TC-325 as monotherapy for acute gastrointestinal bleeding: a multi-center prospective study

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Abstract

Background

Topical hemostatic powders are a reliable second-line approach in acute gastrointestinal (AGIB) bleeding treatment, according to the existing guidelines. Increasing evidence supports the use of TC-325 as monotherapy in specific GI bleeding scenarios. This prospective, multi-center study evaluated the performance of this measure as monotherapy to GI hemorrhage.

Methods

Eighteen centres across Europe, USA, and Australia contributed between 2016 and2022 to an international multicentre prospective regisrty. Adults with AGIB were eligible (melena, hematemesis, hematochezia or Glascow-Blatchford score ≥1 or abnormal Oakland score), or when TC-350 was part of combined hemostasis (adjunctive to clips or thermocautery). The primary endpoint was immediate heamostasis with rebleeding, 7- and 30-day mortality rates being secondary outcomes. Potential associations with risk factors were investigated with statistical significance set for $p \leq 0.05$.

Results

One hundred and ninety patients were included (age=51-81, male:female= 2:1). Peptic ulcer (n=48), upper GI malignancy (n=79), post endoscopic treatment-related hemorrhage (n=37), and lower GI lesions (n=26) were diagnosed. The primary outcome was recorded in 96.3% (95%CI:92.6-98.5) and rebleeding in 17.4% (95%CI:11.9-24.1) when TC-350 was used as primary monotherapy.. 9.9% (95%CI:5.8-15.6) died within 7 days and 21.7% (95%CI:15.6-28.9) within 30 days post hemostasis. Regarding peptic ulcer, the immediate hemostasis was achieved in 88% (95%CI:75-95) of cases and 26% (95%CI:13-43) rebled. Increased ASA score was associated with mortality [OR:23.5 (95%CI:1.60-345); p=0.02]. The primary outcome was achieved in 100% of cases with malignancy and post GI intervention bleeding; 17% and 3.1% recurred, respectively. Twenty-six patients received Hemospray for lower GI bleeding, and in all but one the primary outcome was achieved.

Conclusions

TC-325 powder as monotherapy represents a safe and effective modality especially in malignancy- or post-endoscopic intervention- related bleeding, whereas in bleeding peptic ulcers it could be helpful when the standard of care treatment is not feasible or available to stablise patients.

Keywords: Hemospray, TC-325, Endoscopy, Upper Gastro-intestinal bleeding, Hemospray monotherapy

Introduction

Acute gastrointestinal bleeding (AGIB) is a common medical emergency, especially in the era of the broadly used antithrombotic agents.(1,2) Depending on the origin of the bleeding, it is defined as upper GIB (UGIB), when located proximally to the ligament of Treitz, whereas lower GIB (LGIB) refers to the remaining alimentary tract . The frequency of UGIB follows a reducing trend over the last two decades, probably due to the eradication of *Helicobacter pylori* and the broad prescription of proton pump inhibitors (PPIs).(3) More specifically, UGIB is recorded at a rate of 67 cases per 100,000 population in the United States of America(4) 134 per 100,000 population in the UK(5) and 47 per 100,000 in Spain.(3) Similarly, the incidence of UGIB-related deaths has reduced, as indicated by a database study of peptic ulcer bleeding from the US, conducted between 1989 and 2009, which found that the mortality rate had halved, falling from 4.5 to 2.1%.(6) Although LGIB is more common than UGIB, limited data exist in the literature regarding its prevalence in the general population. It is interesting, though, that the rates of diverticular disease and angiodysplasia-related bleedings increased, probably reflecting the use of antiplatelets and novel anticoagulants.(1,2)

Endoscopic hemostasis represents the mainstay treatment, accompanied with optimized medical care. This is supported by studies revealing a reduction in overall mortality caused by GI bleeding. Gastrointestinal Endoscopy Societies have published thourough guidelines on GI bleeding management, favoring dual hemostasis as the optimal approach in cases of active hemorrhage.(7–9) Mechanical treatment, including a variety of endoscopic clips and bands, provides a reliable and lasting effect, especially when applied to focal lesions and vessels. Similarly, thermal ablation targets on actively bleeding or high-risk spots with equivalent efficacy. Injection with adrenaline solution provides a combined tamponade and vasoconstritive effect, however it is limited by the short duration and needs to be accompanied with another technique.(9) All of these techniques require targeting the bleeding site and fine movements, which may be challenging in difficult positions or big abnormal surfaces, such as malignancies.

