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ENDOSCOPY

Comparison of a Polysaccharide Hemostatic Powder and Conventional Therapy for Peptic Ulcer Bleeding

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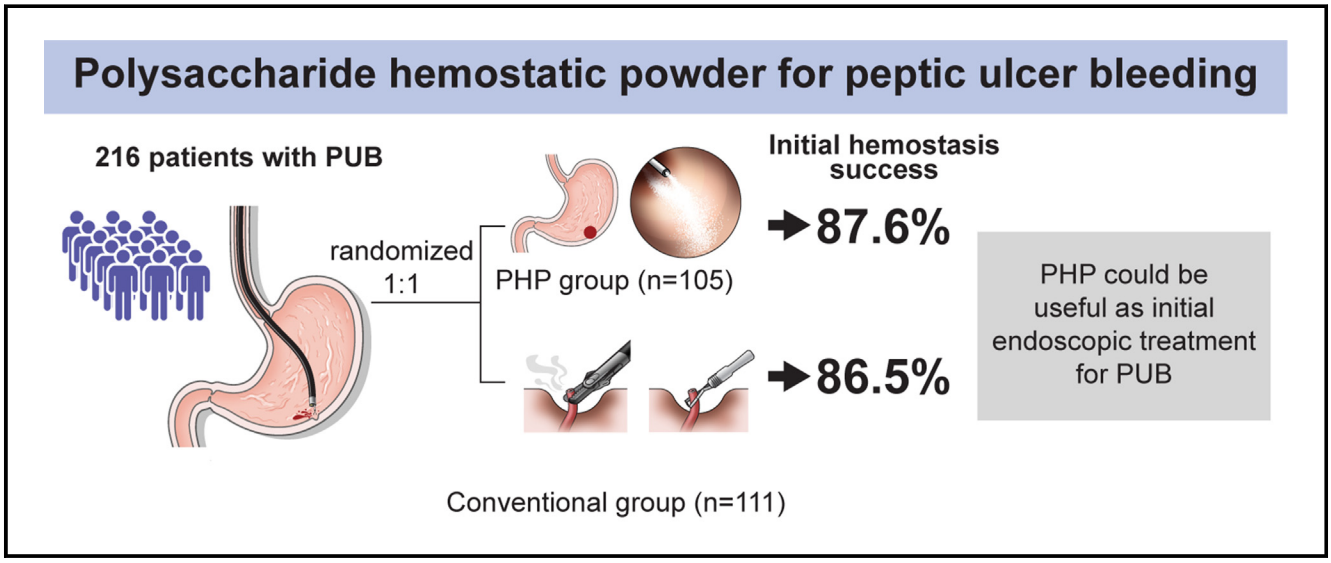

BACKGROUND & AIMS: Hemostatic powders have been clinically used in the treatment of gastrointestinal bleeding. We investigated the non-inferiority of a polysaccharide hemostatic powder (PHP), compared with conventional endoscopic treatments, for peptic ulcer bleeding (PUB).

METHODS: This study was a prospective multi-center, randomized, open-label, controlled trial at 4 referral institutions. We consecutively enrolled patients who had undergone emergency endoscopy for PUB. The patients were randomly assigned to either a PHP or conventional treatment group. In the PHP group, diluted epinephrine was injected, and the powder was applied as a spray. Conventional endoscopic treatment included the use of electrical coagulation or hemoclipping after injection of diluted epinephrine.

RESULTS: Between July 2017 and May 2021, 216 patients were enrolled in this study (PHP group, 105; control group, 111). Initial hemostasis was achieved in 92 of 105 patients (87.6%) in the PHP group and 96 of 111 patients (86.5%) in the conventional treatment group. Re-bleeding did not differ between the 2 groups. In subgroup analysis, the initial hemostasis failure rate in the conventional treatment group was 13.6% for Forrest IIa cases; however, there was no initial

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Abbreviations used in this paper: CUSUM, cumulative sum; NVUGIB, non-variceal upper gastrointestinal bleeding; PHP, polysaccharide hemostatic powder; PPI, proton pump inhibitor; PUB, peptic ulcer bleeding; RCTs, randomized controlled trials; UGIB, upper gastrointestinal bleeding.

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hemostasis failure in the PHP group ($P = .023$). Large ulcer size (≥15 mm) and chronic kidney disease with dialysis were independent risk factors for re-bleeding at 30 days. No adverse events were associated with PHP use.

CONCLUSIONS: **PHP is not inferior to conventional treatments and could be useful in initial endoscopic treatment for PUB. Further studies are needed to confirm the re-bleeding rate of PHP. ClinicalTrials.gov, Number: NCT02717416).**

Keywords: Endoscopy; Hemostasis; Hemostatic Powder; Upper Gastrointestinal Bleeding.

The most common cause of acute upper gastrointestinal bleeding (UGIB) is non-variceal bleeding, and the most common lesions are peptic ulcers of the stomach and duodenum.[1] With the ageing of society and increasing use of antithrombotic agents and non-steroidal anti-inflammatory drugs, the number of patients at high risk of bleeding has increased.[2-5] Therefore, sufficient and effective treatment of acute UGIB is required, which can be clinically challenging in some cases. Conventional endoscopic treatments for acute UGIB, such as epinephrine injection, clipping, electrical coagulation, and argon plasma coagulation, achieve hemostasis in more than 90% of cases.[6] Although conventional endoscopic treatment is considered the gold standard for achieving hemostasis, conventional treatment can be technically challenging, depending on the bleeding site and etiology, and may not be optimal in some cases. Recently, a new modality, hemostatic powder, has been shown to have several advantages over conventional methods in that it is a non-contact method and is easily applied for the treatment of gastrointestinal bleeding.[7] Several hemostatic agents are available on the market; however, prospective randomized controlled trials (RCTs) are still lacking to determine whether they have an effect comparable to that of existing conventional methods. A recent study compared the effectiveness of endoscopic hemostasis between mineral powder (TC-325) and conventional methods in patients with acute non-variceal upper gastrointestinal bleeding (NVUGIB).[8] A polysaccharide hemostatic powder (PHP) with a mechanism similar to that of TC-325, but with different ingredients, has also been recently developed and used in clinical practice.[9] Our group has demonstrated the feasibility of PHP for endoscopic treatment of UGIB and recorded similar effectiveness to conventional treatments.[10] Although PHP has been shown to be effective in UGIB, there has been no multicenter prospective RCT on the efficacy of PHP in peptic ulcer bleeding (PUB). Therefore, we designed a prospective, multicenter RCT to examine the efficacy of PHP in patients with acute PUB with sufficient power to produce conclusive results.

