

Efficacy of novel endoscopic hemostatic agent for bleeding control and prevention: Results from a prospective, multicenter national registry



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ABSTRACT

Background and study aims Topical hemostatic agents emerged as a new treatment modality for gastrointestinal bleeding. The aim of this study was to assess the safety and efficacy of PuraStat for control of active bleeding and for prevention of bleeding after different operative endoscopy procedures.

Patients and methods A national, multicenter, observational registry was established to collect data from ten Italian centers from June 2021 to February 2023. Demographics, type of application (active gastrointestinal bleeding or prevention after endoscopic procedures, site, amount of gel used, completeness of coverage of the treated area), outcomes (rates of intraprocedural hemostasis and bleeding events during 30-day follow-up), and adverse events (AEs) were prospectively analyzed.

Results Four hundred and one patients were treated for active gastrointestinal bleeding or as a preventive measure after different types of operative endoscopy procedures. Ninety-one treatments for active bleeding and 310 preventive applications were included. In 174 of 401 cases (43.4%), PuraStat was the primary treatment modality. Complete coverage was possible in 330 of 401 (82.3%) with difficulty in application in seven of 401 cases (1.7%). Hemostasis of active bleedings was achieved in 90 of 91 pa-

tients (98.9%). In 30-day follow-up 3.9% patients in whom PuraStat was used for prophylaxis had a bleeding event compared with 7.7% after hemostasis. No AEs related to the use of PuraStat were reported.

Conclusions PuraStat is a safe and effective hemostat both for bleeding control and for bleeding prevention after different operative endoscopy procedures. Our results suggest that the possible applications for the use of PuraStat may be wider compared with current indications.

Introduction

Acute gastrointestinal bleeding, from either an upper or lower source, is a common clinical entity that often requires hospitalization and is associated with substantial morbidity and mortality. Although risk assessment protocols and treatment algorithms have been implemented, gastrointestinal bleeding still represents a relevant economic burden for healthcare systems [1].

Endoscopy is a cornerstone of management of gastrointestinal bleeding, for both assessment and treatment. The endoscopic armamentarium for hemostasis is wide, but it can be broadly categorized into injection, mechanical, and thermal methods [2,3].

In recent years, topical hemostatic agents have emerged as a new treatment modality that may have a role in challenging situations, such as management of diffuse bleeding or hemostasis of lesions located in regions difficult to reach endoscopically [4]. These agents (ie. Hemospray, EndoClot) are provided as powder, which is propelled endoscopically via a compressed gas onto the bleeding site. On contact with bodily fluid, the powder turns into a gel and promotes hemostasis by sealing the bleeding site and enhancing clot formation [5].

Use of hemostatic powders, however, is hampered by two main limitations: risk of clogging of the delivery catheter and limited visibility after application, due to the opaque nature of the hemostatic agent.

A novel type of topical hemostatic agent recently has been developed for treatment of oozing bleeding. PuraStat (3D-Matrix Europe SAS, France) is a viscous and transparent biocompatible synthetic peptide solution. On exposure to blood and because of a change in pH and ion concentration, it undergoes self-assembly into fibers and forms a hydrogel barrier that has a hemostatic effect and works as an extracellular matrix scaffold for subsequent healing [6,7].

The first clinical applications of PuraStat were described in various fields, including cardiac surgery [8,9], vascular [10], ear, nose and throat [11,12,13], and general surgery [14,15].

With regard to gastrointestinal endoscopy, PuraStat has proved effective and its use was approved for postprocedural oozing and bleeding from small blood vessels in the gastrointestinal tract as an adjunct hemostatic modality and for reduc-

tion of delayed bleeding after colonic endoscopic submucosal dissection (ESD) [16,17,18].

Further studies investigated the potential role of PuraStat in other indications, such as spontaneous acute gastrointestinal bleeding [19,20,21], post-sphincterotomy bleeding [22,23,24,25,26], post-papillectomy bleeding [27,28], gastric antral vascular ectasia (GAVE) [29], hemorrhagic radiation proctopathy [30], walled-off pancreatic necrosis [31], solitary rectal ulcer syndrome [32], acute intrahepatic biliary duct bleeding [33], bleeding after endoscopic ultrasound-guided hepaticogastrostomy [34], and delayed percutaneous endoscopic gastrostomy (PEG) bleeding [35], with very limited data but initial results seemed promising.

To further investigate the role of PuraStat for various applications, we established a national, multicenter, observational registry with the aim of collecting data about feasibility, effectiveness, and safety and identifying any possible additional field of use other than the current indications.

Patients and methods

Patients

All patients that underwent endoscopy and for whom PuraStat was used were eligible for recruitment in the registry. The study protocol was approved by the Institutional Review Board for Human Research at Humanitas Research and Clinical Center as coordinating center. Written informed consent was obtained from all patients before they underwent the endoscopic procedure at the respective institutions.

