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ORIGINAL ARTICLE

Endoscopic steroid injection reduced frequency of repeat dilation in patients with anastomotic stenosis after esophagectomy

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Abstract
Background The incidence of anastomotic stenosis ranges from 26 to 42 % in patients who have undergone esophagectomy. Stenosis reduces patient quality of life and requires multiple endoscopic balloon dilations (EBDs). We investigated the effects of EBD with intralesional steroid injection on anastomotic re-stenosis after EBD.
Methods We retrospectively analyzed 30 esophageal cancer patients who experienced anastomotic stricture after primary surgical resection. All patients had subtotal esophagectomy and cervical anastomosis with retrosternal reconstruction route. The diagnosis of anastomotic stenosis was based on a dysphagia score of 2 or more. Ten patients were treated with EBD and endoscopic corticosteroid injections (steroid group), and 20 were treated with only endoscopic balloon dilation (control group). In the steroid group, triamcinolone acetonide was evenly injected around the anastomosis. We compared the clinical outcomes.
Results The number of EBDs, measured from the beginning to the release of stricture, was significantly lower in the steroid group than in the control group [2.5 (1–6) vs. 4.5 (1–20), $p = 0.033$]. Moreover, the period between the first dilatation and the release from stenosis in the steroid group was significantly shorter than that in the control group [58.5 days (0–142 days) vs 94.5 days (0–518 days), $p = 0.047$]. Bleeding occurred at the anastomotic site in one case in the steroid group, but was completely controlled by endoscopic hemostasis. No other complications were observed in both groups.
Conclusions Intralesional steroid injection with EBD for treating anastomotic stenosis after esophagectomy is beneficial for reducing the number of repeat EBDs performed and shortening the period before release from stenosis.

Keywords Esophageal cancer · Anastomotic stenosis · Endoscopic balloon dilation · Steroid injection

Abbreviations
EBD Endoscopic balloon dilation

Introduction

Esophageal cancer is one of the most common malignant neoplasms [1], ranking eighth in cancer incidence and sixth in cancer mortality worldwide [2, 3]. Although the effectiveness of chemotherapy or chemoradiotherapy for the treatment of esophageal cancer has been reported [4–10], esophagectomy remains the mainstay for the definitive treatment of this disease [11–13]. Short-term and long-term treatment outcomes have improved due to advanced surgical techniques and perioperative management. However, at present, morbidity, such as pneumonia, anastomotic leakage and recurrent nerve paralysis, still occurs frequently after esophagectomy [14].

The incidence of anastomotic stricture ranges from 26 to 42 % in patients who have undergone esophagectomy [15–17]. Anastomotic stricture reduces oral intake and body weight, leading to a decrease in patient quality of life [18]. Endoscopic balloon dilation (EBD) is the first choice of treatment for anastomotic stricture. However, it has been

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reported that ~80 % of patients who are treated with EBD show re-stenosis and require frequent EBDs thereafter [18].

According to recent reports, intralesional steroid injection is effective for the prevention of stenosis for benign peptic ulcer and endoscopic submucosal dissection [19–21]. However, it is unclear whether intralesional steroid injection is effective for anastomotic re-stenosis after EBD for esophagogastric anastomotic stricture.

In the present study, we retrospectively investigated the effects of EBD with intralesional steroid injection on anastomotic re-stenosis after EBD.

Materials and methods

Patients

This retrospective study included 30 esophageal cancer patients who had anastomotic stricture confirmed by endoscopy after primary surgical resection between March 2009 and March 2011 at the Osaka Medical Center for Cancer and Cardiovascular Diseases in Japan. During this period, we performed surgery on 126 esophageal cancer patients. Of these 126 patients, 90 underwent subtotal esophagectomy, followed by gastric tube reconstruction with a retrosternal route. Of these 90 patients, 36 complained of dysphagia. The diagnosis of anastomotic stenosis is based on a dysphagia score of 2 or more.

The dysphagia score is utilized based on the management of malignant dysphagia as follows: 0, able to eat a normal diet; 1, unable to swallow certain solids; 2, able to swallow semisolid foods; 3, able to swallow liquids only; and 4, unable to swallow liquids [22]. The fiber used in this study was XQ260 or XQ240 with a front-edge size of 9.0 mm (Olympus, Japan). Of the 36 patients with stenosis, 10 were treated with EBD and endoscopic corticosteroid injections (steroid group), and 20 were treated with only endoscopic balloon dilation (control group). The remaining 6 patients were treated with only balloon dilatation initially. However, after repeated balloon dilatation, steroid injection was introduced in the middle of the treatment course. Therefore, these 6 patients were excluded from analysis because they were treated with a mixture of balloon dilation with and without steroid injection. We compared the clinical outcomes between the two groups.

