Topical hemostatic agents in endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Technical and Technology Review

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published online 2025

Bibliography
Endoscopy
DOI 10.1055/a-2646-7556
ISSN 0013-726X

This article is published by Thieme.
Georg Thieme Verlag KG, Oswald-Hesse-Straße 50,
70469 Stuttgart, Germany

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ABSTRACT

Background Gastrointestinal (GI) endoscopy has evolved from a diagnostic tool into a therapeutic modality, leading to a higher incidence of bleeding complications during and after procedures. To address this issue, various hemostatic agents have been developed, including injectable, mechanical, thermal, and topical products. Topical hemostatic agents, available in powder or gel forms, can be used as standalone treatments or as adjuncts to traditional hemostatic therapies to control or prevent bleeding.

Methods This Technical and Technology Review examines the commercially available topical hemostatic agents used in endoscopy, specifically Purastat, TC-325 Hemospray, EndoClot PHS, Nexpowder, Ankaferd Blood Stopper, and CG GEL. A systematic literature review was conducted up to January 2025, focusing on randomized controlled trials (RCTs), meta-analyses, and observational studies. Each product was assessed for its composition, mechanism of action, regulatory status, mode of use, efficacy, safety, and financial considerations.

Results Purastat showed 94% efficacy in acute GI bleeding, reducing delayed bleeding to 4.3% in endoscopic submucosal dissection (ESD) and endoscopic mucosal resection cases, with significantly lower thermal device usage. TC-325 Hemospray achieved 85%–98.5% primary hemostasis in upper and lower GI bleeding, with pooled hemostasis rates of 93.1% and rebleeding rates of 8.9%. It was also effective in malignancy-related bleeding, with hemostasis success up to 100%. EndoClot PHS demonstrated 76%–100% hemostasis efficacy, comparable with TC-325, with rebleeding rates of 24%–25%. It showed prophylactic

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potential post-ESD, with rebleeding rates of 7.3%–9.1%. Nexpowder achieved 94% hemostasis in refractory upper GI bleeds and reduced rebleeding in lower GI bleeds to 5.5% at 28 days. Ankaferd Blood Stopper demonstrated 73%–100% hemostasis across various GI bleeding sources, including peptic ulcers and malignancies, though further data on rebleeding are needed.

Conclusion Topical hemostatic agents offer effective options for managing GI bleeding. Products like Purastat, TC-325 Hemospray, EndoClot PHS, Nexpowder, Ankaferd Blood Stopper, and CG GEL have shown promising results in achieving hemostasis; however, further RCTs and cost-effectiveness analyses are needed to better establish their roles in endoscopic practice.

ABBREVIATIONS

ABS	Ankaferd Blood Stopper
AE	adverse event
APC	argon plasma coagulation
CE	Conformité Européenne
EMR	endoscopic mucosal resection
ERCP	endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
ESD	endoscopic submucosal dissection
FDA	Food and Drug Administration
GI	gastrointestinal
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
UI-EWD	upper intraluminal endoscopic wound dressing

SOURCE AND SCOPE

This European Society of Gastrointestinal Endoscopy (ESGE) Technical and Technology Review addresses the use of hemostatic agents in endoscopy, providing updated guidance on the available products and their uses.

Introduction

The field of gastrointestinal (GI) endoscopy has rapidly evolved from being a predominantly diagnostic to a therapeutic modality. This increase in therapeutic endoscopic procedures comes with a parallel increase in rates of intra- and post-procedural bleeding events. Hemostatic agents that are used to treat or prevent bleeding can be broadly divided into injectables, mechanical, thermal (contact and noncontact) and topical modalities.

Topical agents are endoscopically applied directly onto the surface of a bleeding lesion or prophylactically onto an area that has the potential for delayed bleeding. These topical agents come either in powder or liquid/gel form. Topical hemostatic agents can be used as monotherapy or as an adjunctive treatment with more traditional hemostatic therapies (e. g. thermal, mechanical).

This ESGE Technical And Technology Review will focus on the currently commercially available topical hemostatic agents and will provide guidance on their clinical and technical usage during endoscopic practice.

Methodology and development process

The ESGE Research Committee Chair (L.F.), at the request of the ESGE Executive Committee, commissioned this Technical and Technology Review and appointed two co-leaders (I.M.G. and P.B.) who invited the listed authors to participate in the project development. The authors performed a systematic literature search to prepare an evidence-based, narrative review of the assigned topic.

The literature search was performed on the main scientific databases through until March 2025, focusing on randomized controlled trials (RCTs) and meta-analyses of RCTs. The search was based on the following key words: "topical hemostatic agents," "gastrointestinal bleeding," "Purastat," "TC-325 Hemospray," "EndoClot Polysaccharide Hemostatic System," "EndoClot PHS," "Nexpowder," "UI-EWD," "Ankaferd Blood Stopper," "ABS," "CG GEL," and "CEGP-003." Observational studies were included if they addressed topics not covered in the RCTs. The following issues were reviewed for each agent: composition and mechanism of action, regulatory status, mode of use, evidence, safety, financial aspects, and comparison.

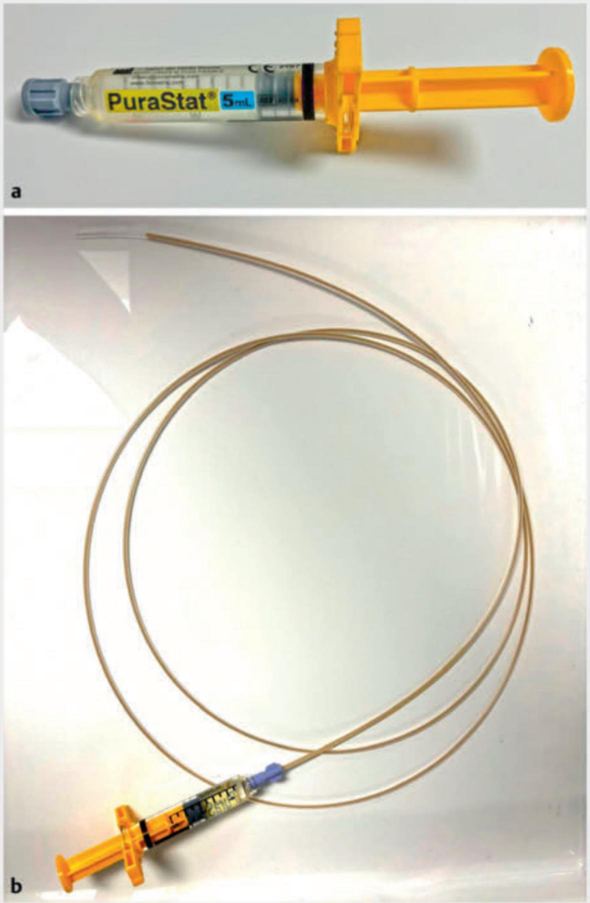
The final draft was reviewed by the ESGE Governing Board and two external reviewers and, after agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised version.

1 Purastat

1.1 Composition and mechanism of action

Purastat is a self-assembling peptide gel that was developed by 3-D Matrix Ltd. (▶ **Fig. 1**) to control exudative hemorrhage from small vessels, vascular anastomoses, and solid organs. Purastat is approved for use to control GI bleeding in the upper and lower GI tracts, including prevention of delayed bleeding after colonic endoscopic submucosal dissection (ESD).

Purastat is built from a chain of three types of amino acids that bond together to form a peptide (RADA 16). This peptide has a shape-forming ability that enables it to self-assemble into fibers that closely resemble human extracellular matrix. Purastat is activated when it meets bodily fluids, including blood, as a change in pH and salt concentration triggers nanofiber net-



▶ **Fig. 1** The Purastat device.

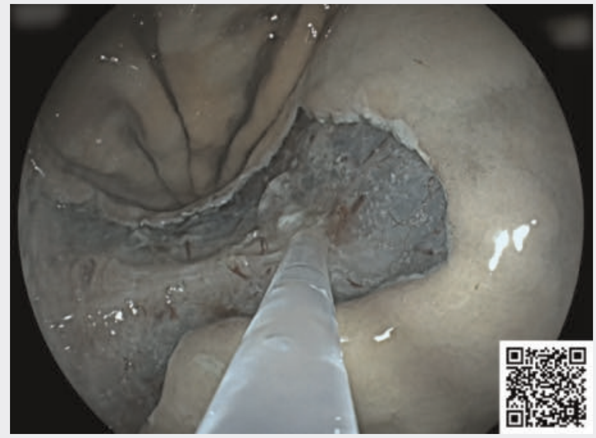
work formation. The matrix sticks to and seals the blood vessel, thereby facilitating hemostasis as a mechanical barrier is formed. This process also facilitates platelet aggregation and activation of the clotting cascade for hemostasis. Purastat is not absorbed by the GI tract mucosa and eventually coalesces and sloughs off into the lumen before being eliminated. It is a safe, nonbiogenic, biocompatible, resorbable peptide hydrogel with no risk of transmissible spongiform encephalopathy.

1.2 Regulatory status

Purastat received Conformité Européenne (CE) marking in 2014 and US Food and Drug Administration (FDA) clearance in 2021. It is also approved in Japan and licensed in Australia.

1.3 Mode of use

Purastat is a transparent viscous gel that is supplied in three syringe sizes (1, 3, and 5 mL) and requires refrigerated storage at a temperature of 2–8 °C (it must not be frozen). The product is provided sterile in the package; it should be used promptly and handled aseptically to avoid contamination. It is applied through a catheter, inserted into the accessory channel of the endoscope with a minimum channel diameter of 2.8 mm. Prior to application, the endoscopist should remove as much blood and fluid from the bleeding site and, for ideal hemostatic action, the Purastat should be applied close to the tissue, directly over the bleeding point. Application of the gel should start from the edge of the lesion so that, by the force of gravity, it moves toward the center of the base, while using gentle suction to bring the edges of the base closer together to enable complete coverage of the resection base (▶ **Video 1**) [1]. Endoscopists should avoid injecting water or aspirating to prevent gel dispersion [2]. The catheter should not be retracted back into the endoscope for several seconds after application of Purastat to prevent gel dislodgment through scope movement or capillary action of catheter withdrawal.



