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Efficacy of hemostatic powders as monotherapy or rescue therapy in gastrointestinal bleeding related to neoplastic or non-neoplastic lesions

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BACKGROUND Hemostatic powder (HP) in gastrointestinal bleeding (GIB) is mainly used as rescue therapy after failure of conventional hemostatic procedures (CHP).

AIM To define the best field of application and the efficacy of HP as first choice monotherapy or rescue therapy.

METHODS We compared the efficacy of HP monotherapy, HP rescue therapy, and CHP in the management of active GIB due to neoplastic and non-neoplastic lesions.

RESULTS A total of 108 patients, 43 treated with HP as either first choice or rescue therapy and 65 with CHP, were included in the study. The most frequent sources of bleeding were peptic ulcer and malignancy. Immediate hemostasis rates were: HP monotherapy = 100% in peptic ulcer and 100% in malignancy; HP rescue therapy = 93.2% in peptic ulcer and 85.7% in malignancy; CHP = 77.9% in peptic ulcer and 41.7 in malignancy. Definitive hemostasis rates were: HP monotherapy = 50% in peptic ulcer and 45.5% in malignancy; HP rescue therapy = 73.3% in peptic ulcer and 85.7% in malignancy; CHP = 69.1% in peptic ulcer and 33.3% in malignancy. No difference was found in terms of additional intervention between the three groups.

CONCLUSIONS HP is highly effective as monotherapy and rescue therapy in GIB. GIB related to malignancy may be the best field of application of HP, but confirmatory studies are necessary.

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Introduction

Gastrointestinal (GI) bleeding (GIB) is one of the most frequent causes of morbidity and mortality worldwide, with annual hospitalization rates of about 150 patients per 100,000 population and an annual mortality rate of 7%–10% [1–3]. Endoscopic hemostasis is the first choice approach and gold standard treatment for GIB. Conventional hemostatic procedures (CHP) include (i) injection agents, (ii) contact thermal devices such as heater probes, multipolar electrocautery probes, (iii) non-contact thermal devices such as argon plasma coagulation (APC), (iv) mechanical devices including hemostatic graspers, band ligators, clips, and loops, and (v) topical agents [3]. Efficacy of endoscopic hemostasis ranges from 67% to 100%, with a re-bleeding rate of 10%–30% [2,3]. Hemostatic powders (HP) were recently introduced for the treatment of acute GIB. Three forms of HP are currently available: Hemospray®, EndoClot®, and Ankaferd

Blood Stopper [4,5]. Several studies [6–14] reported the efficacy of HP as rescue therapy in GIB that cannot be controlled by CHP. However, the use of HP as monotherapy and in GIB from malignant lesions remains to be fully demonstrated.

The aim of the present study was to evaluate the efficacy and safety of HP as rescue therapy and monotherapy in non-vascular GIB from different neoplastic and non-neoplastic lesions not responding to or not amenable to treatment with CHP during emergency digestive endoscopy.

Patients and methods

Study design

From September 2017 to September 2019, all consecutive patients undergoing emergency endoscopy with active GIB at the Gastroenterology Unit of the University Hospital "Tor Vergata" were eligible for the study. Patients with GIB related to portal hypertension, angiodysplasia, or other vascular malformations were excluded as the investigation was focused on evaluating the efficacy of HP in non-vascular GIB. Recruitment was carried out prospectively and included only patients treated in the emergency department or hospitalized in other wards.

After written informed consent was obtained, all patients underwent upper or lower digestive endoscopy (colonoscopy) within 24 h from the occurrence of GIB. Once identified, the bleeding source was treated with CHP consisting of adrenaline infiltration associated with APC and/or hemostatic clip. HP was used as a rescue technique in the event of failure to stop the bleed with CHP, or as first choice monotherapy when a lesion was deemed as either not responding to CHP (e.g. malignancy with multiple oozing sites), at risk of severe adverse events if treated with thermal or mechanical CHP (e.g. large areas of mucosal denudation in esophagus), or not accessible to CHP due to anatomical location. HP used was Endoclot or Hemospray, and in both cases was sprayed over the lesion through a catheter.

After endoscopy, vital signs, hemoglobin, and hemodynamic parameters of all patients were monitored. In the case of re-bleeding, patients underwent a second-look endoscopy with a further hemostatic procedure. Patients not responding to hemostatic procedures underwent radiological embolization and/or surgery. In the case of upper GIB, patients received a high dose of a proton pump inhibitor (e.g. pantoprazole 80–200 mg/24 h by continous intravenous infusion) after the hemostatic procedure. All patients were followed up until the day of discharge and, when possible, in subsequent ambulatory visits. The study population therefore included patients treated with HP used as rescue therapy or first choice monotherapy *versus* patients treated only by CHP.

