SYSTEMATIC REVIEW AND META-ANALYSIS

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Efficacy of Hemospray in Upper Gastrointestinal Bleeding: A Systematic Review and Meta-Analysis

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ABSTRACT

Background & Aims: Hemospray is a non-contact modality of endoscopic hemostasis that has been used in the management of upper gastrointestinal bleeding (UGIB) with varying success. Our aim was to evaluate the efficacy of Hemospray in the management of UGIB.

Methods: An electronic bibliographic search of digital dissertation databases was performed from inception till October 2019. All prospective studies, including randomized controlled trials evaluating the efficacy of Hemospray in the management of UGIB were analysed. The primary outcome was immediate haemostasis and the secondary outcome was rebleeding rate. Subgroup analyses based on etiology of UGIB (tumour-related, variceal, etc) were also performed.

Results: A total of 11 prospective studies, including 4 randomized trials were included for the analysis. The pooled immediate haemostasis rate with Hemospray was 93% (95% CI 90.3-95%, p<0.001). Rebleeding occurred in 14.4% (95% CI 8.8-22.8%, p<0.001) of patients. For the subgroup of tumour-related bleeding, the immediate haemostasis rate was 95.3% (95% CI 89.6-97.3%; p <0.001) and rebleeding rate was 21.9% (95% CI 13.9-32.7%, p <0.001). In patients with variceal bleeding, immediate haemostasis was achieved in 92.7% (95% CI 83.6-96.9%; p<0.001) of patients, with a rebleeding rate of 3.1% (95% CI 0.9-10.2%, p <0.001).

Conclusion: Hemospray shows high immediate haemostasis and low bleeding percentages. The odds were in its favour compared to conventional endoscopic modalities, but not statistically significant. The results are undermined by the risk of bias in the studies. Nevertheless, it is an easy technique that should be further investigated with better studies.

Key words: Hemospray – upper gastrointestinal bleeding – meta-analysis – systematic review.

Abbreviations: FDA: Food and Drug Administration; PUD: peptic ulcer disease; RCT: randomized controlled trial; UGIB: upper gastrointestinal bleeding.

INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is a major cause of hospital admissions and is associated with significant morbidity and mortality. In the year 2012, 67 patients per 100,000 population required inpatient admission in the US [1]. Traditionally available endoscopic modalities for haemostasis include contact thermal devices (heater probe, multipolar electrocautery probes and haemostatic graspers), noncontact thermal devices (argon plasma coagulator, injection needles) and mechanical devices (band ligation, clips and loops) [2]. These haemostatic techniques have significantly contributed to the decrease in inpatient mortality [2, 3]. However, a failure to achieve haemostasis by these conventional endoscopic methods occurs in 8-15% of the cases [4].

TC-325 (Hemospray, Cook Medical, Winston-Salem, North Carolina, USA) is a biologically inert powder that was approved by the Food and Drug Administration (FDA, USA) for endoscopic haemostasis in May 2018 [5]. When the powder comes in contact with water, it acts in an adhesive and cohesive manner to form a mechanical barrier over the bleeding site [6]. It also seems to enhance clot formation and shorten the coagulation time [7]. A recent systematic review elucidated the efficacy of Hemospray as a haemostatic agent in the management of UGIB [8]. However, the quality of evidence was low with significant heterogeneity due to the inclusion of retrospective studies.

We present a meta-analysis of all prospective studies (including randomized trials) on the efficacy of Hemospray in UGIB.

METHODS

Standard Cochrane guidelines and PRISMA statement for systematic review and meta-analysis were followed during the review process [9, 10].

Eligibility criteria

The specific inclusion criteria for the systematic review and meta-analysis were: (1) randomized controlled trials (RCTs) or prospective studies in patients more than 18 years of age with follow up information of UGIB; (2) use of Hemospray as intervention for management of UGIB regardless of etiology of the bleeding, and (3) full text articles available in the English language. Any retrospective study was not eligible.

