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Hemostatic powders for gastrointestinal bleeding: a review of old, new, and emerging agents in a rapidly advancing field

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ABSTRACT

Background and study aims Hemostatic powders are increasingly used to address limitations in conventional endoscopic techniques for gastrointestinal bleeding. Various agents exist with different compositions, characteristics, efficacy, and adverse events (AEs). We sought to review existing hemostatic powders, from preclinical to established agents.

Methods A literature review on hemostatic powders for gastrointestinal bleeding was undertaken through a MEDLINE search from 2000–2021 and hand searching of articles. Relevant literature was critically appraised and reviewed for mechanism of action, hemostasis and rebleeding rate, factors associated with hemostatic failure, and AEs.

Results The most established agents are TC-325 (Hemospray), EndoClot, and Ankaferd Blood Stopper (ABS). These agents have been successfully applied to a variety of upper and lower gastrointestinal bleeding etiologies, in the form of primary, combination, salvage, and bridging therapy. Few AEs have been reported, including visceral perforation, venous embolism, and self-limited abdominal pain. Newer agents include CEGP-003 and UI-EWD, which have shown results similar to those for the older agents in initial clinical studies. All aforementioned powders have high immediate hemostasis rates, particularly in scenarios not amenable to conventional endoscopic methods, but are limited by significant rates of rebleeding. Other treatments include TDM-621 (PuraStat) consisting of a liquid hemostatic agent newly applied to endoscopy and self-propelling thrombin powder (CounterFlow Powder), a preclinical but promising agent.

Conclusions Rapid development of hemostatic powders and growing clinical expertise has established these agents as a valuable strategy in gastrointestinal bleeding. Further research will continue to refine the efficacy and applicability of these agents.

Introduction

Hemostatic powders have been developed to address current limitations of conventional endoscopic treatment for gastrointestinal bleeding. Conventional management, consisting of mechanical clipping, thermocoagulation, and epinephrine injection, is estimated to fail and lead to mortality in 5 % to 10 % of cases [1, 2]. In part, this is due to difficulty applying these methods to bleeding in anatomically challenging areas, lesions

▶ **Table 1** Summary of hemostatic powders for endoscopic application.

	TC-325 (Hemospray)	EndoClot	ABS	ui-EWD (NexPowder)	CEGP-003
Manufacturer	Cook Medical Winston-Salem, North Carolina, USA	EndoClot Plus Santa Clara, California, USA	Ankaferd Health Products Istanbul, Turkey	Next Biomedical Incheon, South Korea	CGBio Seong-Nam, South Korea
Material	Inert mineral powder	Polysaccharides from plant starch	Five herbal extracts	Natural polymer	Natural polymer with epidermal growth factor
Mechanism of action	Forms adhesive seal over bleeding site, concentrates platelets and coagulation factors	Forms gelled matrix to seal bleeding site, causes platelet/coagulation factor concentration from rapid absorption of water, and activation of fibroblasts	Forms encapsulated protein matrix, leading to erythrocyte aggregation	Forms mucoadhesive hydrogel to create mechanical barrier on bleeding site	Forms adhesive gel to create mechanical barrier and promote local wound healing pathways
Reported clinical uses	Peptic ulcer disease, malignant GIB, varices, post-intervention, diverticular disease, portal hypertensive gastropathy/colopathy	Peptic ulcer disease, malignant GIB, varices, post-banding ulcers, post-EMR/ESD, radiation injury, lower GI bleeding	Peptic ulcer disease, malignant GIB, varices, GAVE, post-polypectomy, post-sphincterotomy, vascular lesion, radiation colitis, diverticular bleeding	Peptic ulcer, post-intervention, malignant GIB (carcinoma, GIST, lymphoma).	Peptic ulcer, post-EMR, post-ESD

GIB, gastrointestinal bleeding; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; GAVE, gastric antral vascular ectasia; GIST, gastrointestinal stromal tumor.

with poor visualization, diffuse bleeding, and friable tissue. Further, the success of these techniques depends upon availability of skilled endoscopists and equipment. Hemostatic powders provide a treatment modality that has a minimal learning curve, is atraumatic, accesses anatomically difficult areas, and is broadly applicable to various etiologies of gastrointestinal bleeding. On a healthcare system level, use of hemostatic powders as rescue therapy where conventional therapy fails is projected to lead to economic savings [3]. For upper gastrointestinal bleeding, the 2021 American College of Gastroenterology (ACG) clinical guidelines conditionally recommend endoscopic hemostatic therapy for patients with actively bleeding ulcers, while the 2019 International Consensus guidelines recommend its use only as a temporizing measure toward definitive treatment [4, 5]. These evolving guidelines reflect recent advances in and research about hemostatic powders.

