ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

Section Editor: Todd H. Baron, MD

Hemostatic Spray for the Management of Gastrointestinal Bleeding

John R. Saltzman, MD
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

G&H What treatment modalities have traditionally been available for endoscopic hemostasis of gastrointestinal bleeding?

JS The main endoscopic treatment modalities that have traditionally been used to manage hemostasis of gastrointestinal bleeding are cautery, such as bipolar circumactive probe (BICAP) cautery; hemoclips; or a combination therapy, in which either of the aforementioned modalities is combined with an injection of epinephrine. Combining epinephrine with BICAP cautery or with hemoclips is very effective; however, the use of epinephrine as a monotherapy is not as durable as the combination therapies or as the other single-agent modalities. Typically, physicians do not recommend epinephrine injection by itself. Hemoclips are currently the most widely used method in the United States, with or without injection therapy.

G&H What limitations are associated with these modalities?

JS Several limitations are associated with the traditional endoscopic methods. The location of the lesion may hinder the ability to treat it or may place it at risk for a complication. For example, hemoclips may not be able to be placed on lesions that are located high on the lesser curvature of the gastric wall or on portions of the duodenal bulb, and perforation may occur if cautery is repeatedly applied to a wall of the bowel that is thin. Another major limitation is that these therapies are not completely effective at primary control or at preventing rebleeding. Some patients have such severe bleeding that the site cannot be localized and the cause cannot be determined. Thus, a specific, directed therapy cannot be applied to control the bleeding. Rebleeding can occur in 10% to 20% of patients who are treated with endoscopic modalities, and treatment is usually less effective when it is repeated. Lastly, certain patient groups are more difficult to treat with traditional methods. These include patients who have peptic ulcers that are larger than 2 cm in size or blood vessels that are larger than 2 mm in diameter, patients who have multiple comorbid illnesses, and patients who are taking antithrombotics.

> The mineral material within the hemostatic spray is able to absorb fluid 30 to 40 times its dry weight, and a combination of fluid absorption, clotting, and coating the area results in hemostasis.

G&H Which sprays or powders are available to achieve hemostasis?

JS Hemospray (Cook Medical), a mineral-based product (TC-325), has been widely used for control of gastrointestinal bleeding, and most experience is with this spray therapy. However, there are other therapies available worldwide. Ankaferd BloodStopper (İmmun İlaç Kozmetik LTD) is a plant-based product from Turkey that provides a natural medicine pathway to control bleeding. Data on the use of this product are predominantly from Turkey, and study results show that the spray may have a role in controlling gastrointestinal bleeding. However, the data are still somewhat limited. EndoClot (EndoClot Plus, Inc) is manufactured in California but is not yet available for use in the United States. The spray uses a modified plant starch called absorbable modified polymer, which rapidly absorbs water and causes a procoagulant effect. This product requires a pump technology to deliver the spray, and it is unknown whether the spray is subject to degradation within the gastrointestinal tract due to gastric acid or other digestive enzymes. Currently in development in South Korea is CEGP-003 (CGBio Inc), which is a combination product of an epidermal growth factor and a hydroxyethylcellulose powder. Only 1 preliminary study has been performed that demonstrates that this spray can stop bleeding.

G&H Are any hemostatic sprays approved for use in the United States?

JS Hemospray is the only spray currently available for use in the United States. The US Food and Drug Administration (FDA) approved the hemostatic spray in May 2018, and the majority of studies on hemostatic sprays have been conducted using this product. The hemostatic spray was originally developed in the military to stop bleeding in the field and has since been applied to bleeding in the upper and lower gastrointestinal tract. The mineral material within the hemostatic spray is able to absorb fluid 30 to 40 times its dry weight, and a combination of fluid absorption, clotting, and coating the area results in hemostasis.

G&H How is the hemostatic spray administered?

JS The hemostatic spray is administered through a catheter that is attached to a standard endoscope. A carbon dioxide cartridge is placed on the end of the catheter, and a trigger mechanism sprays the product onto the area that is actively bleeding. The trigger can be pressed repeatedly to allow for as much spray as needed.