Search strategy

The search strategy was designed and conducted by the authors (H.M and A.B). Two reviewers independently and in duplicate searched PubMed, Medline, CENTRAL, EMBASE, Scopus, Web of Sciences and clinical trial registries using multiple search terms (TC-325 or Hemospray or haemostatic powder or microporous polysaccharides) from 1950 till October 2019. All titles and abstracts were identified by the authors and screened to accrue potentially eligible studies. Then, the same reviewers independently assessed all selected full-text manuscripts for the eligibility. Disagreements between two reviewers were resolved through consensus and input from a third reviewer and principal investigator.

Study characteristics and quality assessment

We selected data collection forms for RCTs based on the Cochrane Collaboration risk assessment tool to adhere to principles of sound methodological quality. For each study, we ascertained the methods of randomization sequence, allocation concealment, and identified imbalances in baseline characteristics. We used the terms "low risk" and "high risk" of bias at the study level for scoring system. Quality assessments were also conducted independently, and discrepancies were resolved by consensus.

Outcome measures

Among all the studies on Hemospray use in UGIB, those which measured immediate haemostasis and rebleeding rate were analysed in detail. Primary outcome was treatment success defined as immediate haemostasis rate. Secondary outcome was rebleeding rate within 1 to 30 days of index endoscopy. Subgroup analysis with focus on the etiology of the UGIB (tumour-related UGIB; variceal bleeding) was also similarly conducted in terms of immediate haemostasis and rebleeding rate.

Data extraction

Three reviewers (H.M., A.B., G.S.) independently reviewed and abstracted data on immediate and rebleeding for each eligible study. If there were multiple reports stemming from a specific study database, data from the most robust study was extracted with other studies contributing towards bibliography. The reviewers sorted the data separately in all stages of study collection, data extraction and quality assessment. All discrepancies found between 2 reviewers were resolved with consensus and inputs from other authors.

Quantitative data synthesis

All data were analysed by the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ; http://www.meta-analysis.com/). The final pooled risk estimates were obtained using random effects models by the methods of DerSimonian and Laird with inverse variance weighting. Raw data for immediate hemostasis and rebleeding events and non-events from each study were used to calculate a crude odds ratio (OR) for each study. The Cochrane Q and the I^2 statistics were calculated to assess heterogeneity between studies. A p value < 0.10 for chi-square test and I^2 < 20% were interpreted as low-level heterogeneity. Probability of publication bias was assessed using funnel plots and with Egger's test.

RESULTS

The preliminary search yielded 23 studies that evaluated the use of Hemospray in UGIB. We excluded the retrospective studies and only included studies with a prospective design (including randomized trials). Finally, 11 studies (with a total of 609 patients) met the inclusion criteria for the meta-analysis as shown in Fig. 1 (PRISMA flowchart) [11-21] and detailed in Table I. Subgroup analyses were also performed in regard to the etiology of bleeding (tumour-related and variceal bleeding).

Immediate haemostasis

Immediate haemostasis was defined as successful control of bleeding during the index endoscopy, as determined by the endoscopist. The pooled rate for immediate haemostasis across all studies was 93.0% (95% CI 90.3-95.0%, p<0.001) with no significant statistical heterogeneity. The Forest plot is shown in Fig. 2. Subgroup analyses were performed based on the etiology of bleeding: tumour related bleeding and variceal bleeding. In the subgroup of tumour-related gastrointestinal bleeding, the pooled immediate haemostasis rate was 95.3% (95% CI 89.6-97.3%; p <0.001) and no significant statistical heterogeneity as shown in Fig. 3. In the variceal bleeding subgroup, the pooled immediate hemostasis rate was 92.7% (95% CI 83.6-96.9%; p<0.001) and no significant statistical heterogeneity. The Forest plot is shown in Fig. 4.

We also performed a separate analysis of the three included RCTs in non-variceal UGIB. This was performed as these RCTs compared Hemospray to conventional endoscopic modalities in terms of achieving immediate haemostasis. The analysis, shown in Fig. 5, revealed that the odds of achieving immediate haemostasis are more than three times with Hemospray as compared to standard conventional therapy (OR 3.46; 95% CI 0.39-30.31). However, this was not statistically significant (p=0.27) and could be attributed to the limited number of RCTs comparing Hemospray with standard conventional therapy.

