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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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REVIEW

Anticoagulation and antiplatelet management in gastrointestinal endoscopy: A review of current evidence

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Abstract

The role of endoscopic procedures, in both diagnostic and therapeutic purposes is continually expanding and evolving rapidly. In this context, endoscopists will encounter patients prescribed on anticoagulant and antiplatelet medications frequently. This poses an increased risk of intraprocedural and delayed gastrointestinal bleeding. Thus, there is now greater importance on optimal pre, peri and post-operative management of anticoagulant and/or antiplatelet therapy to minimise the risk of post-procedural bleeding, without increasing the risk of a thromboembolic event as a consequence of therapy interruption. Currently, there are position statements and guidelines from the major gastroenterology societies. These are available to assist endoscopists with an evidenced-based systematic approach to anticoagulant and/or antiplatelet management in endoscopic procedures, to ensure optimal patient safety. However, since the publication of these guidelines, there is emerging evidence not previously considered in the recommendations that may warrant changes to our current clinical practices. Most notably and divergent from current position statements, is a growing concern regarding the use of heparin bridging therapy during warfarin cessation and its associated risk of increased bleeding, suggestive that this practice should be avoided. In addition, there is emerging evidence that anticoagulant and/or antiplatelet therapy may be safe to be continued in cold snare polypectomy for small polyps (< 10 mm).

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Core Tip: The current position statements and guidelines from the major gastroenterology societies have provided endoscopists with an evidenced-based systematic approach to pre, peri and post-operative management of patients on anticoagulant and/or antiplatelet therapy, in the context of both low and high-risk endoscopic procedures. While there is sufficient evidence on the index bleeding risk for common endoscopic procedures in the absence of anticoagulant and/or antiplatelet use, the evidence surrounding the bleeding risk on anticoagulant and/or antiplatelet therapy is variable among different publications and is still evolving. In this review, we have summarised the available evidence, provided an overview, and described our recommended practical approach to anticoagulant and/or antiplatelet management in common endoscopic procedures. Finally, we have compared our recommendations against the current guidelines from the major gastroenterology societies to assimilate a new working reference, and to highlight any knowledge gaps and directions for future research.

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INTRODUCTION

Contemporary management of patients with atrial fibrillation (AF), venous thromboembolism (VTE) and acute coronary syndromes (ACS) requires the use of an expanding range of anticoagulant and antiplatelet agents. Similarly, the type and range of endoscopic procedures has evolved rapidly, and screening for neoplasia has increased the frequency of procedures per se. In this context, endoscopists will encounter patients prescribed on anticoagulant and antiplatelet medications frequently, and thus an informed and systematic approach to pre, peri and post-operative management is of great importance.

The major risk of anticoagulant and antiplatelet therapy is gastrointestinal bleeding, especially within the first 30 d following an endoscopic procedure[1]. Optimal management involves minimising the risk of post-procedural bleeding (PPB) on one hand, without significantly increasing the risk of a thromboembolic event on the other. Thromboembolic events [including stroke, myocardial infarction (MI) or pulmonary embolism] often have serious, irreversible consequences compared to gastrointestinal bleeding, which if detected early and managed appropriately is of minor consequence. The old wisdom that the brain or heart cannot be replaced, whilst blood or fluid can be readily transfused holds true.

In recent years, a wealth of literature relating to anticoagulant and antiplatelet use has emerged, including a number of position statements and guidelines from the major gastroenterology societies in Europe, the United States of America and Asia. These documents, along with the research studies from which they are based, should logically form the basis of future recommendations. The purpose of this review therefore is to firstly evaluate the index bleeding risk associated with common endoscopic procedures in the absence of anticoagulant and/or antiplatelet use. We then aim to consider the major research studies relating to anticoagulant and antiplatelet use in this context, and to compare the available evidence against the relevant major guidelines mentioned, to assimilate a new working reference, and to highlight any knowledge gaps and directions for future research.

SEARCH STRATEGY

We performed a structured literature review using Ovid Medline, considering articles from January 1, 2011 to January 1, 2020, with the intention of identifying relevant

research potentially not included in recent guidelines[2-4]. Medical Subject Headings (Supplementary material) were formulated relating to the anticoagulant and antiplatelet agents of interest [aspirin, thienopyridine (clopidogrel, prasugrel, ticagrelor), warfarin, direct oral anticoagulants (DOACs) (dabigatran, rivaroxaban, apixaban), heparin bridging therapy (HBT)], all relevant endoscopic procedures, and "bleeding" rates. Case reports, abstracts, commentaries, letters, and editorials were not considered. Relevant articles were retrieved and reviewed, with data tabulated (Tables 1-56)

COMMON ENDOSCOPIC PROCEDURES AND THE INDEX POST-PROCEDURE BLEEDING RISK IN THE ABSENCE OF ANTICOAGULANT AND/OR ANTIPLATELET USE

A summary of the relevant studies evaluating the index PPB risk for common endoscopic procedures, in the absence of anticoagulant and/or antiplatelet use, are outlined in Tables 1-16.

DIAGNOSTIC ENDOSCOPIC PROCEDURES

Diagnostic endoscopy and colonoscopy with biopsy (Table 1)

Endoscopic biopsy is a minimally invasive procedure that is commonly undertaken during diagnostic endoscopies and colonoscopies to diagnose a range of conditions (*e.g.*, neoplasia, coeliac disease, *Helicobacter pylori)*. The risk of PPB is low, ranging from 0.12%-0.98% in published studies[5-7].

Diagnostic ± therapeutic push or device assisted enteroscopy/balloon enteroscopy (Table 2)

Double balloon enteroscopy (DBE) allows for detailed and direct visualisation and assessment (diagnostic) of the small bowel and application of endoscopic intervention. The risk of PPB associated with DBE is 0.5%, but increases with therapeutic intervention[8,9]. The study by Wang *et al*[9] recorded seven episodes of PPB in 1531 DBEs (0.5%), with all associated with therapeutic polypectomy. There were no reported incidences of PPB in the studies for diagnostic-only DBE.

Endoscopic ultrasound ± fine needle aspiration (Table 3)

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) with a 22G FNA needle is the gold standard diagnostic tool for pancreatic and upper gastrointestinal tract lesions. A 22G FNA needle is generally preferred, but the procedure can also be performed with either 19G or 25G needles. The reported risk of PPB varies according to needle gauge, ranging from 2.1% with 25G needles to 4.3% with 22G needles[10-17]. Of note, both the study by Vilmann *et al*[13] and Inoue *et al*[17] observed an associated immediate/intraprocedural bleeding risk of 0.7%-1%. However, in both studies, the bleeding was self-limited and did not require any further endoscopic intervention.

Published data on the use of 19G needles is more limited compared to the evidence available for both the 22G and 25G needles. A 19G needle is more rigid than its smaller gauge counterparts. This makes adequate positioning of the endoscope and manipulation technically more difficult[18]. However, successful use of 19G needles has been shown to yield superior diagnostic accuracy and better diagnostic tissue acquisition compared to the 22G and 25G needles[18,19]. There were no reported incidences of PPB in any of the studies[18-20], although two studies observed an associated immediate/intraprocedural bleeding risk of 1.0%-1.8%[19,20] with 19G needle use.

Endoscopic retrograde cholangiopancreatography (diagnostic) (Table 4)

With advancements in imaging modalities, such as magnetic resonance cholangiopancreatography (MRCP), the role for diagnostic only endoscopic retrograde cholangiopancreatography (ERCP) is rare. ERCP is now predominantly considered an interventional procedure (endoscopic sphincterotomy, papillotomy, biliary stone removal and insertion of biliary stents). Diagnostic ERCP rarely causes PPB with a rate of 0.3%-1.66% reported[21-25].

In all of the studies, PPB was most commonly observed in diagnostic ERCP when

Table 1 Diagnostic endoscopy and colonoscopy with biopsy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Fujita *et al*[5]	2015	Japan	Retrospective	3671	Endoscopic biopsy	No medications	Incidence of PPB 0.98%
Ara *et al*[6]	2015	Japan	Prospective	3758	Endoscopic biopsy	No medications	Incidence of PPB 0.12%
Yuki *et al*[7]	2017	Japan	Prospective	263	Endoscopic biopsy	No medications	No incidence of PPB

PPB: Post-procedural bleeding.

Table 2 Diagnostic ± therapeutic push or device assisted enteroscopy/balloon enteroscopy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Yamamoto *et al*[8]	2015	Japan	Prospective	120	DBE	No medications	No incidence of PPB
Wang *et al*[9]	2020	Japan	Retrospective	1531	DBE	No medications	Incidence of PPB 0.5%

DBE: Double balloon enteroscopy; PPB: Post-procedural bleeding.

Table 3 Endoscopic ultrasound ± fine needle aspiration

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Song *et al*[18]	2010	South Korea	Prospective	117	EUS + FNA	No medications	No incidence of PPB
Uehara *et al*[10]	2011	Japan	Retrospective	115	EUS + FNA	No medications	No incidence of PPB
Suzuki *et al*[11]	2012	United States	Prospective	20	EUS + FNA	No medications	No incidence of PPB
Lee *et al*[12]	2013	South Korea	Prospective	188	EUS + FNA	No medications	Incidence of PPB 2.1% (25G group). Incidence of PPB 4.3% (22G group)
Vilmann *et al*[13]	2013	Denmark	Prospective	135	EUS - FNA	No medications	No incidence of PPB
Yang *et al*[14]	2015	South Korea	Retrospective	76	EUS + FNA	No medications	No incidence of PPB
Mavrogenis *et al*[15]	2015	United States	Prospective	28	EUS + FNA	No medications	No incidence of PPB
Ramesh *et al*[19]	2015	South Korea	Prospective	100	EUS + FNA	No medications	No incidence of PPB. Incidence of immediate/intraprocedural bleeding 1.0%
Park *et al*[16]	2016	Denmark	Prospective	56	EUS + FNA	No medications	No incidence of PPB
Inoue *et al*[17]	2017	Japan	Retrospective	742	EUS + FNA	No medications	No incidence of PPB
Iwashita *et al*[20]	2018	South Korea	Prospective	110	EUS + FNA	No medications	No incidence of PPB. Incidence of immediate/intraprocedural bleeding 1.8%

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; PPB: Post-procedural bleeding.

sphincterotomy was required to obtain better access. Sphincterotomy is associated with an up to five-fold increased risk of PPB[21,23-25] and will be discussed further in the "ERCP with sphincterotomy" section (Table 9).

Table 4 Endoscopic retrograde cholangiopancreatography (diagnostic)

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Masci *et al*[21]	2001	Italy	Prospective	782	ERCP (diagnostic)	No medications	Incidence of PPB 1.13%
Williams *et al*[22]	2007	United Kingdom	Prospective	5264	ERCP (diagnostic)	No medications	Incidence of PPB 0.9%
Cotton *et al*[23]	2009	United States	Retrospective	11497	ERCP (diagnostic)	No medications	Incidence of PPB 0.3%
Coelho-Prabhu *et al*[24]	2013	United States	Retrospective	1072	ERCP (diagnostic)	No medications	Incidence of PPB 1.4%
Rotundo *et al*[25]	2020	United States	Retrospective	555	ERCP (diagnostic)	No medications	Incidence of PPB 1.66% (teaching hospital). Incidence of PPB 1.49% (nonteaching hospital)

ERCP: Endoscopic retrograde cholangiopancreatography; PPB: Post-procedural bleeding.

THERAPEUTIC ENDOSCOPIC PROCEDURES

Conventional polypectomy/hot snare polypectomy (Table 5)

Conventional polypectomy, also referred to as hot snare polypectomy (HSP), uses electrosurgical current through a polypectomy snare and is the standard practice for polyp resection and prevention of colorectal cancer. It has been associated with a colorectal cancer mortality reduction over 30 years. Numerous published studies have identified the overall risk of PPB post conventional polypectomy to be around 0.05%-3.0%[26-42]. Larger polyp sizes (> 10 mm), polyps located in caecum and ascending colon, and pedunculated polyps are all associated with an additional increased risk of overall PPB[33,36,41,43].

Cold snare polypectomy and endoscopic mucosal resection (Tables 6 and 7)

Aside from conventional polypectomy (HSP), other polypectomy techniques are often utilised, specifically cold snare polypectomy (CSP) and endoscopic mucosal resection (EMR). The chosen method is often dependent on polyp characteristics. Hot biopsy forceps (HBF) are insulated monopolar electrocoagulating forceps, allowing for biopsy and electrocoagulating tissue simultaneously[44]. HBF were previously used for polypectomy of diminutive polyps, but have since fallen out of favour due to its poorer *en-bloc* resection rate, and increased rate of significant injury to the pathology tissue compared to CSP[45]. HBF was not a focus for this review and will not be discussed further given it is no longer commonly practiced.

The European Society of Gastrointestinal Endoscopy (ESGE) clinical guidelines[46] recommends the use of CSP technique for removal of diminutive polyps ≤ 5mm and sessile polyps 6-9 mm in size because of its superior safety profile. Studies have shown that CSP is superior to HSP in resection of polyps ≤ 10 mm, with a shorter procedure time[27] and no statistically significant difference in complete resection rate[27,39], or delayed bleeding rates[27,37-40]. The risk of delayed PPB in CSP is shown to be very low with no incidences (0%) observed in any of the studies[27,37-39,47,48]. This is comparable to HSP with an incidence rate of 0%-0.5% for polyps ≤ 10 mm[27,37-40]. However, there is an increased risk of immediate/intraprocedural PPB in CSP for small polyps (< 10 mm), with three studies[27,39,48] showing an intraprocedural bleeding rate of 2.7%-9.1%, compared to 1%-3.5% in HSP[27,39].

Conventionally, HSP (for polyps > 10 mm in size) and EMR (for polyps > 20 mm in size, particularly if sessile) have been the standard of care in the removal of these larger polyps, as it is considered more efficacious in minimising the risk of intraprocedural bleeding. The ESGE clinical guideline on colorectal polypectomy and EMR[46] still recommends HSP as the preferred technique for polyps 10-19 mm in size and EMR for polyps ≥ 20 mm. This is due to its ability to cauterise the resected tissue, while also providing additional ablation to the residual tissue, promoting complete haemostasis[40]. The risk of intraprocedural and delayed PPB with EMR in polyps < 10 mm is 1.7%[48] and 0%-1.7%[48,49], respectively. Risk of delayed PPB is higher with increasing polyp size. So *et al*[50] found an incidence of 6.3% in polyps with a mean size of 34 mm.

