REVIEW ARTICLE

Topical hemostatic agents: a systematic review with particular emphasis on endoscopic application in GI bleeding CME

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GI bleeding (GIB) remains a major cause of morbidity and mortality worldwide. Endoscopic management of GIB could be challenging, despite the existing advancements in hemostatic techniques; there are unmet needs for the introduction of topical hemostatic agents in management of profound venous or arterial GIB and malignant lesions with a large surface area that are not quite amenable to traditional endoscopic hemostatic techniques. Many topical hemostatic agents have been developed over the past 50 years with widespread medical applications.[1] The introduction of topical hemostatic agents in the modern surgical era can be traced back to 1909, when Bergel first discussed the use of topical fibrin for hemostasis. This class of preparations, known as fibrin sealants, marked the beginning of wide spectrum of topical hemostatic agents with various mechanisms of action.

Gelatin-based hemostatic agents[2] and cyanoacrylate adhesives[3] were 2 more common topical hemostatic agents introduced in the 1940s.[1] In the 1970s, a new class of agents, namely, microfibrillar collagen products, were synthesized by purifying and processing bovine collagen[4]; these were then manipulated to different hemostatic agents that were used in various surgical specialties for achieving hemostasis. In 1998, the U.S. Food and Drug Administration approved Tisseel, the first commercial fibrin sealant. These compounds were used as surgical hemostatic and adhesive material.[5] Other topical hemostatic agents, including topical thrombin,[6] endoscopic spray of clotting factors,[7] and topical sucralfate,[8] have been introduced in limited clinical data with various outcomes. More recently, additional agents have been adapted to digestive endoscopy and the management of GIB. We review the mechanisms of action of powder-based topical hemostatic agents and their efficacy and safety profiles, while attempting to predict their potential utility in digestive endoscopy. Reviews on topical hemostatic agents as they apply to other clinical applications can be found elsewhere.[9]

Abbreviations: ABS, Ankaferd BloodStopper; GIB, bleeding.

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METHODS

A computerized systematic literature review from January 1950 through August 2012, by using OVID MEDLINE, EMBASE, CENTRAL, and ISI Web of Knowledge 5.6 was initiated. Articles were selected by using a combination of MeSH headings and text words related to Hemospray, nanopowder, hemostatic or haemostatic agent, granule or powder, TC-325, Ankaferd BloodStopper, microporous polysaccharides hemosphere, and Arista. Recursive searches and cross-referencing were also carried out by using a "similar articles" function; hand searches of articles were identified after an initial search. We included all adult human studies in French or English and also included abstracts.

STUDY SELECTION

Of an initial 3167 articles, we identified 112 articles relevant to the topic of topical hemostatic agents. We then focused the study selection on 2 powder-based topical hemostatic agents that have been used endoscopically in the GI tract: Ankaferd BloodStopper® (ABS) and TC-325. Of note, microporous polysaccharide hemosphere has been used in non-GIB with no clinical data in the literature on GI endoscopic application. Of 112 articles, 86 were on ABS, including 82 published articles in addition to 4 abstracts. Twenty-one articles on ABS did not have any published abstracts. We also identified 5 published articles on TC-325 with 3 poster presentations. We briefly mention EndoClot for which all pertinent information was obtained through review of the manufacturer's Web site, and at the time of writing this manuscript, no published peer-reviewed clinical data are available.

CHEMICAL COMPOSITION AND MECHANISM OF ACTION

Table 1 briefly outlines the composition and mechanisms of action of 3 hemostatic compounds of interest.

TABLE 1. Outline of the composition of topical hemostatic agents and summary of their mechanism of action

Agent	Trade Name	Composition	Mechanism of action	Approved human application	Formulation
	Ankaferd BloodStopper	Standardized herbal mixture	Forms protein network, aggregates RBCs, activates clotting cascade	Dental procedures, ambulance, first aid services, schools, fast hemostasis	Tampons, sprays, ampoules
TC-325	Hemospray	Granular mineral-based	Adsorbs H_2O, mechanical tamponade, activates clotting cascade	Recently approved for nonvariceal GI bleed in Canada, Hong Kong, Europe	CO_2 pressurized handheld canister (20 g)
EndoClot	EndoClot	Absorbable modified polymers	Absorbs H_2O and concentrates cells, activates clotting cascade	Intended for adjuvant hemostatic therapy	Pressurized air compressor

RBCs, Red blood cells.

