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Original research

Multicentre randomised controlled trial of a self-assembling haemostatic gel to prevent delayed bleeding following endoscopic mucosal resection (PURPLE Trial)

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ABSTRACT

Background Prophylactic application of a haemostatic gel to the resection field may be an easy way to prevent delayed bleeding, a frequent complication after endoscopic mucosal resection (EMR).

Objective We aimed to evaluate if the prophylactic application of a haemostatic gel to the resection field directly after EMR can reduce the rate of clinically significant delayed bleeding events.

Design We conducted a prospective randomised trial of patients undergoing hot-snare EMR of flat lesions in the duodenum (≥ 10 mm) and colorectum (≥ 20 mm) at 15 German centres. Prophylactic clip closure was not allowed, but selective clipping or coagulation could be used prior to randomisation to treat intraprocedural bleeding or for prophylactic closure of visible vessels. Patients were randomised to haemostatic gel application or no prophylaxis. The primary endpoint was delayed bleeding within 30 days.

Results The trial was stopped early due to futility after an interim analysis. The primary endpoint was analysed in 232 patients (208 colorectal, 26 duodenal). Both groups were comparable in age, sex, comorbidities and lesion characteristics. Preventive measures, such as selective clipping or coagulation, were applied prior to randomisation in 51.9% of cases, with no difference between groups. Delayed bleeding occurred in 14 cases (11.7%; 95% CI 7.1% to 18.6%) after Purastat and in 7 cases (6.3%; 95% CI 3.1% to 12.3%) in the control group ($p=0.227$), with no difference between colorectal and duodenal subgroups.

Conclusion The application of a haemostatic gel following EMR of large flat lesions in the duodenum and colorectum does not reduce the rate of delayed bleeding.

INTRODUCTION

Endoscopic removal of colorectal adenomas that are precancerous lesions contributes to cancer prevention.¹ A similar rationale applies in the duodenum,

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Delayed bleeding is its most common complication of endoscopic resection of flat adenomas in the duodenum and colorectum. Clip closure is the only evidence-based approach to mitigate this problem at least partially. Topical haemostatic agents like haemostatic gels and sprays would be an easier solution, but evidence is largely missing.

WHAT THIS STUDY ADDS

⇒ This is the first randomised controlled trial evaluating a topical haemostatic agent, in this case, a self-assembling peptide hydrogel (PuraStat), as prophylaxis to prevent delayed bleeding in a population where selective prophylactic clipping (but not clip closure of the resection field) or coagulation was performed in half of the cases. There was no significant difference in the bleeding rate between the intervention and the control group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ For now, clip closure of the resection field after endoscopic mucosal resection (EMR) of large polyps in the right colon remains the only evidence-based approach to prevent delayed bleeding. Following colorectal or duodenal EMR, the haemostatic gel tested is not effective in preventing delayed bleeding.

even though larger trials for duodenal adenomas are missing.² Small and medium-sized colorectal adenomas (< 20 mm) are usually removed by simple en bloc snare polypectomy, but larger lesions require more advanced techniques.³ The removal of duodenal compared with colorectal lesions is somewhat more challenging since the duodenal

submucosa is densely vascularised and management of complications (ie, bleeding and perforations) is more difficult.

Endoscopic mucosal resection (EMR) using an electrocautery-enhanced ('hot') snare is the standard approach for the removal of larger flat adenomatous lesions in the duodenum and colorectum.³ Lesions >20 mm often require removal in several pieces, that is, piecemeal EMR. The most common adverse event associated with hot snare EMR is clinically significant delayed bleeding (CSDB) that occurs in 4%–11% after EMR of larger flat lesions in the colorectum^{4–8} and in between 8% and 18% in the duodenum.^{9–11} More than half of these events occur soon (up to 48 hours) after the procedure.¹² For colorectal lesions, location in the right colon has consistently been associated with delayed bleeding risk; other reported risk factors include lesion size, use of anticoagulant medications, patient age and higher American Society of Anesthesiologists score.^{4 12 13}

Since delayed bleeding may create significant patient discomfort and utilisation of healthcare resources, approaches to reduce the bleeding rate following EMR are desirable; preventive clip closure of the resection site has been studied extensively, with some benefit in the right colon,^{4 7 14} but is time-consuming and requires some skills. In contrast, topical haemostatic agents can be applied quickly and easily through the endoscope working channel without much training required.¹⁵ If they were effective in preventing bleeding when applied to a resection field prophylactically, this would be a fast and easy way to reduce delayed post-EMR bleeding.¹⁶ We, therefore, conducted the first randomised controlled trial (RCT) to evaluate whether the prophylactic application of PuraStat, a self-assembling peptide haemostatic hydrogel¹⁷ to the resection field reduces delayed bleeding in colorectal and duodenal lesions.

PATIENTS AND METHODS

Study overview

We conducted a randomised controlled unblinded trial at 15 academic and non-academic referral hospitals in Germany (online supplemental figure S1). The primary objective of this trial was to determine the impact of prophylactic application of a haemostatic gel to the resection field following EMR of large flat polyps in the duodenum or colorectum on delayed bleeding rate.

Study population

Patients with large flat polyps of the duodenum (largest diameter ≥ 10 mm) or colorectum (largest diameter ≥ 20 mm) and an indication for hot snare EMR according to current guidelines^{3 18} were eligible to participate in this study. Exclusion criteria included dual antiplatelet therapy (ie, two antiplatelet agents taken simultaneously), antiplatelet therapy in combination with an inhibitor of plasmatic coagulation, significant pre-existing coagulopathy and planned resection with a technique other than hot snare EMR such as cold snare EMR, endoscopic submucosal dissection (ESD) or full thickness resection. Of note, patients taking either a single antiplatelet agent or a single inhibitor of plasmatic coagulation were allowed to be included in the study. Online supplemental table S1 shows full inclusion and exclusion criteria. Patients with multiple polyps were allowed to participate if the total cumulative of the largest diameters of all lesions resected did not exceed 100 mm. Randomisation, evaluation of the primary endpoint and most other analyses were carried out on a per-patient level. Per polyp analyses are provided in addition and are indicated as such.

