Safety and efficacy of Hemospray® in upper gastrointestinal bleeding

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BACKGROUND: Hemospray (Cook Medical, USA) has recently been approved in Canada for the management of nonvariceal upper gastrointestinal bleeding (UGIB). It achieves hemostasis by adhering to the bleeding site, which contact coagulation efforts may be hampered by further tissue damage and induction of more bleeding (3). In contrast, Hemospray can quickly cover large areas and does not require en face view or a temporary measure or a bridge toward more definitive therapy.

OBJECTIVE: To review the authors’ experience with the safety and efficacy of Hemospray for treating UGIB.

METHODS: A retrospective chart review was performed on patients who required endoscopic evaluation for suspected UGIB and were treated with Hemospray.

RESULTS: From February 2012 to July 2013, 19 patients (mean age 67.6 years) with UGIB were treated with Hemospray. A bleeding lesion was identified in the esophagus in one (5.3%) patient, the stomach in five (26.3%) and duodenum in 13 (68.4%). Bleeding was secondary to peptic ulcers in 12 (63.2%) patients, Dieulafoy lesions in two (10.5%), mucosal erosion in one (5.3%), angiodysplastic lesions in one (5.3%), ampullary in one (5.3%), polypectomy in one (5.3%) and an unidentified lesion in one (5.3%). The lesions showed spurring hemorrhage in four (21.1%) patients, ooze hemorrhage in 11 (57.9%) and no active bleeding in four (21.1%). Hemospray was administered as monotherapy in two (10.5%) patients, first-line modality in one (5.3%) and rescue modality in 16 (84.2%). Hemospray was applied prophylactically to nonbleeding lesions in four (21.1%) patients and therapeutically to bleeding lesions in 15 (78.9%). Acute hemostasis was achieved in 14 of 15 (93.3%) patients. Rebleeding within seven days occurred in seven of 18 (38.9%) patients. Potential adverse events occurred in two (10.5%) patients and included visceral perforation and splenic infarct. Mortality occurred in five (26.3%) patients but the cause of death was unrelated to gastrointestinal bleeding with the exception of one patient who developed hemoperitoneum.

CONCLUSIONS: The high rates of both acute hemostasis and recurrent bleeding suggest that Hemospray may be used in high-risk cases as a temporary measure or a bridge toward more definitive therapy.

Key Words: Efficacy; Hemospray; Safety; Upper gastrointestinal bleeding

Hemospray (TC-325) (Cook Medical, USA), a novel proprietary inorganic powder, has recently been approved in Canada for the management of nonvariceal upper gastrointestinal bleeding (UGIB). One lesion hemorrhagic, was identified in the esophagus of one patient (5.3%), the stomach of five patients (26.3%) and the duodenum of 13 patients (68.4%). The lesions showed spurring hemorrhage in four (21.1%) patients, ooze hemorrhage in 11 (57.9%) and no active bleeding in four (21.1%). Hemospray was administered as monotherapy in two (10.5%) patients, first-line modality in one (5.3%) and rescue modality in 16 (84.2%). Hemospray was applied prophylactically to nonbleeding lesions in four (21.1%) patients and therapeutically to bleeding lesions in 15 (78.9%). Acute hemostasis was achieved in 14 of 15 (93.3%) patients. Rebleeding within seven days occurred in seven of 18 (38.9%) patients. Potential adverse events occurred in two (10.5%) patients and included visceral perforation and splenic infarct. Mortality occurred in five (26.3%) patients but the cause of death was unrelated to gastrointestinal bleeding with the exception of one patient who developed hemoperitoneum.

CONCLUSIONS: The high rates of both acute hemostasis and recurrent bleeding suggest that Hemospray may be used in high-risk cases as a temporary measure or a bridge toward more definitive therapy.