Given the rapid development of several hemostatic powders worldwide and addition of new agents, we provide a comprehensive clinical summary of all therapies, including those not discussed in previous reviews [6–9]. We review more established agents, TC-325 (Hemospray), EndoClot, and Ankaferd Blood Stopper (ABS) as well as newer agents, CEGP-003 and UI-EWD (NexPowder). We also review non-powder, preclinical, and alternative agents with mounting evidence. For each agent, we outline the mechanism of action, supporting clinical or preclinical studies, associated adverse events (AEs), and technical issues.

Methods

A literature search was conducted on MEDLINE from 2000–2021 for the keywords and MeSH headings “gastrointestinal bleeding,” “gastrointestinal hemorrhage,” “hemostatic powder,” “hemospray,” “TC-325,” “EndoClot,” “polysaccharide hemostatic system,” “polysaccharide hemostatic powder,” and “Ankaferd blood stopper.” Relevant studies were reviewed for mechanism of action, rate of immediate hemostasis and rebleeding, factors associated with hemostatic failure, and AEs.

Results

TC-325 (Hemospray)

Mechanism of action

TC-325 (Hemospray) is comprised of bentonite, an inert mineral powder that rapidly absorbs water upon contact with blood, creating an adhesive seal for mechanical tamponade, and concentrating clotting factors (▶ **Table 1**) [10, 11]. The powder is then sloughed off the mucosa and passes through the gastrointestinal tract, which has been demonstrated by multiple studies finding no residue on re-look endoscopy in 24 to 72 hours [10, 12]. TC-325 is propelled by compressed air through a catheter placed in the working channel of the endoscope, allowing for non-contact and non-traumatic spray application in the bleeding area.

▶ **Table 2** Clinical studies with sample size greater than 10.

Study	Country	Design	Intervention	Application	% Forrest Ia/b	Indication	Outcomes	
Sung 2011	Hong Kong	PC, N = 20	TC-325	PUD	1a: 5 %, 1b: 95 %	Primary	I: 95 %	R: 0 % (30 day)
Holster 2013	Netherlands	PC, N = 16	TC-325	UGIB	1a: 25 %, 1b: 25 %	Primary (50 %), rescue (31 %)	I: 81 %	R: 31.3 % (7 day)
Leblanc 2013	France	CS, N = 17	TC-325	UGIB, post-procedure	NR	Primary (66.7 %), rescue	I: 100 %	R: 11.7 % (7 day)
Smith 2014	Europe	RC, N = 63	TC-325	UGIB	1a: 17 %, 1b: 25 %	Primary, combination	I: 76–85 %	R: 15 % (7 day)
Sulz 2014	Switzerland	CS, N = 16	TC-325	UGIB, LGIB	NR	Primary, rescue	I: 94 %	R: 12.5 % (7 day)
Yau 2014	Canada	RC, N = 19	TC-325	UGIB	1a: 26 %, 1b: 11 %	Primary, rescue	I: 93 %	R: 38.9 % (7 day)
Chen 2015	Canada	RC, N = 60	TC-325	UGIB, LGIB	NR	Primary, rescue	I: 99 %	R: 14.3 % (30 day)
Haddara 2016	France	PC, N = 202	TC-325	UGIB	1a: 7 %, 1b: 21 %	Primary, rescue	I: 92–100 %	R: 0–66.7 % (30 day)
Giles 2016	New Zealand	CS, N = 36	TC-325	UGIB	NR	Primary, rescue	I: 100 %	R: 15 % (7 day)
Hagel 2017	Germany	RC, N = 25	TC-325	UGIB, LGIB	NR	Primary, rescue	I: 96 %	R: 37 % (30 day)
Cahyadi 2017	Germany	RC, N = 52	TC-325	UGIB	1a: 0 %, 1b: 39 %	Primary (44.2 %), rescue	I: 98 %	R: 44–52 % (7 day)
Arena 2017	Italy	RC, N = 15	TC-325	Malignant GIB	NR	Primary	I: 93 %	R: 21 % (6 day)
Pittayanon 2018	Canada, Thailand	RC, N = 99	TC-325	Malignant GIB	1a: NR, 1b: 94 %	Primary (88 %), rescue (13 %)	I: 98 %	R 27 % (30 day)
Ramírez-Polo 2019	Mexico	RC, N = 81	TC-325	UGIB, LGIB	NR	Primary (54 %), combination	I: 99 %	R: 20 % (5 day)
Hookey 2019	Canada	PC, N = 50	TC-325	LGIB	NR	Primary, combination, rescue	I: 98 %	R: 10 % (30 day)
Rodriguez De Santiago 2019	Spain	RC, N = 261	TC-325	UGIB	1a: 25 %, 1b: 64 %	Primary, rescue (73.2 %)	I: 94 %	R: 27.4 % (30 day)
Ng 2019	Singapore	CS, N = 10	TC-325	Diverticular bleed	NR	Primary	I: 100 %	R: 0 % (3 month)
Alzoubaidi 2020	UK, France, Germany	PC, N = 314	TC-325	UGIB, LGIB	1a: 17 %, 1b: 60 %	Primary (38 %), combination (45 %), rescue (17.5 %)	I:89.5 %	R: 10.3 % (3 day)
Chahal 2020	Canada	RC, N = 86	TC-325	UGIB, LGIB	1a: 14 %, 1b: 53 %	Primary, combination	I: 88 %	R: 33.7 % (30 day)
Hussein 2020	UK, US, France, Germany	PC, N = 202	TC-325	PUD	1a: 19 %, 1b: 58 %	Primary, combination, rescue	I: 88 %	R:17 % (30 day)