Table I. Description of included studies.

Study	Year and Location	Study Design	Sample Size	Mean Age (years)	Etiology	Location	Immediate Hemostasis	Recurrent Bleeding
Sung et al. [11]	2009-2010 Hongkong	Prospective	20	60.2	PUD only	Stomach – 30% Duodenum – 70%	19/20	2/19
Ibrahim et al. [12]	2013 Belgium Egypt	Prospective	9	66.2	Variceal only	Esophagus – 100%	9/9	0/9
Sulz et al. [13]	2014 Switzerland	Prospective	13	68.2	Nonvariceal - PUD, tumor, post-sphincterotomy, others	Esophagus – 15% Stomach – 39% Duodenum – 46 %	12/13	2/12
Ibrahim et al. [14]	2014-2016 Belgium Egypt	Prospective	30	59.5	Variceal only	Esophagus – 83% Stomach – 10% Duodenum – 7%	30/30	1/30
Pittayanon et al. [15]	2016 Thailand	Prospective	10	63.4	Tumor only	NR	10/10	1/10
Haddara et al. [16]	2013-2015 France/ Europe	Prospective	202	68.9	Non-variceal - PUD, tumor, post-endoscopic, others	NR	195/202	51/191
Kwek et al. [17]	2017 Singapore	Randomized trial	10	67.9	PUD only	Stomach – 40% Duodenum – 60%	9/10	3/9
Ibrahim et al. [18]	2014-2016 Belgium Egypt	Randomized trial	43	58.5	Variceal only	NR	39/43	1/39
Chen et al. [19]	2019 Canada	Randomized trial	8	68.2	Tumor only	NR	8/8	1/8
Baracat et al. [20]	2015-2017 Sao Paolo	Randomized trial	19	57.2	Non-variceal – PUD, tumor, post-sphincterotomy, others	Esophagus – 5%; Stomach-47% Duodenum – 47%	19/19	5/19
Alzoubaidi et al. [21]	2016-2018 London	Prospective	118	71.0	PUD, tumor, variceal, others	NR	156/173	17/156

PUD: peptic ulcer disease; NR: not reported

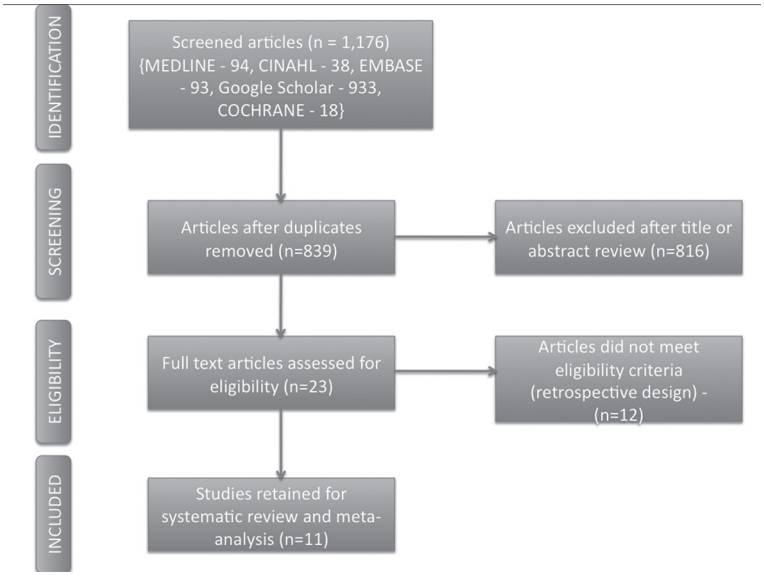

Fig. 1. PRISMA flow diagram of the article selection process.

