Original research

Effectiveness and safety of a haemostatic gel in the treatment of intraprocedural bleeding and prevention of delayed bleeding after advanced endoscopic resection of large and complex gastrointestinal neoplasia: a multicentre prospective observational PuraStat study

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ABSTRACT

Objective PuraStat is a topical haemostatic agent used for treatment and prevention of bleeding. Our aim was to evaluate the efficacy and safety of using PuraStat during advanced endoscopic resection procedures in a multicentre prospective setting.

Design/methods This is a multicentre prospective evaluation on efficacy and safety of PuraStat when used in the treatment of intraprocedural bleeding and prevention of delayed bleeding during the study period from 2019 to 2021. High-risk tissue resections (HRTR) with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) for large and complex lesions from the oesophagus, stomach, duodenum and colon were included. Data on the type of bleed, haemostatic measures used, and efficacy and safety of PuraStat were prospectively collected. A descriptive analysis was performed and expressed as proportions.

Results PuraStat was used in a total of 448 patients with HRTR. PuraStat was used for treatment of intraprocedural bleeding in

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ PuraStat has been recognised as a haemostatic agent during endoscopic resection of GI neoplasia. Small single-centre retrospective studies have shown a potential for PuraStat in reducing delayed bleeding.

WHAT THIS STUDY ADDS

⇒ Our multicentre study supports previously reported benefits of PuraStatin reducing delayed bleeding in high-risk tissue resection (HRTR) in various gastrointestinal locations. The multi-institutional nature of the study supports generalisability of these findings.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may support the broader adoption of PuraStat in clinical practice for haemostasis and prevention of delayed bleeding after advanced endoscopic resection. Further research for indications beyond needs to be performed.

105 patients. Overall haemostatic efficacy in this group was 91.43%. All 448 patients had prophylactic application of PuraStat on the resection base to prevent delayed bleeding. The observed overall delayed bleeding rate for the entire cohort was 1.34%. On subgroup analysis, we found that this was highest in the duodenum (8.69%) followed by 1.80% in the right colon (EMR and ESD). There were no delayed bleeds in the oesophagus, stomach and left colon.

Conclusions Our data demonstrates that PuraStat is safe and appears to be effective in the treatment of intraprocedural bleeding and prevention of delayed bleeding after high-risk endoscopic resections.

Trial registration number NCT03983707.

INTRODUCTION

Endoscopic resections such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) have changed the landscape in managing early neoplasia in gastrointestinal tract.[1] However, intraprocedural and delayed bleeding can still represent a challenge during endoscopic resection.[2] Despite advances in endoscopic techniques and peri-procedural management, the incidence of delayed bleeding after endoscopic resections remains high (up to 8% with gastric ESD,[3 4] up to 11% with colorectal EMR[5 6] and up to 18% with duodenal EMR,[7–9] especially in an increasingly comorbid and ageing cohort taking antithrombotic agents). This complication can significantly impact patient outcomes, often leading to increased morbidity, including hospital readmission with repeat endoscopic interventions, blood transfusion or, in rare cases, surgical interventions. In addition, delayed bleeding also contributes substantially to the overall healthcare burden through prolonged hospital stays and increased resource utilisation. This has led to prophylactic clipping after endoscopic resection of colonic polyps. Trials using prophylactic clippings has shown significant reduction of delayed bleeding after endoscopic resection of colonic neoplasia.[5 6 10 11] Clipping is technically challenging, and data demonstrate that even in trial settings, complete clip closure is only possible in 57% of the cases.[10] Complete clip closure failed predominately in large polyps irrespective of the locations.[10] It is also worth noting that clipping is not an acceptable option for treatment of intraprocedural bleeding as it interferes with further resection. An alternative option is thermocoagulation using haemostatic forceps, but this can be associated with a risk of delayed perforation if significant thermal coagulation in the resection field is used.[12–14]

Consequently, there is a significant interest in developing novel haemostatic agents which are safe, easy-to-use and effective in treating intraprocedural bleeding as well as reducing delayed bleeding.

PuraStat is a synthetic, bioinert, self-assembling peptide (RADA16) that ionises rapidly to form a network of nanofibres when in contact with bodily fluids. This transparent hydrogel acts as a mechanical barrier and blocks the blood flow from damaged vessels. This allows for the intrinsic clotting mechanism to kick in and form a stable clot, resulting in haemostasis. It can be used to control all types of non-variceal gastrointestinal (GI) bleeding, including intraprocedural bleeding during endoscopic resections, either in isolation or as an adjunct to conventional haemostatic methods.[15] A meta-analysis of seven studies with a total of 427 patients with GI bleeding showed haemostatic efficacy of 93% with PuraStat with a rebleeding rate of 8.9%.[16] However, there is significant heterogeneity between the studies; hence, it is difficult to draw firm conclusions.

