

Douglas G. Adler MD, FACP, AGAF, FASGE, Series Editor

## Hemospray for Gastrointestinal Bleeding: Technology Status Update



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### INTRODUCTION

**M**ortality due to upper gastrointestinal bleeding (UGIB) has declined significantly in the last two decades, largely attributable to improved endoscopic practices.<sup>1</sup> A similar downward trend has been observed in lower gastrointestinal bleeding (LGIB).<sup>2</sup> Nonetheless, gastrointestinal bleeding (GIB) is still a major cause of morbidity and mortality in the United States with significant associated healthcare costs. UGIB accounts for about 300,000 hospital admissions yearly with a case fatality rate of 2-3%.<sup>1, 2</sup> Case fatality rate in LGIB is 1.47% with a two fold increase in patients greater than 75 years old.<sup>2</sup>

Endoscopic hemostasis remains first line treatment for GIB. While conventional endoscopic

methods including injectable agents, thermal treatments, argon plasma coagulation (APC), hemostatic clips and other therapies are effective, they often require high level of endoscopic expertise which may not be readily available. Furthermore, these modalities often require precise localization of the bleeding source and may be less effective in patients experiencing large mucosal bleeds, difficult to access lesions or in severe bleeding. Even with high level of endoscopic expertise, rebleeding risk with conventional endoscopic methods is about 5%.<sup>3</sup>

A simple to use hemostatic agent such as a hemostatic powder may potentially impact the endoscopic management of gastrointestinal bleeding, especially in lesions less amenable to conventional endoscopy. This paper aims to describe the efficacy and safety of Hemospray (Cook Medical, Winston Salem NC) in the management of gastrointestinal bleeding.

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## Overview of Hemospray

Hemospray is a hemostatic powder developed for endoscopic therapy of GI bleeding. (Figure 1) Unlike conventional endoscopic methods, Hemospray is non-contact, non-thermal and non-traumatic. It also doesn't require specific lesion targeting to secure hemostasis, although if possible direct spraying of the compound on the lesion is preferable.

According to the manufacturer, Hemospray is metabolically inert, presumably nontoxic and doesn't contain any human or animal allergens. On contact with blood, Hemospray induces hemostasis by absorbing water and forming a mechanical and adhesive barrier over the bleeding site. It causes a dose dependent reduction in median recalcification and clotting time of whole blood, rapidly producing hemostasis.<sup>6</sup> Hemospray is not absorbed by the body and no long-term effects due to ingestion have been documented to date.

Hemospray was first studied in porcine models to control surgically created high-pressure spurting arterial bleeds.<sup>7</sup> Hemostasis was achieved successfully in all study animals as compared to none in control animals. A pilot study of 20 people with peptic ulcer bleeding closely followed and hemostasis was achieved in 95% of cases.<sup>8</sup> These initial results have prompted the evaluation of Hemospray for endoscopic hemostasis in a wide array of bleeding disorders in the upper and lower gastrointestinal tract.<sup>8-16</sup>

## Primary Hemostasis

### Peptic Ulcer Disease

Gastrointestinal bleeding is common in peptic ulcer disease (PUD), accounting for more than 7 in 10 hospitalizations amongst PUD patients annually.<sup>17</sup> (Figure 2 and Figure 3) About a tenth of those with severe bleeding die, a higher risk of death observed in patients with high risk stigmata (active bleeding, non-bleeding visible vessel) and/or duodenal ulcers.<sup>4,17-19</sup> While conventional endoscopic methods are often highly effective, some lesions are not easily amenable to conventional therapy due to difficulties in endoscope positioning, surrounding tissue friability or fibrosis, or other factors. This was evident in a recent large national study that observed that 7% of PUD patients with high risk

stigmata did not receive any endoscopic therapy, with lesions deemed to be too large for endoscopic approaches being a frequently cited reason.<sup>20</sup>

Hemospray has been used successfully both as monotherapy and in conjunction with conventional methods in controlling bleeding due to PUD.<sup>8,9,21,22</sup> Sung et al. used Hemospray monotherapy on 20 patients with Forrest 1a and 1b ulcers and reported immediate hemostasis in 95% of patients.<sup>8</sup> Hemostasis was not secured in one patient who had a pseudoaneurysm and eventually required arterial embolization. Rebleeding occurred in 2 patients within 72 hours but there was no active bleeding on repeat endoscopy.