Inclusion criteria were age > 18 years and patient consent to be included in the study. The exclusion criterion was presence of a known coagulopathy likely to affect risk of bleeding.

Data were collected about patient demographics, comorbidities (i.e. cardiovascular disease, diabetes mellitus, liver disease, renal disease), antithrombotic treatment (antiplatelets, anticoagulants), blood tests (complete blood count and coagulation parameters), and need for blood product transfusion.

PuraStat use was possible in the setting of both active gastrointestinal bleeding (spontaneous or related to endoscopic procedure) and bleeding prevention after endoscopic procedures.

In case of active bleeding, data were collected regarding bleeding severity (mild: ooze from mucosa or resection base; moderate: bleeding visible vessel or clot; severe: arterial spurt), cause and location, whether hemostasis was possible, if PuraStat was the primary or secondary hemostatic treatment, and what other type of hemostatic therapy was used (i. e. injection, thermal, mechanical).

In case of use of PuraStat for prevention after endoscopic procedures, data were collected regarding the type of procedure (i. e. endoscopic mucosal resection [EMR], knife assisted resection [KAR], ESD, sphincterotomy, endoscopic papillectomy, treatment of radiation proctopathy), lesion size and extension (where applicable), length of procedure, if PuraStat was the primary or secondary hemostatic treatment, and if any other hemostatic method was used.

The patient then entered a follow-up period of 30 days in order to collect data about rebleeding after previous hemostasis with PuraStat or post-procedural bleeding after prophylactic application of PuraStat, and how the bleeding event was managed.

The primary endpoints of the studies were the rate of successful hemostasis with PuraStat in case of active bleeding and the rate of post-procedural bleeding after prophylactic PuraStat application. Secondary endpoints were represented by the rebleeding rate after hemostasis with PuraStat in case of active bleeding and completeness of coverage of the area treated with PuraStat for either hemostasis or postprocedural bleeding prevention. Furthermore, data about difficulty of PuraStat application were analyzed.

Finally, data were collected about safety and adverse events (AEs) related to PuraStat.

PuraStat application

Before the start of the study, training sessions about application of PuraStat were provided to investigators involved in the recruiting centers. The investigators from each center were endoscopists with significant experience in therapeutic endoscopic procedures.

The decision about whether employ PuraStat was left to operator discretion, based on the clinical scenario.

Use of PuraStat could be either as the primary and sole hemostatic treatment or as a secondary additional modality after other treatment options (i. e. mechanical, injection, thermal). In consideration of the effectiveness of PuraStat being proven in previous studies, especially for oozing and nonspurting bleeding, in the event of arterial spurting, application of PuraStat was allowed solely as a secondary therapy after a different primary hemostatic modality.

PuraStat was supplied in prefilled syringes available in different volumes (1 mL, 3 mL and 5 mL), according to the extent of the surface that needed to be covered. Delivery of PuraStat was carried out with a dedicated 220-cm endoscopic catheter (Nozzle System Type E) compatible with a 2.8-mm endoscopic working channel.

Data were collected about the total amount of PuraStat applied and percentage of coverage of the treated area, as well as

difficulty of application and the reason for it (i. e. position of the endoscope, blockage or kinking of the catheter).

Statistical analysis

Patient data were collected in a dedicated electronic case report form (eCRF).

Descriptive statistics were calculated: mean value with standard deviation and median value with range were determined for continuous variables; percentages and proportions were determined for categorical variables.

Statistical analysis was performed using chi-squared, Fisher's exact test, and Student's t test, when appropriate. $P < 0.05$ was considered significant.

Potential factors influencing the rebleeding rate after previous hemostasis with PuraStat and the delayed bleeding rate after prophylactic application of PuraStat were tested in a univariate logistic regression model and results were expressed in terms of odds ratios (ORs) and 95% confidence intervals (CIs).

The inferential analysis for time to event data, namely the factors influencing time to rebleeding, was conducted using the Cox univariate regression model to estimate hazard ratios (HRs) and 95% CIs.

Statistical analyses were performed with the R Statistical Software 3.0.2, Survival package (Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 403 patients were recruited in 10 Italian centers from June 2021 to February 2023. Two patients were subsequently excluded for missing essential data.

Ninety-one patients with active gastrointestinal bleeding and 310 patients undergoing postprocedural bleeding prevention were included. Baseline patient characteristics, sorted by indication, are shown in ► **Table 1** and ► **Table 2**.

No AEs or complications related to PuraStat use were reported.

Acute active bleeding

The most relevant cause of acute gastrointestinal bleeding was iatrogenic in 45 cases, 39 of which occurred during an endoscopic intervention. The remaining cases were spontaneous bleeds, such as ulcer bleeding (28), and angiodysplasia (11), followed by other less common etiologies (further details are provided in ► **Table 1** and ► **Table 3**).

