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Efficacy of self-assembling peptide in mitigating delayed bleeding after advanced endoscopic resection of gastrointestinal lesions: A meta-analysis

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Authors
Harishankar Gopakumar[1], Ishaan Vohra[1], Neil R. Sharma[2], Srinivas R. Puli[1]

Institutions
1 Department of Gastroenterology and Hepatology, University of Illinois College of Medicine at Peoria, Peoria, Illinois, United States
2 Parkview Cancer Institute, Interventional Oncology & Surgical Endoscopy (IOSE) division, GI Oncology Tumor Site Team, Fort Wayne, Indiana, United States

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Corresponding author
Harishankar Gopakumar, MD, FACP, Department of Gastroenterology and Hepatology, 530 NE Glen Oak Ave, Peoria, IL USA 61637, United States
Fax: +1-312-872-8570
harishankar.gopakumar@oshealthcare.org
hgopakumarmd@gmail.com

ABSTRACT

Background and study aims Advanced endoscopic resection techniques carry a risk of delayed bleeding (DB). A novel fully synthetic self-assembling peptide (SAP) has shown promising results in mitigating this risk. In this meta-analysis, we evaluated all available data and analyzed the effectiveness of SAP in reducing DB after advanced endoscopic resection of gastrointestinal luminal lesions.

Patients and methods Electronic databases (PubMed, Embase, and Cochrane Library) from January 2010 through October 2022 were searched for publications addressing the use of SAP solution in patients undergoing advanced endoscopic resection of gastrointestinal lesions. Pooled proportions were calculated using fixed (inverse variance) and random-effects (DerSimonian-Laird) models.

Results The initial search identified 277 studies, of which 63 relevant articles were reviewed. The final analysis included data from six studies comprising 307 patients that met inclusion criteria. The pooled rate of DB was 5.73% (95% confidence interval [CI] = 3.42–8.59). Mean patient age was 69.40 years ± 1.82. The weighted mean size of resected lesions was 36.20 mm (95% CI = 33.37–39.02). Endoscopic submucosal dissection was used in 72.69% (95% CI = 67.62–77.48), while endoscopic mucosal resection was used in 26.42% (95% CI = 21.69–31.44) of the procedures. Among the 307 patients, 36% were on antithrombotic medications. No adverse events (AEs) were attributable to using SAP, with a pooled rate of 0.00% (95% CI = 0.00–1.49).

Conclusions SAP solution appears promising in reducing post-procedural DB after advanced endoscopic resection of high-risk gastrointestinal lesions with no reported AEs.

Introduction

Advanced endoscopic resection (ER) is the preferred initial management for large and often pre-malignant lesions. ER is also the procedure of choice for curative resection of early-stage malignant gastrointestinal luminal lesions [1]. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), including hybrid EMRs, and hybrid ESDs, are the commonly used ER techniques [1]. Despite the high technical success rates, delayed post-procedural bleeding remains a complication, with rates of 2% to 15%, especially in high-risk situations despite standard prophylactic techniques [2].

Delayed bleeding (DB) can manifest as overt bleeding with hematemesis, hematochezia, melena, hemodynamic instability, or a 2-g drop in hemoglobin after the first 24 hours [1]. Major risk factors for DB include the resection site, resected lesion size, and antiplatelet, anticoagulant, or nonsteroidal anti-inflammatory drug use [3,4]. Success with techniques employed to reduce DB, such as prophylactic clipping and coagulation, have been suboptimal and have shown varied results. For example, Nishizawa et al. did not find a significant reduction in DB with prophylactic clipping [5], while Pohl et al. [6] noted a decrease from 7.10% to 3.50%. A large randomized controlled trial (RCT) by Feagins et al. found no difference in the rate of post-procedural DB after ER of large colon polyps treated prophylactically with hemostatic clips [7]. Moreover, achieving adequate hemostasis with clips can be challenging even in experienced hands, depending on the site of ER [7]. On the other hand, electrocoagulation has the potential for thermal injury and can also distort the resection base. Topical hemostatic spray powders, due to their opaque nature, will obscure the resection field and are not ideal in the setting of ER. Their effects are also relatively short-lived and less likely to reduce DB. Post-ER DB can often be significant, requiring hospital admission, blood transfusions, and repeat procedures.

