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Hemospray™ in Gastrointestinal Bleeding

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INTRODUCTION

Acute upper and lower gastrointestinal bleeding are common medical emergencies with high rates of morbidity and mortality.[1] Various endoscopic hemostatic treatment modalities exist including injection, thermal and mechanical therapies. These methods have limitations, as they all require technical expertise and, in most, direct tissue contact with the bleeding vessel.[2] Thermal and ligation devices, such as clips, are limited by the need for en face positioning, possible difficulties in deployment and potential complications such as bleeding and perforation. Furthermore, these techniques do not provide rapid enough hemostasis in the case of massive bleeding.[3,4]

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Application of a hemostatic powder to the bleeding site obviates the need for direct contact of an instrument with the vessel or mucosa. Hemospray™ (TC-325, Cook Medical Inc., Winston-Salem, NC, USA) is a novel, highly adsorptive nanopowder made from a proprietary inorganic mineral blend. It contains no human or animal proteins, botanicals or allergens and is nontoxic.[2] It is currently licensed in Europe, Hong Kong and Canada for endoscopic hemostasis of non-variceal upper gastrointestinal bleeding[5,6] and is undergoing Food and Drug Association (FDA) evaluation in the United States (US) for similar use. It is currently only FDA approved for external traumatic uses.[7,8]

Hemospray Application

Technique and Mechanism of Action

The Hemospray delivery device consists of a powder canister (which contains approximately 20 grams of

TC-325 hemostatic powder), a compressed carbon dioxide propellant and a delivery catheter that is introduced through the working channel of the endoscope. Hemospray is deployed through a 7-Fr or 10-Fr catheter in short bursts (each of which contains an average of 1 to 5 grams of powder). When the powder contacts blood, it absorbs water and forms a gel, which acts both cohesively and adhesively to create a stable mechanical barrier that covers the actively bleeding site. Hemospray is neither absorbed nor metabolized by mucosal tissue and the covering formed by the powder eventually sloughs from the lesion and is eliminated via the gastrointestinal tract.[6,9,10] In vitro experiments, whereby Hemospray was added to the plasma of healthy and factor-deficient patients, suggested that Hemospray may also activate the coagulation cascade and platelet function, thereby facilitating local hemostasis.[11] However, these preliminary findings require confirmatory studies.

Safety and Efficacy in Animal Models

Hemostatic powders have been used efficaciously for hemorrhage control in battlefield trauma patients. Swine model studies have raised concerns about the safety of these agents when used to externally pack open vascular injuries. Local and distant thrombi, transmural vessel damage and neurovascular changes have been described with use of WoundStat (a topical hemostatic agent made of smectite granules) in swine model studies.[12,13] While these safety concerns have caused some hesitancy about the use of hemostatic powders in humans with gastrointestinal bleeding, the animal studies involved extreme vascular injury from surgically transected vessels in which the hemostatic material was firmly packed into the wounds, and therefore could have predisposed to thrombus formation.

In a swine model study by Giday et al., 6 animals underwent gastrotomy and creation of a looped vascular bundle, which was placed into the stomach lumen.[2] On subsequent endoscopy the transplanted vascular bundle was punctured using a needle-knife to create Forrest grade Ia (pulsatile) or Ib (oozing) bleeding gastric lesions. Hemospray was then applied. Initial hemostasis was achieved in all animals and there were no signs of re-bleeding at post-procedure day 9. There was no hemostatic powder identified grossly in any stomach specimens, nor was there histologic evidence of powder or thrombosis in any local or systemic tissue samples.

In a randomized controlled animal trial, 10 swine were randomized to endoscopic treatment with Hemospray or sham (through endoscopic monitoring only) after operative creation of gastric arterial bleeding.[14] Initial hemostasis was achieved in all animals treated with Hemospray while those in the sham treatment group all succumbed to uncontrolled hemorrhage. Durable hemostasis up to 24 hours post-treatment was observed in 80% of the treatment group. There was no evidence of foreign body granuloma or embolization in the lung or brain at necropsy in any of the treatment animals sacrificed one week later.

Clinical Applications of Hemospray

A review of the literature using PubMed and Ovid up to February 2014 showed various clinical applications of Hemospray in both upper and lower gastrointestinal bleeding (summarized in Table 1).

