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par

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TRAITEMENT DES HEMORRAGIES DIGESTIVES PAR APPLICATION DE POUDRE HEMOSTATIQUE PAR VOIE ENDOSCOPIQUE: RESULTATS D'UNE ETUDE PROSPECTIVE MULTICENTRIQUE FRANCAISE EN PRATIQUE DE ROUTINE

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Contents

Abbreviations

ASA score: American Society of Anesthesiologists score

CNIL: Commission National de l'Informatique et des Libertés

CRF: Case Report Form

EMR: Endoscopic Mucosal Resection

ERCP: Endoscopic Retrograde Cholangio-Pancreatigraphy

ESD: Endoscopic Sub-mucosal Dissection

Fr: French

GNEDS: Groupe Nantais d'Ethique dans le Domaine de la Santé

GRAPHE: Groupe de Recherche Avancé des Praticiens Hospitaliers en Endoscopie

OR: Odd-Ratio

UGIB: Upper gastro-intestinal bleeding

USA: United States of America

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Engagement de non plagiat

Je soussigné, HADDARA Sami, déclare être pleinement conscient que le plagiat de documents ou d'une partie d'un document publiés sur toutes ses formes de support, y compris l'Internet, constitue une violation des droits d'auteur ainsi qu'une fraude caractérisée. En conséquence, je m'engage à citer toutes les sources que j'ai utilisées pour écrire ma thèse de Docteur en Médecine.

1 Introduction

Upper gastro-intestinal bleeding (UGIB) is a very common disease. Over the past decade, although a decrease in hospitalisation rates due to UGIB has been observed, the mortality rates remain constant around 10% despite progresses in medical treatment and the development of interventional endoscopy (1,2). Indeed, failure of endoscopic hemostasis by conventional methods still occurs in 8-15% of cases (2). In addition, early recurrence of UGIB is observed in 10-25% of cases, which suggests that conventional endoscopic hemostasis is not always optimal (1–5). Among the large variety of situations that can lead to UGIB, specific situations such as hemostasis disorders, large bleeding lesions or GI malignancies are particularly challenging to treat. Therefore, further developments in the endoscopic armamentarium are eagerly needed.

TC-325 (Hemospray™) is a new mineral-based hemostatic powder designed to achieve hemostasis by combining the following mechanisms: creation of a mechanical barrier, absorption of serum fluid components to concentrate clotting factors and activation of the clotting cascade (6). Previous pathophysiological studies demonstrated that TC-325 shortened both in vitro coagulation time and in vivo clot formation time (7). TC-325 has good safety profiles and is completely eliminated of the GI tract after seventy hours (8). However, cautious use is still required since powder impaction in the colon, arterial embolization and allergic reaction are potential adverse events. In pilot studies performed in expert centers, TC-325 has been shown to be effective in various UGIB lesions (9–13). However, no data exist in routine practice on large samples of patients and endoscopists. Therefore, the aim of our multicentre prospective study was to determine the feasibility and efficacy of TC-325 in routine practice.

2 Patients and methods

2.1 Study population

The GRAPHE (Groupe de Recherche Avancé des Praticiens Hospitaliers en Endoscopie) registry collected prospectively data on TC-325 use in 20 centres including 64 different endoscopists between March 2013 and January 2015. All adults patients receiving TC-325 for UGIB were included in the study. All investigators had received previous theoretical and practical training on TC-325 application. Retrospective analysis of demographic, clinical and endoscopic data was performed at the end of the study by a single investigator and a biostatistician. The study was approved by the GNEDS (Groupe Nantais d'Ethique dans le Domaine de la Santé), the institutional review board of Nantes University Hospital and the French administrative authority for data protection (CNIL; Commission Nationale de l'Informatique et des Libertés). All patients received written information and did not oppose the use of their data.

2.2 Procedure and follow-up

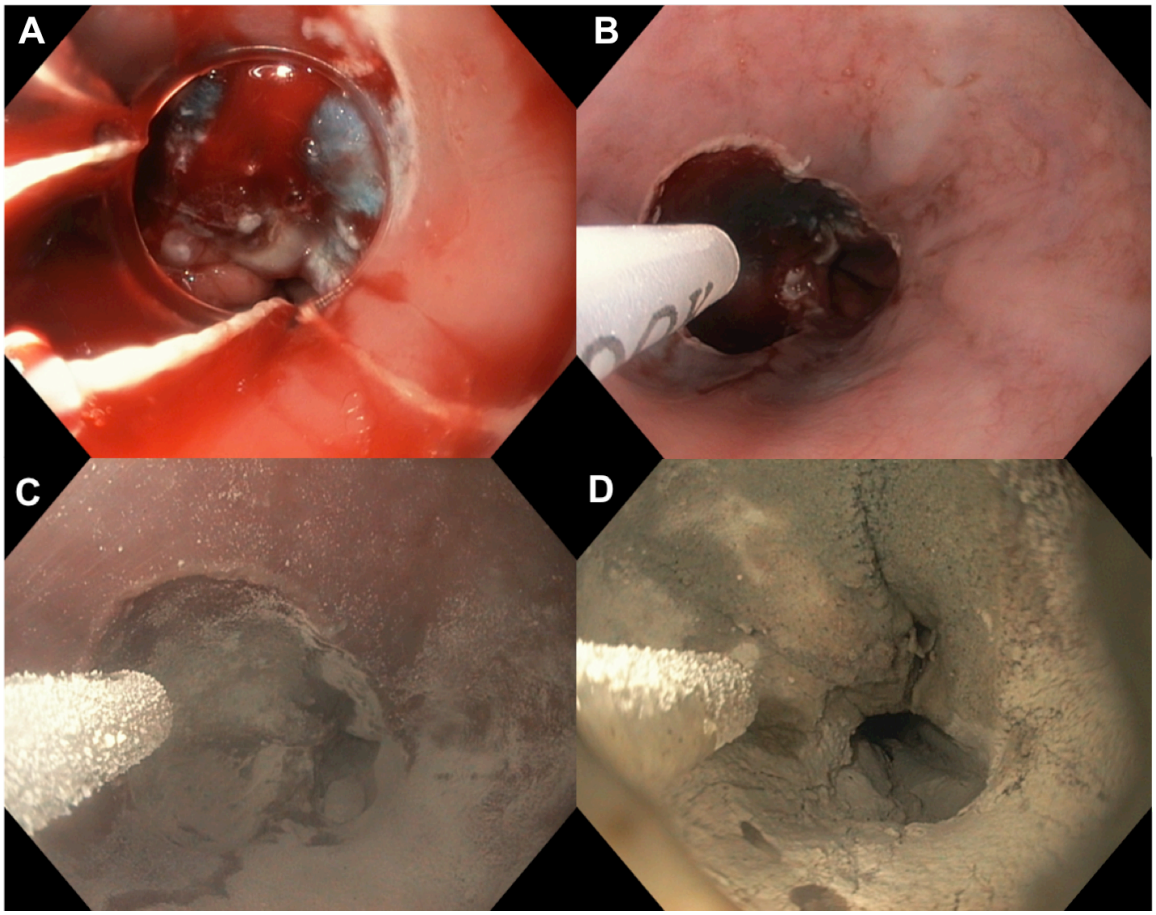
TC-325 (Hemospray™, Cook medical, Winston-Salem, North Carolina, USA) was sprayed endoscopically onto the bleeding site using a 7 or 10 Fr catheter passed through endoscope operative channel and with a built-in carbon dioxide canister to propel the powder (Figure 1). The indication of TC-325 application as a first-line therapy or salvage therapy was at the discretion of the endoscopist. Following the endoscopic procedure, standard medical treatment or adjuvant therapy such as surgery, radiological embolization, radiotherapy or other lines of endoscopic procedures were applied according to the patient's status and the disease evolution. Follow-up data at day 8 and day 30 were collected retrospectively by either a clinical examination or a telephone interview.