Methods

Patients

Between July 2017 and May 2021, we enrolled patients who underwent emergency endoscopy for NVUGIB in this multicenter, open-label, prospective RCT conducted at 4 referral institutions across Korea. Written informed consent was obtained from all patients before enrollment in the study prior to their urgent gastroscopy. Major inclusion criteria were as follows: symptoms of hematemesis, melena, or hematochezia within 72 hours that required emergency endoscopy; exclusion criteria were also as follows: (1) suspected bleeding due to upper gastrointestinal cancer or causes other than PUB; and (2) suspected variceal bleeding among patients with a history of cirrhosis or liver cancer. Other inclusion and exclusion criteria are described in Supplementary Appendix 1. In cases in which lesions had no signs of active or recent bleeding, such as Forrest IIc or III, where endoscopic treatment was unnecessary, the patients were withdrawn from the trial. For Forrest IIb lesions, we attempted to remove blood clots by vigorous irrigation and to identify underlying lesions that required endoscopic hemostasis. If the lesions did not require endoscopic hemostasis, they were not included in this study. A single study coordinator performed randomization using a computer-generated randomization table, and the allocation sequence was concealed until assignment occurred. Patients were randomly assigned at a 1:1 ratio to either the PHP or conventional treatment group. The study protocol was approved by the institutional review boards of each participating institution (4-2016-0027), and the study was registered at ClinicalTrials.gov (identifier 02717416).

Study Treatments

As a general treatment for all enrolled patients with acute UGIB, intravenous fluid therapy was started for hemodynamic stability before endoscopy, and a high-dose proton pump inhibitor (PPI) (Nexium or Pantoloc) (intravenous PPI 80 mg bolus injection, followed by 8 mg/h infusion for 72 hours) was administered. If a bleeding peptic ulcer lesion was confirmed, endoscopic hemostasis was performed. A small amount of 1:10,000 diluted epinephrine was injected initially around the bleeding site in both the PHP and conventional endoscopic groups. The diluted epinephrine was injected at 1∼2 cc per injection, and the total amount did not exceed 6 cc. In the PHP group, the powder was sprayed directly onto the surface of the bleeding site using a 2300-mm catheter through the endoscopic working

channel under continuous airflow, as previously described. While spraying the powder, the catheter tip was placed about 1 to 2 cm away from the lesion (Video 1).[11] Additional powder (up to 3 times) was allowed if the bleeding could not be stopped. In the conventional treatment group, endoscopic treatment was selected at the discretion of the endoscopists, taking into account various conditions, such as location and amount of bleeding and the proficiency of the endoscopists. Conventional endoscopic treatment included electrical coagulation and hemoclipping (through the scope). Electrical coagulation was achieved using hemostatic forceps (Coagrasper; Olympus Co, Tokyo, Japan). If active bleeding persisted when using PHP or conventional endoscopic treatment, additional hemostasis procedures were performed using other hemostasis methods, such as argon plasma coagulation, hemoclipping, or PHP, at the discretion of the endoscopists. At the end of the endoscopy, we asked the endoscopists to rate the difficulty of the endoscopic procedure on a 5-point Likert scale regardless of the success or failure of endoscopic treatment. Experts were defined as those who had more than 1 year of experience in gastrointestinal endoscopy, and trainees were defined as those who had been in the process of learning gastrointestinal endoscopy for less than 1 year.

Perioperative Management and Post Follow-up

Perioperative management and follow-up plan are summarized in Supplementary Appendix 2. The analysis of re-bleeding was based on blood tests and symptoms up to 2 weeks before visiting the outpatient department and confirmed for up to 1 month. The management of antithrombotic agents was defined as follows: (1) for patients receiving aspirin monotherapy for the prophylaxis of coronary artery occlusive disease or cerebrovascular disease (primary prevention), aspirin was discontinued for the duration of the study at the discretion of the investigator; and (2) patients receiving antithrombotic agents for secondary prevention continued them the day after hemostasis if endoscopic hemostasis was successful. For patients with peptic ulcer disease, tests for *Helicobacter pylori* (*H. pylori*) infection, including rapid urease test, were performed. *H. pylori* infection was treated after completing the current clinical trial and ulcer healing.

Study Outcomes

Initial hemostasis success was defined as cessation of bleeding for at least 5 minutes after initial treatment. Re-bleeding was defined as hematemesis, melena, hematochezia, or a decrease in hemoglobin level of $\geq$2.0 g/dL with urgent endoscopy findings showing bleeding in the stomach or a requirement for endoscopic hemostasis. The primary outcome was the rate of initial hemostasis success to investigate the efficacy of PHP for PUB, compared with that of conventional therapy. The secondary outcomes were re-bleeding rates in 30 days, re-bleeding rates according to Forrest classification, and proficiency according to operator or location. If there were any signs of re-bleeding after discharge, patients were instructed to visit our outpatient department or emergency room at any time to receive additional treatment. Therefore, we could assess the time of re-bleeding and the rates of re-bleeding within 30 days.

What You Need to Know

Background

Recently, a new modality, hemostatic powder, has been shown to be effective for the treatment of gastrointestinal bleeding. However, prospective randomized controlled trials are still lacking to compare between polysaccharide hemostatic powder (PHP) and conventional methods.

Findings

The initial hemostasis success rate of the PHP group was not inferior to that of the conventional treatment group. The re-bleeding rate also did not differ between the 2 groups. No adverse events were associated with PHP use.

Implications for patient care

Results highlight that PHP could be an initial endoscopic treatment for peptic ulcer bleeding and is not inferior to conventional endoscopic methods.

Sample Size Calculation

We hypothesised that the endoscopic application of PHP would not be inferior to conventional endoscopic treatment in the control of PUB. Based on a previous study,[12,13] we estimated that the rate of initial hemostasis success of conventional endoscopic treatment was 83%. We chose a non-inferiority margin of -15% as the minimum threshold for an unacceptable loss of efficacy of PHP. The sample size was calculated using a significance level of 0.025 (1-tailed) and a statistical power of 0.8 ($\alpha = 0.025$ [one-tailed]; $1 - \beta = 0.8$). The calculated sample size was 98 patients in each arm, for a total of 226 patients, allowing for a 15% dropout rate.

Statistical Analysis

Continuous variables are presented as means $\pm$ standard deviations, and discrete variables are presented as frequencies (%). The χ^2 test or the Fisher exact test was used to compare categorical parameters. The Student t test was used to compare continuous variables. Logistic regression analysis was used to identify

independent risk factors associated with re-bleeding at 30 days. Only variables with *P*-value < .1 in the univariable logistic regression model were included in multivariable analysis. Differences were considered significant at 2-sided $P < .05$. We assessed the learning curve using the cumulative sum (CUSUM) method (Supplementary Appendix 3).