Recent publications suggest that HSP carries a higher risk of both PPB and

Table 5 Conventional polypectomy/hot snare polypectomy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Gupta *et al*[26]	2012	United Kingdom	Prospective	1200	Polypectomy	No medications	Incidence of PPB 0.67%
Paspatis *et al*[27]	2011	Greece	Prospective	18	Polypectomy	No medications	No incidence of PPB
Singh *et al*[28]	2010	United States	Retrospective	1243	Polypectomy	No medications	Incidence of PPB 1%
Sewitch *et al*[29]	2012	Canada	Prospective	2134	Polypectomy	No medications	Incidence of PPB 0.05%
Feagins *et al*[30]	2011	United States	Retrospective	1849	Polypectomy	No medications	Incidence of PPB 0.32%
Pan *et al*[31]	2012	New Zealand	Retrospective	348	Polypectomy	No medications	Incidence of PPB 0.86%
Manocha *et al*[32]	2012	United States	Retrospective	672	Polypectomy	No medications	Incidence of PPB 3.0%
Kim *et al*[33]	2013	South Korea	Retrospective	7447	Polypectomy	No medications	Incidence of PPB 1.3%
Gavin *et al*[34]	2013	United States	Prospective	20085	Polypectomy	No medications	Incidence of PPB 0.26%
Rutter *et al*[35]	2014	United Kingdom	Retrospective	167208	Polypectomy	No medications	Incidence of PPB 0.65%
Choung *et al*[36]	2014	South Korea	Retrospective	5981	Polypectomy	No medications	Incidence of PPB 1.1%
Gómez *et al*[37]	2015	United States	Prospective	18	Polypectomy	No medications	No incidence of PPB
Suzuki *et al*[38]	2018	Japan	Prospective	27	Polypectomy	No medications	No incidence of PPB. Incidence of immediate/intraprocedural bleeding 3.5%
Kawamura *et al*[39]	2018	Japan	Prospective	402	Polypectomy	No medications	Incidence of PPB 0.5%
Ket *et al*[40]	2020	Australia	Retrospective	258	Polypectomy	No medications	Incidence of PPB 3.5%
Kishida *et al*[41]	2019	Japan	Retrospective	5381	Polypectomy	No medications	Incidence of PPB 0.7%

PPB: Post-procedural bleeding.

perforation compared to CSP in polyps > 10 mm, likely due to the thermal injury of the intestinal wall. A study of resection specimens indicates that the increased risk of delayed bleeding was due to more extensive arterial injury in the submucosal, deep submucosa and muscularis propria layers caused by HSP[40]. In contrast, the removal of polyps > 10 mm by CSP does not cause PPB, with no evidence of bleeding in six studies[40,51-55]. The study by Hirose *et al*[54] reported one case of delayed PPB, but this patient was on warfarin for AF and so was not included in the final analysis. This is compared to a delayed PPB incidence rate of 3.5%, as published in a study by Ket *et al*[40] in the removal of polyps > 10 mm by HSP.

There was limited published data on the time to PPB in patients undergoing HSP in the available studies. The study by Ket *et al*[40] reported the time to PPB in their patient cohort to be between 2 to 7 d post endoscopic procedure. While, the study by Sewitch *et al*[29] had only one complication of PPB (0.05%) which occurred 3 wk post polypectomy. However, this was thought to be more likely in the setting of follow-up treatment rather than the index colonoscopy. A potential limitation is the majority of the studies were retrospective studies, which may have missed subsequent bleeds due to an inadequate follow-up period post procedure.

Endoscopic submucosal dissection (Table 8)

The practice of endoscopic submucosal dissection (ESD) is often required for the

Table 6 Cold snare polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Paspatis *et al*[27]	2011	Greece	Prospective	530	Polyp size 3-8 mm	CSP	No medications	No incidence of PPB. Incidence of immediate/intraprocedural bleeding 9.1%
Ichise *et al*[44]	2011	Japan	Prospective	101	Polyp size < 8 mm	CSP	No medications	No incidence of PPB
Gómez *et al*[37]	2015	United States	Prospective	21	Polyp size < 6 mm	CSP	No medications	No incidence of PPB
Choksi *et al*[51]	2015	United States	Retrospective	15	Polyp size ≥ 10 mm	CSP	No medications	No incidence of PPB
Muniraj *et al*[52]	2015	United States	Retrospective	12	Polyp size ≥ 10 mm	CSP	No medications	No incidence of PPB
Piraka *et al*[53]	2017	United States	Retrospective	94	Polyp size ≥ 10 mm	CSP	No medications	No incidence of PPB
Hirose *et al*[54]	2017	Japan	Retrospective	125	Polyp size ≥ 10 mm	CSP	No medications	No incidence of PPB
Tutticci *et al*[55]	2018	Australia	Prospective	163	Polyp size ≥ 10 mm	CSP	No medications	No incidence of PPB
Zhang *et al*[48]	2018	China	Prospective	212	Polyp size 6-9 mm	CSP	No medications	No incidence of PPB. Incidence of immediate/intraprocedural bleeding 2.7%
Suzuki *et al*[38]	2018	Japan	Prospective	25	Polyp size ≤ 10 mm	CSP	No medications	No incidence of PPB
Kawamura *et al*[39]	2018	Japan	Prospective	394	Polyp size 4-9 mm	CSP	No medications	No incidence of PPB. Incidence of immediate/intraprocedural bleeding 7.1%
Ket *et al*[40]	2020	Australia	Retrospective	346	Polyp size 10-20 mm	CSP	No medications	No incidence of PPB

CSP: Cold snare polypectomy; PPB: Post-procedural bleeding.

Table 7 Endoscopic mucosal resection

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Zhang *et al*[48]	2018	China	Prospective	203	Polyp size 6-9 mm	EMR	No medications	No incidence of PPB. Incidence of immediate/intraprocedural bleeding 1.7%
So *et al*[50]	2019	South Korea	Retrospective	798	Mean polyp size 34 mm	EMR	No medications	Incidence of PPB 6.3%
Kim *et al*[49]	2019	South Korea	Retrospective	717	Polyp size ≥ 6 mm to < 20 mm	EMR	No medications	Incidence of PPB 1.7%

EMR: Endoscopic mucosal resection; PPB: Post-procedural bleeding.

resection of large gastrointestinal lesions *en bloc*, and (compared to CSP and EMR) is associated with a significantly higher risk of PPB between 2.7% to 6.6%[56-63] irrespective of the location of the lesion. This increased risk also translates to a higher risk of immediate/intraprocedural bleeding, reportedly 6.1% in a study by Chen *et al*[63].

ERCP with sphincterotomy (Table 9)

Endoscopic sphincterotomy has now become a standard intervention during ERCP for therapy of pancreaticobiliary diseases, but is commonly associated with complications of PPB. The risk of bleeding post ERCP with sphincterotomy is between 0.45%-9.9%[21,64-71]. Timing of bleeding varied between studies, with Bae *et al*[69] finding the majority of their cases [95 out 108 patients (88.0%)] were from immediate/intraprocedural bleeding. Similarly, Masci *et al*[21] observed a higher occurrence of immediate/ intraprocedural bleeding of 1.1%, compared to only a 0.7% rate of delayed PPB. This is in contrast to the findings from Patai *et al*[66], which found a higher

Table 8 Endoscopic submucosal dissection

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Igarashi *et al*[56]	2017	Japan	Retrospective	722	Gastric ESD	No medications	Incidence of PPB 4.2%
Sato *et al*[57]	2017	Japan	Retrospective	2488	Gastric ESD	No medications	Incidence of PPB 3.9%
Kono *et al*[58]	2018	Japan	Retrospective	814	Gastric ESD	No medications	Incidence of PPB 5.3%
Arimoto *et al*[59]	2018	Japan	Retrospective	783	Colorectal ESD	No medications	Incidence of PPB 3.3%
Yamashita *et al*[60]	2018	Japan	Retrospective	698	Colorectal ESD	No medications	Incidence of PPB 2.7%
Harada *et al*[61]	2020	Japan	Retrospective	286	Colorectal ESD	No medications	Incidence of PPB 6.6%
Manta *et al*[62]	2020	Italy	Retrospective	296	Gastric ESD	No medications	Incidence of PPB 10.1%
Chen *et al*[63]	2020	China	Retrospective	82	Gastric ESD	No medications	Incidence of PPB 3.7%

ESD: Endoscopic submucosal dissection; PPB: Post-procedural bleeding.

Table 9 Endoscopic retrograde cholangiopancreatography with sphincterotomy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Freeman *et al*[64]	1996	United States and Canada	Prospective	2347	ERCP + sphincterotomy	No medications	Incidence of PPB 2%
Masci *et al*[21]	2001	Italy	Prospective	1662	ERCP + sphincterotomy	No medications	Incidence of PPB 0.7%. Incidence of immediate PPB 1.1%
Tzovaras *et al*[65]	2012	Greece	Prospective	50	ERCP + sphincterotomy	No medications	Incidence of PPB 2%
Patai *et al*[66]	2014	Hungary	Prospective	242	ERCP + sphincterotomy	No medications	Incidence of delayed PPB 6.3%. Incidence of immediate/intraprocedural bleeding 2.7%
Tanaka *et al*[67]	2015	Japan	Prospective	360	ERCP + sphincterotomy	No medications	Incidence of PPB 9.9%
Ikarashi *et al*[68]	2017	Japan	Retrospective	816	ERCP + sphincterotomy	No medications	Incidence of PPB 2.2%
Bae *et al*[69]	2019	South Korea	Retrospective	1121	ERCP + sphincterotomy	No medications	Incidence of delayed PPB 1.2%. Incidence of immediate/intraprocedural PPB 8.5%
Lima *et al*[70]	2020	Brazil	Prospective	2137	ERCP + sphincterotomy	No medications	Incidence of PPB 2.2%
Yan *et al*[71]	2020	China	Retrospective	8477	ERCP + sphincterotomy	No medications	Incidence of PPB 1.6%

ERCP: Endoscopic retrograde cholangiopancreatography; PPB: Post-procedural bleeding.

occurrence of delayed PPB of 6.3%, compared to only a 2.7% rate of immediate/intraprocedural bleeding.

Ampullectomy (Table 10)

Endoscopic ampullectomy allows for a minimally invasive nonsurgical intervention option for the treatment of ampullary adenomas, however is associated with significant risk of PPB between 4.9% to 30%[72-79]. The considerably high incidence of PPB of 30% reported in the study by Hopper *et al*[72] was observed in resections of larger sized ampullary adenomas (between 40-60 mm). A limitation of this study was a small sample size of 10. Close monitoring post endoscopic ampullectomy is important.

Endoscopic dilatation (Table 11)

Endoscopic dilatation provides an alternative to surgical intervention, reducing morbidity and prolonging the surgery-free intervals, in patients with symptomatic gastrointestinal strictures. Data from patients with eosinophilic oesophagitis who required dilatation found that PPB was rare (0%-0.3%)[80-84].

Table 10 Ampullectomy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Hopper *et al*[72]	2010	Australia	Prospective	10	Ampullectomy	No medications	Incidence of PPB 30%
Harano *et al*[73]	2011	Japan	Retrospective	28	Ampullectomy	No medications	Incidence of PPB 18%
Patel *et al*[74]	2011	United States	Retrospective	38	Ampullectomy	No medications	Incidence of PPB 5.3%
Salmi *et al*[75]	2012	France	Prospective	61	Ampullectomy	No medications	Incidence of PPB 4.9%
Laleman *et al*[76]	2013	Belgium	Retrospective	91	Ampullectomy	No medications	Incidence of PPB 12.1%
Attila *et al*[77]	2018	Turkey	Retrospective	44	Ampullectomy	No medications	Incidence of PPB 6.8%
Van Der Wiel *et al*[78]	2019	Netherlands	Retrospective	87	Ampullectomy	No medications	Incidence of PPB 12.6%
Alali *et al*[79]	2020	Canada	Retrospective	103	Ampullectomy	No medications	Incidence of PPB 21.4%

PPB: Post-procedural bleeding.

Table 11 Endoscopic dilatation

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Schoepfer *et al*[80]	2010	United States	Prospective	207	Dilatation (EoE)	No medications	No incidence of PPB
Ally *et al*[81]	2013	United States	Retrospective	66	Dilatation (EoE)	No medications	No incidence of PPB
Jung *et al*[82]	2011	South Korea	Retrospective	293	Dilatation (EoE)	No medications	Incidence of PPB 0.3%
Dellon *et al*[83]	2010	United States	Retrospective	70	Dilatation (EoE)	No medications	No incidence of PPB

EoE: Eosinophilic oesophagitis; PPB: Post-procedural bleeding.

Table 12 Colonic stenting

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Meisner *et al*[85]	2011	Denmark	Prospective	439	Colonic stent	No medications	Incidence of PPB 0.5%
van Hooft *et al*[86]	2011	Netherlands	Prospective	47	Colonic stent	No medications	No incidence of PPB
Yoon *et al*[87]	2011	South Korea	Retrospective	373	Colonic stent	No medications	Incidence of PPB 0.3%
Gianotti *et al*[88]	2013	Italy	Prospective	81	Colonic stent	No medications	Incidence of PPB 3.7%

PPB: Post-procedural bleeding.

Table 13 Enteral stenting

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Costamagna *et al*[89]	2012	Italy	Prospective	202	Duodenal stent	No medications	Incidence of PPB 3%

PPB: Post-procedural bleeding.

Colonic, enteral, and oesophageal stenting (Tables 12-14)

Endoscopic placement of self-expandable metallic stent (SEMS), or other various types of stents, is commonly indicated in patients with gastrointestinal obstructive disease secondary to malignancy. It plays an important role in either temporary bridging to surgery, or palliative management in patients with incurable disease[85]. For endoscopic colonic SEMS placement, the risk of PPB is estimated to range from 0.3%-3.7% in several publications[85-88].

A study by Costamagna *et al*[89] reported a similar rate of PPB, compared to colonic stenting, of 3% post endoscopic duodenal stent insertion.

Table 14 Oesophageal stenting

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Oh *et al*[90]	2014	South Korea	Retrospective	1485	Oesophageal stent	No medications	Incidence of PPB 1.7%
Liu *et al*[91]	2016	China	Retrospective	519	Oesophageal stent	No medications	Incidence of PPB 10.4%

PPB: Post-procedural bleeding.