Ankaferd BloodStopper

A unique hemostatic agent, ABS is a derivative of a traditional herbal mixture that has been used topically for centuries in Turkey to terminate bleeding resistant to conventional hemostatic measures.[10] Currently ABS is available in 3 pharmaceutical forms: ABS ampoules, pads, and sprays.[11] In May 2007, Ankaferd Ilac Kozmetik, AS, Turkey, obtained the marketing authorization from TC Ministry of Health, Drug, and Pharmacy General Directorate for all 3 forms within the category of "cosmetics, herbal products not aiming treatment, nutrition support products, nutraceutics and topically applied non-drug products."[12] There is no documented approval on the U.S. Food and Drug Administration Web site.[13] However, according to the Ankaferd Web page, ABS can be used in various areas, including dental offices, emergency departments, schools, and first aid kits.[14] Additional information could not be collected because the manufacturer did not respond to our further queries.

A preparation of 100 mL of ABS is composed of a standardized mixture of plants, including 5 mg *Thymus vulgaris* (dried grass extract), 9 mg *Glycyrrhiza glaba* (dried leaf extract), 8 mg *Vitis vinifera* (dried leaf extract), 7 mg *Alpinia officinarum* (dried leaf extract), and 6 mg *Urtica dioica* (dried root extract).[15] The mechanism of action involves ABS interaction with the endothelium and blood cells, in addition to its influence on angiogenesis, cellular proliferation, vascular dynamics,[16-19] and cell mediators.[20-22] Yilmaz et al[23] suggested that ABS hemostatic actions could be related to its rapid induction (<1 s) of a protein network in human plasma and serum samples. On electron microscopy, erythrocytes and leukocytes aggregate rapidly in the presence of ABS and further contribute to a scaffold formation. Indeed, *in vitro* examination suggests ABS stimulates the formation of the encapsulated protein scaffold network,[15,21] allowing erythrocyte aggregation that then integrates with the classic coagulation cascade.[19,23,24] However, despite the overall hemostatic mechanism of ABS, the exact mechanism of each component is not yet fully understood.[25] In addition to its hemostatic properties, ABS may have therapeutic benefit attributable to possible anti-infective,[26-29] antifungal,[30] antineoplastic, and wound-healing[31] properties that further allow restoring and maintaining tissue hemostasis.[4]

Hemostatic agent TC-325 (Hemospray)

The most novel endoscopic hemostatic technology is a proprietary material, designated as TC-325, with brand name Hemospray (Cook Medical Inc, Bloomington, Ind). It contains no human or animal proteins or botanicals and has no known allergens. TC-325 is a highly absorptive compound with a multimodal mechanism of action. When put in contact with moisture (eg, blood or tissue) in the GI tract, the powder becomes cohesive and adhesive. As a result, TC-325 forms a mechanical barrier that adheres to and covers the bleeding site, achieving very rapid hemostasis, usually within seconds. After approximately 24 to 72 hours (the exact lag time remains unknown but could be shorter), the adherent layer subsequently sloughs off into the lumen from the mucosal wall and is completely eliminated from the GI tract.[32] Although the hemostatic property of this agent is thought to relate principally to its quick application and rapid achievement of full initial hemostasis through mechanical tamponade, absorption of the fluid component of blood ultimately also leads to concentration of clotting factors and cellular elements. Last, it has also been postulated that TC-325 may activate the clotting cascade along with aggregating platelets, forming a fibrin plug.[33-35]