Results

Baseline Characteristics of the Patients and Endoscopic Outcomes

Between July 2017 and May 2021, 234 patients with acute UGIB were screened at 4 institutions across Korea. Of these, 6 patients did not have stigmata of recent bleeding during endoscopy; in 2 patients, the cause of bleeding was a tumor; and in 10 patients, the causes of bleeding were non-peptic ulcer bleeding such as angioectasia, Dieulafoy lesion, and Mallory-Weiss tear bleeding. Of the 216 patients with stigmata of recent bleeding from peptic ulcer enrolled in this study, 105 and 111 were assigned to the PHP and conventional treatment groups, respectively (Figure 1). The baseline characteristics of the patients are shown in Table 1. There were no differences in the baseline characteristics between the PHP and conventional treatment groups. A total of 98 patients were taking antithrombotics. The mean Rockall scores, Glasgow-Blatchford scores, and AIMS65 values were not significantly different between the 2 groups.

Success Rate of Initial Hemostasis

Initial hemostasis success was achieved in 87.6% and 86.5% in the PHP and conventional treatment groups, respectively (Table 2). In the conventional treatment group, initial hemostasis treatment included hemoclipping (n = 56) and electrical coagulation (n = 55) with epinephrine pre-injection. The initial hemostasis success rate was not significantly different between the groups. Initial hemostasis failure occurred in 12.4% and 13.5% (1-sided 97.5% confidence interval CI, -1.1 [−∞ to 7.8]) of patients in the PHP and conventional treatment groups, respectively. Interestingly, in the cases of Forrest IIa classification, the initial hemostasis failure rate in the conventional treatment group was 13.6%, whereas there was no initial hemostasis failure in the PHP group ($P = .023$). Of the 8 patients with Forrest IIa lesions who had immediate hemostasis failure, hemoclipping was used for initial hemostasis in all patients. In the PHP group, all patients underwent hemoclipping as a salvage treatment after initial hemostasis failure. In the conventional treatment group, 2 patients underwent electrical coagulation, 10 patients underwent hemoclipping, 1 patient underwent argon plasma coagulation, and 2 patients received PHP. No adverse events were associated with PHP.

Re-bleeding Rates

A total of 210 patients were followed up for 30 days. The re-bleeding rates were 7.8% and 9.3% in the PHP and conventional treatment groups, respectively. In addition, the 3-day, 7-day, and 30-day re-bleeding rates were also not significantly different between the groups. In subgroup analysis according to Forrest classification, the rates of re-bleeding did not differ between the PHP and conventional treatment groups (Table 3).

Proficiency According to Operator or Location

We calculated the difficulty experienced by endoscopists regarding endoscopic treatment on a Likert scale (1–5) (Table 4). A higher score indicated more difficult cases. In subgroup analysis according to the

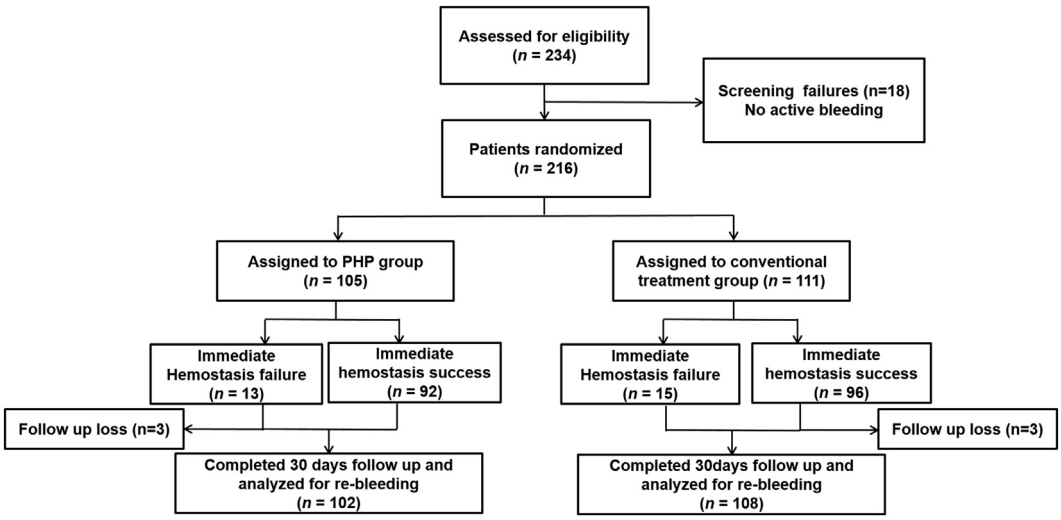

Figure 1. Flowchart for patient inclusion.

Table 1. Baseline Characteristics

Variables	PHP (n = 105)	Conventional treatment (n = 111)	*P*-value
Age, *y*	65.1 ± 15.3	64.3 ± 15.8	.727
Sex			.616
Male	85 (81.0)	86 (77.5)	
Female	20 (19.0)	25 (22.5)	
Comorbidity			
Hypertension	56 (53.3)	62 (55.9)	.785
Diabetes mellitus	29 (27.6)	28 (25.2)	.758
Coronary artery disease	13 (12.4)	17 (15.3)	.561
Cerebrovascular disease	18 (17.1)	12 (10.8)	.238
Liver cirrhosis	3 (2.9)	1 (0.9)	.358[a]
Chronic kidney disease	10 (9.5)	15 (13.5)	.400
Antithrombotic use			
Aspirin	35 (33.3)	44 (39.6)	.397
Clopidogrel	18 (17.1)	23 (20.7)	.603
Other antiplatelet	7 (6.7)	1 (0.9)	.031
Anticoagulants	4 (3.8)	4 (3.6)	1.000
NSAIDs	12 (11.4)	8 (7.2)	.350
Bleeding origin			.493
Gastric ulcer	57 (54.3)	66 (59.5)	
Duodenal ulcer	48 (45.7)	45 (40.5)	
Rockall score[b]	5.33 ± 1.61	5.50 ± 1.67	.469
GBS	9.79 ± 3.63	9.77 ± 3.40	.771
AIMS65	0.95 ± 0.90	0.98 ± 0.88	.959
Location			.665
Duodenum	44 (43.1)	44 (40.7)	
Stomach			
Upper 1/3	10 (9.8)	12 (11.1)	
Middle 1/3	26 (25.5)	22 (20.4)	
Lower 1/3	22 (21.6)	30 (27.8)	
Ulcer size, *mm*			.678
<15	59 (57.8)	59 (54.6)	
≥15	43 (42.2)	49 (45.4)	
Forrest classification			.050
Ia	4 (3.8)	3 (2.7)	
Ib	44 (41.9)	34 (30.6)	
IIa	36 (34.3)	59 (53.2)	
IIb[c]	21 (20.0)	15 (13.5)	

Note: Data are presented as number (%) or mean ± standard deviation.
GBS, Glasgow-Blatchford score; NSAIDs, non-steroidal anti-inflammatory drugs; PHP, polysaccharide hemostatic powder.
[a]Fisher's exact test.
[b]Post-endoscopic Rockall score.
[c]After removing blood clots by vigorous irrigation and identifying underlying lesions requiring endoscopic hemostasis.

operator, the procedure time was longer in the PHP group than in the conventional treatment group among trainees ($P < .001$). In addition, difficulty with the procedure was significantly higher in the PHP group than in the conventional treatment group among trainees ($P < .001$). In contrast, among experts, the procedure time did not differ between the 2 groups (PHP group vs conventional treatment group, 11.23 vs. 10.09 minutes, respectively). Morever, difficulty with the procedure was not significantly different between the PHP and conventional treatment groups of experts.