Table 15 Endoscopic cystogastrostromy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Varadarajulu *et al*[92]	2008	United States	Retrospective	20	ECG	No medications	No incidence of PPB
Melman *et al*[97]	2009	United States	Prospective	45	ECG	No medications	Incidence of PPB 4.4%
Johnson *et al*[93]	2009	United States	Retrospective	24	ECG	No medications	Incidence of PPB 8.3%
Varadarajulu *et al*[96]	2013	United States	Prospective	20	ECG	No medications	No incidence of PPB
Saul *et al*[94]	2016	United States	Retrospective	21	ECG	No medications	Incidence of PPB 9.5%
Saluja *et al*[95]	2019	India	Retrospective	35	ECG	No medications	Incidence of PPB 2.9%

ECG: Endoscopic cystogastrostomy; PPB: Post-procedural bleeding.

Table 16 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Singh *et al*[98]	2012	United States	Retrospective	1541	PEG	No medications	Incidence of PPB 2.7%
Lozoya-González *et al*[99]	2012	Mexico	Retrospective	40	PEG	No medications	No incidence of PPB

PEG: Percutaneous endoscopic gastrostomy; PPB: Post-procedural bleeding.

Table 17 Diagnostic endoscopy and colonoscopy with biopsy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Whitson *et al*[103]	2011	United States	Prospective	280	Endoscopic biopsy	Aspirin (continued)	Incidence of bleeding 0.4%
Ono *et al*[104]	2012	Japan	Prospective	101	Endoscopic biopsy	Aspirin (continued)	No Incidence of PPB
Ara *et al*[6]	2015	Japan	Prospective	3758	Endoscopic biopsy	Aspirin (continued)	No incidence of PPB
Fujita *et al*[5]	2015	Japan	Retrospective	105	Endoscopic biopsy	Aspirin (continued)	Incidence of PPB 0.95%
Yuki *et al*[7]	2017	Japan	Prospective	560	Endoscopic biopsy	Aspirin (continued)	No incidence of PPB
Kono *et al*[105]	2017	Japan	Prospective	221	Endoscopic biopsy	Aspirin (continued)	No incidence of PPB

PPB: Post-procedural bleeding.

However, oesophageal stent insertion for oesophageal obstruction has been reported to be associated with higher risk of PPB compared to both colonic and duodenal stenting, of 1.7%-10.4% in two retrospective studies[90,91]. Liu *et al*[91] defined massive PPB as bleeding that required > 3 units of packed red blood cells and which was complicated by haemorrhagic shock. Massive bleeding was observed in 54 out of 519 of their patients (10.4%) and was associated with fatality within 24 h. Independent risk factors contributing to an increased risk of bleeding (from highest to lowest risk) includes: The presence of accompanying tracheal stent insertion, previous history of radiotherapy and oesophageal fistulae[91].

Table 18 Endoscopic ultrasound ± fine needle aspiration

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Inoue *et al*[17]	2017	Japan	Retrospective	742	EUS + FNA	Aspirin either:(1) Continued (high-risk conditions); (2) Ceased 3 d before	No incidence of PPB
Kawakubo *et al*[106]	2018	Japan	Prospective	85	EUS + FNA	Aspirin(continued)	No incidence of PPB

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; PPB: Post-procedural bleeding.

Table 19 Polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Pan *et al*[31]	2012	New Zealand	Retrospective	145	Size: 2-40 mm (average size 9.6 mm)	Polypectomy	Aspirin (continued)	Incidence of PPB 5.5%
Manocha *et al*[32]	2012	United States	Retrospective	502	Size: 2-50 mm	Polypectomy	Aspirin (continued)	Incidence of PPB 3.2%
Park *et al*[43]	2018	South Korea	Prospective	3887	Size: < 10 mm and ≥ 10 mm	Polypectomy	Aspirin (ceased 5-7 d before and restarted 1 d after)	Incidence of PPB 3.4%
Lin *et al*[107]	2018	United States	Retrospective	20374	Size: < 20 mm and ≥ 20 mm	Polypectomy	Aspirin (continuation or cessation N/S)	Incidence of PPB 0.92%
Kishida *et al*[41]	2019	Japan	Retrospective	12876	Size: < 10 mm and ≥ 10 mm	Polypectomy	Aspirin either: (1) Ceased 3-5 d before (cases before 2012); (2) Continued (cases after 2012)	Incidence of PPB 0.6%
Amato *et al*[108]	2019	Italy	Prospective	1504	Size: ≥ 10 mm	Polypectomy	Aspirin (ceased up to 9 d before)	Incidence PPB 4.2%
Watanabe *et al*[109]	2020	Japan	Retrospective	1050	Size: < 10 mm and ≥ 10 mm	Polypectomy	Aspirin (continued)	Incidence of PPB 4.3%

PPB: Post-procedural bleeding; N/S: Not stated.

Table 20 Cold snare polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Makino *et al*[110]	2018	Japan	Prospective	33	Size: ≤ 10 mm	CSP	Aspirin (continued)	No incidence of PPB
Arimoto *et al*[111]	2019	Japan	Retrospective	501	Size: ≤ 10 mm	CSP	Aspirin (continued)	No incidence of PPB. Incidence of immediate/intraprocedural bleeding 9.8%
Won *et al*[112]	2019	South Korea	Prospective	43	Size: ≤ 10mm	CSP	Aspirin (continued)	No incidence of PPB. Incidence of immediate/intraprocedural bleeding 2.2%

CSP: Cold snare polypectomy; PPB: Post-procedural bleeding.

Endoscopic cystogastrostromy (Table 15)

Endoscopic drainage of contained pancreatic fluid collections (pseudocysts) as a result of acute or chronic pancreatitis, trauma or obstruction, is traditionally considered first-line management over surgical drainage[92-95]. Varadarajulu *et al*[96] reported no significant difference in outcomes of treatment success, complication rates, and need for re-intervention between endoscopic *vs* surgical drainage. Although there were significant benefits in the length of hospital stay post endoscopic cystogastrostomy [median stay of 2 d, compared to 6 d in the surgical group ($P < 0.001$)]. Endoscopic cystogastrostomy is however associated with a significant risk of PPB of between 2.9%-9.5%[92-97].

Table 21 Endoscopic mucosal resection

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Ono *et al*[113]	2019	Japan	Retrospective	1734	Size: Median size 8.5-9.5 ± 5 mm	EMR	Aspirin (continuation or ceased 3 d before)	Incidence of PPB per polyp resection 1.35% (P = 0.81) on antiplatelet therapy (study limited by not differentiating between aspirin *vs* thienopyridine)
So *et al*[50]	2019	South Korea	Retrospective	399	Size: Mean lesion size 34 mm	EMR	Aspirin (ceased day of procedure or 0-4 d before or ceased 5-7 d before or ceased 8-14 d before procedure)	Incidence of PBB 8.2% (either aspirin or thienopyridine monotherapy)
Albéniz *et al*[114]	2020	Spain	Prospective	1034	Size: ≥ 20 mm (mean size 30.5 mm)	EMR	Aspirin (cessation dependent on comorbidities)	Study expressed risk of PPB on antiplatelet monotherapy as OR: 2.51, 95%CI: 0.99-6.34, P < 0.001 (either aspirin or thienopyridine monotherapy)

OR: Odds ratio; EMR: Endoscopic mucosal resection; PPB: Post-procedural bleeding.

Table 22 Endoscopic submucosal dissection

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Igarashi *et al*[56]	2017	Japan	Retrospective	367	Gastric ESD	Aspirin (continued)	Incidence of PPB 12.1%
Furuhata *et al*[115]	2017	Japan	Retrospective	15	Gastric ESD	Aspirin (continued or ceased 3-5 d before)	Incidence of PPB 6.7%
Sato *et al*[57]	2017	Japan	Retrospective	211	Gastric ESD	Aspirin (continued)	Incidence of PPB 5.7%
Kono *et al*[58]	2018	Japan	Retrospective	23	Gastric ESD	Aspirin (continued)	Incidence of PPB 21.7%
Arimoto *et al*[59]	2018	Japan	Retrospective	26	Colorectal ESD	Aspirin (continued)	No incidence of PPB
Oh *et al*[116]	2018	South Korea	Retrospective	94	Gastric ESD	Aspirin either: (1) Ceased 0-4 d before; (2) Ceased 5-7 d before	Incidence of PPB 12.8%
Harada *et al*[117]	2019	Japan	Retrospective	56	Gastric ESD	Aspirin (continued)	Incidence of PPB 10.7%
Nam *et al*[118]	2019	South Korea	Retrospective	31	Gastric ESD	Aspirin (ceased 7 d before)	Incidence of PPB 22.6%
Horikawa *et al*[119]	2019	Japan	Retrospective	50	Gastric ESD	Aspirin (continued)	Incidence of PPB 2.0%

ESD: Endoscopic submucosal dissection; PPB: Post-procedural bleeding.

Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion (Table 16)

The endoscopic placement of percutaneous endoscopic gastrostomy (PEG)/percutaneous endoscopic jejunostomy (PEJ) has a PPB rate of 0%-2.7%[98,99].

COMMON ENDOSCOPIC PROCEDURES AND THE RISK OF POST-PROCEDURE BLEEDING ASSOCIATED WITH EACH ANTICOAGULANT AND ANTIPLATELET AGENT

A summary of the relevant studies evaluating the bleeding risk associated with each anticoagulant and antiplatelet agent for common endoscopic procedures is outlined in

Table 23 Endoscopic retrograde cholangiopancreatography with sphincterotomy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Onal *et al*[120]	2013	Turkey	Prospective	35	Sphincterotomy	Aspirin (within 24 h)	Incidence of PPB 10%
Patai *et al*[66]	2014	Hungary	Prospective	87	Sphincterotomy	Aspirin (continued)	Incidence of delayed PPB 5.8%. Incidence of immediate/intraprocedural bleeding 4.6%
Ikarashi *et al*[68]	2017	Japan	Retrospective	1113	Sphincterotomy	Aspirin (continued)	Incidence of PPB 1.8%
Oh *et al*[121]	2018	United States	Prospective	256	Sphincterotomy	Aspirin (continued)	Incidence of PPB 4.7%
Yamamiya *et al*[122]	2019	Japan	Retrospective	76	Sphincterotomy	Aspirin either: (1) Continued (low-risk conditions); (2) Ceased 3-5 d before (high-risk conditions)	No incidence of PPB in either continuous or cessation group

PPB: Post-procedural bleeding.

Table 24 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Richter *et al*[124]	2011	United States	Retrospective	990	PEG	Aspirin (continued)	Incidence of PPB: (1) ≤ 48 h post-PEG 2.2%; (2) > 48 h post-PEG 1.7%
Singh *et al*[98]	2012	United States	Retrospective	1541	PEG	Aspirin (continued)	Incidence of PPB 3.9%
Lozoya-González *et al*[99]	2012	Mexico	Retrospective	27	PEG	Aspirin (ceased 1-3 d before)	No incidence of PPB
Lee *et al*[123]	2013	South Korea	Retrospective	151	PEG	Aspirin (continued)	No incidence of PPB

PEG: Percutaneous endoscopic gastrostomy; PPB: Post-procedural bleeding.

Table 25 Diagnostic endoscopy and colonoscopy with biopsy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Whitson *et al*[103]	2011	United States	Prospective	350	Endoscopic biopsy	Thienopyridine (continued)	No incidence of PPB
Ono *et al*[104]	2012	Japan	Prospective	101	Endoscopic biopsy	Thienopyridine (continued)	No incidence of PPB
Ara *et al*[6]	2015	Japan	Prospective	3758	Endoscopic biopsy	Thienopyridine either: (1) Continued; (2) Ceased 5-7 d before	No incidence of PPB in either group
Fujita *et al*[5]	2015	Japan	Retrospective	28	Endoscopic biopsy	Thienopyridine (continued)	No incidence of PPB
Yuki *et al*[7]	2017	Japan	Prospective	560	Endoscopic biopsy	Thienopyridine (continued)	No incidence of PPB
Kono *et al*[105]	2017	Japan	Prospective	221	Endoscopic biopsy	Thienopyridine (continued)	No incidence of PPB

PPB: Post-procedural bleeding.

Tables 17-56.

ACETYLSALICYLIC ACID (ASPIRIN) MONOTHERAPY

Acetylsalicylic acid, also known as aspirin, acts by irreversibly inhibiting the cyclooxygenase 1 and 2 enzyme system, resulting in reduction of thromboxane A2 synthesis leading to inhibition of platelet aggregation[100].

Antiplatelet therapy, with aspirin, is first line for secondary prevention of ACS, non-cardioembolic ischaemic stroke and transient ischaemic attack (TIA). In a meta-analysis of randomised controlled trials (RCTs) of aspirin therapy for secondary MI and stroke prevention, there was a 34% reduction in non-fatal MI and a 25% reduction in non-fatal strokes when on long-term aspirin therapy[101].

Interruption of aspirin, in cases of elective endoscopic procedures, is associated with a three-fold increased risk of cardiovascular or cerebrovascular event, with 70% of events occurring within the first 7 to 10 d of withholding antiplatelets[102]. Therefore, withholding aspirin therapy needs to be carefully considered.

Diagnostic endoscopy and colonoscopy with biopsy (Table 17)

Continuing aspirin monotherapy in diagnostic endoscopies and colonoscopies with biopsy is associated with an overall low risk of PPB of 0.4%-0.95% from multiple published studies[5-7,103-105]. There is minimal additive risk in continuing aspirin, as the index bleeding risk in the absence of antiplatelet use is similar, between 0.12%-0.98% (Table 1).

Continuing aspirin without interruption is considered safe in diagnostic endoscopies and colonoscopies with biopsy for patients with indication for aspirin. This recommendation concurs with previous position statements.

EUS ± FNA (Table 18)

The risk of PPB in EUS ± FNA while on continuous aspirin is low. In two recent studies there were no reported incidences of PPB[17,106]. In the study by Inoue *et al*[17], aspirin monotherapy was either continued, in patients considered to be at high-risk of thromboembolism secondary to drug withdrawal, or withheld 3 d before the procedure. There were no incidences of PPB in either subgroup. However, one case of immediate/intraoperative bleeding occurred in the continued aspirin group (1.6%).

Continuing aspirin in EUS ± FNA is safe and recommended to avoid the risk of a thromboembolic event. This concurs with previous position statements.

