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Effectiveness of hemostatic powders in lower gastrointestinal bleeding: a systematic review and meta-analysis

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ABSTRACT

Background and study aims There is limited evidence on the effectiveness of hemostatic powders in the management of lower gastrointestinal bleeding (LGIB). We aimed to provide a pooled estimate of their effectiveness and safety based on the current literature.

Patients and methods Literature review was based on computerized bibliographic search of the main databases through to December 2020. Immediate hemostasis, rebleeding rate, adverse events, and mortality were the outcomes of the analysis. Pooled effects were calculated using a random-effects model.

Results A total of 9 studies with 194 patients were included in the meta-analysis. Immediate hemostasis was achieved in 95% of patients (95% confidence interval [CI] 91.6%–98.5%), with no difference based on treatment strategy or bleeding etiology. Pooled 7- and 30-day rebleeding rates were 10.9% (95%CI 4.2%–17.6%) and 14.3% (95%CI 7.3%–21.2%), respectively. Need for embolization and surgery were 1.7% (95%CI 0%–3.5%) and 2.4% (95%CI 0.3%–4.6%), respectively. Overall, two patients (1.9%, 95%CI 0%–3.8%) experienced mild abdominal pain after powder application, and three bleeding-related deaths (2.3%, 95%CI 0.2%–4.3%) were registered in the included studies.

Conclusion Novel hemostatic powders represent a user-friendly and effective tool in the management of lower gastrointestinal bleeding.

Introduction

Gastrointestinal (GI) bleeding represents a major cause of morbidity and mortality worldwide. Although mortality rate related to lower gastrointestinal bleeding (LGIB) is not as high as that for upper GI hemorrhage, its incidence has increased over time particularly in older patients using antithrombotic therapy [1].

LGIB can be treated successfully through common endoscopic hemostatic techniques including injection therapy, argon plasma coagulation, and clips; however, endoscopic man-

agement can sometimes be challenging for a number of reasons. Among technical issues that may be commonly encountered by the operator are difficulties in obtaining a clear view of the bleeding site for injection or clipping, and the presence of large or multiple sources of bleeding in the case of diverticular disease or malignant lesions, where tissue does not offer adequate binding sites for effective clipping [2].

Therefore, agents that can instantaneously and diffusely stop hemorrhage upon contact with the bleeding site would play a pivotal role in this setting. In this regard, topical hemostatic agents, such as hemostatic powders, represent a valuable option as they are relatively easy to use and have demonstrated promising results in preliminary studies [3].

Among hemostatic topical powders, TC-325 (Hemospray; Cook Medical, Bloomington, Indiana, USA) represents the most investigated agent and was proven to be effective in determining immediate hemostasis in several upper GI bleeding conditions such as variceal hemorrhage or peptic ulcers [3–5]. Other topical agents, such as the starch-derived polysaccharide hemostatic system (EndoClot; EndoClot Plus, Suzhou Industrial Park, China), are also emerging although evidence is more limited [3, 5].

Based on the limited published experience, current guidelines suggest the use of hemostatic topical agents preferentially in high-risk cases as a temporizing measure or a bridge toward more definitive treatment [6]; however, this statement applies to upper GI bleeding and there is very limited evidence on the effectiveness of these agents in LGIB, which is based mainly on small series or single case reports.

The aim of this study was to provide a pooled estimate of the effectiveness and safety profile of hemostatic powders in clinical practice based on the current literature, and thus attempt to determine their potential utility in digestive endoscopy.

Patients and methods

Selection criteria

The literature search strategy was based on the following inclusion criteria: 1) observational or cohort studies enrolling patients with LGIB treated with hemostatic powders; 2) studies published in English; 3) articles reporting hemostatic success or rebleeding rate.

Case reports/series with fewer than five patients, studies not reporting subgroup data concerning LGIB, review articles, and animal models were excluded.

Search strategy

Bibliographic research was conducted on PubMed, EMBASE, Cochrane Library, and Google Scholar including all studies fulfilling the inclusion criteria published until December 2020. The following search strategy was adopted: (((TC-325[MeSH Terms]) OR Hemospray[MeSH Terms]) OR hemostatic powder [MeSH Terms]) OR microporous polysaccharides[MeSH Terms].