In this study, the procedure time for endoscopic hemostasis was analyzed using CUSUM according to location (Supplementary Figure 1). For the stomach, the peak point was reached with the 16th case, which was

Table 2. Results of Immediate Hemostasis

Variables	PHP (n = 105)	Conventional treatment (n = 111)	*P*-value
Immediate hemostasis success	92 (87.6)	96 (86.5)	.842
Immediate hemostasis failure	13 (12.4)	15 (13.5)	
Subgroup analysis of immediate hemostasis failure according to Forrest classification			
Forrest Ia (n = 7)	1/4 (25.0)	2/3 (66.7)	.486[a]
Forrest Ib (n = 78)	12/44 (27.3)	5/34 (14.7)	.269
Forrest IIa (n = 95)	0/36 (0.0)	8/59 (13.6)	.023[a]
Forrest IIb[b] (n = 36)	0/21 (0.0)	0/15 (0.0)	–
Salvage treatment after immediate hemostasis failure			.257
Electrical coagulation	0 (0.0)	2 (13.3)	
Hemoclips	13 (100)	10 (66.7)	
APC	0 (0.0)	1 (6.7)	
PHP	0 (0.0)	2 (13.3)	

Note: Data are presented as number (%).
APC, Argon plasma coagulation; PHP, polysaccharide hemostatic powder.
[a]Fisher exact test.
[b]After removing blood clots by vigorous irrigation and identifying underlying lesions requiring endoscopic hemostasis.

Table 3. Results of re-bleeding after endoscopic hemostasis

Variables	PHP (n = 102)	Conventional treatment (n = 108)	*P*-value
Re-bleeding rate			
3-day	3 (2.9)	1 (0.9)	.358
7-day	6 (5.9)	4 (3.7)	.314
14-day	8 (7.8)	9 (8.3)	.615
30-day	8 (7.8)	10 (9.3)	.808
Re-bleeding rate according to Forrest classification			
Ia	0/4 (0.0)	0/3 (0.0)	–
Ib	3/43 (7.0)	5/33 (15.2)	.283[a]
IIa	3/34 (8.8)	3/58 (5.2)	.666[a]
IIb[b]	2/21 (9.5)	2/14 (14.3)	.664

PHP, Polysaccharide hemostatic powder.
[a]Fisher exact test.
[b]After removing blood clots by vigorous irrigation and identifying underlying lesions requiring endoscopic hemostasis.

considered to be the learning curve when the endoscopist began to perform PHP treatment faster than the mean procedure time. For the duodenum, the peak point was reached with the 24th case. Thus, for the duodenum, more cases were needed for the endoscopist to become proficient. However, there was no difference in time and difficulty of the procedure according to lesion location (stomach vs duodenum) between the PHP and conventional treatment groups.

Risk Factors for Re-bleeding at 30 Days

Univariable analysis revealed that ulcer size larger than 15 mm ($P = .016$) was a significant risk factor for re-bleeding after endoscopy. Multivariable analysis revealed that ulcer size larger than 15 mm and chronic kidney disease with dialysis were independent risk factors for re-bleeding. Initial hemostatic treatments were not associated with re-bleeding (Table 5).

Discussion

In this study, PHP was not inferior to conventional endoscopic treatments for the control of PUB. In PUB, endoscopic treatment is the first-line treatment for controlling bleeding, having been found to reduce re-bleeding, the need for surgery, and mortality.[14] Although endoscopic technique has advanced, re-bleeding and mortality rates persist around 10%.[15] Therefore, various hemostatic methods and devices are being studied to reduce re-bleeding, especially in high-risk patients with PUB, and to improve the outcomes of PUB control.

This is the first, multicenter, prospective RCT undertaken to investigate the efficacy of PHP for PUB with a sufficient sample size in terms of non-inferiority in comparison with conventional treatments. Recently, an RCT was conducted with different agents from PHP to compare the efficacy in the treatment of NVUGIB.[8] The mechanism of PHP derived from starch is similar to that of TC-325. However, the study using TC-325 enrolled a larger proportion of tumor bleeding, for which it is easier to achieve hemostasis using hemostatic powder; in addition, the proportion of tumor bleeding was larger in the TC-325 group than in the conventional treatment group. In our study, we excluded tumor bleeding and causes other than PUB because our focus was the effectiveness of PHP for PUB treatment. When we analyzed clinical outcomes including all causes of NVUGIB other than tumor bleeding, there was no difference in initial hemostasis success and re-bleeding rates between PHP and conventional treatment groups (Supplementary Tables 1–5).

Endoclot (EC, Endo-Clot Inc, Santa Clara, CA) is the name of PHP derived from starch. Although we found that the efficacy of immediate hemostasis to be similar between TC-325 and PHP, there are some technical differences between TC-325 and PHP. First, TC-325 is empirically sprayed at a high pressure and has the advantage of covering a large area; however, the high-pressure application may cause further tissue injury in friable or inflamed mucosa, as well as perforation. In contrast, because PHP is sprayed at a much lower pressure (2.17, 3.04 psi, air compressor) than TC 325 (37 psi, CO_2 canister), it has a disadvantage in that a large amount of powder cannot be applied in a short time. However, it has the advantage of allowing sophisticated manipulation of the targeted area. Using PHP, the operator can slowly spray the optimal amount of hemostatic powder at the appropriate speed.

Conventional endoscopic treatments for hemostasis are challenging for large ulcers, chronic ulcers, high-risk lesions, and lesions with difficult access, such as at the apex of the stomach fundus and the superior duodenal angle of the duodenum. Therefore, there is a need for a novel method that requires minimal technical expertise, is quick to apply, involves no touching that could provoke additional bleeding, and is nonspecific in terms of targeting.[16,17] Hemostatic powders have the advantage of overcoming these challenges. Our study confirms the findings of previous studies, where excellent immediate control of the bleeding source was achieved with a hemostatic powder.[10,18,19]

In the present study, the overall re-bleeding rate was 8.6%, and there was no difference compared with conventional treatments. PHP absorbs water to form a gel matrix that covers the ulcer surface for 3 to 48 hours and accelerates the physiologic clotting system by enhancing the local concentration of coagulating factors.[20] Therefore, PHP was considered to act on bleeding in the early phase (within 2–3 days). However, contrary to expectations, in this study, the overall, 3-day, 7-day, and 30-day re-bleeding rates were not different between the PHP and conventional treatment groups. In addition, in multivariable analysis, ulcer size larger than 15 mm and chronic kidney disease with dialysis were independent risk factors for re-bleeding, and PHP use was not an independent risk factor for re-bleeding.

