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DYNAMIC MANUSCRIPT

Treatment of gastrointestinal bleeding with hemostatic powder (TC-325): a multicenter study

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Abstract

Introduction Hemostatic powder (TC-325) is a new tool for treatment of gastrointestinal bleeding that allows the treatment of large surfaces with active bleeding. The aim was to describe the initial success of TC-325 for the control of GI bleeding.

Materials and methods We did a multicenter cohort study with patients admitted to the endoscopy service for GI bleeding. A format was generated to standardize the information obtained in each center. It was determined whether this treatment had been used as a single therapy or as a combination therapy. Descriptive statistics with medians and ranges, or averages with SD according to distribution.

Results Eighty-one patients with 104 endoscopic procedures were included. The median number of endoscopic procedures was 1 (1–3). In the first procedure, the initial success rate was 98.8% ($n=80$), failure rate was 1.2% ($n=1$), and rebleeding rate was 20% ($n=16$). The majority of rebleeding cases occurred within the first 3 days (12/16, 75%). There was no association between rebleeding and etiology (malignant or benign; $P=0.6$). In first procedure, 44 (54%) cases had monotherapy with TC-325 and 37 (46%) cases had a combined endoscopic therapy. There were no differences in initial success or rebleeding rates when TC-325 was used as monotherapy versus combined therapy ($P=0.7$). The mortality rate was 4% (3/81).

Conclusion TC-325 is effective for achieving initial control of bleeding in patients with different GI etiologies. The rate of bleeding recurrence is considerable in both patients with benign and malignant etiology.

Keywords Hemostatic powder · TC-325 · Active bleeding · Gastrointestinal bleeding · Mexico

Background

Gastrointestinal (GI) bleeding is a common indication for emergency endoscopy. Depending on the etiology, several endoscopic therapeutic options are available. The combination of at least two options has been shown to be effective, and also decreases the incidence of rebleeding [1, 2]. Since 2009, hemostatic powders have been proven to be effective as a treatment for hemorrhage, used first in traumatology and later in endoscopy [3]. One of these hemostatic powders is TC-325 [4] it is a powder with highly absorptive mineral base that has three mechanisms of action: absorbs water, works as a mechanical stopper, and activates the coagulation cascade. The latter, because by absorbing the liquid component of the blood, allows the coagulation factors and cellular components to concentrate. It neither contains allergens, nor proteins of human or animal origin, nor does it have botanical compounds.

The main advantage of hemostatic powders is that they allow the treatment of large surfaces with active bleeding, for which the use of conventional therapies would be ineffective. In most cases, TC-325 is used as an adjuvant therapy with common hemostatic therapies or as a rescue therapy. Because it acts through a topical effect, and is known to be displaced from the target site 2 to 3 days after application,

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it has been assumed to be less effective than other therapies [5]. However, given the almost complete lack of adverse effects, hemostatic powders have become a useful method to achieve immediate hemostasis, and are used in most cases pending a definitive treatment [4].

In "GRAPHE" registry [6], a study conducted in 20 centers in France evaluated the outcomes of treatment with TC-325 in 202 patients, where it was used as initial therapy in 46.5% of the patients and the remaining as salvage therapy. The etiology of bleeding in included patients was ulcer due to peptic acid disease, neoplastic lesions and patients with bleeding related to endoscopic procedures. The conclusion was that TC-325 was associated with a high rate of hemostasis. The simple application and good safety profile have made it the treatment of choice for hemorrhage secondary to tumors or post-endoscopic treatment; however, it also presents a high recurrence rate.

The aim of this study was to describe the initial success of TC-325 for the control of GI bleeding. The secondary objectives included evaluation of the rebleeding rate, adverse events rate, and 30-day mortality.

