Endoscopic tissue shielding to prevent bleeding after endoscopic submucosal dissection: a prospective multicenter randomized controlled trial

Authors
Yosuke Kataoka¹, Yosuke Tsuji¹, Kingo Hirasawa², Kengo Takimoto³-⁴, Tomonori Wada⁵, Satoshi Mochizuki⁶, Ken Ohata⁷, Yoshiaki Sakaguchi⁷, Keiko Nilimi¹-⁸, Satoshi Ono⁹, Shinya Kodashima¹⁰, Nobutake Yamamichi¹, Mitsuhiro Fujishiro¹,¹¹, Kazuhiko Koike¹

Institutions
1 Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
2 Division of Endoscopy, Yokohama City University Medical Center, Kanagawa, Japan
3 Department of Gastroenterology, Takeda General Hospital, Kyoto, Japan
4 Department of Gastroenterology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan
5 Department of Gastroenterology, Sanraku Hospital, Tokyo, Japan
6 Shinagawa Gut Clinic, Tokyo, Japan
7 Department of Gastroenterology, NTT Medical Center Tokyo, Tokyo, Japan
8 Center for Epidemiology and Preventive Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
9 Department of Gastroenterology, Chiba-Nishi General Hospital, Matsudo, Japan
10 Department of Gastroenterology, Teikyo University School of Medicine, Tokyo, Japan
11 Department of Endoscopy and Endoscopic Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

submitted 10.9.2018
accepted after revision 4.2.2019

Bibliography
DOI https://doi.org/10.1055/a-0860-5280
Published online: 12.3.2019 | Endoscopy 2019; 51: 619–627
© Georg Thieme Verlag KG Stuttgart · New York
ISSN 0013-726X

Corresponding author
Yosuke Tsuji, MD, PhD, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan
Fax: +81-3-58009522
ytsuji-tky@umin.ac.jp

ABSTRACT

Background Bleeding after endoscopic submucosal dissection (ESD) is a severe adverse event. Recent reports have described the efficacy of the endoscopic shielding method with polyglycolic acid (PGA) sheets and fibrin glue for the prevention of adverse events after ESD. The aim of the present study was to investigate whether the PGA shielding method provides additional benefit in preventing post-ESD bleeding compared with standard care.

Methods This was a prospective, multicenter, randomized controlled trial. Patients at high risk of post-ESD bleeding were enrolled in the study. Before ESD, patients were randomized to either the PGA group or the control group. After completing ESD in the PGA group, PGA sheets were placed onto the ulcer floor and adhered with fibrin glue. The primary end point was the post-ESD bleeding rate.

Results 140 eligible patients were enrolled from September 2014 to September 2016, and 137 were included in the intention-to-treat analysis (67 in the PGA group and 70 in the control group). Post-ESD bleeding occurred in three patients (4.5 %) in the PGA group and in four patients (5.7 %) in the control group; there was no significant difference between the two groups (P>0.99). Post-ESD bleeding tended to occur later in the control group than in the PGA group (median 12.5 days [range 8–14] vs. 2 days [range 0–7], respectively).

Conclusion The PGA shielding method did not demonstrate a significant effect on the prevention of post-ESD bleeding.

University Hospital Medical Network Clinical Trials Registry UMIN000015091
TRIAL REGISTRATION: prospective multicenter randomized controlled trial UMIN000015091 at http://www.umin.ac.jp
Introduction

Endoscopic submucosal dissection (ESD) for superficial gastric neoplasms has become established as the standard method of treatment in many countries. ESD was first developed in the 1990s as an advanced technique to overcome the limitations of conventional endoscopic mucosal resection (EMR) [1]. ESD has advantages over EMR in that resecting a tumor in an en bloc fashion is possible regardless of tumor size, shape, or ulceration, contributing to accurate histological diagnosis of specimens and a decrease in local recurrence [2–4].

However, ESD is technically difficult and involves a high risk of procedure-related adverse events such as post-ESD bleeding or perforation [2,3,5]. Especially in gastric ESD, post-ESD bleeding is one of the most severe adverse events, and may lead to serious hemorrhagic shock requiring blood transfusion or urgent surgery [6,7]. Therefore, prevention of post-ESD bleeding is a clinically important issue that needs to be addressed.