G&H What are the main advantages of the hemostatic spray?

JS The primary advantage of the hemostatic spray is that it can be used to treat lesions that traditional modalities cannot, whether due to the location of the lesion, the size of the blood vessel, or the risk for complication. It is relatively easy to use, as the endoscope just needs to be placed near the active bleeding site before activating the trigger. Therefore, the hemostatic spray can be used by physicians who are trained in endoscopy but who are not necessarily experts at bleeding control. Importantly, the spray is approved in the United States for both upper and lower gastrointestinal bleeding. It is not approved (and the manufacturer did not seek approval) for control of variceal bleeding, but it may help with managing variceal bleeding in patients with massive bleeding or an obscured source. The spray may also be effective in stopping bleeding in the esophagus and the stomach and in stabilizing the patient, which could prevent the need for a procedure such as a Sengstaken-Blakemore tube placement.

> ... the hemostatic spray is uniquely effective at controlling a wide area and multiple sites of oozing bleeding.

G&H What limitations are associated with the hemostatic spray?

JS The hemostatic spray can only be used on lesions that are actively bleeding. After control of active bleeding, in a lesion that is at high risk for further bleeding, a second modality may need to be applied to prevent rebleeding.

G&H In what ways can the hemostatic spray be combined with conventional endoscopic hemostatic modalities?

JS High-risk bleeding lesions can be initially controlled with the hemostatic spray and followed up with a conventional endoscopic modality to prevent the lesion from rebleeding. Another common indication is to apply hemostatic spray after conventional modalities fail to stop bleeding in order to prevent further bleeding.

G&H What data are available thus far on the safety and efficacy of the hemostatic spray?

JS An increasing number of studies are available, most of which are small case series or retrospective cohort studies. The hemostatic spray appears to be quite safe, with few reported complications, the majority of which were due to other modalities that were applied at the same time as the spray for rescue or to treat the underlying disease. The literature reports that the hemostatic spray is 98% effective during the initial index endoscopy and 96% effective at achieving hemostasis overall. The studies also report a rebleed rate of approximately 18% within 7 days following treatment, although this may be due partly to patient selection (ie, patients with very severe bleeding, at high risk of rebleeding, and/or with several comorbidities), as well as to lesions that require a second modality for control and prevention of rebleeding.

G&H Have there been any head-to-head studies comparing hemostatic spray with existing hemostatic modalities?

JS There have only been a few randomized, controlled trials comparing hemostatic spray with conventional hemostatic modalities. At the World Congress of Gastroenterology at American College of Gastroenterology 2017 Annual Scientific Meeting, Dr Alan Barkun presented the results of a pilot study that randomized 20 patients who had bleeding from a gastrointestinal malignancy to treatment with either hemostatic spray or with argon plasma coagulation. Of the 10 patients who were treated with hemostatic spray, 9 had control of their bleeding with initial hemostasis, compared to 4 of the 10 patients who were treated with argon plasma coagulation. Among the 5 patients in the argon plasma coagulation group who were then treated with hemostatic spray, 4 had control of their bleeding. Patients bleeding from gastrointestinal malignancies constitute a minor but important subgroup, as there is a very high rebleeding rate and, often, there are multiple sites of bleeding. Traditional therapies do not work well, whereas the hemostatic spray is uniquely effective at controlling a wide area and multiple sites of oozing bleeding. Thus, many specialized and academic centers are utilizing hemostatic spray in this difficult-to-treat patient population.

Another trial assessed the management of esophageal variceal bleeding, for which the spray is not currently FDA-approved. Eighty-six patients were randomized to initial treatment with hemostatic spray or to a standard of care. Of the 43 patients who were treated with hemostatic spray, only 5 had further bleeding, whereas 13 patients who received standard of care needed rescue for further bleeding.

G&H What are the current indications for hemostatic spray?