For active bleeding, PuraStat was used as primary treatment modality in 30 patients (33%) and as secondary treatment modality in 61 patients (67%). Hemostasis was achieved in 90 cases (98.9%), with a single case (1.1%) of ineffective hemostasis due to diverticular bleeding that required subsequent radiological embolization.

In the setting of active bleeding, mean and median volumes of PuraStat used were 3.37 mL (\pm 1.51 mL) and 3 mL (range: 1–10 mL) respectively, with complete coverage of the treated area being possible in 76 patients (83.5%) and a mean percentage of coverage of 95% (\pm 12.4%).

► Table 1 Baseline characteristics of patients treated for active bleeding.

Number of patients	91
Sex (n,%)	Male 62 (68.1) Female 29 (31.9)
Age (mean, SD)	68.7 ± 14
Comorbidities (n,%)	None 18 (19.8) Cardiovascular 55 (60.4) Diabetes 21 (23.1) Renal disease 12 (13.2) Liver disease 6 (6.6)
Antithrombotic therapy (n,%)	Antiplatelet 18 (19.8) Anticoagulant 18 (19.8) Both 3 (3.3)
Bleeding location (n,%)	Upper location 62 (68.2) <ul style="list-style-type: none"> ▪ Esophagus 6 (6.6) ▪ Stomach 17 (18.7) ▪ Duodenum 21 (23.1) ▪ Ampulla 18 (19.8)
	Lower location 26 (28.6) <ul style="list-style-type: none"> ▪ Cecum 5 (5.5) ▪ Right colon 6 (6.6) ▪ Left colon 4 (4.4) ▪ Rectum 11 (12.1) ▪ Biliopancreatic 2 (2.2) ▪ Ileum 1 (1.1)
Cause of bleeding (n,%)	Iatrogenic 45 (49.5) <ul style="list-style-type: none"> ▪ Endoscopic intraprocedural 39 (42.9) ▪ ERCP 15 (16.5) ▪ EMR 13 (14.3) ▪ Gastric EMR 1 (1.1) ▪ Duodenal EMR 1 (1.1) ▪ Cecal EMR 2 (2.2) ▪ Right colon EMR 5 (5.5) ▪ Left colon EMR 2 (2.2) ▪ Rectal EMR 2 (2.2) ▪ ESD 4 (4.4) ▪ Gastric ESD 1 (1.1) ▪ Rectal ESD 3 (3.3) ▪ Papillectomy 3 (3.3) ▪ Duodenal EFTR 2 (2.2) ▪ WOPN drainage 1 (1.1) ▪ Intrahepatic lithotripsy 1 (1.1) ▪ Postsurgical 5 (5.5) ▪ Post PEG placement 1 (1.1)

Difficulty in application was reported in three cases (3.3%), all due to endoscope position.

During the follow-up period, seven cases (7.7%) of rebleeding were reported, five of which required endoscopic reintervention and one of which required treatment with interventional radiology.

Details about the outcomes after hemostasis with PuraStat are provided in ► **Table 3** and ► **Table 4**.

Logistic regression analysis was performed for rebleeding events after previous use of PuraStat for hemostasis of active bleeding. The threshold for significance, however, was reached

(Continuation)	
	Ulcer 28 (30.8) <ul style="list-style-type: none"> ▪ Esophageal ulcer 4 (4.4) ▪ Gastric ulcer 11 (12.1) ▪ Duodenal ulcer 9 (9.9) ▪ Rectal ulcer 4 (4.4)
	Angiodysplasia 11 (12.1) Mass lesion 3 (3.3) Mallory-Weiss tear 1 (1.1) Radiation proctopathy 1 (1.1) Diverticular bleeding 1 (1.1) Duodenal necrosis 1 (1.1)
Bleeding severity (n,%)	Mild 34 (37.4) Moderate 52 (57.1) Severe 5 (5.5)
EFTR, endoscopic full-thickness resection; EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; PEG, percutaneous endoscopic gastrostomy; SD, standard deviation; WOPN, wall-off pancreatic necrosis.	

for none of the variables taken into account (details are provided in ► **Table 5**).

Bleeding prophylaxis

Prophylactic application of PuraStat was performed after the following endoscopic procedures: ESD (172), EMR (94), ERCP (8), endoscopic papillectomy (8), KAR (8), WOPN drainage (7), treatment of GAVE (4), polypectomy (3), treatment of gastric mass lesion (3), treatment of radiation proctopathy (2), and pneumatic colorectal anastomosis dilation (1). Further details are provided in ► **Table 2** and ► **Table 6**.