Combination therapy, including at least two of the aforementioned modalities is strongly recommended by current guidelines and supported by high quality of evidence.(8,9)

Although the available modalities offer an adequate effect on hemostasis, single treatment with epinephrine injection is inferior to combination therapies with thermal or mechanical hemostasis. At least in cases with active bleeding, epinephrine injection in the bleeding site followed by cauterization or clipping provides lower rates of rebleeding and need for emergency surgery.(10,11) However, in cases with difficult and unstable endoscopic position, unavailability of sophisticated devices, such as over-the-scope clips, and inadequate endoscopist's experience, combined hemostasis can be impossible.

Topical hemostatic powders offer a treatment modality that is easy to use with minimal learning curve, thus providing a promising alternative, especially when a targeted treatment cannot be provided. Additional benefits include the ability to treat a large surface area and their non-contact nature. TC-325 (Hemospray; Cook Medical, Winston-Salem, North Carolina, USA) is a mineral-based hygroscopic powder that is deployed using a pressurised carbon dioxide cannister. **(Figure 1)** When Hemospray comes into direct contact with blood its triggers a clotting cascade which results in the formation of a coagulum. This leads to a tamponade effect over the bleeding foci by forming an adhesive seal which results in hemostasis. The powder then sloughs off the mucosa over the proceeding 24-72 hours.(12) Althought these hemostatic agents seem to yield an acceptable rate of bleeding cessation, they are currently recommended as rescue theraphy as opposed to primary theraphy.

The aim of this single-arm, prospective, multi-centre international registry study was to evaluate hemostasis outcomes and adverse events in consecutive patients who received hemospray as endoscopic monotherapy for acute GIB, in various locations and with different underlying causes.

Methods

Study design

A prospective international multi-center study was conducted, in form of a registry, to investigate the efficacy of Hemospray on GI bleeding as monotherapy. The Hemospray Registry was presented to the local research ethics committee (London-South East Research Ethics Committee) and received ethical approval in October 2016. (ISRCTN29594250). A total of 18 centres across 3 continents (Europe, USA, Australia) have contributed to the registry between January 2016 – February 2022. The study protocol conformed to the ethical

guidelines of the last revision of Declaration of Helsinki and complied with Good Clinical Practice Guidelines.(13,14) Patients' anonymity is ensured and all of recruited subjects will be informed and consented for their participation in this trial.

Inclusion criteria

Adult patients with evidence of acute GI bleeding were considered as eligible to undergo endoscopic hemostasis with TC-325. Upper GI bleeding was suspected in patients with melena, hematemesis or Glascow-Blatchford score ≥1. Cases with hematochezia and abnormal Oakland score were treated as LGIB, unless evidence of UGIB existed (e.g. increased urea, hemodynamic instability). The final decision for enrollment was at the endoscopists' discretion during the endoscopy. Regarding peptic ulcers, only cases with active bleeding in endoscopy were recruited (Forrest Type 1a and Type 1b).

Patients who did not consent to participate in the study or with prior failed attempts for hemostasis on the same session or previous sessions and those where TC-350 was part of combined hemostasis (adjunctive to clips or thermocautery) were excluded from the final analysis.

Procedure

Following rescusitation with fluids and personalised medical treatment, where needed (e.g. PPIs, red-blood cells transfusion), upper or lower GI endoscopy was offered depending on the suspected area of bleeding.

Upon the identification of the bleeding site, TC-325 was sprayed on the lesion, using the commercially available system (Hemospray; Cook Medical, Winston-Salem, North Carolina, USA). This system includes a canister filled with the powder, a 7 or 10Fr delivery catheter, and a CO_2 pump incorporated to a handle controlling the propulsion of the powder. After obtaining a clear field in front of the bleeding site, the working channel of the endoscope was dried with air inflation, followed by the catheter insertion at 1-2cm from the bleeding lesion. Short bursts under direct vision were performed to release the Hemospray, until the area was completely covered by the powder. The site was then observed for at least 5 minutes to assess for immediate hemostasis or the need for complementary treatment.

Data collection

A predefined online platform was used to insert and keep the records of the enrolled cases, including the variables that were analyzed. Only the primary investigators (NA, RJH) had access to the patients' records across centers.

Outcomes and definitions

Given the different behaviour and impact of the potential bleeding causes and the challenges raised by the location, the outcomes were measured depending on the cause (e.g. peptic ulcer, malignancy, iatrogenic bleeding) and the bleeding site (upper or lower GI) in order to identify any potential benefit from TC-325 related to these variables.