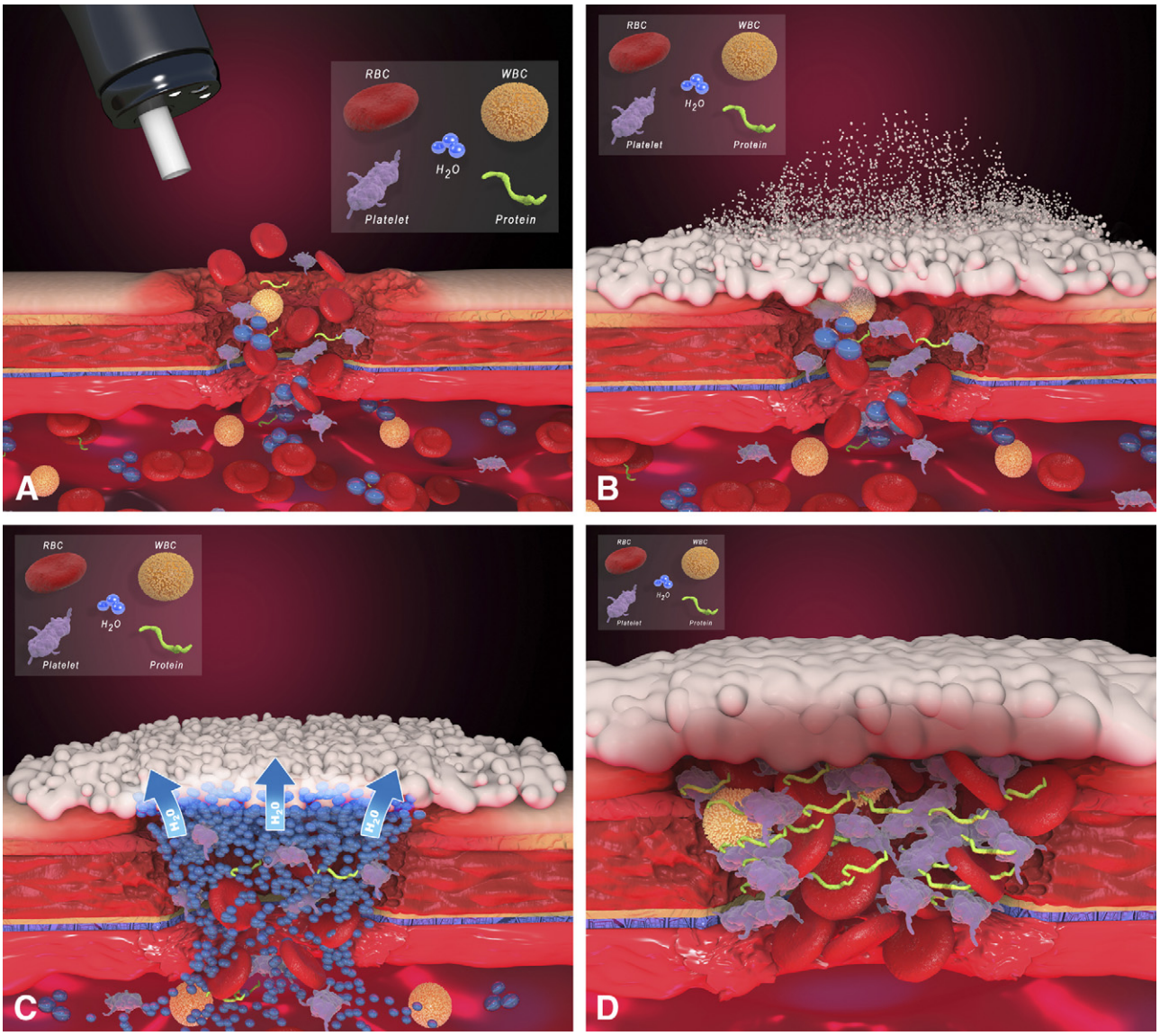

Figure 1. A, Schematic presentation of the targeting by the endoscope of the intraluminal bleeding site. Note extravasation of serum, composed mostly of water, and clotting factors, along with platelets, white blood cells (WBC) and red blood cells (RBC). **B** and **C,** TC-325 application at the bleeding site. As a result of its great ability to absorb water, TC-325 ultimately forms a barrier to prevent further extravasation of blood cells and clotting factors, thus producing a mechanical tamponade that terminates bleeding. **D,** In addition to absorbing water, TC-325 shortens clotting times. It concentrates blood cells and clotting factors, creating a physical lattice that may further favor hemostasis.

In a recent study by Holster et al,[36] the mechanism of action of TC-325 was evaluated in an ex vivo model. Assessment of the extrinsic clotting pathway through prothrombin time analysis revealed a dose-dependent decrease in clotting times in the presence of TC-325. In addition, the authors concluded that alternative hemostatic mechanisms may also be in play. TC-325 concentrates blood cells and clotting factors, creating a physical lattice that may further favor hemostasis.

In summary, TC-325 appears to principally affect hemostasis through its ability to quickly absorb water, creating a physical barrier and a local lattice, delivering a tamponade effect at the bleeding site. It alters clotting times in ex vivo studies, but improved characterization of the clinical implications of these findings and determination of possible additional mechanisms require further study. Figure 1 illustrates the currently postulated mechanisms of action of TC-325.