The use of a self-assembling peptide (SAP), RADA 16, has been reported in recent years as a hemostatic tool with good results across various indications. It is a synthetic 16-amino acid, non-biogenic, biocompatible resorbable peptide that exists as a viscous solution in an acidic environment. When exposed to the physiological pH of blood, interstitial fluid, or lymph, the RADA 16 nanofibers spontaneously crosslink within seconds to form a transparent, stable 3-dimensional (3D) hydrogel [8]. This property has enabled its use as a hemostatic agent. The nanofiber hydrogel structure also closely resembles the 3D structure of extracellular matrices, and this property has been hypothesized to augment wound healing. Its shear-thinning and thixotropic properties allow the product to be delivered to the bleeding site through narrow endoscopic catheters. Its viscous form will enable it to flow and conform to the tissue surface's peaks and troughs. Being transparent, it also does not obscure the view of the resection field [8]. Moreover, it does not alter the surgical site anatomy, as can happen with clips and coagulation. These properties position RADA 16 as a unique tool for controlling intraprocedure and post-procedure bleeding associated with advanced ER. Recently a commercial formulation of RADA 16 (PuraStat; 3D Matrix Ltd, France) has been approved by the US Food and Drug Administration for mild and moderate bleeding post-ESD or EMR, as an adjunct, bridge, prophylactic, or rescue therapy for intraprocedure venous bleeding or prophylactic treatment to prevent post-procedure bleeding. In one of the first studies evaluating the use of SAP in post-ER bleeding, Yoshida et al. reported that it was "remarkably effective" in 92% of patients who underwent gastric ESDs [9]. More extensive and well-devised studies have subsequently evaluated the efficacy, safety, and feasibility of SAP in this setting [10–14]. SAP as a hemostatic agent during ER is considered safe with no adverse events (AEs) related to its use. However, hypersensitivity, pain related to the application of SAP, and thromboembolic events have been proposed as potential complications [9]. We conducted this systematic review of literature and performed a meta-analysis to evaluate the efficacy and feasibility of this novel agent in the prophylaxis of post-procedural DB following advanced ER of gastrointestinal luminal lesions.

Patients and methods

Search methodology

A literature search was conducted using the electronic database engines MEDLINE through PubMed, Ovid, Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Meta-Analysis), EMBASE, ACP journal club, Database of Abstracts of Reviews of Effects (DARE) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines from January 2010 through October 2022 to identify studies addressing the use of this novel SAP, otherwise known as RADA 16 and commercially available as PuraStat in the prevention of DB after advanced ER. Keywords used were EMR, ESD, ER, PuraStat, PuraMatrix, RADA 16, SAP, and gastrointestinal bleeding. The retrieved studies were carefully examined to exclude potential duplicates or overlapping data. An additional literature search was also performed to screen for relevant studies found in the reference list of reviewed studies.

Study eligibility

Published studies were eligible if they reported using novel SAP, RADA 16 or PuraStat, to prevent or reduce the risk of DB following advanced ER. Articles were excluded if they were not in the English language. Studies in animal models, editorials, abstracts with incomplete data, case reports, case series with less than ten patients, and comments were excluded. Studies evaluating the use of SAP for other indications, including management of acute bleeding, were also excluded. Six studies matched the study criteria and two authors reviewed full-text articles independently (HG, IV). Differences were resolved by mutual agreement or review by a third author (SP).

Data extraction and quality assessment

The following data were independently abstracted by two authors (HG, SP) into a standardized form: Study characteristics (primary author, period of study, year of publication, and country of the population studied), study design, baseline characteristics of the study population (number of patients enrolled, participant demographics), and intervention details. The quality of included studies was assessed using a modified version of the Newcastle-Ottawa Scale based on three broad components for the included non-randomized studies and the Jadad scale for the one RCT. Quality was graded as high if the total score was ≥6 from a maximum possible score of 8. Discrepancies were resolved by consensus. Differences were resolved by discussion.