Surgical procedure

Standard operation consisted of subtotal esophagectomy with 2- or 3-field lymph node dissection via right thoracotomy and gastric tube reconstruction. Neoadjuvant chemotherapy or chemoradiotherapy was performed if clinical lymph node metastasis existed before treatment. At the point of reconstruction, we fundamentally adopted a wide gastric tube. When the length of the gastric conduit was not adequate for cervical anastomosis, a narrow gastric tube was adopted. The length of the remnant esophagus used for anastomosis was typically 2–3 cm. The anastomosis was made by hand-sewing end-to-end or end-to-side with vicryl 3-0 (Ethicon, Japan) or by mechanical instrument end-to-side using a 25-mm circular stapler (Ethicon, Japan). A proton pomp inhibitor was used intravenously for a week after esophagectomy and internally thereafter.

Endoscopic procedure

Following diagnosis with anastomotic stenosis, EBD was performed using an 18-mm CRE wire-guided balloon dilator (Boston Scientific Corporation, Watertown, MA, USA). EBD was performed under 3–5 atm for 2–5 min (Fig. 1a). After this procedure, we noted the presence or absence of perforation or bleeding at the site of anastomosis and confirmed the passage of the endoscopic fiber. In the case of

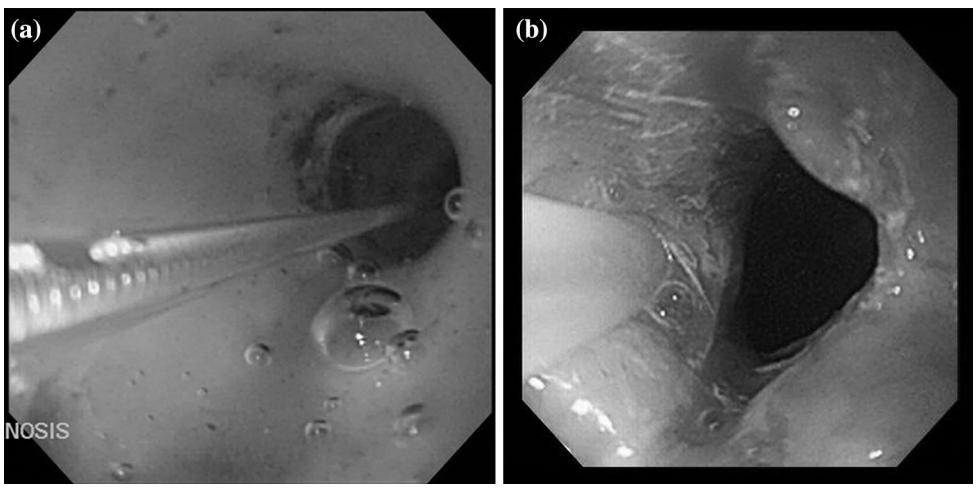

Fig. 1 Endoscopic view after balloon dilation for anastomotic stenosis (**a**). Endoscopic view of triamcinolone injection performed at the anastomotic site after balloon dilation (**b**)

corticosteroid injection, triamcinolone acetonide (Kenacort; 50 mg/5 ml; Bristol–Meyers Squibb Co., Tokyo, Japan) was used. A 25-gauge needle was used to inject the solution evenly into the submucosal layer at 5 points around the circle of the anastomosis (Fig. 1b). Ten milligrams of triamcinolone acetonide was injected into each point. Therefore, a total amount of 50 mg of triamcinolone acetonide was utilized for one EBD procedure. Steroid injection was performed for every repeated EBD.

Follow-up and evaluation

Endoscopic examination was performed on demand for patients complaining of dysphagia. EBD was repeatedly performed when patients experienced persistent dysphagia to solid foods. Release of anastomotic stenosis is defined as a state free from endoscopic dilatation for at least 12 months after the last dilatation. Therefore, the point of release from stricture is the day of the last endoscopic dilatation.

Statistical analysis

Continuous variables are expressed as median (range). The χ^2 test or Fisher's exact test was used to compare the categorized variables. The Wilcoxon test was used to compare the continuous variables. All calculations were performed using JMP v9.0.1 software (SAS Institute Inc., Cary, NC, USA) and a p value of less than 0.05 was considered significant.

