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Hemostatic spray (TC-325) vs. standard endoscopic therapy for non-variceal gastrointestinal bleeding: A meta-analysis of randomized controlled trials

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Authors
Smit S. Deliwala*,[1], Saurabh Chandan*,[2], Babu P. Mohan[3], Shahab Khan[4], Nitin Reddy[5], Daryl Ramai[3], Jay A. Bapaye[6], Dushyant Singh Dahiya[7], Lena L. Kassab[8], Antonio Facciorusso[9], Saurabh Chawla[1], Douglas Adler[10]

Institutions
1 Division of Digestive Diseases, Emory University, Atlanta, Georgia, United States
2 Gastroenterology & Hepatology, Creighton University School of Medicine, Omaha, Nebraska, United States
3 Gastroenterology & Hepatology, University of Utah Health School of Medicine, Salt Lake City, Utah, United States
4 Harvard Medical School, Boston, Massachusetts, United States
5 Department of Internal Medicine, PSG Institute of Medical Science, Coimbatore, Tamil Nadu, India
6 Department of Medicine, Rochester General Hospital, Rochester, New York, United States
7 Department of Internal Medicine, Central Michigan University College of Medicine, Saginaw, Michigan, United States
8 Mayo Clinic, Rochester, Minnesota, United States
9 Gastroenterology Unit, University of Foggia, Foggia, Italy
10 Center for Advanced Therapeutic Endoscopy, Centura Health, Denver, Colorado, United States

Corresponding author
Smit S. Deliwala, Emory University School of Medicine – Division of Digestive Diseases, 615 Michael Street, Suite 201, Atlanta, GA 30303-3073
Phone: +1-810-262-9000
sdeliwa@emory.edu

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

ABSTRACT

Background and study aims Hemospray (TC-325) is a mineral powder with adsorptive properties designed for use in various gastrointestinal bleeding (GIB) scenarios. We conducted a systematic review & meta-analysis of randomized controlled trials (RCTs) comparing TC-325 to standard endoscopic therapy (SET) for non-variceal GIB (NVGIB).

Methods Multiple databases were searched through October 2022. Meta-analysis was performed using a random-effects model to determine pooled relative risk (RR) and proportions with 95 % confidence intervals (CI) for primary hemostasis, hemostasis failure, 30-day rebleeding, length of stay (LOS), and need for rescue interventions. Heterogeneity was assessed using I^2%.

Results Five RCTs with 362 patients (TC-325 178, SET 184) – 123 females and 239 males with a mean age 65 ± 16 years). The most common etiologies were peptic ulcer disease (48 %), malignancies (35 %), and others (17 %). Bleeding was characterized as Forrest IA (7 %), IB (73 %), IIA (3 %), and IIB (1 %). SET included epinephrine injection, electrocautery, hemoclips, or a combination. No statistical difference in primary hemostasis between TC-325 compared to SET, RR 1.09 (CI 0.95–1.25; I^2 43), P = 0.2, including patients with oozing/spurting hemorrhage, RR 1.13 (CI 0.98–1.3; I^2 35), P = 0.08. Failure to achieve hemostasis was higher in SET compared to TC-325, RR 0.30 (CI 0.12–0.77, I^2 0), P = 0.01, including patients with oozing/spurting hemorrhage, RR 0.24 (CI 0.09 – 0.63, I^2 0), P = 0.004. We found no differ-

* These authors contributed equally.

ence between the two interventions in terms of rebleeding, RR 1.13 (CI 0.62–2.07, I^2 26), $P=0.8$ and LOS, standardized mean difference (SMD) 0.27 (CI, −0.20–0.74; I^2 62), $P=0.3$. Finally, pooled rate of rescue interventions (angiography) was statistically higher in SET compared to TC-325, RR 0.68 (CI 0.5–0.94; I^2 0), $P=0.02$.