Outcomes evaluated

The primary outcome evaluated was the efficacy of this novel SAP in preventing post-procedure DB after advanced ER of gastrointestinal luminal lesions. Secondary outcomes assessed were the rate of DB based on the location of ER, AE rates, and the endoscopist reported ease of use of this hemostatic product. An AE was defined as any allergic reaction or hypersensitivity, pain, thromboembolic events, or any other unintended events with an untoward outcome ascribed to the use of SAP by the authors of the included studies.

Statistical analysis

Meta-analysis was performed by calculating pooled proportions. Individual study proportions were transformed into a quantity using the Freeman-Turkey variant of the arcsine square-root transformed proportion. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed-effects model and DerSimonian-Laird method for the random-effects model. The heterogeneity of the studies was evaluated by calculating the I^2 statistic. I^2 values of 0% to 39% were considered non-significant heterogeneity, 40% to 75% moderate heterogeneity, and 76% to 100% considerable heterogeneity. $P>0.10$ rejects the null hypothesis that the studies are heterogeneous. The findings of this meta-analysis are reported using the fixed-effects model, as there was no statistically significant heterogeneity. Forest plots were drawn to show the point estimates in each study in relation to the summary of pooled estimate. The width of point estimates in the Forest plots indicates the assigned weight to that study. The effects of publication and selection bias on the summary estimates were tested by the Egger bias indicator and Begg-Mazumdar bias indicator. Funnel plots were constructed to assess potential publication bias. Microsoft Excel 19 was the software used to perform the statistical calculations for this meta-analysis.

Results

Study characteristics and quality

The initial search identified 277 articles, of which 63 relevant studies were reviewed. Six studies [9–14] that met the inclusion criterion, comprising 307 patients, were included in the final analysis. These 307 patients underwent a total of 322 advanced ER procedures. Mean patient age was 69.40 ± 1.82 years. The pooled mean size of resected lesions was 36.20 mm (95% CI = 33.37–39.02). ESD or hybrid ESD was used in 72.69% (95% CI = 67.62–77.48) of procedures, while EMR or hybrid EMR was used in the other 26.42% (95% CI = 21.69–31.44). Characteristics of included studies and patient demographics are shown in ▶ **Table 1**. PRISMA describing the details of the review process are shown in ▶ **Fig. 1**. The quality of included studies was good as evaluated using Newcastle-Ottawa and Jadad scales shown in ▶ **Table 2** and ▶ **Table 3**, respectively. All the pooled estimates given are estimates calculated by the fixed-effects model. The estimates calculated using fixed and random-effects models were similar.

Primary and secondary outcomes

The overall pooled DB rate post-ER was 5.73% (95% CI = 3.42–8.59). There was no significant heterogeneity, with an I^2 score of 36.20% (95% CI = 0.00 – 73.70). Forest plot showing individual study estimates and the pooled estimate for DB rate is shown in ▶ **Fig. 2**. The Begg-Mazumdar bias indicator gave a Kendall's tau b value of 0.6 ($P = 0.13$), suggesting no publication bias. Funnel plot on publication bias is shown in ▶ **Fig. 3**. None of the reported AEs were attributable to the use of SAP. Hence, the pooled AE rate attributable to using a SAP for managing DB after ER was 0.00% (95% CI = 0.00–1.40). A forest plot showing individual study estimates and the pooled estimate for AE rate is shown in ▶ **Fig. 4**. The rate of DB based on the location of ER was analyzed and showed a pooled rate of 5.64% (95% CI = 2.02–10.92) for esophageal ER, 4.15% (95% CI = 0.37–11.69) for gastric ER, 10.62% (95%f CI = 2.54–23.31) for duodenal ER and 5.07% (95% CI = 1.00–11.99) for colorectal ERs. Forest plots of individual study estimates and the pooled estimates for DB based on location are shown in ▶ **Fig. 5**, ▶ **Fig. 6**, ▶ **Fig. 7**, and ▶ **Fig. 8**. All studies reported that SAP was easy to apply with complete coverage of the resection base and did not add significantly to total procedure time.

