**Title Page**

**A randomised controlled trial of a novel self-assembling peptide for haemostasis in endoscopic submucosal dissection**

**Authors and Affiliations:**

1) Sharmila Subramaniam

i. Department of Gastroenterology, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

2) Kesavan Kandiah

i. Department of Gastroenterology, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

ii. Department of Gastroenterology, St George's University Hospital NHS Trust

London, UK

3) Fergus Chedgy

i. Department of Gastroenterology, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

ii. Department of Gastroenterology, Brighton and Sussex University Hospitals NHS Trust, Brighton and Hove, UK

4) Carole Fogg

i. Department of Research and Innovation, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

ii. School of Health Sciences, University of Southampton,

Southampton SO17 1BJ, UK

5) Sreedhari Thayalasekaran

i. Department of Gastroenterology, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

6) Asma Alkandari

i. Department of Gastroenterology, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

7) Michelle Baker-Moffatt

i. Department of Gastroenterology, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

8) Joanne Dash

i. Department of Gastroenterology, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

9) Mark Lyons-Amos

i. Department of Research and Innovation, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

10) Gaius Longcroft-Wheaton

i. Department of Gastroenterology, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

ii. School of Pharmacy and Biomedical Sciences, University of Portsmouth,

Portsmouth, UK

11) James Brown

i. School of Pharmacy and Biomedical Sciences, University of Portsmouth,

Portsmouth, UK

12) Pradeep Bhandari

i. Department of Gastroenterology, Queen Alexandra Hospital,

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham, Portsmouth, PO6 3LY, UK

ii. School of Pharmacy and Biomedical Sciences, University of Portsmouth,

Portsmouth, UK

**Corresponding Author:**

Professor Pradeep Bhandari (MD, FRCP)

Department of Gastroenterology,

Queen Alexandra Hospital

Portsmouth Hospitals NHS Trust

Southwick Hill Road, Cosham

PO6 3LY, UK

Email: pradeep.bhandari@porthosp.nhs.uk

deep3570@yahoo.co.uk

Tel: 02392286255

**Structured Abstract**

***Background and aims:*** 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 haemostat that may be effective in controlling bleeds 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 to the control group. The secondary aims were to compare the procedure length, time for haemostasis, delayed bleeding rate, adverse events and wound healing between groups.

***Patients and methods:*** This was a single centre randomised controlled trial of 101 patients undergoing ESD. Participants were randomised 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 haemostasis in the interventional group compared to controls (49.3% vs 99.6%, p<0.0001). There was no significant difference in the procedure length, time for haemostasis and delayed bleeding rate in both groups. Complete wound healing at 4 weeks was noted in 48.8% of patients in the interventional group compared to 25% of controls (p=0.02).

***Conclusions:*** This study has demonstrated that Purastat® is an effective haemostat 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 long learning curve. Intraprocedural bleeding (IPB) is a well recognised complication. The usual method of controlling IPB is with electrocautery that is applied through the tip of the knife or via haemostatic 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) associated with female patients, right sided colonic lesions and lesion size >4cm [3].

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

Recently, topical haemostats 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 licensed for use as a haemostat. Its unique transparent gel formulation forms an extracellular scaffold matrix when activated by a 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 haemostasis.

Initial pre-clinical studies investigating this peptide have shown other benefits in addition to its haemostatic 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 favourable outcomes in nasal and cardiothoracic surgery [16,17]. Within endoscopy, its impact on DB and wound healing following ESD has been promising [18,19]. Only one small study of 12 gastric ESD patients assessed its haemostatic efficacy - this showed it was effective in 92% [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 is little data on the efficacy of Purastat® in controlling IPB during ER. However, if it could reduce the need for thermal haemostasis by controlling some bleeds encountered it would improve the safety profile of ESD.

**Aims**

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 haemostat. The secondary aims were to compare the procedure length, time for haemostasis, DB rate, adverse events and wound healing in the interventional arm (Purastat®) and control group.

**Patients/Material and Methods**

**Study Design**

This study was a single centre randomised controlled clinical trial involving patients undergoing oesophageal 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 scheduled for elective oesophageal or colonic ESD for 2-5cm lesions were eligible for participation. Patients under 18 years, unable to provide informed consent, submucosal tumours or lesions with deep submucosal invasion and patients with an inherited or acquired coagulopathy likely to affect the risk of bleeding or where anticoagulant therapy except for aspirin 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 was recorded.