Patients and methods

In this multicenter cohort study, we collected the demographic and clinical information of all patients treated with TC-325 from January 2015 to November 2017 in four third-level hospitals in Mexico City. We reviewed electronic clinical records, as well as electronic and written reports of endoscopic procedures for patients admitted to the endoscopy service of each institution for any of the following diagnoses: GI bleeding (upper or lower), anemia (according to WHO criteria), or decreased hemoglobin level ≥ 3 g/dL. We included patients older than 18 years who were undergoing any type of endoscopic study, in whom the use of TC-325 was documented for the aforementioned diagnoses. We also included studies performed for post-treatment review which involved the use of TC-325. All cases with incomplete clinical information were excluded. Demographic variables, clinical history (co-morbidities), indications, endoscopic findings, and outcomes (initial control of bleeding, rebleeding, treatment failure, 30-day mortality) were assessed. We also documented endoscopic studies that had been previously performed for the diagnosis, use of anticoagulants and/or antiplatelet aggregation agents, transfusion requirements, and whether any other treatments (interventional radiology or surgery) were required to control bleeding. Information on the number of transfused globular packets was obtained by reviewing the nursing records. In the case of patients with neoplasms, we identified whether or not the cause of bleeding was attributable to the cancer diagnosis. In these patients, the clinical stage was recorded, as well as whether or not the outcomes of treatment with surgery or interventional radiology were for management of the neoplasm.

A format was generated to standardize the information obtained in each center. A researcher from each hospital was assigned to obtain information according to the objectives of the study, and all researchers were trained by one of the principal investigators (AIRP). Two identification numbers were assigned: one per study and one per patient. Only the researchers of each center had access to the electronic file of each patient. The study was approved by the ethics committee of each institution.

Indication for the use of TC-325

In all cases, the indication for the use of TC-325 was established (clinical hemorrhage, anemia, hemoglobin reduction). In addition, it was determined whether this treatment had been used as a single therapy or as a combination therapy.

TC-325 application technique

All endoscopists had previously undergone training on the application of hemostatic powder provided by the manufacturer. The powder was applied using a 10-Fr plastic cannula and the introducer handle (with CO_2 canister) provided by the supplier (Cook Medical, Winston-Salem, North Carolina, USA). In all cases, this cannula was introduced through the working channel of a therapeutic gastroscope, colonoscope, or duodenoscope. In the case of enteroscopy, a Soehendra dilator catheter (7 Fr, with the tip cut until the X-ray marker) was used. The application was performed by propelling the powder with the carbon dioxide contained in the cartridge, distributing it on the site of active bleeding, maintaining a distance of at least 2 mm between the site of bleeding (or injury) and the cannula. The amount necessary to achieve hemostasis was applied under direct endoscopic visualization. None of the cases required more than the amount of powder contained in one canister (21 g). Because two of the hospitals are Academic Institutions, some of the cases were treated by trained residents, overseen by the physicians in charge. Videos 1 and 2 show application techniques for different clinical scenarios. Decision about to use TC-325, included if this was used as monotherapy or in combination with other endoscopic treatment, was based in criteria of the physician in charge of each patient. A subsequent endoscopic review for surveillance ("second-look") was not performed in a conventional manner, and was only performed when requested by the treating physician.

Definitions

Hemorrhage was defined as the clinical evidence of bleeding (i.e., the presence of hematemesis, coffee grounds, hematochezia, or rectal bleeding), and/or a hemoglobin decrease ≥ 3 g/dL. According to the outcome, cases were considered as the following: *initial control of bleeding*, where there was an absence of bleeding after endoscopic treatment (cases where the cessation of bleeding was observed due to the use of TC-325 as a single therapy or in combination with another hemostatic treatment); *rebleeding*, where initial control was achieved, but there was a recurrence of clinical hemorrhage or hemoglobin reduction after performing an endoscopic study (considered *early rebleeding* until day 5 after the study); *failure*, where control of bleeding was not achieved at any time; or *death*, where death of the patient was directly related to the hemorrhage. Patients who died due to progression of the underlying disease (such as cancer) were excluded from this definition, as long as the death could not be directly attributed to the bleeding.

We considered the *etiology of the bleeding* in cases with an actively bleeding lesion. Due to the retrospective nature of the study, in cases where a clear diagnosis of the cause of bleeding was not concluded, the narrative part of the endoscopic report and the images (including photos and/or videos) were reviewed to establish the etiology of the bleeding. This assessment was carried out by one of the principal investigators (FITA). In the case of patients who underwent more than one study, and for whom different bleeding etiologies were documented, the second cause of hemorrhage was recorded as a different case.