Relevant reviews and meta-analyses in the field were examined for potential additional suitable studies. Authors of included studies and conference abstracts were contacted to obtain the full text or further information when needed. Manual search on the proceedings of the main international endoscopy and gastroenterology conferences was also performed.

Data extraction was conducted by two reviewers (A.F. and M.P.) and the quality of included studies was assessed by two authors independently (A.F., B.P.M.) according to the Newcastle–Ottawa scale [7]. Disagreements were resolved by discussion and after a third opinion (R.S.).

Outcomes assessed

Immediate hemostasis was defined as achievement of hemostasis after powder application. Other outcomes were rebleeding rate (either at 7 or 30 days), bleeding-related mortality, need for surgery, need for embolization, and adverse event rate.

Statistical analysis

Effectiveness outcomes were pooled from included studies through a random-effects model based on DerSimonian and Laird test, and summary estimates were expressed in terms of rate and 95 % confidence interval (CI). We assessed heterogeneity between study-specific estimates by using the I^2 statistics, with values of < 30 %, 30 %–60 %, 61 %–75 %, and > 75 % suggestive of low, moderate, substantial, and considerable heterogeneity, respectively [8]. Probability of publication bias was assessed through visual inspection of funnel plots.

Several sensitivity analyses were conducted according to the treatment strategy (monotherapy vs. combined vs. rescue), hemostatic agent used (Hemospray vs. Endoclot), etiology of bleeding (restricted to post-polypectomy bleeding), and study design (prospective vs. retrospective). Rescue therapy was defined as use of the powder after failure of another modality to control bleeding.

All statistical analyses were conducted using OpenMeta [Analyst] software. For all calculations, a two-tailed P value of < 0.05 was considered statistically significant.

Results

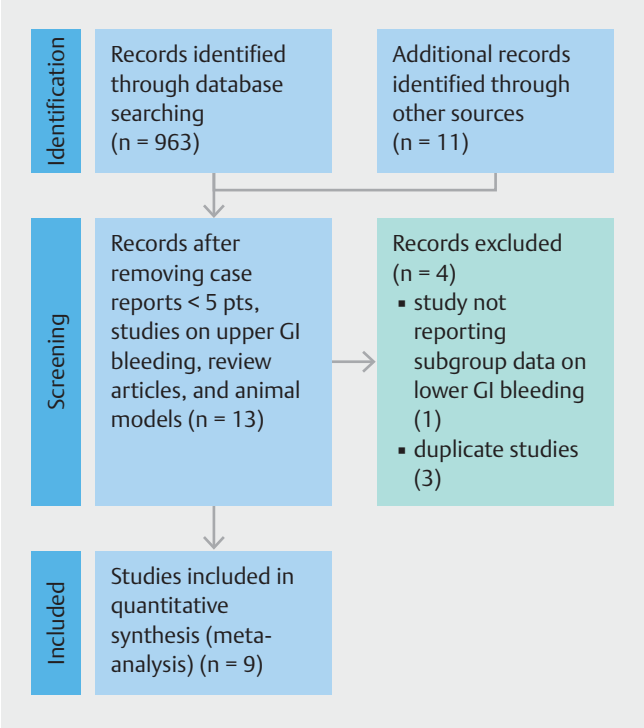
Studies included in the meta-analysis

As shown in ▶ **Fig. 1**, out of 974 studies initially identified, and after exclusion of papers not fulfilling the inclusion criteria, 9 potentially relevant studies [9–17] with 194 patients were included. The main characteristics of the included studies are reported in ▶ **Table 1**.

The period when patients were recruited in the included studies ranged from 2011 to 2019. Out of the studies included, two were prospective [11, 14]; seven studies tested Hemospray [9–13, 15, 17], a single prospective series used EndoClot [14], and a small retrospective case–control study compared the two agents [16].

All studies were Western series, except for a single small retrospective cohort from Singapore [13].

Most of the treated patients were male and the main cause of LGIB was post-polypectomy bleeding. Of note, none of the recruited patients received hemostatic powder treatment for the prevention of post-polypectomy bleeding, instead treatment was applied only in the case of active bleeding. A single



▶ **Fig. 1** Flow chart of the included studies. GI, gastrointestinal; pts, patients.

series included only patients with diverticular bleeding [13], whereas cancer was overall the cause of lower GI hemorrhage in 12 patients (6.2 %).