This was an observational, non-randomized, spontaneous investigation based on routine care procedures and did not receive any financial support from HP manufacturers. The study fulfilled the principles of the Declaration of Helsinki.

Data collection, outcomes, and statistical analysis

We collected demographic and clinical data including sex, age, symptoms at presentation, drugs in active therapy, clinical history of previous GIB, type of lesion causing GIB, hemostatic procedures, recurrent bleeding, additional intervention, number of blood units transfused, and number of days of hospitalization. The risk of patients before endoscopy was defined according to the Rockall score and the Glasgow–Blatchford score. Any adverse events were recorded.

The primary outcome was definitive hemostasis, defined as no further bleeding until discharge. Secondary outcomes were: immediate hemostasis, defined as the stop of bleeding after the hemostatic procedure with no evidence of bleeding after at least three minutes of observation [15]; recurrent bleeding, defined as the occurrence of symptoms (hematemesis, melena, hematochezia, and/or nasogastric tube aspirate with gross blood or coffee-ground material) or signs (hemoglobin drop with/without tachycardia or hypotension) suggesting further GIB within the 1st, 3rd, and 7th day following the hemostatic procedure and

the final day of hospital stay; additional intervention, namely endoscopic retreatment, radiological embolization, and surgery; transfusions, number of blood units required; length of hospital stay, days of hospitalization from endoscopic treatment to discharge; mortality, all deaths related or unrelated to GIB; safety, based on the occurrence of any adverse event, symptom or sign possibly associated with the use of HP.

For this study, the patients were divided into three groups based on hemostastic procedures received: HP Monotherapy, HP Rescue Therapy, and CHP. Data were analyzed using IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, N.Y., USA) and evaluated by univariate analysis, summarized with mean ± standard deviation for continuous variables and percentages for categorical items. Statistical significance was determined using Fisher's exact test or Chi-square test and Student's *t*-test or Kruskal–Wallis test. A P-value of <.05 was considered statistically significant.

Results

A total of 108 patients with active GIB were enrolled in the study, 65 were succesfully treated with CHP, 25 required HP rescue therapy due to persistent bleeding following CHP, and 18 received HP monotherapy. The majority of patients were male (65.7%), only a minority on anticoagulant (13.9%), antiplatelet (12%), or dual therapy (2.8%). A total of 26 patients (24%) had one or more comorbidities, the most frequent being heart diseases (ischemic disease, dilative cardiomyopathy), blood hypertension, chronic obstructive pulmonary disease, and diabetes. Melena was the most frequent (64.8%) sign of bleeding. High-risk scores were found at endoscopy, with a median Rockall score of 5.9 and a Glasgow-Blatchford score of 11.3. The most frequent sources of bleeding were peptic ulcer (66.7%) and malignancy (21.3%) (Table 1). Post-procedural follow-up had an average duration of 28.4 days (range: 2–154).

Table 1. Characteristics of study population at baseline endoscopy. (Table view)

Variable	All	Hemostatic powders		Conventional hemostatic procedures	*p* Value
		First choice	Rescue therapy		
	(*N* = 108)	(*N* = 18)	(*N* = 25)	(*N* = 65)	
Gender, female	37 (34)	3 (16.6)	10 (40)	24 (36.9)	.54
Age (years)	69 ± 15.8	65.8 ± 17.5	72.1 ± 13.4	70.2 ± 17.1	.89
Comorbidity	26 (24)	4 (22.2)	6 (24)	16 (24.6)	1
Alzheimer	1	1	–	–	–
Blood hypertension	22	4	3	15	–
Chronic obstructive pulmonary disease	6	–	2	4	–
Diabetes	6	2	–	4	–
Heart diseases	13	–	3	10	–
Psoriasis	1	–	–	1	–
Renal impairment	4	–	–	4	–
Rheumatoid arthritis	1	–	–	1	–
History of GIB	89 (82.4)	10 (55.5)	19 (76)	60 (92.3)	<.05
Antiplatelets	13 (12)	2 (11.1)	5 (20)	6 (9.2)	.36
Anticoagulant therapy	15 (13.9)	1 (5.5)	6 (24)	8 (12.3)	.58
Dual therapy	3 (2.8)	–	2 (8)	1 (1.5)	.56
Symptoms at presentation					