Therefore, the aim of the study was to assess the safety and efficacy of PuraStat when used as a haemostatic agent for treating intraprocedural bleed as well as preventing delayed bleeding during advanced endoscopic resections.

PATIENTS/MATERIAL AND METHODS

Study design

This was a single-arm prospective multicentre study of patients receiving PuraStat and met the inclusion criteria. It was registered with Clinical Trials Gov and approved by the UK Research Ethics Committee (reference: 18/ES/0093).

Patients were recruited from 10 tertiary UK referral centres between April 2019 and October 2021. Participating centres included in the study were Portsmouth Hospitals University NHS Trust, Nottingham University Hospitals NHS Trust, Gloucestershire Hospitals NHS Foundation Trust, Guy's and St Thomas' NHS Foundation Trust, St Mark's Hospital (London North West University Healthcare NHS Trust), King's College Hospital NHS Foundation Trust, Salford Royal NHS Foundation Trust, Cambridge University Hospitals NHS Foundation Trust, North Tees and Hartlepool NHS Foundation Trust and University Hospitals Birmingham NHS Foundation Trust.

Patients over 18 years of age were enrolled in the study if they received PuraStat and met any of the following criteria:

- Treatment of intraprocedural bleeding during high-risk tissue resection (HRTR) in the oesophagus, stomach, duodenum (ampullary and non-ampullary) and colon.
- Prevention of delayed bleeding during HRTR in the oesophagus, stomach, duodenum (ampullary and non-ampullary) and colon.

HRTR criteria for colon included advanced endoscopic resection of lesions >2 cm either located in the right colon or in a patient taking anti-coagulant/anti-platelet agents irrespective of the location or the size of ≥10 mm of lesion in both the upper and lower GI tract. However, the lesion size of <10 mm was included if lesion was fibrosed due to recurrence and the patient was on anti-coagulant/anti-platelet agents. All procedures were carried out by experienced endoscopists

in each centre using standard hot snare EMR or ESD techniques. Preprocedure anticoagulant management was carried out as per national guidelines.[17] For patients on dual antiplatelet therapy containing aspirin, we continued with aspirin while stopping the other anti-platelet agent (clopidogrel/ticagrelor). For those on aspirin as a single antiplatelet agent, it was up to endoscopist's discretion to either continue or suspend aspirin peri-procedurally. Exclusion criteria include complete clip closure of the resection base.

Each centre used their own diathermy settings with an Erbe generator (VIO 300D or VIO 3) for EMR and ESD. Patients fell into two categories: those requiring treatment for active GI bleeding and those requiring prophylactic measures to prevent delayed bleeding after a HRTR. In all cases, application of PuraStat was performed as per the manufacturer's instructions using a 2200mm-length catheter through the endoscope channel. Topical application of PuraStat for treatment of intraprocedural bleed involves a precise application of a small amount of PuraStat on the bleeding point followed by careful observation looking for haemostasis. Prophylactic application of PuraStat for prevention of delayed bleeding requires a complete coverage of resection base with PuraStat. Early bleeding was defined as bleeding within 24 hours of endoscopic procedure and delayed bleeding as bleeding after 24 hours and up to 28 days post endoscopy. The bleeding should be directly attributed to the procedure and resulted in either a hospital admission or medical intervention including endoscopic treatment or blood transfusion. Intraprocedural bleeding encountered during high-risk resections were classified according to their severity based on classifications used in a previous study.[18] Grade 1 bleeds were mild venous or capillary oozing, Grade 2 were moderate venous bleeds from a visible vessel and Grade 3 were from a spurting arterial vessel.

The efficacy of PuraStat as a haemostatic agent for treatment of intraprocedural bleeding was quantified when PuraStat® was used as a primary haemostatic agent as well as when it was used as a secondary agent following other haemostatic measures. All patients were advised to contact the endoscopy unit if there was any evidence of bleeding within 28 days after the procedure. They were also contacted by research personnel after 24 hours and after 28 days following the procedure to record any evidence of delayed bleeding.

Statistical methods

The statistical analysis for this study was descriptive in nature, performed using SPSS Statistics V.28.0, IBM Corporation.

Categorical variables, such as patient comorbidities, lesion location and resection type, were summarised and presented as frequencies (n) and proportions (%). Continuous data, such as lesion and resection base sizes, were presented as mean and SD. The volume of PuraStat used, being skewed data, was expressed as a median.

