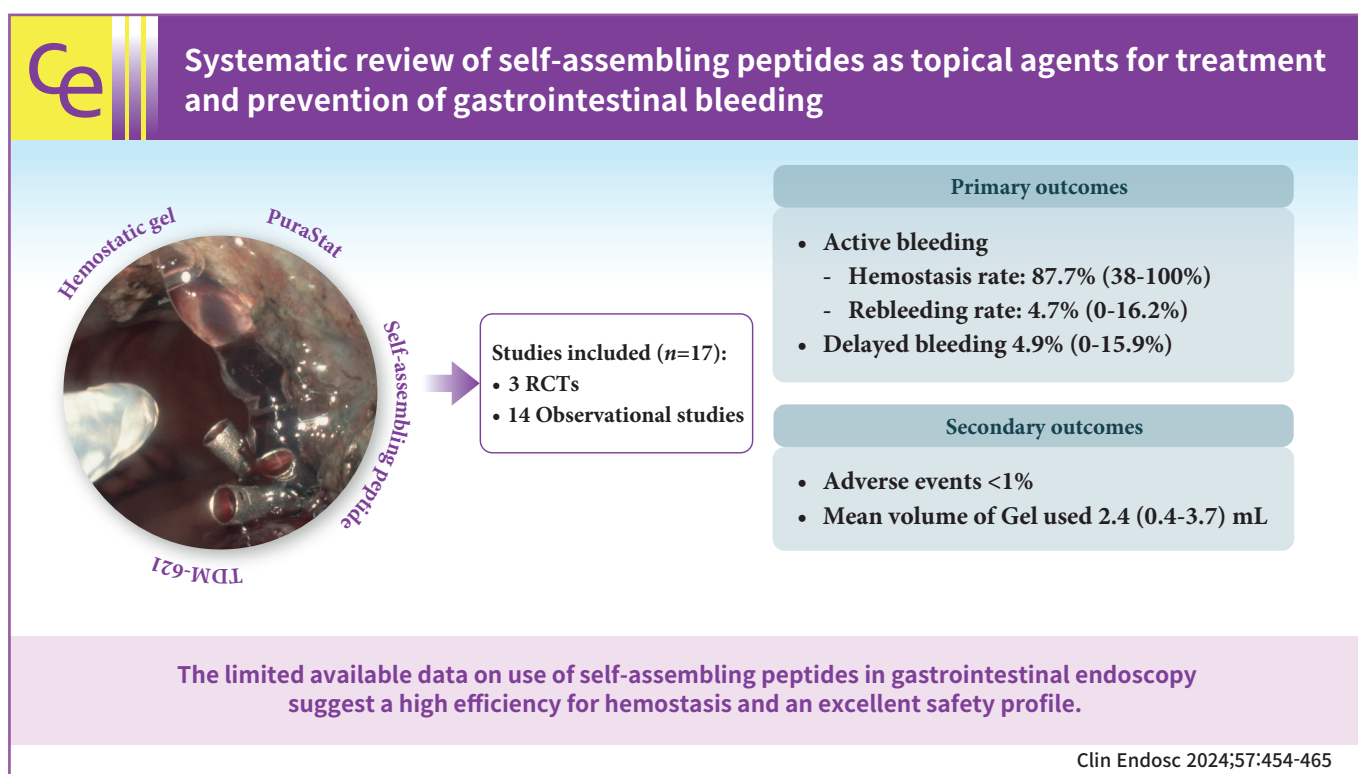**Ce CLINICAL ENDOSCOPY**

Systematic review of self-assembling peptides as topical agents for treatment and prevention of gastrointestinal bleeding

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Ce | Systematic review of self-assembling peptides as topical agents for treatment and prevention of gastrointestinal bleeding

Hemostatic gel · PuraStat · Self-assembling peptide · TDM-621

Studies included (*n*=17):
- 3 RCTs
- 14 Observational studies

Primary outcomes
- **Active bleeding**
  - Hemostasis rate: 87.7% (38-100%)
  - Rebleeding rate: 4.7% (0-16.2%)
- **Delayed bleeding** 4.9% (0-15.9%)

Secondary outcomes
- **Adverse events <1%**
- **Mean volume of Gel used** 2.4 (0.4-3.7) mL

The limited available data on use of self-assembling peptides in gastrointestinal endoscopy suggest a high efficiency for hemostasis and an excellent safety profile.

