Optimization of steroid injection intervals for prevention of stricture after esophageal endoscopic submucosal dissection: A randomized controlled trial

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Abstract

Background and study aims: **Esophageal endoscopic submucosal dissection enables en bloc resection of large superficial esophageal cancer; however, this procedure may induce severe stricture. Intralesional steroid injection is an effective treatment for prevention of stricture after endoscopic resection; however, there have been no studies assessing the duration of such treatment. The aim of this study was to reduce treatment duration and to evaluate the effectiveness of weekly and biweekly steroid injections in preventing esophageal stricture after endoscopic resection.**

Patients and methods: **We performed a randomized controlled trial comparing patients receiving weekly or biweekly intralesional triamcinolone injections. Patients with a mucosal defect greater than 75% (3/4) of the luminal circumference after esophageal endoscopic submucosal dissection for superficial esophageal cancers were enrolled. The primary endpoint was the duration of steroid injection treatment.**

Results: **The median duration of treatment was 37.0 days in the weekly group and 34.2 days in the biweekly group (P = 0.059). Among patients with a mucosal defect larger than 50 mm, there was a significant difference in the median duration of treatment between the weekly and biweekly groups (42.5 days vs 29.0 days, P = 0.013).**

Conclusions: **Biweekly steroid injection of triamcinolone reduces treatment duration, particularly in those with mucosal defects larger than 50 mm.** (Acta gastroenterol. belg., **2016**, 79, **315-320**).

Key words : steroid, esophagus, stricture, ESD

Abbreviations : ESD, esophageal endoscopic submucosal dissection ; EBD, endoscopic balloon dilation ; TR, triamcinolone.

Introduction

Esophageal endoscopic submucosal dissection (ESD) enables *en bloc* resection of a lesion with a sufficient cancer-free margin, irrespective of tumor size (1,2). However, esophageal stricture is known to be one of the major complications of esophageal ESD. Several studies have reported that a reliable predictor of stricture development (3-6) is a mucosal defect of more than 75% (3/4) of the circumference of the esophagus, with stricture development rates reaching as high as 68-100% in such cases (3-6).

A benign esophageal stricture is usually treated by endoscopic balloon dilation (EBD). However, EBD can cause severe complications, such as significant bleeding and perforation, at rates of 0.4% and 0.1-1.1%, respectively (6-8). Frequent EBD sessions are usually required to treat patients with severe stricture, which is associated with a higher risk of complications. Therefore, treatment to prevent stricture, facilitating a reduction in EBD use, is important.

Several studies have suggested the effectiveness of intralesional steroid injections to prevent esophageal stricture after ESD (9-12). Triamcinolone acetonide (TR) is a steroid that can remain in the tissue with long-lasting effects (13). TR injection has been shown to be effective in preventing stricture development, significantly reducing the stricture rate to 10-38%, compared with 66-75% in patients not receiving injection (9-11). Thus, the use of TR injections after esophageal ESD, particularly in patients with large circumferential mucosal defects, has become generally accepted in Japan. Because there have been no reports on the optimum treatment duration or frequency of TR injections, the aim of this study was to optimize the frequency and interval of TR injections in patients who underwent ESD.

Patients and Methods

A total of 33 patients who underwent ESD for superficial esophageal cancer at Kobe University Hospital between September 2010 and December 2011, and who met the following inclusion criteria, were enrolled in the present study: i) lesions were diagnosed within SM1 invasion, preoperatively, ii) no indication of lymph node metastases or distant metastases on computed tomography scanning, and iii) requirement of submucosal dissection involving more than 75% (3/4) of the esophageal circumference. The exclusion criteria were: i) poorly controlled diabetes or adrenal malfunction, ii) congestive cardiac failure, iii) hepatic or renal failure, and iv) active synchronous cancer. Written informed consent was obtained from all enrolled patients.

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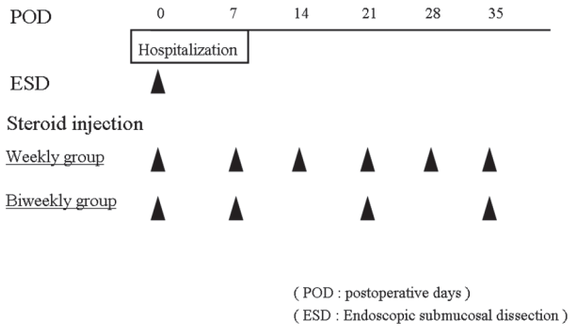

Fig. 1. — Study design

After ESD, the participants were randomly assigned to either the weekly or biweekly treatment groups (Fig. 1) using a random number generated by Excel 2007 (Microsoft Corporation, Redmond, WA). Both groups received intralesional injections of 40 mg of TR on the day of ESD and one week post-ESD, regardless of lesion size. The patients in the weekly group continued to receive injections every 7 days, and the patients in the biweekly group received injections every 14 days until the postoperative ulcer healed completely. Laboratory examination was performed before ESD and 4 and 8 weeks after ESD to assess the adverse events.