For the evaluation of ulcers related to peptic ulcer disease (PUD), the Forrest classification was used. The Borrmann classification was employed for neoplastic gastric lesions, and in the remaining neoplastic lesions only the location was recorded. Likewise, the etiology of "neoplastic lesion" was defined as a macroscopically visible lesion, suggestive of neoplasia, with histopathological diagnosis of malignancy by biopsy. The presence of a visible vessel surrounded by healthy mucosa was considered a "Dieulafoy's lesion". The etiology "post-endoscopic treatment" was recorded when there was a history of a therapeutic or diagnostic endoscopic procedure in the month prior to the hemorrhage event (e.g., sphinterotomy), and the source was documented during a new endoscopic procedure. For patients whose hemorrhage etiology did not correspond to the mentioned classifications, these cases were considered "others".

Statistical analysis

For the statistical analysis, descriptive statistics were used for the demographic characteristics, with medians and ranges presented in the case of continuous variables with a non-normal distribution, and averages with standard deviations in the case of continuous variables with a normal distribution. The categorical variables were analyzed with absolute frequencies, percentages, ratios, and rates. To measure the association between treatment success, recurrence of hemorrhage, and death with the use of TC-325, the Chi square test (X^2) or Fisher's exact test were used depending on the case. Binary variables were used to analyze the number of co-morbidities (less than or greater than one), neoplastic lesion as a cause of bleeding and its relationship with the outcomes of rebleeding and death. A P-value less than 0.05 was considered to indicate statistical significance. The statistical package used for the analyses was STATA version 14.1.

Results

Eighty-one patients with 104 endoscopic procedures were included, 50 (61.8%) of whom were men with a median age of 59 (range 20–94) years. The median number of endoscopic procedures was 1 (range 1–3). Twenty-three (28%) patients required more than one endoscopic study, with 21 (20.2%) patients requiring two studies and two (1.9%) undergoing three studies. The basal clinical and demographic characteristics are presented in Table 1. Table 2 shows the etiologies of the included patients.

In the first procedure, the initial success rate was 98.8% ($n = 80$), failure rate was 1.2% ($n = 1$), and rebleeding rate was 20% ($n = 16$). Twenty-one (26%) patients underwent a second procedure, which was due to rebleeding in 13/21 (62%) patients. Of the patients who underwent a third procedure, all were due to rebleeding.

In first procedure, 44 (54%) cases had monotherapy with TC-325 and 37 (46%) cases had a combined endoscopic therapy (Fig. 1). Table 3 shows the remaining endoscopic therapies used in combination with TC-325.

Bleeding for benign diseases

The initial success rate was 98% (45/46), and the rebleeding rate was 22% (10/46). Among patients, PUD and bleeding post-endoscopic treatment were the most common etiologies (Table 4; Fig. 2). In Table 4, the success and rebleeding rates are presented according to etiology. In the two cases associated with portal hypertension, TC-325 was applied to bleeding esophageal varices as a rescue therapy due to the failure of band ligation. Among the Dieulafoy's lesions, two were located in the stomach (lesser curvature and gastric antrum), one in the gastric antrum, one in the first part of the duodenum, and one in the papilla of Vater. The cases of bleeding after surgical treatment both occurred at the site of esophagogastric anastomosis.

Table 1 Demographic characteristic ($n=81$ cases, 104 procedures)

	N	Percentage (%)
Age (min–max)	59 (20–94)	NA
Sex, *women*	31	38.3
Co-morbidities		
Cancer	40	49.4
Systemic arterial hypertension	21	26
Type 2 diabetes mellitus	14	17.3
Chronic renal failure	6	7.4
Liver cirrhosis	6	7.4
Ischemic cardiopathy	5	6.2
Hematologic diseases	4	4.9
Other co-morbidities	9	11.1
Use of antithrombotic medication	9	11.1
Antiplatelet agents	7	8.6
Anticoagulants	2	2.5
Type of endoscopic study *(first study)*		
Upper endoscopy	59	72.8
Lower endoscopy	13	16
ERCP/duodenoscopy	8	9.9
Enteroscopy	1	1.2
Patients by institution ($n=81$)		
Institution 1	18	22
Institution 2	31	38
Institution 3	16	20
Institution 4	16	20
Indication for endoscopic study		
Hemorrhage	75	93
Decrease in hemoglobin	4	5
Anemia	2	2

