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- Achieving haemostasis in bleeding from small blood vessels and oozing from capillaries of the GI tract following surgical procedures [when haemostasis by ligation or standard means is insufficient or impractical]
- Reduction of delayed bleeding following gastrointestinal endoscopic submucosal dissection (ESD) procedures in the colon

The attached fast facts document refers to the publication:

*"A novel self-assembling peptide for hemostasis during endoscopic submucosal dissection: a randomized controlled trial.*

also describes procedures and contains data which are currently not within the indication of PuraStat.

It concerns, within healing and also the reduction of delayed bleeding, the following procedures/ locations in the attached publication which are not covered by the current indication of PuraStat (indicated with x in table below):

| Location | **ESD** |
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| Colon | Indicated |
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# A novel self-assembling peptide for hemostasis during endoscopic submucosal dissection: a randomized controlled trial

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## ABSTRACT

**Background** Endoscopic submucosal dissection (ESD) is associated with a risk of bleeding. Bleeding is usually treated with diathermy, although this does carry a risk of mucosal thermal injury. Purastat is a topical hemostat that may be effective in controlling bleeding during ESD, thereby reducing the use of heat therapy. The aim of this study was to assess the reduction in heat therapy used in the interventional group (Purastat) compared with the control group. The secondary aims were to compare the procedure length, time for hemostasis, delayed bleeding rate, adverse events, and wound healing between the groups.

**Methods** This was a single-center randomized controlled trial of 101 patients undergoing ESD. Participants were randomized to a control group where diathermy was used to control bleeding or an interventional group where Purastat could be used. Follow-up endoscopy was performed at 4 weeks to assess wound healing.

**Results** There was a significant reduction in the use of heat therapy for intraprocedural hemostasis in the interventional group compared with controls (49.3 % vs. 99.6 %, $P<0.001$). There were no significant differences in the procedure length, time for hemostasis, and delayed bleeding rate between the groups. Complete wound healing at 4 weeks was noted in 48.8 % of patients in the interventional group compared with 25.0 % of controls ($P=0.02$).

**Conclusions** This study has demonstrated that Purastat is an effective hemostat that can reduce the need for heat therapy for bleeding during ESD. It may also have a role in improving post-resection wound healing.

## Introduction

Endoscopic submucosal dissection (ESD) is an effective technique for removal of superficial gastrointestinal (GI) neoplasia. However, its uptake in the West has been hampered by concerns over a high complication rate and the lengthy learning curve. Intraprocedural bleeding (IPB) is a well recognized complication. The usual method of controlling IPB is with electrocautery that is applied through the tip of the knife or via hemostatic forceps [1, 2]. Heat application may result in mucosal thermal injury that can lead to perforation. There is also a risk of post-ESD electrocoagulation syndrome (PEECS), which is associated with female patients, right-sided colonic lesions, and lesions of >4 cm in size [3].

Delayed bleeding is another risk associated with ESD, ranging from 1 % – 15 % depending on lesion location, size, and anticoagulant use [4]. Prophylactic clipping following colonic endoscopic resection showed no benefit [5] and prophylactic coagulation of vessels over the resection base has only been shown to be effective in reducing delayed bleeding post-gastric ESD [6, 7].

Recently, topical hemostats have emerged as alternative non-diathermic modalities to manage bleeding. These are supplied as opaque powders that can be sprayed over the bleeding

point [8, 9]. Purastat (3D-Matrix Europe Ltd., France) is a novel synthetic self-assembling peptide that is licensed for use as a hemostat. Its unique transparent gel formulation forms an extracellular scaffold matrix when activated by the change in pH that occurs upon contact with blood. This matrix forms a stable mechanical barrier over the bleeding site thereby facilitating intrinsic in vivo hemostasis.

Initial preclinical studies investigating this peptide have shown other benefits in addition to its hemostatic properties, including improved wound healing [10 – 14]. The first clinical trial of Purastat was conducted in vascular surgery, where it was used on 33 vascular anastomotic sites in 25 patients [15]. It has also had favorable outcomes in nasal and cardiothoracic surgery [16, 17]. Within endoscopy, its impact on delayed bleeding and wound healing following ESD has shown promise [18, 19]. Only one small study of 12 gastric ESD patients has assessed its hemostatic efficacy – this showed it was effective in 92 % of cases [20]. Purastat has been shown to be safe with no device-related adverse events reported. However, a major limitation of the evidence available is that all the studies have lacked a control group for comparison. There are few data on the efficacy of Purastat in controlling IPB during endoscopic resection. However, if it could reduce the need for thermal hemostasis by controlling some of the bleeds encountered, it would improve the safety profile of ESD.