Polypectomy (Table 19)

The risk of PPB following endoscopic polypectomy in patients on aspirin monotherapy has been considered by a number of groups who performed RCTs. Aspirin use is associated with a three- to six-fold increased relative risk of PPB post endoscopic polypectomy[31], although the absolute risk of PPB is overall still low at 0.6%-5.5%[31,32,41]. Three other studies assessed the risk of PPB when aspirin was withheld at least 3-7 d before the procedure and the associated risk of PPB as a result, was reported to be 0.6%-4.2%[41,43].

The risk of PPB on aspirin monotherapy, either when continued or withheld before the procedure, is overall low at 0.6%-5.5%[31,32,41,43,107-109] and has a similar absolute risk of bleeding in the absence of anticoagulant or antiplatelet use, of 0.05%-3.0% (Table 5). Thus, continuation in all cases is recommended. This concurs with previous position statements.

CSP (Table 20)

There is emerging evidence that aspirin monotherapy in CSP is safe and not associated with an increased risk of PPB. All three studies[110-112] observed no incidences of PPB when aspirin monotherapy was continued. However, two of the studies[111,112] did observe incidences of immediate/intraprocedural bleeding, of 2.2% in the study by Won *et al*[112] to 9.8% in the study by Arimoto *et al*[111]. However, the study by Arimoto *et al*[111] failed to quantify the percentage of immediate/intraprocedural PPB cases on continuous aspirin compared to thienopyridine therapy. Therefore, it is unclear the exact risk of immediate bleeding on aspirin monotherapy alone. Despite this, the reported absolute risk of immediate/intraprocedural bleeding on continued aspirin monotherapy is similar to the bleeding risk in the absence of anticoagulant or antiplatelet use (2.2%-9.8% *vs* 2.4%-9.1%, respectively) (Table 6).

Table 26 Endoscopic ultrasound ± fine needle aspiration

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Inoue *et al*[17]	2017	Japan	Retrospective	742	EUS + FNA	Thienopyridines (ceased 5 d before)	No incidence of PPB
Kawakubo *et al*[106]	2018	Japan	Prospective	30	EUS + FN	Thienopyridines (ceased 5 d before)	No incidence of PPB

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; PPB: Post-procedural bleeding.

Table 27 Polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Singh *et al*[28]	2010	United States	Retrospective	142	Size: < 5 mm or ≥ 10 mm	Polypectomy	Thienopyridine (continued)	Incidence of PPB 3.5%
Feagins *et al*[30]	2011	United States	Retrospective	118	Size: < 20 mm and > 20 mm (average 7 mm)	Polypectomy	Thienopyridine (continued)	No incidence of PPB
Feagins *et al*[125]	2013	United States	Prospective	219	Size: Average 5.2 mm	Polypectomy	Thienopyridine (continued)	Incidence of PPB 2.4%
Lin *et al*[107]	2018	United States	Retrospective	20374	Size: < 20 mm or ≥ 20 mm	Polypectomy	Thienopyridine (ceased 5-7 d before)	Incidence of PPB 0.84%
Kishida *et al*[41]	2019	Japan	Retrospective	12876	Size: < 10 mm or ≥ 10 mm	Polypectomy	Thienopyridine (ceased 5-7 d before)	Incidence of PPB 0.6%
Amato *et al*[108]	2019	Italy	Prospective	1648	Size: ≥ 10 mm	Polypectomy	Thienopyridine (ceased 6 d before)	Incidence of PPB 4.2%
Chan *et al*[126]	2019	China (Hong Kong)	Prospective	216	Size: < 10 mm or ≥ 10 mm (mean size 4.7 mm)	Polypectomy	Thienopyridine (continued)	Incidence of PPB 3.8%
Yu *et al*[127]	2019	United States	Retrospective	6443	N/S	Polypectomy	Thienopyridine (cessation timing N/S)	Incidence of PPB 0.9%
Watanabe *et al*[109]	2020	Japan	Retrospective	45	Size: < 10 mm or ≥ 10 mm	Polypectomy	Thienopyridine (cessation timing N/S)	Incidence of PPB 6.7%

N/S: Not stated; PPB: Post-procedural bleeding.

Table 28 Cold snare polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Makino *et al*[110]	2018	Japan	Prospective	24	Size: ≤ 10 mm	CSP	Thienopyridine (continued)	No incidence of PPB
Arimoto *et al*[111]	2019	Japan	Retrospective	516	Size: ≤ 10 mm	CSP	Thienopyridine (continued)	No incidence of PPB

CSP: Cold snare polypectomy; PPB: Post-procedural bleeding.

The bleeding risk with continued aspirin monotherapy is not shown to significantly increase the risk of bleeding, and continuation in all cases is recommended. This is in accordance with previous position statements.

EMR (Table 21)

Several studies have examined the effects of Aspirin monotherapy and the risk of PPB in EMR[50,113,114]. A study by Albéniz *et al*[114] prospectively assessed the incidence of PPB post EMR in patients who either continued aspirin monotherapy, or had it withheld before EMR. They found that antiplatelet use, either aspirin or thienopyridine monotherapy before EMR, is associated with a two-fold increased relative risk of PPB (OR, 2.51; 95%CI, 2.14-9.63, $P < 0.001$) in lesions ≥ 20 mm. However, the study was limited by not specifying the risk of PPB associated with aspirin monotherapy only.

Another study by So *et al*[50] observed a rate of PPB of 8.2% in EMR of polyps of mean size > 30 mm when on antiplatelet monotherapy. EMR in smaller polyps of < 10 mm was only associated with a 1.35% risk of PPB per polyp resection when on

Table 29 Endoscopic mucosal resection

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Ono *et al*[113]	2019	Japan	Retrospective	1734	Size: Median size 8.5-9.5 ± 5 mm	EMR	Thienopyridines (ceased 3-5 d before)	Incidence of PPB 1.35%
So *et al*[50]	2019	South Korea	Retrospective	399	Size: Mean lesion size 34 mm	EMR (and ESD)	Thienopyridines either: (1) Ceased day of procedure; (2) 0-4 d before; (3) Ceased 5-7 d before; (4) Ceased 8-14 d before	Incidence of PBB 8.2%
Albéniz *et al*[114]	2020	Spain	Prospective	1034	Size: ≥ 20 mm (mean size 30.5 mm)	EMR	Thienopyridines (ceased 5 d before)	Study expressed risk of PPB on antiplatelet monotherapy as OR: 2.51, 95%CI: 0.99-6.34, $P < 0.001$ (either aspirin or thienopyridine monotherapy)

OR: Odds ratio; EMR: Endoscopic mucosal resection; PPB: Post-procedural bleeding.

Table 30 Endoscopic submucosal dissection

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Igarashi *et al*[56]	2017	Japan	Retrospective	90	Gastric ESD	Thienopyridines either: (1) Continued until day of; (2) Ceased 3-7 d before	Incidence of PPB 5.6% (continued). Incidence of PPB 12.5% (ceased)
Ono *et al*[128]	2017	Japan	Prospective	10	Gastric ESD	Thienopyridines (continued)	Incidence of PPB 20%
Sato *et al*[57]	2017	Japan	Retrospective	19	Gastric ESD	Thienopyridines(ceased 5-7 d before)	No incidence of PPB
Oh *et al*[116]	2018	South Korea	Retrospective	56	Gastric ESD	Thienopyridines either: (1) Ceased 0-4 d before; (2) Ceased 5-7 d before	Incidence of PPB 3.6%
Nam *et al*[118]	2019	South Korea	Retrospective	31	Gastric ESD	Thienopyridines(ceased 7 d before)	Incidence of PPB 19.4%

ESD: Endoscopic submucosal dissection; PPB: Post-procedural bleeding.

Table 31 Endoscopic retrograde cholangiopancreatography with sphincterotomy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Patai *et al*[66]	2014	Hungary	Prospective	29	Sphincterotomy	Thienopyridine (continued)	Incidence of delayed PPB 3.5%. Incidence of immediate/intraprocedural bleeding 3.5%
Ikarashi *et al*[68]	2017	Japan	Retrospective	1113	Sphincterotomy	Thienopyridine (ceased 5-7 d before)	Incidence of delayed PPB 3.0%. (study categorised cessation of thienopyridine, warfarin and DOAC into the same "discontinuation" group)
Yamamiya *et al*[122]	2019	Japan	Retrospective	76	Sphincterotomy	Thienopyridine (either continued or ceased 5-7 d or switched to aspirin monotherapy before)	No incidence of PPB in either continuous or cessation group

PPB: Post-procedural bleeding; DOAC: Direct oral anticoagulant.

antiplatelet therapy (aspirin monotherapy either continued or withheld 3 d before) in the study by Ono *et al*[113]. Once again, both studies assessed the risk of PPB on either aspirin or thienopyridine monotherapy together and so did not specify the associated risk of aspirin monotherapy alone. Despite this, the risk of PPB is comparable to the absolute risk of bleeding in the absence of anticoagulant or antiplatelet use of respective size (1.35% *vs* 1.7% in polyps ≤ 10 mm and 8.2% *vs* 6.3% in polyps ≥ 20 mm,

Table 32 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Richter *et al*[124]	2011	United States	Retrospective	990	PEG	Thienopyridines(continued)	No incidence of PPB ≤ 48 h post-PEG. Incidence of PPB > 48 h post-PEG 4%
Singh *et al*[98]	2012	United States	Retrospective	143	PEG	Thienopyridines (ceased on average 2.2 d before)	Incidence of PPB 2.1%
Lozoya-González *et al*[99]	2012	Mexico	Retrospective	24	PEG	Thienopyridines (ceased 1-3 d before)	No incidence of PPB
Lee *et al*[123]	2013	South Korea	Retrospective	81	PEG	Thienopyridines (continued)	No incidence of PPB

PPB: Post-procedural bleeding; PEG: Percutaneous endoscopic gastrostomy.

Table 33 Diagnostic endoscopy and colonoscopy with biopsy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Ono *et al*[104]	2012	Japan	Prospective	101	Endoscopic biopsy	DAPT (continued)	No Incidence of PPB
Ara *et al*[6]	2015	Japan	Prospective	3758	Endoscopic biopsy	DAPT either: (1) Continued; (2) Ceased before	Incidence of PPB on DAPT (continued) 0.35%. No incidence of PPB with DAPT (cessation)
Yuki *et al*[7]	2017	Japan	Prospective	277	Endoscopic biopsy	DAPT (continued)	No incidence of PPB
Kono *et al*[105]	2017	Japan	Prospective	221	Endoscopic biopsy	DAPT (continued)	No incidence of PPB

DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

Table 34 Endoscopic ultrasound ± fine needle aspiration

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Kawakubo *et al*[106]	2018	Japan	Prospective	85	EUS + FNA (for solid lesions only). Pancreatic cysts excluded	DAPT (ceased thienopyridine 5 d before and bridged with aspirin monotherapy)	Incidence of PPB 3.6%

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

respectively) (Table 7).

The risk of PPB with aspirin use is comparable in EMR of polyps < 10 mm[113], but the absolute risk is significantly increased in larger polyp resections ≥ 20 mm[50,114]. Continuation of aspirin monotherapy is thus recommended in EMR (< 20 mm), but should be withheld 7 d before in EMRs (≥ 20 mm). This concurs with previous position statements.

ESD (Table 22)

Continued aspirin monotherapy is associated with a two-fold increased risk of PPB post ESD[58], with numerous published studies reporting the risk of bleeding to be 2.0%-22.6%[56,57,59,115-119]. This is a considerable increased absolute risk of PPB compared to the risk of bleeding in the absence of anticoagulant or antiplatelet use (2.0%-22.6% *vs* 2.7%-6.6%, respectively) (Table 8).

Given the high risk of PPB in ESD, it is recommended aspirin monotherapy should be withheld 7 d before ESD. This concurs with previous position statements.

ERCP with sphincterotomy (Table 23)

Aspirin monotherapy in ERCP with sphincterotomy is associated with an increased

Table 35 Polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Singh *et al*[28]	2010	United States	Retrospective	77	Size: < 5 mm to ≥ 10 mm	Polypectomy	DAPT (continued)	Incidence of delayed PPB 5.2%
Feagins *et al*[30]	2011	United States	Retrospective	118	Size: < 20 mm and > 20 mm	Polypectomy	DAPT (continued)	Incidence of PPB 0.85%
Kishida *et al*[41]	2019	Japan	Retrospective	6382	Size: < 10 mm or ≥ 10 mm	Polypectomy	DAPT either: (1) Ceased 7 d before (before 2012); (2) Bridged with aspirin monotherapy (after 2012)	Incidence of PPB 1.8%
Watanabe *et al*[109]	2020	Japan	Retrospective	50	Size: < 10 mm or ≥ 10 mm	Polypectomy	DAPT (various timing of agent continuation or switching strategies)	Incidence of PPB 6%

DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

Table 36 Cold snare polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Arimoto *et al*[111]	2019	Japan	Retrospective	516	Size: ≤ 10 mm	CSP	DAPT (continued)	No incidence of PPB
Won *et al*[112]	2019	South Korea	Prospective	91	Size: ≤ 10 mm	CSP	DAPT (continued)	Incidence of PPB 2.4%

CSP: Cold snare polypectomy; DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

Table 37 Endoscopic mucosal resection

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Ono *et al*[113]	2019	Japan	Retrospectively	825	Size: Median size ranged from 8.5-9.5 ± 5 mm	EMR	DAPT (thienopyridines ceased and aspirin monotherapy continued)	Incidence of PPB per polyp resection 1.35% (aspirin/thienopyridine/DAPT)
So *et al*[50]	2019	South Korea	Retrospective	399	Size: Mean lesion size 34 mm	EMR and ESD	DAPT (varying patterns of agent continuation or switching strategies)	Incidence of PPB 12.3%

EMR: Endoscopic mucosal resection; DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding; ESD: Endoscopic submucosal dissection.

risk of PPB of 1.8%-10%[66,68,120,121]. Three studies by Patai *et al*[66], Ikarashi *et al*[68], and Oh *et al*[121] continued aspirin and reported the risk of bleeding in their studies to be 5.8%, 1.8%, and 4.7%, respectively. However, the study by Onal *et al*[120] reported an incidence of PPB of 10.0% when aspirin monotherapy was given within the last 24 h. There were no reported incidences of PPB in the study by Yamamiya *et al*[122] in either the continued or withholding aspirin 3-5 d before group.