Institution 1, National Institute of Medical Sciences and Nutrition Salvador Zubirán; Institution 2, National Cancer Institute; Institution 3, Medica Sur Clinical Foundation; Institution 4, Spanish Hospital

The patients grouped as "other" ($n=11$, 14%) included those with post-radiation proctitis ($n=2$), unclassifiable ulcers/friable tissue in the second portion of the duodenum ($n=2$), angiodysplasias in the right colon ($n=1$), grade D esophagitis according to the Los Angeles Classification with an ulcer with visible vessels ($n=1$), venous malformation in the right colon ($n=1$), graft-versus-host disease with gastric involvement ($n=1$), ischemic colitis ($n=1$), diverticular disease ($n=1$), and a case of lower digestive tract hemorrhage with an unidentified etiology ($n=1$).

Bleeding and cancer

There were 35 patients with bleeding secondary to neoplastic lesions, four of whom (11.4%) had no previous diagnosis. There were nine patients with a diagnosis of cancer for whom the GI bleeding had a different etiology: PUD ($n=3$), post-endoscopic treatment ($n=3$), angiodysplasia ($n=2$), and post-surgical treatment ($n=1$). In the 35 patients with GI bleeding secondary to neoplastic lesions, the origin was gastric lesions in 22 (62.8%) patients, colorectal cancer in five (14.3%) patients, duodenal cancer three (8.5%) patients, esophageal cancer in three (8.5%) patients, and tumors in the ampulla of Vater in two (5.7%) patients.

Rebleeding

After the first endoscopic treatment, 16/81 patients had rebleeding. The majority of cases occurred within the first 3 days (12/16, 75%). There was no association between rebleeding and etiology (malignant or benign; $P=0.6$). There was only one case of treatment failure (1/81, 1.2%). This patient had a duodenal ulcer with a visible vessel with jet bleeding, as well as cryptogenic Child C liver cirrhosis. During the emergency endoscopy, no esophageal or gastric varices were observed. The initial treatment was combination therapy consisting of adrenaline injection plus hemoclips, which did not achieve control of bleeding. TC-325 was subsequently applied with initial control of bleeding; however, bleeding was observed 5 min later, so an interventional radiology assessment was requested.

TC-325 as monotherapy versus combined therapy

There were no differences in initial success or rebleeding rates when TC-325 was used as monotherapy versus combined therapy ($P=0.7$; Table 4). In all patients, the sequence was traditional endoscopic therapy completed by TC-325.

Need for interventional radiology and surgery

Two patients were treated by interventional radiology and seven patients underwent a surgical procedure. The two cases treated by interventional radiology were submitted to embolization of the gastroduodenal artery, one for the diagnosis of ulcer Forrest Ia in the duodenal bulb and the other for a tumor in the ampulla of Vater. Of the seven patients who underwent surgery, five were due to rebleeding, while two patients had initial success with TC-325 but the physician in charge decided that surgery was necessary (Fig. 1).

Transfusion requirements

Information about transfusion requirements was only available in 66 (81%) of the 81 patients. Of these, 40/81 (49%) required transfusion of packed red blood cells (PRC). The median number of PRCs required was 1 (range 1–5), with more required by patients with neoplastic lesions as the cause of bleeding ($n=25$).