Sample size

We conducted a preliminary study to evaluate the treatment duration for patients who underwent TR injection weekly or biweekly after esophageal ESD. There was no significant difference in stricture rate between the two groups (p=0.182), but treatment duration was 43.2±9.7 days in the weekly group and 30.8±8.4 days in the biweekly group. Thus, we hypothesized that biweekly steroid injections may reduce treatment duration, and the primary endpoint in this study was defined as the duration of treatment. Based on these preliminary results, we estimated that biweekly steroid injections would reduce the treatment duration by approximately 30%, and the sample size was estimated accordingly. Power analysis indicated that at least 15 patients were required in each group, assuming a 5% significance level and statistical power of 90% using two-sided equivalence.

ESD procedures

ESD was carried out with a Flush knife or Flush knife BT with 1.5 or 2 mm needle length (DK2618JN or DK2618JB; Fujinon, Tokyo, Japan), through a single-channel endoscope (GIF Q240 or Q260J; Olympus Optical Co., Ltd., Tokyo, Japan). A transparent attachment (D-201-11804: Olympus Optical Co., Ltd., or F025/030: Top, Tokyo, Japan) was placed on the tip of the endoscope. A high-frequency electric surgical unit (VIO300D; ERBE, Tűbingen, Germany) was used as the power source for electrical cutting and coagulation. Hyaluronic acid (Mucoup; Johnson and Johnson K.K., Tokyo, Japan) or saline was used for submucosal injection.

Steroid injections

A total of 40 mg of TR (KenacortA; Bristol Myers, Tokyo, Japan) diluted 1:3 with sterile saline was injected into the post-ESD ulcer. We performed 20 injections in aliquots of 2mg (0.2 ml) per session through a 25-gauge endoscopic needle (TOP, Tokyo, Japan) into the residual submucosal layer of the ulcer bed to avoid muscle layer damage (Fig. 2). We confirmed for swelling of the residual submucosal tissue as sign of successful injection into submucosal layer. In those with esophageal stricture, steroid injection was performed after EBD.

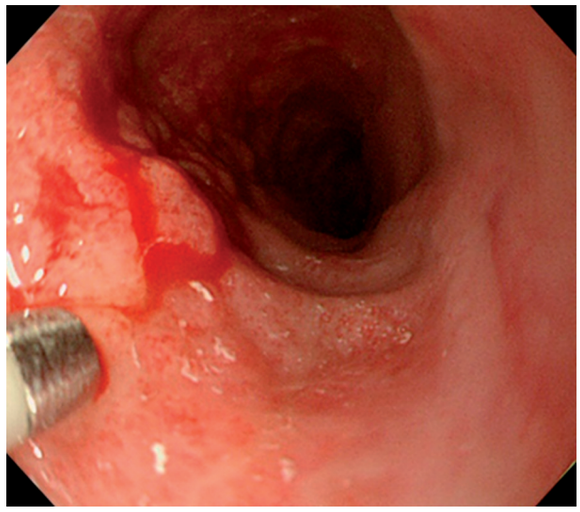

Fig. 2. — Endoscopic image showing triamcinolone injection into the ulcer base

EBD

Stricture was diagnosed when the patient had dysphagia or when an endoscope of 11 mm diameter (GIF-1T240; Olympus Optical Co., Ltd., Tokyo, Japan) was unable to pass the esophageal stenosis. A through-the-scope balloon (CRE; Boston Scientific Japan, Tokyo, Japan) was used for EBD. The balloon was inflated in stages to a maximum diameter of 18 mm. Inflation of the balloon was halted if the patient experienced severe pain, or if exposure of the muscle layer was detected. The final diameter of dilation was decided at the discretion of the endoscopist.

Endpoints

The primary endpoint for this study was the duration of treatment required until ulcer epithelialization without stricture. Secondary endpoints were stricture rate, number of EBD sessions, number of steroid injections, and complication rate.

Statistical analysis

Data analysis was conducted using Stata version 10 (Stata Corp., College Station, TX, USA). All P values were two-tailed. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using Fisher's exact test. P<0.05 was defined as statistically significant.

Ethics

The protocol was approved by the Ethics Committee of Kobe University Hospital, Japan. Patients provided written informed consent before they were randomized into the treatment groups. The URL of the online registry is www.umin.ac.jp/ctr/index.htm, and the clinical trial number is UMIN000005649.

