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Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.15579

GASTROENTEROLOGY

Hemostatic powder TC-325 treatment of malignancy-related upper gastrointestinal bleeds: International registry outcomes

Mohamed Hussein,*,†††,***** Durayd Alzoubaidi,* Michael O'Donnell,§§§§ Alvaro de laSerna,† Paul Bassett,¶¶¶¶ Ioannis Varbobitis,‡ Tricia Hengehold,§ Jacobo Ortiz Fernandez-Sordo,‡ Johannes W Rey,¶ Bu'Hussain Hayee,** Edward J Despott,†† Alberto Murino,†† David Graham,††† Melissa Latorre,§§§§ Sulleman Moreea,‡‡ Phillip Boger,§§ Jason Dunn,¶¶ Inder Mainie,*** Daniel Mullady,§ Dayna Early,§ Krish Ragunath,‡ John Anderson,‡‡‡ Pradeep Bhandari,§§§ Martin Goetz,¶¶¶ Ralf Kiesslich,**** Emmanuel Coron,†††† Enrique Rodriguez de Santiago,† Tamas Gonda,‡‡‡‡ Seth A Gross,§§§§ Laurence B Lovat*,†††,***** and Rehan Haidry*,†††,*****

*Division of Surgery and Interventional Science, University College London (UCL), **Department of Gastroenterology, Kings College Hospital, ††Royal Free Unit for Endoscopy and Centre for Gastroenterology, Royal Free NHS Foundation Trust, ¶¶Department of Gastroenterology, Guy's and St Thomas' Foundation Trust, †††Department of Gastroenterology, University college London hospital (UCLH), *****Wellcome/EPSRC Centre for Interventional and Surgical Sciences (WEISS), University College London, London, ‡NIHR Nottingham Digestive Diseases Biomedical Research Centre, Nottingham University Hospitals, Nottingham, ‡‡Department of Gastroenterology, Bradford Teaching Hospitals Foundation Trust, Bradford, §§Department of Gastroenterology, University Hospital Southampton NHS Foundation Trust, Southampton, ***Department of Gastroenterology, Belfast Health and Social Care Trust, Belfast, ‡‡‡Department of Gastroenterology, Gloucestershire Hospitals NHS Foundation Trust - Cheltenham General Hospital, Cheltenham, §§§Department of Gastroenterology, Portsmouth Hospitals NHS Trust, Portsmouth, ¶¶¶¶Statsconsultancy Ltd, Amersham, UK; †Department of Gastroenterology and Hepatology, Ramon y Cajal University Hospital, IRYCIS, University of Alcala, Madrid, Spain; §Department of Gastroenterology, Washington University School of Medicine in St. Louis, St. Louis, Missouri, ‡‡‡‡Columbia University Medical Centre, §§§§NYU Langone, New York, USA; ¶Department of Gastroenterology, Osnabrück Clinic, Osnabrück, ¶¶¶Sindelfingen-Böblingen Clinic, Böblingen, ****Horst Schmidt Clinics, Wiesbaden, Germany; ††††Department of Gastroenterology, University Hospital Center, Nantes, France

Key words
endoscopy, malignancy, non-variceal, upper gastrointestinal bleeding, upper GI.

Accepted for publication 5 June 2021.

Correspondence
Dr Mohamed Hussein, Division of Surgery and Interventional Science, University College London (UCL), 43-45 Foley Street, London W1W 7TS, UK.
Email: mohamed.hussein@ucl.ac.uk

Declaration of conflict of interest:
M.H. received speaker fees (Cook Medical). R.H received educational grants to support research infrastructure from Medtronic Ltd, Cook Endoscopy (fellowship support), Pentax Europe, C2 Therapeutics, Beamline Diagnostic, Fractyl Ltd. A.M. acted as a consultant for Boston Scientific and GI supply and received academic grants from Fujifilm, Aquilant Endoscopy, Norgine, and Olympus. B.H. received research grants from Fujifilm EU, Olympus UK, Takeda Pharmaceuticals UK, AbbVie UK. The remaining authors have no conflicts of interests to declare.
Financial support: RH (Chief investigator) has received research grant support from Cook Endoscopy to support research infrastructure.