Discussion

Advanced ER techniques are the first-line minimally invasive method for treating large and early neoplastic gastrointestinal luminal lesions. These include EMR, ESD, hybrid EMRs, and hybrid ESDs. Choosing the ideal method depends on lesion size, location, pathology, and available expertise [1]. Intraprocedural and DB are complications associated with advanced ER procedures. These can often be severe, requiring hospital admissions, blood transfusions, and the need for repeat endoscopy or other interventions to treat the bleeding. Our study shows that RADA 16 effectively mitigates the risk of post-ER delayed bleeding across a spectrum of techniques and locations with a pooled DB rate of 5.70%. There were no reported AEs attributable to the use of this product in the control of DB. These results are comparable and better than other modalities used previously to prevent DB after advanced ER [5–7, 15].

The risk for DB is affected by multiple factors such as the choice of ER technique, periprocedure exposure to antithrombotic medications, lesion size, and location [3, 4]. This pooled analysis included patients who underwent different advanced ER procedures, including EMRs, ESDs, hybrid EMRs, and hybrid ESDs. ESD or hybrid ESD was used in about 73%, while EMR or hybrid EMR was used in 26% of the procedures. Hence the findings from this study can be applied to various standard advanced ER procedures. However, data were not available to calculate the pooled effect of SAP in reducing the risk of DB based on ER technique used. DB rates after ER can significantly vary based on the location of the lesion, with studies reporting rates ranging from 0% following esophageal ERs to 20% following duodenal EMRs [16–19]. We analyzed the rate of DB after pro-

▶ **Table 1** Study details and demographics of patients included in this meta-analysis.

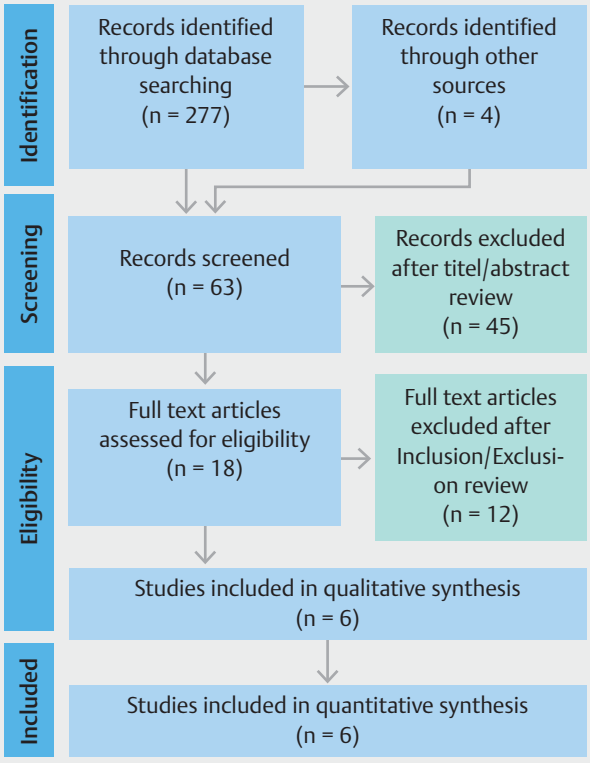
Study, year, location	Study Design	Patients (lesions)	Females, n (%)	Age (yr)	Mean lesion size, mm (SD)	No. EMR	No. ESD	No. DB	No. lesions based on location (DB, n)				
									Esophagus	Stomach	Duodenum	Ampulla	Colon Rectum
Yoshida et al. 2014, Japan [9]	Single-center case series	12 (12)	NR	NR	NR	NR	12	0	0	12 (0)	0	0	0
Pioche et al. 2016, France [10]	Retrospective multicenter	56 (65)	22 (39)	Mean 66.90 (SD 11.40)	37.90 (2.20)	22	40	4	8 (2)	22 (0)	10	3 (1)	22 (1)
Uraoka et al. 2016, Japan [11]	Prospective single-center	45 (51)	12 (27)	Mean 71.90 (SD 8.80)	36.50 (11.30)	0	51	1	NR	NR	NR	NR	NR
Subramaniam et al. 2019, United Kingdom [12]	Prospective single-center	100 (100)	32 (32)	Mean 69.30 (SD NR)	36.70 (21.20)	21	79	3	48(1)	11 (2)	10 (0)	0	31 (0)
Subramaniam et al. 2020, United Kingdom [13]	Prospective single-center RCT	46 (46)	13 (28)	Mean 68.60 (SD 10.60)	33.70 (12.10)	0	46	2	28 (1)	0	0	0	18 (1)
Soons et al. 2021, Netherlands [14]	Prospective single-center	48 (48)	19 (40)	Median 68.50 (55.3–73.0)	NR	48	0	7	16 (1)	0	11 (4)	0	17 (2)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; DB, delayed bleeding; NR, not reported; SD, standard deviation; RCT, randomized controlled trial.