The primary aim of the study was to assess the reduction in the use of heat for treatment of IPB during ESD when Purastat was used as a hemostat. The secondary aims were to compare the procedure length, time for hemostasis, delayed bleeding rate, adverse events, and wound healing in the interventional arm (Purastat) and control group.

# Methods

## Study design

This study was a single-center randomized controlled clinical trial involving patients who were undergoing esophageal and colonic ESD procedures only. It was registered at http://www.clinicaltrials.gov (identifier: NCT02833558) and approved by the South Central Hampshire A research ethics committee (reference: 16/SC/0020).

## Study participants

Patients over 18 years of age scheduled for elective esophageal or colonic ESD for lesions of 2 – 5 cm were eligible for participation. Patients aged under 18 years, unable to provide informed consent, with submucosal tumors or lesions with deep submucosal invasion, with an inherited or acquired coagulopathy likely to affect the risk of bleeding, or receiving an anticoagulant therapy, except for aspirin, that could not be stopped or bridged pre-procedure were excluded. All participants provided written informed consent for the ESD procedure and separate consent for participation in the study. Baseline demographic data were recorded.

## Randomization

All patients recruited were randomized in a 1:1 fashion to either the control or interventional arms. Each participant was allocated a unique trial reference number and computer-generated randomization was carried out at the time of the ESD using a web-based platform (https://www.sealedenvelope.com/).

## Blinding

This was a single-blind study where patients were not informed about their randomization allocation in order to increase reliability during follow-up. Owing to the differences in the interventions, it was not possible to blind the endoscopist performing ESD.

## Endoscopic technique and hemostatic intervention

### Endoscopic submucosal dissection

All esophageal ESD procedures were done with the patient under general anesthetic with a planned overnight hospital stay. Colonic ESD procedures were performed as day-cases with the patient under conscious sedation. Uninterrupted single antiplatelet therapy with aspirin was permitted, while all other anticoagulants were discontinued before the procedure as per national guidelines [21].

One endoscopist (P.B.; lifetime experience of over 500 ESD procedures) performed all of the ESDs. Hybrid ESD was used in cases where significant submucosal fibrosis was anticipated and this was decided on the basis of lesion assessment at the time of the procedure prior to randomization.

A standard lifting solution (500 mL Gelofusine + 1 mL 1:10000 adrenaline + 1 mL 1 % indigo carmine) and the DualKnife or DualKnife J (Olympus Medical UK) were used for all procedures. An Erbe VIO 300 D electrosurgical generator (Erbe Medical, Tübingen, Germany) was used for diathermy. Endocut I (effect 2, cut interval 3, cut duration 3) was used for mucosal incision followed by submucosal dissection on swift coagulation (effect 4, 50 W). The procedure length was measured in minutes as the time taken from the point of submucosal injection to the end of dissection.

### Hemostasis

The start and stop times for each episode of IPB were measured. The number of bleeds that stopped spontaneously without treatment was recorded. We used the definitions described in an earlier study to classify the bleeds into three grades (grade 1, mild oozing; grade 2, moderate non-spurting bleeding with visible vessel; grade 3, arterial spurting) [22].

### Control arm

All patients allocated to the control group received electrocoagulation treatment for IPB. This was applied either via the endoscopic knife tip (swift coagulation mode; effect 4, 50 W) or using a coagulation forceps (Coagrasper; Olympus Medical UK) on soft coagulation mode (effect 4, 80 W). The Coagrasper was used in more severe bleeds.

### Interventional arm

This was a pragmatic real-life study designed to incorporate the use of Purastat into the treatment of IPB in the interventional arm without increasing the complexity of the procedure. Purastat was used for grade 1 and 2 bleeds that were encountered outside the immediate vicinity of the tip of the knife or when the bleeding point was not easily accessible for diathermy (e. g. when the bleeding point was not clearly visible because of blood pooling, was situated in the deeper planes or at the edge of an incision where the bleeding vessel was not fully exposed, or where access to the lesion was unstable).