Abstract

Background and Aim: Upper gastrointestinal tumors account for 5% of upper gastrointestinal bleeds. These patients are challenging to treat due to the diffuse nature of the neoplastic bleeding lesions, high rebleeding rates, and significant transfusion requirements. TC-325 (Cook Medical, North Carolina, USA) is a hemostatic powder for gastrointestinal bleeding. The aim of this study was to examine the outcomes of upper gastrointestinal bleeds secondary to tumors treated with Hemospray therapy.
Methods: Data were prospectively collected on the use of Hemospray from 17 centers. Hemospray was used during emergency endoscopy for upper gastrointestinal bleeds secondary to tumors at the discretion of the endoscopist as a monotherapy, dual therapy with standard hemostatic techniques, or rescue therapy.
Results: One hundred and five patients with upper gastrointestinal bleeds secondary to tumors were recruited. The median Blatchford score at baseline was 10 (interquartile range [IQR], 7–12). The median Rockall score was 8 (IQR, 7–9). Immediate hemostasis was achieved in 102/105 (97%) patients, 15% of patients had a 30-day rebleed, 20% of patients died within 30 days (all-cause mortality). There was a significant improvement in transfusion requirements following treatment ($P < 0.001$) when comparing the number of units transfused 3 weeks before and after treatment. The mean reduction was one unit per patient.
Conclusions: Hemospray achieved high rates of immediate hemostasis, with comparable rebleed rates following treatment of tumor-related upper gastrointestinal bleeds. Hemospray helped in improving transfusion requirements in these patients. This allows for patient stabilization and bridges towards definitive surgery or radiotherapy to treat the underlying tumor.

LBL is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre and the CRUK Experimental Cancer Medicine Centre at UCL. RH and LBL are supported by the Wellcome/EPSRC Centre for Interventional and Surgical Sciences (WEISS) at UCL (203145Z/16/Z).

Background

Tumor-related upper gastrointestinal (UGI) bleeding accounts for 5% of all UGI bleeds.[1] It can present in a number of ways ranging from chronic low volume bleeding to acute hemodynamic compromise.[2] Bleeding occurs following local invasion of the tumor causing vessel damage.[3] Endoscopy is the first line treatment; however, standard modalities have variable hemostasis rates as low as 40% and high rebleed rates up to 30%.[4] Most importantly, these interventions often reduce the transfusion requirements of blood products that will often impact significantly on the quality of life and long-term outcome of these patients. Limitations of current treatment methods are the requirement of a degree of expertise and direct tumor surface contact. These are a difficult cohort of patients to treat in view of their poor underlying clinical status, comorbidities, friable and diffusely bleeding tumor tissue surface causing a high level of unsuccessful endoscopic hemostatic outcomes.[3]

Embolization, radiotherapy, and surgery can provide a more definitive management for these patients. However, in the setting of an acute UGI bleed, surgery is associated with higher rates of morbidity and mortality, and radiotherapy is not so useful in acute GI bleed scenarios albeit effective during subacute blood loss, and interventional radiological embolization is associated with high rebleed rates.[5] An effective hemostatic endoscopic therapy is required as a bridge towards more definitive management and to minimize transfusion requirements in patients being managed conservatively. Low level blood loss and blood product requirements can physiologically compromise these patients and preclude towards definitive oncotherapy. A systematic review showed a 65% increase in mortality in cancer patients with anemia.[6]

TC-325 (Hemospray; Cook Medical, Winston-Salem, North Carolina, USA) is a hemostatic mineral-based powder. It consists of an inorganic and absorbable powder that is sprayed across the bleeding tumor surface formulating an adherent and stable barrier achieving hemostasis[7] (Fig. 1). Current American Gastroenterological Association guidelines recommend the use of hemostatic powder noncontact endoscopic options in diffuse malignancy bleeding.[8]

Our group previously briefly published overall outcomes from the international hemospray registry showing promising initial outcomes on 50 patients with malignancy-related UGI bleeds. We now present more than double the number of patients and assess new and important outcomes and subanalysis.[9]

The aim of this study is to assess immediate hemostasis rates following treatment with Hemospray. Secondary outcomes included 30-day rebleeding rate, change in transfusion requirements, and 7-day and 30-day mortality following treatment.