Hemostatic powders were used mainly as monotherapy (▶ **Table 1**).

None of the included studies reported any cases of admission to the intensive care unit due to lower GI bleeding, and only one patient in the study by Holster et al. [12] experienced hypovolemic shock.

Quality was deemed low in four studies [12, 15–17] and moderate/high in the remaining studies. Details on methodological characteristics and quality of included articles are shown in **Supplementary Table 1s**.

Immediate hemostasis

As depicted in ▶ **Fig. 2**, immediate hemostasis was achieved in 95 % of patients (95 %CI 91.6 %–98.5 %), with evidence of low heterogeneity (I^2 = 17.9 %). There was no evidence of publication bias, as reported in **Supplementary Fig. 1s** (P = 0.43).

The findings of the main analysis were confirmed in sensitivity analyses performed according to treatment strategy (monotherapy vs. combined vs. rescue), bleeding etiology (restricted to post-polypectomy bleeding), and study design (prospective vs. retrospective) (▶ **Table 2**), with considerably low heterogeneity (I^2 ranging from 0 % to 27.8 %).

Of note, use of EndoClot led to a lower rate of immediate hemostasis (80 %, 95 %CI 62.1 %–97.8 %).

Rebleeding rate and other outcomes

As reported in ▶ **Fig. 3** and ▶ **Table 3**, the pooled 7-day rebleeding rate was 10.9 % (95 %CI 4.2 %–17.6 %), with evidence of moderate heterogeneity (I^2 = 38.9 %). The 30-day bleeding recurrence rate was slightly higher (14.3 %, 95 %CI 7.3 %–21.2 %) (▶ **Fig. 4**, ▶ **Table 3**), again with a striking difference in favor of Hemospray compared with EndoClot. As depicted in **Supplementary Fig. 2s** and **Fig. 3s**, there was no evidence of publication bias concerning the two outcomes (P = 0.33 and P = 0.25, respectively).

Overall, only four patients needed to be treated with embolization (1.7 %, 95 %CI 0 %–3.5 %) whereas six patients were treated with surgery within 30 days (2.4 %, 95 %CI 0.3 %–4.6 %) (▶ **Table 3**). Furthermore, two patients (1.9 %, 95 %CI 0 %–3.8 %) experienced mild abdominal pain after powder application, and three bleeding-related deaths were registered in the included studies (2.3 %, 95 %CI 0.2 %–4.3 %). As reported in ▶ **Table 3**, heterogeneity concerning the aforementioned outcomes was low or absent.

Discussion

Although conventional endoscopic hemostatic therapies constitute the landmark in the management of GI bleeding, these treatments have their limitations, such as the risk of perforation, worsening of bleeding, and possible difficulty of use when applied to large, friable bleeding surfaces such as hemorrhage arising from tumors or diverticula.

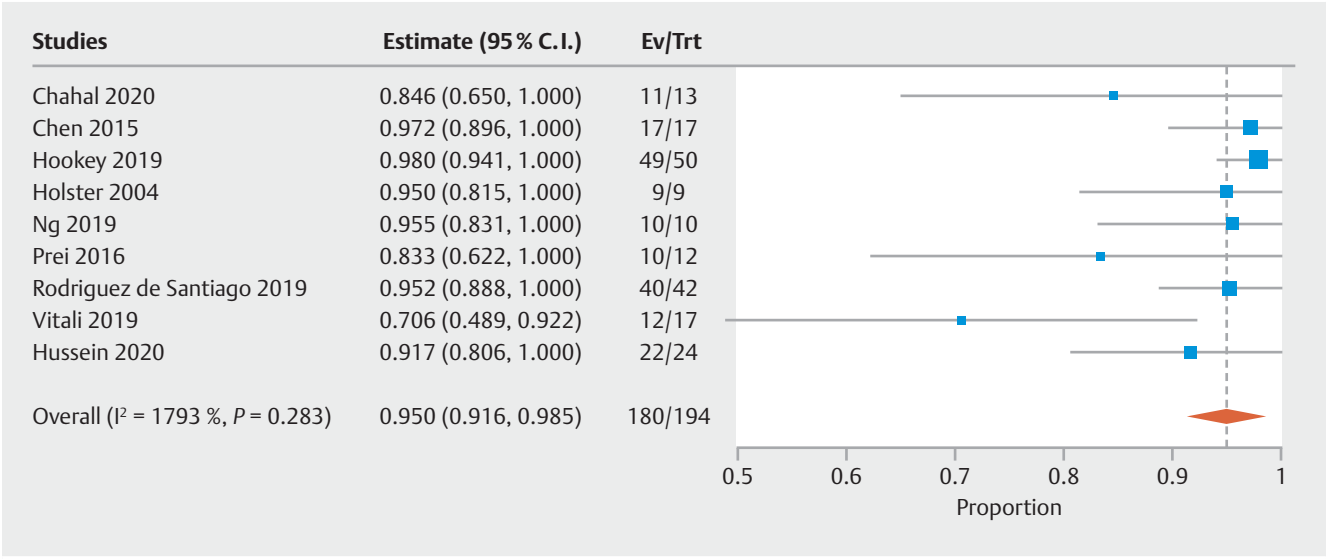
Novel hemostatic products, such as Hemospray and EndoClot, have recently been adapted to digestive endoscopy, and have shown promising results in upper GI bleeding and animal models [3–5].