JS The indications for hemostatic spray are broad, and include nonvariceal bleeding in the upper or lower gastrointestinal tract, including bleeding from peptic ulcer disease, and bleeding from other lesions, such as a Dieulafoy lesion or an arteriovenous malformation. The spray can also be used in patients who undergo an endoscopic therapy that provokes bleeding (eg, endoscopic mucosal resection, endoscopic submucosal dissection, sphincterotomy) that cannot be controlled with other modalities. Other uses include for the control of bleeding from diverticula, in portal hypertensive gastropathy with multiple areas of oozing bleeding, and following polypectomy, typically when other modalities have failed to control the bleeding.

Off-label use includes control of gastric or esophageal varices in patients who have bleeding that either cannot be controlled with standard therapies or that is so severe that standard therapy cannot be applied.

G&H How difficult is hemostatic spray to apply?

JS Overall, hemostatic spray is simple to apply. However, the delivery system has to be kept very dry, as the powder will attach to any fluid and clog the catheter. To avoid inadvertently suctioning fluid onto the catheter tip, I typically flush the delivery catheter with air several times before placement and then remove the suction from the endoscope once the delivery catheter is placed. I also remove the water jet to avoid accidentally clearing the area with water. Staff education and training is key to understanding the delivery system.

G&H How widespread is the use of hemostatic spray in clinical practice?

JS The US experience is limited to approximately 6 months, as hemostatic spray first became available in June 2018 following its May approval. In academic centers, hemostatic spray is typically used in difficult patient populations, such as those with bleeding gastrointestinal malignancies, or following failure of other therapies, rather than as a primary therapy. In the clinical practice setting, the spray is being used more widely as a primary therapy to stop bleeding, especially among physicians who are not comfortable with the current modalities or for whom the other modalities are not available. The use

of hemostatic spray will likely become more common the longer it is available.

G&H What are the priorities of research?

JS One of the main research priorities is to conduct prospective studies as well as randomized, controlled trials comparing hemostatic spray to traditional modalities for the treatment of standard lesions. It would also be beneficial to study the efficacy of hemostatic spray in difficult patient populations, such as in patients on anticoagulants or antithrombotics or in patients with an elevated international normalized ratio. Cost-effective studies are also needed for the use of this therapy. Currently, hemostatic spray is more expensive by itself than any other single endoscopic therapy available; however, the spray may be more advantageous by reducing the length of stay in the hospital or intensive care unit and decreasing the use of blood products, particularly in high-risk patient groups or patients with rebleeding. Additionally, more data are needed regarding the application of the spray in the colon as well as off-label use in esophageal and gastric variceal bleeding.

Dr Saltzman has no relevant conflicts of interest to disclose.

Suggested Reading

Barkun AN, Adam V, Lu Y, Chen YI, Martel M. Using Hemospray improves the cost-effectiveness ratio in the management of upper gastrointestinal nonvariceal bleeding. *J Clin Gastroenterol*. 2018;52(1):36-44.

Changela K, Papafragkakis H, Ofori E, et al. Hemostatic powder spray: a new method for managing gastrointestinal bleeding. *Therap Adv Gastroenterol*. 2015;8(3):125-135.

Chen YI, Barkun AN. Hemostatic powders in gastrointestinal bleeding: a systematic review. *Gastrointest Endosc Clin N Am*. 2015;25(3):535-552.

Haddara S, Jacques J, Lecleire S, et al. A novel hemostatic powder for upper gastrointestinal bleeding: a multicenter study (the "GRAPHE" registry). *Endoscopy*. 2016;48(12):1084-1095.

Ibrahim M, El-Mikkawy A, Abdel Hamid M, et al. Early application of haemostatic powder added to standard management for oesophagogastric variceal bleeding: a randomised trial [published online May 5, 2018]. *Gut*. doi:10.1136/gutjnl-2017-314653.

Pittayanon R, Rerknimitr R, Barkun A. Prognostic factors affecting outcomes in patients with malignant GI bleeding treated with a novel endoscopically delivered hemostatic powder. *Gastrointest Endosc*. 2018;87(4):994-1002.

Sinha R, Lockman KA, Church NI, Plevris JN, Hayes PC. The use of hemostatic spray as an adjunct to conventional hemostatic measures in high-risk nonvariceal upper GI bleeding (with video). *Gastrointest Endosc*. 2016;84(6):900-906.e3.