Study intervention

Hot snare EMR including peri-interventional management of anticoagulant medications was performed according to the centres' standard procedure. To treat intraprocedural bleeding, all haemostatic tools except for topical haemostatic agents were allowed. If use of such an agent was deemed necessary to address intraprocedural bleeding, the patient was excluded from the trial prior to randomisation. Within the trial, the use of haemostatic clips was regulated as follows: 'clip closure', that is, the use of clips in order to adapt the margins of the resection field thereby partially or fully closing it was not allowed. If partial or full clip closure of the resection field was deemed necessary for any reason, the patient was excluded from the trial prior to randomisation. 'Selective clipping', that is, the application of one or more clips within the resection field without moving the margins of the resection field was allowed, but only prior to randomisation and only if the resection field remained open (ie, no adaption of its margins). Specifically, selective clipping prior to randomisation could be performed in order (1) to treat intraprocedural bleeding, (2) to treat intraprocedural deep mural injury or perforation and (3) to prevent delayed bleeding (eg, by selectively clipping visible vessels within the resection field). All of these measures were documented in the case report form. Again, if clipping resulted in partial or complete closure of the resection field, the patient was excluded from the trial prior to randomisation. Thus, only patients where the resection field remained open were randomised and subsequently included in the analysis. Like selective clipping, coagulation within the resection field could be applied to treat intraprocedural bleeding or to seal non-bleeding visible vessels within the resection field; this also had to be documented in the case report form. Margin coagulation in order to prevent adenoma recurrence was allowed but not obligatory in the trial. When margin coagulation was applied, it had to be done prior to randomisation and to be documented in the case report form. After randomisation, patients allocated to the gel group had haemostatic gel applied to the resection field; apart from this study intervention, no other measures to prevent bleeding were allowed after randomisation.

After complete resection, randomisation was performed using opaque envelopes and patients were thus allocated to the control (no prophylaxis) or intervention (haemostatic gel) group. The group assignment was done by a computer-generated randomisation list with stratification for colorectal and duodenal polyp localisation. Each patient was randomised only once. In the intervention group, the haemostatic gel was applied according to the manufacturer's instructions aiming to cover the entire resection field with gel (online supplemental figure S2). In patients with multiple lesions allocated to the intervention group, it was mandatory to apply gel to the resection fields of all lesions larger than 5 mm. There were two scheduled follow-up visits: (1) a telephone interview 30 ± 2 days after the study procedure and (2) a repeat endoscopy 63 ± 7 days after the study procedure. The timing of the repeat endoscopy was chosen in order to conform to the German guideline for follow-up after piecemeal resection of colorectal lesions.

Outcomes

The primary outcome of this trial was the rate of CSDB from the resection site within 30 days after hot snare EMR. CSDB was defined as clinical evidence of delayed bleeding directly related to the EMR procedure and resulting in one or more of the following: (1) transfusion of blood products, (2) unplanned endoscopy, (3) radiological intervention, (4) surgical intervention,

Table 1 Patients characteristics at baseline

	All participants (n=234)		Colorectal lesions (n=208)		Duodenal lesions (n=26)	
	Haemostatic gel (n=120)	Control group (n=114)	Haemostatic gel (n=107)	Control group (n=101)	Haemostatic gel (n=13)	Control group (n=13)
Female sex, % (n)	38 (46)	39 (44)	37 (40)	38 (38)	46 (6)	46 (6)
Age						
Mean (SD)	67 (9)	68 (11)	66 (9)	67 (12)	72 (8)	72 (9)
BMI*						
Mean (SD)	26.5 (5.2)	26.7 (4.7)	26.5 (5.2)	27.1 (4.6)	26.2 (4.9)	24.1 (4.6)
ASA class, % (n)						
I	43.3 (52)	39.5 (45)	47.7 (51)	40.6 (41)	7.7 (1)	31 (4)
II/III	56.7 (68)	60.5 (69)	52.3 (56)	59.4 (50)	92.3 (12)	69 (9)
Comorbidities affecting the Coagulation, % (n)	31.7 (38)	30.7 (35)	29.9 (32)	30.7 (31)	46.2 (6)	30.8 (4)
Antiplatelet/anticoagulant agent, % (n)						
Antiplatelet agent	19.2 (23)	14.9 (17)	17.8 (19)	14.9 (15)	30.8 (4)	15.4 (2)
Anticoagulant agent	10.8 (13)	19.3 (22)	11.2 (12)	20.8 (21)	7.7 (1)	7.7 (1)
None	70 (84)	65.8 (75)	71 (76)	64.4 (65)	61.5 (8)	76.9 (10)
Patients with more than one lesion, % (n)	24.2 (29)	35.1 (40)	26.2 (28)	38.6 (39)	7.7 (1)	7.7 (1)

*No BMI data for three participants in the haemostatic gel group and four participants in the control group.
ASA, American Society of Anesthesiologists; BMI, body mass index.

(5) prolongation of hospital stay, (6) emergency room visit or (7) admission to hospital care. In a prespecified subgroup analysis, we investigated the possible effect of polyp location (ie, proximal vs distal colon; colon vs duodenum), anticoagulant medication, size of the resection field and pre-existing conditions that predispose to bleeding. A per patient analysis was carried out to assess the primary outcome. Even though patients with multiple polyps were permitted, we opted against a per polyp analysis for the primary outcome because this would have required re-endoscopy after every bleeding event to identify the culprit lesion.