There are currently two established effective bleeding prevention methods: proton pump inhibitors (PPI) to promote healing of ulcers after gastric ESD [8,9], and coagulation of visible vessels in the post-ESD ulcers [6]. However, even with these preventive methods, the rate of post-ESD bleeding is approximately 5% [2,10,11], signifying that post-ESD bleeding cannot be completely prevented with only these methods of standard care.

Several reports have revealed that the use of antithrombotic agents and large resection size (≥40 mm) are significant risk factors for post-ESD bleeding [10,12–19]. Considering the increasing population of patients taking antithrombotic agents and the expanded indications for ESD, including large intramuscosal gastric cancer [20], the number of patients at high risk for post-ESD bleeding is expected to increase. Therefore, the development of another effective prevention method for post-ESD bleeding is desirable.

Recent reports have described the shielding method, using polyglycolic acid (PGA) sheets and fibrin glue, as a method of preventing ESD-related adverse events [21–24]. PGA sheets are widely used in surgical fields as an absorbable material to reinforce suturing [25,26]. In the field of endoscopic intervention, Takimoto et al. originally reported the efficacy of shielding the ulcer after duodenal ESD using PGA sheets and fibrin glue to prevent delayed perforation [21]. Tsuji et al. performed a prospective pilot study to investigate the efficacy of this shielding method to prevent bleeding after gastric ESD in high risk patients – those taking antithrombotic agents or those who were expected to undergo large resections (≥40 mm). The study indicated that PGA sheets and fibrin glue could decrease the rate of post-ESD bleeding (PGA group 6.7% vs. control group 22.0%; P=0.04) [23]. Based on these reports, we hypothesized that PGA sheets and fibrin glue can decrease bleeding after gastric ESD in high risk patients.

In order to verify the additional effect of this method to prevent post-ESD bleeding compared with standard care, the Polyglycolic Acid and fibrin Glue to ERadicate Bleeding Ulcer in the Stomach ESD for Risked patient (PAGER BUSTER) trial was designed. This study is the first randomized controlled trial (RCT) on the efficacy of the shielding method for the prevention of bleeding after gastric ESD.

Methods

Study design

This multicenter, open-label, prospective RCT (PAGER BUSTER trial) was undertaken in six referral institutions across Japan. The study protocol was approved by the ethics committee of each participating institution, and the study was registered at the University Hospital Medical Network Clinical Trial Registry (UMIN) on 9 September 2014 (UMIN000015091). After ethics approval and study registration, patient enrollment began on 17 September 2014. The study was conducted in accordance with the Declaration of Helsinki, and all participating patients gave written informed consent before enrollment. The trial investigators collected and analyzed the data, and all co-authors made the decision to submit the manuscript for publication.

Patients

Patients who were scheduled for ESD of gastric adenoma or early gastric cancer and who were at high risk of post-ESD bleeding were enrolled in the study. High risk patients were defined as those with regular intake of antithrombotic agents or those expected to undergo large mucosal resection (≥40 mm).

Patients were eligible to participate in the trial if they fulfilled all of the following inclusion criteria: 1) at least one of the high risk criteria mentioned above; 2) age ≥20 years; 3) Eastern Cooperative Oncology Group Performance Status 0, 1 or 2; 4) preoperative computed tomography showing no lymph node or other organ metastasis; 5) hemoglobin ≥9 g/dL, platelet ≥100 000/mm³, aspartate aminotransferase and alanine aminotransferase ≤100 IU/L, and creatinine ≤2.0 mg/dL in the laboratory blood test performed within 1 month before enrollment.

Patients were excluded if they had at least one of the following exclusion criteria: 1) upper gastrointestinal endoscopic intervention within 28 days before enrollment; 2) multiple mucosal defects after ESD for multiple lesions; 3) history of allergy to PPI or components of fibrin glue; 4) requirement for heparin bridge therapy; 5) those who had developed unstable angina or myocardial infarction within 3 months before enrollment. The reason for excluding the patients under heparin bridge therapy was that the PGA shielding method was not effective for these patients according to the report by Tsuji et al. (post-ESD bleeding rate 42.9% in the PGA group vs. 33.3% in the control group; P>0.99) [23].