▶ **Table 2** (Continuation)

Study	Country	Design	Intervention	Application	% Forrest Ia/b	Indication		Outcomes	
Lau 2020	China, Hong Kong	RCT, N = 224	TC-325, CHT	UGIB	NR	Primary		I: 97 %	R: 8 % (30 day)
Hussein 2021	UK, US, France, Germany, Spain	PC, N = 105	TC-325	Malignant UGIB	NR	Primary, rescue, combination		I: 97 %	R: 15 % (30 day)
Becq 2021	France	RC, N = 152	TC-325	Urgent GIB	NR	Primary, rescue		I: 79 %	R: 41 %
Facciorusso 2021	Italy	CR, N = 65	TC-325	LGIB	NR	Primary, combination, rescue		I: 100 %	R: 9 % (30 day)
Sinha 2016	UK	RC, N = 20	TC-325, epinephrine	UGIB	1a: 60 %, 1b: 40 %	Rescue, combination		I: 95 %	R: 9–25 % (7 day)
Kwek 2017	Singapore	PC, N = 10	TC-325, CHT	PUD	1a: 10 %, 1b: 40 %	Primary		I: 90 %	R: 33.3 % (4 week)
Vitali 2019	Germany	PC, N = 154	TC-325 (n = 111), EndoClot (n = 32)	UGIB, LGIB	1a: 11 %, 1b: 66 %	Primary Rescue (47 %)	TC-325	I: 83 %	R: 24 %
							EndoClot	I: 81 %	R: 25 %
Ibrahim 2019	Belgium, Egypt	RCT, N = 43	TC-325, Pharmacologic	Variceal bleed	NR	Combination		I: 88 %	R: 12 % (12 hour)
Baracat 2020	Brazil	RCT, N = 19	TC-325 with epinephrine, CHT	UGIB	1a: 16 %, 1b: 84 %	Combination		I: 100 %	R: 28 % (7 day)
Chen 2020	Canada	RCT, N = 10	TC-325, CHT	UGIB, LGIB	NR	Primary, rescue		I: 90 %	R: 20 % (180 day)
Paoluzi 2021	Italy	PC, N = 43	TC-325 (n = 33), EndoClot (n = 10), CHT (n = 65)	UGIB, LGIB	1a: 7 %, 1b: 37 %	Primary, rescue		I: 86–100 %	R: 20–50 % (30 day) *PUD only
Beg 2015	UK	RC, N = 21	EndoClot, CHT	UGIB	1a: 24 %, 1b: 76 %	Rescue		I: 100 %	R: 4.8 %
Park 2018	Korea	CC, N = 30	EndoClot, CHT	UGIB	1a: 17 %, 1b: 70 %	Primary, combination		I: 97 %	R: 3.3 % (30 day)
Huang 2014	China	PC, N = 82	EndoClot	Post-EMR	NR	Prophylaxis, primary		I: 90 %	R: 7 % (3 day)
Prei 2016	Germany	PC, N = 70	EndoClot	UGIB, LGIB	1a: 1 %, 1b: 66 %	Primary (80 %), rescue		I: 83 %	R: 11 % (3 day)
Kim 2018	Korea	RC, N = 12	EndoClot	Malignant GIB	1a: 0 %, 1b: 100 %	Primary, rescue (41.6 %)		I: 100 %	R: 16 % (3–5 day)
Hahn 2018	Korea	PC, N = 33	EndoClot	Post-ESD	NR	Prophylaxis		I: 100 %	R: 9 %
Hagel 2020	Germany	RC, N = 43	EndoClot	UGIB	1a/b: 18.6 %	Primary, rescue, prophylaxis		I: 100 %	R: 24 % (1 day)
Kurt 2010	Turkey	CS, N = 10	ABS	Malignant GIB	NR	Primary		I: 100 %	R: 0 % (7–48 day)
Kurt 2010	Turkey	RC, N = 26	ABS	UGIB, LGIB	NR	Primary, combination		I: 100 %	R: NR