In our study, a significant difference in initial hemostasis failure between PHP and conventional treatments was not identified in patients with Forrest I lesions. However, in Forrest IIa or IIb cases, our study showed that PHP had 100% initial hemostasis success rates, unlike conventional treatments: initial hemostasis failure was recorded in 13.6% in the conventional endoscopic treatment group, whereas there was no initial hemostasis failure in the PHP group. We believe that the reasons for this are related with the advantages of PHP, such as being a non-traumatic method that poses no additional tissue injury. In other words, for Forrest IIa lesions, PHP may warrant better initial hemostasis and show comparable rebleeding rate compared with conventional treatments. However, this finding should be carefully interpreted because it was our secondary endpoint, and the Forrest IIa lesions were unevenly allocated in both

Table 4. Proficiency according to operator or location

Variables	PHP (n = 105)	Conventional treatment (n = 111)	*P*-value
Operator			< .001
Trainees	16 (15.2)	49 (44.1)	
Experts	89 (84.8)	62 (55.9)	
Procedure time, *min*	14.53 ± 10.82	13.86 ± 8.09	.611
Difficulty of procedure			.260
Very easy	12 (11.4)	7 (6.3)	
Easy	30 (28.6)	30 (27.0)	
Average	32 (30.5)	45 (40.5)	
Difficult	26 (24.8)	20 (18.0)	
Very difficult	5 (4.8)	9 (8.1)	
Difficulty of procedure	2.83 ± 1.08	2.95 ± 1.02	.411
Subgroup analysis according to operator			
Procedure time by trainee, *min*	32.88 ± 8.53	18.63 ± 7.26	< .001
Difficulty of procedure by trainees			.011
Very easy	0 (0.0)	2 (4.2)	
Easy	1 (6.3)	13 (27.1)	
Average	3 (18.8)	21 (43.8)	
Difficult	9 (56.3)	9 (18.8)	
Very difficult	3 (18.8)	3 (6.3)	
Difficulty of procedure by trainees	3.88 ± 0.81	2.94 ± 0.94	.001
Procedure time by experts, *min*	11.23 ± 7.34	10.09 ± 6.62	.331
Difficulty of procedure by experts			.087
Very easy	12 (14.0)	5 (8.3)	
Easy	28 (32.6)	15 (25.0)	
Average	28 (32.6)	24 (40.0)	
Difficult	17 (19.8)	10 (16.7)	
Very difficult	1 (1.2)	6 (10.0)	
Difficulty of procedure by experts	2.64 ± 1.01	2.95 ± 1.08	.073
Subgroup analysis according to location			
Procedure time in stomach, *min*	13.23 ± 10.03	12.93 ± 8.22	.856
Difficulty of procedure in stomach			.666
Very easy	7 (11.9)	5 (7.6)	
Easy	21 (35.6)	19 (28.8)	
Average	21 (35.6)	29 (43.9)	
Difficult	9 (15.3)	10 (15.2)	
Very difficult	1 (1.7)	3 (4.5)	
Difficulty of procedure in stomach	2.59 ± 0.95	2.80 ± 0.95	.219
Procedure time in duodenum, *min*	16.20 ± 11.67	15.23 ± 7.78	.642
Difficulty of procedure in duodenum			.329
Very easy	5 (10.9)	2 (4.4)	
Easy	9 (19.6)	11 (24.4)	
Average	11 (23.9)	16 (35.6)	
Difficult	17 (37.0)	10 (22.2)	
Very difficult	4 (8.7)	6 (13.3)	
Difficulty of procedure in duodenum	3.13 ± 1.17	3.16 ± 1.09	.916

Note: Data are presented as number (%) or mean ± standard deviation.
PHP, Polysaccharide hemostatic powder.

groups. More clinical trials may be required for reaching a definitive conclusion.

According to previous studies, the re-bleeding risk of Forrest Ia lesions with hemostatic powder remains controversial.[8,16,21] Therefore, to date, it has been recommended mainly as rescue therapy.[16,21] However, in our study, re-bleeding risk was not higher with PHP in any group according to Forrest classification. We believe that many factors can affect the efficacy of hemostatic powders, such as lesion characteristics, bleeding amount, and spurting speed, even in Forrest Ia cases. Therefore, more RCTs are needed to confirm whether hemostatic powders may be used as a first or rescue endoscopic treatment for PUB, especially Forrest I lesions.

Generally, hemostatic powder application is thought to be a simple technique that can be performed by an endoscopist with basic endoscopy experience. In this study, difficulty with PHP varied between experts and trainees. Before the start of the study, we expected that

Table 5. Risk factors for re-bleeding at 30 days

	Univariable analysis		Multivariable analysis	
	Re-bleeding (95% CI)	*P*-value	Re-bleeding (95% CI)	*P*-value
Age	1.016 (0.983–1.051)	.347		
Gender				
Male	Ref	.050		
Female	2.758 (1.000–7.606)		2.752 (0.961–7.883)	.059
Comorbidity				
Hypertension	2.294 (0.787–6.686)	.128		
Diabetes mellitus	0.749 (0.236–2.379)	.624		
Coronary artery disease	0.732 (0.160–3.360)	.688		
Cerebrovascular disease	1.222 (0.332–4.506)	.763		
Liver cirrhosis[a]	1.102 (0.008–10.949)	.954		
CKD on dialysis	4.067 (0.994–16.635)	.051	5.209 (1.168–23.235)	.031
Antithrombotics use				
Aspirin	0.815 (0.293–2.266)	.695		
Clopidogrel	0.838 (0.231–3.045)	.788		
Other antiplatelets[a]	0.572 (0.004–4.903)	.721		
Anticoagulants	1.555 (0.180–13.391)	.688		
NSAIDs	0.536 (0.067–4.252)	.555		
Bleeding origin				
Gastric ulcer	Ref			
Duodenal ulcer	0.972 (0.372–2.452)	.953		
Rockall score (mean ± SD)[b]	1.041 (0.777–1.395)	.786		
GBS (mean ± SD)	1.030 (0.894–1.188)	.682		
AIMS65 (mean ± SD)	1.078 (0.622–1.868)	.788		
Location				
Duodenum	Ref			
Stomach				
Upper 1/3	0.685 (0.070–3.306)	.608		
Middle 1/3	1.435 (0.466–4.236)	.342		
Lower 1/3	0.893 (0.246–2.853)	.859		
Ulcer size,[c] *mm*				
<15	Ref			
≥15	3.719 (1.275–10.850)	.016	4.421 (1.416–13.800)	.010
Forrest classification				
Ia	Ref			
Ib	1.808 (0.189–242.380)	.689		
IIa	1.271 (0.130–170.881)	.767		
IIb[d]	2.076 (0.187–286.459)	.545		
PHP use as an initial hemostatic treatment	0.834 (0.316–2.204)	.714	0.987 (0.357–2.731)	.980
Operator		.783		
Trainees	Ref			
Experts	0.866 (0.310–2.418)			