Hemostatic powder particles swell and become cohesive and adhesive, creating a barrier layer that covers the bleeding site and acts as tamponade achieving very rapid hemostasis, usually within seconds; furthermore, absorption of the fluid component of blood ultimately also leads to concentration of clotting factors and cellular elements [18]. However, some concerns have been raised on the risk of rebleeding because the powder swells and hardens only in the presence of moisture and disappears within a short period of time [19]. Therefore, further data are needed to confirm the role of these agents, particularly in LGIB.

Hemostatic powders could be of particular value in the case of neoplastic bleeding where successful and durable hemostasis is rarely achieved by endoscopic means owing to the large surface area and the specific characteristics of tumoral tissue that do not allow effective clipping. Moreover, in the case of diverticular bleeding, the main issue in conventional endoscopic hemostasis is identification of the exact source of bleeding, especially because active bleeding has often stopped by the time endoscopy is performed. Hemostatic powder may be perfectly adapted to use in these conditions owing to its ability to cover large or not clearly evident areas of bleeding without touching the tissue [18].

▶ **Table 1** Characteristics of the studies included in the systematic review and meta-analysis.

Study and country	Study period/ design	Powder[1]	Sample size, n	Age, years[2]	Male sex, n (%)	Antithrombotic agents, n (%)	Etiology (polypectomy/cancer/ diverticula/ other), n (%)	Location (left-/ right-sided), n (%)	Monotherapy/ combined/ rescue, n (%)
Chahal 2020 [9][3] Canada	2014–2018 Retrosp.	Hemospray	13	61.9 (15.2)	6 (46.2)	4 (30.8)	5 (38.4) 1 (7.7) 1 (7.7) 6 (46.2)	NR	2 (15.4) 11 (84.6) 0
Chen 2015 [10][3] Canada	2011–2013 Retrosp.	Hemospray	17	NR	8 (47.1)	4 (23.5)	6 (35.3) 2 (11.7) 0 9 (53)	NR	17 (100) 0 0
Hookey 2019 [11] Canada	2013–2016 Prosp.	Hemospray	50	64.6 (12.5)	36 (72)	16 (32)	38 (73.1) 0 1 (1.9) 11 (21.9)	30 (58.6) 20 (41.4)	13 (25) 21 (40.3) 16 (30.7)
Holster 2014 [12] Spain/Holland	2011–2013 Retrosp.	Hemospray	9	63 (22–79)	5 (55.5)	4 (44.5)	4 (44.5) 1 (11.1) 1 (11.1) 3 (33.3)	4 (44.5) 5 (55.5)	6 (66.7) 0 3 (33.3)
Ng 2019 [13] Singapore	2016–2017 Retrosp.	Hemospray	10	64 (53–74)	5 (50)	3 (30)	0 0 10 (100) 0	7 (70) 3 (30)	9 (90) 1 (10) 0
Prei 2016 [14][3] Germany	2012–2014 Prosp.	EndoClot	12	67 (13)	NR	NR	NR	4 (33.3) 8 (66.7)	NR
Rodriguez de Santiago 2019 [15][3] Spain	2011–2018 Retrosp.	Hemospray	42	67 (15)	NR	NR	18 (42.8) 2 (4.7) 0 22 (52.5)	NR	NR
Vitali 2019 [16][3] Germany	2013–2017 Retrosp.	Hemospray (9 pts) EndoClot (7 pts) Both (1 pt)	17	NR	NR	10 (58.8)	NR	NR	Primary: 10 (58.8) Rescue: 7 (41.2)
Hussein 2020 [17][4] Multicenter	2016–2019 Retrosp.	Hemospray	24	NR	16 (66.6)	9 (37.5)	5 (20.8) 6 (25) 0 13 (54.2)	NR	15 (62.5) 8 (33.3) 1 (4.2)