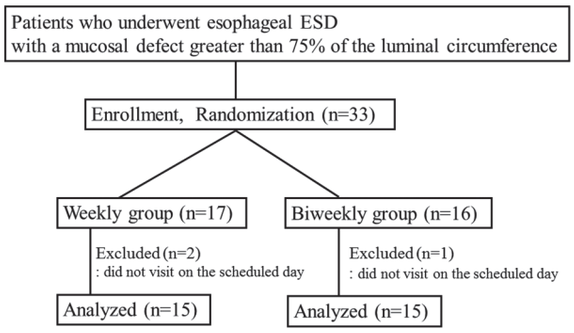

Fig. 3. — Flow chart of study participants

Results

In the present study, 33 patients who satisfied the inclusion criteria were enrolled. Seventeen patients were assigned to the weekly group and 16 to the biweekly group (Fig. 3). Three patients did not complete the regimen, and their data were excluded (2 patients in the weekly group who did not keep to their scheduled appointments, and 1 in the biweekly group who was not administered a steroid injection on the scheduled day). There were no significant differences in demographic characteristics between the two groups, as summarized in Table 1.

Treatment outcomes of all patients are shown in Table 2. The median duration of treatment was 37.0 days (range: 27-57 days) in the weekly group and 34.2 (range: 8-50 days) in the biweekly group. Similar numbers of patients developed post-operative stricture (5 in the weekly group and 6 in the biweekly group), and there was no significant difference in the number of EBD treatments required between the two groups. Of note, the weekly group required significantly more steroid injections than the biweekly group (p<0.001). No serious

Table 1. — **Demographic data for weekly and biweekly groups**

	Weekly group [n=15]	Biweekly group [n=15]	*p*-value
Age (mean±SD; yr)	69.5±8.2	66.3±5.7	0.157
Gender (M / F)	14 / 1	14 / 1	1.000
Absence of reflux esophagitis	0	0	1.000
Localization of esophageal cancer			
Ut-Mt	1	1	
Mt	11	7	
Mt-Lt	2	2	0.469
Lt	1	4	
Lt-Ae	0	1	
Longitudinal diameter of mucosal defect (mean±SD; mm)	60.0±19.0	60.0±13.0	0.917
Circumferential extension of mucosal defect (75-82%, 83-91%, 92-99%, 100%)	2,4,8,1	4,7,4,0	0.308
Macroscopic type (0-IIa/ IIb/ IIc)	3/6/6	4/5/6	1.000
Histologic depth (EP/ LPM/ MM/ SM1/ SM2)	6/5/2/0/2	2/9/3/1/0	0.175

Location in esophagus: Ut, upper thoracic ; Mt, middle thoracic ; Lt, lower thoracic ; Ae, abdominal esophagus.
Histologic depth: EP, epithelium ; LPM, lamina propria mucosa ; MM, muscularis mucosa ; SM, submucosa.

Table 2. — **Treatment outcomes in all patients [n=30]**

	Weekly group [n=15]	Biweekly group [n=15]	*P*-value
Median duration of treatment (range ; days)	37.0 (27-76)	34.2 (8-50)	0.059
Stricture rate (%)	5/15 (33.0)	6/15 (40.0)	0.893
Median EBD times (range)	0 (0-7)	0 (0-5)	0.847
Median steroid injection times (range)	6.0 (4-13)	4.0 (2-5)	<0.001
Adverse event (%)	2/15 (13.3)	0/15 (0.0)	0.483

Table 3. — **Treatment outcomes in patients with lesions of longitudinal diameter ≥5cm [n=21]**

	Weekly group [n=10]	Biweekly group [n=11]	*P*-value
Median duration of treatment (range ; days)	42.5 (29-76)	29.0 (8-50)	0.022
Stricture rate (%)	4/10 (40.0)	4/11 (36.4)	0.608
Median EBD times (range)	0 (0-7)	0 (0-3)	0.599
Median steroid injection times (range)	6.5 (5-13)	4.0 (2-5)	<0.001
Adverse event (%)	1/10 (10)	0/11 (0.0)	0.476

complications occurred in either group. In the weekly group, two patients experienced candida esophagitis. They were asymptomatic and required no additional intervention. In the biweekly group, no complications occurred. Serum electrolyte values were normal and abnormal elevation of blood glucose was not observed in any of the participants, suggesting no obvious adverse effects due to the steroid injections.

We further analyzed treatment outcomes based on lesion size; Table 3 shows the treatment outcomes of patients with lesions of over 50 mm in diameter. There were no significant differences in stricture rate, number of EBD sessions, or complication rate between the two groups. However, the median duration of treatment was significantly shorter in the biweekly group (29.0 days, range: 8-50 days) than in the weekly group (42.5 days, range: 29-57 days) (p=0.022). Accordingly, the median number of steroid injections was significantly fewer in the biweekly group (4.0 times, range: 2-5 times) than in the weekly group (6.5 times, range 5-13 times) (p<0.001).