For bleeding prevention, PuraStat was used as the primary treatment modality in 144 patients (46.5%) and as secondary treatment modality in 166 patients (53.5%).

In the setting of bleeding prevention, mean and median volumes of PuraStat used were 3.32 mL (± 1.23 mL) and 3 mL (range: 1–6 mL), respectively, with complete coverage of the treated area being possible in 254 patients (81.9%) and a mean percentage of coverage of 98.8% (± 5.2%).

Difficulty in application was reported in four cases (1.3%), all due to endoscope position.

During the follow-up period, 12 cases (3.9%) of delayed bleeding were reported, seven of which required endoscopic reintervention and one of which required treatment with interventional radiology.

Details about the outcomes after prophylaxis with PuraStat are provided in ► **Table 6** and ► **Table 7**.

Predictive factors for postprocedural delayed bleeding

Logistic regression analysis was performed for delayed bleeding events after previous use of PuraStat for postprocedural bleeding prevention.

In particular, upper gastrointestinal bleeding had an OR of 1.49 (0.91–1.88; $P = 0.09$), although it was not statistically sig-

► **Table 2** Baseline characteristics of patients undergoing postprocedural bleeding prevention.

Number of patients	310
Sex (n,%)	Male 165 (53.2) Female 145 (46.8)
Age (mean, SD)	69 ± 12.2
Comorbidities (n,%)	None 107 (34.5) Cardiovascular 178 (57.4) Diabetes 40 (12.9) Renal disease 13 (4.2) Liver disease 7 (2.3)
Antithrombotic therapy (n, %)	Antiplatelet 57 (18.4) Anticoagulant 32 (10.3) Both 4 (1.3)
Bleeding location (n,%)	Upper location 103 (33.2) <ul style="list-style-type: none"> ▪ Esophagus 10 (3.2) ▪ Stomach 53 (17.1) ▪ Duodenum 22 (7.1) ▪ Ampulla 18 (5.8)
	Lower location 200 (64.5) <ul style="list-style-type: none"> ▪ Ileocecal valve 2 (0.6) ▪ Caecum 20 (6.5) ▪ Right colon 32 (10.3) ▪ Transverse colon 11 (3.6) ▪ Left colon 27 (8.7) ▪ Rectum 108 (34.8)
	Biliopancreatic 7 (2.3)
Endoscopic procedure (n,%)	ESD 172 (55.5) <ul style="list-style-type: none"> ▪ Esophageal ESD 6 (1.9) ▪ Gastric ESD 42 (13.6) ▪ Cecal ESD 5 (1.6) ▪ Right colon ESD 7 (2.3) ▪ Transverse colon ESD 6 (1.9) ▪ Left colon ESD 10 (3.2) ▪ Rectal ESD 96 (31)

nificant. The threshold for significance was not reached for any of the variables considered (► **Table 8**). Time-to-event analysis confirmed this trend (HR 0.38, 95% CI 0.12–1.21; $P = 0.09$) (► **Fig. 1**).

Logistic regression analysis was performed for delayed bleeding events in patients receiving antithrombotic and antiplatelet therapy. Even in these cases, the threshold for significance was not reached for any of the variables taken into account (► **Table 8**). In the case of rebleeding within 30 days after hemostasis with PuraStat, antiplatelet drug had an OR of 1.43 (95% CI 0.91–2.32; $P = 0.21$) and anticoagulant use had an OR of 1.35 (95% CI 0.71–2.30; $P = 0.77$). In the case of delayed bleeding within 30 days after bleeding prevention with PuraStat, antiplatelet and anticoagulant use had ORs of 1.41 (95% CI 0.76–2.51; $P = 0.78$) and 2.64 (95% CI 0.88–3.67; $P = 0.18$), respectively.

(Continuation)

	EMR 94 (30.3) <ul style="list-style-type: none"> ▪ Esophageal EMR 3 (1) ▪ Gastric EMR 2 (0.6) ▪ Duodenal EMR 20 (6.5) ▪ Ileocecal valve EMR 2 (0.6) ▪ Cecal EMR 15 (4.9) ▪ Right colon EMR 25 (8.1) ▪ Transverse colon EMR 5 (1.6) ▪ Left colon EMR 13 (4.2) ▪ Rectal EMR 9 (2.9)
	ERCP 8 (2.6) Papillectomy 8 (2.6)
	KAR 8 (2.6) <ul style="list-style-type: none"> ▪ Esophageal KAR 1 (0.3) ▪ Gastric KAR 3 (1) ▪ Left colon KAR 4 (1.3)
	WOPN drainage 7 (2.3) Treatment of GAVE 4 (1.3)
	Polypectomy 3 (1) <ul style="list-style-type: none"> ▪ Duodenal polypectomy 2 (0.6) ▪ Rectal polypectomy 1 (0.3)
	Treatment of gastric mass lesion 3 (1) Treatment of radiation proctopathy 2 (0.6) Pneumatic anastomotic dilation 1 (0.3)

EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; GAVE, gastric antral vascular ectasia; KAR, knife assisted resection; SD, standard deviation; WOPN, walled-off pancreatic necrosis.