Conclusions Our analysis shows that for acute NV GIB, including oozing/spurting hemorrhage, TC-325 does not result in higher rates of primary hemostasis compared to SET. However, lower rates of failures were seen with TC-325 than SET. In addition, there was no difference in the two modalities when comparing rates of rebleeding and LOS.

Introduction

Acute gastrointestinal bleeding (GIB) is a medical emergency and carries significant morbidity and mortality [1,2]. Endoscopy is the diagnostic and therapeutic procedure of choice and is often indicated within the first 24 hours [3,4].

Over the years, numerous therapeutic options have been developed to provide the optimal strategy for hemostasis; however, success rates often vary depending on the location of the lesion, etiology, patient factors, and endoscopist expertise. The existing armamentarium includes injection needles, thermal devices, electrocoagulation probes, forceps, clips (through-the-scope and cap-mounted), endoscopic suturing, banding devices, and hemostatic powders [5,6]. However, technical aspects such as difficult anatomic position of the bleeding lesion (including the posterior wall of the duodenal bulb and the lesser curvature of the gastric body) and intense or diffuse bleeding may impact the efficacy of some of these therapeutic modalities [7].

The use of an inorganic hemostatic powder, such as Hemospray (Cook Endoscopy, Winston Salem, NC) or TC-325, has become popular in the last few years for various GIB scenarios, including for non-variceal and malignant bleeding lesions [8]. Systematic reviews of observational cohort studies have reported high rates of initial hemostasis (>90%) and >15% rate of recurrent bleeding with TC-325 use [9,10]. Recently published outcomes from a 5-year international multicenter registry reported a 100% hemostasis rate with Hemospray use in malignant bleeds and suggested that its use as monotherapy is feasible in routine clinical care [11]. Additionally, a cost-effectiveness analysis found Hemospray economical as a first-line strategy [12].

The American College of Gastroenterology (ACG), as a conditional recommendation, suggests using hemostatic spray in non-variceal upper GIB for bleeding ulcers [4]. In contrast, the European Society of Gastrointestinal Endoscopy (ESGE) preferred its use in cases of refractory GIB [1]. However, both these recommendations were backed by very low-quality evidence. While multiple prior meta-analyses have been conducted to better address our gap in knowledge [13–16], comparative outcomes with standard endoscopic therapy (SET) have yet to be thoroughly evaluated.

Recently, several randomized controlled trials (RCTs) have reported outcomes of TC-325 compared to SET in non-variceal GIB (NVGIB), especially high-risk peptic ulcers and malignant bleeding lesions [17–19]. The aim of the study was to systematically appraise the published literature and compare the efficacy of Hemospray (TC-325) to SET in patients with NVGIB.

Methods

Protocol and registration

This review was designed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement to identify studies reporting clinical outcomes of hemostatic power (Hemospray or TC-325) [20].

Eligibility criteria, literature search, and search strategy

A librarian conducted a systematic search of several databases and conference proceedings, including EBM reviews via Ovid, Ovid Embase (1974+), Ovid Medline (1946+including epub ahead of print, in-process, and other non-indexed citations), PubMed, EMBASE, Google Scholar, LILACS, SCOPUS, and Web of Science databases in October 2022. Keywords used in the literature search included a combination of "TC-325", "Hemostatic powder", "Hemospray", "gastrointestinal bleeding," OR "GI bleeding". The search was restricted to studies on human subjects in English. Duplicates were filtered using EndNote. Reference lists of identified sources were cross-checked for additional relevant studies by SD and LK). The complete search strategy is available in Supplementary Appendix-A.

Study selection

[Heading 2]We included RCTs comparing Hemospray to standard therapy in patients with NVGIB. Studies were included irrespective of whether they were performed in inpatient or outpatient settings, follow-up time, and country of origin if they provided the appropriate data needed for the analysis. Our exclusion criteria were as follows: (1) observational cohort studies reporting outcomes of TC-325 without a comparative arm; (2) single patient case reports and case series studies; (3) studies with sample size <10 patients; (4) studies reported on variceal bleeding; and (5) studies performed in the pediatric population (Age <18 years). In cases of multiple publications from a single research group reporting on the same patient cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained. The retained studies were determined based on the publication timing (most recent) and/or the sample size of the study (largest). PRISMA Flowchart for study selection and PRISMA Checklist are provided in Supplementary Fig. 1 and Supplementary Appendix B,

respectively. Reference lists of evaluated studies were examined to identify other studies of interest.