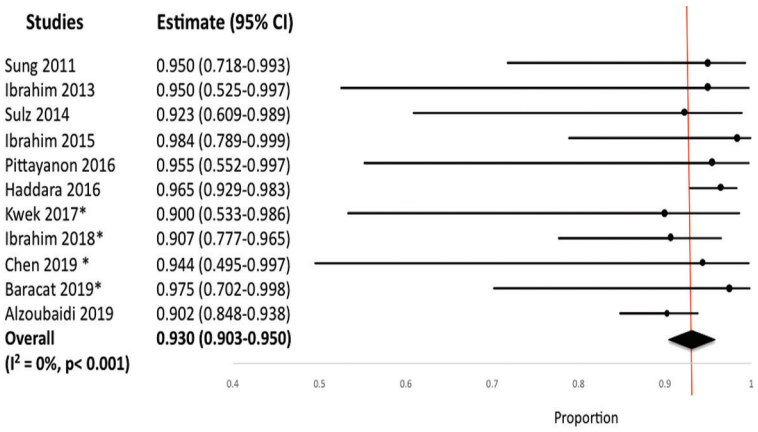

Fig. 2. Pooled Immediate Hemostasis Rate.

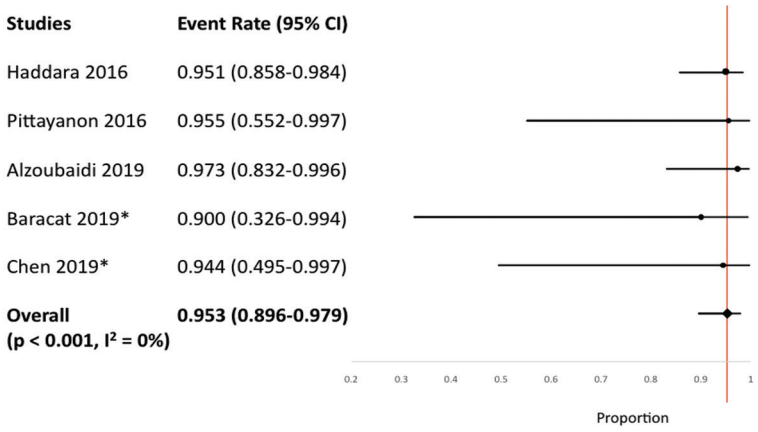

Fig. 3. Hemostasis Rate for Tumor Bleeding.

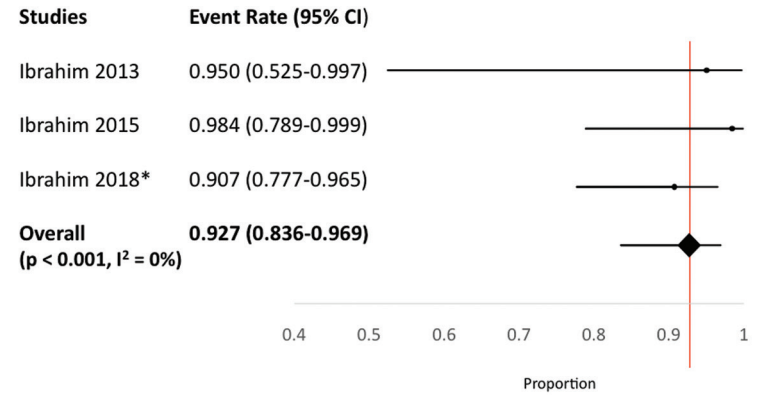

Fig. 4. Hemostasis Rate for Variceal Bleeding.

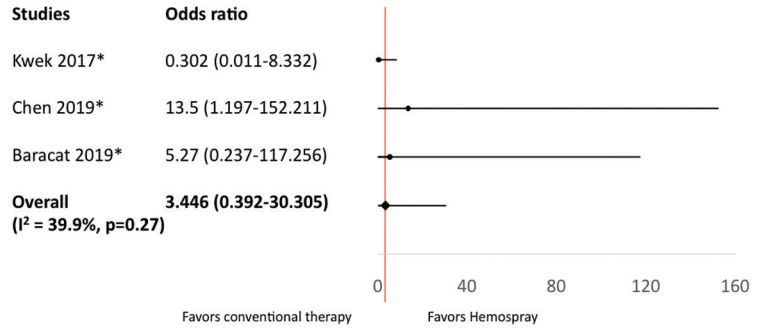

Fig. 5. Hemospray vs Conventional therapy in NVUGIB.