**Randomisation**

All patients recruited were randomised in a 1:1 fashion to either the control or interventional arms. Each participant was allocated a unique trial reference number and computer generated randomisation 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 randomisation allocation in order to increase reliability with follow up. Due to the differences in the interventions it was not possible to blind the endoscopist performing ESD.

**Endoscopic technique and haemostatic intervention**

**Endoscopic submucosal dissection**

All oesophageal ESD procedures were done under general anaesthetic with a planned overnight hospital stay. Colonic ESD procedures were daycases with 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 (PB-lifetime experience of over 500 ESD procedures) performed all ESD. Hybrid ESD was used in cases where significant submucosal fibrosis was anticipated and this was decided based on lesion assessment at the time of the procedure prior to randomisation. In approximately 10% of cases, there was a conversion from ESD to hybrid ESD due to technical difficulty or if time/patient tolerance proved a constraint.

A standard lifting solution (500ml Gelofusine + 1ml 1:10000 adrenaline + 1ml 1% indigocarmine) and the Dual or Dual-J knife (Olympus Medical UK) were used for all procedures. An Erbe VIO 300D electrosurgical generator (Erbe Medical, Tubingen, 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, 50W). The procedure length was measured in minutes as the time taken from the point of submucosal injection to the end of dissection.

**Haemostasis**

The start and stop times for each 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 3 grades (Grade 1: mild oozing; Grade 2: moderate non-spurting bleeding with visible vessel; Grade 3: arterial spurter) [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, 50W) or using a coagulation forceps (Coag-grasper, Olympus Medical UK) on soft coagulation mode (effect 4, 80W). The Coag-grasper 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 where the bleeding point was not clearly visible due to blood pooling, bleeding points situated in the deeper planes or at the edge of an incision where the bleeding vessel is not fully exposed or access to the lesion was unstable).

Purastat® was applied via a bespoke catheter inserted through the endoscope accessory channel (Figure 1). The volume of Purastat® used and the time to haemostasis 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 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 Coag-grasper 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 haemostasis.

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 both groups. 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 oesophageal ESD received high dose proton pump inhibitor therapy (40mg bd 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 (DB, perforation, unexpected hospital admissions) related to the ESD were recorded on this visit. DB was defined as overt haemorrhage occurring between 24 hours to 30 days post-procedure and requring medical intervention (endoscopic/radiological/surgical management) with or without a blood transfusion. Immediate/early rebleeding was defined as overt haemorrhage occurring within the first 24 hours post-procedure requiring intervention as above.

All follow up endoscopies were carried out by 2 experienced endoscopy fellows who were blinded to the randomisation. 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 (Figure 2).

**Outcomes**

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

Secondary outcomes measured were total procedure length, time taken for haemostasis using Purastat® compared to diathermy, proportion of patients with complete wound healing, scarring and healing ulceration present at follow up endoscopy and complication rates in both 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-square or Fisher's exact tests for categorical variables (e.g gender, co-morbidities, anti-thrombotic agents, en-bloc resection, location, circumference, procedure type). Chi-square tests were also used to compare differences between the primary endpoints in both arms and secondary endpoints (DB, adverse events, wound healing). p values obtained were 2-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 was based on the primary outcome measure of reducing the number of IPB requiring heat for haemostasis. As there is a lack of data on haemostasis in ESD, the sample size calculation has been based on assumptions derived from ESD expert experience. We assumed that haemostasis would be required on average 10 times per patient (with a standard deviation of 5). We hypothesised that Purastat® would reduce the number 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**

101 patients were recruited and randomised into two groups from May 2016 to April 2018. 3 patients were withdrawn from the study - 2 had aborted ESD procedures and 1 had a lesion best suited for EMR so did not proceed to ESD. There were 5 patients in the Purastat® arm and 2 in the control arm that did not have IPB. Therefore, an intention to treat analysis was performed on the remaining 91 patients (Figure 3).

**Baseline patient and procedure characteristics**

There were no significant differences between the patient and lesion characteristics in both 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 (e.g cardiorespiratory conditions, diabetes, previous cardiovascular accident). About 40% of patients in both groups had been on anticoagulant therapy which was stopped before the procedure. A similar proportion of patients (37-42%) underwent hybrid ESD which reflects the lower en-bloc resection rates.