Variable	All	Hemostatic powders		Conventional hemostatic procedures	*p* Value
		First choice	Rescue therapy		
	(*N* = 108)	(*N* = 18)	(*N* = 25)	(*N* = 65)	
Melena	70 (64.8)	9 (50)	19 (76)	42 (64.6)	.21
Hematemesis	42 (38.8)	7 (38.9)	10 (40)	25 (38.4)	.84
Hematochezia	7 (6.5)	3 (16.6)	1 (4)	3 (4.6)	.15
Rockall Score	5.9 ± 1.6	5.5 ± 1.4	6.6 ± 1.5	6 ± 1.8	.45
Glasgow-Blatchford Score	11.3 ± 4.3	9.9 ± 2.2	11.6 ± 1.4	12 ± 2.7	<.05
Endoscopic findings					
Peptic ulcer	72 (66.7)	4 (22.2)	15 (60)	53 (81.5)	<.05
Forrest IA	15 (13.9)	–	3 (12)	12 (18.5)	–
Forrest IB	57 (52.8)	4 (22.2)	12 (48)	41 (63)	–
Malignancy	23 (21.3)	11 (61.1)	7 (28)	5 (7.7)	<.01
Post-endotherapy	–	–	–	–	1
Sphincterotomy	6 (5.5)	–	2 (8)	4 (6.1)	–
ESD	1 (0.9)	–	1(4)	–	–
Others	–	–	–	–	.68
GvHD-related esophageal ulcers	1 (0.9)	1 (5.5)	–	–	–
CHT-related esophageal ulcers	1 (0.9)	1 (5.5)	–	–	–
Colonic ulcer	1 (0.9)	1(5.5)	–	–	–
Diverticular disease	3 (2.8)	–	–	3 (4.6)	–

CHT: chemotherapy; ESD: endoscopic submucosa dissection; GvHD: graft-versus-host disease.
Values are *N* (%) or mean ± standard deviation.

Peptic ulcer disease

Seventy-two patients had GIB due to actively bleeding peptic ulcers, classified as Forrest IA in 15 patients and Forrest IB in 57 patients. Outcomes according to hemostatic procedure and Forrest score are shown in Table 2 and Figure 1. Of these 72 patients, 68 were treated with CHP, 53 of whom achieved immediate hemostasis (77.9%), while 15 required HP rescue therapy due to persistent bleeding. HP rescue therapy achieved immediate hemostasis in 14/15 patients (93.2%), while one patient did not respond and underwent surgery. The remaining four patients were treated with HP as first choice monotherapy due to difficult anatomical access (posterior wall of the apex of duodenal bulb) and all achieved immediate hemostasis (100%). Recurrent bleeding occurred in 6/53 patients (11.3%) who responded to CHP, in 3/14 patients (21.4%) who responded to HP rescue therapy, and in 2/4 patients (50%) treated with HP monotherapy. Of the six patients who re-bled following CHP, three re-treated with CHP achieved definitive hemostasis, while the remaining three underwent radiological embolization (two patients) or surgery (one patient) after failure of a further hemostasis attempt with CHP and HP. Of the three patients who re-bled following HP rescue

therapy, two were successfully re-treated with HP achieving definitive hemostasis, while one required surgery after unsuccessful radiological embolization. Both patients who re-bled following HP monotherapy were re-treated with HP; one patient achieved definitive hemostasis, while the other underwent surgery. The definitive hemostasis rate was similar in all three groups (11/15 [73.3%] in the HP Rescue Therapy Group, 2/4 [50%] in the HP Monotherapy Group, and 47/68 [69.1%] in the CHP Group). No differences were found when comparing immediate hemostasis rates and recurrent bleeding rates in the three groups. Mortality occurred in 3/72 patients (4.1%). Two patients, treated with CHP and suffering from ischemic heart disease, died of myocardial infarction. A third patient died during surgery after failure of HP rescue therapy and radiological embolization. No differences were found when comparing units of blood transfused and length of hospital stay in the three patient groups.