The primary endpoint was defined as the rate of immediate endoscopic hemostasis using the Hemospray device. This was defined as the intraprocedure observation of bleeding cessation within the first 5 minutes post monotherapy with TC-325, without recurrence on the same session. The 5 minutes threshold was also used in previous studies, representing a reasonable comparator.(15)

Rebleeding rates, diagnosed when clinical hemorrhage was observed (new hematemesis or melena associated with hemodynamic change following index treatment) or drop in haemoglobin >2g/L, were considered as a secondary outcome.(16,17) Moreover, 7- and 30-day all cause mortality rates were calculated. As for any interventional procedure, the frequency and the severity of adverse events were also evaluated.

Follow-up

A 30 days follow up was agreed, either with a face-to-face clinic review or telephone consultation, to assess for recurrence or adverse events.

Statistical analysis

Data analysis was performed using the Statistical Package for Social Science Software for Windows (IBM SPSS Statistics, Version 28.0. Armonk, NY: IBM Corp). Continuous variables are presented as mean (± standard deviation; SD) and categorical variables are shown as percentages.

We examined the association between the recorded independent variables and the outcomes. Logistical regression was performed in two stages. Firstly, association between each factor and outcomes was examined separately as a univariable analysis. If several

factors showed a statistically significant association with the primary outcomes, we then examined the join association between the factors and primary factors as part of a multivariable analysis. Where appropriate we adopted a backwards selection procedure to omit non-significant variables from the final model.

Odds ratios (OR) and their 95% CIs were derived from each variable coefficient in the final model. Statistical significance was considered for P values ≤0.05 (two tailed).

Results

One hundred and ninety patients were finally included in our cohort and received TC-325 as monotherapy between January 2016 and February 2022. The age ranged between 51 and 81 years with median being 66-71 years among subgroups, and the male to female ratio was 2:1. Immediate hemostasis was yielded in 96.3% (95%CI: 92.6-98.5; 183/190) of patients with an overall recurrence rate of 17.4% (95%CI: 11.9-24.1; 28/161). Sixteen out of 161 patients [9.9% (95%CI: 5.8-15.6)] died withing 7 days post-hemostasis with this outcome raised to 21.7% (95%CI: 15.6-28.9; 35/161) after one month.

Four subgroups were identified, including cases with bleeding peptic ulcer (n=48), upper GI malignancy (n=79), post endoscopic treatment-related hemorrhage (n=37), and lower GI lesions (n=26). **Table 1** depicts the main information of these subgroups.

Peptic ulcer related bleeding

Fourty eight patients with Forrest Ia or Ib ulcer were included out of a total 74 cases with ulcer related bleeding **(Figure 2)**, provided the mechanism of action of Hemospray which, after contacting with blood, becomes cohesive and adhesive, creating a barrier layer that tamponades the bleeding lesion, promotes the concentration of clotting factors and cellular elements and may activate the clotting cascade.(18) Immediate hemostasis was achieved in 42/48 patients equating to a rate of 88% (95%CI:75-95).**(Table 2)** The Blatchford score was borderline associated to failed haemostasis, with every 5-unit increase in the Blatchford score resulting to increasing odds of no haemostasis by 5-fold (p=0.05).

The secondary outcomes **(Table 2)** were assessed in 38 patients, who attended follow-up. Regarding rebleeding, 26% (95%CI:13-43; 10/38) presented with recurrence. Seven patients [11% (95%CI:3-25)] died within 7 days after index hemostasis, whereas the respective ratio within 30 days was 26% (95%CI:13-43; 10/38). Our univariate analysis

revealed that the increased American Society of Anaesthesiologists (ASA) score was associated with 30 day mortality, as 6% of patients with an ASA of I/II died in comparison to 44% of those with an ASA grade of III/IV. The odds of death were 12 times higher for patients with higher ASA grades (p=0.03), and the significance was preserved in a multivariable analysis as well [OR: 23.5 (95%CI:1.60-345); p=0.02].

Upper GI malignancy

Seventy-nine patients were recruited in this subgroup, which included 19 cases with esophageal cancer, six with esophagogastric junction cancer, 51 with gastric, and three with duodenal cancer. The primary outcome was achieved in 100% (79/79) of upper GI malignancy cases, regardless the location or the size of the lesion. **(Figure 3)**

Sixty nine patients provided information about rebleeding and twelve of them [17% (95%CI:9-28)] reported recurrence. The median tumour size was 30mm (IQR: 19-50) and there was a tendency for rebleeding of lesions larger than 40mm compared to smaller ones (27% vs 10%), albeit marginally non-significant (p=0.09). Likewise, the mortality rates were calculated for those patients (69) who attended follow-up. The mortality rate within seven days was 7% (95%CI:2-16; 5/69), raised to 25% (95% CI:15-36; 17/69) within 30 days. The hemodynamic instability was associated with increased risk of 30-day mortality by 9-fold risk of death for unstable patients compared to the stable ones [OR:8.89 (95%CI:1.58-49.9); p=0.01].