Upper Gastrointestinal Bleeding

Various Causes of Upper GI Bleeding[1]

A multicenter, international SEAL (Survey to Evaluate the Application of Hemospray in the Luminal Tract) cohort study assessed the use of Hemospray in non-variceal upper gastrointestinal bleeding in 10 pilot sites across Europe.[15] A total of 63 patients were treated with Hemospray as either primary monotherapy (in 55 patients) or combination second-line therapy (in 8 patients). The etiology of the bleeding was gastroduodenal ulcer in 48% of patients, with the remaining etiologies attributable to various other non-variceal causes. Primary hemostasis was achieved in 85% of patients who received Hemospray monotherapy, the remainder required additional endoscopic hemostatic adjuvant interventions or angiographic embolization. Of the patients for whom initial hemostasis was achieved with Hemospray monotherapy, 15% developed re-bleeding within 7 days. Of the 8 patients treated with Hemospray when standard endoscopic therapies had failed, all 8 (100%) achieved hemostasis with Hemospray. However, 25% of these patients re-bled within 7 days. There were a total of 4 deaths within 7 days, none of which was due to bleeding. Of the patients with peptic ulcer bleeding, 36% failed to achieve either primary or sustained hemostasis with Hemospray. This is higher than expected when compared to published data from controlled studies in ulcer bleeding, but likely

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attributable at least in part to patient selection. While this was an uncontrolled, solely observational study with no set protocol for Hemospray use, it provides some insight into the efficacy and safety of Hemospray in non-variceal upper gastrointestinal bleeding.

Peptic Ulcer Bleeding

In a prospective, single-arm pilot clinical study by Sung et al., consecutive adults with confirmed peptic ulcer bleeding (Forrest class Ia or Ib) were treated with Hemospray.[10] The majority of ulcers (70%) were located in the duodenum, while 30% were in the stomach. Routine second-look endoscopy at 72 hours post-treatment and phone follow-up at 30 days were performed in all participants. Of the 20 total patients in the study (18 men, mean age of 60 years), acute hemostasis was achieved in 95% (19/20) of patients. The one patient for whom Hemospray failed had a pseudoaneurysm that required arterial embolization (the only patient with Forrest Ia ulcer bleeding). Two patients had recurrent bleeding within 72 hours (detected clinically by hemoglobin drop), but neither had active bleeding identified at repeat endoscopy. There were no major adverse events, mortality, or treatment-related adverse events (including systemic embolization, bowel obstruction or allergic reaction) during the 30-day follow-up period. At the routine second-look endoscopy at 72 hours, Hemospray had been eliminated from the stomach and duodenum in all patients. All patients at follow-up endoscopy had clean-based ulcers, and had received high-dose proton pump inhibition co-administration.

Portal Hypertensive Bleeding

Esophageal Variceal Bleeding

A prospective, non-randomized pilot study by Ibrahim et al. evaluated the efficacy of Hemospray in 9 patients with acute esophageal variceal bleeding: 3 with active hemorrhage and 6 with stigmata of recent bleeding.[16] The application of Hemospray produced hemostasis in all patients, and a second dose was required in only one case. Follow-up endoscopy was performed at 24 hours post-intervention in all patients, at which time hemostatic powder had been eliminated from the upper gastrointestinal tract in all patients, and the entire cohort then underwent elective variceal band ligation. No cases of recurrent bleeding or Hemospray-related adverse events were reported. These findings highlight Hemospray as a potential bridge to definitive therapy (either transjugular intrahepatic portosystemic shunt [TIPS] or band ligation) in acute esophageal variceal bleeding, especially in cases when immediate hemostasis is otherwise difficult to achieve. Currently, Hemospray is not recommended for use in variceal hemorrhage by the manufacturer due to theoretical concerns about possible systemic embolization.[3]

