitudinal length of ESD ulcer, mean±SD, mm	46.7±11.3	44.8±14.7	0.40
Depth of invasion			
T1a	33	26	1.00
T1b	6	5	
Number of cases showing muscle damage	6	4	0.52
En bloc resection	100%	100%	

Patch method			
Small size	30		
Large size	9		
Volume of steroid injection 1st time			
40mg		7	
More than 80mg		24	
Number of injection			
Once		27	
More than twice		4	
Additional surgery	6	2	0.22

PGA: polyglycolic acid

Table 2: Stricture formation and endoscopic balloon dilation

	PGA sheet (n=33)	Injection of steroid (n=29)	p-value
Frequency of stricture	3 (9.1%)	3 (10.3%)	1.00
Days between ESD and stricture development (mean±SD)	23.7±8.7	30.7±10.3	0.51
Median number of EBD	0	0	0.95
Number of EBD (mean±SD)	0.057±0.24	1.9±5.1	

ESD: endoscopic submucosal dissection, EBD: endoscopic balloon dilation, PGA: polyglycolic acid, SD: standard deviation

Table 3: Subgroup analysis of the relationship between stricture development and the extent of ESD

	PGA sheet (n = 33)	Injection of steroid (n = 29)	p-value
No. of cases with mucosal defect ≤75% of circumference (A)	17	17	
No. of stricture cases among A (%)	0	2 (11.8%)	0.24
No. of cases with >75% of circumference (B)	16	12	
No. of stricture cases among B (%)	3 (18.8%)	1 (8.3%)	0.41

Table 4: The correlation between the occurrence of the post-ESD stricture and the detachment rate of the PGA sheet in 1 week

		The detachment of PGA sheet in 1 week		p-value
		positive	negative	
Post-ESD stricture	positive	3	0	0.021
	negative	7	23	

Table 5: The correlation between the occurrence of the post-ESD stricture and the interval from ESD to intralesional injection

		The interval from ESD to injection		p-value
		immediately	a few days later	
Post-ESD stricture	positive	2	1	0.10
	negative	26	0	

Table 6: Some dedicated statements to injection variables in the literature

Study	Number	Timing of intervention	Dose	Concentration	Stricture rate
Hashimoto[6)]	21	POD3, 7, 10	18-62 mg	10 mg/ml	19%
Hanaoka[7)]	30	POD0	100 mg	5 mg/ml	10%
Funakawa[19)]	35	POD0, 7, 14	NA	5 mg/ml	51%
Nagami[23)]	12	POD0	40-80 mg	4 mg/ml	8.1%

POD: post-operative days, NA: not available

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