In a small study by Kwek et al. comparing the effectiveness of Hemospray monotherapy to conventional modalities, initial hemostasis was achieved in 90% (9/10) and 100% (10/10) of cases respectively.<sup>9</sup> In the Hemospray group, 7 of 10 patients had duodenal ulcers and initial hemostasis was achieved in 6 of these. Of note, case of Hemospray failure involved a patient with a Forrest 1b posterior duodenal wall ulcer. Hemostasis was eventually achieved with conventional endoscopy. Cahyadi et al. recorded immediate hemostasis with Hemospray in 18 patients with PUD related bleeding whose lesions were deemed not amenable to endoscopy (due to difficult anatomical situation or diffuse bleeding without definite source) or after conventional endoscopic failure.<sup>22</sup> Similarly, Smith et al. reported success in a report of 5 patients who were treated with Hemospray as second line after the failure of conventional endoscopy.<sup>21</sup>

Hemospray has been used as an adjunct to conventional endoscopic methods to control PUD bleeding. Sinha et al. used Hemospray in addition to Adrenaline (8 cases) and Hemospray in addition to Adrenaline with clips or thermal devices (12 cases).<sup>23</sup> Immediate hemostasis was achieved 95% (19/20) of cases. The failure case occurred in the group that had Hemospray, Adrenaline with clips/thermal devices and hemostasis was secured by embolization to the gastroduodenal artery.

### Tumor Bleeding

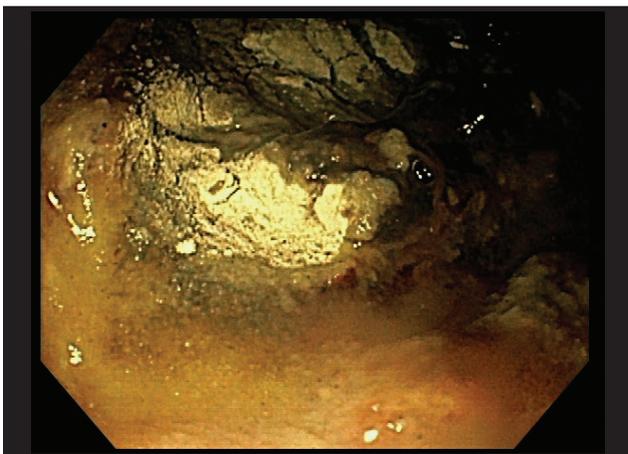
Gastrointestinal tumor bleeding accounts for 2.6 – 5% of UGIB.<sup>24-27</sup> Bleeding is the initial symptom of gastrointestinal tumor in about half of cases making late stage presentation a common phenomenon.<sup>24</sup>



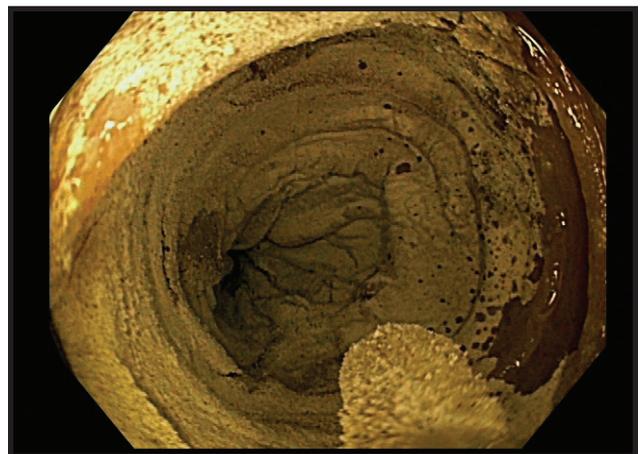
**Figure 1.** Hemospray device and catheter. Image courtesy of Cook Medical.



**Figure 2.** Duodenal ulcer prior to endoscopic Hemospray therapy. Image courtesy Andrew Gawron MD.



**Figure 3.** Same ulcer as in Figure 1 after Hemospray. Image courtesy Andrew Gawron MD.



**Figure 4.** Photo of the colon after Hemospray was used to treat diffuse friability and bleeding. Image courtesy Andrew Gawron MD.

Compared to other causes of UGIB, mortality in gastrointestinal tumor is quite high regardless of endoscopic therapy likely reflecting the severity of the underlying disease.<sup>24,28</sup> However, endoscopic hemostasis is pivotal to managing tumor bleeding and has been shown to reduce the need for blood transfusions or emergent surgery, often acting as a therapeutic bridge to palliative surgery, radiation or chemotherapy.<sup>29-31</sup> Rebleeding after endoscopic treatment is however very high in tumor bleeding.