Purastat was applied via a bespoke catheter inserted through the endoscope accessory channel (▶ **Fig. 1**). The volume of Purastat used and the time to hemostasis was measured. If a bleed was not controlled by either Purastat or diathermy, the endoscopist was permitted to use other treatment modalities.

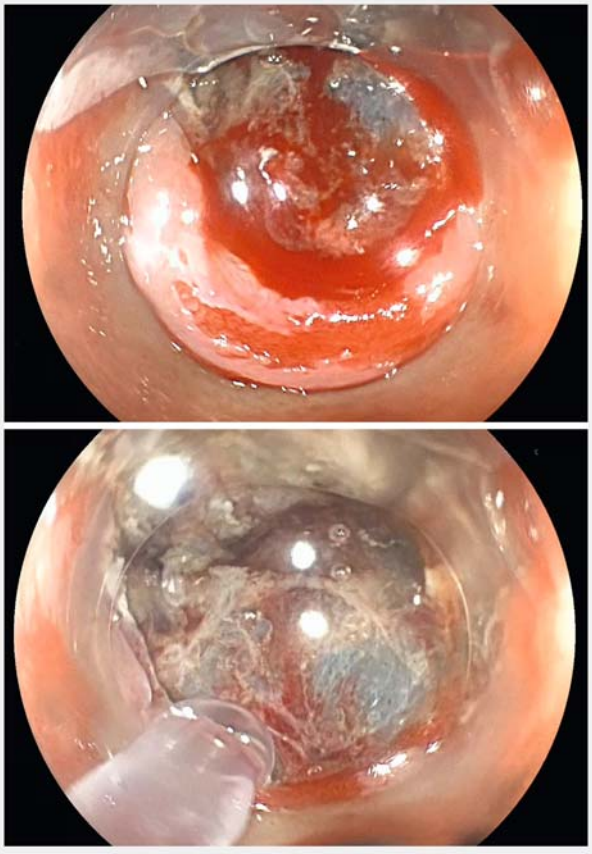
Our previous experience with Purastat demonstrated that it worked best in grade 1 and 2 bleeds, but not in grade 3 bleeds [22]. Therefore, the study protocol permitted the use of diathermy with the endoscopic knife tip (in grade 1 & 2 bleeds) if the bleeding point was clearly visible in the immediate vicinity of the knife and the Coagrasper in grade 3 spurting bleeds where Purastat was not recommended. This strategy addressed any potential ethical dilemmas regarding the value of withdrawing the knife and inserting the catheter for Purastat delivery when the knife could achieve safe hemostasis.

Purastat was applied over the resection base at the end of all procedures in the interventional arm. No other treatment (prophylactic coagulation or clipping) was carried out in either group. The ease of application was recorded and any issues encountered (e. g. catheter blockage, interference with visibility or electrical conductivity through the knife).

## Follow-up

All patients undergoing esophageal ESD received high dose proton pump inhibitor therapy (40 mg twice daily omeprazole or equivalent) for 8 weeks post-procedure. All patients returned approximately 4 weeks post-procedure for a repeat endoscopy to inspect the resection site. Complications or adverse events (delayed bleeding, perforation, unexpected hospital admissions) related to the ESD were recorded at this visit. Delayed bleeding was defined as overt hemorrhage occurring between 24 hours and 30 days post-procedure and requiring medical intervention (endoscopic/radiological/surgical management), with or without a blood transfusion. Immediate/early rebleeding was defined as overt hemorrhage occurring within the first 24 hours post-procedure requiring intervention as above.

All follow-up endoscopies were carried out by two experienced endoscopy fellows who were blinded to the patient's randomization. We adapted the wound healing categories based on the Sakita and Fukutomi ulcer staging classification [23]. The categories used were healing ulceration, scarring, and complete healing (▶ **Fig. 2**).



▶ **Fig. 1** Endoscopic views showing the application of Purastat for intraprocedural bleeding.