CI, Confidence interval; CKD, chronic kidney disease; GBS, Glasgow-Blatchford score; NSAIDs, non-steroidal anti-inflammatory drugs; PHP, polysaccharide hemostatic powder.
[a]Firth method.
[b]Post-endoscopic Rockall score.
[c]Size was measured as a diameter of the long axis of ulcer.
[d]After removing blood clots by vigorous irrigation and identifying underlying lesions requiring endoscopic hemostasis.

hemostatic powder would be easier to apply in all groups; however, there was an unexpected difference between the experts and trainees. Among experts, procedure times and difficulty with the procedure did not differ between the PHP and conventional treatment groups. However, among trainees, the procedure time was longer in the PHP group than in the conventional treatment group, and difficulty with the procedure was significantly higher in the PHP group than in the conventional treatment group. We believe that since PHP is a new method, low familiarity

may have affected the rate of difficulty among trainees, whereas it had little effect on experts. In addition, we analyzed the learning curve of PHP because there are still no data on this subject. We observed that there were different learning curves depending to the location of the bleeding. For the duodenum, more cases were needed to manage PHP: probably because the duodenum has a narrow lumen and is angulated, thus performing a satisfactory procedure could be challenging for the operator. In light of the experience of those who participated in this study, we believe that 16 cases are acceptable to overcome the learning curve associated with PHP use.

This study has some limitations. First, the participating endoscopists were not blinded to the treatment. Second, this study included patients from 4 academic teaching hospitals in South Korea. Therefore, there was a difference in the patient groups in the referral hospital, compared with the primary hospital. In addition, electrocoagulation using hemostatic forceps**,** which are used as one of main treatments in this study is monopolar. However, the type of electrocoagulation device varies based on endoscopic practice location. For this reason, more studies comparing PHP with various thermal therapies, including bipolar electrocautery, may be required to generalize our findings. Third, there is some possibility that epinephrine might affect the hemostatic effect of the PHP, even though the amount administered was small. However, epinephrine was also used in the conventional group, and it is widely used before the main endoscopic hemostasis in clinical practice because of accessibility and low cost. Therefore, the use of epinephrine is designed to maximize the main hemostatic effects of both PHP and other modalities as an additional treatment, rather than monotherapy. Lastly, additional large RCTs are needed to confirm the re-bleeding rate of PHP as the primary outcome. Despite these limitations, however, this study is meaningful because multicenter prospective RCTs on PHP effects are lacking, and PHP use is increasing.

Conclusion

In conclusion, PHP could be an initial endoscopic treatment for PUB and is not inferior to conventional endoscopic methods. Further RCTs are needed to confirm the re-bleeding rate of PHP.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.02.031.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Appendix 1

Patients

Inclusion criteria were as follows: (1) age above 19 years; (2) symptoms of hematemesis, melena, or haematochezia within 72 hours that required emergency endoscopy; and (3) an absolute neutrophil count $\geq$1500/mm^3, platelets $\geq$100,000/mm^3, international normalized ratio $\leq$2.5, activated partial thromboplastin time $\leq$1.5 $\times$ normal value (IU/L), total bilirubin $<$2.0 $\times$ normal value (mg/dL), aspartate aminotransferase and alanine aminotransferase $\leq$2.5 $\times$ normal value (IU/L) in laboratory blood tests performed before enrollment. Exclusion criteria were as follows: (1) sensitivity to starch or starch-derived ingredients; (2) suspected bleeding due to upper gastrointestinal cancer or causes other than peptic ulcer bleeding; (3) suspected variceal bleeding among patients with a history of cirrhosis or liver cancer; (4) coagulation disorders, such as hemophilia and thrombocytopenic purpura; (5) suspected bleeding due to previous upper endoscopy or procedures, such as biopsy, polypectomy, and endoscopic submucosal dissection and stent insertion; and (6) unsuitability for endoscopy due to unconsciousness or anatomical reasons. The study protocol was approved by the institutional review boards of each participating institution (4-2016-0027), and the study was registered at ClinicalTrials.gov (identifier 02717416). All authors had access to the study data and reviewed and approved the final manuscript.

Supplementary Appendix 2

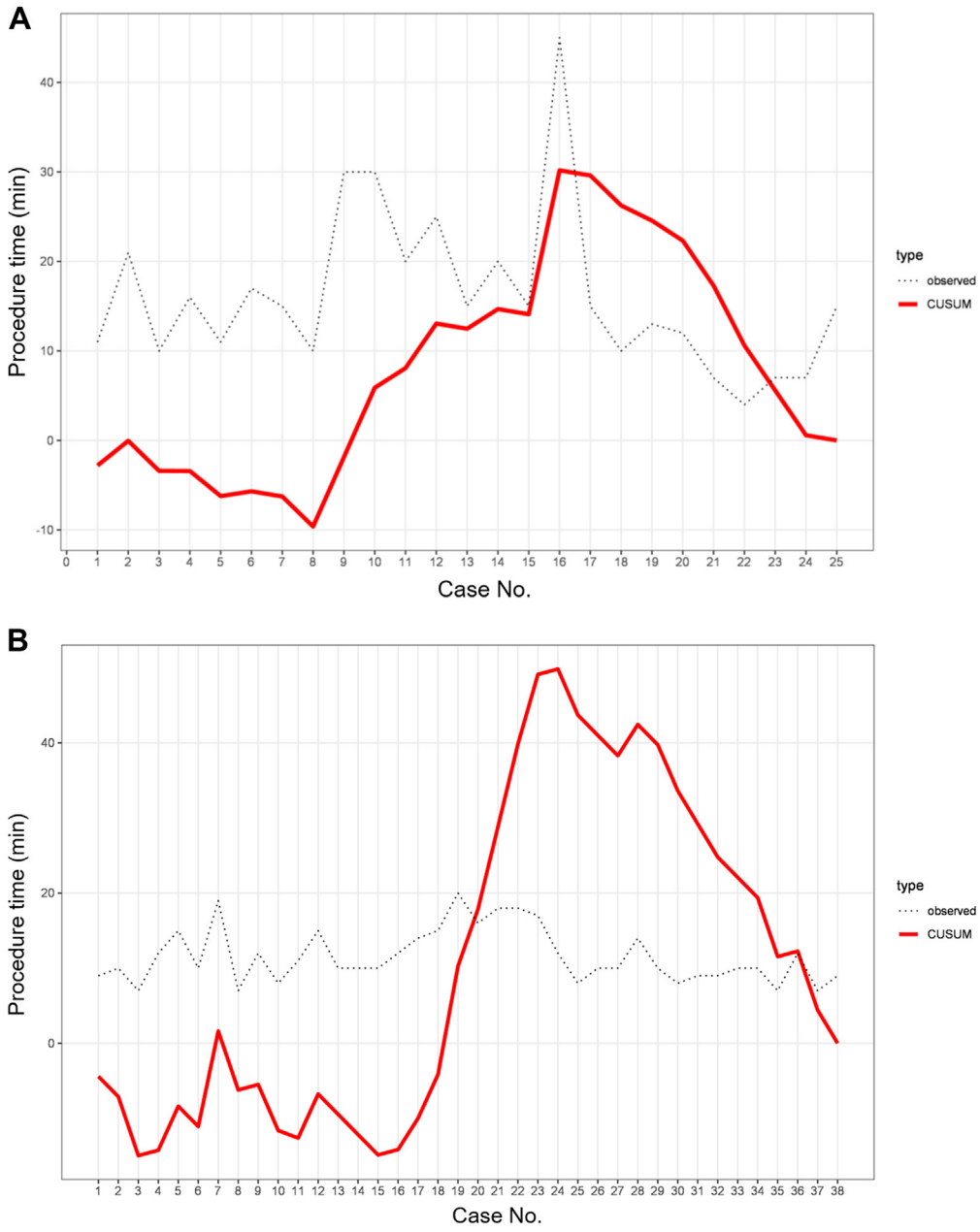
Perioperative Management and Post Follow-up