Post Upper GI endoscopic therapy

Post-procedure bleeding was diagnosed and treated with TC-325 after various procedures, as presented in **Figure 4.**

An optimal rate of immediate hemostasis was achieved [100% (95%CI:91-100); 37/37], for all of the different procedures. Only one case of endoscopic mucosal resection (EMR) [3.1% (95%CI:0-16); 1/32] presented with rebleeding, with the defect been 50mm and the resected lesion 22.5mm. One patient died within the first seven and thirty days [3.1% (95%CI:0-16); 1/32].

Lower GI bleeding

A total of 26 patients received Hemospray for LGIB, and in all but one the primary outcome was achieved [96%(95%CI:80–100); 25/26]. Follow-up information was available in 22 cases with a rebleeding rate of 23% (95%CI:8-45; 5/22). The univariable analysis revealed that age and hemodynamic status were significantly associated with rebleeding. More specifically, for every 10-year increase in age the risk of rebleeding was reduced by 5-fold (p=0.03), whereas it was 18 times higher in patients who were hemodynamically unstable when compared to those who were hemodynamically stable (p=0.04). 14% (95%CI:3-35; 3/22) of cases died within the first week post-hemorrhage and 32% (95% CI: 14-55%; 7/22) within the first month; none of the factors included in our regression models was linked with 30-day mortality.

Adverse Events

A single complication was reported in the registry with the endoscopist reporting catheter blockage during the treatment of a duodenal ulcer. Despite this, immediate hemostasis was achieved and there were no reports of rebleeding.

Discussion

This prospective multi-center study assessed the efficacy of hemospray as monotherapy in different GI bleeding scenarions, thereby indicating a yield of immediade hemostasis in 88-100% of cases. The highest rates were recorded in malignancy and post-endoscopic intervention related bleeding, where TC-325 was universally successful. Interestinly, these two subgroups were associated with the lowest rates of recurrent hemorrhage (17% and 3.1%, respectively), whereas one fourth of peptic ulcers and LGI lesions rebled. A recent meta-analysis assessed the pooled rates of 19 studies, including 212 cases where Hemospray was used as monotherapy. Their outcomes were similar to ours with the immediate hemostasis rates being 91% (95%CI: 79-96), regardless the combined use with other modalities, the intensity of bleeding, and its cause, and the early rebleeding rates were 21% (95%CI; 14-31).(19) Regarding mortality, approximately 25% of peptic ulcer and upper GI malignancy cases of our registry died within the first month post-hemorrhage, especially when and advanced ASA score was recorded or the patients presented unstable, respectively. Only one patient died post-EMR, whereas the higher mortality rates were

detected among patients with LGIB, however none of the evaluated variables was associated with this outcome.

Treating active peptic ulcer-related bleeding requires at least two hemostatic techniques with hemostatic powders, such as TC-320, considered for refractory or recurrent cases.(9) Hemospray monotherapy yielded bleeding cessation in 88% (95%CI:75-95) of cases, however the recurrence rate was considerable [26% (95%CI:13-43)], accompanied with a similarly high mortality rate within the first month [26% (95%CI:13-43)]. Interestingly, the increasing ASA score, reflecting the patients' comorbidities and perioperative risk, was an independent predictor of mortality with an OR: 23.5. In another study of our group, 202 patients were recruited to receive monotherapy with hemospray (25%), combined treatment (75%) or Hemospray as a rescue measure (25%) and the overall hemostasis rate was 88%, without difference among subgroups. Similarly, there was no difference considering rebleeding rates (17%) and early mortality (12%), however the one-month mortality rates were significantly lower when a combined hemostasis approach was applied compared to monotherapy ($p<0.001$).(15) Despite the theoretical risk of failure and rebleeding in cases with spurting hemorrhage (Forrest Ia), it is not homogenously supported by the literature.(15,20) The high rates of immediate hemostasis and the non-inferiority compared to the combined approach for this outcome, reveal a significant role for TC-325 in achieving a direct effect on the active bleeding site, especially when combined hemostasis cannot be achieved, as happens in difficult position, marginally stable patients, or unclear field. Hemospray could be used in these cases as a bridge therapy, in order to gain time with primary control before a second look endoscopy, especially when resources are limited, or when the patient needs to be transferred to another center for definitive treatment. However, the significantly higher rates of mortality in monotherapy cases with comorbidities imply the need for confirmation of hemostasis with a second endoscopy and complementary treatment where needed. Potential causes associated with these rates need to be assessed by future studies, thereby evaluating the clinical approach policies post-hemospray monotherapy for peptic ulcer, including restarting feeding, transfusion policy and antithrombotics continuation.