The absolute risk of PPB with continued aspirin use is increased compared to the absolute risk of bleeding in the absence of anticoagulant or antiplatelet use in ERCP with sphincterotomy (1.8%-10% *vs* 0.3%-1.66%, respectively) (Table 9). However, the absolute bleeding risk on continued aspirin is still overall low. Therefore, we recommend continuing aspirin monotherapy in ERCP with sphincterotomy, but caution is advised. This concurs with previous position statements.

PEG/ PEJ insertion (Table 24)

Aspirin use, whether continued or ceased before PEG/PEJ insertions, has not been shown to be associated with an increased risk of PPB. In two retrospective studies[99,123] there were no reported incidences of PPB when aspirin monotherapy was continued. However, two other studies[98,124] observed a bleeding rate of 1.7%-3.9%. The divergent results may be explained in part by case definition, where Singh *et al*[98] included GI bleeding from any source post PEG insertion (as opposed to bleeding confirmed as

Table 38 Endoscopic submucosal dissection

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Sato *et al*[57]	2017	Japan	Retrospective	75 (2378)	ESD	DAPT (ceased thienopyridine before and bridged with aspirin monotherapy)	Incidence of PPB 30.7%
Kono *et al*[58]	2018	Japan	Retrospective	6 (872)	ESD	DAPT (ceased thienopyridine 7 d before and bridged with aspirin monotherapy)	Incidence of PPB 67.7%
Oh *et al*[116]	2018	South Korea	Retrospective	51 (215)	ESD	DAPT either: (1) Ceased 5-7 d before (discontinuation group); (2) Ceased 0-4 d before (continuation group)	Incidence of delayed PPB 27.5% (14/51)
Harada *et al*[117]	2019	Japan	Retrospective	59 (597)	ESD	DAPT either: (1) Ceased thienopyridine 5 d before and bridged with aspirin monotherapy (high-risk conditions); (2) DAPT ceased > 5 d before (low-risk conditions)	Incidence of PPB 23.1% (aspirin monotherapy bridging). Incidence of PPB 5.0% (DAPT ceased)

ESD: Endoscopic submucosal dissection; DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

Table 39 Endoscopic retrograde cholangiopancreatography with sphincterotomy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Mok *et al*[130]	2017	United States	Prospective	50	Sphincterotomy	DAPT (continued)	Incidence of PPB 3.6%
Yamamiya *et al*[122]	2019	Japan	Retrospective	76	Sphincterotomy	DAPT either: (1) Continued; (2) Ceased 5-7 d. And switched to aspirin monotherapy before	No incidence of PPB in either continuous or cessation group

DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

Table 40 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Lee *et al*[123]	2013	South Korea	Retrospective	40 (1625)	PEG	DAPT (ceased 4 d before)	Incidence of PPB on DAPT 2.5%
Singh *et al*[98]	2012	United States	Retrospective	122 (1541)	PEG	DAPT	Incidence of PPB 2.5%
Lozoya-González *et al*[99]	2012	Mexico	Retrospective	91	PEG	DAPT (ceased 1-3 d before)	Incidence of PPB 0%

PEG: Percutaneous endoscopic gastrostomy; DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

caused by PEG insertion).

The absolute risk of PPB post PEG/PEJ insertion on continued aspirin monotherapy is comparable to the overall risk of bleeding in the absence of anticoagulant or antiplatelet use (1.7%-3.9% *vs* 2.7%, respectively) (Table 16). Thus, the overall bleeding risk is considered low and continuation of aspirin monotherapy in all cases is recommended. This concurs with previous position statements.

P2Y12 RECEPTOR ANTAGONIST/THIENOPYRIDINE (CLOPIDOGREL, PRASUGREL, TICAGRELOR) MONOTHERAPY

P2Y12 receptor antagonists includes clopidogrel, ticagrelor and prasugrel. Both clopidogrel and prasugrel are thienopyridines, an active metabolite that irreversibly binds to the P2Y12 receptor and prevents activation of the GPIIb/IIIa receptor, thereby inhibiting platelet aggregation[100]. Platelet aggregation is affected for the life of the platelet. Platelet function returns to baseline 5 to 7 d after withdrawal of clopidogrel. Ticagrelor is a different class of agent that also binds to the P2Y12 receptor but is reversible.

Table 41 Diagnostic endoscopy and colonoscopy with biopsy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Fujita *et al*[5]	2015	Japan	Retrospective	47	Endoscopic biopsy	Warfarin (continued)	No incidence of PPB. Risk of immediate/intraprocedural bleeding 4.3%
Ara *et al*[6]	2015	Japan	Prospective	3758	Endoscopic biopsy	Warfarin either: (1) Continued; (2) Ceased before	No incidence of PPB on continuous or Warfarin cessation
Ono *et al*[104]	2012	Japan	Prospective	101	Endoscopic biopsy	Warfarin (continued)	No Incidence of PPB
Yuki *et al*[7]	2017	Japan	Prospective	277	Endoscopic biopsy	Warfarin (continued)	No incidence of PPB
Kono *et al*[105]	2017	Japan	Prospective	221	Endoscopic biopsy	Warfarin (continued)	No incidence of PPB when on warfarin monotherapy

PPB: Post-procedural bleeding.

Table 42 Endoscopic ultrasound ± fine needle aspiration

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Inoue *et al*[17]	2017	Japan	Retrospective	742	EUS + FNA	Warfarin (ceased 4 d before)	No incidence of bleeding in either discontinuation warfarin or HBT
Kawakubo *et al*[106]	2018	Japan	Prospective	85	EUS + FNA	Warfarin (ceased 3 d with HBT before)	Incidence of PPB with HBT 4%

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; PPB: Post-procedural bleeding; HBT: Heparin bridging therapy.

Diagnostic endoscopy and colonoscopy with biopsy (Table 25)

Continued thienopyridine monotherapy is considered safe in diagnostic endoscopies and colonoscopies with biopsy. In several published studies there were no reported incidences of bleeding[5-7,103-105].

Continuing thienopyridine monotherapy is recommended in all cases. This concurs with previous position statements.

EUS ± FNA (Table 26)

Data pertaining to PPB secondary to EUS/FNA in patients where thienopyridine monotherapy is continued is limited. However, two studies from Japan[17,106] assessed the risk of bleeding on thienopyridine monotherapy when withheld 5 d before EUS ± FNA. Both studies did not observe any incidences of PPB. This is compared to a reported absolute risk of PPB between 2.1%-4.3% in the absence of anticoagulant or antiplatelet use (Table 3).

Given the current lack of high-quality evidence assessing the safety of EUS ± FNA on continued thienopyridine monotherapy, and the moderate risk of PPB associated with EUS ± FNA in the absence of anticoagulant or antiplatelet use, withholding thienopyridine 5-7 d before is recommended in all cases. This concurs with previous position statements.

Polypectomy (Table 27)

The risk of PPB attributed with conventional polypectomy while on thienopyridine monotherapy has been considered in numerous comparative studies, where the agent was ceased 5-7 d pre-procedure in the control arm. Four studies[28,107,125,126] assessing the risk of PPB on continued thienopyridine reported PPB in 2.4%-3.8%.

Continued thienopyridine is associated with a significant increased risk of immediate/intraprocedural bleeding. The study by Feagins *et al*[125] observed an incidence of immediate/intraprocedural bleeding of 7.3%, compared to only 4.7% in their control group. This was a similar finding in a recent RCT by Chan *et al*[126], which reported the risk of immediate/intraprocedural bleeding to be 8.5% when on continued thienopyridine, compared to only 5.5% in their control group.

Table 43 Polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Horiuchi *et al*[133]	2014	Japan	Prospective	35	Size: ≤ 10 mm	Polypectomy	Warfarin (continued)	Incidence of PPB 14%
Beppu *et al*[134]	2014	Japan	Retrospective	20	Size: ≥ 20 mm and < 20 mm	Polypectomy	Warfarin ± HBT (ceased at least 5 d before)	Incidence of PPB 52.2%
Yanagisawa *et al*[1]	2018	Japan	Retrospective	486	Size: < 10 mm or ≥ 10 mm	Polypectomy	Warfarin ± HBT (ceased 3-5 d before)	Incidence of PPB 13.7%. Incidence of PPB on HBT 21.7%
Lin *et al*[107]	2018	United States	Retrospective	427	Size: < 20 or ≥ 20 mm	Polypectomy	Warfarin ± HBT (ceased 3-5 d before)	Incidence of PPB 0.66%
Yu *et al*[127]	2019	United States	Retrospective	3471	N/S	Polypectomy	Warfarin ± HBT (ceased before procedure)	Incidence of PPB 1.2%
Kishida *et al*[41]	2019	Japan	Retrospective	6382	Size: < 10 mm or ≥ 10 mm	Polypectomy	Warfarin ± HBT (ceased 3-4 d before)	Incidence of PPB 2.3%. Incidence of PPB with HBT 20% (study did not discern rates between warfarin *vs* DOAC)
Amato *et al*[108]	2019	Italy	Prospective	n=1504	Size: ≥ 10 mm	Polypectomy	Warfarin(ceased median 5 d before)	Incidence of PPB 8.5% (anticoagulant monotherapy)(study did not discern rates between warfarin *vs* DOAC)

PPB: Post-procedural bleeding; HBT: Heparin bridging therapy; DOAC: Direct oral anticoagulant; N/S: Not stated.

Table 44 Cold snare polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Horiuchi *et al*[133]	2014	Japan	Prospective	35	Size: ≤ 10 mm	CSP	Warfarin (continued)	No incidences of PPB
Makino *et al*[110]	2018	Japan	Prospective	69	Size: ≤ 10 mm	CSP	Warfarin (continued)	No incidences of PPB. Incidence of immediate/intraprocedural bleeding 5.7%
Arimoto *et al*[111]	2019	Japan	Retrospective	501	Size: ≤ 10 mm	CSP	Warfarin (continued)	No incidences of PPB. Incidence of immediate/intraprocedural bleeding 9.8%

CSP: Cold snare polypectomy; PPB: Post-procedural bleeding.

Five other studies[41,107-109,127] looked at the risk of PPB when thienopyridine was withheld 5-7 d before endoscopic polypectomy. The reported rate of PPB was between 0.6%-6.7%. Although the associated risk of PPB is still higher compared to the risk of bleeding in the absence of anticoagulant or antiplatelet use, this would be considered safer practice than continuing thienopyridine monotherapy.

The absolute risk of PPB while on thienopyridine, either when continued or when withheld 5-7 d before, is slightly increased compared to the rate of bleeding when not on any anticoagulant or antiplatelet agents (0.6%-6.7% *vs* 0.05%-3%, respectively) (Table 6). As highlighted, there is emerging evidence to suggest the risk of delayed PPB is not greatly increased while on continuation thienopyridine monotherapy. However, given the associated high risk of immediate/intraprocedural bleeding, temporary cessation between 5-7 d before is recommended. This concurs with previous position statements.

CSP (Table 28)

There is emerging evidence to suggest that thienopyridine monotherapy may be safely continued in CSP for polyps ≤ 10 mm. Two studies[110,111] reported no incidences of PPB after CSP on continued thienopyridine monotherapy. However, both these studies were small retrospective studies. Larger, RCTs, are still required before this can be safely recommended as standard practice.

Given the current paucity of high-quality evidence, withholding thienopyridine 5-7

Table 45 Endoscopic mucosal resection

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Fujita *et al*[135]	2018	Japan	Prospective (non-HBT group). Retrospective (HBT group)	43/41	Size: < 10 mm (mean size 7.2-7.8 mm ± 2.2-3.2 mm)	EMR	Warfarin ± HBT (ceased morning of)	No incidence of PPB (non-HBT group). Incidence of PPB 9.8% (HBT group)
Ono *et al*[113]	2019	Japan	Retrospective	24	Size: Median size ranged from 8.5-9.5 ± 5 mm between groups	EMR	Warfarin ± HBT either: Continued; ceased 3 d before procedure	Incidence of PPB (without HBT) 10%. Incidence of PPB (with HBT) 21.4%
So *et al*[50]	2019	South Korea	Retrospective	1197	Size: Mean lesion size 34 mm	EMR	Warfarin either: Ceased day of; 0-4 d before; ceased 5-7 d before; ceased 8-14 d before	Incidence of PPB 16.7% (specific PPB rates between warfarin and DOACs N/S). Incidence of PPB (HBT group) 35.7%
Albéniz *et al*[114]	2020	Spain	Prospective	76	Size: ≥ 20 mm (mean size 30.5 mm)	EMR	Warfarin (ceased 5 d before with HBT)	Increased risk of PPB with anticoagulant use (OR: 4.54, 95%CI: 2.14-9.63, $P < 0.001$). Incidence of PPB not specified in study

EMR: Endoscopic mucosal resection; HBT: Heparin bridging therapy; PPB: Post-procedural bleeding; N/S: Not stated; OR: Odds ratio.

Table 46 Endoscopic submucosal dissection

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Igarashi *et al*[56]	2017	Japan	Retrospective	67	ESD	Warfarin ± HBT either: (1) Received till day of; (2) Ceased 3-7 d before; (3) HBT 3-7 d before	Incidence of PPB 10.0% (warfarin and DOAC combined). Incidence of PPB 10.8% (HBT group)
Sato *et al*[57]	2017	Japan	Retrospective	93	ESD	Warfarin ± HBT (ceased 3-5 d before)	Incidence of PPB 5.9% (without HBT). Incidence of PPB (with HBT) 30.7%
Furuhata *et al*[115]	2017	Japan	Retrospective	253	ESD	Warfarin ± HBT (ceased 3-4 d before)	Incidence of PPB 7.3% (Warfarin and DOAC combined). Incidence of PPB 28.8% (with HBT)
Yoshio *et al*[132]	2017	Japan	Retrospective	97	ESD	Warfarin ± HBT (ceased 4-5 d before)	No incidence of PPB (without HBT). Incidence of PPB (with HBT) 31.6%
Harada *et al*[136]	2017	Japan	Prospective	45	ESD	Warfarin ± HBT either: (1) Continued; (2) Switched to HBT	Incidence of PPB 9.1% (warfarin continued). Incidence of PPB 21.7% (HBT)
Kono *et al*[58]	2018	Japan	Retrospective	872	ESD	Warfarin ± HBT (ceased 1-3 d before with or without HBT)	Incidence of PPB 6.4% (without HBT). Incidence of PPB 29% (with HBT) (warfarin and DOACs combined)
Yamashita *et al*[60]	2018	Japan	Retrospective	650	ESD	Warfarin with HBT	Incidence of PPB 26.3% (with HBT)
Nam *et al*[118]	2019	South Korea	Retrospective	1942	ESD	Warfarin ± HBT (ceased 7 d before)	Incidence of PPB 3.2%
Harada *et al*[61]	2020	Japan	Retrospective	26	ESD	Warfarin ± HBT either: (1) Continued; (2) Ceased 4-5 d ± HBT before	Incidence of PPB 7.7%

ESD: Endoscopic submucosal dissection; HBT: Heparin bridging therapy; PPB: Post-procedural bleeding; DOAC: Direct oral anticoagulant.

d before CSP is recommended and concurs with previous position statements. However, with larger studies evaluating the safety of continued thienopyridine monotherapy in CSP, amendments to future position statements may be indicated.