Secondary outcomes included adverse events other than delayed bleeding, wound healing and rate of residual/recurrent polyps at the time of follow-up endoscopy. For the evaluation of wound healing, the Sakita-Miwa Classification was used (online supplemental table S2);¹⁹ briefly, this classification divides ulcer healing into three stages (active, healing and scarring) with two substages per stage thus translating the wound healing process into categorical data.

Statistical planning and analysis

For the power analysis, we assumed 30% duodenal and 70% colorectal polyps with expected CSDB rates of 18% and 8% without gel prophylaxis, respectively. Randomisation was stratified to guarantee a balanced allocation of duodenal and colorectal lesions to the two groups, but we did not prespecify that 30% duodenal and 70% colorectal must be reached nor did we implement a recruiting mechanism to guarantee this. Assuming that gel prophylaxis would be as effective as clip closure,^{4 7 13} a reduction to 2% significant postprocedural bleeding in the haemostatic gel arm was assumed.^{4 14} As outlined above, these assumptions applied to a population where 'selective clipping' within the resection field as deemed necessary was allowed prior to randomisation, but 'clip closure' (ie, adaption of the resection margins) was not allowed.

We planned for the inclusion of 248 patients, randomised 1:1 to haemostatic gel prophylaxis (intervention) versus no haemostatic gel prophylaxis (control). This was intended to detect differences between the treatment groups with a power of 80% at a significance level of 5% using a two-sided Fisher's exact test.

There were significant uncertainties regarding the expected bleeding rates and the number of lesions per patient. Furthermore, the rate of recruitment of patients with lesions in sections of the bowel with higher or lower bleeding risk over the planned recruitment phase was difficult to predict. Thus, we planned an interim analysis after 200 patients had reached the 3-month follow-up. We chose this late time point assuming a relatively low event rate and given that the effect size to be expected was difficult to estimate given the limited data available. Depending on the observed effect size (ie, difference in postprocedural bleeding rates between the groups at the time of the interim analysis), the study protocol allowed for (1) discontinuation of the study (if effect size non-existent or larger than expected), (2) upwards adjustment of the number of patients to be included, that is, including more cases than initially planned (if effect present but effect size smaller than expected) or (3) continuation of the study as planned (effect size as expected; inclusion of planned case number). Of note, this does not correspond to a statistically based formal stopping rule,²⁰ but represented a prespecified pragmatic approach where the observed effect size dictated how to proceed with the trial. Alternatively, group sequential designs with interim analyses could have been considered. The sequential probability ratio test could have been used to examine futility and early proof of efficacy. However, the recruitment of patients lesions in intestinal segments with a low risk of bleeding during the course of the study could have impaired the consistency of the results, so we opted against it. No toxicities have been observed with haemostatic gel tested here during years of clinical application, so the risk of exposing patients to toxicity was considered very low in this trial. For this reason, we considered a non-rigorous stopping rule acceptable.

Data were analysed with R Core Team 2024. Categorical data are expressed as count (percentage) and continuous data are expressed as medians (quartiles) and means (SD). The primary objective was examined using a two-sided Fisher's exact test. A logistic regression model was applied, linking both treatment group and localisation to delayed bleeding. Delayed bleeding for selected risk factors was examined using the difference in proportions (95% CIs). Furthermore, bivariable logistic regression

Table 2 Polyp characteristics of main lesions

	Colorectal lesions			Duodenal lesions		
	All lesions (n=208)	Haemostatic gel (n=107)	Control group (n=101)	All lesions (n=26)	Haemostatic gel (n=13)	Control group (n=13)
Localisation, % (n)						
Duodenum	0 (0)	0 (0)	0 (0)	100 (26)	100 (13)	100 (13)
Coecum	23 (47)	22 (24)	23 (23)	0 (0)	0 (0)	0 (0)
Colon ascendens	34 (71)	34 (36)	35 (35)	0 (0)	0 (0)	0 (0)
Colon transversum	20 (42)	20 (21)	21 (21)	0 (0)	0 (0)	0 (0)
Colon descendens	4.8 (10)	5.6 (6)	4.0 (4)	0 (0)	0 (0)	0 (0)
Sigma	11 (23)	10 (11)	12 (12)	0 (0)	0 (0)	0 (0)
Rectum	7.2 (15)	8.4 (9)	5.9 (6)	0 (0)	0 (0)	0 (0)
Paris classification, % (n)						
I	24 (50)	22.4 (24)	25.7 (26)	23.1 (6)	15.4 (2)	30.8 (4)
I+II	10.6 (22)	10.3 (11)	10.9 (11)	7.7 (2)	15.4 (2)	0 (0)
II	60.1 (125)	60.7 (65)	59.4 (60)	69.2 (18)	69.2 (9)	69.2 (9)
Other	4.8 (10)	6.5 (7)	3.0 (3)	0 (0)	0 (0)	0 (0)
None	0.5 (1)	0 (0)	1.0 (1)	0 (0)	0 (0)	0 (0)
Size of polyp in mm*						
Median (Q1, Q3)	30 (25 35)	30 (25 38)	30 (22 35)	18 (15 24)	20 (15 25)	15 (12 20)
Mean (SD)	32 (13)	33 (14)	30 (12)	20 (10)	24 (12)	16 (5)
Size of resection area (cm ²)*						
Median (Q1, Q3)	7 (4 11)	7 (5 10)	7 (4 11)	3.3 (2.0, 6.2)	4.9 (2.5, 12.0)	2.4 (2.0, 3.5)
Mean (SD)	10 (11)	10 (10)	9 (12)	5.2 (5.0)	7.2 (6.3)	3.2 (2.1)
Histology, % (n)						
Low-grade adenoma	44 (90)	45 (48)	42 (42)	85 (22)	92 (12)	77 (10)
High-grade adenoma	23 (47)	24 (26)	21 (21)	7.7 (2)	7.7 (1)	7.7 (1)
Hyperplastic polyp	2.9 (6)	0.9 (1)	5.1 (5)	0 (0)	0 (0)	0 (0)
Sessil serrated lesion	24 (49)	22 (24)	25 (25)	0 (0)	0 (0)	0 (0)
Traditional serrated adenoma	0.5 (1)	0 (0)	1.0 (1)	0 (0)	0 (0)	0 (0)
Adenocarcinoma	3.9 (8)	3.7 (4)	4.0 (4)	0 (0)	0 (0)	0 (0)
Other histology	2.4 (5)	3.7 (4)	1.0 (1)	7.7 (2)	0 (0)	15 (2)
Unknown	0.9 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)