▶ **Table 2** Modified Newcastle-Ottawa scale assessing quality of included non-randomized studies.

	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability	Assessment of outcome	Follow-up long enough for outcome to occur	Adequacy of follow-up	Quality score	Quality
Yoshida et al. 2014 [9]	[1]	NA	[1]	[1]	NA	[1]	[1]	[1]	6	High
Pioche et al. 2016 [10]	[1]	NA	[1]	[1]	NA	[1]	[1]	[1]	6	High
Uraoka et al. 2016 [11]	[1]	NA	[1]	[1]	NA	[1]	[1]	[1]	6	High
Subramaniam et al. 2019 [12]	[1]	NA	[1]	[1]	NA	[1]	[1]	[1]	6	High
Soons et al. 2021 [14]	[1]	NA	[1]	[1]	NA	[1]	[1]	[1]	6	High

NA, not applicable.
[1] Indicates that the study meets criterion in the respective column. A score of 6 was considered high quality.

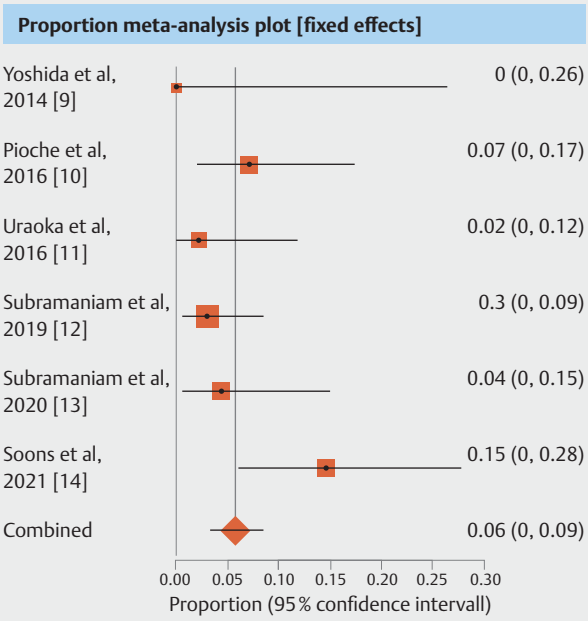


▶ **Fig. 1** Preferred Reporting Items for Systematic reviews and Meta-Analysis describing the details of the review process. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. doi: 10.1136/bmj.n71 For more information, visit: http://www.prisma-statement.org/

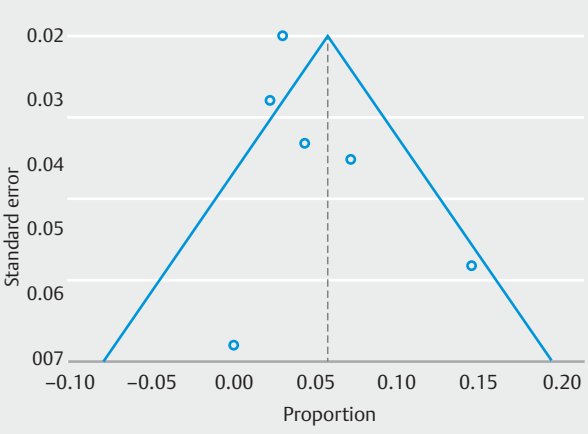
▶ **Table 3** Jadad Quality assessment tool for randomized control trial included in this meta-analysis.