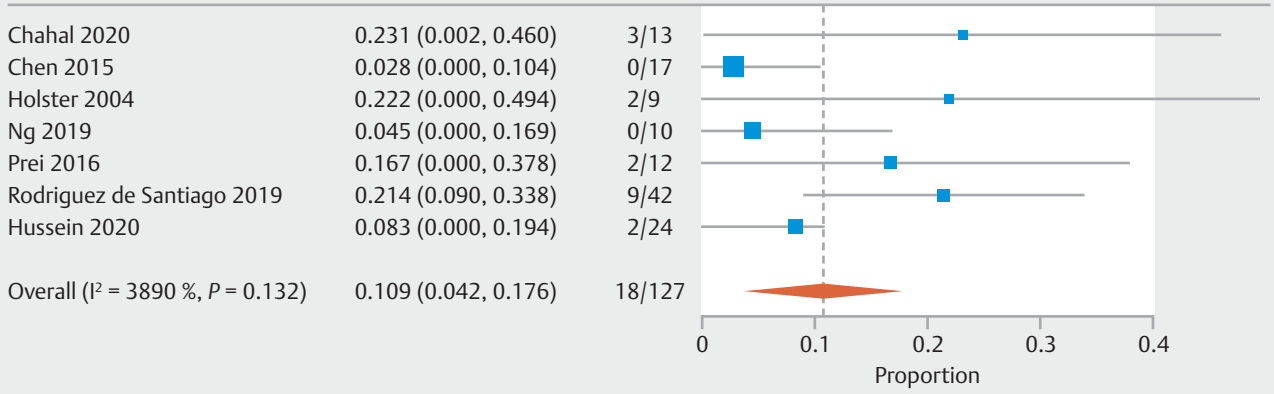
▶ **Fig. 2** Pooled analysis of immediate hemostasis rate achieved with hemostatic powders. Immediate hemostasis was achieved in 95 % of patients (95 %CI 91.6 %–98.5 %), with evidence of low heterogeneity (I^2 = 17.9 %). CI, confidence interval.

▶ **Table 2** Sensitivity analyses. Pooled estimates of immediate hemostasis, obtained according to treatment strategy, hemostatic agent, bleeding etiology, and study design.

Subgroup	Studies, n	Patients, n	Immediate hemostasis rate, % (95 %CI)	Within-group heterogeneity, I^2, %
Treatment strategy				
▪ Monotherapy	5	60	96.5 (92–100)	0
▪ Combined	3	30	93.8 (85.4–100)	0
▪ Rescue	4	27	91.3 (80.2–100)	27.8
Hemostatic agent				
▪ Hemospray[1]	8	175	96.2 (93.5–99.7)	0
▪ EndoClot[2]	2	19	80 (62.1–97.8)	0
Etiology				
▪ Post-polypectomy	4	66	97 (93–100)	0
Study design				
▪ Prospective	2	62	94.5 (82.2–100)	18.5
▪ Retrospective	7	132	93.9 (89.8–98.1)	16.5

CI, confidence interval.
[1] Hemospray; Cook Medical, Bloomington, Indiana, USA.
[2] EndoClot; EndoClot Plus, Suzhou Industrial Park, China.