## Outcomes

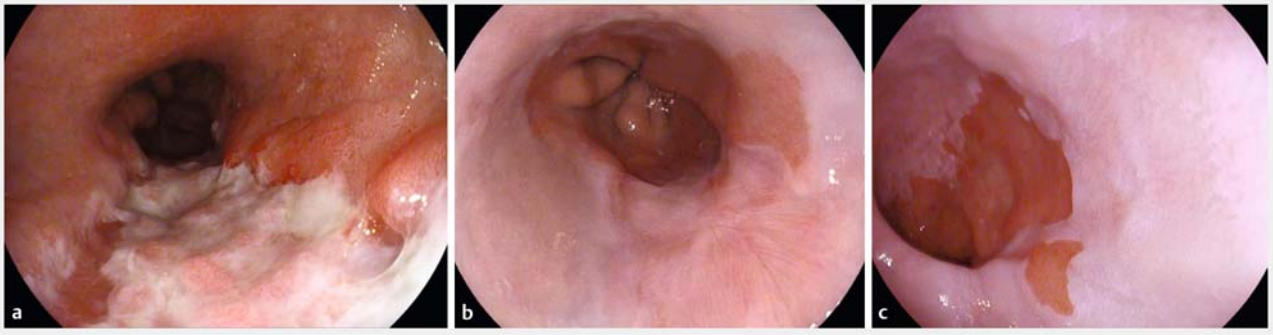
The primary outcome was the mean reduction in intraprocedural heat therapy required when Purastat was used for hemostasis in ESD.

Secondary outcomes measured were: total procedure length; time taken for hemostasis using Purastat compared with diathermy; proportion of patients with complete wound healing, scarring, and healing ulceration present at follow-up endoscopy; and complication rates in the two arms.

## Statistical methods and sample size calculation

An intention-to-treat analysis was performed. Baseline characteristics were compared using the independent *t* test for continuous variables (e. g. age and lesion size) and chi-squared or Fisher's exact tests for categorical variables (e. g. sex, co-morbidities, anti-thrombotic agents, en bloc resection, location, circumference, procedure type). Chi-squared tests were also used to compare differences between the two arms in the primary end point and the secondary end points (delayed bleeding, adverse events, wound healing). *P* values obtained were two-sided and a *P* value of $<0.05$ was considered significant in all cases. Statistical analyses were carried out using SPSS version 24.

The sample size calculation utilized the *t* test for two independent samples and was based on the primary outcome meas-




▶ **Fig. 2** The stages of wound healing of the resection base following endoscopic submucosal dissection were categorized as: **a** healing ulceration; **b** scarring; **c** complete healing.

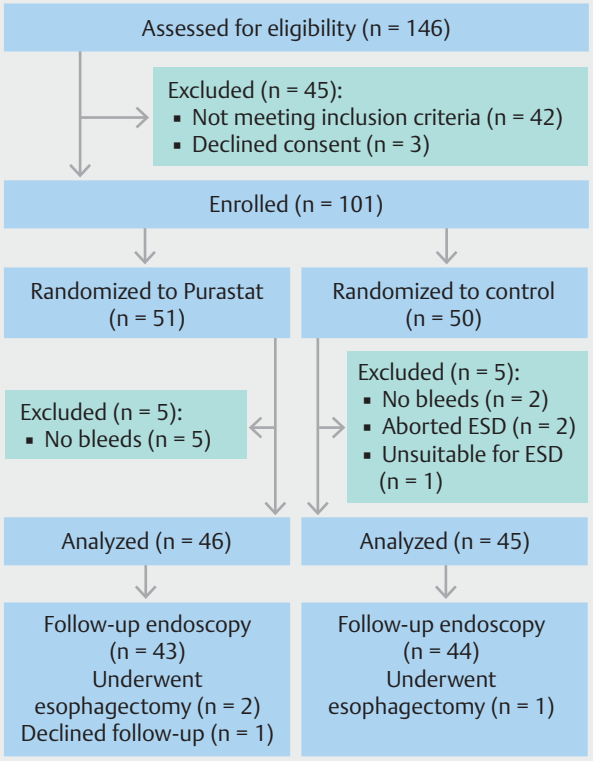
ure of reducing the number of episodes of IPB requiring heat for hemostasis. As there is a lack of data on hemostasis in ESD, the sample size calculation was based on assumptions derived from ESD expert experience. We assumed that hemostasis would be required on average 10 times per patient (with a standard deviation of 5). We hypothesized that Purastat would reduce the number of episodes of IPB requiring heat treatment by 30 %. To detect this difference with 80 % power (assuming a two-sided significance level of 5 %), the study would require 45 patients in each trial arm (90 patients in total). The recruitment target was increased by 10 % to 100 patients in order to account for study withdrawals. The sample size calculation was performed using R for Windows (version 3.5.3).