EMR (Table 29)

The impact of thienopyridine monotherapy and the associated risk of PPB in EMR have not been directly evaluated in published studies. As per with aspirin monotherapy, the same three studies[50,113,114] examined the incidence of PPB associated with both aspirin and thienopyridine monotherapy, generally withheld 3-5 d before, in

Table 47 Endoscopic retrograde cholangiopancreatography with sphincterotomy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Paik *et al*[137]	2018	South Korea	Retrospective	96	Sphincterotomy	Warfarin with HBT	Incidence of delayed PPB 7.3%
Muro *et al*[138]	2020	Japan	Retrospective	149	Sphincterotomy	Warfarin either: (1) Continued; (2) With HBT	Incidence of PPB 8.3% (warfarin continued). Incidence of PPB 4.0% (with HBT)
Yamamiya *et al*[122]	2019	Japan	Retrospective	76	Sphincterotomy	Warfarin: (1) Continued; (2) With HBT	No incidence of PPB in either continuous or HBT group
Ikarashi *et al*[68]	2017	Japan	Retrospective	1113	Sphincterotomy	Warfarin either: (1) Ceased 4-5 d before; (2) With HBT	Incidence of delayed PPB 3.0% (study categorised cessation of thienopyridine, warfarin and DOAC into the same "discontinuation" group). Incidence of PPB 8.0% (with HBT)

HBT: Heparin bridging therapy; PPB: Post-procedural bleeding.

Table 48 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Lee *et al*[123]	2013	South Korea	Retrospective	71	PEG	Warfarin (continuation or cessation details N/S)	Study findings expressed as an OR. Increased risk of PPB with anticoagulant use (OR: 7.26, 95%CI: 2.23-23.68, P = 0.001)
Singh *et al*[98]	2012	United States	Retrospective	326	PEG	Warfarin ± HBT	Without HBT group: (1) Incidence of PPB 5.4% (without HBT); (2) Increased risk of PPB without HBT (OR: 1.08, 95%CI: 0.47-2.49, P = 0.860). HBT group: (1) Incidence of PPB with HBT 7.9% (11/140); (2) Increased risk of PPB with HBT (OR: 2.66, 95%CI: 1.18-5.99, P = 0.018)
Lozoya-González *et al*[99]	2012	Mexico	Retrospective	91	PEG	Warfarin either: (1) Ceased > 48h with HBT before; (2) Ceased 1-5 d before	No incidence of PPB

N/S: Not stated; OR: Odds ratio; PEG: Percutaneous endoscopic gastrostomy; HBT: Heparin bridging therapy; PPB: Post-procedural bleeding.

Table 49 Diagnostic endoscopy and colonoscopy with biopsy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Fujita *et al*[5]	2015	Japan	Retrospective	5 (7939)	Endoscopic biopsy	DOAC (continued)	No incidence of PPB
Ara *et al*[6]	2015	Japan	Prospective	394 (3758)	Endoscopic biopsy	DOAC either: (1) Continued; (2) Ceased before	No incidence of PPB(in both continuous and DOAC cessation group)
Yuki *et al*[7]	2017	Japan	Prospective	45 (549)	Endoscopic biopsy	DOAC (continued)	No incidence of PPB
Kono *et al*[105]	2017	Japan	Prospective	51 (221)	Endoscopic biopsy	DOAC (continued)	No incidence of PPB

PPB: Post-procedural bleeding; DOAC: Direct oral anticoagulant.

the same group (antiplatelet group). Therefore, determining the direct impact of thienopyridine monotherapy can only be estimated.

Albéniz *et al*[114] found that antiplatelet use with, either aspirin or thienopyridine monotherapy before EMR, is associated with a two-fold increased relative risk of PPB (OR, 2.51; 95%CI, 2.14-9.63, P < 0.001) in lesions ≥ 20 mm. Another study by So *et al*[50] observed a rate of PPB of 8.2% in EMR of polyps of mean size > 30 mm when on either

Table 50 Endoscopic ultrasound ± fine needle aspiration

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Kawakubo *et al*[106]	2018	Japan	Prospective	85	EUS + FNA	DOAC (ceased 48 h with HBT before)	No incidence of PPB with HBT

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; HBT: Heparin bridging therapy; PPB: Post-procedural bleeding.

Table 51 Polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Beppu *et al*[134]	2014	Japan	Retrospective	1 (52)	Size: ≥ 20 mm and < 20 mm	Polypectomy	DOAC (ceased at least 5 d before)	Expressed as OR. Increased risk of PPB with DOAC use (OR: 10.2, 95%CI: 2.7-38.3, P = 0.0006)
Yanagisaw *et al*[1]	2018	Japan	Retrospective	73 (436)	Size: < 10 mm or ≥ 10 mm	Polypectomy	DOAC (ceased 24-48 h before ± HBT)	Incidence of PPB 13.8%
Yu *et al*[127]	2019	United States	Retrospective	1590 (611487)	N/S	Polypectomy	DOAC (ceased before)	Incidence of PPB 0.6%
Kishida *et al*[41]	2019	Japan	Retrospective	87 (6382)	Size: < 10 mm or ≥ 10 mm	Polypectomy	DOAC (ceased 24-48 h before)	Incidence of PPB 2.3% (study did not discern rates between warfarin *vs* DOAC)
Amato *et al*[108]	2019	Italy	Prospective	1504	Size: ≥ 10 mm	Polypectomy	DOAC (ceased median 5 d before)	Incidence of PPB 8.5% (study did not discern anticoagulant rates between warfarin *vs* DOACs)

DOAC: Direct oral anticoagulant; OR: Odds ratio; PPB: Post-procedural bleeding.

Table 52 Cold snare polypectomy

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Makino *et al*[110]	2018	Japan	Prospective	17 (172)	Size: ≤ 10 mm	CSP	DOAC (continued)	Incidence of PPB 1.2%
Arimoto *et al*[111]	2019	Japan	Retrospective	65 (501)	Size: ≤ 10 mm	CSP	DOAC (continued)	No incidence of PPB

CSP: Cold snare polypectomy; DOAC: Direct oral anticoagulant; PPB: Post-procedural bleeding.

aspirin or thienopyridine monotherapy.

However, the risk of PPB in EMR for smaller polyps of < 10 mm, although still associated with an increased bleeding risk, is not as high when compared to larger polyp resections (≥ 20 mm). The study by Ono *et al*[113] reported a 1.35% risk of PPB per polyp resection when on either aspirin or thienopyridine monotherapy.

Overall, the absolute risk of PPB is increased with thienopyridine use, particularly in lesions ≥ 20 mm in size, compared to the risk of bleeding in the absence of anticoagulant or antiplatelet use of respective size (1.35%-8.2% *vs* 1.7%-6.3%, respectively) (Table 7).

Given the increased absolute risk of PPB associated with thienopyridine use, withholding thienopyridine monotherapy 5-7 d before is recommended in all cases. This concurs with previous position statements.

ESD (Table 30)

Thienopyridine monotherapy is associated with a four-fold increased relative risk of PPB (OR, 4.26, 95%CI, 1.36-13.29, P = 0.13)[116] in ESD, with a reported incidence of 3.6%-19.4%[56,57,116,118] even when withheld 5-7 d before.

It is apparent that withholding thienopyridine monotherapy for an extended period of time is required to decrease PPB risk. A study by Oh *et al*[116] compared the risk of bleeding when thienopyridines were withheld at either 0-4 d or 5-7 d before EMR. The two patients in the study who developed PPB (3.6%) both had their thienopyridine ceased on the day of the EMR procedure.

Another study by Igarashi *et al*[56] also assessed the risk of PPB when thienopyridine

Table 53 Endoscopic mucosal resection

Ref.	Year	Country	Study design	*n*	Polyp morphology	Procedure	Medication	Relative risk
Fujita *et al*[135]	2018	Japan	Prospective (non-HBT group) and retrospective (HBT group)	84	Size < 10mm (mean size 7.2-7.8 ± 2.2-3.2 mm	EMR	DOAC ± HBT (ceased morning of)	Incidence of PBB 2.3% (non-HBT). No incidence of PPB (HBT)
Ono *et al*[113]	2019	Japan	Retrospective	825	Size median size 8.5-9.5 ± 5 mm between groups	EMR	DOACs (ceased day of)	Incidence of PPB 6.5%
So *et al*[50]	2019	South Korea	Retrospective	399 (1197)	Size mean lesion 34 mm	EMR and ESD	DOAC (ceased day of procedure or 0-4 d before or ceased 5-7 d before or ceased 8-14 d before procedure)	Incidence of PPB 16.7% (anticoagulant group) (study did not specify the risk comparing warfarin and DOAC individually)
Albéniz *et al*[114]	2020	Spain	Prospective	977	Size ≥ 20mm (mean size 30.5 mm)	EMR	DOAC (ceased 48-72 h before)	Expressed as OR (OR: 4.54, 95%CI: 2.14-9.63, $P < 0.001$) (anticoagulant use) (specific PPB rates between warfarin and DOACs not specified)

EMR: Endoscopic mucosal resection; DOAC: Direct oral anticoagulant; ESD: Endoscopic submucosal dissection; HBT: Heparin bridging therapy; OR: Odds ratio; PPB: Post-procedural bleeding.

Table 54 Endoscopic submucosal dissection

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Igarashi *et al*[56]	2017	Japan	Retrospective	30	ESD	DOAC (ceased 3-7 d before)	Incidence of PPB 10.0% (warfarin and DOAC combined)
Sato *et al*[57]	2017	Japan	Retrospective	18	ESD	DOAC (ceased 24-48 h before)	Incidence of PPB 5.6%
Yoshio *et al*[132]	2017	Japan	Retrospective	24	ESD	DOAC: (1) Rivaroxaban/Apixaban ceased 2 d before; (2) Dabigatran ceased 1-2 d before	Incidence of PPB on Rivaroxaban 45.5%. No incidence of PPB on dabigatran or apixaban
Kono *et al*[58]	2018	Japan	Retrospective	872	ESD	DOAC either: (1) Ceased 1-3 d before; (2) Ceased 2 d before with HBT	DOACs ceased 1-3 d before without HBT group: (1) Incidence of PPB 6.4%; (2) Warfarin and DOACs with HBT: Incidence of PPB 29%
Yamashita *et al*[60]	2018	Japan	Retrospective	650	ESD	DOAC (ceased morning of)	Incidence of PPB 22.2%
Harada *et al*[61]	2020	Japan	Retrospective	25	ESD	DOAC (ceased 1 d before ± HBT)	Incidence of PPB 16%

DOAC: Direct oral anticoagulant; ESD: Endoscopic submucosal dissection; HBT: Heparin bridging therapy; OR: Odds ratio; PPB: Post-procedural bleeding.

was withheld on the day of the procedure and found the risk of bleeding to be 5.6%.

Ono *et al*[128] observed the risk of PPB in patients on dual antiplatelet therapy (DAPT) undergoing an ESD, where aspirin was ceased but thienopyridine monotherapy continued. The observed rate of PPB reported was 20%.

The absolute risk of PPB in ESD is high irrespective of whether thienopyridine monotherapy is continued or withheld 5-7 d before the procedure and when compared to the PPB risk in the absence of anticoagulant or antiplatelet use (5.6%-20% *vs* 2.7%-6.6%, respectively) (Table 8). In all circumstances, thienopyridine monotherapy should not be continued and withheld 5-7 d before. This concurs with previous position statements.

ERCP with sphincterotomy (Table 31)

There are currently limited studies evaluating the risk of PPB associated with thienopyridine monotherapy use in ERCP with sphincterotomy. One study by Patai *et al*[66] assessed the risk of bleeding on continued thienopyridine and found the incidence of immediate/intraprocedural and delayed PPB to both be at 3.5%.

Table 55 Endoscopic retrograde cholangiopancreatography with sphincterotomy

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Yamamiya *et al*[122]	2019	Japan	Retrospective	76	Sphincterotomy	DOAC either: (1) Continued; (2) Switched to HBT before	No incidence of PPB in either continuous or HBT group
Muro *et al*[138]	2020	Japan	Retrospective	62 (149)	Sphincterotomy	DOAC: (1) Continued; (2) With HBT	No incidence of PPB (continued DOAC). Incidence of PPB 6.5% (HBT)

DOAC: Direct oral anticoagulant; HBT: Heparin bridging therapy; PPB: Post-procedural bleeding.

Table 56 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion

Ref.	Year	Country	Study design	*n*	Procedure	Medication	Relative risk
Lee *et al*[123]	2013	South Korea	Retrospective	71 (1625)	PEG	DOAC (N/S whether continued or ceased before)	Study expressed risk of PPB as OR (OR: 7.26, 95%CI: 2.23-23.68, P = 0.001) (included both warfarin and DOAC)

DOAC: Direct oral anticoagulant; OR: Odds ratio; PPB: Post-procedural bleeding; PEG: Percutaneous endoscopic gastrostomy.

However, when thienopyridine is withheld 5-7 d before ERCP with sphincterotomy, the risk of bleeding is lower and found to be only 3.0% in one study by Ikarashi *et al*[68] This study was limited by analysing the risk of bleeding associated with thienopyridine, warfarin and DOAC use together. It did not directly analyse the risk thienopyridine has on PPB alone. Another study by Yamamiya *et al*[122] did not observe any incidence of PPB in their study in patients on thienopyridine.

There is an increased absolute risk of PPB with thienopyridine use, when withheld 5-7 d before, compared to in the absence of anticoagulant or antiplatelet use (0%-3% *vs* 0.3%-1.66%, respectively) (Table 9).

Given the increased absolute risk and current limited evidence of the safety on continuation thienopyridine and risk of bleeding post ERCP, it is recommended that thienopyridines should be withheld 5-7 d before the procedure. This concurs with previous position statements.