**Intraprocedural Bleeding & Primary Outcome (Table 2)**

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 both groups (95.3% vs 97.4%) or the mean number of bleeds per patient (5.0 vs 6.0). The majority of bleeds in both groups were Grade 1 and 2 bleeds.

There was a 50% reduction in the number of IPB treated by diathermy in the interventional arm. Diathermy was used for 109/221 (49.3%) of bleeds requiring treatment in the Purastat® arm. In 100/109 bleeds this was due to the severity or location of the bleed in the immediate vicinity of the knife tip whereas 9/109 were due to unsuccessful treatment with Purastat®. 112 bleeds were treated with Purastat® as a primary haemostat and 9 following application of diathermy. Purastat® achieved complete haemostasis in 92.6% of these bleeds (112/121).

**Secondary Outcomes (Table 3)**

The mean length of time for haemostasis using Purastat® was similar compared to diathermy (70 vs 78 seconds, p=0.14). Total procedure time was also similar (74 and 80 minutes for the interventional and control arms respectively). Only a small amount of Purastat® was required (mean of 0.43mls per bleed) for haemostasis and for prophylactic coverage of the resection base (mean of 2.03mls per patient).

**Delayed Bleeding and Adverse Events**

There were 2 delayed bleeds in each arm (DB rate 4.3% and 4.4%). All bleeds were managed endoscopically and no further episodes of rebleeding post-endoscopy occurred. There was 1 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 reported to 'interfere with visibility' in 2 patients - both had multiple IPB within close proximity necessitating repeated applications of the gel in the same field of resection.

**Wound healing (Table 4 and 5)**

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 to controls (48.8% vs 25%, p=0.02). However, in a subgroup analysis according to location no significant difference between the groups was noted in wound healing post oesophageal ESD. This was in contrast with 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-recognised complication of ESD. IPB can prolong procedure time, increase the risk or complexity of the ESD and compromise dissection planes. DB can lead to additional length of stay and increases 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 investigates the use of a novel haemostat 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 haemostat for mild to moderate IPB during ESD and led to a significant reduction in the use of diathermy for haemostasis. This is the first randomised controlled study using this haemostat and both groups of patients were well matched in terms of risk factors for bleeding. 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 endpoints given the sample size required. Therefore, the number of 'heat-treated bleeds' was used as a surrogate marker and designated primary outcome measure. Purastat® may have a role in prevention of PEECS though existing literature has not assessed this. In this trial, there were no cases of PEECS in both arms 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 haemostasis as visibility was maintained after application. There were no instances of early rebleeding in both groups.

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 3ml vial of haemostat 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 conduction of current in this field. In 2 cases, it was found to interfere with visibility although the gel could be removed by vigorous flushing.

The overall DB rate in this study was low (4%) and no difference was noted between both groups. It is encouraging to note that there was no increase in DB in the interventional arm which may permit us to infer that the haemostatic efficacy of Purastat® is sustained. In a previous study where Purastat® was used prophylactically following gastric ESD, the DB 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].

Purastat® may have beneficial effects on wound healing as noted in pre-clinical animal studies [10]. The extracellular scaffold matrix promotes cell regeneration and connective tissue repair which may accelerate wound healing. It has been trialled for use in the prevention of oesophageal strictures after ER in porcine models where the stricture rate in the interventional group was significantly 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 to 54% in the control group at 4 weeks. However, we noted that there was no difference in the stages of wound healing in the oesophageal ESD patients. This may be because of high dose proton pump inhibitor therapy and the timing of follow up in oesophageal lesions where healing may be accelerated. In colorectal ESD, 82% of patients in the Purastat® group achieved complete healing or scarring compared to 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 DB in this group as two previous studies using Purastat® prophylactically post gastric ESD have shown low DB rates (0-2%) although both lacked control groups [18,19]. A matched control study assessing the haemostatic effects of Purastat® following gastric ER would increase our understanding of its properties. Secondly, given the paucity of data on IPB during ESD, we assumed that oesophageal and colonic ESD would have a similar incidence of bleeding and therefore did not power the study to stratify recruitment and randomisation 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 week 1 and 2 post ESD. This may have affected accurate assessment of transition between 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 DB as the focus was to understand its basic principles of efficacy and safety.