2.3 Demographic and outcome data collection

Demographic data, medical history, ASA score and previous treatment were collected. In addition, biological parameters as well as endoscopic data were assessed. The ease of procedures was notified by the endoscopists on 5-points Likert scale from 0 (impossible) to 4 (very easy). Adverse events were noted, as

well as patient's clinical evolution at day 8 and day 30 after the initial endoscopic procedure.

Figure 1. Active bleeding after esophageal EMR (1A). TC-325 catheter passed through the endoscope operative channel (1B). TC-325 was sprayed onto the bleeding site (1C). Hemostasis was obtained after TC-325 application (1D).



2.4 Definitions

All upper gastrointestinal lesions were classified into four categories: ulcers, malignant lesions, post-endoscopic bleedings and others. Ulcers were further classified using the Forrest classification. Malignant lesions were defined by all spontaneous bleeding from a malignant lesion. Post-endoscopic bleedings were defined by all bleeding after endoscopic interventions. Each lesion, which was not included in one of the previous categories, was classified in the "Other lesions" category. In contrast to first-line therapy, salvage therapy was defined by the application of TC-325 because of persistent bleeding after conventional endoscopic methods (hemoclips, diluted epinephrine injections, bipolar

coagulation and/or argon plasma coagulation) either during the same endoscopic procedure, or after failure of previous endoscopic attempts.

2.5 Statistical analysis

Statistical analysis was performed using Stata 14 software (StataCorp LP, College Station, TX, USA). Quantitative variables were expressed as mean ± standard deviation and qualitative variables were expressed as percentages. Odds-ratios (OR) were computed by using logistic regressions. Multivariate analyses were performed by logistic regressions. Significant variables in the univariate analysis ($P < 0.25$) were included in a multivariate model using an ascending procedure ($P < 0.05$). Three dummy variables were created: hemoglobin level ≥ 8g/dL, creatinine level ≥ 15mg/L and an ASA score ≥ 3.

All patients data were reported on an anonym standardized Case Report Form (CRF) and were sent by email or fax to the clinical Centre of investigations from University Nantes Hospital and were stored in the clinical Centre of investigations.

3 Results

3.1 Study population

A total of 202 patients (140 male, 62 female) with 69±15 years of age were treated by TC-325 for an UGIB. Categories were as follows: ulcers (n=75; 37%), malignant lesions (n=61; 30%), post-endoscopic bleedings (n=36; 17%) and others (n=31; 16%). Patients' characteristics are summarized in Table 1. At initial presentation, 53 patients (26%) had hypotension. Distribution of ASA scores was as follows: ASA I (n=9; 4%), ASA II (n=49; 24%), ASA III (n=93; 46%), ASA IV (n=46; 24%) and ASA V (n=5; 2%). Death occurred in 30 patients and was directly attributed to the bleeding in 7 cases. Due to missing data, 3 and 4 patients were excluded from analysis at day 8 and day 30, respectively. In total, 50/187 (27%) patients required additional treatment: surgery in 16 (32%) cases, second-look endoscopy in 18 (36%) cases, radiological embolization in 5 (10%) cases, arterial embolization followed by surgery in 2 (4%) cases and a radiation therapy in 7 (14%) cases. Data concerning the type of additional treatment were missing for 2 patients. Patients treated by TC-325 as a first-line or salvage therapy required additional treatment in 15/86 (17%) and 35/101 (35%) of cases, respectively.

Table 1. Baseline characteristics of patients to lesions sub-type (n=202)

	Overall (n=202)	**Ulcers (n=75)**	**Malignant lesions (n=61)**	**Post endoscopic bleedings (n=35)**	**Others (n=31)**
Age, mean ± SD, years	68.9 ± 14	69.7 ± 17	70.6 ± 17	68.1 ± 13	64.2 ± 18
Sex, % (n)					
Male	69.3 (140)	70.7 (53)	72.1 (44)	68.6 (24)	61.3 (19)
Female	30.7 (62)	29.3 (22)	27.9 (17)	31.4 (11)	38.7 (12)
ASA Score, mean ± SD	2.9 ± 0.9	3 ± 0.8	3 ± 0.8	2.5 ± 0.85	3.1 ± 1.0
Hemoglobin level, mean ± SD, g/dL	8.6 ± 2.3	7.8 ± 1.6	8.1 ± 1.9	11.2 ± 2.7	8.5 ± 2.2
Platelet count, mean ± SD, G/L	213 ± 132	194 ± 109	251 ± 149	239 ± 146	156 ± 109
Prothrombin Time, mean ± SD	70 ± 22	65 ± 21	72 ± 21	89 ± 16	63 ± 23
Creatinine level, mean ± SD, mg/L	11.7 ± 9	12.8 ± 11	11.2 ± 8	8.5 ± 3	13.3 ± 7
Initial hypotension, % (n)	26 (53)	33.3 (25)	21.3 (13)	14.3 (5)	32.4 (10)
Salvage therapy, % (n)	53.5 (108)	80 (60)	27.8 (17)	34.3 (12)	61.3 (19)
Antiplatelet agents, % (n)	24.9 (47)	29.6 (21)	18.2 (10)	28.2 (9)	22.6 (7)
Anticoagulants, % (n)	21.7 (41)	26.8 (19)	23.6 (13)	6.2 (2)	22.6 (7)

SD, Standard Deviation; n, Number of cases.

3.2 Immediate hemostasis and re-bleeding rates

Overall immediate hemostasis was achieved in 97% of cases, independently whether TC-325 was used as first-line (97%) or salvage therapy (96%). The type of lesion did not influence immediate hemostasis, which was achieved in 96% of ulcers, 95% of malignant lesion, 97% of post-endoscopic bleedings and 100% of other causes of bleeding.