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Background/Aims: Gastrointestinal bleeding is a significant and potentially lethal event. We aimed to review the efficiency and safety of self-assembling peptides for the treatment and prevention of gastrointestinal tract bleeding.

Methods: We conducted a systematic search for studies describing the endoscopic use of self-assembling peptides for treatment or prevention of bleeding in the gastrointestinal tract in a parallel, independent fashion. The primary outcomes were rates of successful initial hemostasis, delayed bleeding, and rebleeding. The secondary outcomes were adverse events and ease and volume of gel used.

Results: Seventeen studies were analyzed. Overall success rate of self-assembling peptides in gastrointestinal bleeding was 87.7% (38%–100%), regardless of etiology or associated treatments. Rebleeding rate ranged from 0% to 16.2%, with a mean of 4.7%, and overall delayed bleeding rate was 5% (range, 0%–15.9%). Only three adverse events were reported in a pooled number of 815 patients. The volume of gel used varied (0.43 to 3.7 mL) according to indication and type of bleeding.

Conclusions: The limited available data on the use of self-assembling peptides in gastrointestinal endoscopy suggest a high efficiency and good safety profile.

Keywords: Hemostatic; Gel; PuraStat; Self-assembling peptide; TDM-621

INTRODUCTION

Gastrointestinal (GI) bleeding is a clinically significant and potentially lethal event. Endoscopic intervention is indicated in the vast majority of cases, and a wide range of techniques and devices have demonstrated its efficacy and safety. However, rebleeding remains a frequent occurrence[1] and is sometimes more difficult to treat because of previous interventions. Based on the nature of the lesion, guidelines recommend multiple endoscopic modalities to ensure effective hemostasis,[2,3] and treating lesions with multiple bleeding points or diffuse bleeding can be resource-intensive.[4] Moreover, the ever-expanding scope of and access to advanced therapeutic endoscopy (i.e., endoscopic submucosal resection [ESD], hybrid resection techniques, and third space endoscopy) are associated with an increased risk of iatrogenic hemorrhagic adverse events, for which preventative action is desirable.[5]

In general, few therapeutic options are designed to address both acute bleeding and prevent delayed post-procedural hemorrhage, and only hemostatic clip placement has been shown to reduce delayed bleeding in the management of large polyps.[6] The ideal hemostatic tool for interventional endoscopists should be easy to use, safe, and accessible; ensure immediate and prolonged hemostasis; allow wide field coverage; and be repeatedly used in the same session.

Recently, a new class of hemostatic devices in the form of proprietary, gel-forming, self-assembling peptides (SAP) has become available. Knowledge of self-assembling nanotechnology has progressed since the early 90s[7,8] and led to the development of TDM-621, a sterile synthetic peptide that forms a collagen-like fibrous network upon exposure to fluids under physiological conditions.[9] This network functions as a mechanical barrier, occludes bleeding points, and promotes tissue regeneration. Interest in its use as a topical hemostatic agent in various surgical settings, spanning cardiovascular surgery,[6] otolaryngology,[10] cervical endocrine surgery,[11] and abdominal surgery,[12] has grown in recent years. Under the name PuraStat (3-D Matrix Ltd.), this device has recently become commercially available and gained United States Food and Drug Administration premarket approval for use in mild and moderate bleeding post ESD or endoscopic mucosal resection (EMR) and as prevention for post-procedural bleeding.[13] However, the experience is limited, and its optimal use in the GI setting is under exploration.

We conducted a systematic review of the current data on the efficiency and safety of SAP in the treatment and prevention of bleeding in the GI tract.

METHODS

The study was designed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist and registered in the PROSPERO database on November 7, 2022 (CRD42022373735).

Eligibility criteria

For the purposes of this review, all prospective and retrospective studies describing the endoscopic use of SAP for treatment or prevention of bleeding in the GI tract were eligible. Full texts and abstracts published in English were included, and animal and laboratory studies were excluded.

Literature sources and search strategy

Three investigators (VD, MS, SV) conducted a parallel, independent, exhaustive search of major electronic databases—Medline, Web of Science, Scopus, ScienceDirect, clinicaltrials.gov, and proceedings from major congresses (i.e., Digestive Disease Week, European Society of Gastrointestinal Endoscopy Days, World Congress of GI Endoscopy)—on November 7, 2022. The search strategy included the following key terms: PuraStat, TDM-621, SAP, and hemostatic gel.