As this was a prospective, single-arm, observational study designed to evaluate efficacy and safety, the analysis was confined to descriptive statistics. No formal hypothesis testing or inferential statistics was conducted. Patient recruitment for this study concluded in October 2021, and the database was locked prior to this final analysis.

Table 1 Baseline characteristics of the 501 patients enrolled in the study

	HRTR (n=448)
Patients with more than one comorbidity, n (%)	213 (47.54)
Cardiovascular disease	162 (36.16)
Respiratory disease	71 (15.85)
Chronic liver disease	13 (2.91)
Cerebrovascular accident	20 (4.46)
On anti-thrombotic therapy	117 (26.11)
Aspirin	44 (9.82)
Aspirin not withheld peri-procedurally	26/44 (59.1)
Warfarin	11 (2.46)
Clopidogrel, ticagrelor	29 (6.47)
Heparin	2 (0.45)
Direct oral anti-coagulant (rivaroxaban, apixaban, edoxaban)	47 (10.49)

RESULTS

Four hundred and forty-eight consecutive patients were prospectively recruited into the study for HRTR. Patient comorbidities are described in table 1. This was a high-risk population with 47.54% having significant comorbidities and 26.11% taking anti-platelet/anti-coagulant.

Procedure and lesion characteristics

Among the 448 HRTR, there were 219 EMR, 227 ESD and two ampullectomies. Lesions were located in the oesophagus (91, 20.31%), stomach (59, 13.17%), duodenum (46, 10.27%), right colon (111, 24.78%), left colon (43, 9.6%) and rectum (98, 21.88%). The mean overall lesion size was 40.46 (SD 21.05) mm with mean size in oesophagus being 35.07 (SD 20.27) mm, stomach 30.22 (SD 15.74) mm, duodenum 31.5 (SD 19.5) mm, right colon 44.33 (SD 21.08) mm, left colon 47.09 (SD 25.35) mm and rectum 45.17 (SD 20.21) mm. The mean overall resection base size was 46.03 (SD 22.68) mm. 110 (24.5%) of the cases had clips applied at the resection base; 28.4% in upper GI, 24.1% in right colon and 21.4% in left colonic lesions. The mean number of clips applied was 4.2 per resection base. Clip placements were either focal across exposed superficial muscle fibres or partial closure with no intent of complete closure. Lesion location

Table 2 Lesion and resection characteristics

	Number of cases
Resection type	
ESD	227
EMR	219
Ampullectomy	2
Location	Number of cases
Oesophagus	91 (20.31%)
Stomach	59 (13.17%)
Duodenum	46 (10.27%)
Right colon	111 (24.78%)
Left colon	43 (9.6%)
Rectum	98(21.88%).
Morphology (Paris classification)	Number of cases
Is	95 (21.3%)
Ip	10 (2.24%)
IIa	151 (33.85%)
IIb	26 (5.83%)
IIc	13 (2.91%)
IIa+Is	81 (18.16%)
IIa+IIb	28 (6.28%)
IIa+IIc	41 (9.19%)
Missing	1 (0.24%)
Prophylactic clip closure of the base	110 (24.5%)
	Mean size in mm (SD)
Lesion size	40.46 (21.05)
Resection base size	46.03 (22.68)

based on resection techniques (EMR or ESD) is available in online supplemental material and table 2.

Efficacy of PuraStat as an intraprocedural haemostatic agent

PuraStat was used in the treatment of 105 acute bleeding episodes in patients undergoing HRTR as shown in table 3. Of these, 25 (23.8%) were in oesophagus, 15 (14.3%) in stomach, 10 (9.5%) in duodenum, 24 (22.9%) in right colon, five (4.8%) in left colon and 26 (24.8%) in rectum. Of all 105 acute bleeding episodes, 34 (32.4%) were in the EMR group, while the rest, 71 (67.6%) in the ESD group. The breakdown of location of acute bleeding episodes based on resection type can be found in the online supplemental material. The majority of the bleeds were grade 1 and 2 bleeds. PuraStat was used as a primary haemostat in 64 intra-procedural bleeds and achieved haemostasis in 92.19% (59/64 bleeds). The remaining 7.8% (5/64) bleeds where PuraStat failed to work were all grade 3 bleeds (spurting) requiring thermocoagulation with a coagrasper. PuraStat was used as a secondary haemostat in 41 cases after another primary haemostatic modality (thermocoagulation) failed to stop the bleeding completely and was effective in 37/41 (90.24%) cases. The overall haemostatic efficacy in HRTR group was 96/105 (91.43%) as shown in table 3.