Methods

All consecutive patients with an underlying UGI malignancy treated with TC-325 and presenting with a malignancy-related UGI bleed were included. They were treated endoscopically with Hemospray either as monotherapy, in combination with standard of care adjuncts or as rescue therapy. The decision to use Hemospray was at the endoscopists' discretion. All endoscopists were trained on the use of Hemospray.

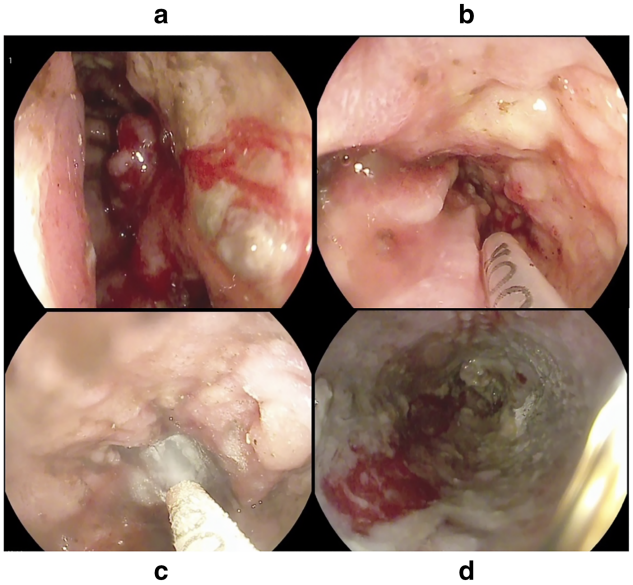

Figure 1 A bleeding esophageal tumor (a) Hemospray is applied (b and c), and immediate hemostasis is achieved (d).

Patients were recruited from 17 centers in the United Kingdom, the United States, France, Germany, and Spain (January 2016 to March 2020). All patients provided informed consent for the procedure and study inclusion.

All patients were scored using both the Rockall and Blatchford scoring systems. The Blatchford score helps assess the likelihood patients will need urgent endoscopic intervention.[10] The Rockall score estimates mortality in patients with an active UGI bleed.[11]

The following definitions were used during the study:

- Immediate hemostasis: Complete cessation of bleeding 5 min after the Hemospray application.
- Reduction in blood products: Reduction in the number of blood units transfused 21 days after treatment with Hemospray compared with 21 days before treatment.
- Hemospray monotherapy: Hemospray is used alone to treat a bleed following which the site is viewed for 5 min to assess for immediate hemostasis.
- Hemospray combination therapy: Hemospray is used in combination with either one or two other standard of care adjuncts to treat a bleed. The site is viewed for 5 min to assess for immediate hemostasis. The order that Hemospray is used was at the endoscopists' discretion.
- Hemospray rescue therapy: One or more standards of care devices are used to treat a bleed following which there is persistent intraprocedural bleeding during the same endoscopic session; therefore, Hemospray is used as a rescue therapy.
- Rebleeding: A drop in hemoglobin (> 2 g/L) or new melena/hematemesis with hemodynamic instability or requirement of further blood products following the index procedure with Hemospray treatment.

The primary outcome was immediate hemostasis rates following endoscopic treatment of a malignancy-related UGI bleed with

Hemospray. Secondary outcomes were reduction in blood transfusion requirements, 30-day rebleed rates, and 7- and 30-day mortality.

Patients were followed up for 30 days after the completion of the index procedure. The number of units of blood transfused was collected 3 weeks before and 3 weeks after treatment with Hemospray. All the data were inputted into an anonymized and customized database.

The study received ethical approval (London - South East Research Ethics Committee) (ISRCTN registry with study ID ISRCTN29594250). All participating centers received local approval.

Statistical analysis

For the binary outcomes, the occurrence of each outcome was quantified as a percentage of patients in which the outcome occurred.

Factors associated with each outcome were examined. For the binary outcomes, the analyses were performed using logistic regression. The separate association between each factor and the outcomes were examined separately in a series of univariate analyses.