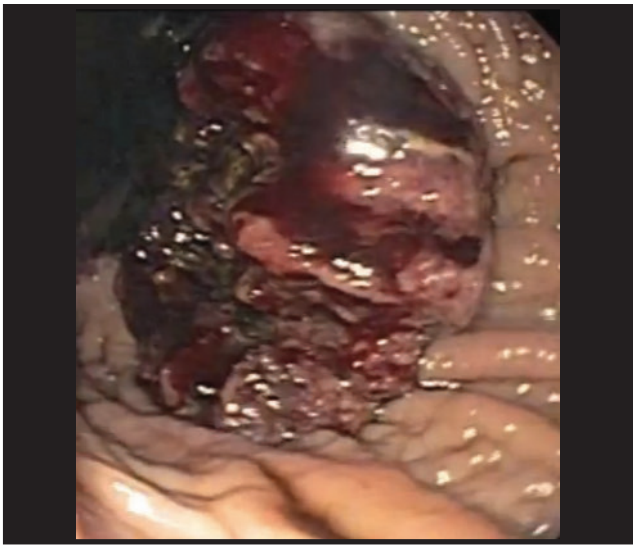

Figure 1.

Gastric Variceal Bleeding

There are two case reports describing the use of Hemospray in gastric variceal bleeding, both after injection therapy with N-butyl-2-cyanoacrylate (Histoacryl™) with lipiodol failed. In one of the patients, it served as a bridge to TIPS, and in the other it was definitive therapy as TIPS was contraindicated due to underlying cardiomyopathy.[17,18]

Portal Hypertensive Gastropathy

Hemospray has been used successfully in 3 patients with diffuse bleeding from portal hypertensive gastropathy.[6]

Patients on Antithrombotic Therapy

Antithrombotic therapy (ATT) includes antiplatelet therapy and anticoagulants and can give rise to life-threatening gastrointestinal hemorrhage. Holster et al. evaluated the relative efficacy of Hemospray in patients with bleeding on ATT (n = 8) compared with those without ATT (n = 8).[19] Successful initial hemostasis

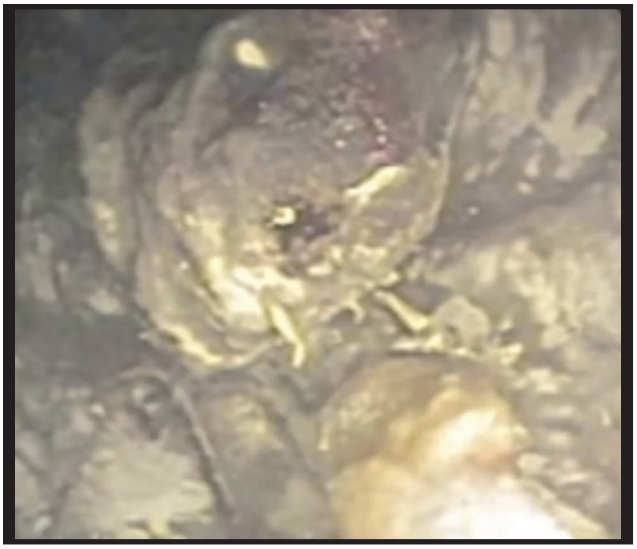

Figure 2.

was achieved in all 8 (100%) of the non-ATT patients and in 5/8 (63%) of the patients on ATT (p = 0.20). For the 3 patients on ATT for whom Hemospray failed, 2 had spurting arterial bleeds controlled with subsequent clipping and the other patient required angiography with coil embolization. Re-bleeding within 7 days was observed in 5 of the 16 patients (3 in the ATT group and 2 in the non-ATT group). In 2 of the 3 ATT cases, Hemospray had been applied to spurting arterial vessel bleeding, and in both of the non-ATT cases, Hemospray had been applied for peptic ulcer related arterial bleeds. No deaths occurred up to 30 days after Hemospray application in either group.

Malignant Tumor Bleeding

Both primary and metastatic tumors of the gastrointestinal tract are at risk of bleeding. Bleeding from malignancy can be induced by tumor necrosis and is often diffuse and widespread.[20] Conventional endoscopic hemostatic therapies (such as heater probe, electrocautery and argon plasma coagulation [APC]) are associated with high rates of recurrent bleeding compared to other non-malignant causes of gastrointestinal bleeding.[21] Chen et al. described 5 cases in which Hemospray was used to treat upper gastrointestinal bleeding due to gastroduodenal tumors.[22] Hemospray was successful in achieving immediate and sustained hemostasis in 4 of the 5 patients, but failed in a patient with severe metastatic disease and disseminated intravascular coagulation. In a study by Leblanc et al., 5 patients with active upper gastrointestinal bleeding due to malignancies of the esophagus, stomach or pancreas were treated with Hemospray.[20] Hemospray was used as first-line therapy in 4 of the 5 patients, and as rescue therapy in the fifth for persistent bleeding despite placement of hemostatic clips. Immediate hemostasis was successful in all 5, with recurrent bleeding in 2 patients. Figure 1 shows a gastric tumor with diffuse bleeding prior to the use of Hemospray. Figure 2 shows complete hemostasis of the same lesion following the application of Hemospray.