▶ **Video 1** Purastat is applied after submucosal dissection of a gastric lesion.
Online content viewable at:
https://doi.org/10.1055/a-2646-7556

1.4 Evidence

1.4.1 Prophylactic use after endoscopic tissue resection to prevent delayed bleeding

Initial studies of Purastat were retrospective analyses of its prophylactic use post-endoscopic resection to prevent delayed bleeding. Pioche et al. conducted a study in 56 patients (with 65 lesions, 43 in the upper GI tract and 22 in the lower GI tract) undergoing either ESD, endoscopic mucosal resection (EMR), or ampullectomy [3]. Many of these resected lesions (44.6%) were in patients with a high bleeding risk (i. e. on antithrombotic therapy, with cirrhosis and portal hypertension, or duodenal resections > 2 cm). Four delayed bleeds were encountered, accounting for a delayed bleed rate of 6.2%. In a study of 47 patients (53 lesions) undergoing gastric ESD, Uraoka et al. demonstrated a delayed bleeding rate of just 2.0% (1/51) [4]. A UK-based registry of 100 patients who had had Purastat applied over their post-ESD/EMR resection base reported a delayed bleeding rate of 3% (one esophageal and two gastric bleeds, with notably no delayed bleeds in the duodenum or colon) [1]. These findings were later echoed in an RCT of 101 patients randomized to either Purastat or conventional diathermy for bleed control in esophageal and colonic ESD, which demonstrated a delayed bleeding rate of 4.3% in the Purastat arm, although no significant difference was shown with the control group [5].

In contrast, a smaller study limited to Purastat application post-EMR in 48 patients (17 esophageal, 13 duodenal, and 18 colorectal lesions) showed that delayed bleeding rates were almost 16% in the entire cohort, including four bleeds in the duodenum [6]. Gomi et al. evaluated the effects of Purastat use in preventing delayed bleeding post-gastric ESD in 101 patients compared with a historical cohort of 297 patients, but did not demonstrate a significant difference (5.9% vs. 6.7%; $P = 0.78$) [7]. The authors postulated that this may be due to a non-enduring hemostatic effect of Purastat and the location of the ESD on the gastric lesser curve/anterior wall, which may be subject to gravitational forces that could alter the duration of contact of Purastat with the resection site.

A recent meta-analysis of six studies (307 patients) using Purastat for the prevention of delayed bleeding after endoscopic resection reported a pooled rate of delayed bleeding of 5.7% (stratified pooled delayed bleeding rates of approximately 4%–5% in the esophagus, stomach, and colon; 10% in the duodenum), despite a high proportion of patients being on antithrombotic therapy (36%) [8]. This suggests that Purastat may have an overall benefit in reducing delayed bleeds, particularly in high risk patients (e. g. cirrhotic patients, patients on anticoagulant therapy) and for lesions in high risk locations (e. g. in the duodenum, where delayed bleeding rates can be as high as 20%).

The impact of Purastat on delayed bleeding after EMR was explored in 232 patients (208 colon and 26 duodenal polyps) in a recently published RCT involving 15 centers in Germany by Drews et al. [9]. Delayed bleeding was reported in 14 cases (11.7%; 95%CI 7.1%–18.6%) after Purastat and in seven cases (6.3%; 95%CI 3.1%–12.3%) in the control group ($P = 0.23$). The authors concluded that Purastat, when used prophylactically after colonic and duodenal EMR, did not reduce the risk of delayed bleeding. The trial included lesions with wide-ranging bleeding risks, and selective clipping and coagulation (snare tip, coagulation forceps, or argon beamer) were allowed during the procedure to treat intraprocedural bleeding and after completion of the resection, thereby potentially introducing a bias. The study was prematurely terminated owing to futility after an interim analysis.

1.4.2 Hemostatic efficacy

1.4.2.1 Efficacy in the treatment of endoscopy-related bleeding Several studies have now demonstrated Purastat's hemostatic efficacy (▶ **Table 1**) [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22]. Indeed, the earliest study on this, which was limited to 12 patients undergoing gastric ESD and EMR, showed that Purastat was effective in all patients [10]. A prospective single-center UK registry demonstrated hemostatic efficacy in 75% of intraprocedural bleeding during endoscopic resection and noted that Purastat was most effective on oozing or moderate venous vessel bleeds, rather than arterial spurting bleeds [1]. A single-center RCT of 101 patients undergoing esophageal and colonic ESD found a significant reduction in the use of heat therapy for intraprocedural

▶ **Table 1** Evidence on the efficacy of Purastat.

Authors, year of publication	Country	Study design	Patients (lesions) where Purastat used, n	Indication	Application	Outcomes
Yoshida, 2014 [10]	Japan	Retrospective case series	12	Post-EMR/ESD of gastric tumors	Monotherapy	11/12 complete hemostasis; no delayed bleeds
Pioche, 2016 [3]	France	Prospective observational	56 (65)	Post-endoscopic resection (UGI + LGI + ampullectomy)	Prophylactic application over the resection base	4 delayed bleeds (6.2%)
Uraoka, 2016 [4]	Japan	Prospective observational	57 (53)	Post-gastric ESD	Prophylactic (post-procedure); wound healing	1/51 delayed bleeds (2.0%); 96% active wound healing at week 1; 19% scarring stage at week 4; 98% scarring stage at week 8
Subramaniam, 2019 [1]	UK	Prospective observational	100	Intraprocedural bleeding and post-endoscopic resection (EMR/ESD) in the esophagus, stomach, duodenum, and colorectum	Monotherapy (n = 64); prophylactic application over the resection base	Hemostasis in 75%; delayed bleeding rate = 3%

▶ **Table 1** (Continuation)

Authors, year of publication	Country	Study design	Patients (lesions) where Purastat used, n	Indication	Application	Outcomes
Drews, 2025 [9]	Germany	RCT	120	Prevention post-endoscopic resection (EMR) in colorectal and duodenal lesions	Prophylactic application over the resection base	Clinically significant delayed bleeding occurred in 14 cases (11.7%) in the hemostatic gel group and 7 cases (6.3%) in the control group; no significant difference
De Nucci, 2020 [2]	Italy	Prospective observational	77	Acute UGI and LGI bleeding (including 50 post-endoscopic resection)	Rescue therapy after two modalities	Hemostasis in 90.9%; recurrence of bleeding in 10.4%
Subramaniam, 2021 [5]	UK	Single-center RCT	46	Active bleeding and post-endoscopic resection (esophageal and colonic ESD)	Monotherapy (121 bleeds); combination therapy (9 bleeds); prophylactic application over the resection base	Reduction in heat therapy for hemostasis by 50% in Purastat arm; successful primary hemostasis with Purastat in 92.6%; 4-week wound healing rate of 49% (Purastat) vs. 25% (controls)
Soons, 2021 [6]	Netherlands	Prospective observational	48	Post-endoscopic mucosal resection (esophagus, duodenum, and colorectum)	Prophylactic application over the resection base	Delayed bleeding in 7 patients (15.9%), with 4/7 in the duodenum (57.1%)
White, 2021 [11]	UK	Prospective observational	21	Refractory radiation proctopathy	4-weekly intervals (up to 3 times)	Reduction in bleeding episodes from 4.5 to 2 in the 7 days before the first and third treatments; improvement in hemoglobin and endoscopic score
Branchi, 2022 [12]	Germany	Prospective observational	111	Acute UGI and LGI bleeding (including 28 post-endoscopic resection)	Monotherapy; rescue therapy	Primary hemostasis in 94%; secondary hemostasis in 75%; 7-day rebleeding rate of 12%; 30-day rebleeding rate of 16%
Ishida, 2022 [13]	Japan	Retrospective case series	6	Endoscopic sphincterotomy bleeding	Monotherapy	Primary hemostasis in 100%
Uba, 2022 [14]	Japan	Retrospective	26	Endoscopic sphincterotomy bleeding	Monotherapy (n = 23); combination therapy (n = 3)	Primary hemostasis in 23/26 (88.4%)
Lesmana, 2023 [15]	Indonesia	Retrospective	41	Endoscopic sphincterotomy bleeding	Monotherapy (n = 34); combination therapy (n = 7)	Hemostasis rates in monotherapy + combination therapy of 100%; no rebleeding

▶ **Table 1** (Continuation)

Authors, year of publication	Country	Study design	Patients (lesions) where Purastat used, n	Indication	Application	Outcomes
Kubo, 2023 [16]	Japan	Retrospective	6	Acute UGI bleeding (peptic ulcer + gastric varices)	Combination therapy with hemoclips	Hemostasis in 100%: no rebleeding
Uraoka, 2023 [17]	Japan	Multicenter RCT (7 centers)	86	Gastric and rectal ESD	Combination therapy with coagulation forceps vs. coagulation forceps alone	Number of coagulations with hemostatic forceps reduced in the Purastat arm (1.0 vs. 4.9); time to achieve hemostasis longer in the Purastat arm: no difference in delayed bleeding rates
Dhindsa, 2023 [18]	Worldwide	Meta-analysis	427 patients (7 studies)	Acute GI bleeding including during endoscopic resection	Combination and monotherapy	Pooled rate of hemostasis 93.1%; Pooled rebleeding rate 8.9%
Gopakumar, 2023 [8]	Worldwide	Meta-analysis	307 patients (6 studies)	Post-endoscopic resection in the UGI and LGI tract	Prophylactic application to reduce risk of delayed bleeding	Pooled rate of delayed bleeding 5.7%
Gomi, 2024 [7]	Japan	Retrospective case control	101	Post-gastric ESD	Prophylactic application over the resection base	No difference in delayed bleeding rate vs. control group (5.9% vs. 6.7%)
Yang, 2024 [19]	USA	Multicenter prospective	43	Stricture prevention post-esophageal ESD	Prophylactic application over the resection base	Stricture rate of 20.9% (7/43); 80% after circumferential ESD; postoperative bleeding rate 6.9%
Maselli, 2024 [20]	Italy	Prospective observational	401	Active UGI + LGI bleeding and post-endoscopic resection (EMR, ESD, and ampullectomy)	Monotherapy and combination therapy; prophylactic application over the resection base	Hemostasis in 98.9%; rebleeding rate of 7.7%; delayed bleeding rate of 3.9%
Binda, 2023 [21]	Italy	Retrospective case series	10	Prevention and treatment of bleeding following endoscopic necrosectomy	Monotherapy and combination therapy; prophylactic application after EUS-guided necrosectomy	Hemostasis in 100% (3/3); no rebleeding; prevention of bleeding achieved in 6/7 (85.7%)
Oza, 2024 [22]	USA	Case series	10	Treatment of non-healing anastomotic ulcers following PPI treatment	Monotherapy following 8 weeks of PPI treatment	Ulcer healing in 9/10 patients (90%)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; LGI, lower gastrointestinal; PPI, proton pump inhibitor; RCT, randomized controlled trial; UGI, upper gastrointestinal.

hemostasis when Purastat was used as a primary hemostat compared with controls (49.3% vs. 99.6%; $P<0.001$) [5]. It is also worth noting that the use of Purastat did not adversely affect the en bloc resection rates, which were in fact higher in the interventional arm (76%) compared with the control group (69%). A subsequent multicenter Japanese RCT in gastric and rectal ESD also showed a significant reduction in hemostatic forceps use when Purastat was used beforehand (1.0 [SD 1.4] vs. 4.9 [SD 4.2] in the control group; $P<0.001$) and successful primary hemostatic rates of 62.2% [17]. The procedure time reported in both RCTs remained similar between the intervention and control groups, suggesting the application of Purastat does not prolong the procedure compared with diathermy. This suggests that Purastat can be an effective adjunct to thermal modalities to treat intraprocedural bleeding during ESD.