▶ **Table 2** (Continuation)

Study	Country	Design	Intervention	Application	% Forrest Ia/b	Indication	Outcomes	
Karaman 2012	Turkey	PC, N = 30	ABS	UGIB	NR	Primary, combination	I: 87 %	R: 0 % (7 day)
Gungor 2012	Turkey	PC, N = 26	ABS	UGIB	1a: 15 %, 1b: 85 %	Primary, combination	I: 73 %	R: 16–33 % (NR)
Bang 2018	Korea	RCT, N = 35	CEGP-003, CHT	UGIB	1a: 0 %, 1b: 86 %	Primary	I: 100 %	R: 9 % (3 day)
Park 2019	Korea	PC, N = 17	UI-EWD	UGIB	1a: 12 %, 1b: 88 %	Rescue	1: 94 %	R: 19 % (30 day)
Park 2019	Korea	RC, N = 56	UI-EWD	UGIB	1a: 0 %, 1b: 64 %	Primary	I: 96 %	R: 4 % (7 day)
Shin 2021	Korea	RC, N = 41	UI-EWD	Malignant GIB	1a: 7 %, 1b: 93 %	Primary, rescue	I: 100 %	R: 26 % (28 day)

PC, prospective cohort; RC, retrospective cohort; CS, case series; RCT, randomized controlled trial; TC-325, Hemospray; ABS, Ankaferd Blood Stopper; UI-EWD, NexPowder; CHB, conventional hemostatic treatment (mechanical, thermal, chemical therapy); UGIB/LGIB, upper/lower gastrointestinal bleeding; PUD, peptic ulcer disease; I, immediate hemostasis rate; R, recurrent bleeding rate.

Clinical evidence

TC-325 is the most studied and widely used hemostatic powder on the market, with studies on its clinical use in many settings of gastrointestinal bleeding (▶ **Table 2**). TC-325 has been successfully applied to many etiologies including peptic ulcer disease, malignant gastrointestinal bleeding, post-procedure gastrointestinal bleeding (endoscopic mucosal resection, sphincterotomy, ampullary resection, and polypectomy), variceal bleeding, portal hypertensive gastropathy/colopathy, and diverticular bleeding [12–41]. Of particular note is successful use in clinical scenarios not amenable to traditional endoscopic methods, such as malignant gastrointestinal bleeding with friable surfaces or diverticular bleeding. A study of urgent after-hours endoscopic hemostasis using TC-325 showed similar efficacy between "more" and "less" experiences endoscopists, demonstrating its ease of use [36].

Recent meta-analyses have studied use of TC-325 in both primary and secondary settings. Chahal et al. described 27 clinical studies with 1916 patients with upper gastrointestinal bleeding of various etiologies. Pooled hemostasis was 94.5 % and rebleeding rate was 9.9 % in 3 days, and 17.6 % in 30 days. The addition of TC-325 to conventional treatment led to a higher rate of immediate hemostasis compared with conventional treatment alone with odds ratio of 4.40 [42]. Similarly, a systematic review of lower gastrointestinal bleeding, including nine studies with a total of 194 patients, observed an immediate hemostasis rate of 96.2 % and a 7-day rebleeding rate of 19.5 % [9]. When compared to conventional hemostatic therapy, TC-325 had similar efficacy in initial hemostasis and rebleeding rates [13–16]. When added to pharmacotherapy, TC-325 use was associated with lower rebleeding rates compared to pharmacotherapy alone [17].