PEG/PEJ insertion (Table 32)

The estimated risk of PPB post endoscopic PEG/PEJ insertion associated with thienopyridine monotherapy, when withheld 1-3 d before, is reported to be 0%-2.1% in several published studies[99].

The study by Richter *et al*[124] evaluated the associated risk of PPB when thienopyridine monotherapy was continued. It reported a bleeding rate of 4%.

The absolute risk of PPB with thienopyridine use, when continued or withheld 1-3 d before, is increased when compared with the risk of bleeding in patients in the absence of anticoagulant or antiplatelet use (2.1%-4% *vs* 2.7%, respectively) (Table 16).

Given the increased absolute risk of PPB when thienopyridine monotherapy is continued, it is recommended that thienopyridine should be withheld 5-7 d before PEG/PEJ insertion. This concurs with previous position statements.

DUAL ANTIPLATELET THERAPY (DAPT) (ASPIRIN + P2Y12 RECEPTOR ANTAGONIST/THIENOPYRIDINE)

DAPT of aspirin plus a P2Y12 receptor antagonist (thienopyridine) is most commonly indicated for the management of ACS. In percutaneous coronary intervention (PCI), such as drug eluding stent (DES) or bare metal stent (BMS) insertion, indication to remain on DAPT for a given period is paramount in order to prevent stent thrombosis. The current Cardiac Society of Australia and New Zealand (CSANZ) guidelines[129] on DAPT duration post PCI, recommends patients should remain on DAPT for 12 mo. Risk of stent thrombosis increases after 5 d without antiplatelet therapy with an approximate risk of 40% for MI and death[2]. There is emerging evidence that

prolonged therapy of up to 3 years for patients with prior MI demonstrates a relative reduction in cardiovascular death (RR: 0.85, 95%CI: 0.74-0.98), and recurrent MI (RR: 0.70, 95%CI: 0.55-0.88). However, there is an associated increase incidence of bleeding events (RR: 1.73, 95%CI: 1.19-2.50) with no improvement in non-cardiovascular death or overall mortality[129]. In patients with a high bleeding risk and low risk for recurrent ischaemic events, a shorter duration of treatment such as 6 mo could be considered, but not ideal. The minimum duration of uninterrupted DAPT should be at least 30 d for BMS, and 3 mo for DES.

Diagnostic endoscopy and colonoscopy with biopsy (Table 33)

Continued DAPT in diagnostic endoscopies and colonoscopies with biopsy has an overall low risk of bleeding. Three studies[7,104,105] reported no incidences of PPB post biopsy. While the study by Ara *et al*[6] only reported one episode of bleeding post biopsy on continued DAPT (0.35%). The absolute risk on continued DAPT is comparable to the reported risk of PPB in the absence of anticoagulant or antiplatelet use (0.35% *vs* 0.12%-0.98%) (Table 1).

Overall, DAPT is considered safe and is recommended to be continued in all cases. This concurs with previous position statements.

EUS ± FNA (Table 34)

There is currently a scarcity of evidence evaluating the risk of PPB in patients on DAPT undergoing EUS ± FNA. Although a study by Kawakubo *et al*[106] reported of risk of PPB of 3.6%, when thienopyridine was withheld 5 d before and bridged with aspirin monotherapy, in patients initially on DAPT. This is comparable to the absolute risk of PPB of 2.1%-4.3% in the absence of anticoagulant or antiplatelet use (Table 3).

Given the limited evidence regarding the safety of continued DAPT in EUS± FNA, it is recommended that thienopyridine should be withheld 5-7 d before with bridging aspirin monotherapy (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

Polypectomy (Table 35)

The risk of PPB is reportedly significantly increased in patients on continued DAPT undertaking endoscopic polypectomy. A study by Singh *et al*[28] reported a three-fold increased relative risk of PPB when DAPT is continued (OR: 3.69; 95%CI, 1.60-8.52, P = 0.002), with the incidence rate of PPB on continuation DAPT between 0.85%-6%, as reported in several published studies[28,30,41,109].

The study by Kishida *et al*[41] considered the risk of bleeding when either, both aspirin and thienopyridine were withheld (before 2012), or only thienopyridine withheld and bridged with aspirin monotherapy. In this study, the incidence of PPB was reported to be 1.8%.

The absolute risk of PPB post polypectomy when thienopyridine is withheld and bridged with aspirin monotherapy is comparable to the overall risk of PPB in the absence of anticoagulant or antiplatelet use (1.8% *vs* 0.05%-3.0%, respectively) (Table 5).

Given the high risk of bleeding complications on continued DAPT, it is recommended that thienopyridine is withheld 5-7 d before and bridged with aspirin monotherapy (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

CSP (Table 36)

In CSP, there is emerging evidence to suggest the risk of bleeding on continued DAPT is overall low and estimated to be around 2.4% in a recent RCT by Won *et al*[112]. However, this study was limited by a small sample size of 91 patients. Thus, larger RCTs are still required before this can be safely recommended as standard practice.

In a retrospective study by Arimoto *et al*[111], they reported no incidences of PPB in their DAPT group. Despite this, uninterrupted DAPT appears to be associated with a significant increased risk of immediate/intraprocedural bleeding between 4.8%-17.8%[111,112]. This is significantly higher compared to the reported rates of immediate/intraprocedural bleeding in the absence of anticoagulant or antiplatelet use (2.4%-9.1%, Table 6).

Given the current paucity in high-quality evidence and significant increased risk of

immediate/intraprocedural bleeding, withholding thienopyridine 5-7 d before and bridging with aspirin monotherapy is recommended in CSP (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

EMR (Table 37)

Two recent studies[50,113] retrospectively assessed the indirect effects of DAPT use, when thienopyridine was withheld and bridged with aspirin monotherapy before EMR. The study by Makino *et al*[110] observed a risk of PPB per polyp resection of 1.35% when on antiplatelet therapy (monotherapy or DAPT). However, this study was limited by not quantifying the exact risk of PPB on DAPT alone.

Another study by So *et al*[50] found DAPT use was associated with a two-fold increased relative risk of bleeding (OR: 2.14; 95%CI, 0.63-7.32, $P = 0.226$) in lesions ≥ 20 mm, with a reported incidence of PPB of 12.3% post EMR.

The relative and absolute risk of PPB with DAPT is higher compared to the risk of bleeding in the absence of anticoagulant or antiplatelet use (1.35%-12.3% *vs* 1.7%-6.3%, respectively) (Table 7).

The risk of PPB associated with DAPT use in EMR is considerably high and precautions should be made to reduce this risk. In lesions < 20 mm, withholding thienopyridine 5-7 d before and bridging with aspirin monotherapy is recommended (unless contraindicated). In lesions ≥ 20 mm withholding both thienopyridine and aspirin is the safest recommendation with regards to bleeding risk.

If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

ESD (Table 38)

The absolute risk of PPB in ESD in the absence of anticoagulant or antiplatelet use is high (2.7%-6.6%, Table 8). DAPT use before ESD is associated with a reported two- to three-fold increased relative risk of bleeding in two studies[116,117], even after withholding thienopyridine 5-7 d before and bridged with aspirin monotherapy only. The study by Sato *et al*[57] found that DAPT use was a significant independent risk factor for PPB than what was reported in the two other studies (OR: 10.33, 95%CI, 6.06-17.59, $P < 0.001$).

Several studies have reported the absolute risk of bleeding post ESD to be 23.1%-67.7%[57,58,116,117]. In the study by Harada *et al*[117] they compared the risk of bleeding with bridging aspirin monotherapy *vs* discontinuation of both thienopyridine and aspirin > 5 d before the procedure. The reported incidence of PPB in this study was 23.1% and 5.0%, respectively.

Continuing DAPT in ESD is not recommended given the significant increased risk of PPB. Withholding both thienopyridine and aspirin is the safest recommendation with regards to bleeding risk. However, if this cannot be undertaken due to risk of thromboembolism, then withholding thienopyridine 5-7 d before procedure and switching to bridging aspirin monotherapy is otherwise recommended (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

ERCP with sphincterotomy (Table 39)

There have been limited published studies assessing the risk of bleeding with DAPT in ERCP with sphincterotomy. Two studies by Mok *et al*[130] and Yamamiya *et al*[122] analysed the incidence of bleeding when DAPT was continued and reported an absolute risk of PPB of 0%-3.6%. This compares to an overall risk of PPB of 0.45%-9.9% in the absence of anticoagulant or antiplatelet use (Table 9).

These two studies may suggest that continued DAPT in ERCP with sphincterotomy may be safe. However, evidence is limited due to a lack of large, high-quality studies. For now, it is recommended that thienopyridine is withheld 5-7 d before and bridged with aspirin monotherapy only (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

PEG/PEJ insertion (Table 40)

Several studies have found DAPT use to be associated with a 2.5% absolute risk of

PPB post PEG/PEJ insertion[98,123]. The study by Lee *et al*[123] ceased DAPT at least 4 d (range 4-10 d) before the PEG procedure. Whereas, the study by Singh *et al*[98] did not clearly specify the DAPT management regime. In the study by Lozoya-González *et al*[99] there were no reported incidences of PPB in any of their patients on DAPT, which was ceased 1-3 d before the PEG procedure. The absolute risk of PPB while on DAPT is comparable to the overall risk of PPB in the absence of anticoagulant or antiplatelet use (2.5% *vs* 2.7%, respectively) (Table 16).

Given current studies have only evaluated the risk of bleeding when DAPT is ceased before a PEG procedure, and yielded similar rates of PPB compared to in the absence of anticoagulant or antiplatelet use, it is recommended that thienopyridine is withheld 5-7 d before and bridged with aspirin monotherapy only (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

VITAMIN K ANTAGONIST (WARFARIN)

Warfarin is a vitamin K antagonist, which inhibits the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and the antithrombotic factors protein C and S[100]. The duration of action of warfarin is 5 d. Current evidence supports the shifting trend that DOACs are more efficacious and safer than warfarin[131]. Furthermore, warfarin needs to be withheld for a longer period and generally HBT is required, further increasing the risk of PPB and the length of hospital stay[132].

Despite the rise in DOAC use, warfarin is still commonly encountered in certain conditions such as mechanical heart valve prosthesis, AF with mitral stenosis, and CKD patients where DOACs are contraindicated. Thus, its management in peri-endoscopic period is still very relevant.

Diagnostic endoscopy and colonoscopy with biopsy (Table 41)

Continuation of Warfarin therapy in diagnostic endoscopies and colonoscopies with biopsy is considered safe and overall is not associated with an increased risk of gastrointestinal bleeding. Four prospective and one retrospective study did not report any incidences of PPB on continued warfarin monotherapy[6,7,104,105].

The study by Kono *et al*[105] observed PPB in one case on continued warfarin. However, this patient was also on an antiplatelet agent and thus, had an increased overall risk of bleeding. In this case, endoscopic haemostasis was required with good clinical outcome.

Overall, continuing warfarin therapy is considered safe in diagnostic endoscopies and colonoscopies with biopsy in all cases. This concurs with previous position statements.

EUS ± FNA (Table 42)

Withholding warfarin at least 4 d before EUS ± FNA without HBT does not appear to increase the risk of PPB compared to the absolute risk of bleeding in the absence of anticoagulant or antiplatelet use (0%-4% *vs* 2.1%-4.3%, respectively) (Table 3).

The study by Inoue *et al*[17] found no incidences of PPB in their cohort of patients who had warfarin ceased 4 d before EUS ± FNA. However, HBT was found to be associated with an increased risk of bleeding, without reducing the risk of thromboembolic event relating to warfarin interruption, in the study by Kawakubo *et al*[106]. In this study, there was one case (4%) of PPB in a patient on HBT after EUS ± FNA and none in the warfarin cessation without HBT group. No thromboembolic events occurred in either the warfarin cessation or HBT group.

We recommend withholding warfarin 5 d before EUS ± FNA based on current evidence available. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

Polypectomy (Table 43)

Warfarin use is associated with a high-risk of PPB in endoscopic polypectomy, irrespective of whether warfarin is withheld with or without HBT before the procedure. The study by Horiuchi *et al*[133] reported a 14% risk of PPB with continued warfarin use. However, when warfarin is withheld 3-5 d before the procedure, the

absolute risk of bleeding is reported to be 0.7%-13.5%, according to several studies[1,41,107,108,127].

HBT is indicated in patients with high-thromboembolic risk patients as per current guidelines[2-4]. However, HBT has been shown to be associated with higher risk of bleeding without significantly reducing the risk of a thromboembolic event. A study by Yanagisawa *et al*[1] compared the risk of PPB and thromboembolic event in its analysis and found withholding warfarin with HBT, compared to withholding warfarin without HBT, yielded a higher rate of PPB (21.7% *vs* 13.7%, respectively) without providing significant difference in the prevention of a thromboembolic event. Two cases of a thromboembolic event were reported in this study. However, this occurred in both groups, one in the HBT group and the other in the withholding warfarin without HBT.

Another study by Lin *et al*[107] also associated HBT with a ten-fold increased relative risk of PPB in their cohort (OR: 10.3, P = 0.0001), with the incidence of bleeding on HBT reported at 14.9% compared to only 0.7% in the warfarin discontinuation without HBT. Similarly, there was no difference in the rate of thromboembolic event in both groups. No thromboembolic events occurred in the study.

Warfarin use is associated with an absolute increased risk of bleeding in endoscopic polypectomies irrespective of whether warfarin is withheld or not. The risk of bleeding while on warfarin, even when withheld 3-5 d before polypectomy, compared to the risk of bleeding in the absence of anticoagulant or antiplatelet use is significantly increased (0.7%-13.5% *vs* 0.05%-3.0%, respectively) (Table 5). The studies also suggest that HBT is associated with a significantly increased risk of PPB, without reducing the risk of thromboembolic event in high-risk patients.

To minimise the risk of PPB, it is recommended that warfarin be withheld 5 d before the procedure. HBT is associated with an increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

CSP (Table 44)

There is emerging evidence that continuing warfarin therapy in CSP for polyps ≤ 10 mm does not increase the risk of PPB. It is theorised the reason for bleeding after polypectomy is due to submucosal vessel damage from electrocautery. CSP does not involve electrocautery and therefore, may decrease the risk of bleeding[133].

Three recent studies looking at the bleeding risk without warfarin cessation uniformly reported no incidences of PPB[110,111,133]. However, there is an associated increased risk of immediate/intraprocedural bleeding when on continued warfarin of 5.7%-9.8%[111,133].