For 24 hours after endoscopy, patients were fasted, intravenous fluid therapy was administered, and proton pump inhibitor) infusion was continued. If there was no evidence of bleeding after 24 hours of endoscopy, water intake was started, followed by a liquid and soft diet. After cessation of high-dose proton pump inhibitor infusion, the patients received 40 mg pantoprazole (Pantoloc) orally once a day for 28 days. Patients were discharged on the second or third day after endoscopy if no re-bleeding events were reported. They were instructed to visit the outpatient department 2 weeks ($\pm$3 days) after discharge to evaluate re-bleeding and to undergo blood tests.

Supplementary Appendix 3

Statistical Analysis

We assessed the learning curve using the cumulative sum (CUSUM) method, which is a statistical technique designed to quantitatively assess learning curves. In this study, the CUSUM of the procedure time was defined as CUSUM $= \sum_{i=1}^{n}(X_i - \mu)$, where x_i is an individual procedure time and μ is the mean of the procedure time in all cases. The CUSUM of the procedure time was analysed using data for one endoscopist who performed most of the procedures. By plotting the outcomes in the CUSUM curve, the slope revealed a performance trend. The breakpoint was defined as the period during which the slope gradient was achieved at the plateau. In this study, the breakpoint was considered the learning curve period. A subgroup analysis was performed according to the operator. Statistical analyses were performed using SPSS version 23.0 for Windows (SPSS Inc., Chicago, IL) and R package, version 3.4.3 (http://www.R-project.org).



Supplementary Figure 1. Procedure time and cumulative sum of the procedure time (CUSUMOT) graph. (*A*) Stomach; (*B*) Duodenum.

Supplementary Table 1. Baseline Characteristics

Variables	PHP (n = 110)	Conventional treatment (n = 116)	*P*-value
Age, *y*	64.8 ± 15.8	64.0 ± 15.8	.725
Sex			.454
Male	88 (80.0)	88 (75.9)	
Female	22 (20.0)	28 (24.1)	
Comorbidity			
Hypertension	59 (53.6)	64 (55.2)	.817
Diabetes mellitus	29 (26.4)	29 (25.0)	.815
Coronary artery disease	13 (11.8)	17 (14.7)	.530
Cerebrovascular disease	19 (17.3)	13 (11.2)	.191
Liver cirrhosis	3 (2.7)	1 (0.9)	.359[b]
Chronic kidney disease	10 (9.1)	15 (12.9)	.358
Antithrombotic use			
Aspirin	35 (31.8)	45 (38.8)	.273
Clopidogrel	20 (18.2)	23 (19.8)	.753
Other antiplatelet	7 (6.4)	1 (0.9)	.032[b]
Anticoagulants	4 (3.6)	4 (3.4)	.939
NSAIDs	12 (10.9)	8 (6.9)	.288
Bleeding origin			.239[b]
Gastric ulcer	57 (51.8)	66 (56.9)	
Duodenal ulcer	48 (43.6)	45 (38.8)	
Angiodysplasia	2 (1.8)	3 (2.6)	
Dieulafoy	3 (2.7)	0 (0.0)	
Mallory-Weiss tear	0 (0.0)	2 (1.7)	
Rockall score[a]	5.35 ± 1.59	5.47 ± 1.67	.554
GBS	9.83 ± 3.62	9.69 ± 3.48	.771
AIMS65	0.97 ± 0.94	0.97 ± 0.87	.991
Location			.315
Duodenum	49 (44.5)	46 (39.7)	
Stomach			
Upper 1/3	10 (9.1)	16 (13.8)	
Middle 1/3	29 (26.4)	23 (19.8)	
Lower 1/3	22 (20.0)	31 (26.7)	
Ulcer size, *mm*			.789
<15	64 (58.2)	65 (56.0)	
≥15	46 (41.8)	51 (44.0)	
Forrest classification			.020
Ia	5 (4.5)	6 (5.2)	
Ib	47 (42.7)	34 (29.3)	
IIa	36 (32.7)	61 (52.6)	
IIb[c]	22 (20.0)	15 (12.9)	

Note: Data are presented as number (%) or mean ± standard deviation.
GBS, Glasgow-Blatchford score; NSAIDs, non-steroidal anti-inflammatory drugs; PHP, polysaccharide hemostatic powder.
[a]Post-endoscopic Rockall score.
[b]Fisher exact test
[c]After removing blood clots by vigorous irrigation and identifying underlying lesions requiring endoscopic hemostasis.

Supplementary Table 2. Results of Immediate Hemostasis

Variables	PHP (n = 110)	Conventional treatment (n = 116)	*P*-value
Immediate hemostasis success	96 (87.3)	101 (87.1)	.964
Immediate hemostasis failure	14 (12.7)	15 (12.9)	
Subgroup analysis of immediate hemostasis failure according to Forrest classification			
Forrest Ia (n = 11)	1/5 (20.0)	2/6 (33.3)	> .999[a]
Forrest Ib (n = 81)	13/47 (27.7)	5/34 (14.7)	.166
Forrest IIa (n = 97)	0/36 (0.0)	8/61 (13.1)	.024[a]
Forrest IIb[b] (n = 37)	0/22 (0.0)	0/15 (0.0)	–
Salvage treatment after immediate hemostasis failure			.067[a]
Electrical coagulation	0 (0.0)	2 (13.3)	
Hemoclips	14 (100)	10 (66.7)	
APC	0 (0.0)	1 (6.7)	
PHP	0 (0.0)	2 (13.3)	

Note: Data are presented as number (%).
APC, Argon plasma coagulation; PHP, polysaccharide hemostatic powder.
[a]Fisher exact test.
[b]After removing blood clots by vigorous irrigation and identifying underlying lesions requiring endoscopic hemostasis.