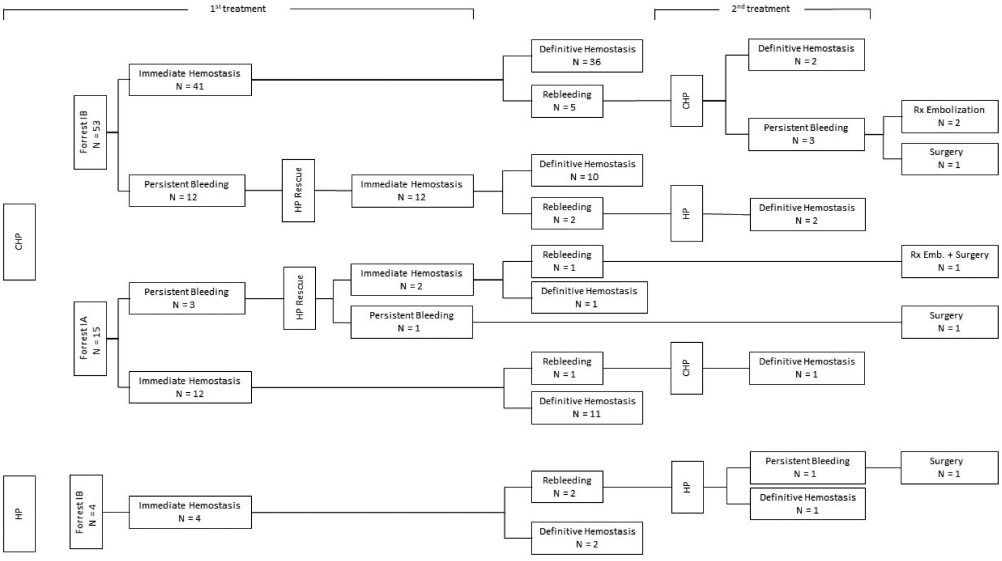

Figure 1. Outcome of patients with gastrointestinal bleeding due to peptic ulcer according to hemostatic procedures and Forrest score. CHP: conventional hemostatic procedures; HP: hemostatic powder.

Table 2. Outcomes in patients with benign ulcer (intention-to-treat). (Table view)

Variables	Hemostatic Powders		Conventional hemostatic procedures
	First choice	Rescue therapy	
No. patients	4	15	68
Forrest score			
IA	–	3	15
IB	4	12	53
Response to treatment			
Persistent bleeding	–	1 (6.7)	15 (22)
Immediate hemostasis	4 (100)	14 (93.2)	53 (77.9)
Stable hemostasis	2 (50)	11 (73.3)	51 (75)
Definitive hemostasis	2 (50)	11 (73.3)	47 (70.5)
Cumulative recurrent bleeding			
≤1 day	–	–	2 (2.9)
≤3 days	2 (50)	3 (20)	4 (5.8)
≤7 days	2 (50)	3 (20)	6 (9.4)
≤30 days	2 (50)	3 (20)	6 (9.4)
Patients requiring transfusion	4 (100)	11 (73.3)	27 (39.7)
Units of blood transfused	2 ± 0.81	1.53 ± 1.24	1.70 ± 1.32
Additional intervention			
Endoscopic hemostasis	1	2	3

Variables	Hemostatic Powders		Conventional hemostatic procedures
	First choice	Rescue therapy	
Radiological embolization	–	1	2
Surgery	1 (25)	2 (13.3)	1 (1.9)
Length of hospital stay (days)	13.2 ± 4.2	25.4 ± 20.8	20.3 ± 18.3
Mortality due to any cause	–	1 (6.7)	2 (2.9)

Values are *N* (%) or mean ± standard deviation.

Malignancy

Twenty-three patients had GIB due to malignancy, 14 of whom had primary and nine metastatic cancer. The source of bleeding was the stomach in 15 patients, the duodenum in six patients, and the colon/rectum in two patients; in all cases bleeding was oozing from multiple sites. Characteristics of the lesions, hemostatic procedures, and outcomes are shown in Table 3. CHP was used in 12 patients, five of whom achieved hemostasis while seven required HP rescue therapy due to persistent bleeding. The remaining 11/23 patients were treated with HP as first choice monotherapy. HP achieved immediate hemostasis in 6/7 patients when used as rescue therapy and in all 11 patients when used as monotherapy. Immediate hemostasis rates in patients treated with HP rescue therapy and in those treated with HP monotherapy were significantly higher than in patients treated with CHP (85.7% and 100% *versus* 41.7%, respectively, $p<.02$). The outcomes of patients with malignancy following hemostatic procedures are shown in Figure 2. Of the five patients who responded to CHP, one re-bled on the 2nd day after the procedure, underwent surgery after failure of re-treatment with APC, and was subsequently discharged. No re-bleeding occurred in the other four patients, three of whom were discharged and one died of his underlying disease. Of the six patients who responded to HP rescue therapy, none re-bled, five were discharged, and one died of their underlying disease. Of the 11 patients treated with HP monotherapy, five did not bleed again and were discharged, while six had recurrent bleeding (three on the 2nd day and the other three on the 9th, 13th, and 18th day after the procedure), four of whom died of their underlying disease and two were re-treated with HP achieving definitive hemostasis and discharged. The definitive hemostasis rate was similar in the three groups (6/7 [85.7%] in the HP Rescue Therapy Group, 5/11 [45.5%] in the HP Monotherapy Group, and 4/12 [33.3%] in the CHP Group).