EndoClot Polysaccharide Hemostatic System

EndoClot[37] (EndoClot Plus Inc, Santa Clara, Calif) consists of absorbable modified polymers and is intended to be used as adjuvant hemostatic agent to control bleeding in the GI tract.[38] It is a biocompatible, nonpyogenic, and starch-derived compound that rapidly absorbs water from serum and concentrates platelets, red blood cells, and coagulation proteins at the bleeding site to accelerate the clotting cascade.[39] The interaction of the polymer particles

with blood produces a matrix that seals the bleeding tissue. The particles are subsequently cleared from the bleeding site with no residual remaining a few hours to days after the application, depending on the amount used. The manufacturer's Web site[40] claims that the particles have been widely used in open surgery and have proved to be safe and effective; however, we identified no peer-reviewed publications to date on this product.

Additional information could not be collected because the manufacturer did not respond to our queries. In addition, there is no documented approval on the U.S. Food and Drug Administration Web site.[13]

EXPERIMENTAL MODEL STUDIES: EFFECTIVENESS AND SAFETY

Ankaferd BloodStopper

The ABS effectiveness in various nonendoscopic applications in animal models has been described, including heparin-induced epistaxis,[41-44] head and neck,[45] ocular,[46-48] urological,[49-56] dental,[57-62] orthopedic,[63-65] plastic,[66] cardiothoracic surgeries,[10,67] renal trauma,[68,69] and aortic and hepatic parenchymal bleeding.[70-75] A short-term toxicity assessment of ABS in an in vivo animal experimental model study by Bilgili et al[76] revealed no mucosal, hematologic, hepatologic, nephrologic, or biochemical toxicity. Although multiple studies have confirmed the safety profile of ABS, caution needs to be taken in certain surgical procedures, including intraperitoneal,[77,78] ocular,[46,79] and vascular applications,[80] as ABS intravascular delivery is contraindicated for the presumable risk of embolization. ABS has also been used as a successful alternative therapy to ethanol[81] in an animal model of nonresectable hepatocellular carcinoma. ABS application in postcaustic esophageal injury in a rat model study[82] was associated with a decreased rate of stenosis, inflammation, and mortality. Therefore, animal model studies have shown ABS to be an effective hemostatic agent in various settings with minimal toxicity to date.

TC-325 (Hemospray)

There exist few published animal models on TC-325 to date. TC-325 has been deemed in biocompatibility testing to be nontoxic (A. Barkun, personal communication, Cook Medical Inc, Bloomington, Ind). Giday et al[83] evaluated the efficacy and safety of TC-325 in a randomized, controlled animal model study of spurting arterial bleeding. Hemostasis was achieved in all 5 treated animals within the first hour, but in none of the controls. No active rebleeding was noted in 80% of the treatment arm animals, along with evidence of a healed gastric lesion on necropsy with no foreign body granuloma formation or embolization to distant organs. In addition, Giday et al[84] also evaluated the safety profile of TC-325 in a porcine animal model of severe gastric bleeding (ie, Forrest grade IA or IB). The study showed neither TC-325 particles nor thromboembolic events in local, regional, or systemic tissues on gross or histological evaluations. The study showed no evidence of bowel obstruction or coagulopathy or any effect on the healing process at the surgical site associated with TC-325 application. In conclusion, limited animal experimentation so far has suggested the safety of TC-325.

CLINICAL EXPERIENCE

Ankaferd BloodStopper

ABS exists in various formulations, including tampons, sprays, and ampoules.[15] ABS can be applied through the operating channel of diagnostic endoscopes by injecting the content of 50-mL vials through a disposable catheter (model PW-205L; Olympus Corp, Tokyo, Japan).[85] It has been used in the nonendoscopic management of various forms of acute hemorrhage, including epistaxis,[86] dental,[87] head and neck,[88-90] and urological surgeries and pediatric cases,[90] in addition to those with bleeding disorders.[90-92] ABS use has been described in both upper and lower GIB[93,94] of various etiologies. In a retrospective study[95] of 10,711 patients with upper and/or lower endoscopy procedures, excluding subjects with malignancies, the product was successfully used in 26 patients with hemorrhage secondary to Mallory-Weiss tears, polypectomies, and Dieulafoy lesions. Others reported success in lower GIB after polypectomy,[96] radiation colitis,[97] and a Dieulafoy lesion[98] with spurting hemorrhage having failed epinephrine injection and hemoclips.[99] Purnak et al[100] reported successful use of ABS as an adjunctive agent in a thrombocytopenic, coagulopathic patient with a bleeding gastric ulcer. It has also been successfully applied to variceal bleeding, both as a bridge to definitive treatment and as rescue for failed conventional therapy including banding and *N*-butyl-2-cyanoacrylate.[101-104] ABS thus may have a role to play as an alternative therapy in the management of patients with refractory variceal hemorrhage.[105] Rapid successful endoscopic hemostasis with ABS was also reported in a retrospective study of 10 patients with neoplastic GIB,[85] with no immediate adverse events and with subsequent reduction in tumor-associated vascularization.[106]