1.4.2.2 Efficacy in the treatment of upper and lower GI bleeding Purastat has also been noted to be effective in acute upper and lower GI bleeding. In a study of 111 patients with acute GI bleeding, Branchi et al. showed hemostatic efficacy rates of 94% when Purastat was used as a primary hemostatic agent; most of these bleeds were peptic ulcer, tumor, or angiodysplasia related [12]. The success rates (absence of rebleeding) were 91% at 3 days and 87% at 7 days after primary use, 87% and 81%, respectively, in all study patients. The overall rebleeding rate was 12% at 7 days and 16% at 30 days and, in the five patients who required surgery, temporary hemostasis and stabilization was achieved in all cases [12]. De Nucci reported a case series of 77 patients where Purastat was used as salvage therapy after failure of two hemostatic modalities and noted an initial hemostatic rate of 90%, with a rebleeding rate of 10% [2]. Maselli et al. [20] recently published a large Italian registry of Purastat application in 401 patients (n = 91 for hemostasis and n = 310 for prevention of bleeding). About half of the 91 patients had iatrogenic bleeds and 30% had peptic ulcer bleeds. This study was unique in utilizing Purastat in unconventional settings (e. g. for walled-off pancreatic necrosis drainage, angiodysplasia, gastric antral vascular ectasia, and post-percutaneous endoscopic gastrostomy). Overall hemostasis rates were 98.9%, although there were no details provided on the hemostasis rates stratified by clinical indication. In the 30-day follow-up period, the bleeding event rate following prophylactic use of Purastat was 3.9%, and rebleeding rate following hemostasis for active bleeding was reported as 7.7% (with five patients requiring endoscopic reintervention and one requiring treatment with interventional radiology) [20].

Binda et al. reported the use of Purastat for bleeding control in a multicenter pilot study of 10 patients undergoing endoscopy-guided walled-off pancreatic necrosis drainage [21]. In seven cases, Purastat was used for post-direct endoscopic necrosectomy bleeding prevention; in three cases, it was used to manage active bleeding: two cases being oozing that was successfully controlled, and one being a massive spurting bleed from a retroperitoneal vessel, which required subsequent angiography; no rebleeding occurred.

The evidence for Purastat as a hemostat has also been validated in a recent meta-analysis including seven studies with 427 patients. This study reported a pooled rate of successful hemostasis in 93.1%, with a rebleeding rate of 8.9% and no significant difference in hemostasis rates between monotherapy and combination therapy [18].

1.4.2.3 Efficacy in the treatment of endoscopic retrograde cholangiopancreatography-related bleeding Purastat has also been reported to be effective in the treatment of endoscopic retrograde cholangiopancreatography (ERCP)-related bleeds (sphincterotomy). A small series of six patients by Ishida et al. reported its efficacy and safety for sphincterotomy-related bleeding [13]. Another recent publication from Japan compared the use of Purastat with conventional modalities of treatment for sphincterotomy-related bleeds in a retrospective cohort of 62 patients [14]. The authors reported that Purastat was as effective as conventional modalities in achieving hemostasis; however, the mean procedure time was significantly shorter in patients treated with Purastat (9.4 vs. 15.4 minutes; $P=0.01$) and it was associated with a lower adverse event (AE) rate (including pancreatitis). A case series of 100 patients reported from Indonesia compared the outcome of conventional modalities of sphincterotomy bleed treatment with Purastat or a fibrin sealant (Beriplast; Aventis-Behring Ltd., Germany) and found both topical agents to be as effective as conventional hemostasis treatment, and with a lower delayed bleeding rate [15]. In these ERCP studies on Purastat use (unlike those for acute GI bleeding), the nature of the bleeding tended to be oozing bleeds, which is where the strength of Purastat lies. Oozing bleeds fall within the product's indication for usage; it should be noted that Purastat is not recommended for spurting bleeds.

1.4.2.4 Efficacy in the treatment of radiation proctopathy-related bleeding Purastat has also been used in the management of radiation proctopathy. A prospective UK case series of 21 patients demonstrated that repeated applications of Purastat could reduce the number of rectal bleeding episodes, improve the overall endoscopic grade of proctopathy, and improve the mean hemoglobin concentration, without any side effects [11]. This is an interesting area that deserves further evaluation.

1.4.3 Wound healing

Two studies have evaluated wound healing with Purastat application post-ESD [4, 5]. Uraoka et al. reported transition to the wound healing stage in 96% by 1 week post-gastric ESD [4], whilst Subramaniam et al. showed that complete wound healing was achieved by 4 weeks in almost 50% of patients compared with 25% of controls, with significant improvements in healing post-colonic ESD [5]. This effect of Purastat in modulating tissue healing has also been explored in the prevention of esophageal strictures after extensive esophageal ESD, as reported in a recent case series of 43 patients from the USA [19]. It may also play a role in treating anastomotic ulcers as shown by Oza et al. in their multicenter case series where 9/10 patients showed clinical improvement after failure to improve on proton pump inhibitor therapy [22].

1.4.4 Safety, financial aspects, and comparison

Purastat is technically easy to use, with no reports of catheter clogging and additionally, owing to its transparent nature, it does not impair endoscopic visualization, thereby permitting ongoing endoscopic therapy if required. Maselli et al. highlighted that, in the few cases where technical difficulties arose, this was related to instability of the endoscope's position [20]. Purastat is a sterile product and needs to be stored in a refrigerator prior to use. It is safe to use, is not systemically absorbed, and no AEs directly related to Purastat have been reported in the currently available biomedical literature. Given its flexible through-the-scope delivery catheter, it can be applied to bleeding in areas with difficult access.

There are no studies evaluating the financial aspects or cost-effectiveness of Purastat use. There are also no studies directly comparing Purastat with other topical hemostatic agents, although it has been used in combination with other hemostatic modalities successfully and has been shown to slow down bleeding enough to achieve complete hemostasis with endoscopic clips or thermal treatments, such as argon plasma coagulation (APC) [2, 16].

1.5 Summary

Purastat appears to be an effective hemostatic agent, which also has potential for reducing delayed bleeding, managing acute oozing GI bleeding, and favorably modulating tissue healing.

2 TC-325 Hemospray

2.1 Composition and mechanism

TC-325 (commercially available as Hemospray; Cook Medical, Winston-Salem, North Carolina, USA) (▶ **Fig. 2**) consists primarily of bentonite, an inert mineral that quickly absorbs water upon contact with blood. This absorption creates an adhesive seal, mechanical tamponade, and concentrates clotting factors without directly engaging the clotting cascade [23].

2.2 Regulatory status

TC-325 received initial FDA clearance as Hemospray in 2018; however, in 2023, it was recalled after receiving complaints that the handle and/or activation knob had cracked or broken when the device was activated. The recall applied to all lots manufactured from 16 January 2017 to 15 January 2020. After this issue was resolved, the company announced that the device was again available. Another issue, addressed by the company, was the adherence of the powder to the tip of the endoscope, causing difficulties in handling or removing the scope, especially when the product was applied with the scope in retroflexion. The company provided detailed instructions on how to avoid this risk.

▶ **Fig. 2** The Hemospray (TC-325) device.

2.3 Mode of use

The technical application of Hemospray is generally considered to be straightforward; however, the aforementioned drawbacks raise some considerations regarding the device's feasibility. Avoiding prolonged direct contact of the powder with the tip of the endoscope by using short intermittent sprays is recommended to reduce the risk of the powder's adherence, and ensure technical success and safety. The high pressure from the CO_2 flow also constitutes a risk of perforation, thereby warranting cautious and intermittent release of the powder.

In a comparative study, endoscopists evaluated TC-325 against standard endoscopic treatments (i. e. mechanical clipping, thermal cautery, or injection therapy). The investigators found that 78% considered TC-325 easier to use than endoscopic clips, 63% easier than APC, 54% easier than a bipolar contact thermal probe, and 46% easier than injection therapy [24]. Conversely, a minority found the application of TC-325 to be more challenging than other modalities (9% for injection therapy, 6% for a bipolar probe, and 4% for endoscopic clips), so creating some ambiguity regarding the feasibility of TC-325 in real life [24].

This evidence documents the need for dedicated training, although there is a lack of specific evidence regarding the necessary training and maintenance of competency. According to the recent ESGE curriculum on training in basic endoscopy, achieving competency in hemostasis requires 10–25 procedures, although this number is somewhat arbitrary and is not exclusive to hemostatic powders [25].

2.4 Evidence

2.4.1 Hemostatic efficacy

2.4.1.1 Efficacy in the treatment of upper GI bleeding Hemospray has been extensively studied, particularly in the context of actively bleeding lesions (▶ **Table 2**) [23, 24, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45]. Most studies have focused on its use in treating GI bleeding with active hemorrhage due to benign (Forrest Ia or Ib) (▶ **Fig. 3**) or malignant lesions [45].

Prospective cohort studies have shown high success rates in achieving primary hemostasis, ranging from 85% to 98.5% [24, 42], with primary hemostasis rates not significantly affected by antithrombotic use (63% in patients on antithrombotics vs. 100% in patients not using antithrombotics; rebleeding within

▶ **Table 2** Evidence on the efficacy of TC-325 (Hemospray) treatment.