Discussion

TR is a long-acting synthetic corticosteroid, and is approximately five times as effective as hydrocortisone (14). In vivo data suggest that TR is effective at breaking down mature collagen, and should theoretically reduce fibrosis (13). Although several reports have clarified the effectiveness of intralesional TR injection in preventing esophageal stricture after ESD, the intervals of injections varied among these reports. Takeuchi *et al*. (9) performed 2 injections per week, while Hashimoto *et al*. (10) performed a total of 3 sessions within 2 weeks. Because TR remains active for 3-4 weeks in local tissue (15), we investigated whether the frequency of TR injection can be optimized by testing different intervals of injection treatment.

In an analysis of all patients, the biweekly group tended to require shorter treatment duration than the weekly group, although this difference was not significant. However, this difference became significant when analyzing patients with lesions with a longitudinal diameter of over 50 mm; the treatment duration in the biweekly group was shorter than in the weekly group. This may be explained by the fact that steroids can delay ulcer healing (16). Importantly, there was no significant difference in stricture rate between the groups. This suggests that frequent steroid injection may slow ulcer healing without the beneficial effect of avoiding stricture development.

In previous studies, it is reported that stricture rates were between 10-38% (9-11). On the other hand, the stricture rate observed in the present study is 36.7% which was relatively high compared with those previously reported. In the present study, the dose of TR used per session was 40 mg, which was within the range of doses previously used, and the total amount administered was also similar to previous reports. However, Hanaoka *et al*. (11) reported the results of single session of 100 mg TR injection immediately after ESD reduced stricture rate to only 10%. This dose is higher than the dose we used in a session. The difference of TR amount injected in early stage of ulcer healing may influence the occurrence of stricture. Furthermore, in our series, 46.7% of the enrolled patients had a defect greater than 83% around the circumference, and all patients who developed stricture after ESD were those who required circumferential resection of greater than 83% (data not shown). Although previous studies enrolled patients requiring circumferential resection of greater than 75%,

further detailed information regarding the degree of the mucosal defects were not provided. Thus the high incidence of strictures observed in our study may partly be explained by possible inclusion of a larger number of patients who needed wider dissection.

In the present study, no serious complications were observed, and there were only two minor complications of asymptomatic candida esophagitis. However, an animal study of TR injection into exposed esophageal submucosa resulted in periesophageal abscess formation in all 4 pigs tested (17). Although such a problem has not yet been reported in humans, attention should be paid to the possible risk of steroid injection compromising local immunity.

One case of delayed perforation after TR injection into the proper muscle layer has also been reported (18), and although the exact mechanism of delayed perforation by steroid injection is not fully understood, a previous report suggested that TR may inhibit stricture formation by modifying the appearance and proliferation of myofibroblasts in the proper muscle layer. Therefore, steroid injection into the proper muscle layer should be avoided. Because the esophageal wall becomes extremely thin after ESD, unintentional puncture into the deep layer may occur, even with precautions taken. Thus, to reduce the risk of possible deep injection, a reduction in the number of injections is required.

Systemic prednisolone administration is an alternative treatment for prevention of esophageal stricture after ESD (19). In one study, a remarkably low stricture rate was reported (5% in the steroid group, 32% in the EBD group), which was better than rates reported in previous studies on local TR injections, as well as our study; however, these results should be interpreted carefully. The cumulative dose of systemic administration of prednisolone was nearly 1000 mg, a level which may trigger steroid-related adverse events (14); therefore, such exposure may increase risks, including abnormal blood glucose elevation and opportunistic infections. Accordingly, disseminated nocardiosis during oral prednisolone administration following esophageal ESD has been previously reported (20). The dose of steroids required for TR local injection is approximately 54-500 mg of TR, which is equivalent to 67.5-625 mg of prednisolone (9-11). Furthermore, local injection is considered to have reduced systemic effects. Thus, the selection of systemic or local use of steroids to prevent esophageal stricture should be carefully decided, depending on the case.

Other treatments, including the use of biodegradable stents (21,22) or autologous oral mucosal sheets (23), may improve stricture, although the clinical evidence of their effectiveness remain to be established (24).

The present study included the limitations of relatively small sample size and performance in a single center. However, to the best of our knowledge, this is the first report addressing the frequency and interval of TR injections for the prevention of stricture after ESD. A larger randomized controlled trial is warranted to confirm the results of this study.

Conclusion

A biweekly injection protocol significantly shortened the treatment duration in cases with large lesions without increasing stricture rate, compared with weekly injections.

The present results suggest that treatment frequency can be reduced from a weekly to biweekly schedule.

Conflicts of interests

All authors declare no conflict of interest.

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