While TC-325 has a high immediate hemostasis rate, particularly in scenarios unsuitable for conventional treatment, there is a significant rebleeding rate. Multiple studies have demonstrated that the risk of rebleeding is highest within the first week following TC-325 application, likely due to sloughing off the protective seal, thus limiting its efficacy in high-risk lesions that are prone to rebleeding. Multiple prognosticators for rebleeding have been identified including high-risk stigmata (Forrest 1a lesion) [8, 23, 31, 43], use as salvage therapy [8, 22, 23], and clinical indicators of more severe gastrointestinal bleeding such as syncope, hypotension, and higher Blatchford Score (▶ **Table 3**).

Adverse events

As evidence for TC-325 has been accruing since 2011, there have been several reports of AEs related to its use (▶ **Table 4**). Minor AEs include self-limited abdominal pain immediately after spraying, which has been attributed to visceral distension from the CO_2 propellant [16, 23, 31]. Several cases of viscus perforation have been identified following use of TC-325, though in many cases it is difficult to discern whether the cause was TC-325, endoscope trauma, or friable tissue from the underlying condition [12, 21, 25, 31, 36, 39]. There has been a case of biliary obstruction when TC-325 was applied to post-sphincterotomy bleeding [44]; however, there are also cases of

▶ **Table 3** Factors associated with recurrent bleeding and failure of TC-325 (Hemospray).

Category	Factor
Clinical Presentation	Syncope [33] Melena [23] American Society of Anesthesiologists physical status score (ASA) ≥ III [23] Blatchford score [32] Hypotension [31]
Investigations	Creatinine ≥ 15 mg/L [23] International normalized ratio (INR) ≥ 1.3 [28]
Medications	Vasoactive drugs [31] Anti-thrombotic/coagulant therapy [19]
Endoscopic Findings	Spurting vessel (Forrest class Ia) [8, 23, 25, 31]
Management	Use as salvage therapy [8, 22, 23]

successful application without complications [45]. Two thromboembolic events have been described, possibly due to embolism of the powder into the low pressure venous system, leading to a splenic infarct [21] and pulmonary embolism in a patient with a known factor II prothrombotic mutation [31]. There are two reports of congealed powder leading to adhesion of the endoscope to the mucosa, particularly when TC-325 is sprayed in retroflexion, and led to one case of retained endoscope for 48 hours [12, 46].

Spray catheter occlusion has been reported in several studies. To prevent this, some operators utilize prolonged insufflation following blood aspiration to dry the working channel prior to powder application [40].

EndoClot

Mechanism of action

EndoClot is composed of absorbable modified polymers (AMP) derived from plant starch. Upon contact with blood, polymers rapidly absorb water to form a protective gel matrix and concentrate coagulation factors (▶ **Table 1**) [47]. EndoClot has also been shown to activate fibroblasts and growth factors to promote wound healing [48]. The AMP are degraded by endogenous amylase and glucoamylase in the gastrointestinal tract, leaving no residual powder on re-look endoscopy after 24 hours [49].

Clinical evidence

EndoClot has been studied in settings of gastroinestinal bleeding prophylaxis as well as primary, rescue, and combination treatment with conventional endoscopic methods (▶ **Table 2**). Similar to TC-325, EndoClot has been applied to a variety of upper and lower gastrointestinal bleed settings, including malignant bleeding, peptic ulcer disease, varices, and radiation injury. As primary or secondary treatment, EndoClot has immediate hemostasis rates of 83 % to 100 % and recurrent bleeding rates of 11 % to 23 % [43, 50, 51].

Preventive use following high-risk endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), including Forrest 1a lesions, showed rebleeding rates of 7.3 % at 3 days [52, 53]. Rebleeding occurred after 48 hours in the post-ESD cohort, suggesting protection from the gel matrix for the duration that it resides on the mucosal surface. There was also a signal toward superior ulcer healing after using EndoClot, as re-look endoscopy showed a lower proportion of post-procedural Forrest IIa ulcers compared to other studies without use of EndoClot [52].