Rebleeding Rate

We defined rebleeding for our analysis as endoscopic visualization of rebleeding during a second-look endoscopy or any new episode of overt bleeding (hematemesis, melena) with a drop in haemoglobin after the index endoscopy. The included studies had varying definitions for rebleeding event. The time to rebleeding ranged from 12 hours to 30 days post index endoscopy across the studies [11-21]. The pooled rebleeding

rate across all studies was 14.4% (95% CI 8.8-22.8%, p<0.001) as shown in Fig. 6. The lack of uniformity led to substantial statistical heterogeneity (I^2 = 61.9%) and these results should therefore be interpreted with caution.

Subgroup analyses were also performed on the basis of etiology of UGIB: tumour related bleeding and variceal bleeding. In the subgroup of tumour-related bleeding, the pooled rebleeding rate was 21.9% (95% CI 13.9%-32.7%, p <0.001) and no significant statistical heterogeneity. The Forest plot for tumour related rebleeding is shown in Fig. 7. The subgroup of variceal bleeding revealed a pooled rebleeding rate of 3.1% (95% CI 0.9%-10.2%, p <0.001) and no statistical heterogeneity, as shown in Fig. 8.

Safety of hemospray

The three potential side-effects of Hemospray include an allergic reaction to the powder, intestinal obstruction (as a consequence of sloughing off the powder from the gastrointestinal wall) and systemic embolization. The FDA contraindicates the use of Hemospray in the presence of a suspected or confirmed gastrointestinal perforation, which should always be kept in mind before considering its use.

None of the above-mentioned side-effects were reported uniformly across the included studies. Only Baracat et al. [20] reported a case of distal esophageal perforation before or during the use of Hemospray. Therefore, limited data was available for the analysis of safety of Hemospray from the included studies and statistical analysis was not feasible.

Publication bias

Publication bias of the published studies was evaluated using Funnel plot shown in Fig. 9. The observed effect was close to the imputed effect using a random model. Egger's test confirmed no significant publication bias with a p value of 0.22.

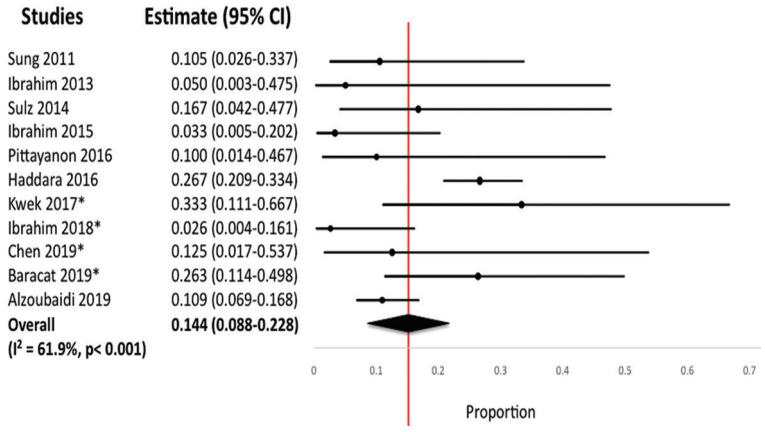

Fig. 6. Pooled Rebleeding Rate.

