Hemospray® Endoscopic Hemostat

The summary of clinical data presented below will be available on the Cook Medical website at **CookMedical.com/HemosprayData**

SUMMARY OF CLINICAL DATA

Cook Medical reports on 3 clinical studies and 1 survey of the use of Hemospray® Outside the United States (OUS). In addition, information from published literature of relevant studies comprising the treatment of 522 patients with Hemospray® was also evaluated. The first study was a feasibility study conducted in Hong Kong. The Survey to Evaluate the Application of Hemospray® in the Luminal Tract (SEAL) was conducted in Canada, Denmark, England, France, Germany, Italy and Holland with over 100 patients, primarily with upper gastrointestinal bleeding. Hemospray® is approved for use in upper gastrointestinal nonvariceal bleeding in Europe and both upper and lower gastrointestinal nonvariceal bleeding in Canada. There were two additional studies which include the Hemostasis of Active GI Luminal Tract Bleeding (HALT) study and A Prospective Observational Cohort Study of Hemospray® for Lower Gastrointestinal Hemorrhage (APPROACH) study. Published clinical literature information was cited for use as historical control data for evaluation of each of these single-armed studies.

The feasibility study was completed on 20 patients who presented with non-variceal upper gastrointestinal bleeding (NVUGIB). All 20 patients included in this study presented with melena at hospital admission, 7 of whom also had concurrent hematemesis. Nineteen patients were diagnosed with a Forrest 1b ulcer and 1 patient had Forrest 1a bleeding. Most ulcers were in the duodenum 14 (70%), and the remaining 6 (30%) were in the stomach. The number of syringes of Hemospray® used for each patient ranged between 1 and 7, with most patients (13/20, 65%) receiving only 1 syringe (20g Hemospray® powder). One patient with an unrecognized submucosal pseudoaneurysm failed all modalities of treatment including Hemospray®. Angioembolization was ultimately required to successfully stop the bleeding. Acute (procedural) hemostasis was achieved in 19 of 20 patients (95%). There were no treatment-related or procedure-related serious adverse events. Two patients met the study definition of recurrent bleeding or rebleeding within 72 hours. However, in both patients, no active bleeding was observed at the treated lesion sites at the planned second-look endoscopy. Neither patient reported adverse events nor serious adverse events at 30-day follow-up.

The SEAL registry survey included data from 89 evaluable patients collected from 2013-2015 in the European Union and Canada primarily with upper gastrointestinal bleeding. Acute hemostasis was achieved in all (100%) cases. There were no unanticipated adverse events or serious adverse events attributed to Hemospray®.

Holster I.L, et. al., published a study of patients with upper gastrointestinal bleeding who were on antithrombotic therapy. Patients on antithrombotics had 63% initial hemostasis with a 38% rebleeding rate following Hemospray® treatment. The majority of patients on antithrombotic therapy were on antiplatelet therapy with only a few patients on anticoagulants.

The HALT trial began on December 15, 2011 and was designed to study the safety and effectiveness of Hemospray® in treating upper GI bleeds (UGIB), specifically Forrest 1a and 1b actively bleeding ulcers. The HALT trial continues to enroll patients in Canada and Europe with an ultimate goal of 80 patients. An interim report of the study's findings on 64 patients was performed. The data lock was instituted on August 24, 2016. The HALT study was initiated with Version 1 of the Hemospray® device (55 psi CO2 canisters), but all sites were converted to the Version 2 device (37 psi CO2 canisters) effective January 2013. There are 10 enrollment sites. Initial hemostasis was achieved using Hemospray® as a single-modality treatment method in 88.9% (56/63) of cases. Initial hemostasis was defined as patients with hemostasis at the conclusion of the index procedure, where 'index procedure' is considered to be the application of Hemospray® and a 5-minute observation period. Patients that did not achieve initial hemostasis with Hemospray® were treated with a variety of different techniques including clips, injection with epinephrine and hemostasis clips, injection and argon beam therapy, injection and thermal probe, conversion to surgical repair, and proton pump inhibitor (PPI) therapy.

Fifty-five patients completed their 30-day follow-up; eight patients exited the study prior to completion of 30-day follow-up. Of these eight, one patient died 2 days after the procedure, and one patient died 18 days after the procedure. Both deaths occurred after surgical intervention, one for bowel perforation and one for rebleeding, resulting in death from postoperative liver failure and pneumonia, respectively. Six other patients were lost to follow up prior to completing the study follow-up schedule.

The second study is the Canadian APPROACH study. APPROACH is designed to collect safety and performance data on nonvariceal lower gastrointestinal bleeding (NVLGIB). Although the rate of occurrence and mortality in NVLGIB is lower than UGIB, bleeding in the lower GI tract can become clinically significant and/or exacerbate existing co-morbidities. This prospective, single-arm, post-market study collected data on the safety and effectiveness of the Hemospray® device. The study enrolled 50 patients at 4 clinical sites in Canada. Patient enrollment and data collection were completed in October and November 2016, respectively. Hemostasis was achieved after the index procedural use of Hemospray® as an initial, supplemental, or rescue intervention treatment method in 98% of cases. Hemostasis, defined as the absence of persistent bleeding at the conclusion of the index colonoscopy, was achieved in all but one patient who had a visibly oozing and spurting bleed. One SAE was reported as a patient died from gastrointestinal bleeding secondary to pre-existing chronic idiopathic thrombocytopenia 27 days after the procedure. Six episodes of clinical signs and symptoms of lower GI bleeding were reported in five patients. Three of these cases were confirmed to have a recurrent bleed at the study lesion site. Two additional post-operative serious adverse events were reported in which clinical signs and symptoms of lower GI bleeding were not noted. Forty-eight patients completed their final follow-up. One patient exited the study prior to completion of the 14-day and 30-day follow-ups. No other patients were lost to follow up prior to completing the study follow-up schedule.