*Largest diameter.

models linking each of the risk factors and the treatment group to CSDB were calculated. A $p < 0.05$ was considered significant.

Patient and public involvement

Patients or the public were not directly involved in this study, including but not limited to the trial design, patient recruitment, conduct of the trial, analysis of data and manuscript preparation.

RESULTS

Patient inclusion

Between May 2022 and January 2024, 234 patients were randomised into the control (n=114) or haemostatic gel (n=120)

group. At this time, the recruitment was stopped due to futility based on the results of a prespecified interim analysis. Thus, the study was terminated early, but the number of cases randomised reached 94.4% (234 out of 248) of the initially planned number.

The primary endpoint could be evaluated in 232 out of 234 cases (online supplemental figure S3). Two patients were excluded due to death from a cardiac cause shortly after the procedure (n=1) and small polyp size (n=1). Baseline characteristics were comparable between the groups (table 1, online supplemental table S3 and S4). When only main lesions were considered, there was no size difference in the colorectum (median diameter 30mm for both gel and control group); the

Table 3 Measures prior to randomisation

	Treatment of intraprocedural bleeding		Treatment of deep mural injury/perforation		Bleeding prophylaxis prior to randomisation	
	Gel group (n=120)	Control group (n=113)	Gel group (n=120)	Control group (n=113)	Haemostatic gel (n=120)	Control group (n=113)
Any measure						
Yes, % (n)	32.5 (39)	34.5 (39)	0.8 (1)	1.8 (2)	51.7 (62)	52.2 (59)
TTS clip application	15 (18)	17.7 (20)	0.8 (1)	1.8 (2)	28.3 (34)	31.9 (36)
Suprarenin injection	1.7 (2)	1.8 (2)	–	–	8.3 (10)	6.2 (7)
Snare tip coagulation	21.7 (26)	22.1 (25)	–	–	13.3 (16)	14.2 (16)
Haemostatic forceps	10.8 (13)	6.2 (7)	–	–	10 (12)	7.1 (8)
Argon plasma coagulation	0	0.9 (1)	–	–	–	–
No, % (n)	67.5 (81)	65.5 (74)	99.2 (119)	98.2 (111)	48.3 (58)	47.8 (54)
TTS, through the scope.						

Table 4 Clinically significant delayed bleeding events

	Clinically significant delayed bleeding		P value
	Yes, % (n)	No, % (n)	
All lesions (n=232)			
Haemostatic gel (n=120)	11.7 (14)	88.3 (106)	0.227
Control group (n=112)	6.3 (7)	93.8 (105)	
Colorectal lesions (n=206)			
Haemostatic gel (n=107)	9.3 (10)	90.7 (97)	0.359
Control group (n=99)	5.1 (5)	95.0 (94)	
Duodenal lesions (n=26)			
Haemostatic gel (n=13)	30.8 (4)	69.2 (9)	0.642
Control group (n=13)	15.4 (2)	84.6 (11)	

duodenal lesions were somewhat larger in the gel group (median diameter 20 mm vs 15 mm), but this was not significant (table 2).

Histopathology showed about half of the lesions resected to be low-grade adenomas. Malignancy was detected in 2.2% of lesions resected and 3.4% of patients included in the final analysis. Procedural information is shown in online supplemental table S5. In total, 368 lesions were resected (178 in the haemostatic gel and 190 in the control group). Polyp characteristics of

all lesions resected can be found in online supplemental table S6 and S7.

Selective clipping and coagulation (snare tip, coagulation forceps or argon beamer) were allowed during the procedure to treat intraprocedural bleeding and after completed resection but before randomisation to prevent bleeding from visible vessels. Selective clipping was also allowed to treat deep mural injury or perforation. Any clips and/or coagulation methods for bleeding prevention prior to randomisation were used in 51.7% of patients in the haemostatic gel group and 52.2% of patients in the control group (table 3). 57.6% of patients (55.8% in colorectal and 73.1% in duodenal) did not obtain focal clipping prior to randomisation.

In the intervention group, a mean of 3.3 ± 1.4 mL of haemostatic gel was applied. In two cases, two packages (5 mL) of haemostatic gel were used. Haemostatic gel application was technically successful in all (100%) of cases.