Key Words: Efficacy; Hemospray; Safety; Upper gastrointestinal bleeding

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Received for publication October 17, 2013. Accepted November 3, 2013

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Can J Gastroenterol Hepatol Vol 28 No 2 February 2014
METHODS

From February 2012 to July 2013, 19 patients who required endoscopic evaluation for suspected UGIB were treated with Hemospray. A retrospective chart review was performed collecting demographic data (age and sex); clinical data (symptoms, vital signs, medical history and medications); diagnostic data (complete blood count, renal function, coagulation study and endoscopic findings); and therapeutic data (resuscitative measures, hemostatic interventions and hemostatic outcomes). All patients provided written informed consent for study participation. The study was approved by the institutional review board.

Patients were resuscitated as needed to achieve hemodynamic stability before undergoing endoscopy. Hemospray was used as monotherapy (Hemospray only); first-line modality (Hemospray followed by conventional endoscopic therapy) or rescue modality (conventional endoscopic therapy followed by Hemospray) at the discretion of the endoscopist. Hemospray was delivered through a 10 Fr catheter that was inserted into the working channel of a therapeutic endoscope (Olympus, Japan). The bleeding site was observed for 5 min under endoscopy and, if recurrent bleeding occurred, Hemospray was reapplied as needed to a maximum of 20 g (one canister). Endoscopy was repeated and Hemospray was reapplied as needed in patients with clinical or laboratory evidence of recurrent bleeding.

The primary end point was acute hemostasis (defined as endoscopic observation of bleeding cessation for \( >5 \) min). The secondary end points were: recurrent bleeding at seven and 30 days (defined as clinical presentation of hematemesis or melena; hemoglobin level decrease \( >20 \) g/L within 48 h or direct visualization of active bleeding at the previously treated lesion at repeat endoscopy); mortality at seven and 30 days (related to gastrointestinal bleeding); and adverse events in hospital (related to Hemospray use). Hemospray failure was defined as the inability to achieve acute hemostasis after application of \( 20 \) g of Hemospray or recurrent bleeding despite application of Hemospray on two separate occasions.

RESULTS

Patient characteristics (Table 1)

A total of 19 patients (mean age 67.6 years; range 29 to 94 years; five [26.3%] women) with UGIB were treated with Hemospray during the study period (February 2012 to July 2013).

Clinical presentation included hematemesis in eight (42.1%) patients, melena in 17 (89.5%), presyncope in eight (42.1%) and syncope in one (5.3%). Physical examination revealed hypotension (systolic blood pressure <90 mmHg) in nine (47.4%) patients and tachycardia (heart rate >100 beats/min) in 10 (52.6%). Laboratory investigations showed a mean hemoglobin nadir of 72.3 g/L (normal range 135 g/L to 170 g/L), thrombocytopenia (platelets <150×10^9/L) in nine (47.4%) patients and coagulopathy (international normalized ratio \( >1.2 \)) in seven (38.9%).

Medication review found the use of antiplatelet agents in 11 (57.9%) patients and anticoagulants in 10 (52.6%). Acetylsalicylic acid, clopidogrel and heparin (therapeutic dose) were administered to one patient who presented with unstable angina before cardiac catheterization (patient 4) and another who was admitted for transfemoral closure of severe mitral prosthetic paravalvular leak (patient 2). Warfarin and heparin (therapeutic dose) were given to one patient who had developed bilateral deep vein thrombosis in the lower extremities (patient 7).

Endoscopic findings (Table 2)