Hemospray (TC-325)

The product was recently approved in Hong Kong, Canada, and some European countries for clinical use. There has been only limited published clinical experience to date. Sung et al[32] evaluated the safety and effectiveness of TC-325 for hemostasis in 20 consecutive adults with confirmed peptic ulcer bleeding (Forrest score Ia or Ib). The powder was delivered at gastroscopy in short bursts by means of a CO_2 pressurized spray catheter positioned 1 to 2 cm from the bleeding site (each canister delivers up to a total of 20 g, with a maximal allowed dosing of 150 g). Up to 2 full canisters of TC-325 (40 g) were applied during endoscopy within 24 hours of hospital admission after hemodynamic stabilization. Second-look endoscopy was performed

at 72 hours. Acute hemostasis was successfully achieved in 95% (19/20 patients). The hemoglobin level decreased in 2 patients within 72 hours without active bleeding noted at repeat endoscopy. One patient was found to have a pseudoaneurysm requiring arterial embolization. No major side effects, mortality, treatment- or procedure-related serious adverse events were noted over the 30-day follow-up. Recently, Moosavi et al[107] described the therapeutic and prophylactic applications of TC-325 as initial or rescue therapy in 4 patients with disparate benign upper and lower GIB lesions (Fig. 2). Hemostasis was achieved in all patients, except in the postsphincterotomy bleed, where TC-325 application resulted in a transient obstruction of the biliary opening, which ultimately resolved after vigorous water irrigation; the bleeding halted with traditional hemostatic methods.

Most recently, Chen et al[108] demonstrated the novel application of TC-325 in managing malignant bleeding of the esophagus, stomach, and duodenum in 5 patients. Immediate hemostasis was achieved in all patients. One patient rebled. The authors concluded that TC-325 is a promising agent in the management of acute malignant GIB, both as an adjuvant and as a bridge to more definitive treatment; a hemostatic powder appears especially well adapted for this difficult indication, allowing treatment of a large surface area with multiple bleeding points while causing minimal tissue trauma.

Furthermore, preliminary results of the SEAL survey (Survey to Evaluate the Application of HemospraySM in the Luminal Tract), a worldwide, multicentered clinical registry of 97 patients (ages 18-80 years) who received TC-325 for the management of acute GI hemorrhage, either as a single or adjuvant modality. Acute hemostasis was noted in 92%, with TC-325 used as monotherapy in 58% of patients. Bleeding lesions were mostly found in the duodenum (40.2%) and stomach (28.9%) followed by esophagus (20.6%) and other locations (10.3%). The most common bleeding lesions were peptic ulcers (40.2%) followed by a diverse range of underlying etiologies. Hemostasis was achieved in less than 10 minutes in more than 70% of cases by using less than 1 canister per patient. No adverse events, such as embolism and bowel obstruction, have been noted in any of these cases.

Finally, quite recently, but in contradiction to the manufacturer's labeling (presumably because of the fear of embolization), Holster et al[109] released a successful case report of TC-325 in the management of a patient with variceal bleeding.