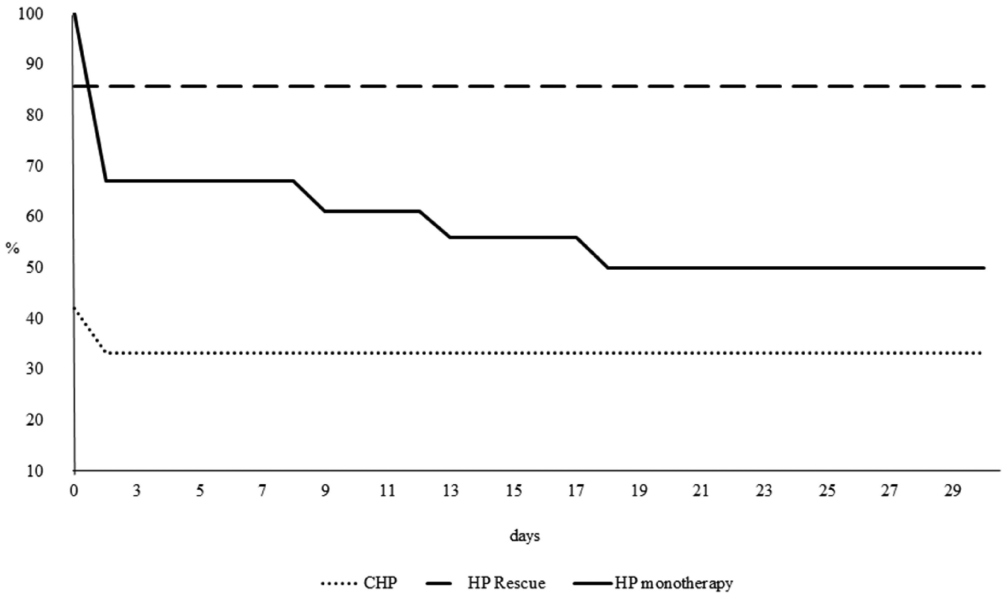

Figure 2. Efficacy of HP in patients with gastrointestinal bleeding due to neoplastic lesions. Immediate and definitive hemostasis rates achieved by HP used as first choice and rescue therapy were higher than those achieved by CHP. CHP: conventional hemostatic procedures; HP: hemostatic powder.

Table 3. Characteristics of lesions, hemostastic procedures, and outcomes in 23 patients with malignancy. (Table view)

No.	Site of Bleeding	Primary/ Metastatic	First Choice Hemostatic Procedure	Rescue Therapy	Immediate Hemostasis	Re-bleeding	Additional Intervention	Outcome
1	Duodenum	Metastatic, colon	H	No	Yes	Yes	No	Died from underlying disease
2	Stomach	Metastatic, melanoma	H	No	Yes	No	No	Discharged
3	Duodenum	Primary	H	No	Yes	Yes	No	Died from underlying disease
4	Stomach	Primary	H	No	Yes	Yes	H	Discharged
5	Stomach	Primary	E	No	Yes	No	No	Discharged
6	Stomach	Primary	E	No	Yes	No	No	Discharged
7	Stomach	Primary	APC	H	Yes	No	No	Elective surgery, Discharged
8	Stomach	Primary	APC	H	Yes	No	No	Discharged
9	Stomach	Primary	APC, Clip	H	Yes	No	No	Elective surgery, Discharged
10	Stomach	Primary	APC, Clip	H	No	No	Surgery	Discharged
11	Stomach	Metastatic, pancreas	H	No	Yes	Yes	No	Died from underlying disease
12	Stomach	Metastatic, pancreas	H	No	Yes	No	No	Elective surgery, Discharged
13	Duodenum	Metastatic, pancreas	APC	H	Yes	No	No	Discharged
14	Duodenum	Metastatic, pancreas	H	No	Yes	Yes	H	Discharged
15	Duodenum	Metastatic, pancreas	APC	H	Yes	No	No	Died from underlying disease
16	Stomach	Metastatic, lymphoma	APC	H	Yes	No	No	Discharged
17	Rectum	Metastatic, lymphoma	H	No	Yes	Yes	No	Died from underlying disease
18	Colon	Primary	H	No	Yes	No	No	Elective surgery, Discharged
19	Stomach	Primary	APC	No	Yes	No	No	Discharged
20	Duodenum	Metastatic, pancreas	APC	No	Yes	No	No	Died from underlying disease
21	Stomach	Metastatic, pancreas	APC	No	Yes	Yes	APC	Elective surgery, Discharged
22	Stomach	Primary	APC	No	Yes	No	No	Discharged
23	Stomach	Primary	APC	No	Yes	No	No	Discharged

APC: argon plasma coagulation; E: Endoclot®; H: Hemospray®.

Of the 23 patients with GIB due to malignancy, 17 had an advanced unresectable tumor; 11 were discharged for palliative treatment and six died (mortality: 26%) from malignancy-related complications other than GIB. Of the six remaining patients, five underwent elective surgery and one emergency surgery due to failure of hemostatic procedures.