The change in transfusion requirements was measured on a continuous scale. This was measured by the difference in the number of units of blood transfused 21 days before and 21 days after treatment with Hemospray. Initially, the change in blood units between time points was examined. The change in values was found to be approximately normally distributed, and thus, the paired *t*-test was used for analysis.

Results

Between January 2016 and March 2020, 105 patients were enrolled into the study. Sixty-seven percent of patients were male. The median age is 71 (interquartile range [IQR], 60–98) years of age. The median overall Rockall score was 8 (IQR, 7–9), and median Blatchford score was 10 (IQR, 7–12). Sixty-nine over one hundred and five (66%) of the malignancies were in the stomach and 30/105 (29%) in the esophagus (Table 1). Six over one hundred and five (6%) were spurting malignancy-related bleeds, 81/105 (77%) were oozing bleeds, and 13/105 (12%) had a visible vessel/adherent clots on endoscopy.

Table 1 Demographics of the patient cohort

January 2016 to March 2020 (*N* = 105)	
Median age, years (IQR)	71 (60–98)
Male (%)	70/105 (67%)
Female (%)	35/105 (33%)
Antiplatelets (%)	12/103 (12%)
Anticoagulation (%)	17/103 (17%)
Median lesion size, mm (IQR)	25 (12–44)
ASA physical classification	
3	43/103 (42%)
4	23/103 (22%)
5	1/103 (1%)
Tumor location	
Esophagus/GOJ	30/105 (29%)
Stomach	69/105 (66%)
Duodenum	6/105 (6%)

ASA, American Society of Anesthesiologists; GOJ, gastroesophageal junction; IQR, interquartile range.

Table 2 Overall outcomes following treatment with Hemospray

Variable	Outcomes (*N* = 105)	Rockall score	Blatchford score
Hemostasis	102/105 (97%)	8 (IQR, 7–9)	10 (IQR, 7–12)
Rebleeding	13/87 (15%)	7 (IQR, 7–8)	10 (IQR, 9–12)
7-day mortality	4/90 (4%)	8	13 (IQR, 11–14)
30-day mortality	18/90 (20%)	8 (IQR, 7–9)	12 (IQR, 10–15)

IQR, interquartile range.

Immediate hemostasis was achieved in 102/105 (97%) patients following treatment with Hemospray. Rebleeding occurred in 13/87 (15%) of patients within 30 days of treatment. Nine over thirteen (69%) of rebleeds were more than 4 days after treatment. Of the 13 patients with rebleeding, three patients had one repeat endoscopy within 30 days of index endoscopy. On two endoscopies, there was no bleeding that required treatment, and on one endoscopy, a repeat treatment with Hemospray on Day 26 following index endoscopy was performed. Patients with oozing bleeds achieved a 98% immediate hemostasis rate, 16% 30-day rebleed rate and 20% 30-day mortality following treatment with Hemospray. Seventy-two percent of these patients were treated with Hemospray monotherapy.

All-cause mortality within 30 days occurred in 18/90 (20%) patients (Table 2). Mortality and rebleeding data were missing for 15 patients. A median number of eight Hemospray applications were required to achieve hemostasis. In the three patients where immediate endoscopic hemostasis was not achieved, two patients were managed conservatively, and one patient was treated with a further endoscopic session with argon plasma coagulation (APC). One of the patients managed conservatively was the only mortality within 30 days.

Twelve patients had a repeat endoscopy within 30 days of their index procedure. Eight of the patients overall had no bleeding evident on the repeat endoscopy, and therefore, no intervention was required. In the four remaining patients, one patient had further treatment with APC, one patient had a further treatment with Hemospray, one patient was managed conservatively, and one patient proceeded to have surgery.

Seventy over one hundred and five (67%) patients received Hemospray treatment as a monotherapy, where an immediate hemostasis rate of 100% was achieved with a 30-day rebleed rate of 15%. Twenty-six over one hundred and five (25%) patients received treatment as part of a combination therapy, where an immediate hemostasis rate of 88% was achieved and 30-day rebleed rate of 18% (Table 3). There were no complications associated with the use of Hemospray.