Data abstraction and quality assessment

Data on study-related outcomes were abstracted onto an a priori-designed Google sheet by two authors (NR, JAB), while two authors (SD, SC) completed the quality scoring independently [21]. The Jadad scale was used to assess the quality of studies. A score of 2 or less is considered low, 3 to 4 is moderate, and 5 is of excellent quality [22].

Outcomes assessed

The primary outcome was primary hemostasis, defined as endoscopically verified cessation of bleeding for 3 to 5 minutes or control of bleeding within 30 days of randomization, defined as achievement of endoscopic hemostasis by the assigned treatment modality during the first endoscopy and no recurrent bleeding after endoscopic hemostasis.

The second outcomes were as follows. Failure to achieve hemostasis was defined as recurrent bleeding during index intervention necessitating cross-over to alternative therapeutic modality. Rebleeding was defined as a drop in hemoglobin of 2 g/dL or more, a new episode of hematemesis/melena/hematochezia, red blood content from a nasogastric or oro-gastric tube, or rebleeding identified during second look/repeat endoscopy up to 30 days after the index procedure. Length of stay (LOS) was defined as the duration of hospitalization post-index endoscopy. Rescue interventions were failed endoscopic management necessitating rescue intervention, including arteriography, angiography, and/or surgery. Mortality was death from any cause within the first 30 days after index intervention.

Statistical analysis

Meta-analysis techniques were used to calculate the pooled risk ratios (RR) with pooled estimates and 95 % confidence intervals (CI) and mean difference (SMD) using a random-effects model. A continuity correction of 0.5 was added to incident cases before analysis [23] We assessed heterogeneity using Cochran Q statistical test for heterogeneity with I^2 statistics [24–26]. In this, values < 30 %, 31 % to 60 %, 61 % to 75 %, and > 75 % were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively. Publication bias was ascertained qualitatively by visual inspection and quantitatively by the Egger test. When publication bias was present, further statistics using the fail-Safe N test and Duval and Tweedie's 'Trim and Fill' test were used to ascertain the impact of the bias [27]. All analyses were performed using comprehensive meta-analysis (CMA) V3 software (Englewood, New Jersey, United States).

Results

Search results and population characteristics

All search results were exported to EndNote, where 2303 obvious duplicates were removed, leaving 2342 citations. All titles were extracted and screened, and 145 full-length articles were reviewed in detail. A schematic diagram demonstrating our study selection is illustrated in Supplementary Fig. 1.

The final analysis included five RCTs with 362 patients (TC-325 178, SET 184) [17–19, 28,29]. There were 123 females and 239 males (mean age 65 ± 16 years). The most common etiologies of bleeding were PUD in 173 (TC-325 87, SET 86) and upper and lower GI malignancies in 123 and 3 patients, respectively (TC-325 71, SET 55). Other etiologies included Mallory-Weiss in 15 patients, post-sphincterotomy bleeding in four, Dieulafoy lesions in 24, reflux esophagitis, esophageal erosion, ischemic gastritis, gastric amyloidosis, diffuse hemorrhage from erosive gastritis, portal hypertensive gastropathy, angiodysplasia, and antral vascular ectasia in 12 patients. The etiology was not only reported as others in eight and. The mean peptic ulcer size was 11.61 ± 8.4 mm (TC-325 11.58 ± 8.2 mm, standard therapy 11.63 ± 8.68 mm).