No differences were found in the three groups when comparing units of blood transfused, additional interventions, length of hospital stay, and mortality rate.

Miscellaneous

Thirteen patients had GIB due to several other conditions. Six patients with post-sphincterotomy GIB received CHP; four achieved immediate hemostasis, while two required HP rescue therapy, which induced immediate and definitive hemostasis. One patient had post-endoscopic submucosal dissection GIB not responding to CHP and was successfully treated with HP. HP was used as first choice monotherapy achieving immediate and definitive hemostasis in three patients with atypical conditions: a 41-year-old female with acute leukemia and graft-versus-host disease (GvHD) presenting multiple large areas of mucosal denudation with oozing bleeding in the esophagus; a 44-year-old male on chemotherapy with several large areas of mucosal damage with oozing bleeding in the esophagus; and a 34-year-old-male with large ulceration of the cecum with oozing bleeding. Three patients with GIB due to diverticular disease underwent CHP achieving immediate hemostasis. Recurrent bleeding occurred in one patient with post-sphincterotomy GIB and two patients with diverticular disease; in all three patients CHP achieved definitive hemostasis, although one with diverticular disease also underwent surgery. All patients were discharged except one, who had undergone sphincterotomy and died of their underlying disease (cholangiocarcinoma).

Type of HP used, tolerability, safety, efficacy, and ease of application

Of the 43 patients treated with HP, 33 received Hemospray and 10 Endoclot. Both HPs showed an optimal safety, as no adverse events occurred during or after application of HP. The efficacy of the two types of HP was similar (Table 4). Both types of HP were found easy to apply.

Table 4. Efficacy of hemostatic powders in GIB due to different benign and malignant lesions. (Table view)

Lesions	Hemostatic Powder	Patients, N	Immediate Hemostasis, *N* (%)	Definitive Hemostasis, *N* (%)
All	E	10	9 (90)	8 (80)
	H	33	32 (97)	22 (67)
Ulcer				
	E	6	5 (83)	4 (67)
	H	13	13 (100)	9 (69)
Malignancy				
	E	2	2 (100)	2 (100)
	H	16	15 (94)	9 (60)
Miscellaneous				
	E	2	2 (100)	2 (100)
	H	4	4 (100)	4 (100)

E: Endoclot®; H: Hemospray®.

Discussion

The present study confirms that HP is effective in stopping GIB due to neoplastic and non-neoplastic lesions both as monotherapy and rescue therapy. Our findings are in line with the largest studies published to date [12,13,16]. A prospective study of 314 patients treated with Hemospray reported immediate hemostasis in 89.5% of cases, with a re-bleeding rate of 10%, and a definitive hemostasis rate of ~90% [13]. A retrospective nationwide study conducted in Spain involving 261 patients with GIB showed the efficacy of Hemospray in inducing an immediate hemostasis rate of 93%, with a re-bleeding rate of 23%, and a definitive hemostasis rate of 77% [12]. A recent retrospective study including 86 patients treated with HP as rescue therapy and monotherapy described a high rate (88.4%) of immediate hemostasis but a cumulative re-bleeding rate of 33.7% [16]. These data demonstrate that although HP is highly effective in inducing immediate hemostasis, recurrent bleeding may occur in up to about one-third of patients. The discrepancy between rates of recurrent bleeding and consequently of definitive hemostasis in these published studies may be due to the heterogeneity of lesions treated. The retrospective setting and lack of a patient control group represent further limitations. Taken together, the bleeding rates in our study are somewhat higher than in some previous investigations [12,13]. It is possible that comorbidities and general clinical status, expressed by high Rockall score and Glasgow Blatchford score, have in some cases made patients frailer. Indeed, recurrent bleeding rates found in our study are similar to those reported in other works investigating a high percentage of patients with peptic ulcers [16,17]. In our study, more than two-thirds of lesions were actively bleeding ulcers, classified as Forrest 1 A and 1B, which are the most difficult to control with HP [18]. In this context, HP was able to achieve hemostasis in >70% of bleeding ulcers where CHP was not effective. A different mode of action in addition to those of previously performed CHPs is the most likely reason for the effectiveness of HP as a rescue therapy. HP was used as first choice in too few cases of peptic ulcer to determine whether this technique is more useful as monotherapy or rescue therapy.