Results

Patients' characteristics

The clinical and surgical characteristics of the patients are shown in Table 1. Twelve patients had neoadjuvant chemotherapy and 1 received neoadjuvant chemoradiotherapy, while 17 did not undergo neoadjuvant therapy before

Table 1 Baseline characteristics of patients

	Control group ($n = 20$)	Steroid group ($n = 10$)	p value
Age			
(median, range)	63 (37–79)	60.5 (50–74)	0.454
Sex			
Male	18	10	0.540
Female	2	0	
Neoadjuvant chemotherapy			
None	12	5	0.609
Chemotherapy	7	5	
Chemoradiotherapy	1	0	
cT			
cT1–2	12	5	0.706
cT3–4	8	5	
cN			
cN0	11	3	0.260
cN1–3	9	7	
cStage			
cStage0–2	11	4	0.700
cStage3–4	9	6	
Anastomosis			
Hand-sewn	19	8	0.251
Mechanical	1	2	
Gastric tube			
Wide	19	8	0.251
Narrow	1	2	
Anastomotic leakage			
+	0	0	1.000
−	20	10	
Interval between surgery and stenosis (day) (median, range)	49 (34–120)	49.5 (25–83)	0.581

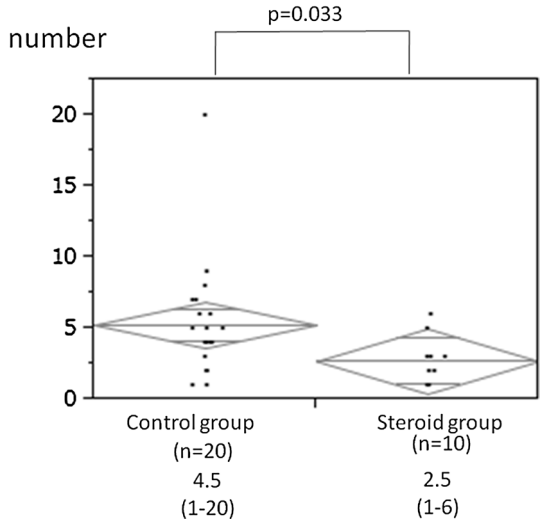

Fig. 2 The number of endoscopic balloon dilatations (EBDs) measured from the beginning to the release of stricture. The number of EBD was significantly lower in the steroid group than in the control group [2.5 (1–6) vs. 4.5 (1–20), $p = 0.033$]

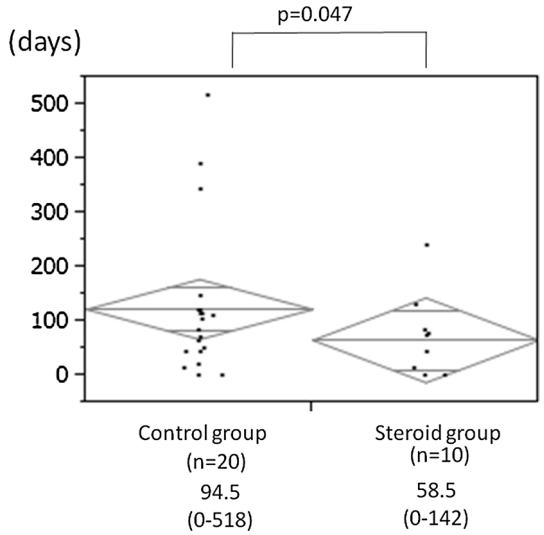

Fig. 3 The period between the first dilatation and the release from stenosis. This period was significantly shorter in the steroid group than in the control group [58.5 days (0–142 days) vs 94.5 days (0–518 days), $p = 0.047$]

surgery. With regard to reconstruction, a wide gastric tube was used in 27 patients, while a narrow gastric tube was used in 3. All patients had cervical anastomosis and a retrosternal reconstruction route. With regard to the anastomosis method, 27 patients received hand-sewn anastomosis, and 3 underwent mechanical anastomosis. No patients had anastomotic leakage. The median interval between surgery and stricture diagnosis was 49 days. There were no significant differences in clinical factors between the two groups.

Clinical efficacy of steroid injection

The number of EBDs, measured from the beginning to the release of stricture, was significantly lower in the steroid group than in the control group [2.5 (1–6) vs. 4.5 (1–20), $p = 0.033$] (Fig. 2). Moreover, the period between the first dilatation and the release from stenosis in the steroid group was significantly shorter than that in the control group [58.5 days (0–142 days) vs 94.5 days (0–518 days), $p = 0.047$] (Fig. 3).