Despite the limitations, this study is the first randomised controlled trial investigating a novel haemostat for control of IPB during ESD. The primary endpoint of the trial was met as Purastat® does significantly reduce the need for heat required for haemostasis. This may improve the overall safety of ESD and highlights an emerging role for this peptide as an adjunct to conventional haemostatic techniques during ESD.

**References**

1. Enomoto S, Yahagi N, Fujishiro M et al. Novel endoscopic hemostasis technique for use during endoscopic submucosal dissection. Endoscopy. 2007;39:E156

2. Hotta K, Yamaguchi Y, Saito Y et al. Current opinions for endoscopic submucosal dissection for colorectal tumors from our experiences: Indications, technical aspects and complications. Dig Endosc. 2012;24(1):110-116

3. Yamashina T, Takeuchi Y, Uedo N et al. Features of electrocoagulation syndrome after endoscopic submucosal dissection for colorectal neoplasm. J Gastroenterol Hepatol. 2016;31(3):615-620

4. Kataoka Y, Tsuji Y, Sakaguchi Y et al. Bleeding after endoscopic submucosal dissection: Risk factors and preventive methods. World J Gastroenterol. 2016;22(26):5927–5935.

5. Nishizawa T, Suzuki H, Goto O et al. Effect of prophylactic clipping in colorectal endoscopic resection: A meta-analysis of randomized controlled studies. United European Gastroenterology Journal. 2017;5(6):859–867.

6. Park CH, Lee SK. Preventing and controlling bleeding in gastric endoscopic submucosal dissection. Clinical Endoscopy 2013;46(5):456–462.

7. Takizawa K, Oda I, Gotoda T et al. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection - An analysis of risk factors. Endoscopy. 2008;40(3):179-183

8. Mourad FH, Leong RW. Role of hemostatic powders in the management of lower gastrointestinal bleeding: A review. Journal of Gastroenterology and Hepatology (Australia). 2018;33(8):1445-1553

9. Huang R, Pan Y, Hui N et al. Polysaccharide hemostatic system for hemostasis management in colorectal endoscopic mucosal resection. Dig Endosc. 2014;26(1):63-68

10. Leung GKK, Wang YC, Wu W. Peptide nanofiber scaffold for brain tissue reconstruction. Methods Enzymol. 2012;508:177-190

11. Xu FF, Wang YC, Sun S et al. Comparison between self-assembling peptide nanofiber scaffold (SAPNS) and fibrin sealant in neurosurgical hemostasis. Clin Transl Sci. 2015;8(5):490-494

12. Luo Z, Wang S, Zhang S. Fabrication of self-assembling d-form peptide nanofiber scaffold d-EAK16 for rapid hemostasis. Biomaterials. 2011;32(8):2013-2020

13. Ye ZY, Zhang HY, Luo HL et al. Temperature and pH effects on biophysical and morphological properties of self-assembling peptide RADA16-1. J Pept Sci. 2008;14(2):152-162

14. Song H, Zhang L, Zhao X. Hemostatic efficacy of biological self-assembling peptide nanofibers in a rat kidney model. Macromol Biosci. 2010;10(11):33-39

15. Masuhara H, Fujii T, Watanabe Y et al. Novel infectious agent-free hemostatic material (TDM-621) in cardiovascular surgery. Ann Thorac Cardiovasc Surg. 2012;18(5):444–451.

16. Lee MF, Ma Z, Ananda A. A novel haemostatic agent based on self-assembling peptides in the setting of nasal endoscopic surgery, a case series. Int J Surg Case Rep. 2017;41:461–464.

17. Giritharan S, Salhiyyah K, Tsang G et al. Feasibility of a novel, synthetic, self-assembling peptide for suture-line haemostasis in cardiac surgery. J Cardiothorac Surg. 2018;13 (1):68. Available from: https://doi.org/10.1186/s13019-018-0745-2

18. Uraoka T, Ochiai Y, Fujimoto A et al. A novel fully synthetic and self-assembled peptide solution for endoscopic submucosal dissection-induced ulcer in the stomach. Gastrointest Endosc. 2016;83(6):1259–1264.

19. Pioche M, Camus M, Rivory J et al. A self-assembling matrix-forming gel can be easily and safely applied to prevent delayed bleeding after endoscopic resections. Endosc Int Open. 2016;4(4):E415-419

20. Yoshida M, Goto N, Kawaguchi M et al. Initial clinical trial of a novel hemostat, TDM-621, in the endoscopic treatments of the gastric tumors. J Gastroenterol Hepatol. 2014;29(S4):77–79.