Characteristics and quality of included studies

Two studies were conducted in Brazil [19, 29], one in Canada [18], and two in Singapore [17, 28]. Bleeding was characterized as Forrest IA in 26 (T-325 13, SET 13), IB in 264 (TC-325 131, SET 133), IIA in 10 (TC-325 4, SET 6), and IIB in two patients (TC-325 1, SET 1). In three studies, hemorrhage was characterized as oozing and spurting [17, 18, 29]. All studies reported using TC-325 as the index intervention, while SET included endoscopic hemoclips, saline adrenaline injections (1:10,000 in four quadrants in 0.5–2 ml aliquots), heater probe, bipolar electrocautery, argon plasma coagulation, and/or laser photocoagulation. In one trial, a combination of epinephrine injection and TC-325 was used [29], while TC-325 was used as monotherapy in all the others. Reported time to verify bleeding cessation during index endoscopy – three minutes [18, 19, 29], five minutes [28], and unspecified [17]. Further details of included studies and patient characteristics are presented in ▶ **Table 1** and ▶ **Table 2**. The majority of included studies were moderate [17, 19, 28] and excellent quality [18] with one low-quality (Supplementary Table 1) [29].

Meta-analysis outcomes

There was no statistical difference in the pooled rates of primary hemostasis between TC-325, 91 % (CI 85.4–94.6) compared to SET, 79.1 % (CI 53.9–92.5), RR 1.09 (CI 0.95–1.25; I^2 43), $P = 0.2$, including in patients with oozing/spurting hemorrhage (Forrest IA, IB), RR 1.13 (CI 0.98–1.3; I^2 35), $P = 0.08$ (▶ **Fig. 1**).

Given the variation in definition of primary hemostasis, as reported by Lau et al, we performed a subgroup analysis excluding this study. We found no statistical difference between the rates of primary hemostasis between the two modalities, RR 1.11 (CI 0.83–1.48; I^2 61), $P = 0.5$. [17].

The pooled rate of failure to achieve hemostasis was higher in SET, 16.5 % (CI 4.4–45.7) compared to TC-325, 4.3 % (CI 1.9–9.5), RR 0.30 (CI 0.12–0.77, I^2 0), $P = 0.01$, including among patients with oozing/spurting hemorrhage (Forrest IA, IB), RR 0.24 (CI 0.09–0.63, I^2 0), $P = 0.004$ (▶ **Fig. 2**).

There were no statistical differences in the pooled rates of rebleeding between TC-325, 20.8 % (CI 10.6–36.6) compared to SET, 18.8 % (CI 8.8–37.3), RR 1.13 (CI 0.62–2.07; I^2 43), $P = 0.7$ (▶ **Fig. 3**).

▶ **Table 1** Study details and population characteristics.

Study	Design	Standard therapy	Total patients		Age (mean, SD, y)		Gender (male/female)		Etiology		Ulcer size (mm)	
			TC 325	Standard	TC 325	Standard	TC 325	Standard	TC 325	Standard	TC 325	Standard
Kwek 2017 [28]	Prospective, RCT, December 2013 to February 2015, single-center, Singapore	Clip + epinephrine injection/coagulation + epinephrine injection	10	10	67.9 (18.4)	72.1 (11.4)	9/1	7/3	PU 10 (Forest IA 1, IB, 4, IIA 4, IIB 1)	PU 10 (Forest IB, 3, IIA 6, IIB 1)	10.3 5.4	13.1 3.2
Baracat 2020 [29]	Prospective, RCT, July 2015 to July 2017, single-center, Brazil	Hemoclips + epinephrine injection	19 (Forest IA/IB)	20 (Forest IA/IB)	57.2 (16.2)	56.5 (15.6)	14/5	12/8	PU 9, Malignancy 4, others 6 (Forest IA 2, IB 16)	PU 8, Malignancy 1, others 11 (Forest IA 1, IB 19)	NR	NR
Chen 2020 [18]	Prospective, RCT, April 2014, dual-center, Canada	Heater probe, bipolar electrocautery, APC, and laser photocoagulation & Injection treatments (Epinephrine injection and Sodium tetradecyl sulfate)	10 (Forest IA/IB)	10 (Forest IA/IB)	68.2 (9.7)	66.1 (20.9)	7/3	8/2	Malignancy 10 (Forest IA 1, IB 9)	Malignancy 10 (Forest IA 0, IB 10)	NR	NR
Lau 2022 [17]	Prospective, RCT, September 2015 to December 2018, Multicenter, Hong Kong, Thailand, Singapore	Heater probe or Bipolar probe or Hemoclips with or without prior injection of diluted Epinephrine	111 (Forest IA/IB)	113 (Forest IA/IB)	68.5 (15.0)	66.3 (16.7)	77/34	73/40	PU 68, malignancy 29, other 14 (Forest IA 9, IB 102)	PU 68, malignancy 13, other 32 (Forest IA 12, IB 101)	11.7 (8.4)	11.5 (9.0)
Costa Martins 2022 [19]	Prospective, RCT, August 2016 to February 2020, single-center, Brazil	Epinephrine injection, clipping, argon plasm coagulation or others	28	31	55 (15.3)	62.1 (12.1)	10/8	12/6	Malignancy 28	Malignancy 31	NR	NR

