



# Efficacy of polyglycolic acid sheets and fibrin glue for prevention of bleeding after gastric endoscopic submucosal dissection in patients under continued antithrombotic agents

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## Abstract

**Background** A novel method for the prevention of bleeding after gastric endoscopic submucosal dissection (ESD) is necessary, as the numbers of patients taking antithrombotic agents have increased. This study aimed to assess the efficacy and safety of the covering method using polyglycolic acid (PGA) sheets and fibrin glue for ESD-induced ulcer in preventing post-ESD bleeding in patients under continued antithrombotic agents.

**Methods** One hundred five consecutive gastric tumors among 84 patients who were treated by ESD under continued antithrombotic agents between April 2014 and September 2015 were enrolled in this study. The patients were classified into two groups, the covering group (52 lesions among 38 patients; those with ESD in whom PGA sheets and fibrin glue were used as the covering method) and the control group (53 lesions among 46 patients; ESD only), and their post-ESD bleeding rates were compared.

**Results** No significant differences were seen in the number and type of antithrombotic agents, lesion location, median procedure time, and median resected specimen size between the groups. ESD was completed in all cases, with no cases of uncontrollable bleeding during the procedure. Post-ESD bleeding occurred in 5.8% (3/52) and 20.8% (11/53) in the covering and control groups, respectively. The post-ESD bleeding rate significantly differed between the groups ( $P = 0.04$ ; odds ratio, 0.23; 95% confidential interval, 0.06–0.89). No adverse events were associated with the use of PGA sheets and fibrin glue.

**Conclusions** The covering method using PGA sheets and fibrin glue has the potential to reduce post-ESD bleeding in patients receiving continued antithrombotic agents.

**Keywords** Endoscopic submucosal dissection · Early gastric cancer · Antithrombotic therapy · Polyglycolic acid sheet · Fibrin glue

## Introduction

Endoscopic examination of patients taking antithrombotic agents has increased with the increased incidence of ischemic heart disease and cerebrovascular disease. The traditional recommendation is to discontinue antithrombotic therapy during the peri-endoscopic period. However,

discontinuation of antithrombotic therapy may lead to serious thrombotic events [1–3]. Recently, guidelines for gastroenterological endoscopy in patients on antithrombotic therapy have been changed to emphasize the risk of thromboembolism caused by discontinuation of antithrombotic therapy rather than the risk of bleeding during the peri-endoscopic period [4, 5]. Consequently, the increase in the risk of bleeding associated with endoscopic procedures is a concern for patients on antithrombotic therapy.

Endoscopic submucosal dissection (ESD) has been widely performed as a standard treatment for early gastric cancer without the possibility of lymph node metastasis [6]. ESD is classified as a gastroenterological endoscopic procedure with high bleeding risk [4, 5]; post-ESD bleeding

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occurs in approximately 5% (range, 0–15.6%) of patients [6]. In addition, some reports indicate that patients on antithrombotic therapy have a greater risk of post-ESD bleeding (21–38%) [7–10]. Post-ESD bleeding causes serious conditions such as hemorrhagic shock, which requires blood transfusion, interventional radiology, or surgery, in some cases. Thus, a new method of preventing post-ESD bleeding in patients on antithrombotic therapy is necessary.

Recently, a covering method using polyglycolic acid (PGA) sheets (Neoveil; Gunze, Kyoto, Japan) and fibrin glue (Beriplast P Combi-Set; CSL Behring Pharma, Tokyo, Japan) for ESD-induced ulcers has been reported to have potential in reducing the risk of post-ESD bleeding [11, 12]. The PGA sheet is a biodegradable suture material that resorbs in approximately 15 weeks. Fibrin glue is a blood-derived product that is used as a surgical tissue adhesive. The combination of PGA sheet and fibrin glue has been widely used in the surgical field [13–15], and it is subsequently being used as a prevention and treatment method for post-ESD adverse events [16–20]. Based on this background information, we assessed the efficacy and safety of the covering method using PGA sheets and fibrin glue in preventing post-ESD bleeding in patients receiving ongoing antithrombotic agents.