Author, year of publication	Country	Design (cases treated, n)	Indication	Application (n or % of cases)	Outcomes
Holster, 2013 [26]	Netherlands	Prospective cohort (16)	UGIB	Monotherapy (11); salvage therapy (5)	Hemostasis: (i) on anti-thrombotics 5/8 (63%); (ii) not on anti-thrombotics 8/8 (100%); rebleeding: (i) on anti-thrombotics 3/8 (38%); (ii) not on anti-thrombotics 2/8 (25%)
Ibrahim 2013 [27]	Belgium and Egypt	Prospective cohort (9)	Variceal bleeding	Monotherapy – bridge to EVL	Hemostasis 9/9 (100%)
Smith, 2014 [24]	Multicenter, European	Prospective cohort (63)	UGIB	Monotherapy (55); combination (8)	Hemostasis 55/63 (87.3%); rebleeding 9/55 (16.4%)
Ibrahim, 2015 [28]	Belgium and Egypt	Prospective cohort (30)	Variceal bleeding	Monotherapy – bridge to EVL	Hemostasis 30/30 (100%); rebleeding 1/30 (3.3%)
Haddara, 2016 [30]	France	Prospective cohort (202)	UGIB-PUD (75); UGIB from malignancy (61); postintervention (35); others (31)	Monotherapy: (i) first line 94 (46.5%); (ii) salvage therapy 108 (53.5%)	Hemostasis 195/202 (96.5%); rebleeding 51/191 (26.7%)
Hagel, 2017 [31]	Germany	Prospective cohort (27)	UGIB 25; LGIB 2	Monotherapy	Hemostasis 26/27 (96.3%); rebleeding 9/27 (33.3%)
Kwek, 2017 [32]	Singapore	RCT (20)	UGIB	Monotherapy	Hemostasis: Hemospray 9/10 (90%) vs. standard treatment 10/10 (100%); rebleeding: Hemospray 3/9 (33.3%) vs. standard treatment 1/10 (10%)
Hookey, 2019 [33]	Canada	Prospective cohort (50)	LGIB	Monotherapy (25%); combination (42.3%); rescue (32.7%)	Hemostasis 49/50 (98%); rebleeding 5/50 (10%)
Ibrahim, 2019 [29]	Belgium and Egypt	RCT (86)	Variceal bleeding	Monotherapy – bridge to EVL	Hemostasis: Hemospray 38/43 (88%) vs. controls 27/43 (63%); rebleeding: Hemospray 3/9 (33.3%) vs. standard treatment 1/10 (10%)
Ramirez-Polo, 2019 [34]	Mexico	Retrospective cohort (81)	UGIB 23; bleeding from malignancy 35; post-procedure 2; other 11	Monotherapy	Hemostasis 80/81 (98.8%); rebleeding 16/80 (20%)
Chen, 2020 [35]	Canada	RCT (20)	Bleeding from malignancy	Hemospray vs. standard endoscopic therapy	Hemostasis: Hemospray 9/10 (90%) vs. standard therapy 4/10 (40%); rebleeding: Hemospray 2/10 (20%) vs. standard therapy 6/10 (60%)
Rodriguez de Santiago, 2019 [36]	Spain	Retrospective cohort (261)	UGIB 219: LGIB 42	First-line 70 (26.8%); rescue 191 (73.2%)	Hemostasis 93.5%; rebleeding 22.9%
Baracat, 2020 [37]	Brazil	RCT (39)	UGIB	Hemospray vs. hemoclip	Hemostasis: Hemospray 19/19 (100%) vs. hemoclip 18/20 (90%)

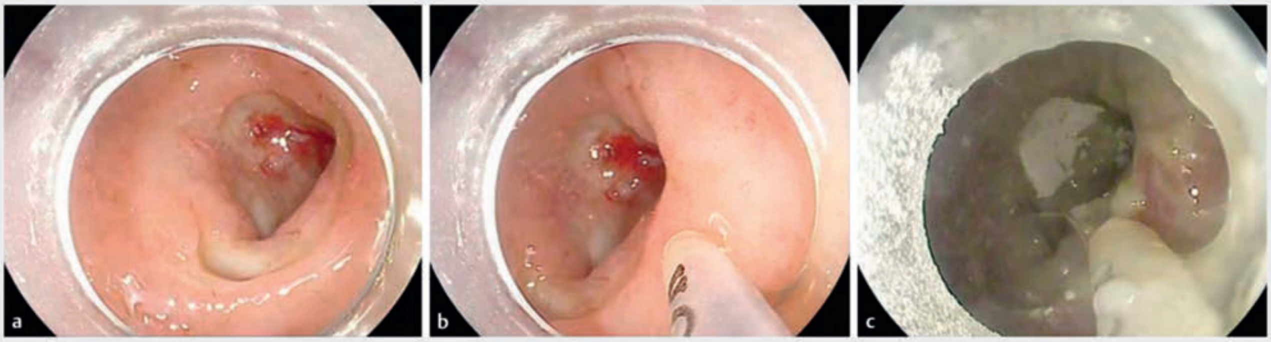
▶ **Table 2** (Continuation)

Author, year of publication	Country	Design (cases treated, n)	Indication	Application (n or % of cases)	Outcomes
Chahal, 2020 [38]	Canada	Retrospective cohort (86)	UGIB 73; LGIB 13	Monotherapy 28 (32.6%); combination 58 (67.4%)	Hemostasis 76/86 (88.4%); rebleeding (33.7%)
Hussein, 2021 [40]	UK	Prospective cohort (202)	UGIB-PUD	Monotherapy 50; combination 101; rescue 51	Hemostasis 178/202 (88%); rebleeding 26/154 (17%)
Hussein, 2020 [45]	Multicenter, international	Prospective cohort (73)	Post-endoscopic procedure	Monotherapy	Hemostasis 73/73 (100%); rebleeding 2/57 (4%)
Becq, 2021 [23]	France	Retrospective cohort (152)	UGIB 109; bleeding from malignancy 43; bleeding from procedure 9	Monotherapy 60 (39.2%); salvage 93 (60.8%)	Hemostasis 121/159 (79.0%)
Hussein, 2021 [39]	International registry	Prospective cohort (105)	UGIB from malignancy	Monotherapy 70; combination 26; rescue 9	Hemostasis 102/105 (97%); rebleeding 13/87 (15%)
Lau, 2022 [41]	Singapore and Hong Kong	RCT (224)	UGIB 136; bleeding from malignancy 33; other 55	Monotherapy vs. standard endoscopic therapy	Hemostasis: Hemospray 100/111 (90.1%) vs. standard therapy 92/113 (91.4%); rebleeding: Hemospray 9/111 (8.1%) vs. standard therapy 10/113 (8.8%)
Sung, 2022 [42]	Multicenter, international	Prospective cohort (67)	UGIB	Monotherapy	Hemostasis 60/66 (90.9%); rebleeding 8/66 (12.1%)
Pittayanon, 2023 [43]	Thailand	RCT (106)	Bleeding from malignancy	Monotherapy 55; crossover after standard endoscopic therapy 15	Hemostasis: Hemospray 55/55 (100%) vs. standard therapy 35/51 (68.6%); rebleeding: Hemospray 1/48 (2.1%) vs. standard therapy 10/47 (21.3%)
Papaefthymiou, 2024 [44]	Multicenter, international	Prospective cohort (190)	UGIB-PUD (48); UGIB from malignancy (79); LGIB (26); postintervention (37)	Monotherapy	Hemostasis 183/190 (96.3%); rebleeding 28/161 (17.4%)

EVL, endoscopic variceal ligation; LGIB, lower gastrointestinal bleeding; PUD, peptic ulcer disease; RCT, randomized controlled trial; UGIB, upper gastrointestinal bleeding.

7 days in 38% and 25%, respectively) [26]. A noninferiority RCT found fewer treatment failures with TC-325 compared with standard endoscopic therapies during index endoscopy (2.7% vs. 9.7%; odds ratio [OR] 0.26, 95%CI 0.07–0.95), whereas no significant differences were observed in terms of recurrent bleeding, the need for further interventions, or 30-day mortality [41]. Overall, bleeding was controlled within 30 days in 90.1% in the TC-325 group and 81.4% in the standard endoscopic therapies group. Another RCT compared TC-325 to hemoclip placement following adrenaline injection and, although primary hemostasis was comparable (100% vs. 90%; $P=0.49$), significantly more patients in the TC-325 group required an additional endoscopy with hemostasis therapy ($P=0.04$); however, these results are limited by the underpowered sample size owing to the available TC-325 devices [37].

A meta-analysis by Deliwala et al. [46] concluded that the overall success of primary hemostasis with TC-325 was equivalent to standard endoscopic therapies (risk ratio [RR] 1.09, 95%CI 0.95–1.25), including in patients with oozing/spurting hemorrhage (Forrest Ia or Ib; RR 1.13, 95%CI 0.98–1.3). However, owing to limited high level evidence, standard endoscopic therapies are recommended as first-line therapy, especially when there are risk factors for rebleeding, such as a Forrest Ia



► **Fig. 3** Endoscopic images showing Hemospray (TC-325) being used to treat oozing bleeding from a peptic ulcer.

lesion, a higher Glasgow–Blatchford score, hypotension, or the use of vasoactive drugs [30, 47].

Hemostatic powders are recommended as complementary to standard endoscopic therapies [48]. In a prospective study, TC-325 was used as monotherapy (25%), in combination therapy (50%), or as rescue therapy (25%), with no significant differences in hemostasis, rebleeding rates, or 7-day mortality amongst the groups [40]; however, 30-day mortality was significantly lower in the combination therapy group ($P < 0.05$) [40]. Chahal et al. [49] summarized 27 clinical studies with 1916 patients with upper GI bleeding of various etiologies. The pooled hemostasis rate was 94.5% and the rebleeding rates were 9.9% and 17.6% at 3 days and 30 days, respectively. The addition of TC-325 to standard endoscopic therapies led to a higher rate of primary hemostasis with an OR of 4.40 (95%CI 1.9–10.4) [49]. A network meta-analysis of 22 studies compared different hemostatic approaches, including mainly studies on TC-325, but also four studies investigating other powders (upper intraluminal endoscopic wound dressing [UI-EWD] and EndoClot) [50]. In terms of the 30-day cumulative rebleeding rate, hemostatic powders combined with standard endoscopic therapies had comparable efficacy to standard endoscopic therapies alone (RR 0.73, 95%CI 0.45–1.13) or over-the-scope (OTS) clipping alone (RR 0.56, 95%CI 0.30–1.05), showing no statistically significant difference [50].

According to a recently published systematic review with meta-analysis of four RCTs (303 patients) that compared TC-325 to standard endoscopic therapies for primary hemostasis of nonvariceal upper GI bleeding, the odds of primary hemostasis were significantly higher with TC-325 compared with standard endoscopic therapies (OR 3.48, 95%CI 1.09–11.18). Furthermore, there was no statistically significant difference between TC-325 and standard endoscopic therapies in terms of rebleeding rates (OR 0.79, 95%CI 0.24–2.55) [46].

2.4.1.2 Efficacy in the treatment of lower GI bleeding TC-325 also shows efficacy in lower GI bleeding, with similar hemostasis and rebleeding rates to those seen for upper GI bleeding [38]; however, the absence of distinct evidence on its use as monotherapy limits its indications to cases where there has been technical or clinical failure of conventional hemostasis techniques, or as an adjunctive treatment. In a prospective study, 50 patients, mainly suffering from post-polypectomy bleeding, underwent treatment with TC-325 (monotherapy 26%, combination treatment 40%, rescue treatment 34%) [33]. Primary hemostasis was achieved in all but one case, with a 10% rebleeding rate within 30 days. Facciorusso et al. [51] reported on a prospective database (65 patients) using TC-325 to treat lower GI bleeding. The main causes of bleeding were immediate post-polypectomy bleeding (46.1%), diverticular disease (18.4%), and colorectal cancer (18.4%). TC-325 was used as monotherapy in 56.9% of cases. Hemostasis was achieved in all cases and rebleeding occurred in 7.7% of cases within 7 days and in 9.2% within 30 days. The authors also meta-analyzed the outcomes of relevant studies, reporting a pooled rate for primary hemostasis of 96.3% (95%CI 93.4%–99.2%), 7-day rebleeding rate of 9.6% (95%CI 4.5%–14.6%), and 30-day rebleeding rate of 12.9% (95%CI 7.2%–18.5%), irrespective of the use of TC-325 as monotherapy or as combination therapy, the cause of lower GI bleeding, or study design [51]. It is however important to note that, in all three cases of spurting bleeding, TC-325 was applied in combination with standard of care, reflecting the difficulty of controlling arterial hemorrhage with hemostatic powders.