There is still very limited evidence on the use of hemostatic powders in LGIB, hence the pressing need to systematically assess the effectiveness and safety profile of these agents in this setting in order to inform guidelines. To the best of our knowledge, this is the first meta-analysis on this topic. Through our meta-analysis of nine studies, we made several key observations. First, hemostatic powders were effective in achieving immediate hemostasis, with a 95 % pooled success rate. This finding could be of particular interest in the case of bleeding sources that are not usually amenable to effective conventional treatments, such as large tumors, where the ability of hemostatic powders to cover a large irregular surface of bleeding may make them an ideal treatment modality. However, even in the context of post-polypectomy bleeding (the most frequent source of bleeding in the included studies), the pooled effectiveness of these agents represents a striking result, suggesting that hemostatic powders may be a valuable tool in the management algorithm of LGIB. However, it should be noted that the heterogeneity of bleeding etiology and the uneven inclusion of different causes of bleeding in the studies call for caution when



▶ **Fig. 3** Pooled analysis of 7-day rebleeding rate after use of hemostatic powders. Rate of bleeding recurrence within 7 days from the index procedure was 10.9 % (95 %CI 4.2 %–17.6 %), with evidence of moderate heterogeneity (I^2 = 38.9 %). CI, confidence interval.

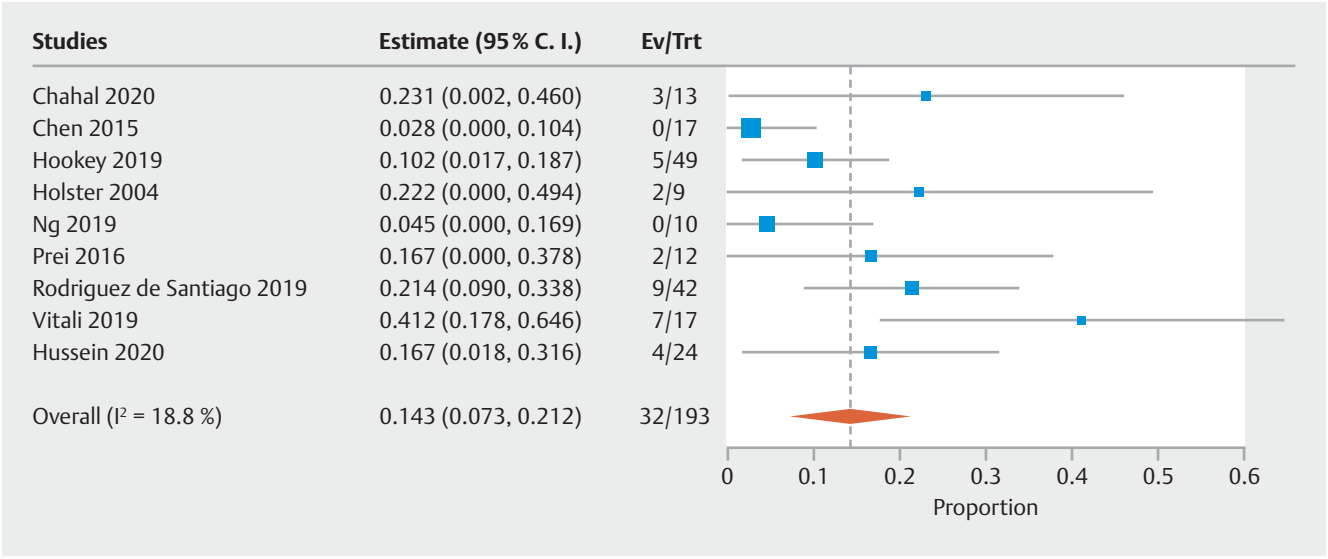
▶ **Table 3** Secondary outcomes.

Outcome and subgroup	Studies, n	Patients, n	Pooled rate, % (95 %CI)	Within-group heterogeneity, I^2, %
7-day rebleeding				
▪ Overall	9	127	10.9 (4.2–17.6)	38.9
▪ Hemospray[1]	8	115	9.8 (3.8–15.8)	19.5
▪ EndoClot[2]	1	12	16.7 (0–37.8)	Not applicable
30-day rebleeding				
▪ Overall	9	193	14.3 (7.3–21.2)	18.8
▪ Hemospray[1]	8	174	12.3 (6–18.7)	19.3
▪ EndoClot[2]	2	19	34 (0–73.3)	71.5
Need for embolization				
▪ Overall	9	194	1.7 (0–3.5)	0
Need of surgery				
▪ Overall	9	194	2.4 (0.3–4.6)	0
Adverse events				
▪ Overall	9	194	1.9 (0–3.8)	0
Mortality rate				
▪ Overall	9	194	2.3 (0.2–4.3)	0

CI, confidence interval.
[1] Hemospray; Cook Medical, Bloomington, Indiana, USA.
[2] EndoClot; EndoClot Plus, Suzhou Industrial Park, China.

interpreting our findings. This is particularly true with regard to specific etiologies, such as diverticular hemorrhage, where the data were based only on a very limited number of patients.