## Patients and methods

### Patients and study design

This study was a nonrandomized, retrospective, single-center study of 916 gastric tumors among 722 patients who were treated by ESD at Shizuoka Cancer Center from April 2014 to September 2015. Patients who were not taking antithrombotic agents or who discontinued antithrombotic agents before ESD were excluded. Ultimately, 105 consecutive gastric tumors among 84 patients under continued antithrombotic agents treated by ESD were enrolled in this study. The patients were classified into two groups based on the use of PGA sheets and fibrin glue: the covering group (52 lesions among 38 patients; those who underwent ESD and the covering method used PGA sheets and fibrin glue) and the control group (53 lesions among 46 patients; ESD only). All patients provided written informed consent for ESD under continued antithrombotic agents, and patients in the covering group provided written informed consent for the use of PGA sheets and fibrin glue before ESD. This study was approved by the ethics committee of Shizuoka Cancer Center (approval no. 28-J82-28-1-2).

### Management of antithrombotic agents

Antithrombotic agents are defined as antiplatelet agents (e.g., low-dose aspirin, cilostazol, or thienopyridine derivatives) or anticoagulants [e.g., warfarin or direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban]. We consulted the prescribing doctor or a board-certified cardiologist before gastric ESD about the risk of thromboembolism caused by discontinuation of antithrombotic agents. Based on the risk assessment of thromboembolism, we explained to all patients the advantages and disadvantages of discontinuation of antithrombotic agents according to the guidelines before ESD. When the patient had a high risk of thromboembolism, or if the patient so desired, we performed ESD under continued antithrombotic agents after obtaining written informed consent.

### ESD procedure and management after ESD

All patients underwent ESD under continued antithrombotic agents. ESD was performed using an IT knife-2 (KD-61 1L; Olympus, Tokyo, Japan), an endoscope with a water-jet function (GIF-Q260 J; Olympus, Tokyo, Japan), and a high-frequency generator (VIO300D; ERBE Elektromedizin, Tübingen, Germany) under sedation with diazepam and pethidine hydrochloride. Hemostasis was performed by Radial Jaw hot biopsy forceps (Boston Scientific Japan, Tokyo, Japan). The details of the ESD procedures and settings have been described previously [21–23]. Immediately after tumor resection, all visible vessels on the ESD-induced ulcer were coagulated to prevent post-ESD bleeding [24].

A second-look endoscopy was performed 1 day after ESD, and endoscopic hemostasis or prophylactic coagulation was employed if active bleeding (Forrest type I) or a visible vessel (Forrest type IIa) was observed. Antithrombotic agents were started after confirmation of hemostasis by second-look endoscopy. A proton pump inhibitor (omeprazole 40 mg/day) was administered intravenously for the first 2 days and, subsequently, orally (rabeprazole 20 mg/day) for at least 2 months. A soft-food diet was started 2 days after ESD. The patients were closely observed after ESD to detect any development of adverse events.

### Covering method using PGA sheets and fibrin glue

After completing the ESD procedure, a PGA sheet cut into 2- to 5-cm pieces that fit the size of the ESD-induced ulcer was grasped by rubber-tipped grasping forceps (FG21-L-1; Olympus, Tokyo, Japan) and carried orally to the ESD-induced ulcer by the endoscope. Then, the PGA sheet was removed from the forceps and placed over the ESD-induced

ulcer with or without hemoclips. If a single PGA sheet could not cover the ESD-induced ulcer, the same procedure was repeated until the entire ESD-induced ulcer was covered. After the ESD-induced ulcer was sufficiently covered, the PGA sheets were fixed in place with fibrin glue consisting of solutions A (fibrinogen) and B (thrombin) using a spraying tube (Fig. 1).