## Results

A total of 101 patients were recruited and randomized into the two groups from May 2016 to April 2018. There were three patients who were withdrawn from the study: two had aborted ESD procedures and one had a lesion better suited for EMR so did not proceed to ESD. There were five patients in the Purastat arm and two in the control arm who did not have any IPB. Therefore, the intention-to-treat analysis was performed on the remaining 91 patients (▶ **Fig. 3**).

### Baseline patient and procedural characteristics

There were no significant differences between the patient and lesion characteristics in the two groups (▶ **Table 1**). Notably, this was a high risk study population with a high proportion of patients (50 % in the Purastat group and 38 % in the control group) having significant co-morbidities, such as cardiorespiratory conditions, diabetes, or previous cerebrovascular accident. About 40 % of patients in each group had been on anticoagulant therapy which was stopped before the procedure. The study protocol permitted conversion from ESD to hybrid ESD (~10 %) for reasons of technical difficulty or if time/patient tolerance proved a constraint. A similar proportion of patients (37 % vs. 42 %) underwent hybrid ESD, which is reflected in the low en bloc resection rates.




▶ **Fig. 3** Flow diagram of the study participants.

### Intraprocedural bleeding and primary outcome

There were 269 bleeds in 45 patients in the control group and 232 bleeds in 46 patients in the Purastat group. There was no significant difference in the proportion of bleeds requiring treatment in the two groups (95.3 % vs. 97.4 %) or the mean number of bleeds per patient (5.0 vs. 6.0) (▶ **Table 2**). The majority of bleeds in both groups were grade 1 and 2 bleeds.

There was a 50 % reduction in the number of episodes of IPB treated by diathermy in the interventional arm. Diathermy was used for 109/221 bleeds requiring treatment (49.3 %) in the Purastat arm. In 100/109 bleeds, this was owing to the severity

▶ **Table 1** Baseline characteristics of the 101 patients enrolled in the study.

| | | Interventional arm (Purastat) n = 46 | Control arm (diathermy) n = 45 | *P* value |
|---|---|---|---|---|
| Age, mean (SD), years | | 68.6 (10.6) | 71.5 (11.2) | 0.22 |
| Lesion size, mean (SD), mm | | 33.7 (12.1) | 36.6 (13.6) | 0.29 |
| Sex, male : female, n | | 33 : 13 | 27 : 18 | 0.27 |
| Co-morbidities present, n (%) | | 23 (50.0 %) | 17 (37.8 %) | 0.24 |
| ▪ Cardiovascular disease | | 20 (43.5 %) | 15 (33.3 %) | 0.39 |
| ▪ Ischemic heart disease | | 6 (13.0 %) | 7 (15.6 %) | 0.77 |
| ▪ Hypertension | | 7 (15.2 %) | 5 (11.1 %) | 0.76 |
| ▪ Atrial fibrillation | | 6 (13.0 %) | 4 (8.9 %) | 0.74 |
| ▪ Valvular abnormalities | | 2 (4.3 %) | 0 | 0.50 |
| ▪ Peripheral vascular disease | | 2 (4.3 %) | 2 (4.4 %) | > 0.99 |
| ▪ Diabetes mellitus | | 2 (4.3 %) | 3 (6.7 %) | 0.68 |
| ▪ Asthma/COPD | | 1 (2.2 %) | 1 (2.2 %) | > 0.99 |
| ▪ Cerebrovascular accident/TIA | | 2 (4.3 %) | 2 (4.4 %) | > 0.99 |
| ▪ Chronic liver disease | | 0 | 0 | > 0.99 |
| On antithrombotic therapy, n (%) | | 19 (41.3 %) | 18 (40.0 %) | 0.90 |
| ▪ Warfarin | | 5 (10.9 %) | 3 (6.7 %) | 0.71 |
| ▪ Novel oral anticoagulant | | 1 (2.2 %) | 3 (6.7 %) | 0.36 |
| ▪ Aspirin | | 7 (15.2 %) | 6 (13.3 %) | > 0.99 |
| ▪ Clopidogrel | | 6 (13.0 %) | 6 (13.3 %) | > 0.99 |
| En bloc resection rate, n (%) | | 35 (76.1 %) | 31 (68.9 %) | 0.44 |
| Location, n (%) | Esophageal | 28 (60.9 %) | 20 (44.4 %) | 0.12 |
| | Colorectal | 18 (39.1 %) | 25 (55.6 %) | |
| Circumference, n (%) | < 50 % | 32 (69.6 %) | 26 (57.8 %) | 0.24 |
| | > 50 % | 14 (30.4 %) | 19 (42.2 %) | |
| Procedure type, n (%) | ESD | 29 (63.0 %) | 26 (57.8 %) | 0.61 |
| | Hybrid ESD | 17 (37.0 %) | 19 (42.2 %) | |