Before ESD, patients were allocated to either the PGA group or the control group at a ratio of 1:1 by minimization method through a web-based system (University Hospital Clinical Trial Alliance Clinical Research Supporting System: UHCT ACReSS). We set the allocation factors as: 1) the tumor location (antrum or body); 2) the facilities where ESD was performed; 3) the stratification of risk – a) continued use of antithrombotic agents and resection size ≥40 mm, b) cessation of antithrombotic agents and resection size ≥40 mm, c) no antithrombotic agents...
and resection size ≥ 40 mm, d) continued use of antithrombotic agents and resection size < 40 mm, e) cessation of antithrombotic agents and resection size < 40 mm.

ESD procedures

ESD was performed in principle according to the standard method using a therapeutic endoscope (GIF-Q260; Olympus Medical, Tokyo, Japan) and an electrosurgical unit (VIO 300D; Erbe, Tübingen, Germany). The procedure consisted of the following steps: 1) marking around the lesion; 2) submucosal injection of 0.2% – 0.4% sodium hyaluronic acid solution or normal saline; 3) mucosal incision and submucosal dissection with an ESD device; 4) coagulation of visible vessels on the ESD ulcer floor by hemostatic forceps [27]. Step 4 was the last procedural step for patients in the control group.

PGA sheet application

After completing ESD procedures, the shielding method with PGA sheets (Neovel; Gunze Co, Osaka, Japan) and fibrin glue (Beriplast P Combi-Set; CSLBehring Pharma, Tokyo, Japan) was performed in the PGA group (Fig.1).

PGA sheet application was performed according to one of the following two methods: 1) a PGA sheet was cut into approximately 2 × 1 cm pieces, and each piece was grasped by hemostatic forceps and delivered onto the ESD ulcer through the working channel until the ulcer was completely covered (step-by-step method) [21]; 2) a PGA sheet cut was cut into a 5 × 5 cm piece, which was grasped by hemostatic forceps and wrapped around the endoscope, and then inserted orally to the ESD ulcer. Clips were then used to anchor and fix the PGA sheet (clip-and-pull method) [28]. After delivery, PGA sheets were adhered to the ESD ulcer using fibrin glue. The choice of delivery was at the discretion of each endoscopist.

Perioperative management and follow-up after ESD

Patients took 10 mg rabeprazole orally for 30 days from the day before ESD. Oral ingestion was prohibited from the morning of ESD until the day after ESD. Laboratory findings and X-ray were checked on the day after ESD. Scheduled second-look endoscopy was not performed, based on the study by Mochizuki et al. [29]. If a patient developed hematemesis, melena or showed a decrease in hemoglobin ≥ 2.0 g/dL, urgent endoscopy was performed at the discretion of the doctor in charge. Post-ESD bleeding was defined as the condition where urgent endoscopy showed clot accumulation in the stomach or endoscopic hemostasis was required. All patients were followed up until 28 days after ESD.

Study outcomes

The post-ESD bleeding rate was set as the primary end point to investigate whether there was an additional benefit of the PGA shielding method for preventing post-ESD bleeding compared with standard care. In addition, risk factors for post-ESD bleeding were analyzed.

The secondary end points were: 1) the rate of post-ESD bleeding in cases where the long diameter of the resected specimen was ≥ 40 mm; 2) the frequency of urgent endoscopy; and 3) adverse events associated with PGA sheets and fibrin glue.

Statistical analysis

All statistical analyses were conducted using JMP version 11 (SAS Institute Inc., Cary, North Carolina, USA). Categorical data were compared using Fisher’s exact test. Continuous data were compared using Student’s t test or the Mann-Whitney U test. All tests were two sided, and a P value of < 0.05 was considered significant.

In the pilot study by Tsuji et al., the post-ESD bleeding rate was 0% in the PGA group and 21.1% in the control group, excluding those under heparin bridge therapy [23]. According to these data, we calculated that 130 patients would give the study a power of 80% to detect the superiority of the PGA shielding method, assuming a rate of post-ESD bleeding to be 4% in the PGA group and 21% in the control group with a two-sided alpha level of 0.05. Finally, we determined the required sample size to be 140 patients (70 patients in each group) taking account of approximately a 5% dropout rate.