Recurrence of bleeding was observed in 27% (57/191) of overall cases at day 8. The bleeding recurrence rate according to the lesion sub-type was 38% (27/71) for ulcers, 25% (14/56) for malignant lesions, 14% (5/35) for post-endoscopic bleedings and 17% (5/29) for others lesions. At day 30, cumulative incidence of re-bleeding rates were 41%, 38%, 18% and 25% for ulcers, malignant lesions, post-endoscopic bleedings and other lesions, respectively (Figure 2A).

When used as a first-line, TC-325 had re-bleeding rates in overall lesions, ulcers, malignant lesions, post-endoscopic bleedings and other lesions, of 17%, 31%, 18%, 13%, and 10% at day 8, respectively. At day 30, cumulative incidences of re-bleeding rates were 27%, 31%, 33%, 14% and 22%, respectively (Figure 2B).

When used as a salvage therapy, re-bleeding rates at day 8 were 35%, 40%, 47%, 17% and 21% in overall lesions, ulcers, malignant lesions, post-endoscopic bleedings and other lesions, respectively. At day 30, cumulative incidence of re-bleeding was 39%, 44%, 50%, 25% and 26%, respectively (Figure 2C). Additional results according to lesions' classification are reported in Table 2.

3.3 Ease and duration of the procedure

TC-325 application was characterized as very easy, easy, moderately easy, hard and impossible in 32%, 55%, 7% 5% and 1% of cases, respectively. In particular, spraying the hemostatic powder was impossible with a duodenoscope in 2 cases, requiring the physician to switch for a gastroscope, thereby allowing successful TC-325 application. Initial catheter obstruction requiring replacement by another catheter occurred in 4 cases. The total duration of the endoscopic procedure, including both the pre-therapeutic and the therapeutic parts, was 30±21 minutes. No severe adverse event was reported. However, a subset of patients reported epigastric pain during TC-325 application when performed without general anesthesia nor sedation (data not shown).

Figure 2. Immediate hemostasis rate after TC-325 application and re-bleedings rates at day 8 and day 30 (2A). Re-bleeding rates at day 8 and day 30 when TC-325 was used as first line therapy (2B) or as salvage therapy (2C).

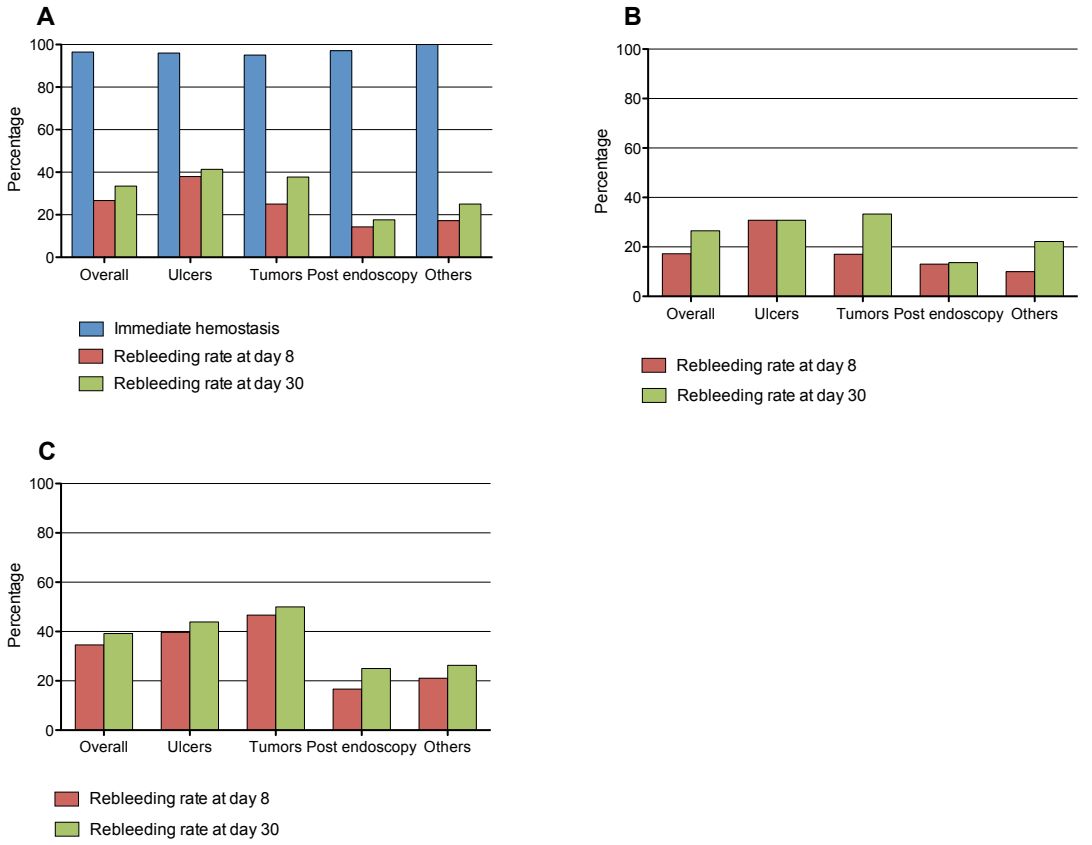


Table 2. Efficacy of TC-325 and follow-up data according to lesion

	Immediate hemostasis	Recurrence of bleedings at day 8	Recurrence of bleedings at day 30	Need for a further treatment
Ulcers Ia, % (n)	93.3 (14/15)	66.7 (10/15)	66.7 (10/15)	60 (9/15)
Ulcers Ib, % (n)	95.4 (41/43)	31.7 (13/41)	35 (14/40)	27.5 (11/40)
Ulcers II, % (n)	100 (14/14)	33.3 (4/12)	41.7 (5/12)	36.4 (4/11)
Malignant lesions, % (n)	95.1 (58/61)	25 (14/56)	37.7 (20/53)	27.8 (15/54)
Sphincterotomy, % (n)	100 (7/7)	28.6 (2/7)	28.6 (2/7)	28.6 (2/7)
EMR, % (n)	92.3 (12/13)	7.7 (1/13)	16.7 (2/12)	7.7 (1/13)
Polypectomy, % (n)	100 (4/4)	0 (0/4)	0 (0/4)	0 (0/4)
ESD, % (n)	100 (2/2)	50 (1/2)	50 (1/2)	50 (1/2)
Biopsy/Puncture, % (n)	100 (3/3)	0 (0/3)	0 (0/3)	0 (0/3)
Oesophageal prosthesis, % (n)	100 (3/3)	33.3 (1/3)	33.3 (1/3)	0 (0/3)
Infundibulotomy/Ampullectomy, % (n)	100 (3/3)	0 (0/3)	0 (0/3)	0 (0/3)
Oesophagitis, % (n)	100 (6/6)	0 (0/6)	20 (1/5)	16.7 (1/6)
Dieulafoy lesions, % (n)	100 (3/3)	33.3 (1/3)	33.3 (1/3)	0 (0/3)
Portal hypertension lesions, % (n)	100 (7/7)	16.7 (1/6)	33.3 (2/6)	33.3 (2/6)
Vascular lesions, % (n)	100 (4/4)	25 (1/4)	25 (1/4)	50 (2/4)
Surgical anastomotic bleeding, % (n)	100 (3/3)	33.3 (1/3)	33.3 (1/3)	33.3 (1/3)
Mallory-Weiss lesions, % (n)	100 (2/2)	50 (1/2)	50 (1/2)	50 (1/2)
Ulceration lesion, % (n)	100 (1/1)	0 (0/1)	0 (0/1)	0 (0/1)
Traumatic endoscopic injury, % (n)	100 (2/2)	0 (0/2)	0 (0/2)	0 (0/2)
Ischemic lesion, % (n)	100 (1/1)	NA	NA	NA
Extra digestive cavity bleeding, % (n)	100 (2/2)	0 (0/2)	0 (0/2)	0 (0/2)