Ninety-nine percent of patients with gastric malignancy-related UGI bleeds achieved immediate hemostasis following treatment with Hemospray with a 30-day rebleed rate of 14%. Ninety-three percent of patients with esophageal malignancy-related UGI bleeds achieved hemostasis following treatment with a 30-day rebleed rate of 17% (Table 4). There was a significantly lower 30-day mortality rate in the gastric cohort *versus* the esophageal

Table 3 Outcomes in the Hemospray monotherapy, combination, and rescue therapy subgroups

Variable	Monotherapy	Combination	Rescue
	(*N* = 70)	(*N* = 26)	(*N* = 9)
Hemostasis	70/70 (100%)	23/26 (88%)	9/9 (100%)
Blatchford	10 (IQR, 7–12)	10 (IQR, 7–13)	12 (IQR, 10–13)
Rockall	8 (IQR, 7–9)	8 (IQR, 7–9)	7, (IQR, 6–9)
Rebleed	9/62 (15%)	3/17 (18%)	1/8 (13%)
7-day mortality	4/62 (6%)	0	0
30-day mortality	14/62 (23%)	4/20 (20%)	0

IQR, interquartile range.

Table 4 Outcomes following treatment based on location of malignancy in the upper gastrointestinal tract

Variable	Esophagus	Stomach	Duodenum
	(*N* = 30)	(*N* = 69)	(*N* = 6)
Hemostasis rate	28/30 (93%)	68/69 (99%)	6/6 (100%)
Blatchford score	10 (IQR, 7–12)	10 (IQR, 8–12)	11 (IQR, 8–12)
Rockall score	8 (IQR, 7–9)	8 (IQR, 7–9)	8 (IQR, 8–9)
30-day rebleed	4/23 (17%)	8/59 (14%)	1/5 (20%)
7-day mortality	2/25 (8%)	2/60 (3%)	0
30-day mortality	9/25 (36%)	9/60 (15%)	0

IQR, interquartile range.

cohort ($P < 0.05$) (Table S1). The odds of 30-day mortality associated with bleeds secondary to gastric malignancies were three times lower than esophageal malignancy-related bleeds following treatment with Hemospray.

Risk factors for rebleeding and 30-day mortality after treatment with Hemospray

There were no factors significantly associated with occurrence of rebleeding (Table S2). Univariable analysis suggested that malignancy site and Blatchford score were significantly associated with 30-day mortality ($P < 0.05$) (Table S1). There was evidence of an association between urea and 30-day mortality of borderline statistical significance ($P = 0.05$).

The effect of Hemospray treatment on transfusion requirements

The mean number of units of blood transfused 3 weeks before treatment was 2.5 units ± 2.0 SD, and the mean number of units transfused 3 weeks following treatment was 1.5 units ± 2.5 in 73 patients. There was a significant reduction in units transfused following treatment with Hemospray therapy ($P < 0.001$) (Table 5). The mean reduction was one unit per patient. There was a significant reduction in transfusion requirements when Hemospray was used as a monotherapy ($P < 0.05$). Figure 2 illustrates the distribution of the changes in blood units from pre-Hemospray to post-Hemospray treatment (Fig. 2). Transfusion data were missing for 32 patients.

Discussion

Our study showed high immediate overall hemostasis rates of 97% and a reasonable rebleed rate of 15% in 105 patients presenting with malignancy-related UGI bleeds treated with Hemospray. Hemospray provides a promising alternative bridging option towards definitive treatment with surgery/radiotherapy in these patients. When sprayed across a tumor surface, it develops adhesive and cohesive properties. It is useful to apply in difficult positions and over a wide tumor surface area.[1] Malignancy-related UGI bleeds are challenging to treat and lead to frequent admissions and transfusion requirements. There is oozing from the tumor surface secondary to angiogenesis.[7] They are difficult to treat with conventional endoscopic modalities due to the large tumor surface area and tumor fragility, which can be exacerbated by direct contact. Loftus *et al* showed immediate hemostasis was achieved in 67% of patients with standard of care endoscopic therapy with re-bleeding in 80% of patients.[12]