### Outcome measurement

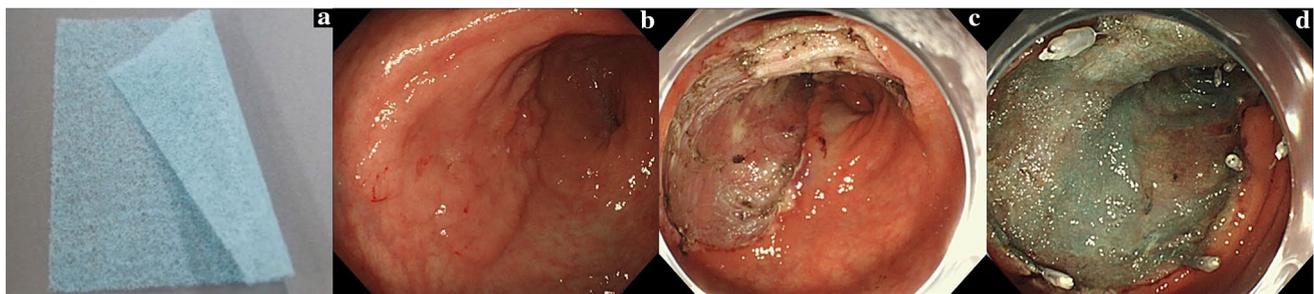
To clarify the efficacy of PGA sheet and fibrin glue, we compared the post-ESD bleeding rates of the two groups. Post-ESD bleeding was defined as a case in which hemorrhage was confirmed by emergency endoscopy after ESD with an apparent sign of bleeding, such as melena or hematemesis. The post-ESD bleeding rate was measured, per ESD-induced ulcer, from the completion of ESD until postoperative day 28.

### Statistical analysis

Fisher's exact tests and  $\chi^2$  tests were used to compare the proportion of categorical variables (such as sex), and Wilcoxon tests were used to compare the median of continuous variables (such as age) between the groups.  $P < 0.05$  was considered statistically significant. All analyses were performed using JMP software version 11 (SAS Institute, Cary, NC, USA).

### Results

The baseline characteristics of each group are summarized in Tables 1 and 2. The rate of patients with multiple tumors was significantly higher in the covering group than in the control group ( $P = 0.02$ ). No significant differences were seen in lesion-based characteristics between the groups in any background factors.



**Fig. 1** Covering method using polyglycolic acid sheets and fibrin glue. **a** Polyglycolic acid (PGA) sheet, 10 × 10 cm (Neoveil). **b** Early gastric cancer located at the anterior wall of the antrum. **c** Artificial

ulcer immediately after gastric endoscopic submucosal dissection (resected specimen size, 98 × 75 mm). **d** After covering method using PGA sheets and fibrin glue

**Table 1** Baseline patient characteristics

Patient	Covering group ( $n = 38$ )	Control group ( $n = 46$ )	$P$ value
Sex (male/female)	33/5	37/9	0.56
Age in years [median (range)]	78.5 (59–91)	78 (51–91)	0.68
Concomitant disease, $n$ (%)			
Hypertension	28 (74)	36 (78)	0.79
Diabetes mellitus	13 (34)	9 (20)	0.14
Ischemic heart disease	9 (24)	19 (41)	0.10
Arrhythmia	8 (21)	10 (22)	0.93
Cerebrovascular disease	17 (45)	12 (26)	0.10
Other arteriosclerotic disease	5 (13)	4 (9)	0.72
Number of lesions, $n$ (%)			0.02
Single	24 (63)	40 (87)	
Multiple	14 (37)	6 (13)	
Number of antithrombotic agents, $n$ (%)			0.28
Single	28 (74)	39 (85)	
Multiple	10 (26)	7 (15)	