Supplementary Table 3. Results of Re-bleeding After Endoscopic Hemostasis

Variables	PHP (n = 107)	Conventional treatment (n = 113)	*P*-value
Re-bleeding rate			
3-day	3 (2.8)	1 (0.9)	.358a[a]
7-day	6 (5.6)	4 (3.5)	.530a[a]
14-day	8 (7.5)	9 (8.0)	> .999
30-day	8 (7.5)	10 (8.8)	.710
Re-bleeding rate according to Forrest classification			
Ia	0/5 (0.0)	0/6 (0.0)	–
Ib	3/46 (6.5)	5/33 (15.2)	.268a[a]
IIa	3/34 (8.8)	3/60 (5.0)	.664a[a]
IIbb[b]	2/22 (9.1)	2/14 (14.3)	.634a[a]

Note: Data are presented as number (%).
PHP, Polysaccharide hemostatic powder.
[a]Fisher exact test.
[b]After removing blood clots by vigorous irrigation and identifying underlying lesions requiring endoscopic hemostasis.

Supplementary Table 4. Proficiency According to Operator or Location

Variables	PHP (n = 110)	Conventional treatment (n = 116)	*P*-value
Operator			< .001
Trainees	18 (16.4)	56 (48.3)	
Experts	92 (83.6)	60 (51.7)	
Procedure time, *min*	14.31 ± 10.76	13.98 ± 8.29	.797
Difficulty of procedure			.260
Very easy	14 (12.7)	8 (6.9)	
Easy	31 (28.2)	31 (26.7)	
Average	33 (30.0)	46 (39.7)	
Difficult	27 (24.5)	22 (19.0)	
Very difficult	5 (4.5)	9 (7.8)	
Difficulty of procedure	2.80 ± 1.09	2.94 ± 1.02	.322
Subgroup analysis according to operator			
Procedure time by trainee, *min*	31.39 ± 9.12	18.98 ± 7.62	< .001
Difficulty of procedure by trainees			.005[a]
Very easy	0 (0.0)	2 (3.9)	
Easy	1 (5.6)	15 (29.4)	
Average	4 (22.2)	22 (43.1)	
Difficult	10 (55.6)	9 (17.6)	
Very difficult	3 (16.7)	3 (5.9)	
Difficulty of procedure by trainees	3.83 ± 0.79	2.92 ± 0.94	< .001
Procedure time by experts, *min*	10.97 ± 7.36	10.06 ± 6.52	.425
Difficulty of procedure by experts			.199
Very easy	14 (15.2)	6 (9.2)	
Easy	30 (32.6)	16 (24.6)	
Average	29 (31.5)	24 (36.9)	
Difficult	17 (18.5)	13 (20.0)	
Very difficult	2 (2.2)	6 (9.2)	
Difficulty of procedure by experts	2.60 ± 1.03	2.95 ± 1.10	.039
Subgroup analysis according to location			
Procedure time in stomach, *min*	12.91 ± 10.02	13.32 ± 8.55	.800
Difficulty of procedure in stomach			.525
Very easy	8 (13.1)	5 (7.1)	
Easy	22 (36.1)	20 (28.6)	
Average	21 (34.4)	30 (42.9)	
Difficult	9 (14.8)	12 (17.1)	
Very difficult	1 (1.6)	3 (4.3)	
Difficulty of procedure in stomach	2.56 ± 0.96	2.83 ± 0.95	.106
Procedure time in duodenum, *min*	16.06 ± 11.48	14.99 ± 7.86	.595
Difficulty of procedure in duodenum			.359
Very easy	6 (12.2)	3 (6.5)	
Easy	9 (18.4)	11 (23.9)	
Average	12 (24.5)	16 (34.8)	
Difficult	18 (36.7)	10 (21.7)	
Very difficult	4 (8.2)	6 (13.0)	
Difficulty of procedure in duodenum	3.10 ± 1.18	3.11 ± 1.12	.978

Note: Data are presented as number (%) or mean ± standard deviation.
PHP, Polysaccharide hemostatic powder.
[a]Fisher exact test

Supplementary Table 5. Risk Factors for Re-bleeding at 30 Days

	Univariable analysis		Multivariable analysis	
	Re-bleeding (95% CI)	*P*-value	Re-bleeding (95% CI)	*P*-value
Age	1.017 (0.984–1.052)	.316		
Gender				
Male	Ref	.075		
Female	2.499 (0.912–6.846)			
Comorbidity				
Hypertension	2.308 (0.794–6.715)	.125		
Diabetes mellitus	0.783 (0.247–2.483)	.678		
Coronary artery disease	0.778 (0.169–3.563)	.745		
Cerebrovascular disease	1.193 (0.325–4.380)	.790		
Liver cirrhosis[a]	1.191 (0.044–32.374)	.917		
CKD on dialysis	4.289 (1.049–17.537)	.043	5.457 (1.210–24.612)	.027
Antithrombotics use				
Aspirin	0.865 (0.312–2.401)	.781		
Clopidogrel	0.836 (0.231–3.030)	.785		
Other antiplatelets[a]	0.619 (0.029–13.224)	.759		
Anticoagulants	1.639 (0.190–14.112)	.653		
NSAIDs	0.567 (0.071–4.496)	.591		
Bleeding origin				
Gastric ulcer	1.341 (0.500–3.598)	.560		
Duodenal ulcer	0.912 (0.340–2.451)	.856		
Angiodysplasia	–	> .999		
Dieulafoy	–	> .999		
Mallory-Weiss tear	–	> .999		
Rockall score[b]	1.044 (0.778–1.400)	.776		
GBS	1.031 (0.896–1.187)	.668		
AIMS65	1.065 (0.621–1.827)	.819		
Location				
Duodenum	0.876 (0.326–2.353)	.793		
Stomach				
Upper 1/3	0.416 (0.053–3.267)	.405		
Middle 1/3	1.795 (0.638–5.056)	.268		
Lower 1/3	0.917 (0.288–2.917)	.883		
Ulcer size,[c] *mm*				
<15	Ref			
≥15	4.183 (1.452–12.053)	.008	4.663 (1.566–13.885)	.006
Forrest classification		.682		
Ia	Ref			
Ib	2.734 (0.130–57.294)	.517		
IIa	1.689 (0.079–36.153)	.737		
IIb[d]	3.184 (0.140–72.215)	.467		
PHP use as an initial hemostatic treatment	1.201 (0.456–3.169)	.711	0.960 (0.362–2.548)	.935
Operator		.816		
Trainees	Ref			
Experts	0.886 (0.318–2.468)			

CI, Confidence interval; CKD, chronic kidney disease; GBS, Glasgow-Blatchford score; NSAIDs, non-steroidal anti-inflammatory drugs; PHP, polysaccharide hemostatic powder; Ref, reference.

[a]Firth method.

[b]Post-endoscopic Rockall score.

[c]Size was measured as a diameter of the long axis of ulcer.

[d]After removing blood clots by vigorous irrigation and identifying underlying lesions requiring endoscopic hemostasis.