A bleeding lesion was identified in the esophagus in one (5.3%) patient, the stomach in five (26.3%) and duodenum in 13 (68.4%). Bleeding originated from peptic ulcers in 12 (63.2%) patients, Dieulafoy lesions in two (10.5%), mucosal erosion in one (5.3%), angiodysplastic lesions in one (5.3%), ampullary site in one (5.3%), polypectomy site in one (5.3%) and an unidentified lesion in
TABLE 2
Endoscopic findings

| Patient | Location | Lesion | Stigmata |
|---------|----------|--------|----------|
| 1       | Gastric (prepylorus) | Ulcer | Oozing, clot |
| 2       | Gastric (cardia, fundus) | No discrete lesions | Adherent clots |
| 3       | Gastric (incisura) | Ulcers × 3 (5 mm) | Oozing |
| 4       | Gastric (fundus) | Angiodysplastic lesions × few | Oozing |
| 5       | Duodenal (D1/D2) | Ulcer | Multiple red spots, clean base |
| 6       | Duodenal (D2) | Ulcers × several | Spurting, visible vessel |
| 7       | Duodenal (D1/D2) | Ulcer (2 cm) | Oozing, large clot |
| 8       | Duodenal (D1/D2) | Dieulafoy lesion | Oozing |
| 9       | Duodenal (D1/D2) | Ulcer | Oozing, visible vessel |
| 10      | Esophageal (mid, 34 cm to 36 cm) | Dieulafoy lesions × 2 | Oozing, clot |
| 11      | Gastric (lesser curve) | Ulcer with distal varices (3 cm) | Oozing, surrounding clot |
| 12      | Duodenal (bulb) | Ulcer (hemi circumferential) | Spurting, visible vessel, adherent clots |
| 13      | Duodenal (D1/D2) | Ulcers × 2 (1.5 cm) | Spurting, visible vessel |
| 14      | Duodenal (D2) | Ulcers × 3 (hemi circumferential) | Adherent clots |
| 15      | Duodenal (D1/D2) | Erosion (linear) | Oozing |
| 16      | Duodenal (D1/D2) | Polyectomy site (3 cm, sessile) | Bleeding artery |
| 17      | Duodenal (major papilla) | Ulcer at ampullectomy site | Oozing, visible vessels × 4 |
| 18      | Duodenal (D1/D2) | Ulcers × multiple (7 mm to 8 mm) | Spurting, visible vessel |
| 19      | Duodenal (bulb) | Ulcer | No active bleeding |

D1 First part of the duodenum; D2 Second part of the duodenum

TABLE 3
Hemostatic interventions

| Patient | Hemospray* | Injection (volume) | Thermal | Mechanical (frequency) | Transarterial embolization | Surgical oversewing |
|---------|------------|--------------------|---------|-----------------------|---------------------------|---------------------|
| 1       | Rescue modality | Epinephrine (8 mL) | – | Clips (× 3) | – | – |
| 2       | Monotherapy | – | – | – | – | – |
| 3       | Monotherapy | – | – | – | – | – |
| 4       | Rescue modality | Epinephrine (4 mL) | – | – | – | – |
| 5       | Rescue modality | Epinephrine (8 mL) | BICAP cauter | Clips (× 2) | Yes | – |
| 6       | Rescue modality | Epinephrine (16 + 9 mL) | Cautery | Clips (× 5) | – | – |
| 7       | Rescue modality | Epinephrine (12 mL) | – | – | – | – |
| 8       | Rescue modality | Epinephrine (15 mL × 2) | Gold probe | – | – | – |
| 9       | Rescue modality | Epinephrine (6 mL) | BICAP cauter | – | – | – |
| 10      | Rescue modality | Epinephrine (2 + 6 mL) Tromboject sclerosant (2.5 mL) | – | Bands (× 5) | – | – |
| 11      | Rescue modality | Epinephrine (4 mL) | – | Clips (× 4) | – | – |
| 12      | Rescue modality | – | – | Clips (× 2) | Yes | – |
| 13      | Rescue modality | Epinephrine (8 mL) | Gold probe | Clips (× 6) | – | – |
| 14      | Rescue modality | Epinephrine x 2 | BICAP cauter | Clips (× 3) | – | Yes |
| 15      | Rescue modality | Epinephrine (3 mL) | – | – | – | – |
| 16      | Rescue modality | Epinephrine (3 mL) | Hot biopsy forceps | Clips (× 2) | – | – |
| 17      | First modality | Epinephrine (4.5 mL) | Hot cautery forceps | – | – | – |
| 18      | Rescue modality | Epinephrine (10 mL) | BICAP cauter | – | – | – |
| 19      | Rescue modality | Epinephrine (3 mL) | Cautery | – | – | – |