**Table 2** Lesion-based characteristics

Lesion	Covering group (n = 52)	Control group (n = 53)	P value
Type of antithrombotic agents, n (%)			0.43
Low-dose aspirin	8 (15)	17 (32)	
Cilostazol	11 (21)	6 (11)	
Thienopyridine derivatives	7 (13)	9 (17)	
Dual antiplatelet therapy	11 (21)	8 (15)	
Warfarin	3 (6)	3 (6)	
DOAC	7 (13)	7 (13)	
Warfarin with antiplatelet agents	5 (10)	3 (6)	
Location, n (%)			0.29
Upper third	10 (19)	9 (17)	
Middle third	16 (31)	24 (45)	
Lower third	26 (50)	20 (38)	
Resected specimen size			
Median (range), mm	43 (20–100)	38 (20–100)	0.08
≤40 mm, n (%)	21 (40)	29 (55)	0.17
>40 mm, n (%)	31 (60)	24 (45)	
Ulceration, n (%)			0.98
Negative	49 (94)	49 (92)	
Positive	3 (6)	4 (8)	

DOAC direct oral anticoagulant

Treatment outcomes are summarized in Table 3. ESD was completed in all lesions, with no cases of uncontrollable bleeding during the procedure. There were no differences in median procedure time and en bloc resection rate between the groups. The median time required to cover ESD-induced ulcers using PGA sheets and fibrin glue was 15.5 min (range, 3–50 min). The PGA sheets were confirmed to have dropped away from two ESD-induced ulcers at second-look endoscopy, and prophylactic coagulation was performed in one of the ESD-induced ulcers at that time.

Post-ESD bleeding occurred in 5.8% (3/52) in the covering group and 20.8% (11/53) in the control group. There was a significant difference in the post-ESD bleeding rate between the groups [ $P = 0.04$ ; odds ratio (OR), 0.23; 95% confidential interval (CI), 0.06–0.89].

The clinical course is shown in Fig. 2. Of the three cases with post-ESD bleeding in the covering group, bleeding occurred after 7 h from ESD in one case, and second-look endoscopy performed on the next day confirmed that the PGA sheets dropped away from the ESD-induced ulcers in the two other cases.

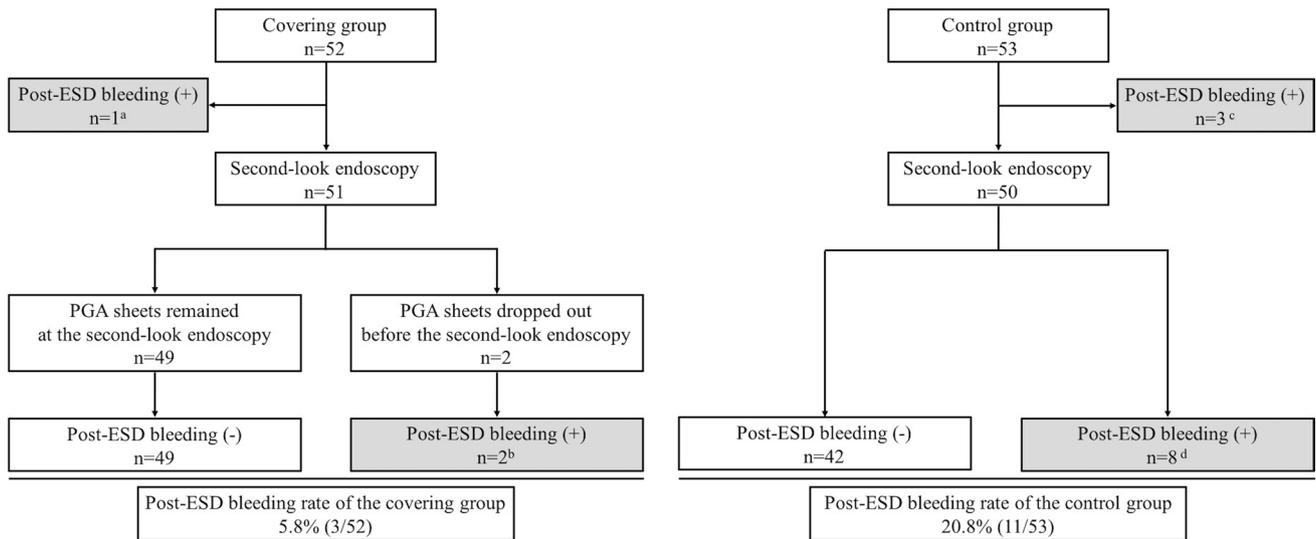
The timing of post-ESD bleeding is shown in Fig. 3. Post-ESD bleeding occurred within 17 days. All cases of post-ESD bleeding were controlled by endoscopic hemostasis and did not require interventional radiology or surgery. Blood transfusion was required in two patients in each group. No thromboembolism or adverse events associated with PGA sheets and fibrin glue were observed in the follow-up period.