	Subramaniam et al. 2020 [13]
Described as randomized[1]	1
Described as double-blinded[1]	0
Description of withdrawals[1]	1
Randomization method described and appro-priate[2]	1
Double blinding method described and appro-priate[2]	0
Total score	3

A total score of 3 or more indicates good quality trials
[1] A study receives a score of 1 for Yes and 0 for No.
[2] A study receives a score of 0 if no description is given, 1 if the method is described and appropriate, and – 1 if the method is described but inap-propriate.

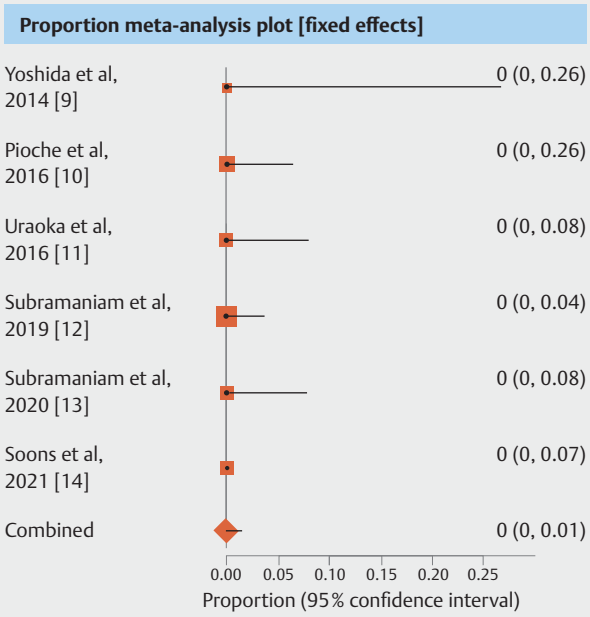


▶ **Fig. 2** Forest plot showing individual study rates and the pooled estimate for DB rate.

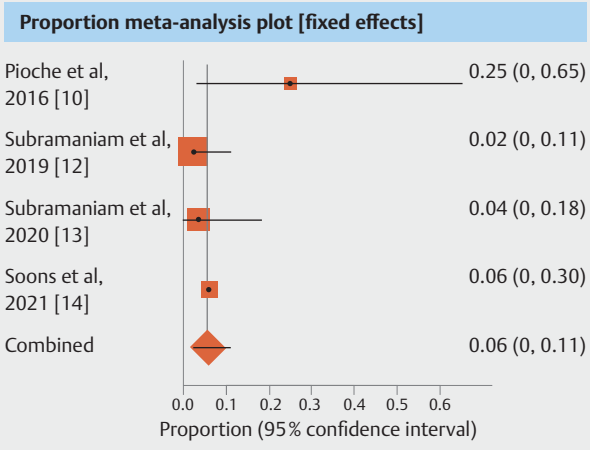


▶ **Fig. 3** Funnel plot of publication bias for DB rate.

phylactic SAP based on the location of ER and showed a pooled rate of 5.60 % for esophagus, 4.15 % for gastric, 10.60 % for duodenal, and 5.07 % for colorectal ERs. DB in the esophagus is considered rare, with reported rates between 0 % and 0.7 % [16, 17]. However, this can change considerably with periprocedure antithrombotic use or coexistent conditions such as severe liver disease. Horie et al. evaluated the role of antithrombotic drug use on DB after ER of esophageal lesions [20]. They found that the post-ER bleeding rate was 0.3 % in the group without antithrombotic drug use, consistent with prior reported rates. DB rates were 4.5 % in the aspirin-continued group and 2.9 % in the aspirin-discontinued group. However, in the group of individuals on direct oral anticoagulants, the DB rates were much higher at 13 % [20]. Hence the rate of DB in esophageal ER can