Discussion

Gastrointestinal bleeding is a condition often encountered in clinical practice, which is associated with high morbidity and mortality. Furthermore, with operative endoscopy procedures becoming more advanced and complex, bleeding is a well-known and common AE that may present either during the procedure or up to several days after it and which may be the cause of a longer hospital stay.

In recent years and since its introduction, PuraStat has emerged as an effective and safe hemostatic agent that may be helpful for both providing hemostasis for acute bleeding and preventing rebleeding or delayed bleeding events after various operative endoscopy procedures.

To the best of our knowledge, this registry collects data about the largest study population in which PuraStat has been used, for either hemostasis of acute gastrointestinal bleeding or prophylaxis of delayed bleeding following an endoscopic procedure.

PuraStat proved to be an excellent hemostatic agent for acute gastrointestinal bleeding as a primary or secondary modality, with an overall rate of successful hemostasis of 98.9%. Its effectiveness was shown in different bleeding settings: upper gastrointestinal, lower gastrointestinal and biliopancreatic,

► Table 3 Details about treatments for active bleeding.

Number of patients	91
PuraStat as primary modality	30 (33)
Other primary treatment modality + PuraStat as secondary modality	61 (67)
<ul style="list-style-type: none"> ▪ Injection ▪ Thermal ▪ Mechanical ▪ Combination of different modalities 	<ul style="list-style-type: none"> ▪ 17 (18.7) ▪ 6 (6.6) ▪ 16 (17.6) ▪ 22 (24.1)
Cause of bleeding treated with PuraStat alone	Endoscopic intraprocedural 16 <ul style="list-style-type: none"> ▪ EMR 7 ▪ Gastric EMR 1 ▪ Duodenal EMR 1 ▪ Right colon EMR 3 ▪ Rectal EMR 2 ▪ ESD 2 ▪ Rectal ESD 2 ▪ ERCP 6 ▪ Papillectomy 1
	Ulcer 7 <ul style="list-style-type: none"> ▪ Esophageal ulcer 2 ▪ Gastric ulcer 2 ▪ Duodenal ulcer 1 ▪ Rectal ulcer 2
	Angiodysplasia 2 <ul style="list-style-type: none"> ▪ Esophageal angiodysplasia 1 ▪ Rectal angiodysplasia 1
	Mallory-Weiss tear 1 Anastomotic bleeding 1 Duodenal mass lesion 1 Duodenal necrosis 1 Post PEG placement 1
Cause of bleeding treated with injection of a hemostatic agent + PuraStat	Endoscopic intraprocedural 7 <ul style="list-style-type: none"> ▪ EMR 1 ▪ Right colon EMR 1 ▪ ERCP 5 ▪ Papillectomy 1
	Ulcer 8 <ul style="list-style-type: none"> ▪ Gastric ulcer 3 ▪ Duodenal ulcer 5
	Duodenal angiodysplasia 1 Radiation proctopathy 1
Cause of bleeding treated with thermal hemostasis + PuraStat	Endoscopic intraprocedural 2 <ul style="list-style-type: none"> ▪ EMR 2 ▪ Right colon EMR 1 ▪ Left colon EMR 1
	Angiodysplasia 3 <ul style="list-style-type: none"> ▪ Cecal angiodysplasia 1 ▪ Right colon angiodysplasia 2
	Duodenal mass lesion 1

(Continuation)

Cause of bleeding treated with mechanical hemostasis + PuraStat	Endoscopic intraprocedural 5 <ul style="list-style-type: none"> ▪ EMR 2 ▪ Cecal EMR 1 ▪ Left colon EMR 1 ▪ ESD 1 ▪ Gastric ESD 1 ▪ ERCP 1 ▪ WOPN drainage 1
	Ulcer 4 <ul style="list-style-type: none"> ▪ Gastric ulcer 3 ▪ Rectal ulcer 1
	Angiodysplasia 3 <ul style="list-style-type: none"> ▪ Gastric angiodysplasia 1 ▪ Duodenal angiodysplasia 2
	Anastomotic bleeding 3 Diverticular bleeding 1
Cause of bleeding treated with combination modality + PuraStat	Endoscopic intraprocedural 9 <ul style="list-style-type: none"> ▪ EMR 1 ▪ Cecal EMR 1 ▪ ESD 1 ▪ Rectal ESD 1 ▪ ERCP 4 ▪ Papillectomy 1 ▪ Duodenal EFTR 2
	Ulcer 9 <ul style="list-style-type: none"> ▪ Esophageal ulcer 2 ▪ Gastric ulcer 3 ▪ Duodenal ulcer 3 ▪ Rectal ulcer 1
	Angiodysplasia 2 <ul style="list-style-type: none"> ▪ Duodenal angiodysplasia 1 ▪ Cecal angiodysplasia 1
	Gastric mass lesion 1 Anastomotic bleeding 1
Cases of rebleeding within 30 days	After PuraStat as primary treatment 3 <ul style="list-style-type: none"> ▪ Gastric ulcer 1 ▪ Duodenal ulcer 1 ▪ Anastomotic bleeding 1
	After mechanical hemostasis + PuraStat 1 <ul style="list-style-type: none"> ▪ Gastric ESD 1
	After injective hemostasis + PuraStat 1 <ul style="list-style-type: none"> ▪ Duodenal ulcer 1
	After combination modality + PuraStat 2 <ul style="list-style-type: none"> ▪ Rectal ESD 1 ▪ Duodenal angiodysplasia 1

EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; PEG, percutaneous endoscopic gastrostomy; WOPN, walled-off pancreatic necrosis.

► **Table 4** Outcomes after hemostasis (active bleeding) with PuraStat.

Effectiveness of hemostasis (n, %)	Effective 90 (98.9) Not effective 1 (1.1)
Rebleeding within 30 days (n,%)	7 (7.7)
<ul style="list-style-type: none"> Previously treated lesion 	Duodenal ulcer 2 Gastric ESD 1 Gastric ulcer 1 Duodenal angiodysplasia 1 Rectal ESD 1 Colorectal anastomosis bleeding 1
<ul style="list-style-type: none"> Previous bleeding severity 	Mild 2 Moderate 5 Severe 0
<ul style="list-style-type: none"> Antithrombotic therapy 	None 3 On therapy (discontinued) 4
<ul style="list-style-type: none"> Previous coverage with PuraStat 	Complete 6 Incomplete (50%) 1

ESD, endoscopic submucosal dissection.

spontaneous, or related to different kinds of operative endoscopy procedures.

With regard to previous hemostasis with PuraStat, the rebleeding rate was low (7.7%) and in the majority of patients (85.7%), it was self-limiting or it could be managed with endoscopic reintervention.

In the context of postprocedural bleeding prevention, the data appeared promising as well, with delayed bleeding occurring in only 3.9% of patients, typically following endoscopic resection (ER) procedures (i.e. EMR, ESD, endoscopic papillectomy), and once again, it was self-limiting in nature or manageable with an endoscopic reintervention in the vast majority of patients (91.7%). The effectiveness of PuraStat application for bleeding prevention was studied in a wide array of endoscopic procedures involving the upper, lower, and biliopancreatic tract.

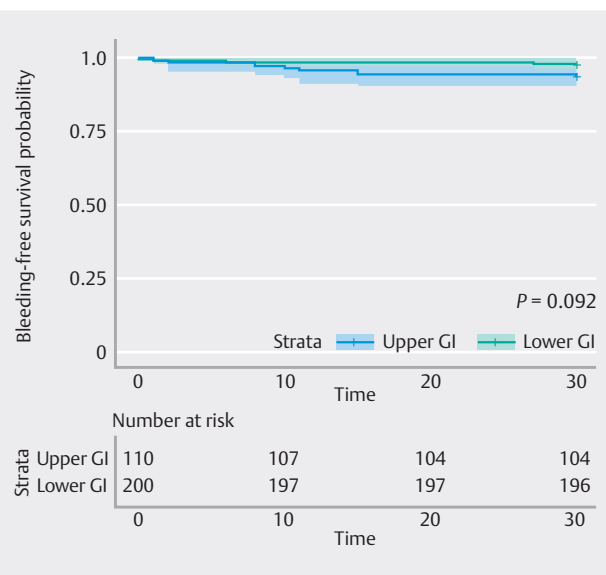
Of note, in the setting of prevention of post-procedural bleeding, PuraStat showed a higher magnitude of effect in the lower gastrointestinal tract (OR 1.49, 95% CI 0.91–1.88). Its use led to a 49% decrease in post-procedural bleeding in lower gastrointestinal as compared with the upper gastrointestinal, although the significance threshold was not reached ($P = 0.09$), probably because the study was underpowered to detect this difference. Larger cohorts are needed to assess this important clinical issue. However, given the low event rate and the specific subsets of patients (prevention of postprocedural bleeding), a sample size of more than 1000 patients would be required to register a significant difference; unfortunately, such a huge sample size is very difficult to collect.

Regarding technical aspects, PuraStat delivery proved simple, with only a few cases of difficult application due to complex endoscope position. Nonetheless, near-complete coverage of the treated lesion was possible in almost all patients. Moreover, the safety profile of PuraStat proved excellent, with no reported AEs related to its application.