Table 2 Etiology of bleeding for all included procedures ($n=104$)

Etiology	First study ($n=81$) *n* (%)	Second/third study ($n=23$) *n* (%)	Overall ($n=104$) *n* (%)
Neoplastic lesion	35 (43.2)	6 (26)	41 (39.4)
Acid-peptic disease (ulcer)	14 (17.3)	3 (13)	17 (16.3)
After endoscopic treatment	12 (14.8)	1 (4.3)	13 (12.5)
Post cyanoacrylate ulcer	1	0	1 (0.9)
Post argon plasma ulcer	1	0	1 (0.9)
Sphinterotomy	5	1	5 (4.8)
Ampulectomy	1	0	1 (0.9)
ESD (during the procedure)	1	0	1 (0.9)
Polypectomy	3	0	3 (2.8)
Dieulafoy's lesion	5 (6.1)	0	5 (4.8)
Post-surgical treatment	2 (2.5)	0	2 (1.9)
Variceal	2 (2.5)	0	2 (1.9)
Other etiology	11 (13.6)	3 (13)	14 (13.5)
Subtotal	81	13	94 (90.4)
Second-look	–	10	10 (9.6)
Total	81	23	104

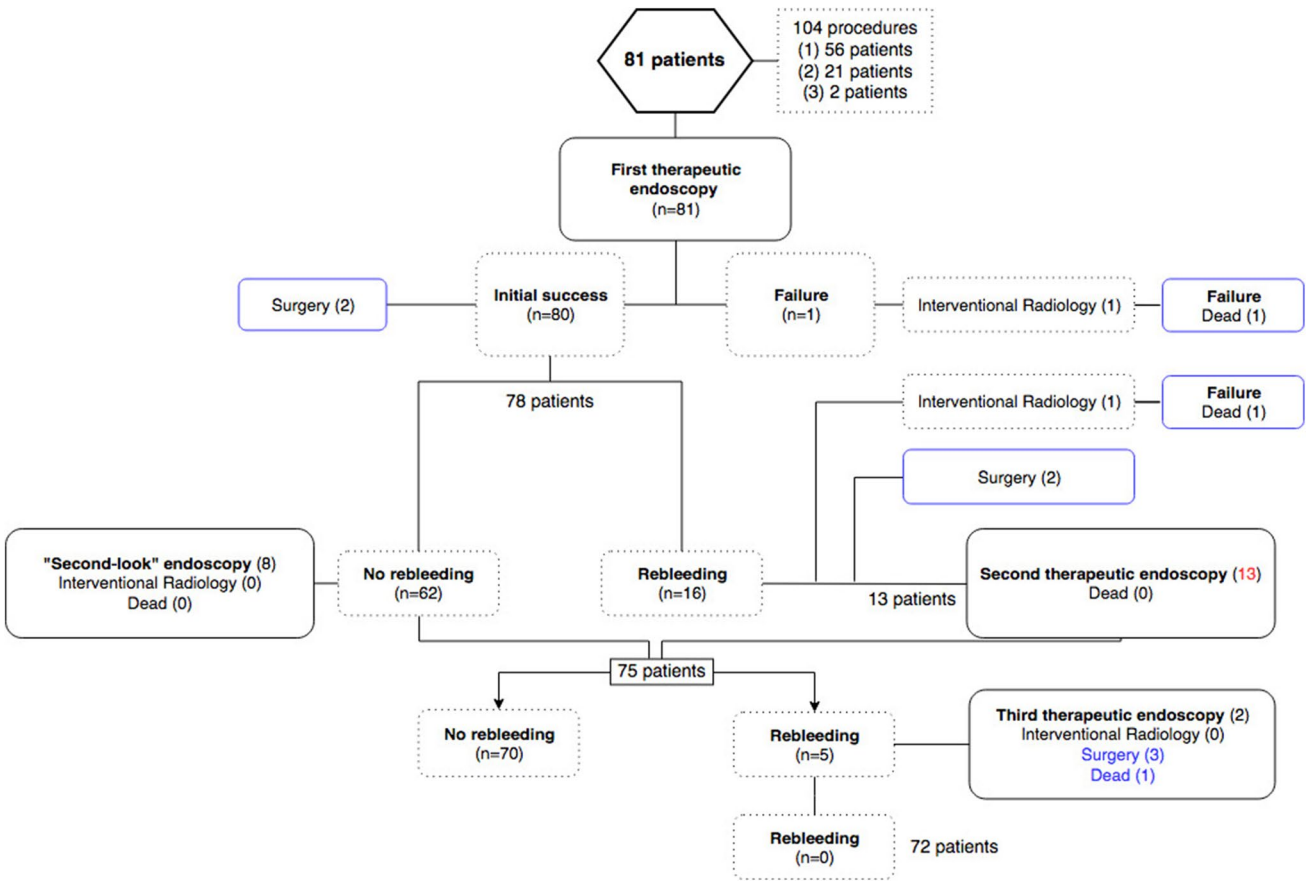

Fig. 1 Flowchart of included patients

Table 3 Combined endoscopic therapies including TC-325 ($n=37$)