n, Number of cases; EMR, Endoscopic Mucosal Resection; ESD, Endoscopic Sub-mucosal Dissection; NA, Patient died from another cause

3.4 Predictive factors for bleeding recurrence

Univariate analysis showed that exteriorisation of melena at initial presentation, creatinine levels > 15 mg/L and TC-325 used as salvage therapy were predictive of bleeding recurrence at day 8. At day 30, exteriorisation of melena at initial presentation, creatinine levels > 15mg/L, and ASA score ≥ III were predictive of bleeding recurrence. However, multivariate analysis showed that only melena exteriorisation and TC-325 used as salvage therapy were significantly predictive of bleeding recurrence at day 8. At day 30, only melena exteriorisation and pulsatile bleeding at initial endoscopy were predictive of bleeding recurrence.

Conversely, parameters significantly associated with fewer bleeding recurrence were: post-endoscopic bleeding etiology and obtention of endoscopic hemostasis following TC-325 application during the procedure at day 8 and day 30. In addition, previous antiplatelet or anticoagulant therapy was also associated with lower bleeding recurrence by univariate analysis. By multivariate analysis, the only predictive factor of lower bleeding recurrence rate was the obtention of initial hemostasis following TC-325 application at day 8 and day 30 (Table 3). Sub-stratification analysis by lesion type showed that Forrest Ia ulcers were significantly associated with bleeding recurrence at day 8, but not at day 30, by multivariate analysis (Table 4). Other lesions sub-types were not associated with bleeding recurrences (data not shown).

Table 3. Predictive factors for bleeding recurrence after application of TC-325 for overall lesions

	Univariate analysis				Multivariate analysis			
	8 days re-bleeding		30 days re-bleeding		8 days re-bleeding		30 days re-bleeding	
Value	**OR**	***p***	**OR**	***p***	**OR**	***p***	**OR**	***p***
Male sex	1.10	0.790	1.09	0.795				
Age	0.99	0.559	0.99	0.385				
Hematemesis	0.64	0.216	0.62	0.173				
Melena	**2.64**	**0.006**	**2.30**	**0.011**	**2.81**	**0.006**	**2.88**	**0.003**
Hematochezia	2.29	0.057	1.68	0.236				
No Bleeding	0.83	0.757	1.21	0.724				
Initial hypotension	1.41	0.353	1.08	0.833				
Hemoglobin level ≥ 8g/dL	0.70	0.283	0.65	0.183				
Platelet level	1.00	0.464	1.00	0.120				
Prothrombin time	1.00	0.463	1.00	0.828				
Creatinine level > 15 mg/L	**2.61**	**0.025**	**2.57**	**0.032**				
Active bleeding:								
No bleeding	ref	0	ref					
Oozing	2.34	0.276	1.31	0.662				
Pulsatile	4.5	0.085	3.03	0.129			**3.11**	**0.023**
Lesion sub-type								
Ulcers	ref		ref					
Malignant lesions	0.54	0.121	0.86	0.679				
Post endoscopy bleedings	**0.27**	**0.016**	**0.30**	**0.019**				
Salvage therapy	**2.54**	**0.008**	1.79	0.070	**2.48**	**0.013**		
Initial hemostasis	**0.13**	**0.018**	**0.19**	**0.050**	**0.10**	**0.009**	**0.15**	**0.034**
ASA ≥ 3	2.01	0.079	**2.49**	**0.017**				
Antiplatelet	0.45	0.077	**0.38**	**0.026**				
Anticoagulant	1.00	0.993	1.14	0.729				

Table 4. Predictive factors for bleeding recurrence after application of TC-325 for ulcers

	Univariate analysis				Multivariate analysis			
	8 days re-bleeding		30 days re-bleeding		8 days re-bleeding		30 days re-bleeding	
Value	**OR**	***p***	**OR**	***p***	**OR**	***p***	**OR**	***p***
Male Sex	1.00	0.944	1.22	0.711				
Age	1.02	0.280	1.00	0.743				
Hematemesis	0.68	0.471	0.55	0.272				
Melena	0.70	0.517	0.85	0.763				
Hematochezia	2.65	0.081	2.17	0.162				
Initial hypotension	1.40	0.513	1.27	0.644				
Hemoglobin level ≥ 8g/dL	0.82	0.204	0.81	0.181				
Platelet level	1.00	0.725	1.00	0.453				
Prothrombin time	0.99	0.421	1.00	0.599				
Creatinine level > 15 mgl/L	3.48	0.052	3.68	0.054				
Active bleeding:								
No bleeding	ref		ref					
Oozing	2.06	0.532	2.5	0.427				
Spurting	8	0.103	8	0.103				
Forrest								
Ulcers II	ref		ref					
Ulcers Ib	0.93	0.92	0.75	0.675				
Ulcers Ia	4	0.092	2.8	0.199	**4.24**	**0.02**		
Salvage therapy	1.48	0.552	1.76	0.391				
ASA ≥ 3	1.65	0.404	1.99	0.252				
Antiplatelet	0.32	0.072	0.42	0.148				
Anticoagulant	0.82	0.725	0.75	0.627				

4 Discussion

The present study is the largest registry on TC-325 performed in routine practice conditions for the treatment of UGIB. Indeed, based on a nationwide network of 64 endoscopists from 20 different centres, this database including 202 patients confirms the excellent feasibility and immediate efficacy of this hemostatic powder.

Tables 5, 6 and 7 report the results of the published literature about TC-325 in malignant lesions bleeding, post endoscopic bleeding and peptic ulcer bleeding.