Results

Patients

We enrolled 140 eligible patients from September 2014 to September 2016 at six facilities across Japan (Fig.2). A total of 68 patients were assigned to the PGA group and 72 patients to the control group. After excluding three patients (ESD cancellation in 2, consent withdrawal in 1), 67 patients in the PGA group and 70 patients in the control group were included in the intention-to-treat analysis. The baseline characteristics of the patients and tumors are shown in Table 1. The patient characteristics...
were evenly distributed between the two groups, including age and use of antithrombotic agents.

**ESD procedure and PGA sheet application**

All ESD procedures were completed without life-threatening events and 137 ESD ulcers were created. The rate of en bloc resection was 100% and the rate of R0 resection was 92.0% \((127/137)\) (Table 1). Intraoperative perforation occurred at a rate of 2.2% \((3/137)\). All three perforations were managed by endoscopic clipping. The mean resection size was 47.5 mm \((SD 12.9 mm)\) in the PGA group and 51.3 mm \((SD 16.1 mm)\) in the control group \((P=0.23)\).

In the PGA group \((step-by-step method 24; clip-and-pull method 43)\), complete shielding was achieved in 61 ESD ulcers \((91.0\%)\), and partial shielding was achieved in 6 ESD ulcers \((step-by-step method 3; clip-and-pull method 3)\). The mean procedure time for applying PGA sheets and fibrin glue was 25.5 minutes \((SD 15.0 minutes)\). The mean procedure time of the clip-and-pull method was significantly shorter than that of the step-by-step method \((21.5 vs. 32.7 minutes, respectively; P=0.03)\).

**Primary end point**

Post-ESD bleeding occurred in 4.5% \((3/67)\) in the PGA group and in 5.7% \((4/70)\) in the control group (Table 2a). There was no significant difference in post-ESD bleeding rate between the two groups \((P>0.99)\). Details of the post-ESD bleeding cases are shown in Table 2b. Endoscopic hemostasis was achieved in all bleeding cases, and only one case from the control group required blood transfusion. For the post-ESD bleeding cases in the PGA group, all three ESD ulcers had been completely covered with PGA sheets. In the control group, post-ESD bleeding tended to occur later than in the PGA group \((median 12.5 days [range 8–14] vs. 2 days [range 0–7 days], respectively)\) (Fig. 3).

---

**Table 1** Baseline characteristics of patients and endoscopic submucosal dissection procedures.

<table>
<thead>
<tr>
<th></th>
<th>PGA group ((n=67))</th>
<th>Control group ((n=70))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>72.9 (8.8)</td>
<td>73.0 (9.4)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>36 (53.7)</td>
<td>35 (50.0)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>12 (17.9)</td>
<td>17 (24.3)</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>9 (13.4)</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Antithrombotic agent therapy, n (%)</td>
<td>24 (35.8)</td>
<td>28 (40.0)</td>
</tr>
<tr>
<td>Continued use/cessation</td>
<td>5/19</td>
<td>8/20</td>
</tr>
<tr>
<td>ESD procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor location, antrum/body, n</td>
<td>19/48</td>
<td>19/51</td>
</tr>
<tr>
<td>Resection size, mean (SD), mm</td>
<td>47.5 (12.9)</td>
<td>51.3 (16.1)</td>
</tr>
<tr>
<td>Resection time, mean (SD), minutes</td>
<td>138.6 (77.4)</td>
<td>137.1 (80.5)</td>
</tr>
<tr>
<td>Preventive coagulation time, mean (SD), minutes</td>
<td>10.5 (5.6)</td>
<td>8.8 (4.7)</td>
</tr>
<tr>
<td>En bloc resection, n (%)</td>
<td>67 (100)</td>
<td>70 (100)</td>
</tr>
<tr>
<td>R0 resection, n (%)</td>
<td>60 (89.6)</td>
<td>67 (95.7)</td>
</tr>
<tr>
<td>Intraoperative perforation, n (%)</td>
<td>2 (3.0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Pathological diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size, mean (SD), mm</td>
<td>23.8 (11.2)</td>
<td>26.9 (15.2)</td>
</tr>
<tr>
<td>Adenoma, n</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Differentiated carcinoma, n</td>
<td>50</td>
<td>62</td>
</tr>
<tr>
<td>Undifferentiated carcinoma, n</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Mixed carcinoma, n</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Carcinoma depth, M/SM/MP, n</td>
<td>48/16/1</td>
<td>59/9/0</td>
</tr>
</tbody>
</table>

PGA, polyglycolic acid; SD, standard deviation; ESD, endoscopic submucosal dissection; M, mucosa; SM, submucosal; MP, muscularis propria.