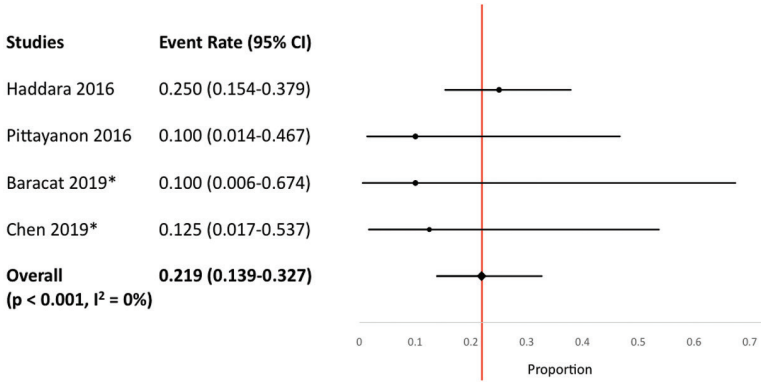

Fig. 7. Tumor Rebleeding Rate.

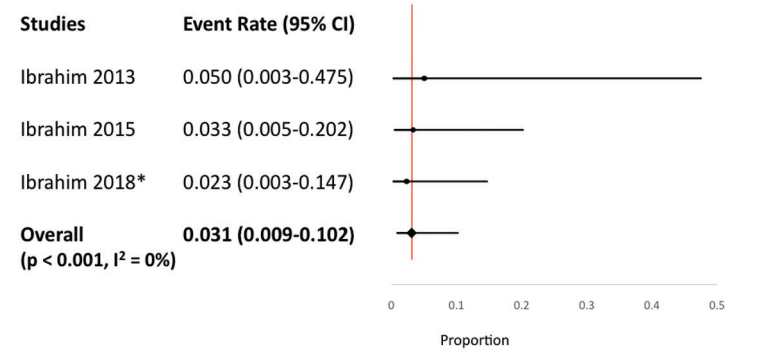

Fig. 8. Variceal Rebleeding Rate.

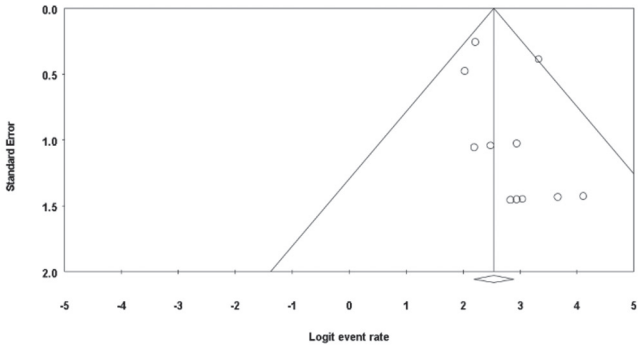

Fig. 9. Funnel Plot for publication bias.

Study quality and assessment

The Cochrane risk assessment tool [22] was utilized to assess the quality of the RCTs in the analysis as shown in Figs. 10 and 11. All the RCTs utilized random sequence generation either in blocks or 1:1 generation, which is an adequate method of reducing selection bias. However, only Chen et al. [19] described the concealment process in detail. They selected patients who were considered to have a malignant lesion, thereby creating possible selection bias. Therefore, selection bias in the cohorts cannot be completely excluded from the studies. Similarly, three out of the four trials did not describe the blinding process and therefore, performance bias and observer bias cannot be ascertained. However, all the studies reported all the outcomes decreasing the possibility of attrition and reporting bias.

Newcastle-Ottawa Scale [23] was utilized to assess the quality of prospective studies as summarized in Table II. All the prospective studies had documented bleeding during endoscopy with cases representative of population where Hemospray would be used. However, lack of controls and adjustment of confounders in the studies (except Pittayanon et al. [15]) indicates inadequate comparability. All the prospective studies did have adequate follow up of the cohort to determine the outcomes to ascertain results.

DISCUSSION

The management of UGIB is an ever-growing area of interest and research. The efficacy of Hemospray in the management of UGIB has recently been illustrated in a systematic review and meta-analysis by Facciorusso et al [8]. The need for another meta-analysis stems from the fact that their analysis included a large number of retrospective studies, limiting their results owing to the low quality of included studies. There was moderate to high level of statistical heterogeneity across the different analyses. Additionally, since their analysis, three more prospective studies (including two randomized trials) evaluating Hemospray in UGIB have been published, adding to the body of literature and further necessitating the need for another analysis. Our analysis includes only prospective studies and therefore provides robust results supporting the use of Hemospray as an effective agent for haemostasis in UGIB, regardless of the etiology of bleeding. We report a pooled immediate haemostasis rate of 93.0% and a rebleeding rate of 14.4%. Subgroup analyses for various etiologies of UGIB have also yielded similar results. For our primary outcome of immediate haemostasis, there is no statistically significant heterogeneity across all analyses.