Two patients (10 %) needed only one EBD to obtain complete cure in the control group, while 3 (30 %) needed only one dilatation in the steroid group. However, this difference did not reach significance ($p = 0.300$). One patient in the control group and 2 in the steroid group complained of anastomotic stenosis and required only one EBD again 3 months after the last dilatation. In these 3 patients, the periods between release from stenosis to true last dilatation were 4, 4 and 12 months, respectively.

Table 2 Complications after endoscopic balloon dilatation

	Control group ($n = 20$)	Steroid group ($n = 10$)
Bleeding	0	1
Perforation	0	0
Others	0	0

Complications

One major adverse event occurred in the steroid group. At the time of the second EBD, bleeding occurred at the anastomotic site, but was completely controlled by endoscopic monopolar soft coagulation. No bleeding-related adverse events occurred in the control group. No other complications, such as perforation or esophagitis, were observed in the steroid or control group (Table 2).

Discussion

In the present study, we found that intralesional steroid injection of EBD is effective in preventing re-stenosis after EBD for esophagogastric stricture. This intralesional injection significantly decreased the number of repeat EBDs until the release of stenosis and shortened the period from the first EBD to the release of stenosis. Vann et al. [18] have reported that the average number of repeated EBDs for the treatment of esophagogastric stenosis is 5, similar to controls. They also have analyzed risk factors for the development of anastomotic stenosis after esophagectomy,

including cardiovascular disease, gastric tube reconstruction and postoperative anastomotic leakage. Moreover, they have shown that anastomotic leakage, preoperative chemoradiotherapy and the early development of stricture are independently associated with the development of refractory stenosis. In our studies, these factors were not associated with refractory stenosis. Instead, lack of steroid injection was the only factor associated with this condition.

The mechanism of anastomotic stenosis after esophagectomy is unknown. Hirdes et al. [23] have reported that it involves ischemia-induced chronic inflammation. The tip of the gastric tube becomes ischemic under reconstruction because of ligation of the left gastric artery and left epiploic artery. Chronic inflammation induced by ischemia produces scarring and fibrosis, resulting in stenosis. Steroids inhibit the migration and activation of leukocytes and fibroblasts, thereby suppressing edema and collagen formation. Intralesional steroid injection potentially inhibits re-fibrosis caused by EBD.

The incidence of anastomotic stenosis in this study is comparable to previous reports. However, the frequency reached 40 %, which is high in practice. The cause of high frequency is unknown. However, it may be due to the method of anastomosis. Recently, mechanical anastomosis using linear stapler has been reported [24, 25]. According to these reports, the incidence of anastomotic stenosis ranged from 12.5 to 15 %. To avoid anastomotic stenosis, an appropriate anastomotic method should be adopted.

It has been reported that intravenous administration of steroids is also equally effective for the prevention of re-stenosis after EBD via intralesional steroid injection [26, 27]. However, in the case of intravenous treatment, the risk of infection and/or development of an aggravated state in diabetes patients must be considered. For this reason, in this study, we used local steroid injection. The injection procedure and dose of triamcinolone acetonide used were according to our previous report [20].

With regard to adverse events, in this study, bleeding was observed in one case in the steroid group, requiring endoscopic hemostasis. Perforation and other adverse events were not observed in this study. However, delayed perforation occurred after steroid injection with EBD after endoscopic submucosal dissection for superficial esophageal cancer [28]. Therefore, careful follow-up was essential.

Hirdes et al. [23] have demonstrated in a multicenter randomized clinical trial that endoscopic steroid injection does not reduce dysphagia after endoscopic dilation in patients with anastomotic stricture after esophagectomy. In their study, 45 % of patients in the steroid group remained dysphagia free for 6 months compared with 36 % in the control group. However, this difference did not reach statistical significance. In our study, there was also no significant difference in the proportion of patients with re-stenosis between the steroid group and control group. Moreover, there was no difference in the mean period between the first dilatation and second dilatation in both groups. However, in our study, intralesional steroid injection was effective in reducing the number of EBDs.

In summary, we have demonstrated that adding steroid injection to endoscopic balloon dilation results in a statistically significant reduction in repeat dilation and a shortening of the period between the first dilation and release of stenosis. This study was retrospective, and the sample size was small. In future, we will conduct a prospective, randomized controlled study.

Conclusion

Intralesional steroid injection with EBD for treating anastomotic stenosis after esophagectomy is beneficial for reducing the number of repeat EBD procedures and shortening the period before release from stenosis.

Ethical Statement Our studies were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and subsequent revisions. Written informed consent was obtained from participants.

Conflict of interest There are no financial or other relations that could lead to a conflict of interest. There are no non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript.

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