Diverticulosis is the most common cause of acute lower GI bleeding; however, an actively bleeding diverticulum is rarely detected during colonoscopy. Applying a factor that covers a large surface of a bleeding area, such as a part of the colon with diverticula, could theoretically ameliorate the risk of rebleeding; however, the risk of complications, such as perforation owing to the high release pressure, should be taken into account. Ng et al. [52] evaluated the performance of TC-325 in 10 cases with diverticular bleeding. In nine cases, the TC-325 was applied to an adherent clot, whereas one patient had spurting bleeding that was initially treated with hemostatic clips. No rebleeding occurred; however, these results require careful interpretation because of the low methodological quality of this study [52].

2.4.1.3 Efficacy in the treatment of GI malignancy-related bleeding TC-325 is promising in the treatment of malignancy-related bleeding. Results from international registries, using prospectively collected data, have shown primary hemostasis rates of 97%–100% with TC-325 [39]. Rebleeding occurred in 15% of patients within 30 days of treatment, with the malignancy site and the Blatchford score being significantly associated with 30-day mortality (P < 0.05). Interestingly, the mean number of units of blood transfused was significantly reduced by one unit per patient post-hemostasis treatment (P < 0.001) [39]. Pittayanon et al. [43] randomized 106 patients with malignancy-related GI hemorrhage to undergo hemostasis with TC-325 or standard endoscopic therapies. Primary hemostasis was achieved in 100% of cases receiving TC-325, compared with 68.6% in the standard endoscopic therapies group (OR 1.45, 95%CI 0.93–2.29; P < 0.001). Rebleeding within 30 days was significantly lower in the TC-325 group (2.1% vs. 21.3%; OR 0.09, 95%CI 0.01–0.80), and the application of TC-325 was the only significant variable predictive of reduced recurrent bleeding at 30 days. Likewise, the rebleeding rate was lower at 6-month follow-up in the TC-325 group (OR 0.26, 95%CI 0.08–0.86) [43]. In a crossover RCT, including 20 cases with both upper (85%) and lower (15%) GI malignancies, primary hemostasis was achieved in 90% of patients initially treated with TC-325 versus 40% in the standard endoscopic therapies group (P = 0.06) [35]. There was an overall hemostasis rate at index endoscopy (before or after crossover) of 87.7% in the patients treated with TC-325. Recurrent bleeding over the next 6 months was 20% in the TC-325 group compared with 60% in the standard endoscopic therapies group; however, this difference was not significant, likely owing to the limited sample size (P = 0.17).

Two similar meta-analyses were published recently, summarizing the evidence of RCTs on TC-325 efficacy compared with standard endoscopic hemostasis in the treatment of malignancy-related bleeding [53, 54]. Both studies confirmed the superiority of Hemospray over alternatives in terms of immediate hemostasis (RR 1.48, 95%CI 1.26–1.74; OR 46.6, 95% CI 5.89–369.1). Saeed et al. [53], who included four RCTs (227 patients) with upper GI malignancy, revealed similar rates of 30-day rebleeding between TC-325 and comparators, whereas Alali et al. [54], who included three RCTs (160 patients), demonstrated superiority of Hemospray in preserving the hemostatic effect (30-day rebleeding OR 0.28, 95%CI 0.11–0.70). All-cause mortality and the need for nonendoscopic treatment were not affected by the type of hemostasis in either study [55].

2.4.1.4 Efficacy in the treatment of interventional endoscopy-related bleeding Interventional endoscopy is associated with risks of AEs including hemorrhage, and TC-325 has been considered to have a potential role in prevention and treatment. Although postintervention bleeding has been evaluated as a subgroup in most studies of TC-325, there are some data focusing on this indication alone. In a prospective study of patients with post-endoscopic intervention bleeding (27% on antithrombotics), 73 subjects received TC-325 [45]. The primary hemostasis rate was 100%, regardless of the use of TC-325 as monotherapy, combination, or rescue therapy after any procedure (i. e. EMR, ESD, ampullectomy, sphincterotomy, and biopsy). Likewise, the rebleeding and 30-day mortality rates did not differ among the subgroups, with only two patients presenting with rebleeding.

2.4.1.5 Efficacy as salvage therapy Early prospective studies investigated the role of hemostatic powders as salvage therapy in cases of refractory/persistent bleeding. Sulz et al. [56] recruited 16 patients, with 14 receiving TC-325 as rescue therapy after failed conventional endoscopic hemostasis treatment. Hemostasis using TC-325 was achieved in 13/14 patients (92.9%), with only one patient having recurrent bleeding. A large prospective study confirmed that the hemostasis rates after the use of TC-325 in refractory bleeding cases were as high as in cases where it was used as primary treatment [30].

2.4.1.6 Efficacy in the treatment of esophageal variceal bleeding The role of TC-325 has been investigated for the treatment of esophageal variceal bleeding. Two prospective studies used TC-325 as the primary treatment for bleeding esophageal varices, with 100% primary hemostasis, and a successful bridge to elective band ligation [27, 28]. In a subsequent randomized trial, these same investigators assessed the efficacy of TC-325 application within 2 hours of admission, followed by elective band ligation the next day, compared with the standard approach of band ligation at the time of early endoscopy. Rescue endoscopy before the planned banding was necessary in 12% and 30% of the TC-325 group and the control group, respectively (P = 0.03). Additionally, 6-week survival was significantly higher in the TC-325 group (7% vs. 30%; P = 0.006) [29]. However, these data are not enough to support topical hemostatic powder use in cases of variceal bleeding and hemostatic powders should be reserved for those cases where standard variceal hemostasis modalities have failed or are unavailable [57].

2.4.2 Safety, technical failure, financial considerations, and comparison

The existing literature supports an overall good safety profile for TC-325; however, there are some reports of AEs. Abdominal pain is the most frequently reported AE, with rare cases of thromboembolism or perforation being reported, although it is not clear whether the TC-325 was responsible for these incidents or they were caused by the underlying medical condition [58]. As previously mentioned, a theoretical cause of perforation could be the high pressure of the CO_2 and this can be controlled by intermittent release of the agent.

The only well-established technical AEs include the risk of catheter occlusion and retention in the endoscope, particularly when the powder is released with the scope in retroflexion. This complication raised complaints to the company, resulting in a temporary withdrawal of the product, albeit the global rate of occurrence of difficulty or inability to maneuver or remove the endoscope or adhesion of the endoscope to tissue was 0.014% and subsequent patient harm occurred in 0.004%. To prevent catheter occlusion, prolonged insufflation following blood aspiration to dry the working channel prior to powder application is recommended [59]. In addition, reports regarding cracking of the handle or activation knob led to a voluntary recall, until the issue was resolved.

There are no studies evaluating the financial aspect or cost-effectiveness of TC-325 use. There are also no RCTs directly comparing TC-325 with other topical hemostatic agents.

2.5 Summary

TC-325 appears to be an effective hemostatic agent for hemostasis of nonvariceal upper and lower GI bleeding, for GI tumor-related bleeding, and for the management of interventional endoscopy-related bleeding. TC-325 should be considered as salvage therapy when standard endoscopic therapies fail. Comparative studies with other topical hemostatic agents and financial considerations do not exist and are still needed.

3 EndoClot Polysaccharide Hemostatic System (EndoClot PHS)

3.1 Composition and mechanism

EndoClot Polysaccharide Hemostatic System (EndoClot PHS; Olympus) (▶ **Fig. 4**) is a single-use endoscopic hemostatic system designed to control GI bleeding. It consists of a polysaccharide hemostatic powder and a specific air-pressure powder delivery system. The hemostatic powder is composed of absorbable modified polymers, which are polysaccharide particles derived from plant starch. These particles absorb water from blood, leading to the concentration of platelets, red blood cells, and coagulation proteins. This process accelerates the natural clotting cascade, forming a gel-like matrix that acts as a mechanical barrier to protect the bleeding site and control bleeding for several days. The exact adherence to the mucosa of the gel-like matrix is unknown, but the residence time in the GI tract is likely limited, ranging from a few hours to 48 hours. EndoClot PHS is not absorbed or metabolized by the mucosa, but it is eliminated through physical forces and enzyme degradation by endogenous amylase and glucoamylase [60, 61].

3.2 Regulatory status

EndoClot PHS was developed by EndoClot Plus, Inc. and launched in Europe in 2011. Since 2014, it has been manufactured in Suzhou Industrial Park, China. The US FDA cleared EndoClot PHS for the control of bleeding in the upper and lower GI tract in January 2021. It is now distributed in the USA, Europe, the Middle East, and Africa by Olympus.

3.3 Mode of use

EndoClot PHS includes the absorbable modified polymer hemostatic powder (2 g or 3 g) (▶ **Fig. 4a**) and a single-use powder applicator that consists of a 2300-mm delivery catheter, a powder/air mixing chamber, and a connecting tube that connects the applicator to an external reusable air source that operates on rechargeable batteries or AC power (EndoClot Air Compressor) (▶ **Fig. 4b**).

To use the EndoClot system, the endoscopist uses the following step-by-step guide: (i) the air compressor is connected to the delivery catheter and activated for high flow; (ii) the delivery catheter is inserted through the endoscope working channel (minimum diameter 2.8 mm), while the powder chamber is held upright to avoid spillage as the catheter is inserted (▶ **Fig. 4c**) – the high flow of air during insertion prevents wet particles entering the catheter and inducing clotting during the application process; (iii) the catheter tip is positioned at the bleeding site, keeping 1–2 cm distant from the site to avoid catheter clogging – direct contact of the catheter tip with any fluid must be avoided to prevent catheter blockage caused by reverse flow; (iv) the air flow is reduced to low; (v) the applicator is angled to 45° and the powder chamber is gently tapped to release the powder into the mixing chamber (▶ **Fig. 4d**) – the pressure coming from the air compressor propels the powder through the catheter, distributing it over a wide area.

3.4 Evidence

3.4.1 Hemostatic efficacy

3.4.1.1 Efficacy in the treatment of GI bleeding Müller-Gerbes et al. reported the first clinical experience of the EndoClot PHS in patients with upper GI bleeding. EndoClot PHS was used as monotherapy in 16 cases and as an adjunctive modality to other conventional hemostatic interventions in five cases, with effective hemostasis achieved in 20/21 patients (95%) [60]. Since then, EndoClot PHS has been applied in various GI

▶ **Fig. 4** Photographs of the EndoClot Polysaccharide Hemostatic System (EndoClot PHS) showing: **a** the cannister containing the absorbable modified polymer hemostatic powder; **b** the applicator (powder/gas mixing chamber, delivery catheter and connecting tube to external gas source) and air compressor: **c** the powder chamber being held in the upright position during catheter insertion; **d** the powder chamber (held at a 45° angle) and applicator during the powder release.