RCT, randomized controlled trial; NR, not reported.

▶ **Table 2** Study outcomes.

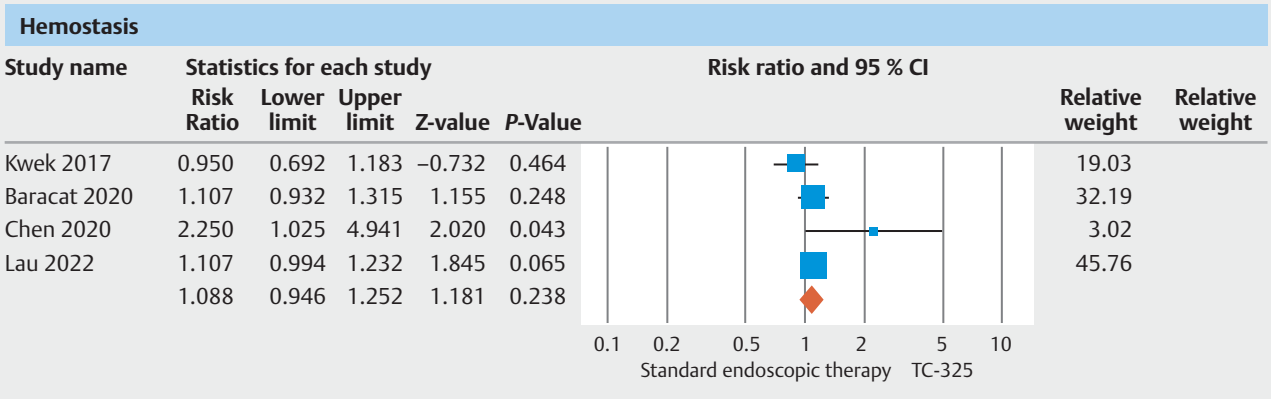
Study	Outcomes									
	Primary hemostasis		Failure		Rebleeding (30 d)		Length of hospital stay (range)		Rebleeding treatment	
	TC 325	Standard	TC 325	Standard	TC 325	Standard	TC 325	Standard	TC 325	Standard
Kwek 2017 [28]	9/10	10/10	1/10	0/10	3/10	1/10	NR	NR	2 endoscopy 1 angiography	1 endoscopy 0 angiography
Baracat 2020 [29]	19/19	18/20	0/19	2/20	5/19	3/20	11.00 (10.09)	5.94 (3.82)	1 surgery	0 surgery
Chen 2020 [18]	9/10	4/10	1/10	6/10	2/10	6/10	14.6 (9.9)	9.4 (6.1)	1 angiography 4 radiation 1 surgery	1 angiography 3 radiation 2 surgery
Lau 2022 [17]	100/111	92/113	3/111	11/113	9/111	10/113	6 (1–90) (after randomization)	6 (1–107) (after randomization)	8 endoscopy 2 angiography 1 surgery	10 endoscopy 4 angiography 0 surgery
Costa Martins 2022 [19]	22/22	NR	0/18	NR	9/28	6/31	17.4 (± 17.7)	12.8 (± 14.1)	1 surgery 0 arteriography 12 radiotherapy	2 surgery 16 radiotherapy 2 arteriography

NR, not reported.