BICAP Bipolar electrocoagulation; First modality (Hemospray [*Cook Medical, USA] followed by conventional endoscopic therapy); Monotherapy (Hemospray only); Rescue modality (Conventional endoscopic therapy followed by Hemospray)

Hemostatic interventions (Table 3)
Hemospray was administered as monotherapy in two (10.5%) patients, first modality in one (5.3%) and rescue modality in 16 (84.2%). Other hemostatic modalities were injection methods in 16 (84.2%) patients, thermal methods in 10 (52.6%), mechanical methods in nine (47.4%), transarterial embolization in two (10.5%) and surgical oversewing in one (5.3%). Importantly, all four patients with spurt- ing hemorrhage were found to have hemodynamic instability, thrombocytopenia and coagulopathy.

Hemostatic outcomes (Table 4)
Hemospray was applied prophylactically to nonbleeding lesions in four (21.1%) patients and therapeutically to bleeding lesions in 15 (78.9%). Among patients with bleeding lesions, acute hemostasis was achieved in 14 of 15 (93.3%). The one patient who did not achieve acute hemosta- sis essentially had Hemospray failure and, ultimately, required transarterial embolization for spurtting hemorrhage. Recurrent bleeding was found in seven of 18 (38.9%) patients and all developed within seven days of Hemospray application to lesions with spurting hemor- rhage in two, oozing hemorrhage in three and no active bleeding in two. One of these patients required transarterial embolization and another required surgical oversewing. Repeat endoscopy was per- formed in seven (38.9%) patients and all occurred within seven days with the exception of one patient who received it at seven weeks. Four of these patients were found to have active bleeding of the previously treated lesion at repeat endoscopy, and Hemospray was reapplied to the one patient who only had minor oozing with acute hemostasis once again achieved.

Adverse events (Table 4)
Adverse events potentially related to Hemospray use were identified in two (10.5%) patients. One patient developed acute abdominal distension
with hemoperitoneum on diagnostic paracentesis in the hours following Hemospray application; however, a coroner’s autopsy was not performed to determine whether visceral perforation had occurred. This patient was admitted with severe mitral prosthetic paravalvular leak requiring percutaneous transfemoral closure. He had a history of hypertension, coronary artery disease, atrial fibrillation, congestive heart failure and chronic kidney disease. Another patient developed radiological evidence of new-onset splenic infarct on abdominal computed tomography scan after Hemospray use. This patient was admitted for a compound fracture of the left proximal tibia requiring open reduction and internal fixation. She had a history of hepatic steatosis, cholelithiasis, end-stage renal disease, gout and osteoporosis.

Mortality (Table 4)
Mortality occurred in five (26.3%) patients; however, with the exception of the patient who had developed hemoperitoneum and hypovolemic shock on day 0, the cause of death in the other four patients was not directly related to gastrointestinal bleeding. These included hospital-acquired pneumonia on day 13; hemodialysis withdrawal secondary to arteriogenous fistula blockage on day 21; acute renal failure and newly diagnosed cryptogenic cirrhosis on day 12; and methicillin-susceptible bacteremia and ventilator-acquired pneumonia on day 74.

DISCUSSION
Our study examined the use of Hemospray in UGIB (n=19), which originated from peptic ulcers in 63.2% of patients. Hemospray was frequently administered as a rescue modality (84.2%), with an overall rate of acute hemostasis in 93.3% and rebleeding in 38.9% of patients. In the largest four case series performed by Sung et al (3 [n=20]), Smith et al (4 [n=82]), Holster et al (6 [n=16]) and Leblanc et al (12 [n=17]), Hemospray was used as monotherapy in 50% to 95%, first modality in 0% to 19% and rescue modality in 0% to 33% of patients, with an overall rate of acute hemostasis in 81% to 100%, and recurrent bleeding in 11% to 31%. The higher rates of recurrent bleeding and Hemospray use as a rescue modality in our study could be due to selection bias in the tertiary care setting, with frequent encounters of thrombocytopenia (47.4%), coagulopathy (38.9%), antiplatelet use (57.9%), anticoagulant use (52.6%) and spurring hemorrhage (21.1%).