Endoscopic therapy	n[a]	Percentage (%)
Adrenaline	20	24.7
Heat	5	6.2
Hemoclips	14	17.3
Endoloop	1	1.2
APC	10	12.3
Endoscopic band ligation	2	2.5
Cyanoacrilate	1	1.2

Only includes the first study

APC argon plasma coagulation

[a]Some patients underwent more than one endoscopic therapy

Death

The mortality rate was 4% (3/81). Two of the three deaths occurred within 3 days of the endoscopic procedure. Two (2.5%) patients died due to adenocarcinoma of the ampulla of Vater, and one was due to bleeding from a duodenal ulcer.

Discussion

According to our results, the use of TC-325 is useful and safe in patients with GI bleeding, with both benign and malignant etiologies.

Several studies have demonstrated the usefulness of TC-325 in the treatment of both upper and lower GI bleeding. In the present study, we show its usefulness in several bleeding conditions, with a good number of patients and an acceptable rebleeding rate. In the present cohort, neoplastic lesions were the most frequent cause of bleeding, which may have been due to reference bias, as two of the institutions are public reference centers. The gastric cancers were considered remarkable in 22 patients, most of which were Borrmann III. The source of bleeding was not always the neoplastic lesion in patients with cancer, which is important to highlight as these patients could be stigmatized, and other injuries may be overlooked as a result. In the group of patients who experienced bleeding after endoscopic treatment, TC-325 was useful in all cases for initial control, with only one case of rebleeding observed (in a patient with sphincterotomy). According to our results, TC-325 is useful as a monotherapy for the management of bleeding secondary to endoscopic treatments. A frequent clinical scenario is bleeding due to PUD. In our experience, ulcers of the bulb are difficult to manage with conventional endoscopic therapy and have high rebleeding rates. In fact, two of the three

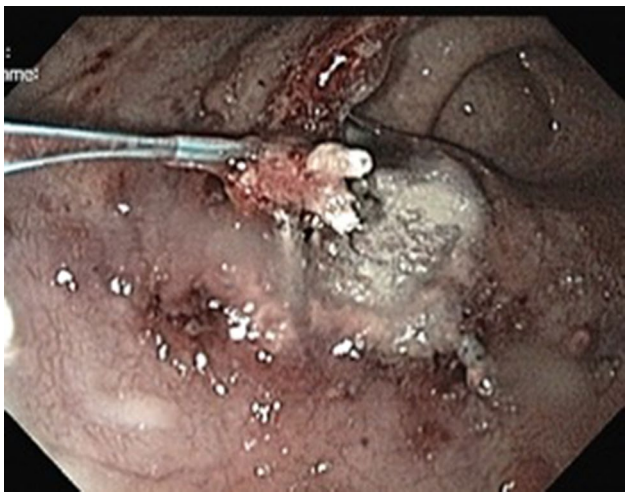

Fig. 2 Application of TC-325 on the bleeding site following hot snare polypectomy in an 18-year-old woman with inflammatory polyps and severe anemia. Initially, polypectomy with hot snare was performed, with previous lifting at the base of the polyp. A 1.5-cm defect was observed, and closure was performed using the "King closure" technique. However, the defect persistence was observed at the distal edge. TC-325 was applied to complement the closure. The photo shows the final appearance of the defect after endoscopic treatment