SD, standard deviation; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; ESD, endoscopic submucosal dissection.

of the bleed or the location being in the immediate vicinity of the knife tip, whereas 9/109 uses of diathermy were because of unsuccessful treatment with Purastat. There were 112 bleeds that were treated with Purastat as a primary hemostat and nine that were treated following the application of diathermy. Purastat achieved complete hemostasis in 92.6 % of these bleeds (112/121).

## Secondary outcomes

The mean length of time for hemostasis using Purastat was similar compared with diathermy (70 vs. 78 seconds, $P = 0.14$) (▶ **Table 3**). The total procedure time was also similar (74 vs. 81 minutes for the interventional and control arms, respectively). Only a small amount of Purastat was required (mean of 0.43 mL per bleed) for hemostasis and for prophylactic coverage of the resection base (mean of 2.03 mL per patient).

## Delayed bleeding and adverse events

There were two delayed bleeds in each arm (delayed bleeding rate 4.3 % vs. 4.4 %). All bleeds were managed endoscopically and no further episodes of rebleeding occurred post-endoscopy. There was one perforation in the interventional arm, which was unrelated to the application of Purastat and attributed to the lesion histology (submucosally invasive cancer).

## Technical feasibility

Purastat was rated as easy to apply with complete coverage of the resection base achieved in the interventional arm. It was re-

▶ **Table 2** Comparison of intraprocedural bleeding (IPB) and hemostat use between the two groups.

| | | Interventional arm (Purastat) n = 46 | Control arm (Diathermy) n = 45 | *P* value |
|---|---|---|---|---|
| Total episodes of IPB, n | | 232 | 269 | N/A |
| Episodes of IPB that stopped spontaneously, n (%) | | 11 (4.7 %) | 7 (2.6 %) | 0.20 |
| Episodes of IPB that required hemostasis, n (%) | | 221 (95.3 %) | 262 (97.4 %) | 0.20 |
| Severity of bleeding, n (%) | Grade 1 | 105 (47.5 %) | 151 (57.6 %) | 0.03 |
| | Grade 2 | 102 (46.2 %) | 101 (38.5 %) | 0.09 |
| | Grade 3 | 14 (6.3 %) | 10 (3.8 %) | 0.21 |
| Episodes of IPB treated with heat, n (%)[1] | | 109 (49.3 %) | 261 (99.6 %)[2] | 0.001 |
| Episodes of IPB treated with Purastat, n (%)[3] | | 121 (54.8 %) | 0 | N/A |
| Successful hemostasis achieved with Purastat, n (%) | | 112/121 (92.6 %) | N/A | N/A |

NA, not applicable.
[1] Includes nine bleeds treated with heat following unsuccessful hemostasis with Purastat.
[2] One bleed required the use of endoscopic clips for safe hemostasis.
[3] Includes the use of Purastat for hemostasis in nine bleeds following unsuccessful diathermy.

ported to "interfere with visibility" in two patients: both had multiple sites of IPB within close proximity necessitating repeated applications of the gel in the same field of resection.