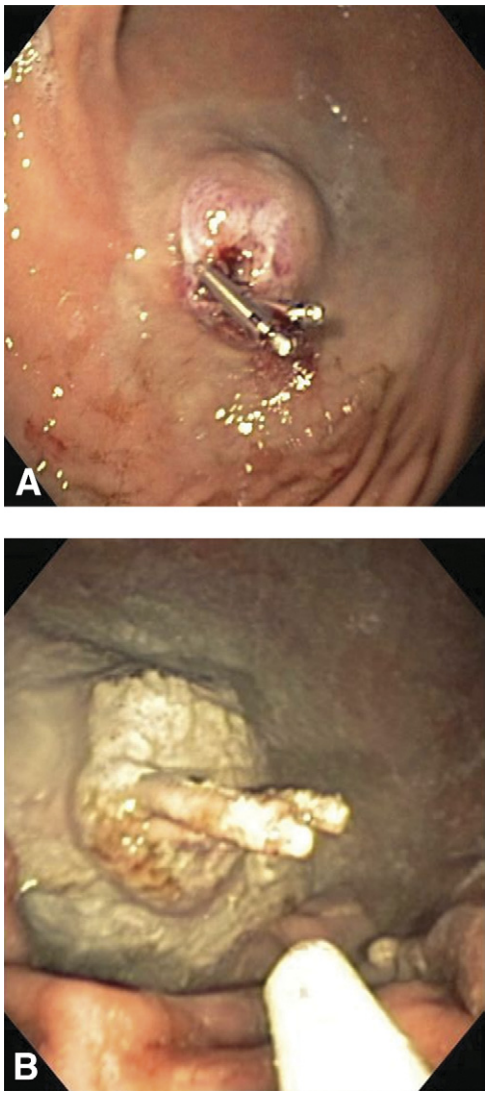

Figure 2. A, Endoscopic image of a bleeding ulcer that was suboptimally controlled with epinephrine injection and clipping. **B**, TC-325 application terminated the bleed. Note the clip covered with TC-325 powder. *The suppositions behind the different postulated roles of the hemostatic powders in GI bleeding require validation in high-quality clinical outcome studies. Includes gastric antral vascular ectasia (GAVE), portal gastropathy, which are associated with lower risk of acute rebleed and other benign pathologies with multiple or large surface area sources of bleeding. Topical hemostatic agents can also facilitate the diagnostic process; these may allow the endoscopist in certain cases to better visualize the area and subsequently pinpoint any persistent bleeding site. The hemostatic powder can be used before or after conventional methods of hemostasis, applied at that same setting or at a second-look procedure.

BENEFITS AND LIMITATIONS OF HEMOSTATIC POWDERS IN DIGESTIVE ENDOSCOPY

Potential benefits of hemostatic powders in digestive endoscopy

From the limited published clinical experience and the authors' additional unpublished experience with TC-325, it would appear that the topical hemostatic powders currently available are effective hemostatic agents in both therapeutic and prophylactic applications, alone or in combination (as initial agent or after conventional techniques or as rescue therapy), both in the upper and lower GI tracts with a possibility for subsequent repeated therapies. Preliminary results have shown that it is an effective technique in rapidly terminating active hemorrhage in a matter of a few seconds. Once it is applied to the hemorrhage site, it allows the endoscopist in certain cases to better visualize the area and subsequently pinpoint any

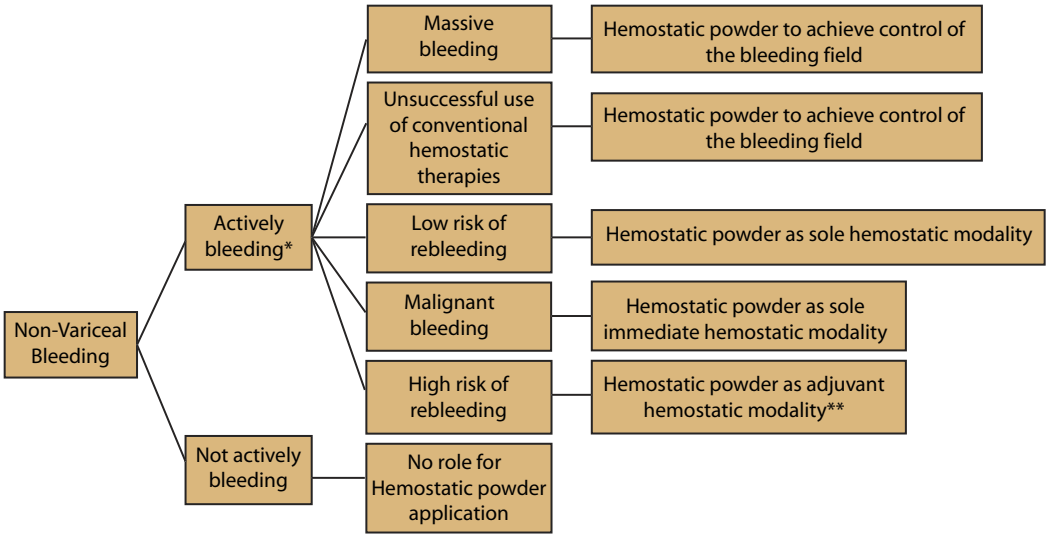

Figure 3. Algorithm for approach to management of acute nonvariceal bleeding and the role of hemostatic agents.