EndoClot has also been compared to conventional therapy and TC-325. Observational studies have shown that EndoClot had similar 30 day rebleeding rates compared to conventional treatment, in both primary and combination settings [49, 54]. Studies comparing TC-325 and EndoClot have found similar rates of hemostasis and rebleeding, though research with larger sample sizes and randomized design are lacking [39, 40]. Similar to TC-325, EndoClot also has limited residence time in the gastrointestinal tract, its application may be limited in lesions at high risk of rebleeding, as evidenced by high rates of recurrent bleeding in 24 to 72 hours.

Adverse events

No AEs were reported in reviewed clinical studies, however, there remains a theoretical risk of perforation, intestinal obstruction, embolism, and allergic reactions.

Ankaferd Blood Stopper

Mechanism of action

Developed in Turkey, ABS is composed of herbal extracts from five different plants, *Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum,* and *Urtica dioica* (▶ **Table 1**) [55]. Upon contact with moisture, ABS forms an encapsulated protein network that facilitates erythrocyte aggregation, leading to hemostasis [56]. Other reported mechanisms of action include inhibition of fibrinolysis and anti-coagulant pathways, as well as angiogenesis and cellular proliferation to promote wound healing [22].

Clinical evidence

Several cohort studies have been conducted in cases of gastrointestinal bleeding of various etiologies treated with ABS as monotherapy or combined with conventional treatment (▶ **Table 2**). Overall, the rate of immediate hemostasis ranges from 73 % to 100 % and rebleeding rate ranges from 0 % to 33 % [57–60]. In a series of 10 patients with malignant gastrointestinal bleeding, all had complete hemostasis up to 48 days until definitive management with surgery, suggesting a role as bridging therapy [58]. Case reports have also shown successful use of ABS for variceal bleeding [61–63], rectal ulcers [64], radiation colitis [65, 66], post-polypectomy [67], and diverticular bleeding [68]. ABS was also effective in a case of post-sphincterotomy bleeding with no associated complications [55]. Interestingly, in a case series of patients with gastric and rectal carcinoma, ABS application led to decreased tumor microvessel densi-

▶ **Table 4** Adverse events and technical issues.

Study, year	Intervention(s)	Case(s)	N (%)	Adverse events
Smith 2014	TC-325	Severe proximal portal hypertensive gastropathy	1/4 (25 %)	Perforated viscus following use of TC-325 which led to hemostasis, not candidate for surgery and died of sepsis.
Yau 2014	TC-325	UGIB	1/19 (5.3 %)	Abdominal distension and hemoperitoneum on paracentesis hours post-TC-325, suspected perforation.
		UGIB, in patient admitted with tibial fracture	1/19 (5.3 %)	New onset splenic infarct on abdominal computed tomography scan after TC-325 use.
Smith 2014	TC-325	UGIB	2/63 (3 %)	Endoscope transiently adherent to esophageal mucosa when TC-325 was sprayed in retroflexion.
Hagel 2017	TC-325	Diffuse bleeding in gastric wall	1/27 (3.7 %)	Immediate perforation after Hemospray administration, managed with laparotomy.
Pittayanon 2018	TC-325	Malignant GIB	1/88 (11.4 %)	Cardiac arrest of unclear cause as TC-325 was used, subsequent death 4 days later.
Rodriguez de Santiago 2019	TC-325	Esophageal ulcer secondary to GI graft vs host disease	1/261 (0.4 %)	Esophageal perforation after TC-325 use.
		Unknown GIB in woman with factor II prothrombotic mutation	1/261 (0.4 %)	Pulmonary thromboembolism 48 hours after TC-325 use.
Vitali 2019	TC-325	Unknown GIB	2/154 (1.3 %)	Perforation after TC-325 use.
Becq 2021	TC-325	Deep peptic ulcer	1/152 (0.7 %)	Perforation after TC-325 use.
Beyazit 2013	ABS	Gastroduodenal amyloidosis	Case report	Perforation of duodenum after ABS application.
Technical Issues				
Hagel 2020	EndoClot	UGIB	1/43 (2.3 %)	Occlusion of spray catheter.
Beg 2015	EndoClot	UGIB	2/21 (9.5 %)	Occlusion of spray catheter.
Smith 2014	TC-325	UGIB	3/64 (4.8 %)	Occlusion of application catheter.
			1/64 (1.6 %)	Occlusion of endoscope instrument channel.
			1/64 (1.6 %)	Malfunction of the CO_2 propellant cartridge.
Rodriguez de Santiago 2019	TC-325	GIB	5/261 (1.9 %)	Occlusion of spray catheter.
			1/261 (0.4 %)	Occlusion of endoscope instrument channel.
Park 2019	UI-EWD	UGIB	2/56 (3.6 %)	Occlusion of spray catheter.