### Wound healing

The median length of follow-up was 30 days in both groups. There was a significant increase in the proportion of patients achieving complete wound healing in the Purastat group compared with controls (48.8 % vs. 25.0 %, $P = 0.02$) (▶ **Table 4**). However, in a subgroup analysis according to location, no significant difference between the groups was noted in wound healing post-esophageal ESD (▶ **Table 5**). This was in contrast to colorectal ESD, where a higher proportion of patients in the control group were noted to have ulceration over the resection site during follow-up endoscopy (56 % vs. 17.6 %, $P = 0.01$), indicative of incomplete wound healing.

## Discussion

Bleeding is a well recognized complication of ESD. IPB can prolong the procedure time, increase the risk or complexity of the ESD, and compromise the dissection planes. Delayed bleeding can lead to additional length of stay and increases the morbidity associated with the procedure. Thus far, conventional treatment of IPB has been carried out using diathermy, which can increase the risk of thermal injury. Our study investigated the use of a novel hemostat to tackle procedure-related bleeding, with the aim of reducing the amount of heat therapy required.

We demonstrated that Purastat is a safe and viable hemostat for mild to moderate IPB during ESD and led to a significant reduction in the use of diathermy for hemostasis. This is the first randomized controlled study using this hemostat and both groups of patients were well matched in terms of their risk factors for bleeding. There was only limited conversion from ESD to hybrid ESD, which did not have a significant effect on the pri-

▶ **Table 3** Comparison of secondary outcomes between the two groups.

| | Interventional arm (Purastat) n = 46 | Control arm (diathermy) n = 45 | *P* value |
|---|---|---|---|
| Procedure length, mean (SD), minutes | 74.2 (48.7) | 80.7 (56.6) | 0.56 |
| Time for hemostasis per bleed, mean (SD), seconds | 70.0 (76.1) | 77.6 (274.2) | 0.14 |
| Immediate/early rebleeding, n | 0 | 0 | |
| Delayed bleeding, n (%) | 2 (4.3 %) Esophageal 1 Colonic 1 | 2 (4.4 %) Esophageal 1 Colonic 1 | 0.98 |
| Perforation, n (%) | 1 (2.2 %) | 0 | 0.32 |

SD, standard deviation.

▶ **Table 4** Comparison of wound healing between the two groups.

| Wound healing categories | Interventional arm (Purastat) n = 43 | Control arm (diathermy) n = 44 | *P* value |
|---|---|---|---|
| Complete healing, n (%) | 21 (48.8 %) | 11 (25.0 %) | 0.02 |
| Scarring, n (%) | 11 (25.6 %) | 13 (29.5 %) | 0.69 |
| Healing ulceration, n (%) | 11 (25.6 %) | 20 (45.5 %) | 0.05 |

▶ **Table 5** Subgroup analysis of wound healing according to lesion location.

| | Esophageal (n = 45) | | | Colorectal (n = 42) | | |
|---|---|---|---|---|---|---|
| | Purastat (n = 26) | Control (n = 19) | *P* value | Purastat (n = 17) | Control (n = 25) | *P* value |
| Complete healing | 14 (53.8 %) | 7 (36.8 %) | 0.26 | 7 (41.2 %) | 4 (16.0 %) | 0.07 |
| Scarring | 4 (15.4 %) | 6 (31.6 %) | 0.20 | 7 (41.2 %) | 7 (28.0 %) | 0.38 |
| Healing ulceration | 8 (30.8 %) | 6 (31.6 %) | 0.96 | 3 (17.6 %) | 14 (56.0 %) | 0.01 |

mary end point, given the ratio of conventional to hybrid procedures was similar in the two arms.

There is limited literature available on the amount of energy needed to cause a full-thickness perforation; however, it is widely accepted that any use of monopolar electrocoagulation current on an ESD base carries the risk of thermal injury and can lead to PEECS. The incidence of PEECS and perforation in ESD is low and it would not have been pragmatic to power a trial with these end points, given the sample size required. Therefore, the number of "heat-treated bleeds" was used as a surrogate marker and was designated the primary outcome measure. Purastat may have a role in prevention of PEECS, although the existing literature has not assessed this. In this trial, there were no cases of PEECS in either arm, so we may not draw any firm conclusions from this. Nevertheless, a non-diathermic modality that allows the endoscopist to use heat judiciously will continue to make ESD safer. This is relevant as the ESD expertise in the West is currently not as good as in Japan and the risks are higher in the learning curve phase [24, 25].