Table 3 Haemostatic efficacy of PuraStat

PuraStat use in intraprocedural bleeding in HRTR	
As a primary modality of haemostasis	**Number of cases**
Number of bleeds	64
Number of bleeds successfully controlled	59
Haemostatic efficacy	59/64 (92.19%)
As a secondary modality of haemostasis	**HRTR**
Number of bleeds	41
Number of bleeds successfully controlled	37
Haemostatic efficacy	37/41 (90.24%)
Overall	**HRTR**
Number of bleeds	105
Number of bleeds successfully controlled	96
Haemostatic efficacy	96/105 (91.43%)

HRTR, high-risk tissue resection.

Table 4 Delayed bleeding rate

Delayed bleeding rate in prophylactic use of PuraStat	**HRTR**
Number of patients	448
Number of delayed bleeds	6
Delayed bleeding rate	6/448 (1.34%)

HRTR, high-risk tissue resection.

Efficacy of PuraStat in prevention of delayed bleeding

PuraStat was also applied prophylactically in all 448 cases of HRTR to prevent delayed bleeding. Table 4 shows the delayed bleeding rate across all categories of patients. Only six of 448 patients (1.34%) experienced delayed bleeding after endoscopic resection. Four of six bleeds were managed conservatively and settled spontaneously after a period of observation, while the other two bleeds were treated endoscopically. Table 5 shows the delayed bleeding rates according to location and type of resection. It is noteworthy that four out of six delayed bleeds were seen in patients with duodenal EMR. This equates to a delayed bleed rate of 9.09% (4/44) in patients with duodenal EMR after prophylactic application of PuraStat. 1/87 (1.15%) right colonic EMR and 1/24 (4.17%) right colonic ESD had delayed bleeding despite application of PuraStat. No delayed bleeding was observed following oesophageal, gastric and left colonic EMR or ESD. None of the patients who had delayed bleeding were on any antithrombotic medications.

Technical feasibility and amount of PuraStat used

It was technically feasible to use PuraStat in almost all patients in this study. There were no PuraStat or catheter-related issues for application of PuraStat. Only one centre reported difficulties with its application in seven HRTR patients, mainly due to endoscopic

Table 5 Delayed bleeding rate in HRTR group according to procedure and location

Delayed bleeding rate	Oesophagus	Stomach	Duodenum	Right colon (caecum, ascending + transverse)	Left colon (descending + sigmoid + rectum)
EMR	0/12 (0%)	0/15 (0%)	4/44 (9.09%)	1/87 (1.15%)	0/63 (0%)
ESD	0/79 (0%)	0/44 (0%)	0/2 (0%)	1/24 (4.17%)	0/78 (0%)
Total	0/91 (0%)	0/59 (0%)	4/46 (8.69%)	2/111 (1.80%)	0/141 (0%)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HRTR, high-risk tissue resection.

positioning (five), mucosal fold (one) and spastic bowel (one).

A median of 3 mL of PuraStat was used for prevention of delayed bleeding. A smaller volume with a median of 0.8 mL was required for haemostasis intraprocedurally.

DISCUSSION

Topical haemostatic agents have been gaining momentum given their safety profile, efficacy and relative ease of use. PuraStat, in the form of a transparent gel, has shown promising results in the treatment and prevention of bleeding. However, most of the reported data comes from small or single-centre studies.[18–20] This is a large multicentre study evaluating the efficacy of PuraStat as a haemostatic agent in high risk advanced endoscopic resections.

The findings from our study corroborate previous research[18] on haemostatic efficacy of PuraStat, showing a high rate of intraprocedural haemostasis achieved, when used as a primary haemostatic agent (92%). It is also interesting to note that PuraStat was also highly effective (90% success rate) as a secondary haemostatic agent following failure of conventional therapy. The primary haemostatic efficacy of PuraStat compares favourably with a previous small, single-centre preliminary study on PuraStat use in endoscopic resection where intraprocedural haemostasis was achieved in 75% of cases.[18] The increased haemostatic efficacy (91%) seen in this study may be related to increased knowledge and experience in the use of PuraStat application to maximise coverage of the bleeding point or better bleed selection. The secondary haemostatic efficacy is not dissimilar to the rates quoted by de Nucci *et al* who studied the use of PuraStat purely as rescue therapy in upper and lower GI bleeds, including iatrogenic bleeds following endoscopic resection and sphincterotomy.[21]