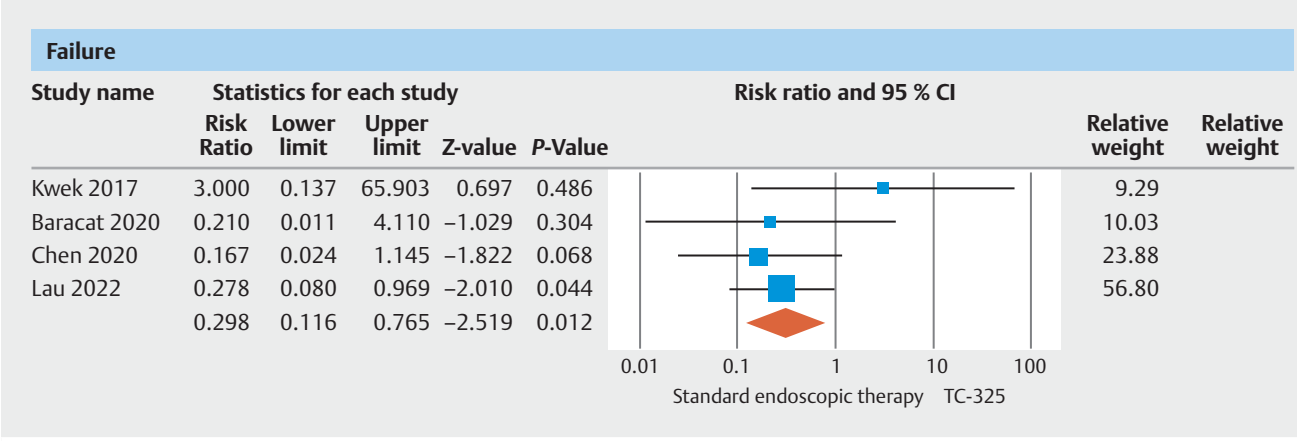
There was no statistical difference in the overall LOS between TC-325 and SET, with standardized mean difference (SMD) 0.27 (CI, –0.20–0.74; I^2 62), P=0.3 (Supplementary Fig. 2).

Pooled rates of rescue interventions necessitating arteriography and/or angiography were higher in SET, 20% (CI 1.7–78.4) compared to TC-325, 13.2% (CI 1.3–16.5), RR 0.68 (CI 0.5–0.94, I^2 0), P=0.02 (Supplementary Fig. 3). There was no statistical difference in the pooled rates of rescue surgery between TC-325, 4.3% (CI 1.7–10.7) and SET, 4% (CI 0.9–15.8), RR 1.11 (CI 0.3–3.7; I^2 0), P=0.9 (Supplementary Fig. 4).