Published medical literature on 532 Hemospray® applications in 522 patients from Europe, Canada, and Asia report 97% hemostasis on index endoscopy and a 22% rate of rebleeding. Ninety-one percent of the literature reports are on the treatment of upper gastrointestinal bleeding with Hemospray®, while 9% of the reports include lower gastrointestinal bleeding cases. The literature reports consisted of the following levels of evidence:

- Level II: 12 registry-derived studies
- Level IV: single-arm retrospective or prospective studies, case series and case reports.

The information consists of thirty studies in which there were 532 Hemospray® applications in 522 patients. A 97% hemostasis rate was achieved with an overall re-bleeding rate of 23%. There were 2 instances of bowel perforation, which may have been attributed to the use of Hemospray®, and 2 aspiration pneumonias, which could not be attributed to Hemospray®. There were no reports of bowel powder impaction or thromboembolic events.

An additional 5 cases of emergency use Hemospray® application in critically ill, high-risk surgical patients in the United States were reported. Hemospray® was used after all other modalities of endoscopic treatment failed. Hemospray® stopped the upper gastrointestinal bleeding in all patients; none died of recurrent bleeding, and one died from progression of lymphoma during the time interval report. Examples of the types of bleeding included duodenoduodenostomy anastomotic bleeding, multiple esophageal ulcers in a coagulopathic patient, nonvariceal gastric bleeding in a patient with hepatitis C-associated cirrhosis and end-stage liver disease, and radiation esophagitis resulting in diffuse multiple bleeding ulcers.

Table 1: Summary of Hemospray® Clinical Experience

Study	N	Hemostasis on Index Endoscopy (%)	Re-bleed Rate (%)	30-day Mortality (%)	Bowel Perforation (%)	Powder Impaction (%)	Thromboembolic Event
Feasibility Study	**20**	95	10	0	0	0	0
SEAL Survey	**89**	100	19	5.6	3.4	0	0
HALT Study	**64**	97	20	3.2	3.1	0	0
APPROACH Study	**50**	100	10	2	0	0	0
Hemospray® Literature *	**522**	97.4	22	10.7	0.4	0	0
Emergency Use	**5**	100	0	20	0	0	0
Total	**750**	97.8	20.2	11.6	0.9	0	0

***Includes patients from the Feasibility Study and SEAL survey**

Two hundred eighty (280) OUS complaints were reported to the company [1.1.2013-12.31.2016]. Ten percent (10%) of these complaints required medical intervention. There were 4 deaths reported in the complaint data. Two deaths were related to patient co-morbidities and 2 may have been related to the device – one perforation, sepsis, and death, possibly from bowel over-inflation, and one death from exsanguination due to device malfunction. Table 2 below summarizes the complaint data, stratified by Risk Severity Score (RSS)a. A RSS score less than 3 does not represent clinical events. Scores 5 and above required medical intervention.

Table 2: Risk Severity Score

RSS Value:	2	3	4	5	6	7	10
Number of Complaint Reports	**1**	**246**	**3**	**16**	**4**	**6**	**4**
Description of Harm	Label damage	Low impact, loss of all or part of device function; nuisance to patient or end user	Negligible harm; harm not requiring medical intervention	Minor harm; harm requiring medical intervention	Moderate harm; harm requiring medical intervention	Significant harm; harm resulting in hospitalization, major	Critical harm; death.

[a] Risk Severity Score (RSS) Requiring Medical Intervention

RSS 10: 4 deaths – 2 comorbidities, 1 perforation sepsis, 1 device malfunction resulting in exsanguination

RSS 7: 5 re-bleed, 1 perforation requiring surgery

RSS 6: less significant re-bleed, 1 requiring surgery

RSS 5: re-bleed, stricture, failed hemostasis

Conclusions:

- Hemospray® has been used as primary treatment of nonvariceal gastrointestinal bleeding, rescue therapy, adjunctive therapy, bridging therapy, and, in some cases, prophylactic therapy after polyp excision or mucosectomy. Both upper gastrointestinal and lower gastrointestinal nonvariceal bleeding have been treated with Hemospray® outside the United States with few reports of device-related adverse events and possible device-related adverse events. In all these clinical applications of Hemospray®, initial hemostasis was achieved in over 95% of patients.
- The HALT and APPROACH studies were prospective, OUS, single-armed studies that demonstrated the effectiveness of Hemospray® in treating both upper and lower gastrointestinal bleeding.
- Complaint data resulted in label warnings and device manufacturing changes to limit the risk of bowel perforation and device malfunction.
- In patients on antithrombotic therapy (ATT), Hemospray® treatment resulted in 63% initial hemostasis and 38% re-bleed rate. (Holster et.al., 2013)

Pediatric Extrapolation:

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

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