**Table 3** Treatment outcomes

	Covering group (n = 52)	Control group (n = 53)	P value
Procedure time in minutes, median (range)	34 (7–116)	39 (8–185)	0.12
En bloc resection rate, % (n)	100 (52/52)	98.1 (52/53)	0.99
Covering time by PGA sheets and fibrin glue in minutes, median (range)	15.5 (3–50)	–	
Retention rate of PGA sheets at second-look endoscopy, % (n) <sup>a</sup>	96.1 (49/51)	–	
Prophylactic coagulation rate at second-look endoscopy, %, (n) <sup>a</sup>	2.0 (1/51)	18.0 (9/50)	0.008
Post-ESD bleeding rate, % (n)	5.8 (3/52)	20.8 (11/53)	0.04

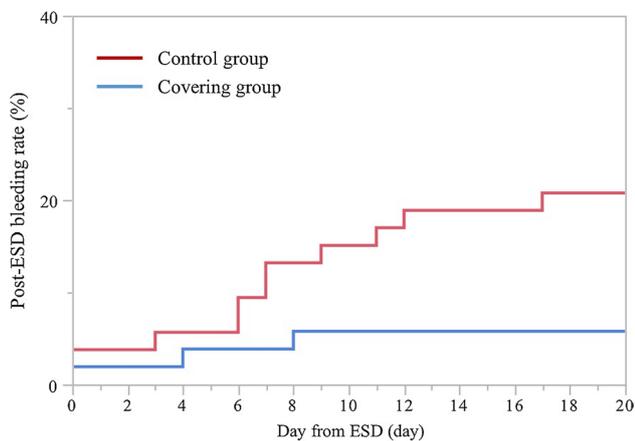
ESD endoscopic submucosal dissection, PGA polyglycolic acid

<sup>a</sup>Patients with post-ESD bleeding before second-look endoscopy were not included



**Fig. 2** Clinical course after endoscopic submucosal dissection (ESD). <sup>a</sup>Thienopyridine derivatives ( $n = 1$ ); <sup>b</sup>warfarin ( $n = 1$ ) and DOACs ( $n = 1$ ); <sup>c</sup>low-dose aspirin ( $n = 1$ ), thienopyridine derivatives ( $n = 1$ ), and warfarin with antiplatelet agents ( $n = 1$ ); <sup>d</sup>low-dose aspirin

( $n = 3$ ), dual antiplatelet therapy ( $n = 2$ ), warfarin ( $n = 1$ ), DOACs ( $n = 1$ ), and warfarin with antiplatelet agents ( $n = 1$ ). DOACs direct oral anticoagulants, ESD endoscopic submucosal dissection, PGA polyglycolic acid



**Fig. 3** Timing and rate of post-ESD bleeding. ESD endoscopic submucosal dissection

## Discussion

In the present study, we demonstrated the efficacy and safety of the covering method using PGA sheets and fibrin glue for ESD-induced ulcers in preventing post-ESD bleeding in patients under continued antithrombotic agents. Our study showed that this covering method significantly reduced the risk of post-ESD bleeding, and no adverse events associated with PGA sheets and fibrin glue occurred.