Main outcome

CSDB occurred in 14 cases (11.7%; 95% CI 7.1% to 18.6%) in the haemostatic gel group and 7 cases (6.3%; 95% CI 3.1% to 12.3%) in the control group (table 4; figure 1A). This difference was not statistically significant ($p=0.277$). In the subgroup

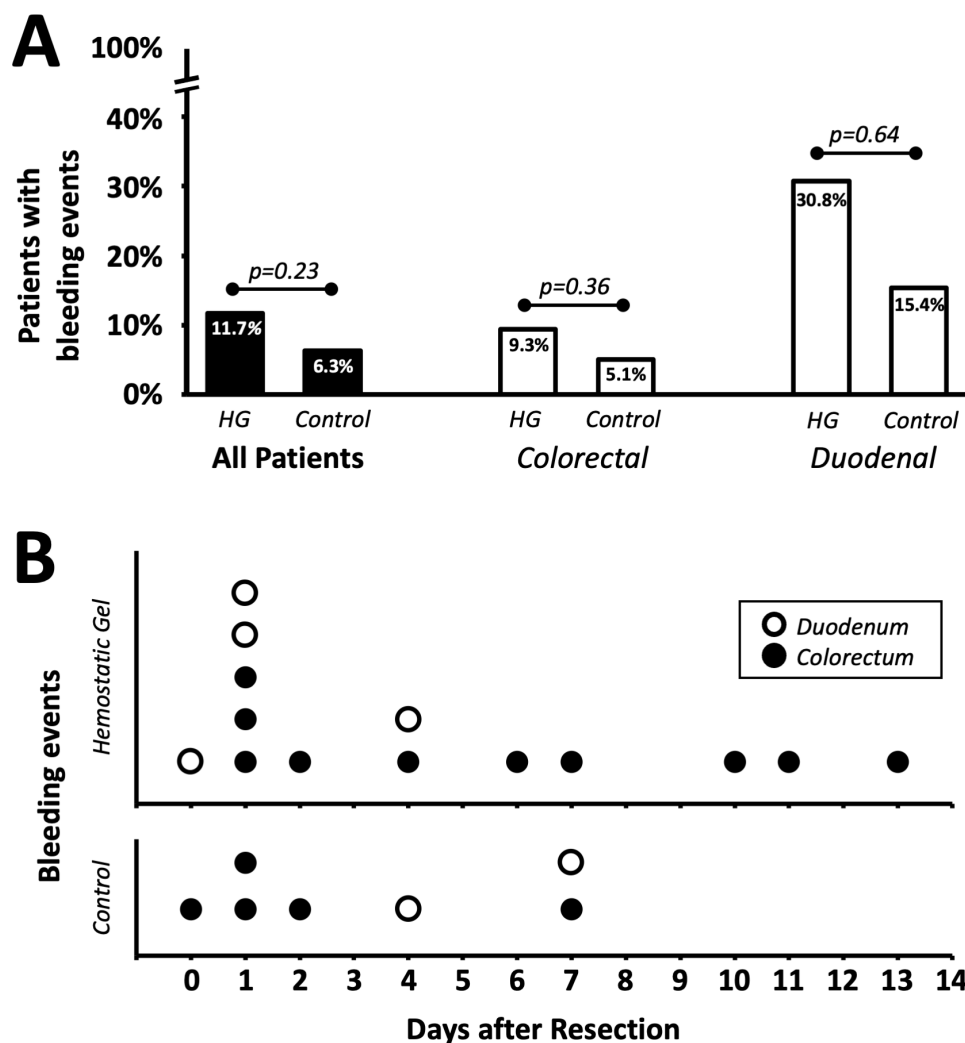


Figure 1 Outcome: primary endpoint. (A) CSDB rate overall and stratified by colorectal versus duodenal location. Within-group differences were tested for statistical significance using Fisher's exact test. (B) Timing of CSDB events. CSDB, clinically significant delayed bleeding; HG, haemostatic gel.

Table 5 Clinically significant delayed bleeding events in patients without clip measures

	Clinically significant delayed bleeding		P value
	Yes, % (n)	No, % (n)	
All lesions (n=133)			
Haemostatic gel (n=71)	9.9 (7)	90.1 (64)	0.174
Control group (n=62)	3.2 (2)	96.8 (60)	
Colorectal lesions (n=114)			
Haemostatic gel (n=60)	5 (3)	95 (57)	0.62
Control group (n=54)	1.9 (1)	98.1 (53)	
Duodenal lesions (n=19)			
Haemostatic gel (n=11)	36.4 (4)	63.6 (7)	0.339
Control group (n=8)	12.5 (1)	87.5 (7)	

with colorectal lesions, the delayed bleeding rates were 9.3% (95% CI 5.2% to 16.4%) and 5.1% (95% CI 2.2% to 11.3%) in the haemostatic gel and control group, respectively. In the subgroup with duodenal lesions, the CSDB rates were 30.8% (95% CI 12.7% to 57.6%) and 15.4% (95% CI 4.3% to 42.2%) in the haemostatic gel and control group, respectively. In the post hoc analysis of patients where no selective clipping prior to randomisation was performed for any reason, there were also numerically more bleeding events in the gel group, but again the difference was not statistically significant (table 5).

In the overall cohort, the median time between the intervention and the diagnosis of bleeding was comparable between the groups (2 vs 3 days, respectively) with half of bleeding events occurring within 48 hours after the procedure (figure 1B). Of note, in the subgroup of colorectal lesions, the median time until postprocedural bleeding was 1 day (range 0–7 days) in the control group compared with 5 days (range 1–13 days) in the gel group. Subgroup analysis evaluating additional factors potentially associated with risk of postprocedural bleeding did not show any subgroup where gel application might be advantageous (online supplemental figure S4).

Secondary outcomes

There were no statistically significant differences in terms of prespecified secondary outcomes (transfusion requirement, unplanned endoscopy, readmission to hospital care) between the groups. An endoscopic assessment of wound healing conforming to the prespecified time window was available for 290 lesions in 190 patients. The majority of resection fields were fully healed at this time point and there was no statistically significant difference between the groups (online supplemental table S8).