UGIB, upper gastrointestinal bleeding; GIB, gastrointestinal bleeding.

ty, hypothesized to be due to inhibition of angiogenesis, suggestive of anti-tumor properties [69].

Adverse events

A single AE has been noted in the case of a patient with gastroduodenal amyloidosis who developed duodenal perforation following ABS application, however authors concluded that it is unknown if this was due to the disease process itself [70]. There is also a risk of vascular embolization with ABS application to variceal bleeding; however, it has been successfully used in several cases reports of variceal bleeding [61–63].

CEGP-003

Mechanism of action

CEGP-003 is composed of absorbable and adhesive macromolecules of hydroxyethylcellulose with epidermal growth factor (EGF) (▶ **Table 1**). Beyond forming an adhesive seal when in contact with water, the EGF component promotes wound healing by activating EGF receptors and intracellular pathways of wound healing [71].

Clinical evidence

Bang et al. conducted a randomized controlled trial comparing CEGP-003 with epinephrine injection as primary intervention for upper gastrointestinal bleeding (▶ **Table 2**). Bleeding etiologies included peptic ulcer disease (20.5 %), post-EMR bleeding

(15.1 %), and post-ESD bleeding (64.4 %). Thirty-five patients randomized to CEGP-003 had an immediate hemostasis rate of 100 % with recurrent bleeding at a rate of 8.6 %, compared to 37 patients in the epinephrine arm with only 89.2 % achieving immediate hemostasis and 2.7 % rebleeding at 3 days post-procedure. Statistically, the rebleeding rate was not significantly higher for CEGP-003 but numerically it is more than double that of the epinephrine arm. However, as epinephrine injection is rarely used as monotherapy for hemostasis, further research is required before CEGP-003 can be considered comparable to standard of care in gastrointestinal bleeding [71].

Adverse events

No AEs related to CEGP-003 have been reported; however, given the limited number of studies, further research is required.

UI-EWD (NexPowder)

Mechanism of action

UI-EWD (NexPowder) is composed of oxidized dextran and succinic anhydride, which is converted to an adhesive hydrogel upon contact with moisture (▶ **Table 1**). The resulting hydrogel cross-links within itself and with adjacent tissue to create a mechanical barrier to promote hemostasis. As it does not require clot formation to achieve hemostasis, UI-EWD does not require active bleeding. This provides it a potential role in prophylaxis, such as post-procedure or following primary hemostasis achieved with conventional endoscopic techniques. Other advantages include a liquid coating technology to improve delivery without catheter occlusion, prevent particle scattering, and a distinctive blue color for improved visualization of treated areas [72, 73].

Clinical evidence

While UI-EWD is the newest development in hemostatic powders for clinical use, initial results are promising (▶ **Table 2**). Park et al. studied 17 patients with refractory gastrointestinal bleeding of various etiologies (including peptic ulcer disease, post-intervention, and malignancy), of which 12 % were Forrest class 1a and 88 % were Forrest class 1b. Immediate hemostasis was achieved in 94 % of patients and 30-day rebleed rate was 19 %. For Forrest 1a lesions, immediate hemostasis was only achieved in 50 %, suggesting it is likely inadequate in the highest risk lesions similar to other hemostatic powders [74].

When used as monotherapy in upper gastrointestinal bleeding in 56 patients, rate of immediate hemostasis was 96.4 % and 30-day rebleed was noted in only 3.7 %. Patients in this study had similar bleeding etiologies of peptic ulcer, post-intervention, anastomotic site, and malignant bleeding; however, this population had lower-risk stigmata as Forrest 1a lesions were excluded and only 64.5 % of lesions were Forrest 1b. Importantly, the hydrogel remained attached in 39 % of patients after 3 days, suggesting an improvement in residence time from previous hemostatic powders [75]. Shin et al. studied UI-EWD use as monotherapy or rescue in 41 patients with malignant bleeding, including carcinoma, gastrointestinal stromal tumor, and lymphoma. Immediate hemostasis rate was high at 97.5 % and rebleeding rate was 22.5 % in 28 days [76].