**Table 2a** Results of bleeding after endoscopic submucosal dissection (ESD), a Rate of post-ESD bleeding.

<table>
<thead>
<tr>
<th>Primary end point</th>
<th>PGA group ((n=67))</th>
<th>Control group ((n=70))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-ESD bleeding, n (%)</td>
<td>3 (4.5)</td>
<td>4 (5.7)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

PGA, polyglycolic acid; ESD, endoscopic submucosal dissection; POD, postoperative day.
Secondary end points
The results of the secondary end points are shown in Table 3. Prior to enrollment, 104 patients were expected to undergo large-sized resection, whereas 105 resected specimens were ≥40 mm. In these 105 patients, the rate of post-ESD bleeding was 6.0% (3/50) in the PGA group and 5.5% (3/55) in the control group (P > 0.99).

The rate of urgent endoscopy in the PGA group tended to be lower than in the control group (7.5% and 12.9%, respectively; P = 0.40). The reasons for urgent endoscopy other than bleeding symptoms were delayed perforation in one patient, which was successfully closed by clips and managed conservatively, and pyloric stenosis in one patient, which required distal gastrectomy following unsuccessful balloon dilation. Both occurred in the control group.

There were no adverse events associated with PGA sheets and fibrin glue.

Risk factors for post-ESD bleeding
In univariate analysis, intake of multiple antithrombotic agents (P = 0.03) and lesions in the lesser curvature (P = 0.045) were significant risk factors (Table 4). No multivariate analysis was performed because post-ESD bleeding only occurred in seven patients.

Discussion
This study is the first RCT to investigate the effect of PGA sheets and fibrin glue for the prevention of post-ESD bleeding. Previously, Tsuji et al. reported that the PGA shielding method decreased the risk of post-ESD bleeding in a nonrandomized trial with historical control subjects [23]. Moreover, Kawata et al. reported that the PGA shielding method might exert a preventive effect on delayed bleeding in patients who underwent gastric ESD while continuing with their antithrombotic therapy [30]. However, the present study could not demonstrate a significant additional effect of the PGA shielding method over standard care to prevent bleeding. One possible reason for this result might be the unexpected low bleeding rate in the control group. Several reports have indicated that taking antithrombotic agents (odds ratio [OR] 2.67 – 5.44) and a large mucosal resection (OR 2.15 – 3.25) are risk factors for post-ESD bleeding [10, 12 – 14, 16, 31]. However, post-ESD bleeding occurred at a rate of only 5.1% in the control group of the present study, which is almost equivalent to that of low risk patients; this result implies that the inclusion criteria in the study were not optimal.
### Table 3  Secondary end points.

<table>
<thead>
<tr>
<th></th>
<th>PGA group (n=67)</th>
<th>Control group (n=70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with resection size ≥ 40 mm, n</td>
<td>50</td>
<td>55</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>• Post-ESD bleeding, n (%)</td>
<td>3 (6.0)</td>
<td>3 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Cases requiring urgent endoscopy, n (%)</td>
<td>5 (7.5)</td>
<td>9 (12.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>• Reasons for urgent endoscopy</td>
<td>3 post-ESD bleeding 1 hematochezia (without endoscopic hemostasis) 1 melena (without endoscopic hemostasis)</td>
<td>4 post-ESD bleeding 1 melena (without endoscopic hemostasis) 2 hemoglobin decrease ≥ 2 g/dL (without endoscopic hemostasis) 1 delayed perforation 1 pyloric stenosis</td>
<td></td>
</tr>
</tbody>
</table>

PGA, polyglycolic acid; ESD, endoscopic submucosal dissection.