The immediate hemostasis rate is impressive either in our study (96%) or in the published literature regardless of the source of bleeding directly linked to the haemostasis ability of the nanopowder due to the triple mechanism of action:

- Concentration of clot factors on the bleeding site
- Formation of a mechanical barrier
- And enhancement of the clot formation.

Moreover TC-325 works in emergency as an "extinguisher". It's a non-contact endoscopic hemostatic device with a distance spray that didn’t need particular high endoscopic skill contrary to other endoscopic haemostatic tools like mechanical therapy (hemoclips) and thermal therapy. This method of pulverization explains the absence of difference in term of immediate haemostatic rate when TC-125 is used in first line therapy or in a rescue matter after a previous endoscopic hemostatic procedure. This ease of use is confirmed in our study as 87% of physicians consider the use of the device easy or very easy. Only 4 obstructions of the catheter happened although 81% (163/202) of the procedures were performed with a 7 french catheter. Several difficulties with lateral viewing endoscope have been reported by physicians due to the plicate of the plastic sheath with the elevator. This issue is classic with all hemostatic devices used in case of bleeding during Endoscopic Retrograde Cholangio-Pancreatigraphy (ERCP) but is less challenging with the haemostatic powder because the pulverization could be as effective replacing the lateral viewing endoscope by a classic gastroscope contrary to other hemostatic devices that need a perfect visualisation and position in front of the post sphincterotomy bleeding site.

In our survey, overall hemostasis rate with TC-325 was 96.5%, 96.81% in first line therapy and 96.3% in rescue therapy. Our finding confirmed the high rate TC-325's initial hemostasis in first line therapy and in rescue therapy suggested by others studies despite high rate of malignant lesions (30.2%) and initial severity of clinical situations (26.2% of initial hypotension, 71.29% of patients ≥ ASA III).

In addition, we show that melena exteriorisation at initial presentation, salvage therapy and Forrest Ia ulcers are predictive factors of bleeding recurrence at day 8. Conversely, initial hemostasis following TC-325 application is associated with lower risks of bleeding recurrence at day 8 and day 30 highlighting the need for an immediate hemostasis to change the natural history of upper gastro-intestinal bleeding. No severe adverse event was noted but it's important to note that the pressure induced by the CO2 burst has been regularly painful.

In the sub group of tumour's bleeding, results are very impressive with an immediate hemostatic efficacy at 95% and a small early re-bleeding rate at 25%. The delayed re-bleeding rate at 30 days was 37%. Our results are quite similar with previous reports resumed in Table 5 with 37 patients with bleeding tumours treated with TC-325 in 5 case series. Bleeding was stop in 100% of cases and 32% of patients presented an early re-bleeding. Bleeding malignant lesions of the gastro-intestinal tract is a very challenging situation, leading to multiple hospitalizations and transfusion. Endoscopic hemostasis is difficult because of frequent oozing bleedings due to neoangiogenesis. Classical endoscopic hemostatic tools (epinephrine injection, hemoclips) are of limited value because of the fragility of the tumoral tissue. Until TC-325, Argon Plasma Coagulation and laser coagulation were considered as the treatment of choice for bleeding tumours due to its ability to treat the entire tumoral tissue (14). However, it's not always simple in particular in large tumours and could be a long procedure that needs multiple sessions of treatment. In terms of efficacy, one of the largest series of more than 100 bleeding gastric cancers (15) reported a re-bleeding rate of more than 40% at 3 day after a thermal treatment with electrocoagulation or argon plasma coagulation. Recently a large study of 103 upper gastro-intestinal bleeding tumours (16) of various locations reported a 86% immediate efficacy with classical endoscopic hemostatic tools. The 30 days re-bleeding rate was

high around 50%. Even if these different results are not strongly comparable due to the methodology, the very high immediate hemostatic rate, the low early re-bleeding rate, the ease of use of the delivery system in all location, and the ability to cover large tumours in a non-contact matter make of this powder as the treatment of choice for gastrointestinal tumour's bleeding. Of course due to the natural history of gastro-intestinal tumour's bleeding, all endoscopic hemostatic modalities including TC-325 are not definitive, and can be considered as a bridge toward a more radical treatment (surgery, radiotherapy) according to the therapeutic project of the patient (palliative versus curative condition).

Table 5. Results of the literature of TC-325 in malignant lesions bleedings

Author	Journal	Date	Method	No of patients included	No of bleeding malignant lesions	Immediate efficacy	Re-bleeding rate
Chen (13)	GIE	2012	Case series	5	5	5	1
Holster (17)	Endoscopy	2012	Case series	16	2	2	0
Leblanc (12)	GIE	2013	Case series	17	5	5	2
Smith (10)	J of clinical gastroenterology	2013	Case series	63	6	6	2
Chen (18)	Endoscopy	2014	Case series	50	19	19	7
TotaL				**151**	**37**	**37/37 (100%)**	**12/37 (32.4%)**
GRAPHE		**2015**	**Case series**	**202**	**61**	**58/61 (95%)**	**14/56 (25%)**

In the post-endoscopic bleeding subgroup, TC-325 pulverization allowed an immediate hemostatic rate of 97% (34/35) with an 8 days re-bleeding rate of 14.7% (5/34). Our results agree with the previous reports with 51 patients treated in the literature (Table 6) before our study with an immediate haemostatic rate of 98% and a 4% re-bleeding rate. Interventional endoscopic techniques are constantly growing with the possibility of ever-larger resection of superficial cancerous lesion. Bleeding is one of the most frequent and one of the most challenging complications of these techniques. It occurs in 2% of cases after sphincterotomy (19), 2 to 10% after Gastric ESD (20,21), 1 to 2% after oesophageal EMR (22), and between 5 to 10% after ampullectomy (23,24). The endoscopic treatments of choice in theses cases are either adrenaline injection in

cases of oozing bleeding without visible vessels and hemoclips or thermal therapy in cases of spurting bleeding or visible vessels. However hemoclips and thermal therapy are very challenging and sometimes impossible with side-viewing endoscopes and can be very difficult to use in other difficult location (retrovision) even with classic gastroscope. Moreover in cases of post resection scars, hemoclips and even more thermal therapy could be dangerous with the risk of injury of the muscularis propria layer. Finally clipping scar after extended resection could modify the appearance during the follow-up and make it difficult to analyse and to resect a possible recurrence (25). Like in tumour's bleeding, according to the reported efficacy, the ease of use, the security profile and the sus-mentioned theoretical disadvantages of other endoscopic modalities, TC-325 could probably become a treatment of choice for post endoscopic bleeding, but confirmation in randomised control trials are necessary.