Duplicates were removed, and the remaining titles and abstracts were screened and reviewed for eligibility and appropriateness by three independent reviewers (VD, MS, SV). In cases of disagreement, another investigator (AV) made the final decision regarding study eligibility and inclusion. In cases where studies by the same authors had overlapping cases, we opted to include the largest and most recent series in the analysis. The final list was reviewed independently by PB and AV.

Study quality assessment

We used the methodological index for non-randomized studies (MINORS) criteria[14] for cohort studies and the modified Jadad scale[15] for the quality assessment of randomized controlled trials (RCTs). Seven of the 17 studies were available only as abstracts, and points were assigned to categories that were explicitly presented in the study or could be inferred from the abstract.

Outcome measures

The primary outcomes were the rates of successful initial hemostasis, delayed bleeding, and rebleeding. (1) Hemostasis: endoscopically confirmed absence of bleeding after the intervention without adjunctive modalities. The initial use of another modality (e.g., thermal and adrenaline injection) that did not stop the bleeding, with subsequent intervention was allowed. (2) Rebleeding: presence of hemorrhagic signs (i.e., hematemesis, melena, hematochezia, drop in hemoglobin level, drop in blood pressure, and increased heart rate) after initial successful hemostasis. (3) Delayed bleeding: presence of hemorrhagic signs after a resection procedure employing SAP as prophylaxis.

The secondary outcomes were adverse events, ease of use, and quantity of the substance used.

Data extraction

We extracted data regarding the type of study, bleeding source (upper/lower GI tract), number of patients, number of treated lesions, type of bleeding (oozing/spurting), indication for use (prophylaxis and hemostasis), outcomes, adverse events, ease of use, quantity required to treat a lesion, and associated methods for hemostasis (injection, clipping, and diathermy).

Data analysis

We coded the data and performed a descriptive analysis using IBM SPSS for Windows ver. 20.0 (IBM Corp.). Data analysis included descriptive statistics computed for continuous variables, expressed as mean and standard deviation. Categorical variables are described as counts and percentages.

RESULTS

The preliminary search yielded 776 studies. Figure 1 shows the flow chart of the manuscripts included in the final analysis according to the PRISMA reporting guidelines. We excluded case reports (15 articles) and included only retrospective or prospective studies (randomized or non-randomized). Finally, after eliminating duplicates and studies by the same authors
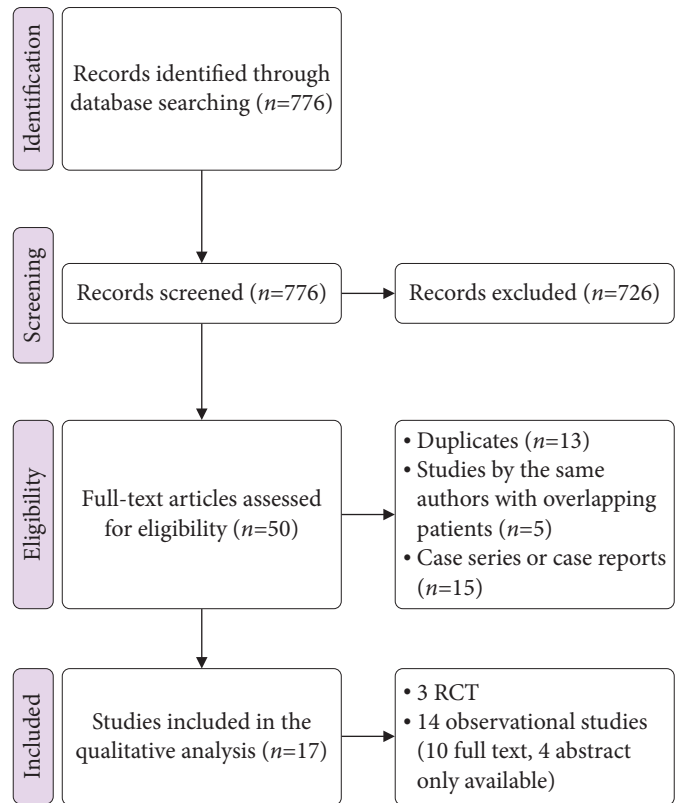

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-Analysis flowchart of the article selection process. RCT, randomized controlled trial.

with overlapping patients, 17 studies (with 925 patients) met the inclusion criteria, as detailed in Table 1.[16-32]

A total of three RCTs and 14 observational studies were retrieved for full-text analysis. Of these 17 studies, 10 included patients with upper and lower GI bleeding; five, only upper GI bleeding; and two, only lower GI bleeding. Six studies reported the type of bleeding; in four studies, only oozing bleeding was treated, while two reported both oozing and spurting bleeding. The purpose of using SAP was hemostasis in nine studies, prophylaxis of delayed bleeding after resection in five studies, and

both treatments for intraprocedural bleeding and post procedural prophylaxis in three studies.