Adverse events

Besides the main outcome events for delayed bleeding detailed above, there was one duodenal perforation in the gel group that, after a protracted course eventually resulted in the death of the patient. One patient in the control group died of a cardiac event within 24 hours of the intervention; this was considered potentially related to the study procedure. There were three instances of postpolypectomy syndrome (one in the gel groups and two in the control group). There were no additional adverse events considered related to the study procedures, and no adverse events were related to the haemostatic gel used. Of note, three more patients died during the study period from causes deemed unrelated to the study procedure. This included progression of a pre-existing malignant disease (n=1), newly diagnosed

malignant disease (n=1) and trauma resulting from a fall 27 days after the trial procedure (n=1).

DISCUSSION

Since colon EMR is common and larger lesions such as advanced adenomas occur in 4%–6%²¹ or more²² of all (screening) colonoscopy procedures, even smaller rates of postprocedural adverse events become relevant, both from the patient perspective as well as for economic reasons. Postprocedural bleeding events after conventional hot EMR have been reported in 6%–10% of cases²³ and often lead to additional care, readmissions or reinterventions. Preventive measures have been tried: coagulation of residual vessels at the resection site²⁴ has been shown not to be effective in preventing post-EMR bleeding. A meta-analysis of randomised trials on preventive clipping has demonstrated some effect at least in subgroups, that is, those with large right-sided polyps, with relative reduction of 30%–40%.²⁵ However, clipping may be time-consuming, not fully effective and costly. Thus, easier methods of bleeding prevention are desirable. Cold snare resection of larger adenomas would be ideal since postprocedural bleeding is almost abolished, but recurrence rates seem to be substantially higher,^{8 26} so further studies with possibly additional measures are to be awaited.

PuraStat, a common THA which is also known as TDM-621, is a self-assembling peptide hydrogel that can be applied to the resection field through a catheter that is inserted into the endoscope working channel.¹⁷ Application of the gel is fast and easily accomplished in almost any location. Moreover, the agent is transparent and does not obscure the resection field. It is thus easily possible to apply the gel after other tools (eg, clips) have already been applied or to use any additional haemostatic tool subsequently. Being available for about 10 years now, PuraStat has been used for both prevention and treatment of gastrointestinal (GI) bleeding, but without good evidence²⁷; mostly case series have stated some effectiveness.^{28–31} A recent randomised trial showed that Purastat can be helpful during ESD, but had no effect on postprocedural bleeding.³² A recent retrospective analysis of gastric ESD cases also found no difference either.³³

Thus, our multicentric RCT is the first to assess the issue of postprocedural bleeding after colonic and duodenal EMR. Overall, as well as in subgroups, application of a haemostatic peptide hydrogel to the resection field following EMR did not result in a decreased post-EMR bleeding rate. The overall post-EMR bleeding rate we observed for colorectal lesions (7.3%) was comparable to what could be expected based on existing data on colorectal EMR (4%–11%).^{4–8} As expected, the overall bleeding rate following duodenal EMR (23.1%) was higher than for colorectal lesions, but it was also higher than in most published studies (8%–18%).^{9–11} Of note, these studies were retrospective analyses, some of prospectively collected databases, at single or few expert centres. Reporting of adverse events is likely to be more complete in randomised trials.

In our study, the bleeding rate in the intervention group was numerically higher than in the control group; however, this difference was not statistically significant. In any case, it seems highly unlikely that a larger study in the same indication would turn the results and reveal a benefit. The observation that the postprocedural bleedings in the colon occurred later than in the control group (5 hours vs 1 hour) is first based on a post hoc analysis and has, therefore, limited reliability. Second, even if so, this cannot necessarily be regarded as an advantage, since even in healthcare systems with a high rate of in-patient performance

of more extended EMR, patients would have been discharged after 5 days.

There are several limitations to our study: Group allocation was stratified only for duodenal versus colorectal location, but not for other possible risk determinants such as polyp size, right-sided colonic location or anticoagulant use. However, post hoc stratification of the cohort for these and other factors did not reveal any subgroup with an indication of a benefit of gel application following EMR.

Another issue to be discussed is the high rate of preventive measures after EMR consisting of selective clipping (ie, placement of a single or few focal clips within the resection field) or coagulation methods, mostly for non-bleeding visible vessels. This was allowed by the study protocol and was done in about half of the cases in both groups and seems to reflect common practice in the participating centres. To our knowledge, there are no data on selective clipping of visible vessels to prevent bleeding after EMR of large polyps, in contrast to randomised trials on clip closure of the resection wound.^{4 7 14 34 35} Interestingly enough, a study looking at clipping for bleeding prevention using an insurance database (no effect could be shown) included all cases with at least one clip used and could not specify whether clips were used to close the resection site or be placed at visible vessels only (ie, selective clipping). Overall, clips were used in about half of 657 lesions.³⁵ A survey among 428 Dutch and 69 foreign gastroenterologists regarding whether they used clips remained somewhat unclear whether the case-based inquiry clearly differentiated between these two options (clip closure vs selective clipping); of the 190 replies included, overall the 'none' option (no clipping) was chosen in 27.8% of all case questions, while only 6.8% never clipped.³⁴ Interestingly, of the randomised clip closure trials, detailed information on any other preventive measures before clip closure is available from only one of them: In the Spanish randomised trial performed between 2016 and 2018,¹⁴ coagulation of submucosal vessels by means of snare-tip, forceps or argon plasma coagulation was performed when the endoscopist considered it necessary and was finally used in 48% in the control group and in 53% in the group which then underwent clip closure. This was done despite a prior randomised trial in 2015 could not show any effect of prophylactic coagulation.³⁶ Thus, it seems likely, that in clinical practice many endoscopists perform techniques even if they are not evidence based or evidence would suggest otherwise.