To date, this is the largest study investigating the use of Hemospray in this cohort of patients. The next largest study was in a cohort of 79 patients with UGI malignancy-related bleeds, which showed an immediate hemostasis rate of 97.7% in the overall cohort (UGI and LGI malignancy bleeds) and a rebleeding rate of 27.3% all of which were in patients with UGI malignancies.[7] This study assesses outcomes in both upper and lower GI malignancy-related bleeds, whereas our study focuses on UGI malignancy-related bleeding. The presence of gastric juices in the stomach has a potential effect on the formation of fibrin clots therefore contributing to prolonged bleeding and having an effect on rebleeding rates.[13] We assess the outcomes based on the locations of the tumor in the UGI tract to help better determine which tumors will respond favorably to Hemospray. We subdivide the method of treatment into the monotherapy, combination, and rescue therapy subgroups. We hope this will help guide not just when to use Hemospray but how in these situations. Another new important factor we investigated was the change in transfusion requirements before and after treatment with TC-325 to try and help determine whether such treatment has an important role in slowing down bleeding. Our data also provide generalizability with results from 17 centers *versus* 2 centers on the second largest study.[7]

Other studies also showed a high immediate hemostasis rate.[14] A randomized controlled trial of 20 patients showed an immediate hemostasis rate of 90% in the TC-325 cohort *versus* 40% in the standard of care group. Recurrent bleeding after 180 days was 20% in the TC-325 cohort *versus* 60% in the standard of care cohort.[3] Another study of 10 patients showed a 14-day rebleed rate of 10% in the Hemospray group *versus* 30% in the standard of care group.[4] Table S3 summarizes the outcomes from studies evaluating Hemospray treatment in malignancy-related bleeding (Table S3).

Historically APC and laser therapy were considered treatments of choice for malignancy-related UGI bleeds. The disadvantage of such methods is that multiple treatment sessions are necessary. They are also not efficient for treating a large tumor surface. A retrospective study of 25 patients with malignancy-related

Table 5 Change in transfusion requirements after Hemospray treatment in upper gastrointestinal bleeds secondary to tumors

Variable		*N*	Blood units	Change in blood units	*P* value
			Mean ± SD	Mean (95% CI)	
All patients treated with Hemospray (monotherapy, combination and rescue therapy)	Pre-Hemospray	73	2.5 ± 2.0	0	< 0.001
	Post-Hemospray	73	1.5 ± 2.5	−1.0 (−1.6, −0.4)	
Patients treated with Hemospray monotherapy	Pre-Hemospray	45	2.3 ± 2.0	0	< 0.05
	Post-Hemospray	45	1.4 ± 2.5	−0.9 (−1.6, −0.1)	

CI, confidence interval; SD, standard deviation.

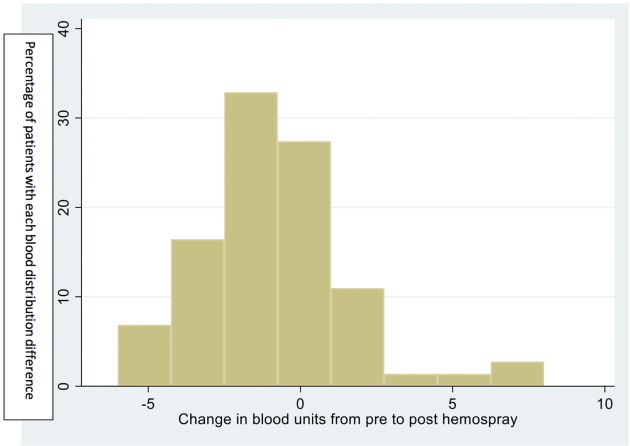

Figure 2 Histogram of the distribution of changes in blood units from pre-Hemospray to post-Hemospray treatment.

UGI bleeds treated with APC showed an initial hemostasis rate of 73% and 30-day rebleed rate of 33%.[15] Hemospray is noncontact and has a spray effect over a large tumor surface.