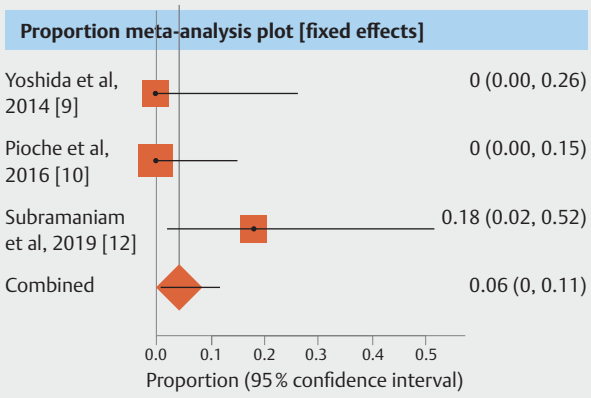


▶ **Fig. 4** Forest plot showing individual study rates and the pooled estimate for adverse event rate.

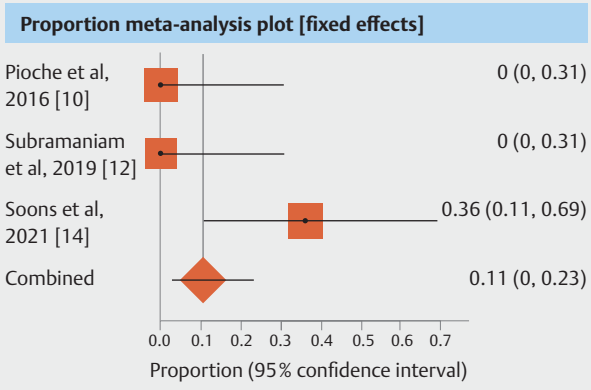


▶ **Fig. 5** Forest plot showing the individual study rates and the pooled estimate of DB in the esophagus.

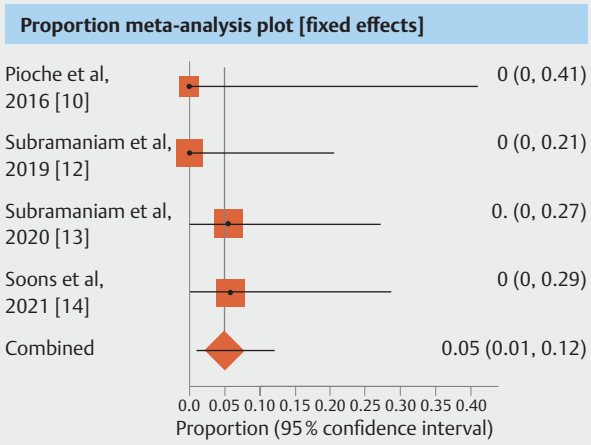
vary widely (0.3%–13%) depending on periprocedure antithrombotic use. Similarly, in a large nationwide multicenter study evaluating perioperative management of antiplatelet agents and the risk of post-ESD bleeding in early gastric cancer, Miura et al. reported that among aspirin users, the continuation group experienced significant post-ESD bleeding [21]. The rate of post-ESD bleeding was approximately 10% to 20%, irrespective of the status of antiplatelet agent administration among dual antiplatelet therapy users in this study [21]. Other studies have reported DB rates after gastric ESDs to be between 4% and 9% [22–24]. There is wide variability in the reported



▶ **Fig. 6** Forest plot showing the individual study rates and the pooled estimate of DB in the stomach.



▶ **Fig. 7** Forest plot showing the individual study rates and the pooled estimate of DB in the duodenum.



▶ **Fig. 8** Forest plot showing the individual study rates and the pooled estimate of DB in the colorectum.