▶ **Table 3** Evidence on the efficacy of EndoClot PHS.

Author, year	Country	Design (cases treated, n)	Indication	Application (number of cases)	Outcomes
Müller-Gerbes, 2013 [60]	Germany	Case series (21)	UGIB	Monotherapy (5); combination (16)	Hemostasis 20/21 (95%)
Huang, 2014 [65]	China	Prospective cohort (82)	Post-EMR (colon)	Monotherapy	Hemostasis 18/20 (90%); post-EMR bleeding 6/82 (7.3%)
Beg, 2015 [61]	UK	Retrospective cohort (21)	UGIB	Rescue	Hemostasis 21/21 (100%); rebleeding (30-day): 1/21 (4.8%)
Prei, 2016 [62]	Germany	Prospective cohort (70)	UGIB (58); LGIB (12)	Monotherapy; rescue	Hemostasis 53/70 (76%); rebleeding 8/70 (11%)
Kim, 2018 [63]	Korea	Retrospective series (12)	UGIB from gastric malignancy	Monotherapy (7); combination (5)	Hemostasis 12/12 (100%); rebleeding 2/12 (16%)
Park, 2018 [66]	Korea	Prospective cohort (37)	UGIB	Monotherapy (13); combination (24)	Hemostasis 36/37 (97.3%); rebleeding 2/37 (5.4%)
Hahn, 2018 [67]	Korea	Prospective cohort (44)	Post-ESD (stomach)	Prophylaxis, primary	Post-ESD bleeding 4/44 (9.1%)
Vitali, 2019 [64]	Italy	Prospective cohort (32)	UGIB (25); LGIB (7)	Rescue (15); monotherapy (11); combination (6)	Hemostasis 26/32 (81%); rebleeding 8/43 (25%)
Hagel, 2020 [68]	Germany	Retrospective cohort (43)	UGIB; postintervention (EMR, ESD, sphincterotomy)	Rescue (17); monotherapy (5); combination (12); postintervention (9)	Hemostasis 37/43 (86%); rebleeding 9/43 (21%)
Jung, 2023 [69]	Korea	RCT (105)	Peptic ulcer bleeding	Combination with epinephrine injection	Hemostasis 92/105 (87.6%); rebleeding 8/102 (7.8%)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LGIB, lower gastrointestinal bleeding; RCT, randomized controlled trial, UGIB, upper gastrointestinal bleeding.

bleeding settings, including tumor bleeding, either as a single agent or in combination with other conventional interventions, or as rescue therapy after endoscopic hemostasis failure [61, 62, 63, 64]. As a primary or secondary treatment, EndoClot PHS has been shown to be effective in achieving hemostasis in 76%–100% of cases, with recurrent bleeding rates ranging from 5.1% to 25%. Details of the clinical studies are reported in ▶ **Table 3** [60, 61, 62, 63, 64, 65, 66, 67, 68, 69]. Limited data exist for the use of EndoClot PHS for lower GI bleeding [62, 64].

One multicenter, noninferiority RCT involving 216 patients with peptic ulcer bleeding and major stigmata of recent hemorrhage compared EndoClot PHS with conventional treatments (electrical coagulation with hemostatic forceps or clipping) [69]. In both groups, epinephrine injection was used as the initial treatment and, where initial hemostasis failed, salvage treatment with alternative hemostatic methods was applied at the discretion of the endoscopist. Initial successful hemostasis (the primary study outcome) was similar between the EndoClot PHS and conventional groups (92/105 patients [87.6%] vs. 96/111 patients [86.5%], respectively). The rebleeding rates also did not differ significantly between the two groups (7.8% vs. 9.3%, respectively). Notably, when restricting the analysis to patients with actively bleeding ulcers (Forrest Ia and Ib), failure of hemostasis was slightly higher in the EndoClot PHS group (13/35 patients; 37.1%) than in the conventional group (7/29; 24.1%). This suggests that, for patients with actively bleeding peptic ulcers, achieving initial hemostasis before applying EndoClot PHS may help to reduce the failure rate.

Vitali et al. [64] compared endoscopic outcomes in 154 bleeding patients (137 with upper GI bleeding, mainly from peptic ulcers, 17 with lower GI bleeding) treated with TC-325 (n = 111 patients) and EndoClot PHS (n = 32 patients) as primary or salvage therapy. The comparison revealed similar rates of short-term hemostasis (81.2% vs. 82.9%) and rebleeding (25.0% vs. 24.3%). Park et al. [66] prospectively compared 40 patients treated with EndoClot PHS and 303 patients treated with conventional hemostasis therapy for high risk upper GI bleeding lesions (Forrest Ia, Ib, IIa). In the EndoClot PHS group, the rates of primary hemostasis and 30-day rebleeding were 97.3% and 5.4%, respectively. These rates were comparable to those observed in the conventional group, both before and after propensity score matching, which included the Glasgow–Blatchford score and Forrest classification. In a subgroup analysis, no significant differences in primary hemostasis or rebleeding rates were noted between EndoClot PHS used as monotherapy or combined with a conventional hemostatic method. According to the authors, this suggests that EndoClot PHS and conventional therapy may have similar effectiveness; however, the nonrandomized study design and small sample size, which included only five spurting lesions (Forrest class Ia), call for caution in generalizing these conclusions.

3.4.1.2 Efficacy in the treatment of interventional endoscopy-related bleeding Prophylactic use following high risk EMR and ESD showed rebleeding rates of 7.3% and 9.1%, respectively [65, 68]. Rebleeding occurred after 48 hours, suggesting protection from the gel matrix may be limited to the duration that it resides on the mucosal surface [67]. Nevertheless, owing to the absence of a control arm, the effectiveness of EndoClot PHS in reducing the risk of delayed bleeding remains unclear. Currently, no data are available on the use of EndoClot PHS for treating procedure-related bleeding.

3.4.2 Safety and financial aspects

None of the published studies have reported any AEs directly related to EndoClot PHS; however, a few instances of technical issues, such as catheter blockages, have been reported [70]. There remains a theoretical risk of intestinal obstruction, embolism, perforation, and allergic reactions. The risk of perforation is considered very low, given that EndoClot is applied at a relatively low pressure. The risk of allergic reactions is likely negligible, given that EndoClot PHS does not contain any human or animal proteins.

There are currently no studies available that evaluate the financial impact or cost-effectiveness of EndoClot PHS.

3.5 Summary

EndoClot PHS appears to be an effective hemostatic agent, either as monotherapy or in combination with other endoscopic hemostasis treatment modalities, mainly for the primary hemostasis of nonvariceal upper GI bleeding, for tumor-related bleeding, and for the prevention of interventional endoscopy-related bleeding. Well-performed RCTs comparing it with other topical hemostatic agents and the assessment of financial considerations over other hemostatic modalities are needed.

4 Nexpowder

Upper intraluminal endoscopic wound dressing (UI-EWD; commercially available as Nexpowder; Medtronic, Minneapolis, Minnesota, USA) (▶ **Fig. 5**) was originally developed by Nextbiomedical, Incheon, South Korea to overcome the technical challenges of other commercially available topical hemostatic powders [71]. These technical challenges include delivery catheter clogging and impaired endoscopic visualization owing to scattering of the hemostatic powder.

▶ **Fig. 5** The Nexpowder device.

4.1 Composition and mechanism

UI-EWD is a biocompatible natural polymer (no human or animal proteins) consisting of aldehyde dextran and succinic acid modified ε-poly (l-lysine) [71]. Upon contact with moisture, these two materials immediately convert into an adhesive hydrogel, creating a mechanical barrier to promote hemostasis. The reaction between UI-EWD and water forms a Schiff base and multiple crosslinks within the hydrogel and between the hydrogel and the tissues. In addition, a liquid coating process applied to the powder using a fluidized bed granulator modifies the water absorption capacity of UI-EWD. This liquid coating technology allows UI-EWD to be delivered without clogging of the delivery catheter or scattering of the powder particulate matter and, in addition, provides a blue color at the treatment site [70].

4.2 Regulatory status

UI-EWD (Nexpowder) was cleared by the US FDA in 2022, as a hemostatic device for intraluminal GI use, and specifically for hemostasis of nonvariceal upper GI bleeding [72]. In addition to FDA certification, Nexpowder has obtained CE medical device regulation certification for use in Europe. Nextbiomedical has submitted an application to the FDA to extend the indication for Nexpowder to include the treatment of lower GI bleeding, which is currently under evaluation (koreabiomed.com). It is currently in use in more than 30 countries, including the USA and Europe.

4.3 Mode of use

UI-EWD is an inert powder developed for endoscopic hemostasis. The powder is delivered by a battery-powered delivery system through a 7.5-Fr catheter inserted through the working channel of the endoscope. There are 3 g of UI-EWD powder supplied in each commercial kit, with a shelf-life of 15 months [73]. The hemostatic mechanism of action of UI-EWD is the formation of a physical barrier to achieve hemostasis, and the presence of blood is not required for this to occur. Prior to application of the powder, it is important to remove blood and fluids from the treatment area, the powder chamber must be kept upright to prevent accidental spillage, and the catheter must not come into contact with liquids, as this could cause the powder to coagulate inside the catheter. Therefore, it is recommended that the endoscope channel is thoroughly cleaned with air before the procedure and an angle of approximately 45° relative to the application site is maintained to optimize powder dispersion. Notably, UI-EWD was specially designed to elimi-

► **Table 4** Evidence on the efficacy of UI-EWD (Nexpowder).

Author, year	Country	Design (cases treated, n)	Indication	Application (number of cases)	Outcomes
Park, 2019 [71]	Korea	Prospective pilot study (17)	Refractory UGIB	Rescue monotherapy	Immediate hemostasis 16/17 (94.1%); rebleeding within 30 days 3/16 (18.8%)
Park, 2019 [74]	Korea	Retrospective cohort (56)	Nonvariceal UGIB	Monotherapy	Immediate hemostasis 54/56 (96.4%); rebleeding within 30 days 2/54 (3.7%)
Shin, 2021 [75]	Korea	Retrospective cohort (41)	Upper GI tract tumor bleeding	Rescue therapy	Immediate hemostasis 40/41 (97.5%); rebleeding within 28 days 10/40 (22.5%)
Cha, 2022 [76]	Korea	Retrospective cohort (55)	LGIB	Rescue therapy (38); monotherapy (17)	Rebleeding within 28 days 3/55 (5.5%)

LGIB, lower gastrointestinal bleeding; UGIB, upper gastrointestinal bleeding.

nate the effects of high application pressures and minimize the risk of perforation.

4.4 Evidence

4.4.1 Hemostatic efficacy

Currently there are limited clinical data available evaluating the efficacy and safety of UI-EWD, and only a single retrospective study comparing UI-EWD with conventional hemostasis modalities in lower GI bleeding. There are no studies comparing UI-EWD with other available topical hemostatic agents. All of the published studies are from South Korea. Details are reported in ► **Table 4** [71, 74, 75, 76].