RCTs compared SAP with conventional hemostasis techniques. Choi et al.[25] compared the use of PuraStat with epinephrine spray in patients with post endoscopic sphincterotomy or post-papillectomy bleeding. SAP showed significantly higher successful primary hemostasis rates than epinephrine spray (100% vs. 85.4%, $p=0.026$). There were no significant statistical differences between the two agents in delayed bleeding (2.4% vs. 7.3%). A study conducted by Subramaniam et al.[18] evaluated

Table 1. Description of included studies

Study	Type of study	No. of patients treated	Location	Type of bleeding	Prophylactic use	Included patients
Arndtz et al. (2021)[16]	Prospective, multicenter, observational-descriptive	226	U-L	NA	Yes	EMR, ESD, RP, others
Branchi et al. (2022)[17]	Prospective, multicenter, observational-descriptive	111	U-L	O-S	No	EMR, ESD, GDU, others
Subramaniam et al. (2019)[18]	Prospective, single-center, observational-descriptive	100	U-L	O	Yes	EMR, ESD
Uedo et al. (2022)[19]	Prospective, multicenter, interventional, randomized	86	U-L	NA	No	ESD
de Nucci et al. (2020)[20]	Prospective, multicenter, observational-descriptive	77	U-L	O-S	No	EMR, ERCP, GDU, others
Pioche et al. (2016)[21]	Retrospective multicenter, observational-descriptive	56	U-L	NA	Yes	EMR, ESD
Subramaniam et al. (2021)[22]	Prospective, single-center, interventional, randomized, single-blind	46	U-L	O	No	ESD
Uraoka et al. (2016)[23]	Prospective, single-center, observational-descriprive	45	U	NA	Yes	ESD
Soons et al. (2021)[24]	Prospective, single-center, observational-descriptive	44	U-L	NA	Yes	EMR
Choi et al. (2022)[25]	Prospective, multicenter, interventional, randomized, single-blind	41	U	NA	No	ERCP
Labianca et al. (2021)[26]	Prospective, single-center, observational-descriptive	24	U-L	NA	No	EMR, ERCP, GDU
White et al. (2021)[27]	Prospective, single-center, observational-descriptive	21	L	NA	No	RP
Woolley et al. (2022)[28]	Retrospective, multicenter, observational-descriptive	17	U	NA	Yes	EMR, AMP
Yoshida et al. (2014)[29]	Prospective, single-center, observational-descriptive	12	U	O	No	EMR, ESD
Soriani et al. (2018)[30]	Prospective, single-center, observational-descriptive	7	U-L	NA	Yes	EMR, ESD
Stammers et al. (2021)[31]	Prospective, single-center, interventional, non-randomized	6	L	NA	No	RP
Ishida et al. (2022)[32]	Retrospective, single-center, observational-descriptive	6	U	O	No	ERCP

U, upper gastrointestinal tract; L, lower gastrointestinal tract; NA, not applicable; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; RP, radiation proctopathy; O, oozing; S, spurting; GDU, gastro-duodenal ulcer; ERCP, endoscopic retrograde cholangiopancreatography; AMP, ampullectomy.

the reduction in the need for coagulation for bleeding control related to ESD when the PuraStat was used. The authors reported a significant reduction in the use of diathermy for intraprocedural hemostasis in the interventional group compared to controls (49.3% vs. 99.6%, $p<0.001$), with no significant differences in the procedure length, time for hemostasis, and delayed bleeding rate. Lastly, Uedo et al.[19] investigated the efficacy of PuraStat in reducing the need for coagulation forceps in the case of oozing bleeding lasting more than 3 minutes during ESD and found that the SAP group had significantly fewer uses of forceps than the control group (1.0 ± 1.4 vs. 4.9 ± 5.2, $p<0.001$), without serious safety concerns.