Post-Therapeutic Intervention Bleeding

Hemospray has been used in 12 patients who developed upper gastrointestinal bleeding after therapeutic endoscopic interventions.[20] Bleeding occurred after esophageal endoscopic mucosal resection (EMR) in 5 patients, after duodenal EMR in 4 patients, after ampullary resection in 2 patients and after biliary sphincterotomy in 1 patient. Lesion diameter ranged from 10 mm to 90 mm. Hemospray was used as initial therapy in 8 of these patients and as rescue therapy (after standard hemostatic therapy failed) in 4 patients. Recurrent bleeding was suspected but not confirmed on repeat endoscopy 48 hours after Hemospray application in two of the 12 patients. No recurrent bleeding occurred in any of the 12 patients during follow-up at 7 days and 30 days post-treatment. In the only published U.S. case report of Hemospray, a young patient with a metal biliary stent placed for malignant biliary obstruction developed a bleeding duodenal ulcer from stent migration.[8] Because of its location and anatomic distortion, conventional endoscopic hemostatic interventions failed and the patient continued to bleed despite gastroduodenal artery embolization. An investigational device exemption was approved for use of Hemospray, and hemostasis was finally achieved. The patient was discharged home 6 days later with no further bleeding episodes.

Lower Gastrointestinal Bleeding

Lower gastrointestinal bleeding accounts for 20-40% of acute gastrointestinal bleeding cases. This type of bleeding can be massive and therefore requires prompt and durable hemostasis. Conventional hemostatic modalities include clips and thermal coagulation.[9] The role of Hemospray in lower gastrointestinal bleeding has recently been studied. In a multi-center European case series by Holster et al., nine patients with active

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lower gastrointestinal bleeding of various causes (post-polypectomy, colorectal anastomosis, rectal ulcer, diverticular, proctitis and cecal adenocarcinoma) were treated with Hemospray, either as initial or salvage therapy.[9] Immediate hemostasis was successful in all 9 patients (100%), but re-bleeding occurred in 2 of the 9 patients (22%) within 7 days. Both of these patients were on aspirin and had initial pulsatile arterial bleeds. Successful hemostasis was eventually achieved in these patients with clip placement and arterial embolization.

Soulellis et al. were the first group to report Hemospray application in the lower GI tract describing

Table 1. Summary of Literature Using Hemospray™ in Upper and Lower Gastrointestinal Bleeding

Indication	Reference	Location	Publication Year	Study Type	Number of Patients	% Immediate Hemostasis	% Early Re-bleed
Upper GI Bleeding							
Various causes	Smith et al.[15]	10 European centers	2013	Multicenter, prospective registry	63	85%	15%
Peptic ulcer bleeding	Sung et al.[10]	Hong Kong	2011	Prospective, single-arm pilot study	20	95%	10.5%
Esophageal variceal bleed	Ibrahim et al.[16]	Belgium, Egypt	2013	Prospective, non-randomized study	9	100%	0%
Gastric variceal bleed	Holster et al.[17] Stanley et al.[18]	Netherlands United Kingdom	2012 2013	Case report Case report	1 1	100% 100%	0% 0%
Portal hypertensive gastropathy	Smith et al.[6]	United Kingdom	2014	Case series	3	100%	0%
Various causes, on or off ATT	Holster et al.[19]	Netherlands	2013	Retrospective	8 not on ATT 8 on ATT	100% 63%	25% 37.5%
Tumor bleeding	Leblanc et al.[20] Chen et al.[22]	France Canada	2013 2012	Case series Case series	5 5	100% 100%	40% 20%
Post therapeutic intervention	Leblanc et al.[20] Sargon et al.[8]	France United States	2012 2013	Case series Case report	12 1	100% 100%	16.7% 0%
Lower GI Bleeding							
Various causes	Holster et al.[9] Soulellis et al.[23]	Netherlands Canada	2014 2013	Retrospective Case series	9 4	100% 100%	22% 0%
H1N1 cecal ulcer	Granata et al.[24]	Italy	2013	Case report	1	100%	0%