Table 6. Results of the literature of TC-325 in post endoscopic bleedings

Author	Journal	Date	Method	No of patients included	No of post-endoscopic bleeding	Immediate efficacy	Rebleeding rate
Holster (17)	Endoscopy	2012	Case series	16	2	2	1
Moosavi (26)	Endoscopy	2013	Case report	1	1	1	0
Leblanc (12)	GIE	2013	Case series	17	12	12	0
Smith (10)	J. of clinical gastroenterology	2013	Case series	63	10	9	0
Tarantino (27)	Endoscopy	2014	Case report	1	1	1	0
Yau (28)	Canadian journal of gastroenterology	2014	Case series	19	2	2	1
Curcio (29)	Digestive endoscopy	2014	Case report	1	1	1	0
Appleby (30)	QJM	2014	Case report	1	1	1	0
Chen (18)	Endoscopy	2014	Case series	60	20	20	0
Ivekovic (31)	Endoscopy	2015	Case report	1	1	1	0
Total				**180**	**51**	**50/51 (98%)**	**2/50 (4%)**
GRAPHE		**2015**	**Case series**	**202**	**35**	**34/35 (97%)**	**5/34 (14.7%)**

The place of the TC-325 powder in the therapeutic arsenal for peptic ulcer bleedings is still difficult to define despite our very large study with 72 ulcers

treated in a rescue matter or in first-line monotherapy. Indeeed despite an impressive immediate hemostatic efficacy in 95% of bleeding ulcers, the early re-bleeding was very frequent at 40%; 71.4% for Forrest Ia ulcers and 31.7% for Forrest Ib ulcers. These results are close to those previously published in the literature (Table 7) with a 73% re-bleeding rate in Forrest Ia and a 12.5% re-bleeding rate in Forrest Ib. Systematic reviews and meta-analyses (1,32,33) reported early re-bleeding rate around 10 and 20% in peptic ulcer bleeding following endoscopic therapy.

Table 7. Results of the literature of TC-325 in bleeding ulcers

Author	Journal	Date	Method	No of patients included	No of bleeding ulcers (T/Ia/Ib)	Immediate hemostasis (T/Ia/Ib)	Early re-bleeding rate (T/Ia/Ib)
Sung (9)	Endoscopy	2011	Case series	20	T: 20 Ia: 1 (5%) Ib: 19 (95%)	T: 19 (95%) Ia:0 (0%) Ib: 19 (100%)	T: 2/19 (10.5%) Ia: na Ib: 2/19 (10.5%)
Holster (17)	Endoscopy	2012	Case series	16	T:9 Ia: 5 (55.5%) Ib: 4 (44.5%)	T: 8 (88.9%) Ia: 4/5 (80%) Ib: 4/4 (100%)	T: 3/8 (37.5%) Ia: 3/4 (75%) Ib: 0/4 (0%)
Smith (10)	J of clinical gastroenterology	2013	Case series	63	T: 27 Ia: 11 (41%) Ib: 16 (59%)	T: 21 (77.8%) Ia: 5/11 (45.4%) Ib: 16/16 (100%)	T: 4/5 (80%) Ia: 4/5 (80%) Ib: 0/16 (0%)
Masci (33)	Scandinavian j of gastroenterology	2014	Case series	13	T: 13 Ia: 4 (31%) Ib: 9 (69%)	T: 10 (77%) Ia: 1/4 (25%) Ib: 9/9 (100%)	T: 2/10 (20%) Ia: 1/1 (100%) Ib: 1/9 (11.9%)
Yau (28)	Canadian j of gastroenterology	2014	Case series	19	T: 9 Ia: 4 (44.5%) Ib: 5 (55.5%)	T: 8 (88.9%) Ia: 3/4 (75%) Ib: 5/5 (100%)	T: 3/8 (37.5%) Ia: 2/3 (66.7%) Ib: 1/5 (20%)
Chen (18)	Endoscopy	2014	Case series	60	T: 15 Ia: 3 (20%) Ib: 12 (80%)	T: 14 (93.3%) Ia: 3/3 (100%) Ib: 11/12 (91.7%)	T: 5/14 (35.7%) Ia: 1/3 (33.3%) Ib: 4/11 (36.3%)
Total				181	T: 93 Ia: 28 (30%) Ib: 65 (70%)	T: 80/93 (86%) Ia: 15/28 (53.6%) Ib: 64 (98%)	T: 19/80 (23.8%) Ia: 11/15 (73%) Ib: 8/64 (12.5%)
GRAPHE		**2015**	Case series	202	T: 72 Ia: 15 (21%) Ib: 43 (60%) II: 14 (19%)	T: 69/72 (96%) Ia: 14/15 (93.3%) Ib: 41/43 (95.3%) II: 14/14 (100%)	T: 27/67 (40%) Ia: 10/14 (71.4%) Ib: 13/41 (31.7%) II: 4/12 (33.3%)

However these meta-analyses included all types of gastro-duodenal ulcers according to the Forrest classification with a much higher proportion of peptic ulcer with low risk stigmata (Forrest IIc and III) and a small proportion of peptic ulcer with very high risk of re-bleeding (Forrest Ia and Ib). In our study as in the published literature, TC-325 has been used primarily for these ulcers (21% of

Forrest Ia ulcers and 60% of Forrest Ib ulcers). This very high proportion of very high-risk ulcers is linked to the design of the study. Indeed, this case series was not a consecutive one and a selection bias is obvious with the use of TC-325 mostly in very high-risk procedures. It's well known that the rate of re-bleeding increases linearly with the proportion of Forrest Ia and Ib ulcers treated.

Indeed, in a recent study published last year that included 431 patients suffering from peptic ulcer bleeding (34), 18,6% presented early re-bleeding. Only 4.5% and 18.4% of patients respectively presented a Forrest Ia or Ib ulcer. In the subgroup analysis, the Forrest Ia and Ib ulcers presented an early re-bleeding in 58.8% and 26% although the immediate hemostatic rate was high at 93% with the use of the recommended bitherapy (adrenaline injection and a second modality) in 79% of cases. In our study, Forrest Ia ulcers were clearly identified as the single significant risk factor of early re-bleeding with an odds ratio of 4.24 (p = 0.02).

Moreover the gravity of our patients with peptic ulcer bleeding is sustained by their comorbidities reported in Table 1: the mean ASA score was III, the proportion of patients under antiplatelet or anticoagulants agents was 40% and 25% presented an initial hypotension at initial presentation. All these data have been previously identified as risk factors of mortality, failure of endoscopic therapy or re-bleeding in the literature.

Data are lacking about size and precise location of ulcers (posterior wall of the bulb, retrovision in gastric location). In these cases, classical endoscopic therapies are very challenging in particular clips and thermal therapies; TC-325 could probably become one of the best alternatives available in these cases.