These initial results suggest that UI-EWD has high immediate hemostasis rate and low rebleeding rate when used in less acute gastroinestinal bleeding. A particular advantage is the prolonged residence time of the hydrogel that provides a mechanical seal, which may be especially well-suited for lesions with high-risk stigmata that may rebleed. However, the initial hemostasis rate for Forrest 1a lesions was low at 50 % so the role of UI-EWD in high-risk lesions remains undefined [74]. Further research is needed, particularly in comparison to conventional methods and other hemostatic powders.

Adverse events

Despite the liquid coating technology, clogging of the spray catheter was noted in 3.6 % of patients, which was easily addressed with using another catheter [75]. No procedure-related AEs have been observed to date, though the number of clinical studies remains limited with this novel agent.

Other treatments

Self-propelling thrombin powder (CounterFlow Powder)

Self-propelling thrombin powder (SPTP; CounterFlow Powder) is a new hemostatic powder with unique properties to deliver the clotting factor directly to damaged bleeding vessels. Still in preclinical study, SPTP is adapted for endoscopic use from a gauze formulation that was used to successfully manage non-compressible hemorrhage [77, 78].

SPTP is composed of porous calcium carbonate microparticles loaded with thrombin and formulated with an organic acid. Protonated tranexamic acid has been included as the organic acid component for its potent anti-fibrinolytic properties. Contact with blood leads to effervescence of the powder, propelling thrombin to penetrate deep into the bleeding lesion to initiate hemostasis and stabilize clots [77]. This direct activity is demonstrated by improved hemostasis when SPTP was added to non-compression dressings in a porcine model of lethal femoral artery hemorrhage and a sheep model of turbinate bleeding [78–80].

As it has high hemostatic potential from thrombin, the mechanism of SPTP is likely well-suited to higher risk gastrointestinal bleeding with exposed vessels. In a porcine model of Forrest class Ia and Ib upper gastrointestinal bleeding, hemostasis was successfully achieved at all sites [81]. Previous non-gastrointestinal bleeding studies showed that SPTP is safe and well-tolerated with no evidence of toxicity or thromboembolism [77, 78].

TDM-621 (PuraStat)

While not a powder formulation, TDM-621 (PuraStat; 3 D Matrix Europe SAS, Caluire-et-Cuire, France) is a topical hemostatic agent for surgical wounds that has been newly applied to endoscopic therapy with positive results. It is a transparent gel comprised of a specific sequence of amino acids that self-assemble into beta protein sheets upon contact with neutralizing fluid, forming a hydrogel scaffold similar to human extracellular ma-

trix [82]. As the hydrogel is transparent, visibility of the bleeding area and endoscope views remain unaffected. The gel formulation also prevents clogging of the catheter channel [83].

Compared to diathermy in a randomized controlled trial of post-ESD patients, TDM-621 had similar hemostasis and rebleeding, but superior wound healing at 4 weeks [84]. A prospective observational study was conducted using TDM-621 as primary and secondary treatment in 111 patients with gastrointestinal bleeding. The rate of immediate hemostasis was 94% and rebleeding rate was 16% at 30 days [85]. TDM-621 has also shown efficacy in refractory radiation proctopathy [86], post-EMR/ESD bleeding [87], and as rescue therapy in acute gastrointestinal bleeding [88]. No AEs or technical failures have been reported to date.

Conclusion

The last decade has shown rapid advancements in endoscopic hemostasis technology with development of several hemostatic powders. These powders have demonstrated their role for various bleeding etiologies and particularly in clinical scenarios where conventional treatment fails. Substantial rates of early rebleeding, likely due to sloughing off of the protective seal, limit their use as definitive monotherapy in current guidelines. Further, technical issues of catheter occlusion and impaired visual field are uncommon but reduce the usability of hemostatic powders. To address these challenges, iterative improvements have been made, exemplified by the design behind new agents, though further study to delineate their clinical efficacy is still underway. Ongoing research and development of hemostatic powders, as well as evolving clinical expertise to optimize their use, will propel endoscopic hemostasis into the future.

Competing interests

Dr. Kastrup is the inventor on patents and intellectual property, and Dr. Ali-Mohamad, Dr. Donnellan, and Dr. Kastrup are involved in commercialization activities related to self-propelling thrombin powder.

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