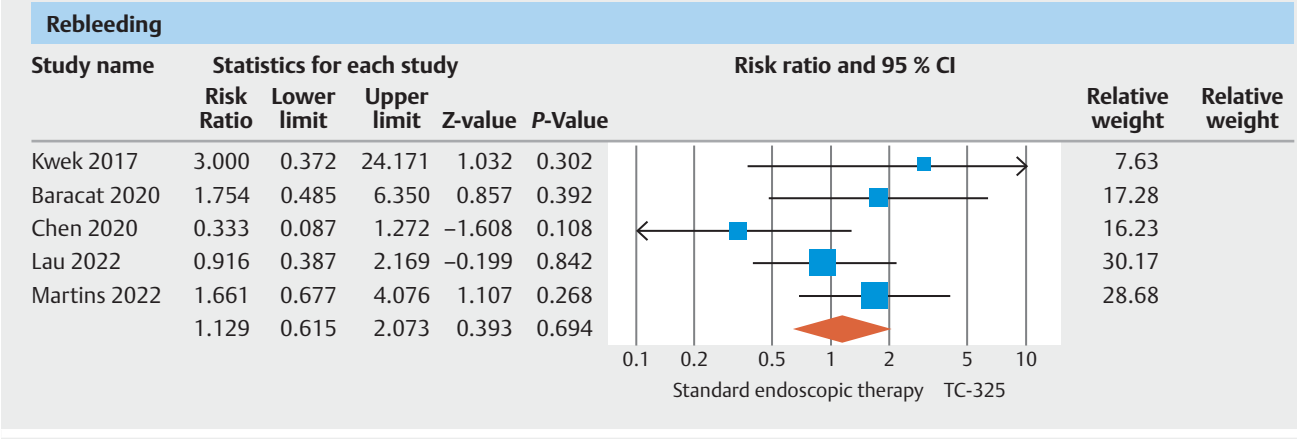
Pooled rates of all-cause mortality were higher in TC-325, 18.9% (CI 10.6–31.4), compared to SET, 14.9% (CI 10.2–21.3), however, the difference between the two was not statistically significant, RR 1.14 (CI 0.69–1.9, I^2 0), P=0.6 (Supplementary Fig. 5).



▶ **Fig. 1** Forest plot of primary hemostasis.



▶ **Fig. 2** Forest plot of failure to achieve hemostasis.



▶ **Fig. 3** Forest plot of rebleeding.

Validation of meta-analysis results

Sensitivity analysis

To assess whether any study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its impact on our main summary estimate. While numerically higher, we found no statistical difference in the pooled rates of primary hemostasis between TC-325 and SET groups, RR 1.13 (CI 0.98–1.3; I^2 35), $P=0.08$. Upon sensitivity analysis and removing the study by Kewk et al, we noticed that the difference did reach statistical significance. This may be because of several reasons. Firstly, this manuscript was from a pilot feasibility study where only 20 patients were randomized to TC-325 and SET. Furthermore, only 40 % (8/20) had actively bleeding Forrest Ia or Ib ulcers. Five of these patients received Hemospray (including one ulcer that extended into the retroperitoneum), and only three with Forrest Ia or Ib ulcers received standard dual therapy. Since TC-325 requires active bleeding to achieve hemostasis and is not recommended for patients with non-bleeding vessels, data regarding initial hemostasis and rebleeding rates from this study are difficult to assess [28].

Heterogeneity

We assessed the dispersion of the calculated rates using the CI and I^2 percentage values. The overall distribution of effects was minimal to low based on the 95 % CI and I^2% values across included studies.

Publication bias

Based on visual inspection of the funnel plot and quantitative measurement that used the Egger regression test, there was no evidence of publication bias for hemostasis and failure (Egger's 2-tailed z = 0.31, p = 0.81 and Egger's 2-tailed z = 0.60, $P=0.74$) (Supplementary Fig. 6 and Supplementary Fig. 7).

Discussion

Our analysis, based on data from randomized controlled trials (RCTs), shows that among patients with NVGIB, there is no significant difference in the rates of primary hemostasis, rebleeding, length of hospital stays, or need for rescue surgery between Hemospray (TC-325) and standard endoscopic therapy (SET). Our findings suggest that monotherapy with TC-325

may be a viable option for NVGIB, including actively bleeding peptic ulcers and malignancies, even though TC-325 is not typically used in this manner and can be cost-prohibitive.