The primary outcomes for studies that used SAP as a treatment for active bleeding and those employing SAP as prophylaxis against delayed bleeding are summarized in Tables 2, 3, respectively.[16-18,20-30,32] We could not extract data from two out of the 12 studies reporting SAP usage for hemostasis because only their abstracts were accessible. Of the eight studies that evaluat-

ed the efficacy in preventing delayed bleeding, six followed patients for 30 days after the intervention. We could not retrieve information on follow-up from the study by Arndtz et al.[16] owing to its availability only in abstract format and from the study by Uraoka et al.[23] because it was not presented.

Hemostasis

The 12 studies that reported data on hemostasis included 756 patients. The overall success rate was 87.7% (38.1%–100%), regardless of bleeding etiology or associated treatments. The vast majority of the uses were for intraprocedural bleeding, both in the upper and lower digestive tracts, with success rates between 75% and 100%. Meanwhile, the success rate for achieving hemostasis was only 38.1% when SAP was employed to manage bleeding associated with radiation proctitis (Table 2).

Rebleeding rate

In the 12 studies that reported the use of PuraStat for hemostasis, the rebleeding rate was 4.7% (range, 0%–16.2%). The follow-up period from the initial hemostasis ranged from 1 to 30 days. The highest rebleeding rates were found in the studies by Branchi et al.[17] (16.2%) and de Nucci et al.[20] (10.3%). In a study by de Nucci et al.,[20] rebleeding occurred in eight patients: two colonic cancers with oozing-type, two duodenal ulcers with spurting-type bleeding and oozing-type bleeding, one duodenal mucosal resection with oozing-type bleeding, one gastric ulcer with spurting-type bleeding, and two gastric cancers with oozing-type bleeding (Table 2).

Delayed bleeding

The mean delayed bleeding rate was 4.9% (range, 0%–15.9%), based on results from eight studies. There were 393 prophylactic applications in 495 patients, all representing EMR or ESD

Table 2. Summary of primary outcomes of self-assembling peptide for active bleeding

Study	Hemostasis (%)	Rebleeding (%)
Ishida et al. (2022)[32]	100	0
Choi et al. (2022)[25]	100	2.4
Arndtz et al. (2021)[16]	92	8
Branchi et al. (2022)[17]	88.3	16.2
Subramaniam et al. (2021)[22]	92.6	0
Labianca et al. (2021)[26]	100	0
White et al. (2021)[27]	38.1	4.8
de Nucci et al. (2020)[20]	90.9	10.4
Subramaniam et al. (2019)[18]	75	NA
Yoshida et al. (2014)[29]	100	0
Overall	87.7	4.7

NA, not applicable.

Table 3. Summary of primary outcomes of self-assembling peptide for prophylaxis

Study	Procedure	Follow-up (day)	Delayed bleeding (%)
Woolley et al. (2022)[28]	EMR, AMP	30	5.9
Subramaniam et al. (2021)[22]	ESD	30	4.3
Soons et al. (2021)[24]	EMR	30	15.9
Arndtz et al. (2021)[16]	EMR, ESD, RP, others	NA	2.3
Subramaniam et al. (2019)[18]	EMR, ESD	30	3
Soriani et al. (2018)[30]	EMR, ESD	30	0
Pioche et al. (2016)[21]	EMR, ESD	30	6.1
Uraoka et al. (2016)[23]	ESD	NA	1.9
Overall		30	4.9

EMR, endoscopic mucosal resection; AMP, ampullectomy; ESD, endoscopic submucosal dissection; RP, radiation proctopathy; NA, not applicable.

performed in the esophagus, stomach, duodenum, colon, or rectum, with the exception of six patients for whom it was applied for spontaneous bleeding in the upper digestive tract and 22 patients for whom it was used for radiation proctitis. The study by Soons et al.,[24] which had the highest delayed bleeding rate (15.9%), included patients who underwent EMR for lesions in the esophagus, duodenum (>1 cm), and colon (>2 cm). All patients with delayed bleeding underwent piecemeal resection. In a study by Subramaniam et al.,[18] delayed bleeding occurred in three patients (3%) treated for antral gastric cancers and esophageal adenocarcinoma. Pioche et al.[21] reported delayed bleeding in four patients (6.1%): two following esophageal resection, one after ampullectomy, and one rectal ESD, who also needed reintroduction of heparin post-procedure. All patients were managed by an endoscopist. Uraoka et al.[23] encountered a single delayed bleeding (1.9%) in a gastric resection managed during second-look endoscopy. Soons et al.[24] reported delayed bleeding in seven cases (15.9%), all of which underwent piecemeal resection, and three of them used antithrombotics; one in the esophagus, four in the duodenum, and three in the colorectum. All but one were managed with hemostatic clip placement (Table 3).