Antithrombotic therapy is a risk factor for post-ESD bleeding. However, antithrombotic therapy should be

continued, if possible, for patients at high risk for thromboembolism, because bleeding is an acceptable complication compared to thromboembolism [25]. Furthermore, the post-ESD bleeding rate was not significantly different between patients who did or did not discontinue antithrombotic therapy [26]. A previous study reported that thromboembolism during the peri-endoscopic period only occurred in patients who had discontinued antithrombotic therapy [26–28]. In our study, the post-ESD bleeding rate of the covering group was similar to the post-ESD bleeding rates of patients without antithrombotic therapy in previous reports (5.5%; range, 2.0–7.0%) [10, 12, 24, 28, 29]. Our results suggest that the covering method using PGA sheets and fibrin glue allows ESD to be performed in patients who are taking antithrombotic agents without the increased risk of post-ESD bleeding and thromboembolism.

Guidelines recommend that warfarin should be replaced with heparin before an endoscopic procedure with a high bleeding risk [4, 5]. However, some studies reported that patients with heparin replacement have a higher risk of post-ESD bleeding (24–38%) [8, 30, 31]. Tsuji et al. [11] reported that all patients experiencing post-ESD bleeding after the application of PGA sheets and fibrin glue had received heparin replacement. Thus, we think that using this method with ESD for patients under continued warfarin or DOAC therapy is a valid and feasible strategy in preventing post-ESD bleeding. Further, this method eliminates the need for prolonged hospitalization for heparin replacement.

The present study showed that PGA sheets can cover large ESD-induced ulcers, even those 10 cm in size. The use of hemoclips [32] or detachable snares with hemoclips [33] in closing ESD-induced ulcers to prevent post-ESD bleeding has been reported previously. However, complete closure of large ESD-induced ulcers using those methods is technically difficult, with a complete closure rate of about 60% [32, 33]. The advantage of the covering method using PGA sheets and fibrin glue is the possibility of completely covering the ESD-induced ulcer regardless of size and location. The large size of the resected specimen is also a risk factor for post-ESD bleeding [30, 34]. Therefore, patients on antithrombotic agents and with a large ESD-induced ulcer are considered good candidates for this method.

Interestingly, the present study showed that post-ESD bleeding occurred in two cases in which the PGA sheets dropped away from the ESD-induced ulcer before second-look endoscopy. Therefore, using the PGA sheets to cover the ESD-induced ulcer over a longer period can potentially further reduce the rate of post-ESD bleeding. Fukuda et al. [12] reported that small PGA sheets were retained on the ESD-induced ulcer for a significantly longer time compared to large PGA sheets. Furthermore, they demonstrated that the post-ESD bleeding rate tended to be lower. On the other hand, there is a possibility that small PGA sheets require a longer time to cover the ESD-induced ulcer than large PGA sheets. In future studies, we must develop techniques that more easily and quickly cover the ESD-induced ulcer with PGA sheets while allowing such sheets to be retained on the ulcer for a longer period of time.

Our study has several limitations. The study was a retrospective, nonrandomized, single-center study with a small number of cases. There was a bias in patient selection for the application of PGA sheets and fibrin glue. Although PGA sheets and fibrin glue tended to be used for large ESD-induced ulcers, the post-ESD bleeding rate of the covering group was significantly lower than that of the control group. In the future, a large, multicenter, prospective, randomized control study is necessary.

In conclusion, our results suggested that the covering method using PGA sheets and fibrin glue is an effective and safe method for reducing post-ESD bleeding in patients under continued antithrombotic agents. We believe that this covering method allows patients to undergo ESD while continuing their use of antithrombotic agents without increased risk of post-ESD bleeding and thromboembolism.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Human rights statement** All procedures followed were in accordance with the ethical standards of the responsible committee on human

experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

**Informed consent** Informed consent or a substitute for such consent was obtained from all patients before inclusion in our study.

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