The action of HP in absence of mechanical contact with the bleeding surface and the possibility of spreading the powder over a large surface allowing the simultaneous treatment of multiple bleeding points indicate that HP is particularly effective in the treatment of cancer-related GIB. Currently, there is no gold standard treatment for GIB from GI malignancy. Despite its frequent use in clinical practice, APC is associated with temporary efficacy and high recurrent bleeding rates in GIB due to malignancy [19]. Data regarding the use of HP in patients with GIB caused by malignancy refer mainly to retrospective series and to few prospective studies including small series of patients [20,21]. Only one recent pilot randomized controlled study on 20 patients with GI from malignant lesions reported a greater efficacy of Hemospray monotherapy in inducing immediate hemostasis with a lower rate of recurrent bleeding compared to CHP [22]. Findings from our study suggest that HP monotherapy is a straightforward procedure and is more effective than CHP in stopping GIB due to malignancy. HP is also effective in stopping hemorrhage in patients not responding to CHP. Although the difference was not statistically significant because of the limited number of patients enrolled in our study, immediate and definitive hemostasis rates achieved by HP were about two and three times greater than CHP in cancer-related GIB, respectively. Thus, cancer-related GIB may be the best field of application of HP, even when used as first choice monotherapy, especially in the presence of lesions with multiple oozing sites. Studies on larger populations will be necessary to confirm this hypothesis.

As the main concern about the use of HP is recurrent bleeding and consequently the need for additional intervention, it is crucial to know when another bleeding episode is more likely to occur in clinical practice. In our study, almost all recurrent bleedings occurred within the first 3–7 days after treatment with HP. A large proportion of patients who re-bled achieved definitive hemostasis following re-treatment with HP. This finding is in line with a recent study reporting recurrent bleeding mainly within the first 7–10 days with rates leveling off during the subsequent follow-up period [16].

As far as concerns the safety, Food and Drugs Administration has reported embolization, bowel obstruction and allergic reaction as potential adverse events to Hemospray® [23]. Although no adverse

events are generally reported with the use of HPs [18], two studies describe mild abdominal pain, gastric perforation, and esophageal perforation in a child with GvHD, and pulmonary thromboembolism in a patient with a history of venous embolism [12,24]. In the present study, safety was deemed as good in the absence of adverse events during the use of Hemospray® and Endoclot®.

Some difficulties may occur in the release of HP as it coagulates when in contact with fresh blood. During an emergency endoscopy with active GIB, it is necessary to aspire blood from the lumen of the digestive tract, and presence of blood in the working channel may determine coagulation of HP causing occlusion of the catheter. We encountered this inconvenience at the beginning of our experience with HP. To overcome the issue, we successfully introduced the maneuver of a prolonged insufflation following blood aspiration to dry the working channel immediately before the spraying of HP.

The strengths of our study lie in the prospective collection of data and the inclusion of a cohort of patients with cancer-related GIB who were followed up after the hemostatic procedure. Data derived from such patients will help to better understand the role of HP in controlling cancer-related GIBs, for which a specific treatment of choice has not yet been well defined. The main drawback of our investigation is that the allocation of treatment to HP monotherapy *versus* CHP was not randomized, possibly resulting in a selection bias. While this precludes drawing any definitive conclusions, we intend to validate the current findings in a randomized study. In addition, the relatively small population did not allow for the multivariate analysis of factors potentially influencing the outcome according to the different procedures and thus limited the power of the study. We used two different types of HP, which showed similar efficacy. To the best of our knowledge, only one previous study directly compared the two different HPs for the treatment of GI bleeding and found no difference in terms of short- and long-term hemostasis and recurrent bleeding [25]. Thus, the use of different HPs should not, in our opinion, have influenced the outcomes in our patients.

In conclusion, HP is highly effective when used as monotherapy and rescue therapy for stopping GIB related to benign and malignant lesions. Early recurrent bleeding may occur in up to one-third of patients treated. HP may find its best application in malignancy-related GIB, but confirmatory large prospective studies are necessary.

Acknowledgments

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Disclosure statement

Drs. Omero Alessandro Paoluzi, Carla Cardamone, Antonio Aucello, Benedetto Neri, Enrico Grasso, Mario Giannelli, Laura Di Iorio, Giovanni Monteleone, and Giovanna Del Vecchio Blanco have no conflicts of interest or financial ties to disclose.

References

[1] Lanas A, García-Rodríguez LA, Polo-Tomás M, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. *Am J Gastroenterol*. 2009;104(7):1633–1641.

[2] Hearnshaw SA, Logan RFA, Lowe D, et al. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut*. 2011;60(10):1327–1335.

[3] Fukuda S, Shimodaira Y, Watanabe K, et al. Risks for rebleeding and in-Hospital mortality after gastrointestinal bleeding in a tertiary referral center in Japan. *Digestion*. 2020;101(Suppl. 1):31–37.

[4] Weilert F, Binmoeller KF. New endoscopic technologies and procedural advances for endoscopic hemostasis. *Clin Gastroenterol Hepatol*. 2016;14(9):1234–1244.

[5] Jacques J, Legros R, Chaussade S, et al. Endoscopic haemostasis: an overview of procedures and clinical scenarios. *Dig Liver Dis*. 2014;46(9):766–776.