Table 4 Bleeding control achieved with TC-325 in the first study

	Overall ($n=81$)		Success		Rebleeding	
	n	%	n	%	n	%
By type of therapy						
Monotherapy	44	54	44	100	8	18
Combined therapy	37	46	36	97.3	8	22
By etiology						
Neoplastic lesion	35	43	35	100	6	17
Acid-peptic disease (ulcer)	14	17	13	93	4	29
After endoscopic treatment	12	14.8	12	100	1	8
Dieulafoy's lesion	5	6.1	5	100	0	0
Variceal	2	2.5	2	100	0	0
Post-surgical treatment	2	2.5	2	100	1	50
Other etiology	11	14	11	100	4	36

deaths occurred in patients with these ulcers. This outcome has been reported in previous studies [2, 3]. In patients with variceal bleeding, some authors found that the initial use of TC-325 improves the outcome regardless of whether vasoactive drugs were used [7]. In our series, only two patients were treated for variceal hemorrhage, in whom TC-325 was used as a second-line treatment after failure of conventional treatment (band ligation).

The rebleeding rate (20%) observed in this study is high, but is similar to that reported in previous studies. Pittayanon et al. [8] found a reduction in the rate of rebleeding at day 14 (10% vs. 30%) as well as a reduced mortality rate (10% vs. 30%) in patients treated with TC-325, demonstrating its use as a promising therapy for achieving initial hemostasis. In our study, the highest frequency of rebleeding was associated with neoplastic lesions. An absence of rebleeding beyond day 14 could be due to patients having been given more definitive therapies before they presented rebleeding, as shown in other studies [7, 9]. Based on these results, treatment with TC-325 could be useful as a bridging treatment before more definitive treatment in some cases. These patients, in addition to those with neoplastic lesions with recurrent bleeding, are those who would benefit most from initial treatment with TC-325, by allowing improvement of the patient's general condition and potentially even reducing the need for transfusion.

According to our results, the use of a combined therapy with traditional endoscopic treatment plus TC-325 is a highly effective strategy, with no adverse events and acceptable rates of rebleeding. One factor to consider is the cost of adding TC-325 to traditional endoscopic treatment; however, some studies have emphasized that the effectiveness of hemostatic therapies is improved when TC-325 is used concomitantly [7, 9], in addition to an improved cost-effectiveness ratio [9]. In our study, we did not observe any differences in clinical success or the rebleeding rate in patients who received TC-325 treatment as monotherapy versus patients who received combined therapy including TC-325. The results of the current study do not allow us to reach any conclusions about cost.

There are some limitations of our study which should be noted. Firstly, the retrospective nature of the study and the combination of different etiologies do not allow for conclusive analysis of causes represented by a few patients. Our study included a significant number of patients with neoplastic lesions, and it is possible that the stage of the neoplasm may influence the probability of bleeding or recurrence; however, this analysis could not be performed. In relation to the strengths of this study, we were able to confirm the ease and usefulness of TC-325 by endoscopists with different levels of expertise. Furthermore, we demonstrated the utility of TC-325 to control bleeding after endoscopic treatment, with an excellent initial control rate (92%) and low probability of rebleeding (8%) achieved. In addition, there were no adverse effects associated with the administration of this hemostatic powder in patients with bleeding from the ampulla of Vater or bleeding associated with portal hypertension in our study. In an unintentional way, all included patients had at least one of the following situations: diffuse bleeding (patients with bleeding neoplastic lesion), coagulations disorders (liver chronic diseases, hematologic diseases), or patients with use of antiplatelets or anticoagulants drugs (Table 1). Probably, these situations justified the use of TC-325 (combined or as monotherapy) in an empirical way by the doctor in charge of each patient in particular. We consider that, this situation should skew the results in an unfavorable way for results with the use of TC-325 (or any other endoscopic therapy), and despite this, the results were not discouraging.

Conclusion

TC-325 is effective for achieving initial control of bleeding in patients with different GI etiologies. The rate of bleeding recurrence is considerable in both patients with benign and malignant etiology.

Compliance with ethical standards

Disclosures Drs. Ariadna Iraís Ramírez-Polo, Jorge Casal-Sánchez, Angélica Hernández-Guerrero, Luz María Castro-Reyes, Melissa Yáñez-Cruz, Louis Francois De Giau-Triulzi, Javier Vinageras-Barroso, Félix Ignacio Téllez-Ávila have no conflict of interest or financial ties to disclose.

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