According to our results and previous published studies, TC-325 could not be recommended as a first line therapy in Forrest Ia peptic ulcer bleeding but due to the high immediate hemostatic rate, it can serve as a bridge until a second attempt of endoscopic therapy, a radiological embolization or a surgical procedure. In Forrest Ib ulcers, data are promising but other well designed studies (consecutive or randomized) are needed to confirm the real place of this device (monotherapy or rescue therapy?). Until now a bitherapy with epinephrine injection and another modality chosen between thermal therapy and clip is still the recommended endoscopic therapy for peptic ulcer bleeding Forrest Ia and Ib.

In other situations (esophagitis, Dieulafoy lesions, portal hypertension lesions, vascular lesions, surgical anastomotic bleeding, Mallory-Weiss lesions) results are promising with a 100% immediate hemostatic rate, and TC-325 can be considered as a new tool available for these lesions.

Despite a power linked to the number of patients treated (202), the number of physicians involved (64) and the number of participating specialized centres (20), this study has a lot of limitations. First it's a retrospective analysis of prospective collected data and some data is missing. Moreover, the non-consecutive inclusion of patients with the possibility to use of TC-325 left to the physician's discretion has led to a major selection bias with a majority of very serious patients that do not represent routine practice of upper-gastro-intestinal bleeding. This bias explains the high mortality rate (15%) limiting the analysis of re-bleeding at 8 and 30 days. Finally, no consensus about the support of upper gastro-intestinal bleeding was decided previously to the study and differences could be found between the different physicians in particular for the choice of the hemostatic endoscopic therapy.

5 Conclusion

To conclude, our multicentre data obtained in routine practice conditions confirm the high immediate haemostatic rate, the excellent feasibility and the safety profile of the haemostatic powder applied endoscopically for gastrointestinal bleeding, even after failure of conventional methods. This new method of endoscopic hemostasis could probably become one of the treatments of choice in cases of tumour's and post endoscopic bleedings. This registry showed that TC-325 is not better than conventional haemostatic methods to prevent re-bleeding in ulcers, particularly in Forrest Ia ulcers, but is effective to reduce the need of radiological embolization and surgery in salvage therapy and could particularly be interesting in difficult locations or in large size ulcers where conventional endoscopic therapy are often failing. However cost-effectiveness and prospective consecutive or controlled studies are necessary to define the exact place of TC-325 in the armamentarium of endoscopic hemostasis. Such studies are urgently needed, because the ease of use of this device results in daily practice in a frequent use in first-line even in peptic ulcer bleeding where the level of evidence is low.

Bibliography

1. Hearnshaw SA, Logan RFA, Lowe D, Travis SPL, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut. 2011 Oct;60(10):1327–35.

2. Lau JYW, Barkun A, Fan D, Kuipers EJ, Yang Y, Chan FKL. Challenges in the management of acute peptic ulcer bleeding. Lancet Lond Engl. 2013 Jun 8;381(9882):2033–43.

3. Lu Y, Loffroy R, Lau JYW, Barkun A. Multidisciplinary management strategies for acute non-variceal upper gastrointestinal bleeding. Br J Surg. 2014 Jan;101(1):e34–50.

4. Chung IK, Kim EJ, Lee MS, Kim HS, Park SH, Lee MH, et al. Endoscopic factors predisposing to rebleeding following endoscopic hemostasis in bleeding peptic ulcers. Endoscopy. 2001 Nov;33(11):969–75.

5. Barkun A, Sabbah S, Enns R, Armstrong D, Gregor J, Fedorak RNN, et al. The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): Endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. Am J Gastroenterol. 2004 Jul;99(7):1238–46.

6. Barkun AN, Moosavi S, Martel M. Topical hemostatic agents: a systematic review with particular emphasis on endoscopic application in GI bleeding. Gastrointest Endosc. 2013 May;77(5):692–700.

7. Holster IL, van Beusekom HMM, Kuipers EJ, Leebeek FWG, de Maat MPM, Tjwa ETTL. Effects of a hemostatic powder hemospray on coagulation and clot formation. Endoscopy. 2015 Jul;47(7):638–45.

8. Sung JJY, Luo D, Wu JCY, Ching JYL, Chan FKL, Lau JYW, et al. Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. Endoscopy. 2011 Apr;43(4):291–5.

9. Sung J, Luo D, Wu J, Ching J, Chan F, Lau J, et al. Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. Endoscopy. 2011 Apr 31;43:291–

5.

10. Smith LA, Stanley AJ, Bergman JJ, Kiesslich R, Hoffman A, Tjwa ET, et al. Hemospray Application in Nonvariceal Upper Gastrointestinal Bleeding: Results of the Survey to Evaluate the Application of Hemospray in the Luminal Tract. J Clin Gastroenterol. 2013 Dec 10;

11. Smith LA, Morris AJ, Stanley AJ. The use of hemospray in portal hypertensive bleeding; a case series. J Hepatol. 2014 Mar 1;60:457–60.

12. Leblanc S, Vienne A, Dhooge M, Coriat R, Chaussade S, Prat F. Early experience with a novel hemostatic powder used to treat upper GI bleeding related to malignancies or after therapeutic interventions (with videos). Gastrointest Endosc. 2013 Jul;78(1):169–75.

13. Chen Y-I, Barkun AN, Soulellis C, Mayrand S, Ghali P. Use of the endoscopically applied hemostatic powder TC-325 in cancer-related upper GI hemorrhage: preliminary experience (with video). Gastrointest Endosc. 2012 Jun;75(6):1278–81.

14. Jacques J, Legros R, Chaussade S, Sautereau D. Endoscopic haemostasis: an overview of procedures and clinical scenarios. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2014 Sep;46(9):766–76.

15. Kim Y-I, Choi IJ, Cho S-J, Lee JY, Kim CG, Kim M-J, et al. Outcome of endoscopic therapy for cancer bleeding in patients with unresectable gastric cancer. J Gastroenterol Hepatol. 2013 Sep;28(9):1489–95.

16. Sheibani S, Kim JJ, Chen B, Park S, Saberi B, Keyashian K, et al. Natural history of acute upper GI bleeding due to tumours: short-term success and long-term recurrence with or without endoscopic therapy. Aliment Pharmacol Ther. 2013 Jul;38(2):144–50.

17. Holster I, Kuipers E, Tjwa E. Hemospray in the treatment of upper gastrointestinal hemorrhage in patients on antithrombotic therapy. Endoscopy. 2012 Dec 19;45:63–6.

18. Chen Y-I, Barkun A, Nolan S. Hemostatic powder TC-325 in the management of upper and lower gastrointestinal bleeding: a two-year experience at a single institution. Endoscopy. 2015 Feb;47(2):167–71.

19. Bakman Y, Freeman ML. Update on biliary and pancreatic sphincterotomy. Curr Opin Gastroenterol. 2012;28(5):420–6.

20. Facciorusso A. Endoscopic submucosal dissection vsendoscopic mucosal resection for early gastric cancer: A meta-analysis. World J Gastrointest Endosc. 2014;6(11):555.