additional clinical uses of Hemospray.[23] Indications included post-polypectomy bleeding, after conventional hemostatic therapy with clips, thermal probe, and epinephrine injection had failed. Hemospray was also used successfully in a left-sided colonic Dieulafoy's lesion after clip placement and epinephrine injection failed. Lastly, the investigators also reported its use in radiation proctopathy after argon plasma coagulation caused more bleeding. Granata et al. described a single case report of Hemospray application for refractory cecal ulcer bleeding in a patient with influenza A (H1N1) virus who was being treated with extracorporeal membrane oxygenation for respiratory failure.[24] Re-bleeding had occurred after initial hemostasis with fibrin glue injection, whereas rescue therapy with Hemospray resulted in durable hemostasis.

CAUTIONARY NOTE AND COMPLICATIONS

A recent review suggested that because the Hemospray powder only binds to actively bleeding sites, its short contact time on the lesion may limit its use as monotherapy and may contribute to re-bleeding.

Feared complications of Hemospray use include bowel obstruction, systemic embolization and perforation. There have been no reports of bowel obstruction to date. Due to fear of systemic embolization, the manufacturers do not recommend use of Hemospray in variceal bleeding (where theoretically the powder could enter the venous circulation and embolize). However, some authors report that the outflow pressure of the device (when used correctly) is 12 mmHg, which should be less than intravariceal pressures, suggesting the embolization risk may be overstated.[23] In the available published literature where Hemospray was used in esophageal and gastric varices, there was no clinical evidence of systemic embolization. There has been only one reported case of perforation after endoscopic application of Hemospray in a patient with active portal hypertensive gastropathy-related bleeding. It was unclear whether the perforation was a result of endoscopy itself or directly due to the application of Hemospray.[6] This potential risk is related to the requisite carbon dioxide pressure used during application, which is approximately 12 mmHg with the catheter 1 to 2 cm from the target lesion, but reaches 55 mmHg if the catheter is incorrectly placed in direct contact with the mucosa.[23]

There is one report of Hemospray causing transient biliary obstruction when applied to a bleeding biliary orifice after sphincterotomy done for biliary stone removal. Biliary patency was restored with water irrigation and prodding open of the papillotomy orifice, but caution is recommended when applying Hemospray near small orifices adjacent to bowel lumen, such as a biliary or pancreatic sphincterotomy site.[25] In one case series, a female patient experienced abdominal pain after each burst of Hemospray application that resolved on its own post-procedure.[9] Device-related complications have included clumping of the powder within the catheter when the biopsy port is exposed to a moist or wet environment and transient adherence of the endoscope to the mucosa.[8,15]

SUMMARY

Hemospray has some distinct advantages over conventional endoscopic hemostatic modalities. It is easy to use and appears relatively safe and efficacious for various causes of both upper and lower gastrointestinal bleeding. Based on the limited available studies, it may have reduced efficacy in spurting arterial ulcer bleeds and in patients on ATT, primarily due to delayed re-bleeding that may exceed the residency time of the product more so than failure to achieve initial immediate hemostasis. In fact, Hemospray may be the most effective product available today in achieving immediate hemostasis. Unfortunately, Hemospray has not been compared in head-to-head controlled comparisons with conventional hemostatic therapies and hence the relative efficacy of this treatment is unknown. Hemospray has been successfully used in combination with other therapeutic modalities in some cases, and when lightly applied, the mucosal topography is preserved.

Its greatest applicability is as rescue therapy in massive hemorrhage when other therapies fail, or as a bridge to more definitive therapy (such as transferring the patient to a more specialized center, application in the context of a marked coagulopathy or in active variceal bleeding as a bridge to TIPS or band ligation under more controlled conditions). It may also be particularly adapted in diffusely bleeding lesions that involve large surface areas, especially in malignant bleeding in which the noncontact application may be particularly advantageous. While Hemospray appears promising as an adjunctive endoscopic hemostatic agent, prospective, controlled studies and resulting cost-effective analyses are urgently needed before more specific recommendations can be made regarding its use in patients with gastrointestinal bleeding. ■

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