Associated treatments

SAP was used as the first and only line of treatment for hemostasis in five studies (Yoshida et al.[29] 2014, Subramaniam et al.[18] 2019, Subramaniam et al.[22] 2021, Choi et al.[25] 2022, and Ishida et al.[32] 2022). The mean success rate of hemostasis in these five studies was 93.5%, and the average rebleeding rate was 0.6% (Table 4). When SAP was used as first line treatment followed by another complementary technique or as second line treatment, the success rate was 81.8% and the rebleeding rate was 7.8%. Among the studies that evaluated delayed bleeding prophylaxis, three used SAP as the first and only line of treatment (Subramaniam et al.[22] 2021, Soons et al.[24] 2021, and Subramaniam et al.[18] 2019). These had an average rebleeding rate of 7.7% at 30 days compared to 2.8% for the studies that used the SAP

gel along with other adjuvant techniques (i.e., Hemospray [Cook Medical], hot diathermy forceps,[21] monopolar forceps[30]).

High-risk patients

Data on patients considered to be at a high risk of bleeding owing to ongoing treatment with antithrombotics were available from 12 studies. Eleven studies included a total of 194 (20.9%) patients on antithrombotic medication. One study excluded patients taking anticoagulants or antifibrinolytics (Yoshida et al.[29] 2014).

Safety

Data regarding adverse events were explicitly reported in 14 studies with a pooled number of 815 patients. Three adverse events were recorded in total (rate, <1%): one perforation unrelated to SAP treatment (Subramaniam et al.[22] 2021), one case of mild elevation of uremic acid and transaminases (Yoshida et al.[29] 2014), and one case of hyperamylasemia after endoscopic sphincterotomy (Ishida et al.[32] 2022).

Technical aspects

The volume of gel required to achieve hemostasis varied according to the purpose of the intervention and the type of bleeding. Eight studies reported the volume needed for hemostasis, with a mean volume of 2.4 mL, ranging from 0.4 to 3.7 mL, and six studies reported the volume needed to prevent delayed bleeding, with a mean volume of 2.7 mL, ranging from 2.3 to 3.5 mL. Ten studies reported on the ease of PuraStat use, mainly in a qualitative fashion based on user experience and satisfaction, while three studies also mentioned the average time required for application: 69.5 seconds,[20] 2 minutes,[21] and a median time of 2 minutes,[23] respectively.

Study quality and assessment

Tables 5, 6 summarize the quality of the observational and interventional studies.[16-32] Only one observational study included a comparison group,[31] and most observational studies were

Table 4. Summary of outcomes according to use of associated treatments

Indication	Self-assembling peptide	Hemostasis (%)	Rebleeding (%)
Hemostasis	First and only treatment	93.5	0.6
Hemostasis	Associated to a complementary technique	81.8	7.8
Prophylaxis	First and only treatment	NA	7.7
Prophylaxis	Associated to a complementary technique	NA	2.8

NA, not applicable.

Table 5. Methodological index for non-randomized studies

| Study | | Descriptive studies | | | | | | | Additional criteria for comparative studies | | | | Total |
	A clearly state aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to aim of the study	Loss to follow-up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary group	Baseline equivalence of groups	Adequate statistical analyses	
Stammers et al. (2021)[31]	2	2	1	2	0	2	2	0	2	2	2	2	19
Soons et al. (2021)[24]	2	2	2	2	0	2	2	0					12
Branchi et al. (2022)[17]	2	2	2	2	0	1	2	1					12
Pioche et al. (2016)[21]	2	2	2	2	0	2	2	0					12
Uraoka et al. (2016)[23]	2	2	2	2	0	2	2	0					12
de Nucci et al. (2020)[20]	2	2	2	2	0	1	1	0					10
White et al. (2021)[27]	2	2	0	2	0	2	2	0					10
Subramaniam et al. (2019)[18]	2	0	2	2	0	2	2	0					10
Soriani et al. (2018)[30]	0	2	2	1	0	2	2	0					9
Woolley et al. (2022)[28]	2	0	0	2	0	2	2	0					8
Yoshida et al. (2014)[29]	2	0	1	2	0	1	2	0					8
Labianca et al. (2021)[26]	2	0	1	2	0	0	2	0					7
Arndtz et al. (2021)[16]	2	0	2	0	0	0	0	0					4
Ishida et al. (2022)[32]	0	0	0	0	0	2	2	0					4