This study also showed that the time taken to control IPB did not differ significantly with the modality of treatment used (just over a minute in both). The transparent nature of the gel made it possible for the endoscopist to accurately observe hemostasis as visibility was maintained after application. There were no instances of early rebleeding in either group.

The overall procedure time was also not prolonged in the interventional arm. Purastat was not used for every bleed encountered as, in some bleeds, it was more pragmatic not to exchange the endoscopic knife for the Purastat catheter, given the location of the bleed and access. We felt that this model of tailoring the use of Purastat depending on the type of bleed was the most practical way of using it and anticipate that future users will adopt a similar strategy.

Our study also showed that only a small amount of Purastat was needed. It was feasible, in many cases, for just a single 3-mL vial of hemostat to be used per ESD. We reported on the technical aspects of gel application and found that there were no instances of catheter blockage. The gel did not hamper dissection in the area of application as there were no clinically perceptible differences in the conduction of current in this field. In two cases, it was found to interfere with visibility, although it was possible to remove the gel by vigorous flushing.

The overall delayed bleeding rate in this study was low (4 %) and no difference was noted between the groups. It is encouraging to note that there was no increase in delayed bleeding in the interventional arm, which may permit us to infer that the hemostatic efficacy of Purastat is sustained. In a previous study where Purastat was used prophylactically following gastric ESD, the delayed bleeding rate was noted to be 2.2 % (no direct control group but this figure is lower than the average rate quoted in the literature) [18].

urastat may have beneficial effects on wound healing as noted in preclinical animal studies [10]. The extracellular scaffold matrix promotes cell regeneration and connective tissue repair, which may accelerate wound healing. It has been trialed for use in the prevention of esophageal strictures after endoscopic resection in porcine models, where the stricture rate in the interventional group was lower than the control group (40 % vs. 100 %, $P = 0.2$) [26]. Only one other human clinical trial investigating the wound healing effects of Purastat has been carried out, which demonstrated that 96 % of cases reached the healing stage of post-gastric ESD ulceration after 1 week and 98 % reached the scarring stage by 8 weeks [18]. In our study, almost 75 % of the patients followed up in the Purastat group achieved either complete wound healing or scarring compared with 54 % in the control group at 4 weeks. However, we noted that there was no difference in the stages of wound healing in the esophageal ESD patients. This may be because of the high dose proton pump inhibitor therapy and the timing of follow-up in the esophageal lesions, where healing may be accelerated. In colorectal ESD, 82 % of patients in the Purastat group achieved complete healing or scarring compared with 44 % of controls.

There were several limitations to this study. Firstly, we did not include patients undergoing gastric ESD (where the incidence of bleeding is higher), as the prevalence of early gastric cancer in our population is low. However, Purastat may have a role to play in reducing delayed bleeding in this group as two previous studies using Purastat prophylactically post-gastric ESD have shown low delayed bleeding rates (0 – 2 %), although both lacked a control group [18, 19]. A matched control study assessing the hemostatic effects of Purastat following gastric endoscopic resection would increase our understanding of its properties.

Secondly, given the paucity of data on IPB during ESD, we assumed that esophageal and colonic ESD would have a similar incidence of bleeding and therefore did not power the study to stratify recruitment and randomization according to lesion location. Thirdly, as this was a pragmatic clinical trial designed to fit in with standard clinical practice, we were not able to carry out additional follow-up procedures at weeks 1 and 2 post-ESD. This may have affected accurate assessment of the transition between the stages of wound healing. It was also difficult to assess the impact of Purastat on the incidence of PEECS, given the

lack of data available and small sample size. We acknowledge that Purastat will add to the cost of the procedure, but this study did not assess its cost-effectiveness and impact on delayed bleeding as the focus was to understand the basic principles of its efficacy and safety.

Despite the limitations, this study is the first randomized controlled trial to investigate a novel hemostat for control of IPB during ESD. The primary end point of the trial was met as Purastat does significantly reduce the need for heat treatment required for hemostasis. This may improve the overall safety of ESD and highlights an emerging role for this peptide as an adjunct to conventional hemostatic techniques during ESD.

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### Competing interests

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### Clinical trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT02833558 | Type of study: randomised controlled trial

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