► **Table 5** Logistic regression analysis for rebleeding within 30 days after hemostasis.

Variable	Odds ratio and P value
Sex	OR 1.45 (95% CI 0.78–3.11), $P = 0.51$
Age	OR 0.78 (95% CI 0.56–2.16), $P = 0.67$
Antiplatelet drug use	OR 1.43 (95% CI 0.91–2.32), $P = 0.21$
Anticoagulant drug use	OR 1.35 (95% CI 0.71–2.30), $P = 0.77$
Upper gastrointestinal tract origin of bleeding	OR 1.13 (95% CI 0.76–1.87), $P = 0.94$
Bleeding related to endoscopic procedure	OR 1.78 (95% CI 0.93–2.87), $P = 0.12$
PuraStat as primary treatment modality	OR 1.34 (95% CI 0.77–1.87), $P = 0.56$
Complete coverage	OR 1.34 (95% CI 0.79–2.13), $P = 0.87$
Difficult application	OR 1.11 (95% CI 0.89–2.33), $P = 0.33$

OR, odds ratio; CI, confidence interval.

► **Fig. 1** Bleeding-free survival probability.

This noncomparative study is inevitably limited by the nature of its own design, which did not include a control group or random treatment assignment. Treatment was solely at the discretion of the operator, both for acute bleeding hemostasis and for bleeding prophylaxis, which therefore implies a potential risk of selection bias. In this regard, this study, therefore, can only provide real-world data.

In addition, due to the very low rates of both rebleeding after previous hemostasis and delayed bleeding after operative endoscopy procedures, it is not possible to draw any specific conclusions regarding any potential risk factor for PuraStat inefficacy. However, albeit not reaching the threshold for statistical significance, we can surmise two potential trends. One fa-

► **Table 6** Details about treatments for bleeding prevention.

Treatments for bleeding prevention	
Number of patients	310
PuraStat as primary modality	144 (46.5)
Other primary treatment modality + PuraStat as secondary modality	166 (53.5)
<ul style="list-style-type: none"> ▪ Injection ▪ Thermal ▪ Mechanical ▪ Combination of different modalities 	1 (0.3) 92 (29.7) 31 (10) 42 (13.5)
Endoscopic procedure followed by bleeding prevention with PuraStat alone	EMR 53 <ul style="list-style-type: none"> ▪ Esophageal EMR 2 ▪ Duodenal EMR 10 ▪ Cecal EMR 5 ▪ Ileocecal valve EMR 1 ▪ Right colon EMR 17 ▪ Transverse colon EMR 2 ▪ Left colon EMR 9 ▪ Rectal EMR 7
	ESD 56 <ul style="list-style-type: none"> ▪ Esophageal ESD 4 ▪ Gastric ESD 28 ▪ Cecal ESD 1 ▪ Right colon ESD 3 ▪ Transverse colon ESD 2 ▪ Left colon ESD 3 ▪ Rectal ESD 15
	KAR 6 <ul style="list-style-type: none"> ▪ Gastric KAR 2 ▪ Left colon KAR 4
	Polypectomy 2 <ul style="list-style-type: none"> ▪ Duodenal polypectomy 1 ▪ Rectal polypectomy 1
	Papillectomy 8 ERCP 7 WOPN drainage 7 Treatment of gastric mass lesion 2 Treatment of GAVE 1 Treatment of radiation proctopathy 1 Pneumatic anastomotic dilation 1
Endoscopic procedure followed by bleeding prevention with injection modality + PuraStat	ERCP 1
Endoscopic procedure followed by bleeding prevention with thermal modality + PuraStat	EMR 20 <ul style="list-style-type: none"> ▪ Esophageal EMR 1 ▪ Duodenal EMR 3 ▪ Cecal EMR 7 ▪ Right colon EMR 3 ▪ Transverse colon EMR 2 ▪ Left colon EMR 4
	ESD 65 <ul style="list-style-type: none"> ▪ Esophageal ESD 2 ▪ Gastric ESD 8 ▪ Cecal ESD 2 ▪ Right colon ESD 2 ▪ Transverse colon ESD 1 ▪ Left colon ESD 4 ▪ Rectal ESD 46

► **Table 6** (Continuation)