[6] Holster IL, Kuipers EJ, Tjwa ET. Hemospray in the treatment of upper gastrointestinal hemorrhage in patients on antithrombotic therapy. *Endoscopy*. 2013;45(1):63–66.

antithrombotic therapy. *Endoscopy*. 2013;45(1):65–68.

[7] Smith LA, Stanley AJ, Bergman JJ, et al. Hemospray application in nonvariceal upper gastrointestinal bleeding: results of the survey to evaluate the application of hemospray in the luminal tract. *J Clin Gastroenterol*. 2014;48(10):e89–e92.

[8] Masci E, Arena M, Morandi E, et al. Upper gastrointestinal active bleeding ulcers: review of literature on the results of endoscopic techniques and our experience with Hemospray. *Scand J Gastroenterol*. 2014;49(11):1290–1295.

[9] Yau AH, Ou G, Galorport C, et al. Safety and efficacy of Hemospray® in upper gastrointestinal bleeding. *Can J Gastroenterol Hepatol*. 2014;28(2):72–76.

[10] Sulz MC, Frei R, Meyenberger C, et al. Routine use of hemospray for gastrointestinal bleeding: prospective two-center experience in Switzerland. *Endoscopy*. 2014;46(7):619–624.

[11] Haddara S, Jacques J, Lecleire S, et al. A novel hemostatic powder for upper gastrointestinal bleeding: a multicenter study (the "GRAPHE" registry)). *Endoscopy*. 2016;48(12):1084–1095.

[12] Rodriguez de SE, Burgos-Santamaria D, Perez-Carazo L, et al. Hemostatic spray powder TC-325 for GI bleeding in a nationwide study: survival and predictors of failure via competing risks analysis. *Gastrointest Endosc*. 2019; 90:581–590 e6.

[13] Alzoubaidi D, Hussein M, Rusu R, et al. Outcomes from an international multicenter registry of patients with acute gastrointestinal bleeding undergoing endoscopic treatment with hemospray. *Dig Endosc*. 2020;32(1):96–105.

[14] Ibrahim M, El-Mikkawy A, Abdel Hamid M, et al. Early application of haemostatic powder added to standard management for oesophagogastric variceal bleeding: a randomised trial. *Gut*. 2019;68(5):844–853.

[15] Laine L, Spiegel B, Rostom A, et al. Methodology for randomized trials of patients with nonvariceal upper gastrointestinal bleeding: recommendations from an international consensus conference. *Am J Gastroenterol*. 2010;105(3):540–550.

[16] Chahal D, Lee JGH, Ali-Mohamad N, et al. High rate of re-bleeding after application of hemospray for upper and lower gastrointestinal bleeds. *Dig Liver Dis*. 2020;52(7):768–772.

[17] Baracat FI, de Moura DTH, Brunaldi VO, et al. Randomized controlled trial of hemostatic powder versus endoscopic clipping for non-variceal upper gastrointestinal bleeding. *Surg Endosc*. 2020;34(1):317–324.

[18] Facciorusso A, Straus Takahashi M, Eyileten Postula C, et al. Efficacy of hemostatic powders in upper gastrointestinal bleeding: a systematic review and Meta-analysis. *Dig Liver Dis*. 2019;51(12):1633–1640.

[19] Ofosu A, Ramai D, Latson W, et al. Endoscopic management of bleeding gastrointestinal tumors. *Ann Gastroenterol*. 2019;32(4):346–351.

[20] Chen YI, Barkun AN, Soulellis C, et al. Use of the endoscopically applied hemostatic powder TC-325 in cancer-related upper GI hemorrhage: preliminary experience (with video). *Gastrointest Endosc*. 2012;75(6):1278–1281.

[21] Leblanc S, Vienne A, Dhooge M, et al. Early experience with a novel hemostatic powder used to treat upper GI bleeding related to malignancies or after therapeutic interventions (with videos). *Gastrointest Endosc*. 2013;78(1):169–175.

[22] Chen YI, Wyse J, Lu Y, et al. TC-325 hemostatic powder versus current standard of care in managing malignant GI bleeding: a pilot randomized clinical trial. *Gastrointest Endosc*. 2020;91(2):321–328.

[23] https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170015.pdf.

[24] Hagel AF, Albrecht H, Nägel A, et al. The application of hemospray in gastrointestinal bleeding during emergency endoscopy. *Gastroenterol Res Pract*. 2017;2017:3083481.

[25] Vitali F, Naegel A, Atreya R, et al. Comparison of hemospray® and endoclot™ for the treatment of gastrointestinal bleeding. *World J Gastroenterol*. 2019;25(13):1592–1602.