21. Veitch AM, Vanbiervliet G, Gershlick AH et al. Endoscopy in patients on antiplatelet or anticoagulant therapy, including Direct Oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal endoscopy (ESGE) guidelines. Gut. 2016;65(3):374-389

22. Subramaniam S, Kandiah K, Thayalasekaran S et al. Haemostasis and prevention of bleeding related to ER: The role of a novel self-assembling peptide. United Eur Gastroenterol J. 2019;7(1):155-162

23. Sakita T FH. Ulcer of stomach and duodenum. Endosc diagnosis. 1971;198–208.

24. Fuccio L, Hassan C, Ponchon T et al. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and meta-analysis. Gastrointestinal Endoscopy 2017;86(1):74-86

25. Barret M, Lepilliez V, Coumaros D et al. The expansion of endoscopic submucosal dissection in France: A prospective nationwide survey. United European Gastroenterol J. 2017;5(1):45-53

26. Barret M, Bordacahar B, Beuvon F et al. Self-assembling peptide matrix for the prevention of esophageal stricture after endoscopic resection: a randomized controlled trial in a porcine model. Dis Esophagus. 2017;30(5):1–7.

**Acknowledgments**

The authors would like to thank the Wessex Clinical Research Network (National Institute for Health Research) for their overall contribution with research infrastructure to support the trial. We would also like to acknowledge 3D-Matrix Ltd for the supply of Purastat® for the trial. There was no commercial involvement in the design, implementation, analysis and outcome of the results for this trial. Finally, we thank Lisa Murray for her support with the protocol design and study set up.

**Figure Legends**

Figure 1: Application of Purastat® for intraprocedural bleeding

Figure 2a-c: Stages of wound healing of ESD resection base: (a) Healing Ulceration, (b) Scarring, (c) Complete Healing

Figure 3: Flow diagram of study participants

**Tables**

**Table 1: Baseline characteristics of patients enrolled in the study**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | **Interventional arm (Purastat®)**  **n=46** | **Control arm (Diathermy)**  **n=45** | **Significance** |
| **Age (mean + SD, years)** | | 68.63 (+/- 10.60) | 71.47 (+/- 11.15) | p=0.217 |
| **Lesion size (mean + SD, mm)** | | 33.70 (+/- 12.08) | 36.56 (+/- 13.56) | p=0.291 |
| **Gender (M:F)** | | 33:13 | 27:18 | p=0.274 |
| **All co-morbidities present (n, %)** | | 23 (50%) | 17 (37.8%) | p=0.240 |
| **Cardiovascular disease (n,%)** | | 20 (43.5%) | 15 (33.3%) | p=0.390 |
| **Ischaemic heart disease (n,%)** | | 6 (13.0%) | 7 (15.6%) | p=0.773 |
| **Hypertension (n,%)** | | 7 (15.2%) | 5 (11.1%) | p=0.758 |
| **Atrial fibrillation (n,%)** | | 6 (13.0%) | 4 (8.9%) | p=0.739 |
| **Valvular abnormalities (n,%)** | | 2 (4.3%) | 0 | p=0.495 |
| **Peripheral vascular disease (n,%)** | | 2 (4.3%) | 2 (4.4%) | p=1 |
| **Diabetes mellitus (n,%)** | | 2 (4.3%) | 3 (6.7%) | p=0.677 |
| **Asthma/COPD (n,%)** | | 1 (2.2%) | 1 (2.2%) | p = 1 |
| **Cerebrovascular accident/TIA (n,%)** | | 2 (4.3%) | 2 (4.4%) | p = 1 |
| **Chronic liver disease (n,%)** | | 0 | 0 | p = 1 |
| **All antithrombotic therapy (n, %)** | | 19 (41.3%) | 18 (40%) | p=0.900 |
| **Warfarin (n,%)** | | 5 (10.9%) | 3 (6.7%) | p = 0.714 |
| **Novel oral anticoagulant (n,%)** | | 1 (2.2%) | 3 (6.7%) | p = 0.361 |
| **Aspirin (n,%)** | | 7 (15.2%) | 6 (13.3%) | p = 1 |
| **Clopidogrel (n,%)** | | 6 (13.0%) | 6 (13.3%) | p = 1 |
| **En-bloc resection rate** | | 35 (76.1%) | 31 (68.9%) | p=0.442 |
| **Location** | **Oesophageal** | 28 (60.9%) | 20 (44.4%) | p=0.117 |
| **Colorectal** | 18 (39.1%) | 25 (55.6%) |
| **Circumference** | **<50%** | 32 (69.6%) | 26 (57.8%) | p=0.242 |
| **>50%** | 14 (30.4%) | 19 (42.2%) |
| **Procedure type** | **ESD** | 29 (63.0%) | 26 (57.8%) | p=0.608 |
| **Hybrid ESD** | 17 (37.0%) | 19 (42.2%) |