Arguably, one of the most interesting findings in this study is the low delayed bleeding rate of 1.3% in the entire HRTR cohort. We did not find any delayed bleeding after application of PuraStat following EMR and ESD in the oesophagus, stomach and left colon. The delayed bleed risk following oesophageal and left colonic resection is expected to be low, but historic data would predict a delayed bleed rate of 6%–8% after gastric ESD.[1] The delayed bleed rate in our duodenal EMR cohort was 9.09% which is still significantly lower than the anticipated 18% delayed bleed rate as reported in historic cohorts without PuraStat.[7–9 22] Similarly, another striking finding of our study is a significant reduction in delayed bleeding rate (1.15%) in patients who underwent colonic EMR for large right-sided colonic polyps, in contrast to recent studies reporting a delayed bleeding rate of around 9%–10% in this group of patients.[10] Multiple trials have shown that clip closure of EMR base can significantly reduce the risk of delayed bleeding[6 10] but only if the base is completely closed. However, achieving complete clip closure is technically challenging and it was only achieved in 57% of cases even in experienced hands.[10] Even in the landmark trials on prophylactic clipping in EMR[6 10] and a randomised controlled trial (RCT) of 231 patients,[5] the lowest delayed bleed rates observed with clipping were around 3%. It is notable that our study demonstrated an even lower delayed bleed rate in right colon lesions despite a large average size of 4.4 cm. We also reported only 1 case of delayed bleeding (1/102, 0.98%) after colonic ESD following the use of PuraStat. This is significantly lower than the recently reported delayed bleed rate of 8% following colonic ESD in a western cohort.[23] Our data imply that PuraStat may be considered a potential alternative to clips for prevention of delayed bleeding, especially in the right colon and duodenum, where clipping can be challenging.

Our findings suggest a significant benefit in preventing delayed bleeding after prophylactic use of PuraStat in HRTR. However, it is important to contextualise them with recent evidence. A recent multicentre RCT (the PURPLE trial) evaluated the prophylactic application of PuraStat after colonic and duodenal EMR and reported no benefit.[24] However, that study has been widely criticised for several methodological issues.[25 26] It was likely underpowered and included a heterogeneous population with many low-risk lesions, such as left-sided polyps, sessile serrated lesions and pedunculated polyps. More critically, the trial was confounded by the fact that 84% of patients in both the treatment and control arms received conventional haemostasis like coagulation or clipping before randomisation. This high rate of pre-emptive treatment makes it difficult to isolate the specific effect of PuraStat, thereby questioning the generalisability of the trial's negative findings.

In general, only a small volume (0.8 mL) of PuraStat was required to achieve haemostasis in the HRTR and 3 mL when used to cover resection bases for prevention of delayed bleeding. This is similar to other studies using PuraStat where 3 mL or less are adequate to achieve haemostasis and prevent delayed bleeding.[18 20 27]

Beyond its efficacy, this study also highlights the practical advantages and technical feasibility of using PuraStat. It was easy to use in almost all patients with no significant technical challenges. It was safe with no directly related adverse reactions. It also has a unique advantage over others given its transparent nature, allowing endoscopists to visualise the bleeding point even after the gel has been applied and monitor therapeutic efficacy in real time. PuraStat application did not interfere with ongoing endoscopic resection or further therapy, with no reports of interference with use of cautery over the area. It is worth noting that clipping of bleeding vessels before completion of tissue resection can interfere with further resection, making clips unacceptable options for treatment of intraprocedural bleeding during HRTR. The catheter used to deploy haemostatic powder may get blocked during treatment of bleeding, which can pose a significant challenge compounded by the fact that the resection field can be completely obscured thereafter, impairing visibility and resulting in failure of any further tissue resection. Thermocoagulation of bleeding point remains an effective option but requires technical skill and experience and is associated with a risk of delayed perforation especially in areas with a thinner wall such as the duodenum and right colon and in the stomach where multiple, larger vessels are encountered and thermal damage from cumulative heat treatments can occur.[12–14] This makes PuraStat a safe and effective alternative agent to be used during and after HRTR.

However, our study has certain limitations. As this is a prospective observational study reflecting current clinical practice, the primary limitation is the lack of a control group. It is also worth noting that some of the patients in our study continued to take aspirin peri-procedurally in line with current guidelines[17] and a proportion of patients had focal clip application of the resection base (for mural injury only) which is not uncommon in standard clinical practice. However, due to the low rate of delayed bleeding and the lack of a control group, it was not possible to assess their individual impact on delayed bleeding.

Although a small RCT has previously shown PuraStat can reduce the need for thermocoagulation during ESD, it did not address delayed bleeding after high-risk EMR[20] as addressed in our study.

In conclusion, this is the largest study of its kind with any topical haemostat and provides a real-world insight into the use of PuraStat for treatment and prevention of delayed bleeding during HRTR. It is safe and easy to use, requiring only a small volume. Furthermore, the lack of technical challenges encountered by a range of endoscopists in a multicentre setting provides strong evidence for its generalisability.

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