Our finding that spurring hemorrhage was present in the one patient in whom acute hemostasis was not achieved with Hemospray is consistent with the experience of Sung et al (3) and Holster et al (6); however, Leblanc et al (12) reported effective control of pulsatile bleeding with Hemospray. Recurrent bleeding may be expected to occur because the hemostatic powder does not directly induce healing of the underlying lesion and is sloughed off from the mucosal wall within two to three days, leaving behind a clean remnant (10,11). The high rates of both acute hemostasis and recurrent bleeding suggest that Hemospray is probably best used as a bridge toward more definitive therapy such as transjugular intrahepatic portosystemic shunt in variceal bleeding (8) and radiation therapy in malignancy-related bleeding (11).

One patient in our study developed hemoperitoneum on day 0 and another developed splenic infarct on day 29, although it remained unclear whether these were directly related to Hemospray use. Perforation appears unlikely because the pressure of carbon dioxide is only 12 mmHg when the catheter is placed at 1 cm to 2 cm from the target lesion (10). Embolization also appears unlikely based on the safety study performed in a porcine model by Giday et al (17) using a sevenfold greater dose of Hemospray than that used in most clinical cases; the authors found no histological evidence of powder embolization in systemic tissues including the spleen. In addition, case reports and series in humans have not reported the theoretical risks of Hemospray including thromboembolism, bowel perforation, bowel obstruction, coagulopathy, allergic reaction and powder inhalation (3-13). Transient biliary obstruction has been reported after Hemospray use in post sphincterotomy bleeding (13). However, this did not occur in our patient, who received Hemospray for bleeding from an ampullotomy site because a biliary stent had been previously inserted. Despite its apparent safety from limited data in short-term
studies, Hemospray is contraindicated in variceal bleeding with low venous pressure and numerous collateral shunts due to the risk of thromboembolism (7), and in diverticular bleeding with thin mucosal wall and narrowed bowel lumen due to the risk of perforation and obstruction (10).

Conventional endoscopic therapies have been shown to be effective in increasing the rates of recurrent bleeding, blood transfusion and surgical intervention in UGIB, but the mortality rate has remained at 7% to 10% in the past 30 years (18). It is, therefore, necessary to explore alternative methods of endoscopic hemostasis. Hemospray is a welcome addition to our current armamentarium given its many advantages. First, the ease of application without the need for advanced technical skills is desirable in emergency situations in which expert endoscopists are unavailable (12). Second, accurate localization and precise targeting are not necessary, making it useful in challenging anatomy compounded by endoscope angulations (10). Third, direct mucosal contact does not occur, reducing the risk of further tissue damage that could worsen bleeding and even result in perforation (11,12). Fourth, its ability to cover large areas with multiple bleeding points makes it a suitable choice for hemorrhagic gastritis, gastric antral vascular ectasia, radiation-induced fusion and surgical intervention in UGIB, but the mortality rate has increased in more recent studies, Hemospray being contraindicated in variceal bleeding with low venous pressure and numerous collateral shunts due to the risk of thromboembolism (7), and in diverticular bleeding with thin mucosal wall and narrowed bowel lumen due to the risk of perforation and obstruction (10).

CONCLUSION

Hemospray appears to allow safe control of acute bleeding and may be used in high-risk cases as a temporary measure or a bridge toward more definitive therapy.

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DISCLOSURES: The authors have no financial disclosures or conflicts of interest to declare.