### Table 4  Risk factors for bleeding after endoscopic submucosal dissection (univariate analysis).

<table>
<thead>
<tr>
<th></th>
<th>Post-ESD bleeding (n=7)</th>
<th>No bleeding (n=130)</th>
<th>P value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>78.7 (4.3)</td>
<td>72.8 (9.2)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>5 (71.4)</td>
<td>66 (50.8)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (28.6)</td>
<td>27 (20.8)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>2 (28.6)</td>
<td>18 (13.9)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Antithrombotic agent therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Multiple</td>
<td>2 (28.6)</td>
<td>4 (3.1)</td>
<td>0.03</td>
<td>10.12 (1.42 – 72.75)</td>
</tr>
<tr>
<td>• Monotherapy</td>
<td>1 (14.3)</td>
<td>45 (34.6)</td>
<td>0.45 (0.05 – 4.15)</td>
<td></td>
</tr>
<tr>
<td>• None</td>
<td>4 (57.1)</td>
<td>81 (62.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor location, n (%)</td>
<td></td>
<td></td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>• Antrum</td>
<td>1 (14.3)</td>
<td>37 (28.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Body</td>
<td>6 (85.7)</td>
<td>93 (71.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lesser curvature</td>
<td>6 (85.7)</td>
<td>55 (42.3)</td>
<td>0.045</td>
<td>8.18 (0.96 – 69.92)</td>
</tr>
<tr>
<td>• Others</td>
<td>1 (14.3)</td>
<td>75 (57.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor morphology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Elevating (I or Ia)</td>
<td>2 (28.6)</td>
<td>49 (37.7)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>• Flat/depressed (IIb or IIc)</td>
<td>5 (71.4)</td>
<td>81 (62.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth, submucosal invasion, n (%)</td>
<td>1 (14.3)</td>
<td>24 (18.5)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Ulceration, n (%)</td>
<td>0 (0)</td>
<td>12 (9.2)</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Carcinoma histology, n (%)</td>
<td>7 (100)</td>
<td>126 (96.9)</td>
<td>&gt;0.99</td>
<td></td>
</tr>
<tr>
<td>Operation time, mean (SD), minutes</td>
<td>127.9 (40.9)</td>
<td>138.4 (80.3)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Preventive coagulation time, mean (SD), minutes</td>
<td>9.4 (5.7)</td>
<td>9.6 (5.3)</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Beginner operator (&lt;30 ESD cases), n (%)</td>
<td>1 (14.3)</td>
<td>20 (15.4)</td>
<td>&gt;0.99</td>
<td></td>
</tr>
</tbody>
</table>

ESD, endoscopic submucosal dissection; OR, odds ratio; CI, confidence interval; SD, standard deviation.
Therefore, we investigated whether the type of antithrombotic agent had influenced the results in the current study. There was no significant difference in the distribution of antithrombotic agent types between the two groups \((P = 0.43)\) (▶ Fig. 4). Most of the enrolled patients took aspirin only or relatively low risk antithrombotic agents such as eicosapentaenoic acid, limaprost, or sarpogrelate (▶ Table 5). A recent meta-analysis on the risk factors for post-ESD bleeding revealed that antithrombotic agents \((OR 1.63)\) and large mucosal resection \(> 30\) mm \((OR 2.85)\) are significant risk factors for post-ESD bleeding; however, the study also mentioned that antiplatelet monotherapy with cessation 1 week before ESD is not a significant risk factor for bleeding. In addition, it was described that post-ESD bleeding was associated with the use of anticoagulants and double antiplatelet therapy but not with antiplatelet monotherapy [32].

A univariate analysis on the risk factors for post-ESD bleeding revealed that intake of multiple antithrombotic agents \((P = 0.03)\) and lesions in the lesser curvature \((P = 0.045)\) were significant risk factors (▶ Table 4), which was compatible with the result of the abovementioned meta-analysis [32]. Considering these facts, one possible explanation for the results in the present study is that patients with relatively low risk were enrolled. Patients taking dual antiplatelet therapy or anticoagulants may have been more optimal as a high risk group for post-ESD bleeding. There is a possibility that there may be a group of patients who are at higher risk than those in the present study, and for whom PGA shielding may be more selectively applied.