**Table 2: Intraprocedural bleeding and haemostat use**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | **Interventional arm (Purastat®)**  **n=46** | **Control arm (Diathermy)**  **n=45** | **Significance** |
| **Total number of IPB** | | 232 | 269 | N/A |
| **Number (%) of IPB stopped spontaneously** | | 11 (4.7%) | 7 (2.6%) | p=0.200 |
| **Number (%) of IPB requiring haemostasis** | | 221 (95.3%) | 262 (97.4%) | p=0.200 |
| **Grade of bleeds** | **Grade 1** | 105 (47.5%) | 151 (57.6%) | p=0.027 |
| **Grade 2** | 102 (46.2%) | 101 (38.6%) | p=0.092 |
| **Grade 3** | 14 (6.3%) | 10 (3.8%) | p=0.207 |
| **Number (%) of IPB treated with heat\*** | | 109 (49.3%) | 261 (99.6%)§ | p<0.001 |
| **Number (%) of IPB treated with Purastat®\*\*** | | 121 (54.8%) | 0 | N/A |
| **Successful haemostasis with Purastat®** | | 112/121 (92.9%) | N/A | N/A |

\*Includes 9 bleeds treated with heat following unsuccessful haemostasis with Purastat®

\*\*Includes the use of Purastat® for haemostasis in 9 bleeds following unsuccessful diathermy

§1 bleed required the use of endoscopic clips for safe haemostasis

**Table 3: Secondary outcomes**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Interventional arm (Purastat®)**  **n=46** | **Control arm (Diathermy)**  **n=45** | **Significance** |
| **Procedure length (mean + SD, minutes)** | 74.24 (+/- 48.67) | 80.73 (+/- 56.59) | p=0.558 |
| **Time for haemostasis per bleed (mean + SD, seconds)** | 69.98 (+/- 76.09) | 77.61 (+/-274.18) | p=0.139 |
| **Immediate/early rebleeding** | 0 | 0 |  |
| **Delayed bleeding** | 2 (4.3%)  [1 post oesophageal, 1 post colonic ESD] | 2 (4.4%)  [1 post oesophageal, 1 post colonic ESD] | p=0.981 |
| **Perforation** | 1 (2.2%) | 0 | p=0.320 |

**Table 4: Wound healing in both groups**

|  |  |  |  |
| --- | --- | --- | --- |
| **Wound healing categories** | **Interventional arm (Purastat®)**  **n=43** | **Control arm (Diathermy)**  **n=44** | **Significance** |
| **Complete healing** | 21/43 (48.8%) | 11/44 (25.0%) | p=0.022 |
| **Scarring** | 11/43 (25.6%) | 13/44 (29.5%) | p=0.686 |
| **Healing ulceration** | 11 (25.6%) | 20 (45.5%) | p=0.054 |

**Table 5: Wound healing: Subgroup analysis according to lesion location**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Oesophageal (n=45)** | | **Significance** | **Colorectal (n=42)** | | **Significance** |
|  | **Purastat® (n=26)** | **Control (n=19)** |  | **Purastat® (n=17)** | **Control (n=25)** |  |
| **Complete healing** | 14 (53.8%) | 7 (36.8%) | p=0.264 | 7 (41.2%) | 4 (16.0%) | p=0.072 |
| **Scarring** | 4 (15.4%) | 6 (31.6%) | p=0.202 | 7 (41.2%) | 7 (28.0%) | p=0.379 |
| **Healing ulceration** | 8 (30.8%) | 6 (31.6%) | p=0.955 | 3 (17.6%) | 14 (56.0%) | p=0.014 |