Table 6. The modified Jadad scale for randomized controlled trial studies

Study	Was the study described as randomized?	Was the method of randomization appropriate?	Was the study described as blinding?	Was the method of blinding appropriate?	Was there a description of withdrawals and dropouts?	Was there a clear description of the inclusion/exclusion criteria?	Was the method used to assess adverse effects described?	Was the methods of statistical analysis described?	Total
Subramaniam et al. (2021)[22]	1	1	0.5	1	1	1	1	1	7.5
Uedo et al. (2022)[19]	1	0	0	0	0	1	1	0	3
Choi et al. (2022)[25]	1	0	0.5	0	0	1	0	0	2.5

descriptive. In addition, the quality of interventional studies was low, as two of them lacked important aspects such as details about randomization, blinding, or loss in follow-up management.

DISCUSSION

Our review indicated that SAP are an efficient and safe option for intraprocedural oozing type bleeding that occurs during endoscopic resection in the digestive tract, ensuring hemostasis in >85% of cases and a low rebleeding rate after initial successful hemostasis. Prophylaxis after EMR or ESD is easy to implement and is associated with a low delayed bleeding rate.

Classic hemostatic techniques have a wide range of efficiencies depending on the clinical context in which they are used. The most extensive data comes from peptic ulcer bleeding, where successful hemostasis can be achieved in 75% to 95.1%[33-36] of cases with adrenaline injection, 81.2% to 100%[35,37] with thermocoagulation, and 66.7% to 97.6%[33-38] when standard hemostatic clips are employed. As shown in a Danish nationwide cohort study, the success of endoscopic treatment for this indication has improved significantly over time (94% in 2010–2011 vs. 89% in 2004–2006).[39] The studies we reviewed explored SAP primarily as a hemostatic agent for intraprocedural bleeding (during EMR or ESD) or for bleeding that occurred after these resections. The commonly estimated rates of post-procedural bleeding are low and does not differ between EMR and ESD for neoplastic lesions (1.7%; 95% confidence interval [CI], 0.6%–3.4%] in neoplastic Barrett's, 5% to 10% in gastric lesions, and 2.7% in colorectal lesions).[40-43] Bleeding in these cases can be treated conservatively or with endoscopic hemostasis; however, in some cases, interventional radiology or surgery is required. In our review of SAP performance for this indication, we found that hemostasis could be achieved in 87.7% of cases, with better results reported in studies where PuraStat was employed as the first and only method (93.5%) compared to those that used complementary techniques (81.8%). Furthermore, SAP application for intraprocedural bleeding appeared to reduce the need for thermal coagulation and the risk of complications. Cost considerations must also be taken into account. The healthcare costs associated with uncontrolled bleeding surpass the costs related to SAP use (e.g., 300 to 450 United States dollars (USD)[44] for a mean required volume of 2.4 mL when used for hemostasis). For a 12-month period following the index date, upper gastrointestinal-related healthcare utilization and total healthcare,

medical, and pharmacy costs for upper gastrointestinal bleeding are estimated to be 20,405 USD, including initial hospitalization costs of 11,228 USD.[45]

Any hemostatic agent used in the acute setting is evaluated according to both its immediate success and the durability of the response (i.e., rebleeding). The rate of rebleeding after initial hemostasis with SAP was 4.7%, slightly lower than that obtained with adrenaline injection (14.6%-33.3%),[1-4] hemostatic powders (10.9%–14.4%),[44,45] and over-the-scope clips (OTSC) clips (10.3%)[46-50] and comparable to that achieved with thermal coagulation (3.7%–13.3%),[4,5] or hemostatic clips (2.4%–22.2%).[33-38] Most cases of rebleeding after SAP use could be treated endoscopically, and only a few required referral for surgery.