Malignancy related bleeding is notoriously difficult to treat given the lack of direct target for endotherapy, the tumour tissue friability, the diffuse bleeding and the absence of a sinlge bleeding vessel.(19,21) The widespread application of Hemospray when deployed

makes it a helpful endoscopic treatment option,(21) as indicated by our results with immediate hemostasis achieved in 100% of the cases. Similar studies provide equivalent results regarding immediate efficacy.(22–24) Additionally, TC-325 reduces significantly the required transfusions in this patients group.(24) A recent RCT randomized 106 patients with bleeding malignancy to receive monotherapy with Hemospray or the standard treatment (thermal or mechanical modalities or adrenaline injection alone or in combination). Immediate hemostasis rate was significantly higher using Hemospray compared to the conventional techniques (100% vs 68.6% respectively; $p< 0.001$) and, more interestingly, the recurrence rates were lower in the Hemospray group as well (2.1% vs 21.3%; $p=0.003$).(25) In our cohort, rebleeding occurred in 17% of cases with lesions larger than 4cm presenting a non-significant tendency for recurrence, however data on variables affecting this outcome (e.g. morphology, location of the lesion, coagulation status) need to be elucidated by future studies. Considering mortality, a low number of patients (7%) died during the first week, though this rate was increased within a month, especially among patients who presented with hemodynamic instability. This outcome shows heterogeneity in the literature ranging between 18.9% to 44.9% within 30-days post bleeding, with active bleeding during the endoscopy increasing the risk of death by 2.24.(26,27)

Another field, where Hemospray could represent a reliable choice as monotherapy is post-endoscopic intervention bleeding. In our cohort, the immediate hemostasis was yielded in all of bleeding cases with only one patients presenting with recurrence. This single case occurred following EMR where the lesion was 50mm in size.(28) Similar results of optimal hemostasis are also presented by our group in a relative study, with recurrencies occurring in two post-EMR patients out of fifty-seven (4%).(29) Data on the performance of Hemospray in LGIB is limited, however it seems that it is similar to UGI.(19) Although immediate bleeding cessation was achieved in almost all of our patients, the recurrence rate was relatively high [23% (95%CI:8-45%)], probably reflecting the persistency of LGIB etiology in most cases, such as diverticular disease. Finally, TC-325 is already established in terms of safety, with the most common adverse event being the catheter blockage.

This study has also some limitations, with the most significant one being its non-randomised design with no comparator. Patient selection for monotherapy use was at the discretion of the endoscopist as opposed to a set criteria/protocol which has potentially introduced an element of selection bias. Moreover, detailed aspects regarding macroscopic

features of bleeding lesions or histological diagnosis regarding malignancy were not extracted which could have impacted our outcome measures. A significant drawback is the fact that the exact cause of death for patients was not documented, meaning that we cannot directly attribute rebleeding or immediate hemostasis to mortality.

Endoscopic hemostasis using the TC-325 powder as monotherapy is safe and effective, especially in hemorrhage due to malignant lesions or post-endoscopic intervention. **(Figure 5)** In peptic ulcer-related bleeding it could achieve immediate results when the combined standard of care treatment is not feasible, in order to provide with more time to optimise patients' condition and make a more definite plan. In these cases, a second look endoscopy could be considered to confirm the outcome and intervene when necessary, however this approach should be further evaluated.

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Figure Legents

Figure 1. The Hemospray (TC-325) device

Figure 2. Bleeding peptic ulcer (Forrest Ib) (a), with TC-325 application (b) and immediate hemostasis (c)

Figure 3. Active bleeding from an esophageal malignancy (a). After Hemospray application (b,c) hemostasis was achieved (d)

Figure 4. Causes of GI bleeding post-endoscopic intervention

Figure 5. Proposed algorithm for Hemospray use in GI bleeding

Tables

Table 1. Main characteristics of the recruited sample

Table 2. Study outcomes stratified per cause of bleeding