21. Guo H-M. Endoscopic submucosal dissection vsendoscopic mucosal resection for superficial esophageal cancer. World J Gastroenterol WJG. 2014;20(18):5540.

22. Komeda Y, Bruno M, Koch A. EMR is not inferior to ESD for early Barrett's and EGJ neoplasia: An extensive review on outcome, recurrence and complication rates. Endosc Int Open. 2014;02(02):E58–64.

23. Napoléon B, Gincul R, PONCHON T, Berthiller J, Escourrou J, Canard J-M, et al. Endoscopic papillectomy for early ampullary tumors: long-term results from a large multicenter prospective study. Endoscopy. 2014;46(02):127–34.

24. Palma GDD. Endoscopic papillectomy: Indications, techniques, and results. World J Gastroenterol WJG. 2014;20(6):1537.

25. Pellisé M, Desomer L, Burgess NG, Williams SJ, Sonson R, McLeod D, et al. The influence of clips on scars after EMR: clip artifact. Gastrointest Endosc [Internet]. 2015; Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26364966&retmode=ref&cmd=prlinks

26. Moosavi S, Chen Y, Barkun A. TC-325 application leading to transient obstruction of a post-sphincterotomy biliary orifice. Endoscopy. 2013 Mar 4;45:E130–E130.

27. Tarantino I, Barresi L, Granata A, Curcio G, Traina M. Hemospray for arterial hemorrhage following endoscopic ultrasound -guided pseudocyst drainage. Endoscopy. 2014 Feb 20;46:E71–E71.

28. Yau AHL, Ou G, Galorport C, Amar J, Bressler B, Donnellan F, et al. Safety and efficacy of Hemospray® in upper gastrointestinal bleeding. Can J Gastroenterol Amp Hepatol. 2014 Mar;28:72–6.

29. Curcio G, Granata A, Traina M. Hemospray for multifocal bleeding following ultra-low rectal endoscopic submucosal dissection. Dig Endosc. 2014 Jul;26:606–7.

30. Appleby VJ, Hutchinson JM, Beckett CJ, Moreea S. Use of the haemostatic agent TC-325 in the treatment of bleeding secondary to endoscopic retrograde cholangiopancreatography sphincterotomy. QJM. 2014 Jul 1;

31. Ivekovic H, Bilic B, Markos P, Rustemovic N, Ostojic R, Mönkemüller K. Successful use of Hemospray to control refractory post-polypectomy bleeding. Endoscopy. 2015;47 Suppl 1:E466–7.

32. Kim KB, Yoon SM, Youn SJ. Endoscopy for Nonvariceal Upper Gastrointestinal Bleeding. Clin Endosc. 2014;47:315.

33. Masci E, Arena M, Morandi E, Viaggi P, Mangiavillano B. Upper gastrointestinal active bleeding ulcers: review of literature on the results of endoscopic techniques and our experience with Hemospray. Scand J Gastroenterol. 2014;000–000.

ABSTRACT

Introduction: TC-325, a new hemostatic powder, has shown promising results to treat upper gastrointestinal bleeding (UGIB) in expert centers in pilot studies. The present study reports the feasibility and efficacy of TC-325 in routine practice.

Patients and methods: The data of all patients treated with TC-325 (Hémospray™) were prospectively collected through a national registry. Outcomes were the immediate feasibility and efficacy of TC-325 application, as well as recurrence rate at day 8 and 30. Multivariate analysis using a logistic regression was performed to determine predictive factors of re-bleeding.

Results: A total of 202 patients were enrolled in 20 centres including 64 endoscopists. At endoscopy, an active bleeding was noted in 93% of cases, either pulsatile (13%) or oozing (87%). TC-325 was used as salvage therapy in 53% of cases. The etiology of bleeding was an ulcer (37%), a tumor (30%), post-endoscopic (17%) or other (16%). Application of the hemostatic powder was found to be very easy or easy in 32% and 55%, respectively. The immediate efficacy rate was 97%. Recurrence of UGIB was noted at day 8 and day 30 in 27% and 33%, respectively. Predictive factors of recurrence at day 8 were 1) melena at initial presentation and 2) absence of immediate hemostasis at the end of TC-325 application.

Conclusion: TC-325 shows excellent feasibility and immediate efficacy in routine practice. Although our study was not designed to predict success or failure of this treatment option, it suggests that patients with melena and/or failure of initial hemostasis are at higher risk of re-bleeding.

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Titre de Thèse : Traitement des hémorragies digestives par application de poudre hémostatique par voie endoscopique: résultats d'une étude prospective multicentrique française en pratique de routine.

RESUME

Introduction et objectifs : TC-325 (Hémospray™) est une nouvelle poudre hémostatique endoscopique qui a montré des résultats encourageants pour le traitement des hémorragies digestives hautes dans des études pilotes réalisées dans des centres experts. L'objectif de cette étude était d'évaluer l'efficacité et la faisabilité de TC-325 en pratique de routine.

Méthodes : Tous les patients traités avec TC-325 pour une hémorragie digestive haute ont été inclus prospectivement dans un registre national. Les principaux résultats étaient l'évaluation de la faisabilité et l'efficacité immédiate de TC-325 incluant l'hémostase immédiate mais aussi le taux de récidive à 8 jours et à 30 jours après son application. Une analyse multivariée des facteurs prédictifs de récidive a été réalisée par régression logistique.

Résultats : 202 patients ont été inclus dans 20 centres différents par 64 endoscopistes de mars 2013 à janvier 2015. Au cours de l'endoscopie, un saignement actif a été visualisé dans 93% des cas, ce saignement était pulsatile (13%) ou en nappe (87%). TC-325 a été utilisé en thérapie de sauvetage dans 53% des cas. La lésion visible était un ulcère (37%), une tumeur (30%), une hémorragie dans les suites d'une intervention endoscopique (17%) ou une autre lésion (16%). L'application de TC-325 a été évaluée facile ou très facile respectivement dans 27% et 33% des cas. L'hémostase immédiate a été obtenue chez 97% des patients. Le taux de récidive hémorragique à 8 jours était de 27% et de 33% à 30 jours. Les facteurs prédictifs de récidives à 8 jours étaient 1) la présence initiale de méléna et 2) l'absence d'hémostase à la fin de la procédure.

Conclusion : Cette étude multicentrique réalisée en pratique de routine montre que la faisabilité et l'efficacité de TC-325 sont excellentes. Bien que cette étude n'ait pas été conçue pour évaluer les facteurs prédictifs de succès ou d'échec de l'utilisation de cette poudre hémostatique, elle suggère que les patients présentant du méléna et/ou pour lesquelles l'hémostase n'a pas été obtenue en fin de procédure sont à haut risque de récidive.

Mots clés : Hémorragie digestive haute, Poudre hémostatique, Endoscopie, Urgence.