Current guidelines have suggested using TC-325 as a temporizing measure that should be followed by a second definitive hemostatic modality [30, 31]. This is because TC-325 sloughs off the mucosa and is eliminated from the gastrointestinal tract within 24 hours after application, and subsequent bleeding is common in observational studies of TC-325. Furthermore, SET may fail to achieve successful hemostasis in 8% to 15% of patients with active peptic ulcer bleeding, and rebleeding occurs in 5% to 10% of patients after initial hemostasis using combined endoscopic therapy [32, 33]. Due to its ability to be applied to difficult-to-reach sites and treat large areas where the exact location of bleeding is unknown, TC-325 offers a viable alternative to SET [10, 34]. Our pooled analysis shows similar rates of primary hemostasis between TC-325 monotherapy and SET, adding to the current body of literature on the efficacy of TC-325.

When assessing failure to achieve hemostasis, we found that pooled rates were significantly higher with SET than with TC-325. These results must be reviewed with caution since failure rates of SET were notably higher in two studies [17, 18], which included 62 patients with oozing and/or spurting malignant GIB. However, after analyzing the data after removing the studies, failure rate was 6.2% (1.2%–26%) for TC-325 and 8.5% (2.5%–25.4%) for SET. It is known that endoscopic therapy for malignant GIB is generally less successful and can be technically challenging because of the large surface area of tissue requiring treatment, tissue friability, and underlying coagulopathy. Data regarding the efficacy of SET for malignant GIB is variable, with primary hemostasis rates reported between 31% and 86% and rebleeding rates between 28% and 80% [35–37]. A recent meta-analysis found TC-325 to be highly effective in this scenario with a success rate of 94% and rebleeding rates between 11% to 24% [8]. In our analysis, 126 patients with malignant GIB were included, of which 71 were randomized to TC-325 and 55 to SET. While we found no statistical difference in rates of rebleeding or primary hemostasis between the two modalities, it must be emphasized that our patient population was heterogeneous, including a combination of patients with benign and malignant etiologies of GIB. We believe that further studies are needed to confirm if TC-325 indeed has equivalent efficacy compared to SET when considering specific underlying etiologies of GIB.

There are several strengths to our analysis that are worth mentioning. First, we only included RCTs to give us the most robust evidence of efficacy between TC-325 and SET. Second, as part of our meta-analysis, we performed a comparative pairwise analysis of studies where outcomes of patients with oozing and/or spurting hemorrhage (Forrest IA and IB) were reported and found that the two modalities did not differ in terms of primary hemostasis and rebleeding. Third, we conducted a systematic literature search with well-defined inclusion criteria, careful exclusion of redundant studies, and inclusion of good quality studies with detailed extraction of data and rigorous evaluation of study quality.

This study also has several limitations, most of which are inherent to any meta-analysis. First, our analysis only included five RCTs of a heterogeneous population with various GIB etiologies. In addition, we were unable to report outcomes separately for patients with PUD and malignant GIB. Second, while a vast majority of patients in our analysis with malignant GIB had an upper gastrointestinal source, three patients were included with a lower GIB source. Third, 21 patients required repeat endoscopy to treat rebleeding episodes (TC-325 10, SET 11), there were insufficient data to calculate pooled outcomes of comparison between the two groups. Fourth, while all studies defined primary or initial hemostasis as achieving successful endoscopic hemostasis within 3 to 5 minutes of intervention during the index endoscopy, this outcome was defined differently in the study by Lau et al. Fifth, in one of the included trials, only data regarding rebleeding episodes, LOS, and rescue interventions was reported between the two modalities. Outcomes regarding primary hemostasis were not reported [19]. Most of the trials included in our analysis were performed in similar geographic locations, limiting the generalizability of our results. Finally, we were unable to perform a cost-effectiveness analysis between TC-325 and SET, as the included trials did not report information on the same.

Conclusions

Overall, our analysis demonstrates that compared to SET, TC-325 monotherapy may be an acceptable therapeutic option for patients with acute non-variceal GIB, including those with oozing/spurting hemorrhage from gastrointestinal malignancies and peptic ulcer disease, and those lesions that are difficult to treat with SET. We found no difference in the two modalities when comparing rates of rebleeding and LOS.

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Competing interests

Douglas Adleris a consultant for Boston Scientific. All other authors have no conflict of interest or any economic/personal ties to declare.

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