Bleeding due to gastrointestinal tumor may be diffuse and lack a specific target for endoscopic hemostasis. Furthermore, tumor bleeding often arises from ulcerated or friable mucosa, potentially

limiting the use of mechanical or contact hemostatic methods. As such, a non-contact, non-thermal option like Hemospray may be a good option for providing at least short-term hemostasis. Pittayanon et al. evaluated the effectiveness of Hemospray in 88 patients with tumor bleeding in a large multicenter study.<sup>32</sup> Over 70% were stage 4 tumors and 50 were located in the upper gastrointestinal tract. Hemostasis was achieved with Hemospray in 98% of cases. Definite hemostatic treatment i.e. embolization, chemotherapy, radiotherapy and surgery was associated with improved survival after Hemospray treatment. In smaller studies,

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immediate hemostasis with Hemospray on bleeding due to upper gastrointestinal tumor ranged from 93 to 100%.<sup>22,33–35</sup>

### **Variceal Upper Gastrointestinal Bleeding**

Acute variceal bleeding (AVB) is a leading cause of death in cirrhotic patients, with mortality rates as high as 24% at 6 weeks.<sup>36,37</sup> While gastroduodenal ulcers coexist in a quarter of patients, variceal bleeding accounts for over 50% of UGIB in cirrhotic patients.<sup>38,39</sup> Per conventional endoscopy, sclerotherapy and variceal band ligation (VBL) are frequently utilized to treat bleeding esophageal varices, the latter having superior effects on reducing rebleeding, mortality and fewer esophageal strictures.<sup>40</sup> The combination of VBL with pharmacologic agents demonstrates even better effects on achieving hemostasis and reducing rebleeding than VBL alone.<sup>41</sup> Nonetheless, failure to control bleeding occurs in up to 10% of patients with acute variceal bleeds.<sup>42</sup>

There is emerging evidence on the efficacy of Hemospray in controlling acute variceal bleeding. In a single arm prospective trial, Ibrahim et al. used Hemospray monotherapy in 30 patients with confirmed AVB. Over 80% of varices were in the esophagus and more than half were actively bleeding.<sup>43</sup> With the exception of one patient who required the use of two Hemospray devices due to continued bleeding, others required just one application and immediate hemostasis was achieved in all patients at initial endoscopy.<sup>43</sup> In another study by Ibrahim et al., 100% hemostasis was achieved in all nine patients with AVB treated with Hemospray monotherapy.<sup>44</sup> Ibrahim et al. also studied 86 cirrhotic patients with AVB in a multicenter randomized trial. The study observed that patients who had immediate treatment with Hemospray within 2 hours of admission followed by elective endoscopy treatment at 24 hours had significantly better survival rates at 6 weeks compared to those who had elective endoscopy alone. These patients also had lower rates of rebleeding and need for rescue endoscopy.<sup>45</sup>

### **Lower Gastrointestinal Bleeding**

Lower gastrointestinal bleeding (LGIB) is about a fifth as common as UGIB and more prevalent in

patients older than 65 years.<sup>46</sup> While acute LGIB often resolves spontaneously with supportive care, about 25–40% of cases warrant direct endoscopic therapeutic intervention.<sup>47,48</sup> Conventional endoscopic treatment modalities are often effective at achieving hemostasis. However, in a few cases, bleeding persists warranting the need for other hemostatic options.<sup>49</sup>

Hemospray use in LGIB has been less frequently reported; however some studies have reported on its efficacy in achieving initial hemostasis. (Figure 4) Ivekovic et al. reported the successful use of Hemospray in a patient with spurting post polypectomy bleeding that did not respond to clipping.<sup>50</sup> Similarly, Soulellis et al. also achieved hemostasis with Hemospray in two patients with post-polypectomy bleeding after failure of thermal and mechanical therapy.<sup>51</sup> In a case series, Granata et al. treated four patients with severe LGIB due to ischemic colitis with Hemospray.<sup>52</sup> All four patients were hypotensive and on antithrombotic therapy at presentation. Mean ulcer diameter was quite large at 32 mm. Hemostasis was achieved in all four patients. Less common causes of LGIB in which hemostasis was successfully achieved with Hemospray includes stercoral ulceration, cytomegalovirus induced bleeding, post proctocolectomy bleeding and diclofenac-induced lower GI bleed.<sup>13–16</sup>