The current standard of care for management of nonvariceal UGIB involves combination therapy with two different techniques (injection, cautery, clipping, etc) that require

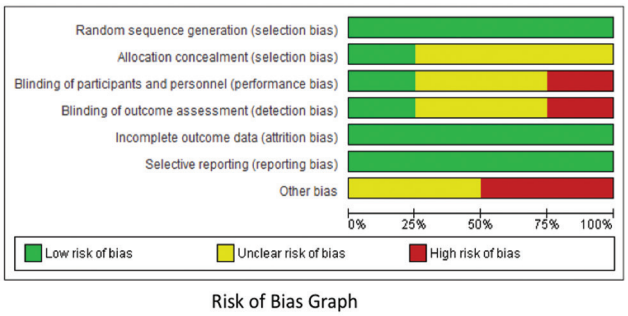

Fig. 10. Cochrane Risk of Bias Graph for RCTs included in the review.

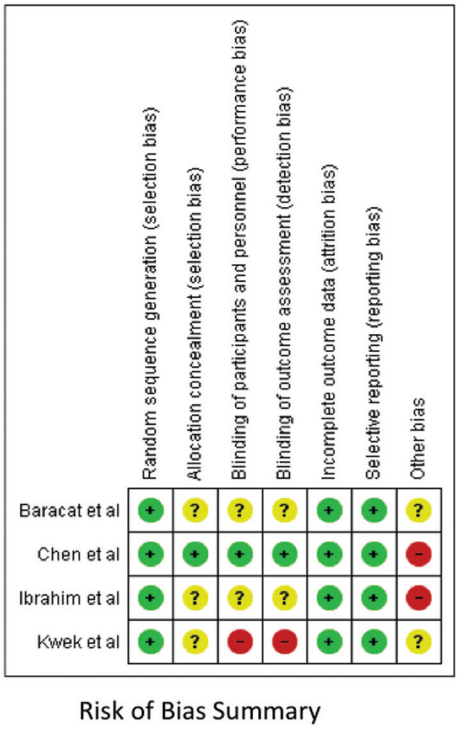

Fig. 11. Cochrane Risk of Bias Summary for RCTs included in the review.

Table II. Newcastle-Ottawa Quality Assessment Scale for the cohort studies evaluated.

Study	Selection	Comparability	Outcome
Sung et al. [11]	**		**
Ibrahim et al. [12] (2013)	**		**
Ibrahim et al. [14] (2015)	**		**
Sulz et al. [13]	***		**
Pittayanon et al. [15]	***	**	***
Haddara et al. [16]	***		**
Alzoubaidi et al. [21]	**		**

direct visualization and contact with the bleeding site [24]. Hemospray is a non-thermal, non-traumatic, non-contact modality that does not require en-face targeting of the bleeding source. Bleeding lesions such as ulcers located at anatomically difficult locations such as the posterior duodenal wall and proximal lesser curve of the stomach, which are difficult to control via conventional endoscopic techniques [25], may be easier to manage with Hemospray. The application of Hemospray involves deployment of the powder through a delivery catheter which is easy to use and does not require a great deal of technical skill or expertise.