Second, hemostatic powders were found to be effective as monotherapy, in combination with conventional treatments, and as a rescue therapy. Spurting bleeding is not common in patients with LGIB, hence hemostatic powders are likely to be effective even when used as single agents. However, although limited by the low number of patients, our meta-analysis seems to suggest an interesting effectiveness profile of Hemospray, even in patients with spurting bleeding, for example in patients with angiodysplasia. Therefore, our findings are in line with those previously reported in patients with upper GI bleeding, where in turn, the use of hemostatic powders was mainly combined with other conventional treatments and rarely characterized by use as monotherapy [5, 20].



▶ **Fig. 4** Pooled analysis of 30-day rebleeding rate after use of hemostatic powders. The 30-day bleeding recurrence rate was 14.3 % (95 %CI 7.3 %–21.2 %), with evidence of low heterogeneity (I^2 = 18.8 %). CI, confidence interval.

Unfortunately, an accurate comparison between the two hemostatic powder devices, namely Hemospray and EndoClot, was not feasible due to the very limited number of studies and patients using the latter. In fact, EndoClot led to a lower rate of immediate hemostasis (80 %), but this finding should be interpreted with caution owing to the aforementioned limitations; further studies are definitely needed in order to assess the real effectiveness of this agent in patients with LGIB.

Interestingly, the pooled 7- and 30-day rebleeding rates were relatively low (10.9 % and 14.3 %, respectively), a finding that is considerably more favorable compared with the performance of hemostatic powders in upper GI bleeding, where previous meta-analyses reported rates of rebleeding around 17 % [5, 20]. A likely explanation of this apparent discrepancy is the spurting bleeding and the difficult-to-treat nature of many upper GI bleeding sources (e. g. peptic ulcers with large diameter and/or difficult anatomy), which usually require multiple treatments. In fact, expert opinion suggests that in these high-risk lesions, where rebleeding rate after hemostatic powder use was reported to be up to 25 % [5], these agents may play a role as a temporizing agent, which could allow for more definitive therapy such as conventional therapy and non-emergency surgery to be arranged [21]. These issues do not frequently occur in patients with LGIB, as reported in our meta-analysis; therefore, hemostatic powders might represent a more definitive and reliable treatment in this setting. Moreover, the pivotal pathogenic role of gastric acid in peptic ulcer bleeding is not applicable to lower GI hemorrhage, and this may be a further reason for the more favorable outcomes observed in this setting. As a consequence, the need for embolization and surgery was extremely low in the literature (1.7 % and 2.4 %, respectively), as well as bleeding-related mortality (2.3 %).

Finally, as expected, hemostatic powder use was extremely safe with only two cases of mild abdominal pain reported to date in patients with LGIB.

There are some limitations to our study. First, the limited number of studies and patients included in the meta-analysis call for further trials and prospective series in order to properly assess the impact of hemostatic powders in patients with LGIB. Moreover, the included cohorts were not homogeneous in terms of bleeding etiology. Therefore, given the prevalence of post-polypectomy bleeding in the included studies, our results should be considered applicable mainly to this specific setting, whereas further data are needed to draw definitive conclusions in other etiologies, such as diverticular bleeding or in patients with colon cancer. Second, a number of variables, such as use of antithrombotic therapy, location of bleeding source, or use of gastric acid-suppressant drugs could not be explored in separate subgroup analyses due to a lack of individual patient data. Third, subanalysis in specific bleeding etiologies, such as diverticular bleeding or angiodysplasia, was not feasible due to the very limited data available.

In conclusion, despite these weaknesses, our study speaks in favor of the use of novel hemostatic powders as a user-friendly and effective tool in the management of LGIB, particularly in patients with post-polypectomy bleeding.

Competing interests

The authors declare that they have no conflict of interest.

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