### **Rebleeding**

Rebleeding after endoscopic hemostasis is an independent predictor of mortality in both UGIB and LGIB.<sup>3,4,53</sup> Endoscopic findings that are predictive of rebleeding include active bleeding at the time of endoscopy, large ulcer size, posterior duodenal location and lesser gastric curve location.<sup>54</sup> Various strategies have been proposed to reduce the risk of rebleeding including avoiding epinephrine monotherapy and the use of dual conventional therapy. Rebleeding occurs in 10–20% of cases despite use of dual therapy.<sup>55</sup>

Studies show rebleeding rates after Hemospray to be highly variable, typically ranging between 15 and 49%.<sup>9,21–23,35,56–58</sup> This variability may be explained by heterogeneity of study populations, studies with small sample size and different modalities of Hemospray use. Certain factors are associated with an increased risk of rebleeding when

Hemospray is used for endoscopic hemostasis. When Hemospray was used as a treatment modality for patients whose ulcers were deemed not amenable to conventional methods i.e. large ulcers or lesions at historically difficult locations to treat, rebleeding rates after initial hemostasis was as high as 49% after 7 days.<sup>22</sup> Rebleeding also appears to be higher when Hemospray is used as salvage therapy i.e. after failure of conventional therapy as compared to primary hemostatic method.<sup>22</sup> Similar to conventional modalities, rebleeding rates are much higher when Hemospray is used to treat spurting arterial bleeding (Forrest 1a ulcers).<sup>9,21,23</sup> However, when treating actively bleeding ulcers, Hemospray may have a higher risk of rebleeding as compared to conventional methods.<sup>9</sup> In fact, at least one study suggests that Hemospray not be used as monotherapy for spurting arterial bleeds due to high risk of rebleeding.<sup>56</sup>

### Safety Issues/Adverse Effects

Despite the benefits of Hemospray or hemostatic powders, there are potential safety issues and reports of adverse events. When Hemospray is used before other hemostatic modalities, there is a risk of obscuring the boundaries of a lesion making it more difficult to implement other hemostatic options if they are needed.<sup>59</sup> Furthermore, there is a risk of catheter obstruction if the delivery device comes into contact with blood.

Per the manufacturer, no more than 3 devices (60g) of Hemospray are to be used in a single patient. Hemospray is not absorbed by the gastrointestinal tract so there is a risk of colonic impaction at higher doses. Up to 150g of Hemospray was utilized in the study by Sung et al., without any report of colonic obstruction.<sup>8</sup> Biliary obstruction after treatment of a post sphincterectomy bleed treated by Hemospray use has been documented.<sup>60</sup> Patency was restored by irrigation and prodding the orifice open with a sphincterotome tip.

Due to its pressurized contents, Hemospray is associated with a risk of bowel perforation and embolization. Hagel et al. documented an 8cm gastric wall perforation after Hemospray was used for a patient with ischemic colitis who presented with melena and generalized peritonitis after total colectomy.<sup>61</sup> Similarly, visceral perforation after Hemospray application has been documented in two other studies although it was unclear if this was directly related to Hemospray use.<sup>62,63</sup>

Hemospray is not currently recommended for primary treatment of variceal bleeding due to the theoretical risk of embolization, although this can be performed in an off-label manner. It is thought that the pressurized contents of Hemospray may overcome the low pressure venous system. However, this adverse event has not been recorded in studies where Hemospray was used for variceal bleeding.<sup>43–45</sup>

### CONCLUSION

Hemospray has potential advantages over conventional methods in the control of gastrointestinal bleeding. It has high primary hemostasis rates in both variceal and non-variceal upper gastrointestinal bleeding. Limited studies also demonstrate high primary hemostasis rates in LGIB. Beyond this, it is simple to use and does not require a high level of endoscopist expertise. It also appears to have a good safety profile, only very few studies documenting serious adverse effects. Hemospray also has some limitations. Despite high primary hemostasis rates, it appears to have higher rates of rebleeding if used to treat spurting arterial bleeding or large, difficult to reach ulcers. It is a single use product and cannot be reused in the same patient if rebleeding occurs at a later date. Furthermore, if the device becomes clogged

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during endoscopy, further use is impossible and another device needs to be used. Going forward, there is need for larger studies to define the optimal role and cost effectiveness of Hemospray in the management of gastrointestinal bleeding. ■

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