In our current study, a hemostasis rate of 100% was achieved when Hemospray was used as a monotherapy with a 30-day rebleed rate of 15%. In the Hemospray combination therapy cohort, there was a lower hemostasis rate of 88% and slightly higher 30-day rebleed rate of 18%. This may be due to disruption of the already fragile tumoral surface when using conventional modalities. The outcomes in the monotherapy cohort of 70 patients suggest that Hemospray could potentially be used as a first line monotherapy in the treatment of GI bleeds in these cohorts of patients as the use of additional standard endoscopic treatments did not show any significant added benefit. A significant improvement in transfusion requirements is also maintained in the monotherapy cohort of patients. Randomized control trials comparing the Hemospray monotherapy *versus* combination therapy subgroups is needed, as well as comparing hemospray *versus* standard of care treatments to confirm these findings.

There was higher hemostasis rate following treatment with Hemospray secondary to gastric malignancies (99%) with a significantly reduced 30-day mortality compared with the esophageal malignancy-related bleeds (15% *vs* 36%) ($P < 0.05$). Gastric cancer is associated with a 5-year survival of approximately 21% *versus* 16% in esophageal cancer.[16] The median survival following palliative treatment is 3–6 months in esophageal cancer.[17] This is likely to explain the higher mortality. Also, a likely contributory factor in this study is that 34% of patients in the esophageal cohort had an ASA grade of 4 or more *versus* 21% in the gastric cohort. Therefore, a larger proportion of patients had more significant comorbidities. A study showed most of the 20 patients treated for malignancy-related UGI bleeds died by 6 months due to the poor prognosis of the underlying diagnosis.[3]

The median Rockall score and Blatchford score were 8 and 10, respectively, in study. This shows a high-risk group of patients from tertiary hospitals that receive complex cancer referrals. The expected rebleed and mortality rate based on this Rockall score is 40%. The outcomes in this study performed better than that. A study showed that the Rockall is a useful scoring system for risk stratifying patients in terms of mortality; however; it was unsatisfactory for predicting rebleeding.[18]

Treatment with Hemospray significantly reduced transfusion requirements ($P < 0.001$). The significant improvement in transfusion requirements remained when Hemospray was used as a monotherapy. Patients can be stabilized and planned for the appropriate definitive intervention of either surgery/radiotherapy. A study of 10 patients treated with Hemospray following malignancy-related UGI bleeds showed that 40% of patients receiving treatment with Hemospray required blood transfusion *versus* 70% of patients in the standard of care arm.[3] Studies have shown that anemia is associated with a low quality of life in cancer patients.[19] We used the time period of 3 weeks before treatment as that is the critical time just before and during admission where more blood transfusion is required secondary to malignancy-related bleeding. We also assessed the number of units of blood required three units after treatment to mirror a similar time period.

There were no complications associated with the use of Hemospray in our current study. The lack of direct contact with a fragile tumor surface may have a role to play here.

There are a number of limitations to the study. It is not a randomized control trial. There may be selection bias as the decision to use Hemospray was at the discretion of endoscopists during the procedure. In future, we will ask endoscopist to include an explanation as to why Hemospray was used in each scenario. More long-term data are required for transfusion requirements to assess whether there is a long-term benefit particularly in patients being managed conservatively in terms of transfusion requirements, hospital readmissions, and requirement for further endoscopies. A limitation is data on whether definitive nonendoscopic

treatments were performed and at what time point were not collected. This is a potential confounding factor on transfusion requirements following index endoscopy. We have adjusted this in the registry such that these data are captured. There was some missing data on rebleeding, mortality, and transfusion. Data on the direct causes of mortality in each patient were not collected. The majority of patients had an ASA of 3 or more and the median Rockall score was 8 suggesting that mortality was likely secondary to underlying significant comorbidities in the majority of cases.

Our data show that Hemospray has a potential role as a first line monotherapy in the endoscopic management of UGI bleeds secondary to malignancy. The noncontact nature of this treatment minimizes disruption of the tumor surface, and it can be used over a wide area. The high hemostasis, reasonable rebleed, and significantly improved transfusion requirement suggest it may be useful as a bridge towards definitive therapy. Randomized control trials are required to confirm these results.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1: Univariable associations with 30-day mortality.
Table S2: Univariable analysis examining factors associated with re-bleeding.
Table S3: Summary from studies investigating outcomes of Hemospray treatment in malignancy related UGI bleeding.