rates of DB following colonic EMRs and colonic ESDs that depend on various factors. Cold snare polypectomy is the recommended ER technique for small colon polyps (< 10 mm). Studies that evaluated the role of EMR for these small colon polyps have reported very low rates of clinically significant delayed post-procedure bleeding rates of around 0.5 % [25]. However, this increases to about 6 % to 7 % with larger polyps and approximately 10 % for polyps > 2 cm in the proximal colon [26–28]. Delayed post-procedure bleeding following colorectal ESDs has been reported to be between 1 % to 5 % in previously reported studies [29–32]. However, most of these studies included only a few patients on antithrombotic medications, while others included patients who were treated prophylactically with hemostatic clips. In a multicenter study evaluating the effect of anticoagulants on DB after colorectal ESDs, Ogiyama et al. described a DB rate of 17.2 % [33]. Duodenal ERs are considered the highest risk for DB, with reported rates of up to 20 % [18, 19]. In their single-center prospective cohort study of 48 patients who all underwent EMR, Soons et al. observed a DB rate of 15.70 % despite prophylactic SAP, which was higher than those reported in other studies [14]. As the authors of this study pointed out, this could have been due to the higher proportion of patients actively on antithrombotic medications at the time of ER, which is not the standard practice. Other observations were the increased proportion of duodenal EMRs in this study and its inherent increased risk for DB [18, 19]. This study also had patients with larger mean lesion size, a known risk factor for DB.

The results of previous studies on SAP and the findings of this meta-analysis support the use of this novel agent in the prophylaxis of DB after advanced ER. With the advancement of ER techniques, various modalities have been evaluated in mitigating the risk of DB. These include the use of prophylactic clipping, coagulation, fibrin glue, and the use of topical polysaccharide hemostats. However, results with these have been suboptimal and varied. No significant reduction in the risk of DB was observed in a meta-analysis evaluating prophylactic clipping for colorectal ESDs [5]. Similarly, no significant difference in DB was observed with prophylactic endoscopic coagulation after wide-field EMR of large sessile colon polyps [34]. A recent RCT of fibrin glue failed to show a preventive effect on overall post-ESD bleeding in high-risk patients undergoing gastric ESDs [15].

This meta-analysis had studies that included a significant proportion of patients on antithrombotic medications (36 %) and patients with other predictors of DB, such as advanced liver disease. For example, in the study by Pioche et al., post-ESD bleeding was observed in a patient with known cirrhosis and esophageal varices. A lesion size > 30 mm is another well-recognized predictor of DB [2]. The pooled mean size of resected lesions in this meta-analysis was about 36 mm and, hence, is representative of lesions at increased risk for DB due to size. Based on these observations, this study is a pragmatic, real-world representation of patients at increased risk for DB after advanced ER of gastrointestinal lesions. Another common observation made by the authors of all the studies included in this meta-analysis was the transparent nature of the SAP agent, which allows visibility for ongoing resections, and the lack of alteration of the resection base. These properties of SAP offer a distinct advantage for "real-time use" during complex resections such as ESD compared to closure devices or coagulation. SAP as a hemostatic is not limited to ER of gastrointestinal luminal lesions. There have also been studies evaluating the utility of SAP as a hemostatic across other indications like cardiac and aortic surgeries [35], liver surgeries [36] and functional endoscopic sinus surgery [37]. These further emphasize the evolving role of this novel agent in the area of hemostasis. To our knowledge, this is the first systematic review and meta-analysis evaluating the efficacy of SAP in reducing the risk of DB after advanced ER of gastrointestinal luminal lesions.

There are a few limitations to this study. All the studies available had relatively small sample sizes, with the largest study having 100 patients. The definition of DB varied slightly across the studies, which could impart some heterogeneity in the reported results. However, this was thoroughly reviewed by the authors to ensure the consistency of the data analyzed. All of the studies included in this meta-analysis were conducted in Europe and Asia with different demographic profiles, in high-volume centers, and were done by experts. Caution must be exercised in interpreting their results when considering a different demographic profile and proceduralist experience. Given the results of this study and some of the proposed benefits such as ease of application, augmented wound healing, and the advantages of being transparent, this novel SAP solution could have a promising role in the management of post-ER bleeding. More extensive well-designed prospective RCTs are needed to establish its true efficacy and potential indications.

Conclusions

The use of a novel SAP solution appears to be promising in reducing the incidence of post-procedural DB after advanced ER of high-risk gastrointestinal lesions with no reported AEs.

Competing interests

Dr. Sharma is a consultant for Boston Scientific, Medtronic, Steris, and Olympus.

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