Even if a direct comparison is not feasible, the data from the analyzed studies are more robust concerning the prevention of delayed bleeding after resection techniques, such as polypectomy, EMR, or ESD. In these cases, there are abundant but conflicting data regarding the prophylactic treatment of the ulcer base with hemostatic clips, indwelling snares, overstitches, suturing, OTSCs, or various polyglycolic sheets.[51-53] Delayed bleeding after prophylactic clipping is encountered in 1.4% to 3.9% of cases,[54-58] whereas 4.9% of patients in whom SAP was used as prophylactic had a bleeding episode within the first 30 days post-intervention. Bleeding prophylaxis was an indication for SAP in most of the early studies analyzed in this review, and some data suggest that the gel also has ulcer-healing-enhancing properties.[19,20]

To correctly position the SAP in the hemostatic armamentarium, we must consider the unique properties of this new method. SAP can be used before or after virtually any other hemostatic method because it forms a transparent gel that conducts current, ensuring that all options remain open to manage challenging bleeding situations. For example, current guidelines recommend the use of two hemostatic methods for actively bleeding peptic ulcers and topical sprays or cap-mounted clips for refractory bleeding.[2] OTSC has shown promising results as first line therapy for the treatment of upper non-variceal GI bleeding, evidenced by Qiu et al.[59] who recently reported a 100% technical success rate (80/80 patients) with a clinical success rate of 91.3% (73/80). In cases of arterial bleeding, SAP is less efficient but can be used as a complementary method to achieve hemostasis. For instance, in a study by de Nucci et al.,[20] SAP showed promise as salvage therapy, after at least two options failed, and had a success rate of 90.9%. Furthermore,

the delivery method using an endoscopic catheter without the risk of clotting makes SAP a good alternative for bleeding in difficult-to-reach anatomical locations. SAP have been used off-label to achieve successful hemostasis in cases that are technically difficult to treat, such as fistula-bleeding after lumen apposing metal stent removal (treatment of an infected pancreatic pseudocyst),[60] biliary tract bleeding (acute intrahepatic biliary duct bleeding following electrohydraulic lithotripsy),[61] or bleeding following percutaneous endoscopic gastrostomy placement.[62] Furthermore, owing to its non-targeted application, the gel is an intriguing option for diffuse bleeding scenarios, such as radiation proctopathy or malignancy-related GI bleeding, for which it has showed high efficiency in achieving hemostasis (94.1%).[63]

In terms of adverse effects, three studies reported perforation,[22] elevation of uremic acid and transaminases,[29] and hyperamylasemia.[32] None of the events were directly related to the use of hemostatic gel. Compared with hemostatic powders, no endoscope blockages or camera obscurations were reported in the reviewed studies. Studies that assessed ease of use reported a high degree of satisfaction with its application among endoscopists. Some authors noted certain difficulties in applying the gel to gravitationally dependent surfaces and a risk of premature rinsing off of the gel owing to peristalsis and mucus formation. Furthermore, no recommendations regarding the optimum quantity of gel can be currently made.

Because SAP was introduced relatively recently in GI endoscopy, there is a natural dearth of well-designed studies. We performed an extensive search of the databases and screened conference proceedings history from past years and clinical trial results, but data from gray literature could have been missed during the process. The main limitations of our study were its qualitative nature and the inability to report statistical results. We were unable to report the results based on the etiology and location of bleeding, as the studies included in this analysis had different designs, making it challenging to integrate them into a cohesive whole. Additionally, these data were not analyzed in the subcategories of the original studies.

Another important aspect is that in most of the studies identified, SAP tended to be used in challenging clinical settings (salvage therapy, severe bleeding, and technically difficult procedures); consequently, the results cannot be applied to common cases. While this might be a good future indication for the widespread use of SAP, further studies on common indications

for hemostasis are needed before recommendations can be made currently.

Hemostatic powders, such as TC-325 (Cook Medical), Endo-Clot (EndoClot Plus), CEGP-003 (CGBio Inc.), UI-EWD (Nexpowder), or Ankaferd Blood Stopper (ABS; Ankaferd Health Products Ltd.) were not included in this analysis because previous comprehensive results on their efficacy in GI bleeding were already available.

The lack of standardization regarding the use of SAP in different settings (treatment or prevention of bleeding in the GI tract) is an important issue identified by our analysis and should be addressed in further prospective multicenter studies using larger samples, with similar definitions of hemostatic or prophylactic success. The hemostatic efficacy of SAP should be compared to that of standard endoscopic therapy in future well-designed randomized trials.

The most important conclusion of our study is that SAP is efficient for the treatment of oozing intraprocedural bleeding during advanced endoscopic resection and has a low rebleeding rate after prophylactic use. Evidently, SAP is safe and can be used even in technically difficult-to-control bleeding situations. Further randomized studies are required to establish the efficacy and optimal indications for SAP.

Ethical Statements

Not applicable.

Conflicts of Interest

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