persistent bleeding site. From the limited available data, these agents seem to exhibit a favorable side-effect profile, most likely secondary to their chemical composition and method of action. The hemostatic powders are easily applied to the bleeding lesions with no complex technical deployment; some of the currently available powder delivery systems, however, require improvement. Therefore, these products could potentially be the initial method of choice in the management of GIB by inexperienced endoscopists. Unlike some other hemostatic techniques, hemostatic powder application does not require en face positioning opposite the source of hemorrhage because the powder diffuses in all directions, nor are these products dependent on very precise targeting to achieve initial hemostasis. Therefore, powders may be the hemostatic method of choice in the management of lesions that are difficult to access endoscopically. As the hemostatic powders can cover large surface areas with multiple bleeding points while minimizing tissue trauma, they appear well adapted to treating malignant tumors of both the upper and lower GI tracts.

Potential limitations of hemostatic powders in digestive endoscopy

Despite their user-friendly application, the hemostatic powders have limitations. The powders can potentially block their applicator delivery system or the accessory channel of the endoscope when prematurely coming into contact with moisture; drying of the accessory channel before application of a hemostatic powder is recommended. Also, until recently, only 10F delivery catheters have been available for TC-325, requiring the use of a therapeutic gastroscope or a colonoscope. A 7F catheter has just been released, but applicator catheter blockage may become more of an issue. Looping of the endoscope also hinders the positioning of the soft catheter sheath of the delivery system. Similarly, ERCP endoscopes are not ideal for the application of the powders because the malleability of the soft catheter over the elevator poses a challenge to optimal powder delivery. Because the powders only adhere to actively bleeding sites, a hemorrhagic field may prevent proper application of the product to the actual bleeding lesion. Although the patient may experience transient discomfort at the time of delivery under CO_2 pressure, no bowel obstruction or thromboembolic event has yet been reported in the limited available clinical data. TC-325 application is contraindicated by the manufacturer in the management of variceal bleeding because of the theoretical risk of thromboembolic events, although, as mentioned previously, ABS has been used in this setting. In addition, caution should be exercised when applying the powders near small orifices such as a biliary or pancreatic sphincterotomy site because there exists the potential for obstruction.

PREDICTING AN OPTIMAL ROLE FOR HEMOSTATIC POWDERS IN GIB IN 2012

Understanding the fundamental mechanisms of action of hemostatic powders (or at least what is known at this time) is critical to postulating their optimal role in GIB. These agents principally act by quickly absorbing water and providing rapid mechanical tamponade at the site of bleeding. They are thus only useful if there is active bleeding and clear access to the hemorrhage source and will otherwise not bind to the targeted mucosal site. They appear helpful in controlling massive bleeding at an initial hemostatic attempt, aiding in acquiring control of the bleeding field. If the main risk of hemorrhage for a given lesion stems from immediate bleeding without a significant risk of delayed rebleeding, a hemostatic powder may suffice as single modality treatment. Indeed, because these

agents can be washed away within hours from the bleeding site, any lesion exhibiting a persistent risk of rebleeding over a more prolonged period of time, such as days, would likely require further treatment either immediately as part of a multimodal approach or subsequently at a second-look setting. The powders also appear effective as rescue therapy at the time of initial hemostasis. They are well adapted to treating malignant GIB. An algorithm highlighting the possible roles of the hemostatic powders is shown in Figure 3. Of course, all of the aforementioned predictions are subject to the accumulation of more extensive experience and high-quality comparative clinical data in particular.

CONCLUSION

Topical hemostatic agents, ie, ABS, have been successfully used in various surgical procedures and endoscopic management of both variceal and nonvariceal GIB as a sole or adjuvant hemostatic agent. Limited clinical data have also shown TC-325 to be a safe and effective powder-based hemostatic agent in management of nonvariceal upper and lower GIB with no serious adverse events. Currently, additional products are being introduced in the market. Randomized, controlled studies and large registries are now required to further define the optimal role of hemostatic powders and their safety in managing patients with GIB.

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