In our study, patients in whom partial or complete clip closure of the resection field was attempted or where clipping resulted in closure of the resection field were excluded from the trial prior to randomisation; however, measures for bleeding prevention before randomisation were frequently applied, namely in half of both study groups: selective clipping before randomisation was done in about 30% of cases and preventive coagulation in 20%–25%. It can only be speculated whether we would have detected different bleeding rates in the absence of preventive (focal) clip or coagulation use. However, in the control group, there was still an overall 7.3% bleeding rate for colorectal lesions and 23.1% for duodenal lesions indicating that there was a significant level of residual risk. In the colon, the bleeding rate was only slightly higher than the 5% reported in the control groups of randomised trial on clip closure summarised in systematic reviews.³⁷ Individual RCTs on clip closure reached bleeding rates comparable to our study, namely 7%⁴ or even 12%,¹⁴ the latter despite other primary prevention methods as mentioned above. Therefore, we consider it unlikely that the preventive measures before gel application greatly influenced bleeding rate.

Clearly, our findings cannot be directly applied to other clinical scenarios such as other locations in the GI tract or other resection techniques like cold snare EMR or ESD. Nevertheless, two ESD studies are in line with our findings regarding postprocedural bleeding.^{32 33} Nonetheless, we believe that the results of the present study are of importance for clinicians, since in interventional endoscopy (as in other fields of medicine), we must aim to use tools and techniques that have proven to be effective and clinically beneficial, while avoiding ineffective measures.

Studies on the haemostatic effects of Purastat in the setting of active bleeding³⁸ were mostly retrospective and/or observational³⁹ and included cases of bleeding refractory to other haemostatic modalities.⁴⁰ Besides its haemostatic properties, the haemostatic gel evaluated here has been reported to promote wound healing. However, in our study, we did not observe a significant difference between the groups in terms of wound healing at the time of follow-up endoscopy (ie, 8–10 weeks after resection). Indeed, most resection fields were fully healed at this point. A study evaluating the use of the gel in ESD found an increased rate of completely healed resection fields at an earlier time point, namely 4 weeks.³² We opted against an earlier endoscopic follow-up that might have been more informative in terms of wound healing, since this would have been outside the time window recommended by the German guideline applicable at the time.¹⁸

Given the number of available THAs, types of GI lesions amenable to endoscopic therapy and resection techniques, there is clearly a need for more high quality—ideally randomised and controlled—data on the effectiveness of preventive strategies as well as strategies to treat active bleeding. For now, clip closure has to be considered the only evidence-based approach to prevent delayed bleeding after EMR at least in the right colon.