In addition, recent technological advancement in ESD might contribute to the reduction in the post-ESD bleeding rate. In 2012, Cho et al. reported that the post-ESD bleeding rate was \(21.1\%\) in continuous aspirin users, concluding that continuous aspirin use increased the risk of post-ESD bleeding [18]. However, many reports have shown that continuous aspirin use does not contribute to post-ESD bleeding [15, 33]. This might be partly because of improvements in the ESD technique itself or in postoperative management. The unpredictably low rate of post-ESD bleeding in the present study might be partly attributed to such advancements in ESD.

In the large-sized \((≥ 40\) mm) resection cases in the present study, only \(5.5\%\) \((3/55)\) of the patients in the control group developed post-ESD bleeding, although prior studies indicated that large mucosal resection was a significant risk factor for post-ESD bleeding [10, 12, 13, 15]. In the present study, it took approximately 10 minutes to perform preventive coagulation of visible vessels on the ESD ulcers (▶ Table 1). To date, no investigations have looked at the association between the time for preventive coagulation and post-ESD bleeding rate; however, especially long preventive coagulation time might have contributed to the low rate of post-ESD bleeding in the large-sized resection cases.

Post-ESD bleeding in the control group occurred more than 7 days after ESD in all four cases, whereas there were no late-phase bleeding events in the PGA group (▶ Fig. 3). Although it is difficult to draw any conclusions from only seven cases of post-ESD bleeding, the PGA shielding method might be effective for the prevention of late-phase bleeding.
Tsujimoto et al. reported that the PGA shielding method promotes healing of ESD ulcers by providing a scaffold function in an animal experiment using the canine stomach model \[34\]. Based on this mechanism there is a possibility that the PGA shielding is not a fast-acting method, which might have contributed to the fact that this method could not prevent the early-phase bleeding. Sato et al. reported that bleeding later than 7 days after ESD tended to occur in the patients taking dual antiplatelet therapy or anticoagulant agents \[35\]. Therefore, the efficacy of the PGA shielding method could be exerted on these high risk patients.

In terms of feasibility of the PGA shielding method, the present study showed that the rate of successful covering of the ESD-induced ulcer by the PGA sheets was satisfactory (91.0%), and the safety of PGA sheets and fibrin glue was elucidated despite a longer procedure time (mean 25.5 minutes). The method of PGA sheet application (step-by-step method or clip-and-pull method) was chosen at the discretion of each endoscopist. The endoscopists at the University of Tokyo tended to choose the clip-and-pull method compared with other facilities: 38 in clip-and-pull and 7 in step-by-step (University of Tokyo) vs 5 and 17, respectively (other study centers). Although the mean procedure time of the clip-and-pull method was significantly shorter than that of the step-by-step method (21.5 vs. 32.7 minutes, respectively; \( P = 0.03 \)), experience of several cases were required in order to master the clip-and-pull technique. It is essential to improve the delivery method of PGA sheets.

There are some limitations to this study. First, the participating facilities were all high volume centers for gastric ESD; therefore, the results of this study may not be applied to low volume centers. Second, our study was an open-label RCT and some biases cannot be eliminated. Double blinding was difficult to conduct because of the nature of the study design; however, for the definition of post-ESD bleeding, urgent endoscopic observation was a requisite for the diagnosis of post-ESD bleeding, minimizing observer bias. Third, second-look endoscopy was not performed in order to make the judgment of post-ESD bleeding. Therefore, how long the PGA sheet remained on the ESD-induced ulcer could not be assessed. The duration of PGA sheet adherence is an issue for future studies to elucidate.

In conclusion, the present study could not demonstrate a significant effect of the PGA shielding method on the prevention of post-ESD bleeding.

**Competing interests**

Drs. Tsuji, Takimoto, and Fujishiro have received lecture fees from GUNZE and CSL Behring.

---

**References**

33. Sanomura Y, Oka S, Tanaka S et al. Continued use of low-dose aspirin does not increase the risk of bleeding during or after endoscopic submucosal dissection for early gastric cancer. Gastric Cancer 2014; 17: 489–496