4.4.1.1 Efficacy in the treatment of upper GI bleeding In an initial publication evaluating the efficacy of UI-EWD in gastric bleeding in a porcine model (n = 8 heparinized male minipigs), Bang et al. [73] reported 100% initial hemostasis with UI-EWD and, at follow-up endoscopy at 6 hours, there was minor bleeding in 10% in the experimental group (n = 5) and 50% in the control group (n = 3). Moreover, UI-EWD hydrogel persisted in 50% of ulcer bases at 42 hours post-application. In the first "in human" pilot study [71], 17 patients who had failed conventional endoscopic hemostasis and had refractory upper GI bleeding (peptic ulcer, postintervention, neoplasm, other) were prospectively enrolled to receive UI-EWD as rescue therapy, with the rates of successful initial hemostasis and rebleeding evaluated. Initial hemostasis occurred in 16/17 patients (94%); rebleeding within 30 days occurred in 3/16 (19%). For Forest Ia lesions, primary hemostasis was only 50%. At second-look endoscopy, performed 24 hours later, UI-EWD remained at the treatment site in 11/16 patients (69%).

In a retrospective study, 56 patients who received UI-EWD as monotherapy for nonvariceal upper GI bleeding (i. e. postintervention, peptic ulcer, anastomotic, and neoplasm bleeding) were evaluated for successful primary hemostasis and rates of rebleeding [74]. Successful primary hemostasis occurred in 54/56 patients (96.4%) and the 30-day rebleeding rate was 2/54 (3.7%); however, there were no Forest Ia lesions included in this cohort. At second-look endoscopy at 24 hours after the procedure, UI-EWD hydrogel remained at the treatment site in 33/47 patients (70.2%) and in 15/38 patients (39.4%) at 72 hours. Catheter clogging was reported in 3.6% of patients [74]. Shin et al. reported on 41 consecutive patients with upper GI tract tumor bleeding (adenocarcinoma, squamous cell carcinoma, gastrointestinal stromal tumor, or lymphoma) where UI-EWD was applied as salvage therapy following the failure of conventional endoscopic hemostasis modalities or as monotherapy [75]. Overall, primary hemostasis with UI-EWD was successful in 40/41 patients (97.5%) and rebleeding within 28 days occurred in 10/40 patients (22.5%). In those patients where UI-EWD was used as monotherapy, primary hemostasis was achieved in 23/23 patients (100%), with rebleeding occurring in 6/23 (26.1%) within 28 days.

4.4.1.2 Efficacy in the treatment of lower GI bleeding In the only study to date evaluating the role of UI-EWD in acute lower GI bleeding, Cha et al. reported on a retrospective cohort of 55 patients with mixed indications (i. e. mainly ulcer bleeding, but also diverticular bleeding, radiation-induced proctopathy, post-procedure and tumor-related bleeding) who received UI-EWD as salvage endoscopic hemostasis therapy (n = 38) or as monotherapy (n = 17) [76]. When compared with a historical cohort of acute lower GI bleeding patients (n = 112) who received conventional endoscopic hemostasis, hemostasis was achieved significantly more often in lesions located at the hepatic flexure (7.3% vs. 0%; P = 0.01) and in lesions > 4 cm (25.5% vs. 8.0%; P = 0.002) when treated with UI-EWD. Moreover, the cumulative rebleeding rates at 28 days were 5.5% in the UI-EWD patients and 17.0% in the conventional endoscopic hemostasis treatment group (P = 0.04).

4.5 Summary

Based on the still limited available evidence, Nexpowder appears to be an effective hemostatic agent, as monotherapy or in combination with other treatment modalities, for the primary hemostasis of nonvariceal upper GI bleeding, for tumor-related bleeding, and for the management of interventional endoscopy-related bleeding. Evidence for lower GI bleeding is less robust. Data for treating delayed or intraprocedural bleeding following endoscopic resection (EMR/ESD) are lacking. The low pressure application improves the safety profile, minimizing the risk of perforation. Studies performed in countries other than South Korea and RCTs comparing it with standard endoscopic therapy and other topical hemostatic agents, as well as the assessment of financial considerations over other hemostatic agents, are still missing.

5 Ankaferd Blood Stopper

5.1 Composition and mechanism

Ankaferd Blood Stopper (ABS; Ankaferd Health Products Ltd., Istanbul, Turkey) (▶ **Fig. 6**) is a novel hemostatic agent that is based on a traditional medicinal plant extract and has been used as a hemostatic agent in Turkish traditional medicine for hundreds of years. ABS is composed of a standardized mixture of the plants *Thymys vulgaris*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Alpinia officinarum*, and *Urtica dioicia* [77]. ABS is approved in Turkey for the management of dermal, external postsurgical, and postdental bleeding, but multiple studies have reported its use in the management of GI bleeding.

The hemostatic effect of ABS is due to the rapid formation of an encapsulated protein network that acts as an anchor for erythrocyte aggregation, leading to hemostasis [78]. In addition, other reported mechanisms of action include inhibition of fibrinolysis and anticoagulant pathways, in addition to wound-healing properties [79]; however, the exact hemostatic effect of ABS remains unknown. Furthermore, ABS has been reported to decrease tumor vascularization in bleeding GI malignancies [80].

5.2 Regulatory status

ABS has obtained CE certification, but has not yet received European Medicines Agency (EMA) approval. It is currently available as a hemostatic agent in several European countries, including Germany, Italy, Greece, Spain, Montenegro, Serbia, and Slovakia. In addition, it is approved in other extra-EU countries, including Turkey, Kuwait, and Panama, amongst others.

5.3 Indications

ABS can be used to manage upper and lower GI bleeding of various etiologies as a primary or rescue therapy, either as monotherapy or in combination with other hemostatic therapies. ABS has been reported in the management of GI bleeding in patients with peptic ulcer disease [81, 82], malignancy [83, 84], varices [85, 86], post-polypectomy bleeding [87, 88], post-sphincterotomy bleeding [89], Mallory–Weiss tear [85, 90], Dieulafoy's lesions [87, 90], gastric antral vascular ectasia [87], diverticulosis [91], and radiation-induced colitis [87, 92, 93]. Furthermore, ABS has been used in patients with solitary rectal ulcer syndrome for its presumed ulcer-healing properties [92].

▶ **Fig. 6** The Ankaferd Blood Stopper device.

Video 2 Ankaferd Blood Stopper is applied topically after duodenal mucosal resection.
Online content viewable at:
https://doi.org/10.1055/a-2646-7556

5.4 Mode of use

ABS is packaged in vials or syringes in liquid form in varying volumes (0.5 mL to 10 mL per syringe). It can be delivered endoscopically to the bleeding lesion using a spray catheter or injection needle (▶ **Video 2**). The topical application of ABS must cover the entire bleeding area. Once applied onto the bleeding area, ABS forms a grayish-yellow coagulum covering the site, which typically disappears within a few days. This discoloration may interfere with endoscopic visualization, so precise application of the agent onto the bleeding site is important. The volume of ABS used has varied in different studies, from as little as 2 mL to as much as 150 mL, depending on the extent of bleeding [77, 94].

5.5 Evidence

5.5.1 Hemostatic efficacy

Several cohort studies and case series have reported on the hemostatic efficacy of ABS, all exclusively from Turkey (▶ **Table 5**) [83, 87, 88, 95, 96, 97, 98, 99]. Gungor et al. reported the efficacy of ABS (as primary or rescue therapy) in 26 patients with nonvariceal upper GI bleeding, the majority secondary to peptic ulcer bleeding [97]. Primary hemostasis was achieved in 73.1% of patients, but rebleeding rates were not reported. Interestingly, this study found a significantly higher failure rate for ABS among patients with coagulopathy and those taking antithrombotics. Kurt et al. reported a primary hemostasis rate of 100% in 26 patients with upper and lower GI bleeding when ABS was used as a first-line or rescue therapy, unfortunately the study did not report the rebleeding rate [87].

One of the largest cohort studies, which included 64 patients with upper (mostly peptic ulcer) and lower GI bleeding of varying etiologies, reported a primary hemostasis rate of 100% and a late rebleeding rate of 1.5% when ABS was used as a first-line or rescue therapy [98]. Of note, most of the patients included in the previous studies had oozing bleeding (Forrest Ib), while a minority had spurting bleeding (Forrest Ia). In fact, ABS was found to be ineffective in patients with spurting bleeding as the forceful arterial pressure prevents ABS from forming a hemostatic plug [100].

Karaman et al. prospectively evaluated the efficacy of ABS in 30 patients with variceal and nonvariceal bleeding, mostly as rescue therapy [88]. Hemostasis was achieved in 87% of cases, with no reported rebleeding up to 1 week postintervention. ABS has shown promising results in managing variceal bleeding (▶ **Fig. 7**) in several small case series and case reports [86, 88, 100].

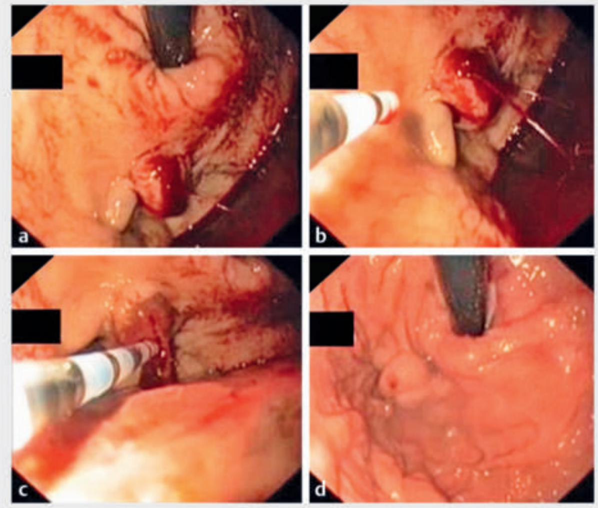
The efficacy of ABS in malignant GI bleeding was evaluated in a retrospective study of 10 patients, where hemostasis was achieved in all patients [87]. The overall primary hemostasis rate reported with ABS varied between 86% and 100%, and a rebleeding rate up to 3% was reported (▶ **Table 5**); these data are similar to those reported with other topical agents in a meta-analysis of 59 studies [101].

Bas et al. compared ABS (alone or as rescue therapy) to standard endoscopic therapy (mostly a combination of injection therapy with endoscopic clips or APC) among patients presenting with nonvariceal upper GI bleeding, mostly duodenal ulcers (50.7%) [99]. The primary hemostasis and rebleeding rates in the ABS group (n = 96 patients) were similar to those observed in the standard endoscopic group (n = 106 patients); however, this study was a retrospective analysis that focused on less experienced endoscopists, and direct comparative data are still lacking for ABS. Nevertheless, these data emphasize the easy application of such therapy, even among less experienced endoscopist in emergency settings.