A particular subgroup of patients that deserves special mention is that of tumour-related bleeds. For malignant UGIB, our subgroup analysis yielded a pooled immediate haemostasis rate of 95.3% with Hemospray, with a rebleeding rate of 21.9%. This compared much more favourably to the reported immediate haemostasis rate of 40% and rebleeding rate up to 30% with conventional endoscopic therapies [26, 27]. Luminal bleeding from gastrointestinal malignancies has always been harder to control with conventional endoscopic techniques because of their friability and diffuse bleeding surfaces. Any mechanical contact with the bleeding surface often risks worsening the bleed or even perforation. A non-contact haemostatic agent such as Hemospray that can target multiple bleeding points seems to be ideal in such cases. We hypothesize that luminal bleeding from GI malignancies might become a standard indication for the use of Hemospray in the future. It can provide a haemostatic bridge for more definitive therapies such as surgery, radiation or radiographic embolization.

Giday et al. [28] evaluated Hemospray in porcine models and found it to be a safe, inert powder with no systemic toxicity. However, a theoretical risk of embolization especially during management of variceal bleeding has been proposed and therefore, it is only approved for use in non-variceal bleeding [5]. The use of Hemospray in variceal bleeding has been studied in two prospective cohort studies and one RCT, all authored by the same group [12, 14, 18]. Our subgroup analysis of these studies yielded an immediate haemostasis rate of 92.7% and a rebleeding rate of 3.1%. There were no reported cases of systemic embolization across all three studies. This has been attributed to the low delivery pressure (<15mmHg) at the tip of the CO_2 catheter, which is almost always lower than the intravariceal pressure [12]. The authors devised a protocol-based application of the powder from the cardia upwards to the mid-esophagus, requiring little expertise while maintaining high success rates. Though the results are promising, further safety analyses are required before the use of Hemospray in variceal bleeding can be standardized.

The main strengths of our analysis are the large number of patients (n=609) and the prospective nature of the included studies, providing a high level of evidence in regard to the efficacy of Hemospray. Our analysis is limited by the clinical and statistical heterogeneity due to varied definitions of the rebleeding rate, with rebleeding times varying from 1 to 30 days amongst the included studies. We believe 72 hours would be an ideal target to evaluate rebleeding with Hemospray as the powder usually sloughs off from the gastrointestinal mucosa within 48-72 hours. Despite including only RCTs and prospective studies, selection and performance biases cannot be completely excluded. One of the ways to decrease the impact of performance bias would be an independent blind researcher analysing the results such as described in Chen et al. [19]. The other would be the utilization of objective measures as outcomes such as blood transfusion, need for repeat endoscopy at a uniform interval or a relook by a different blinded endoscopist. Selection bias in the studies was primarily related to concealment of allocation. This was not described in detail in the RCTs and could skew the results towards favouring Hemospray. Similarly, the lack of controls along with no adjustment for confounders in prospective studies also questions their comparability. Also, since the number of studies is low, the Funnel plot may be underpowered to detect a publication bias and therefore it cannot be completely excluded. Certain groups such as patients on anti-thrombotic therapy or post-sphincterotomy bleeding were also studied but the numbers were too small to arrive at a meaningful conclusion. In another study, Holster et al. [29] studied the use of Hemospray in patients on anti-thrombotic therapy and the results look promising. These groups remain potential indications for the use of Hemospray and should be further evaluated in larger randomized studies, if possible.

CONCLUSIONS

The current evidence cannot prove without any doubt the superiority of Hemospray over conventional endoscopic modalities, since the trials assessing this comparison could not show a statistically significant difference in this respect, although the odds were in its favour. The quality of the trials was not satisfying, thus weakening the evidence. Better conducted randomized studies are required in the future. Nevertheless, its high immediate haemostasis and low rebleeding percentages, along with the previously mentioned odds in its favour, show promise. It has the advantage that it is easy to use and does not require advanced endoscopic expertise. In cases where conventional endoscopic techniques are harder to use or have limited benefits, Hemospray might be an attractive alternative.

Conflicts of interest: None to declare.

Authors' contributions: H.M., A.B.: study concepts and design, literature research; H.M., G.S., S.A., B.A: data acquisition and analysis; A.B. H.M: statistical analysis; H.M., S.A., A.G., G.S.: manuscript drafting; H.M., A.B., A.G., S.A.: manuscript revision for important intellectual content; All authors approved the final version of the manuscript.

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