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REFERENCES

- Brethauer M, Løberg M, Wieszczy P, et al. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. *N Engl J Med* 2022;387:1547–56.
- Vanbiervliet G, Moss A, Arvanitakis M, et al. Endoscopic management of superficial nonampullary duodenal tumors: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2021;53:522–34.
- Ferlitsch M, Hassan C, Bisschops R, et al. Colorectal polypectomy and endoscopic mucosal resection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2024. *Endoscopy* 2024;56:516–45.
- Pohl H, Grimm IS, Moyer MT, et al. Clip Closure Prevents Bleeding After Endoscopic Resection of Large Colon Polyps in a Randomized Trial. *Gastroenterology* 2019;157:977–84.
- Jacques J, Schaefer M, Wallenhorst T, et al. Endoscopic En Bloc Versus Piecemeal Resection of Large Nonpedunculated Colonic Adenomas: A Randomized Comparative Trial. *Ann Intern Med* 2024;177:29–38.
- Sidhu M, Shahidi N, Gupta S, et al. Outcomes of Thermal Ablation of the Mucosal Defect Margin After Endoscopic Mucosal Resection: A Prospective, International, Multicenter Trial of 1000 Large Nonpedunculated Colorectal Polyps. *Gastroenterology* 2021;161:163–70.
- Gupta S, Sidhu M, Shahidi N, et al. Effect of prophylactic endoscopic clip placement on clinically significant post-endoscopic mucosal resection bleeding in the right colon: a single-centre, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2022;7:152–60.
- Steinbrück I, Ebigo A, Kuellmer A, et al. Cold Versus Hot Snare Endoscopic Resection of Large Nonpedunculated Colorectal Polyps: Randomized Controlled German CHRONICLE Trial. *Gastroenterology* 2024;167:764–77.
- Amoyel M, Belle A, Dhooge M, et al. Outcomes of endoscopic mucosal resection for large superficial non-ampullary duodenal adenomas. *Sci Rep* 2022;12:14592.
- Klein A, Nayyar D, Bahin FF, et al. Endoscopic mucosal resection of large and giant lateral spreading lesions of the duodenum: success, adverse events, and long-term outcomes. *Gastrointest Endosc* 2016;84:688–96.
- Basford PJ, George R, Nixon E, et al. Endoscopic resection of sporadic duodenal adenomas: comparison of endoscopic mucosal resection (EMR) with hybrid endoscopic submucosal dissection (ESD) techniques and the risks of late delayed bleeding. *Surg Endosc* 2014;28:1594–600.
- Burgess NG, Metz AJ, Williams SJ, et al. Risk factors for intraoperative and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. *Clin Gastroenterol Hepatol* 2014;12:651–61.
- Albéniz E, Fraile M, Ibáñez B, et al. A Scoring System to Determine Risk of Delayed Bleeding After Endoscopic Mucosal Resection of Large Colorectal Lesions. *Clin Gastroenterol Hepatol* 2016;14:1140–7.
- Albéniz E, Álvarez MA, Espinós JC, et al. Clip Closure After Resection of Large Colorectal Lesions With Substantial Risk of Bleeding. *Gastroenterology* 2019;157:1213–21.
- Jiang SX, Chahal D, Ali-Mohamad N, et al. Hemostatic powders for gastrointestinal bleeding: a review of old, new, and emerging agents in a rapidly advancing field. *Endosc Int Open* 2022;10:E1136–46.
- 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:E415–9.
- PuraStat Website. Im internet. 2024. Available: <https://3dmatrix.com/products/purastat>
- Leitlinienprogramm onkologie (deutsche krebsgesellschaft, deutsche krebshilfe, awmf): s3-leitlinie kolorektales karzinom, langversion 2.1, 2019, awmf registrierungsnummer: 021/007ol. 2019.
- Sakita T, Oguro Y, Takasu S, et al. Observations on the healing of ulcerations in early gastric cancer. The life cycle of the malignant ulcer. *Gastroenterology* 1971;60:835–9.
- Martens MJ, Logan BR. Statistical rules for safety monitoring in clinical trials. *Clin Trials* 2024;21:152–61.
- Wong MCS, Huang J, Huang JLW, et al. Global Prevalence of Colorectal Neoplasia: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol* 2020;18:553–61.
- Brenner H, Altenhofen L, Kretschmann J, et al. Trends in Adenoma Detection Rates During the First 10 Years of the German Screening Colonoscopy Program. *Gastroenterology* 2015;149:356–66.
- Mohapatra S, Fukami N. Prevention of bleeding after EMR of colorectal lesions: when and how? *Lancet Gastroenterol Hepatol* 2022;7:109–10.
- Fahrtash-Bahin F, Holt BA, Jayasekaran V, et al. Snare tip soft coagulation achieves effective and safe endoscopic hemostasis during wide-field endoscopic resection of large colonic lesions (with videos). *Gastrointest Endosc* 2013;78:158–63.
- Yu Z, Albéniz E, Hu J, et al. Prevention of delayed post-polypectomy bleeding by prophylactic clipping after endoscopic colorectal polypectomy: a meta-analysis. *Int J Colorectal Dis* 2022;37:2229–36.
- O'Sullivan T, Cronin O, van Hattem WA, et al. Cold versus hot snare endoscopic mucosal resection for large (≥ 15 mm) flat non-pedunculated colorectal polyps: a randomised controlled trial. *Gut* 2024;73:1823–30.
- 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 Suppl 4:77–9.
- Dhindsa BS, Tun KM, Scholten KJ, et al. New Alternative? Self-Assembling Peptide in Gastrointestinal Bleeding: A Systematic Review and Meta-Analysis. *Dig Dis Sci* 2023;68:3694–701.
- Voiosu A, State M, Drăgan V, et al. Systematic review of self-assembling peptides as topical agents for treatment and prevention of gastrointestinal bleeding. *Clin Endosc* 2024;57:454–65.
- Maselli R, Da Rio L, Manno M, et al. Efficacy of novel endoscopic hemostatic agent for bleeding control and prevention: Results from a prospective, multicenter national registry. *Endosc Int Open* 2024;12:E1220–9.
- Uba Y, Ogura T, Ueno S, et al. Comparison of Endoscopic Hemostasis for Endoscopic Sphincterotomy Bleeding between a Novel Self-Assembling Peptide and Conventional Technique. *J Clin Med* 2022;12:79:12.
- Subramaniam S, Kandiah K, Chedgy F, et al. A novel self-assembling peptide for hemostasis during endoscopic submucosal dissection: a randomized controlled trial. *Endoscopy* 2021;53:27–35.
- Gomi K, Yamamoto Y, Yoshida E, et al. Using a novel hemostatic peptide solution to prevent bleeding after endoscopic submucosal dissection of a gastric tumor. *World J Gastrointest Endosc* 2024;16:168–74.
- Turan AS, Didden P, Peters Y, et al. Factors involved in endoscopists' choice for prophylactic clipping after colorectal endoscopic mucosal resection: a discrete choice experiment. *Scand J Gastroenterol* 2020;55:737–44.

- 35 Chang K, Lee BS, Tekeste T, *et al.* The effect of prophylactic hemoclips on the risk of delayed post-endoscopic mucosal resection bleed for upper and lower gastrointestinal lesions: a retrospective cohort study. *BMC Gastroenterol* 2020;20:60.
- 36 Bahin FF, Naidoo M, Williams SJ, *et al.* Prophylactic endoscopic coagulation to prevent bleeding after wide-field endoscopic mucosal resection of large sessile colon polyps. *Clin Gastroenterol Hepatol* 2015;13:724–30.
- 37 Chen B, Du L, Luo L, *et al.* Prophylactic clips to reduce delayed polypectomy bleeding after resection of large colorectal polyps: a systematic review and meta-analysis of randomized trials. *Gastrointest Endosc* 2021;93:807–15.
- 38 Alali AA, Moosavi S, Martel M, *et al.* Topical hemostatic agents in the management of upper gastrointestinal bleeding: a meta-analysis. *Endosc Int Open* 2023;11:E368–85.
- 39 Branchi F, Klingenberg-Noftz R, Friedrich K, *et al.* PuraStat in gastrointestinal bleeding: results of a prospective multicentre observational pilot study. *Surg Endosc* 2022;36:2954–61.
- 40 de Nucci G, Reati R, Arena I, *et al.* Efficacy of a novel self-assembling peptide hemostatic gel as rescue therapy for refractory acute gastrointestinal bleeding. *Endoscopy* 2020;52:773–9.