5.5.2 Safety and financial considerations

ABS has been demonstrated to be safe in animal studies, even when given in high doses [102]. None of the published human studies have reported any toxicity or AEs directly related to the use of ABS (including any allergic reactions related to its herbal components); however, a case of duodenal perforation was reported in a patient with GI bleeding secondary to gastroduodenal amyloidosis where ABS had been applied 3 days previously to control the bleeding; it remains unclear if this AE was directly related to the use of ABS or to the underlying disease itself [103]. No reports of technical failures or catheter blockages have been reported with ABS use.

There are no data available on the financial considerations.



▶ **Fig. 7** Endoscopic images of the use of the Ankaferd Blood Stopper device showing: **a** active bleeding from an isolated fundal gastric varix; **b** the bleeding area being approached with the catheter; **c** the bleeding being stopped with the topical application of Ankaferd Blood Stopper, which is aimed at the bleeding point; **d** confirmation of hemostasis and the absence of rebleeding on follow-up endoscopy 48 hours later (images used with permission from Ankaferd Health Products Ltd.).

5.6 Summary

ABS may be useful as first-line or rescue therapy, especially in patients with mild–moderate bleeding; however, data supporting the routine use of ABS in the management of GI bleeding remain limited. Studies performed in countries other than Turkey and larger comparative studies are needed to further assess the efficacy of ABS in the treatment of GI bleeding, as well as an assessment of the financial aspects of its use.

6 CG GEL

6.1 Composition and mechanism

CG GEL (previously CEGP-003; CGBio Co., Ltd., Seongnam, South Korea) (▶ **Fig. 8**) is a powder-type endoscopic hemostatic system that is composed of a biocompatible, absorbable, and adhesive macromolecule containing hydroxyethyl cellulose, in addition to epidermal growth factor [104]. Upon contact with blood, CG GEL rapidly absorbs water to concentrate platelets, red blood cells, and coagulation proteins, which accelerate the

► **Table 5** Evidence on the efficacy of CG GEL and Ankaferd Blood Stopper (ABS).

Study	Agent	Country	Design (cases treated, n)	Indication (number of cases)	Application	Outcomes
Bang, 2018 [95]	CG GEL	South Korea	RCT (35)	PUD (6); post-EMR (5); post-ESD (24)	Monotherapy	Hemostasis 35/35 (100%); rebleeding 3/35 (8.6%)
Choi, 2023 [96]	CG GEL	South Korea	RCT (41)	Post-sphincterotomy	Monotherapy	Hemostasis 41/41 (100%); rebleeding 1/41 (2.4%)
Gungor, 2012 [97]	ABS	Turkey	Retrospective cohort (26)	Nonvariceal UGIB (PUD, Dieulafoy, malignancy)	Monotherapy	Hemostasis 19/26 (73.1%); rebleeding 3/26 (15.8%)
Karaman, 2010 [88]	ABS	Turkey	Retrospective cohort (30)	UGIB (variceal, PUD, malignancy, vascular, post-sphincterotomy)	Rescue	Hemostasis 26/30 (86.6%); rebleeding 0/30 (0%)
Kurt, 2010 [87]	ABS	Turkey	Retrospective cohort (26)	UGIB (20); LGIB (6)	Primary; rescue	Hemostasis 26/26 (100%); rebleeding not reported
Kurt, 2010 [83]	ABS	Turkey	Retrospective cohort (10)	Gastric cancer (7); rectal cancer (3)	Monotherapy	Hemostasis 10/10 (100%); rebleeding 0/8 (0%)
Bas, 2021 [98]	ABS	Turkey	Retrospective cohort (64)	UGIB (50); LGIB (14)	Monotherapy; combination	Hemostasis 64/64 (100%); rebleeding 1/64(1.5%)
Bas, 2024 [99]	ABS	Turkey	Retrospective cohort (96)	Non variceal UGIB (PUD, Dieulafoy, malignancy)	Monotherapy; combination	Hemostasis 96/96 (100%); rebleeding 3/96 (3.1%)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LGIB, lower gastrointestinal bleeding; PUD, peptic ulcer disease; RCT, randomized controlled trial; UGIB, upper gastrointestinal bleeding.

► **Fig. 8** The CG GEL delivery system. Source: CGBio, Seoul, South Korea.

physiological clotting cascade. Furthermore, CG GEL forms an adhesive barrier gel that seals the bleeding area and provides a physical barrier to protect it from the acidic gastric environment, further promoting hemostasis. The epidermal growth factor component activates epidermal growth factor receptors and intracellular pathways of wound healing, which promote ulcer healing [105]. The gel is typically excreted from the body within 72 hours.

6.2 Regulatory status

CG GEL is currently approved for the treatment of GI bleeding in South Korea only.

6.3 Indications

CG GEL has been used for hemostasis in patients with non-variceal upper GI bleeding, post-endoscopic resection (EMR/ESD) bleeding [95], and post-sphincterotomy bleeding [96]. Given its epidermal growth factor component, it has been suggested for prophylactic use to prevent bleeding and accelerate healing post-endoscopic resection [105], but human data to support this indication are lacking. No data exist for the use of CG GEL for the management of lower GI or tumor-related bleeding. Furthermore, the role of CG GEL as a rescue therapy after failure of other hemostatic therapy remains unclear.

6.4 Mode of use

The hemostatic powder (3 g in each tube) is delivered to the bleeding area endoscopically via a disposable catheter and a specially designed, battery-powered, continuous air-blowing spray gun. A sufficient amount of the product is sprayed to completely cover the bleeding area, with a maximum dose of 9 g. To avoid catheter clogging, a distance of 1–2 cm should be kept between the catheter tip and bleeding site, and the use of the continuous air-blowing gun may reduce the risk of catheter clogging further, even if the catheter comes into contact with moisture. Upon contact of the powder with moisture, an adhesive gel is formed, which seals the bleeding area to achieve hemostasis. The gel matrix formed by CG GEL sloughs off within

3 days and is excreted naturally through the digestive tract [95].

6.5 Evidence

6.5.1 Hemostatic efficacy

Limited human data exist for the efficacy of CG GEL in the management of GI bleeding and details on clinical studies are reported in ▶ **Table 5** [95, 96].

The first human study was an RCT conducted in South Korea that compared CG GEL (called CEGP-003 at that time) with epinephrine injection monotherapy as a primary therapy for nonvariceal upper GI bleeding [95]. The study included different bleeding etiologies, including peptic ulcer disease (20.5%), post-EMR bleeding (15.1%), and post-ESD bleeding (64.4%). Most lesions were in the stomach and had oozing bleeding (Forrest Ib), while none of the included lesions had spurting bleeding (Forrest Ia). Among the 35 patients randomized to CG GEL, all achieved primary hemostasis, compared with 89.2% of the 37 patients randomized to epinephrine injection. The 3-day rebleeding rate was higher in the CG GEL group compared with the epinephrine injection group (8.6% vs. 2.7%, respectively). These differences were not statistically different, but the rebleeding rate was almost three-fold higher in the CG GEL group compared with epinephrine monotherapy, a treatment that is not recommended to be used as a monotherapy in nonvariceal upper GI bleeding owing to the high risk of rebleeding [106, 107, 108].

The second human study was published recently by Choi et al., who evaluated the safety and efficacy of CG GEL in the treatment of post-endoscopic sphincterotomy or post-papillectomy bleeding when used by experienced endoscopists, comparing CG GEL with epinephrine spray among 82 patients who experienced immediate bleeding after sphincterotomy or papillectomy [96]. The primary hemostasis rate was significantly higher in the CG GEL group compared with epinephrine spray (100% vs. 85.4%; $P = 0.03$), while the rate of delayed bleeding was similar in both groups (2.4% vs. 8.6%; $P = 0.23$), but the procedural time was significantly longer with CG GEL (3.2 vs. 1.9 minutes; $P < 0.001$). Nevertheless, most endoscopists felt that CG GEL was easy to use and expressed a high level of satisfaction with the procedure using CG GEL. The use of epinephrine spray, with its unproven benefit in the setting of post-sphincterotomy bleeding, as a comparative intervention complicates the interpretation of this study's results. Given the methodological issues with the two published RCTs, especially in relation to the endoscopic therapies used in the control arms, caution must be exerted when interpreting the efficacy of CG GEL in the setting of nonvariceal upper GI bleeding.

6.5.2 Safety and financial considerations

None of the published studies have reported any AEs directly related to CG GEL. Choi et al. reported two cases of post-ERCP fever and one case of post-ERCP pancreatitis, but none of these AEs were attributed to the use of the hemostatic powder [96]. No technical failures have been reported so far, including no cases of catheter clogging [95, 96].

Currently, CG GEL is only available commercially in South Korea.

6.6 Summary

The available evidence does not allow any conclusion on the efficacy of CG GEL for the control of GI bleeding. Therefore, further research is required to confirm its efficacy in nonvariceal upper GI bleeding compared with standard hemostatic modalities. In addition, the efficacy of CG GEL in malignant GI bleeding remains to be explored.

Conclusions

This ESGE Technical and Technology review highlights the increasing role of topical hemostatic agents in the field of GI endoscopy. Agents such as Purastat, TC-325 (Hemospray), EndoClot PHS, Nexpowder, Ankaferd Blood Stopper, and CG GEL demonstrate varying degrees of efficacy across different bleeding scenarios. While each product offers unique mechanisms and modes of application, current data largely support their use in specific cases, often as adjuncts to standard endoscopic treatments. In particular, these agents are effective for bleeding control, but caution is needed when considering their efficacy for spurting lesions (Forrest Ia). Maximum efficacy has been demonstrated in studies focused on the treatment of bleeding GI tumors. Stronger and more robust data support the use of hemostatic agents for upper GI bleeding and in the management of intra- and post-procedural bleeding (EMR/ESD), while more data on lower GI bleeding are awaited.

These hemostatic agents represent a very useful tool for less experienced endoscopists, serving as a rescue strategy or as a bridge treatment in facilities without 24/7 services. Despite promising results, comparative studies and evaluations of cost-effectiveness are limited, warranting further research to establish the optimal applications and financial feasibility of these agents in clinical practice. Future studies should also focus on evaluating their safety profiles and enhancing accessibility to newer, more effective hemostatic technologies.

Acknowledgement

We would like to thank Dr. Francesco Vito Mandarino and Professor Marine Camus for their valuable review of this manuscript.

Conflict of Interest

P. Bhandari has received research grants from 3-D Matrix Ltd. (2017 to 2023). I.M. Gralnek has provided consultancy to Medtronic (2022 to present). R.J. Haidry has received research grant support from Pentax Medical, Cook Endoscopy, and AquaMedical (2022 to present). A. Alkandari, A. Alali, A. Papaefthymiou, F. Radaelli, S. Subramaniam, and L. Fuccio declare that they have no conflict of interest.

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