Treatments for bleeding prevention	
	KAR 2 <ul style="list-style-type: none"> ▪ Esophageal KAR 1 ▪ Gastric KAR 1
	Treatment of GAVE 3 Treatment of gastric mass lesion 1 Treatment of radiation proctopathy 1
Endoscopic procedure followed by bleeding prevention with mechanical modality + PuraStat	EMR 17 <ul style="list-style-type: none"> ▪ gastric EMR 2 ▪ Duodenal EMR 7 ▪ Cecal EMR 2 ▪ Ileocecal valve EMR 1 ▪ Right colon EMR 3 ▪ Transverse colon EMR 1 ▪ Rectal EMR 1
	ESD 14 <ul style="list-style-type: none"> ▪ Gastric ESD 3 ▪ Cecal ESD 1 ▪ Right colon ESD 1 ▪ Left colon ESD 3 ▪ Rectal ESD 6
Endoscopic procedure followed by bleeding prevention with combination modality + PuraStat	EMR 4 <ul style="list-style-type: none"> ▪ Cecal EMR 1 ▪ Right colon EMR 2 ▪ Rectal EMR 1
	ESD 37 <ul style="list-style-type: none"> ▪ Gastric ESD 3 ▪ Cecal ESD 1 ▪ Right colon ESD 1 ▪ Transverse colon ESD 3 ▪ Rectal ESD 29
	Duodenal polypectomy 1
Cases of bleeding within 30 days	After PuraStat as primary modality 5 <ul style="list-style-type: none"> ▪ Gastric ESD 3 ▪ Transverse colon EMR 1 ▪ Papillectomy 1
	After mechanical modality + PuraStat 3 <ul style="list-style-type: none"> ▪ ESD 2 ▪ Gastric ESD 1 ▪ Rectal ESD 1
	After thermal modality + PuraStat 3 <ul style="list-style-type: none"> ▪ EMR 2 ▪ Duodenal EMR 1 ▪ Cecal EMR 1 ▪ Rectal ESD 1
	After combination modality + PuraStat 1 <ul style="list-style-type: none"> ▪ Right colon EMR 1

EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; GAVE, gastric antral vascular ectasia; KAR, knife assisted resection; SD, standard deviation; WOPN, walled-off pancreatic necrosis.

► **Table 7** Outcomes after bleeding prevention with PuraStat.

Delayed bleeding (n,%)	12 (3.9)
<ul style="list-style-type: none"> Previously treated lesion 	ESD 6 <ul style="list-style-type: none"> Gastric ESD 4 Rectal ESD 2 EMR 4 <ul style="list-style-type: none"> Duodenal EMR 1 Cecal EMR 1 Right colon EMR 1 Transverse colon EMR 1 Endoscopic papillectomy 2
<ul style="list-style-type: none"> Antithrombotic therapy 	None 7 On therapy (discontinued) 5
<ul style="list-style-type: none"> Previous coverage with PuraStat 	Complete 12 Incomplete 0

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

► **Table 8** Logistic regression analysis for delayed bleeding within 30 days after bleeding prevention.

Variable	Odds ratio and P value
Sex	OR 1.64 (95% CI 0.71–3.23), P = 0.81
Age	OR 1.98 (95% CI 0.88–3.07), P = 0.17
Antiplatelet drug use	OR 1.41 (95% CI 0.76–2.51), P = 0.78
Anticoagulant drug use	OR 2.64 (95% CI 0.88–3.67), P = 0.18
Upper gastrointestinal tract origin of bleeding	OR 1.49 (95% CI 0.91–1.88), P = 0.09
PuraStat as primary treatment modality	OR 1.45 (95% CI 0.71–2.03), P = 0.73
Complete coverage	OR 1.38 (95% CI 0.75–1.88), P = 0.79
Difficult application	OR 1.18 (95% CI 0.73–2.97), P = 0.87

CI, confidence interval; OR, odds ratio.

vors use of PuraStat for hemostasis of intraprocedural bleeding rather than its use for bleeding not related to endoscopic procedures and the other supports the use of PuraStat for bleeding prevention after endoscopic procedures on the lower gastrointestinal tract, rather than the upper gastrointestinal tract.

Nonetheless, we suggest that comparative studies may be necessary to mitigate the impact of confounding variables and enhance the broader applicability of the study findings.

Overall, our data further corroborate the effectiveness of PuraStat as both a treatment modality for both hemostasis and bleeding prevention for the indication for which it is currently approved. Moreover, for the first time, our study provides additional evidence of the efficacy and safety of PuraStat for indications different from the ones for which it is currently approved, such as treatment and prevention of bleeding related to ERCP with sphincterotomy, endoscopic papillectomy, radiation proctopathy, GAVE, EUS-guided WOPN drainage, and pneumatic dilation of colorectal anastomoses.

Conclusions

In conclusion, PuraStat appears to be a safe and effective addition to the endoscopic therapeutic armamentarium for both hemostasis and bleeding prevention, with more and more evidence suggesting a potentially wider number of applications compared with current indications. As a consequence, clinical data from further studies are needed to expand the indications for use of PuraStat and its place in the therapeutic bleeding algorithms.

Conflict of Interest

The authors declare that they have no conflict of interest.

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