Given the current lack of high-quality evidence evaluating the safety with continuing warfarin in CSP, withholding warfarin 5 d before should still be practiced. This concurs with previous position statements. However, with larger studies evaluating the safety of continued warfarin therapy in CSP being currently undertaken, amendments to future position statements may be needed.

EMR (Table 45)

Warfarin use in EMR is associated with over a four-fold increased relative risk of bleeding (OR: 4.54, 95%CI, 2.14-9.63, P < 0.001)[114]. The rate of PPB on warfarin therapy when ceased at least 3-5 d before EMR is between 10%-16.7%, as reported in two retrospective studies[50,113]. This represents an increased absolute risk of bleeding on warfarin therapy compared to the risk of bleeding in the absence of anticoagulant or antiplatelet use (10%-16.7% *vs* 0%-1.7%, respectively) (Table 7).

This risk of bleeding is further increased with concurrent HBT use. HBT is considered to be a significant risk factor for PPB (OR: 5.00, 95%CI, 1.11-22.50, P = 0.036)[50]. From several small studies, the overall risk of PPB is significantly increased when on HBT in EMR, reported to be 9.8%-35.7%[50,113,134,135].

To minimise the risk of PPB, it is recommended that warfarin be withheld 5 d before EMRs. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

ESD (Table 46)

The risk of PPB in warfarin users in ESD is reported to be 3.2%-10.0% when withheld 3-5 d before the procedure[56-58,115,118]. This is similar to the absolute risk of PPB in the absence of anticoagulant or antiplatelet use (3.2%-10% *vs* 2.7%-6.6%, respectively)

(Table 8). HBT continues to be a significant independent risk factor for PPB with a four- to ten-fold increased relative risk of bleeding as estimated in some studies[57,115,132], and a reported incidence of PPB of 10.8%-31.6%[56,57,115,132,136].

Continuing warfarin, as an alternative to HBT, was assessed in two studies[61,136] and was found to have similar risk of PPB compared to when warfarin is withheld 3-5 d before the procedure (7.7%-9.1% *vs* 3.2%-10.0%, respectively). It has been suggested that continuation of warfarin may be a safer alternative to HBT in patients of high-risk of thromboembolism. However, further larger studies are required before this can be safely recommended.

To minimise the risk of PPB, it is recommended that warfarin be withheld 5 d before ESD. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

ERCP with sphincterotomy (Table 47)

Warfarin is associated with a high risk of PPB in ERCP with sphincterotomy. Three studies analysing the incidence of PPB while withholding warfarin with HBT reported a bleeding rate of 4.0%-8.0%[68,137,138]. The study by Muro *et al*[138] reported the risk of bleeding on continued warfarin was slightly higher at 8.3%. This compares to an overall risk of PPB of 0.45%-9.9% in the absence of anticoagulant or antiplatelet use (Table 9).

Continuing warfarin and/or withholding warfarin with HBT are associated with an overall high-risk of PPB in ERCP with sphincterotomy. To minimise the risk of PPB, it is recommended that warfarin be discontinued 5 d before ERCP with sphincterotomy. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

PEG/PEJ insertion (Table 48)

Use of warfarin in PEG/PEJ insertion is a significant independent risk factor for PPB (OR: 7.26, 95%CI, 2.23-23.68, P = 0.001)[123]. The study by Singh *et al*[98] reported an incidence of PPB of 5.4% in the group who had warfarin withheld without HBT. The absolute risk increases to 7.9% with HBT. However, the study by Lozoya-González *et al*[99] reported no incidences of PPB in either group.

Warfarin is a well-established risk factor for bleeding in PEG/PEJ insertion compared to the absolute risk of PPB in the absence of anticoagulant or antiplatelet use (5.4%-7.9% *vs* 2.7%, respectively) (Table 16).

To minimise the risk of PPB, it is recommended that warfarin be withheld 5 d before the procedure. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

DIRECT ORAL ANTICOAGULANTS (DOAC) (DABIGATRAN, RIVAROXABAN AND APIXABAN)

DOAC is a collective term for direct thrombin inhibitors (dabigatran) and other direct factor Xa inhibitors (rivaroxaban and apixaban)[139-141]. DOACs offer an alternative to warfarin in the management of patients with AF and VTE. More recently, DOACs have replaced warfarin as the preferred first line therapy of choice. This is due to its noninferiority at low doses (dabigatran 110 mg BD, rivaroxaban 20 mg daily, apixaban 2.5 mg BD), but superiority at higher doses (dabigatran 150 mg BD, apixaban 5 mg BD), over warfarin in prevention of stroke and thromboembolic events, without increasing the risk of major bleeding in patients with nonvalvular AF[139-141]. DOACs also have other significant logistical benefits over warfarin. Unlike warfarin, DOACs have set doses which do not require regular monitoring with international normalisation ratio (INR) blood tests. Due to its shorter half-lives, DOACs also have a faster onset and offset of action compared to warfarin. However, both dabigatran at high dose (150 mg BD) and rivaroxaban are associated with higher rates of gastrointestinal bleeds compared to warfarin[139,140], and reversibility currently remains a significant safety concern with DOACs. Only dabigatran currently has an available antidote in idarucizumab. This is expected to change with ongoing trials and emerging evidence of antidotes for the other DOACs.

Optimal timing of DOAC cessation should take into consideration the time of maximum effect, half-life and the excretion of the agent. To minimise the risk of PPB, DOACs should be stopped for at least 2 half-lives in all high-risk endoscopic procedures[3]. Both rivaroxaban and apixaban have a relatively short time to maximum effect (2-4 h for rivaroxaban and 1-3 h for apixaban). Rivaroxaban has a half-life between 8-9 h [creatinine clearance (CrCl) > 50 mL/min] and 9-13 h (CrCl > 30-50 mL/min), with 66% of the agent excreted by the kidneys. Whereas apixaban has a half-life between 7-8 h (CrCl > 50 mL/min) and 8-15 h (CrCl 30-50 mL/min), with 25% excreted by the kidneys. Dabigatran was the first DOAC and has a time of maximum effect of 1.25-3 h and its half-life is between 12-14 h (CrCl ≥ 80 mL/min) to 22-35 h (CrCl < 30 mL/min). More cautious peri-endoscopic management is required for dabigatran as the timing of discontinuation is mostly dictated by the patient's CrCl with 80% of the agent excreted by the kidneys[3].

Diagnostic endoscopy and colonoscopy with biopsy (Table 49)

There has been no documented increased risk of PPB in diagnostic endoscopies and colonoscopies with biopsy on continued DOAC therapy from several published studies. Four studies all observed no incidences of bleeding post biopsy in their continuation DOAC group[5-7,105]. This is compared to an already established low risk of PPB in the absence of anticoagulant or antiplatelet use (0.12%-0.98%, Table 1).

DOACs are considered safe to be continued in diagnostic endoscopies and colonoscopies with biopsy. This concurs with previous position statements.

EUS ± FNA (Table 50)

There is currently a paucity of large studies analysing the risk of bleeding while on DOAC therapy in EUS ± FNA. Only one study by Kawakubo *et al*[106] analysed the PPB risk when DOAC therapy was withheld 48 h before the procedure with HBT. There were no reported incidences of bleeding in this study. The absolute risk of PPB in EUS ± FNA is reported to be 2.1%-4.3% in the absence of anticoagulant or antiplatelet use (Table 3).

Given the absolute risk of bleeding in the absence of anticoagulant or antiplatelet use is considerable and with currently only limited evidence of the bleeding risk with DOAC use, it is recommended that DOACs should be withheld at least 48 h before. This concurs with previous position statements.

Polypectomy (Table 51)

DOAC use in polypectomy is associated with a significant increased relative risk of PPB (OR: 17.8, $P < 0.001$) as reported in the study by Yanagisaw *et al*[1]. In this study, the incidence of bleeding in their DOAC group, when DOAC therapy is withheld 24-48 h before the procedure, was 13.8%. The rates of bleeding were similar amongst the different DOAC classes, of dabigatran, rivaroxaban and apixaban, with reported rates of 11.1%, 13.2% and 13.3%, respectively. Another study by Beppu *et al*[134] also observed DOAC use was associated with a ten-fold increased relative risk of bleeding (OR: 10.2, 95%CI, 2.7-38.3, $P = 0.0006$).

Several other studies that withheld DOAC therapy 24-48 h before the procedure (median 5 d in one study[108]), reported an overall incidence of bleeding of 0.6%-13.8%[1,41,108,127]. However, both the study by Kishida *et al*[41] and Amato *et al*[108] analysed the risk of bleeding when on either DOAC or warfarin therapy together, and not as separate agents. This limits the accuracy of the direct effect DOAC therapy has on the risk of bleeding. However regardless, it can be interpreted that DOACs are associated with a significant increased risk.

DOAC use represents a significant increased absolute risk of bleeding compared to the risk of bleeding in the absence of anticoagulant or antiplatelet use (0.6%-13.8% *vs* 0.05%-3.0%, respectively) (Table 5). It is recommended that DOAC therapy should be withheld at least 24-48 h (72 h for dabigatran; in CrCl >50) before polypectomy to minimise the risk of bleeding. This concurs with previous position statements.

CSP (Table 52)

Similar with warfarin, there is emerging evidence from small studies that suggest continuation of DOAC therapy in CSP of polyps ≤ 10 mm is considered safe and does not significantly increase the risk of bleeding[110,111]. This is due to the hypothesis that there is minimal damage to the submucosal vessel in CSP because electrocautery is not involved[133].

The study by Makino *et al*[110] only observed two cases of bleeding post CSP (1.2%). One patient was on dabigatran and the other patient was on apixaban. In the study by

Arimoto *et al*[111] there were no reported incidences of PPB. However, this study did report complications of immediate/intraprocedural bleeding in 11.9% of cases. All cases were adequately controlled with endoscopic haemostasis and did not require further intervention with blood transfusion, admission, and/or surgery.

Although there is emerging evidence suggesting continuation DOAC therapy may be safe in CSP of polyps ≤ 10 mm, until larger studies evaluating the safety of continued DOAC therapy in CSP is undertaken, it is recommended that DOAC therapy should be withheld at least 24-48 h (72 h for dabigatran; in CrCl > 50) before CSP to minimise the risk of bleeding. This concurs with previous position statements.

EMR (Table 53)

Most published studies analysing the risk of PPB in EMR in DOAC users have done so by grouping both warfarin and DOAC monotherapy use together under the umbrella term of "anticoagulant." The risk of bleeding in EMR while on anticoagulant therapy (either warfarin or DOAC) is reported between 5.5%-16.7%[50,113].

However, the risk of bleeding with DOAC use may be overall lower compared to warfarin therapy. In the study by Ono *et al*[113], the risk of bleeding when DOAC has been withheld one day before EMR was reported to be 6.5% per polyp. While another study by Fujita *et al*[135] observed an incidence of 2.3% of PPB in their DOAC group when ceased the morning of EMR.

There is currently limited evidence analysing the risk of bleeding on continued DOAC therapy in EMR. Given this paucity of evidence and to minimise the risk of PPB, it is recommended that DOAC therapy should be withheld at least 24-48 h (72 h for dabigatran; in CrCl > 50) before EMR. This concurs with previous position statements.

ESD (Table 54)

ESD in patients on a DOAC, withheld at least > 24 h before, is reported to be associated with an increased relative risk of PPB compared to the bleeding risk in the absence of anticoagulant or antiplatelet use, in multiple publications[56-58,60,61,132]. The absolute risk of bleeding is, 5.6%-45.5% *vs* 2.7%-6.6%, respectively (Table 8). There have been no studies reporting the rate of PPB on continued DOAC therapy.

The study by Yoshio *et al*[132] reported PPB in five cases on DOAC therapy (45.5%). All five cases were in patients on rivaroxaban. There were no observed cases of PPB in the dabigatran or apixaban group.

HBT is generally not recommended when withholding DOAC therapy, however the study by Kono *et al*[58] analysed the risk of bleeding with HBT during both DOAC and warfarin interruption and observed an incidence of PPB in 29% of cases.

Given the high risk of PPB in ESD procedure associated with DOAC therapy, it is recommended that DOACs should be withheld at least 24-48 h (72 h for dabigatran; in CrCl > 50) without HBT in order to minimise the risk of bleeding. This concurs with previous position statements.

ERCP with sphincterotomy (Table 55)

Two recent small retrospective studies analysing the risk of bleeding when on continued DOAC therapy in ERCP with sphincterotomy reported no incidences of PPB in their studies[122,138]. The risk of bleeding when DOAC therapy was withheld with HBT was also compared in the study by Muro *et al*[138] and found that HBT was a significant risk factor for bleeding. The incidence of PPB in this study was reported in 6.5% of cases. This absolute risk of bleeding when DOAC therapy is withheld compares similarly to the overall risk of bleeding in the absence of anticoagulant or antiplatelet use (6.5% *vs* 0.45%-9.9%, respectively) (Table 9).

These two small studies may suggest that continued DOAC in ERCP with sphincterotomy may be safe. However, until larger RCTs adequately evaluate the risk of bleeding, it is still recommended that DOACs be withheld at least 24-48 h (72 h for dabigatran; in CrCl > 50) without HBT before ERCP with sphincterotomy to minimise the risk of bleeding. This concurs with previous position statements.

PEG/PEJ insertion (Table 56)

Limited data is available that considers the risk of PPB in PEG/PEJ insertion while on DOAC therapy. One study by Lee *et al*[123] evaluated the risk of bleeding when on either warfarin or DOAC monotherapy. It observed a seven-fold increased relative risk of PPB associated with warfarin or DOAC use (OR: 7.26, 95%CI, 2.23-23.68, P = 0.001). However, this study was limited by not specifying the bleeding risk directly related to DOAC therapy use, nor did it specify whether DOAC therapy was continued or

withheld before the procedure.

Given the limited data and significant increased risk of PPB associated with anticoagulant use, it is recommended that DOACs should be withheld at least 24-48 h (72 h for dabigatran; in CrCl > 50) without HBT. This concurs with previous position statements.

DISCUSSION

The current position statements and guidelines from the major gastroenterology societies have provided endoscopists with evidenced-based systematic approaches to pre, peri and post-operative management of patients on anticoagulant and antiplatelet agents in the context of both low and high-risk endoscopic procedures. While there has been sufficient evidence on the index risk of bleeding in common endoscopic procedures in the absence of anticoagulant and/or antiplatelet use, the evidence surrounding bleeding risk while on anticoagulant and/or antiplatelet agents is still evolving.

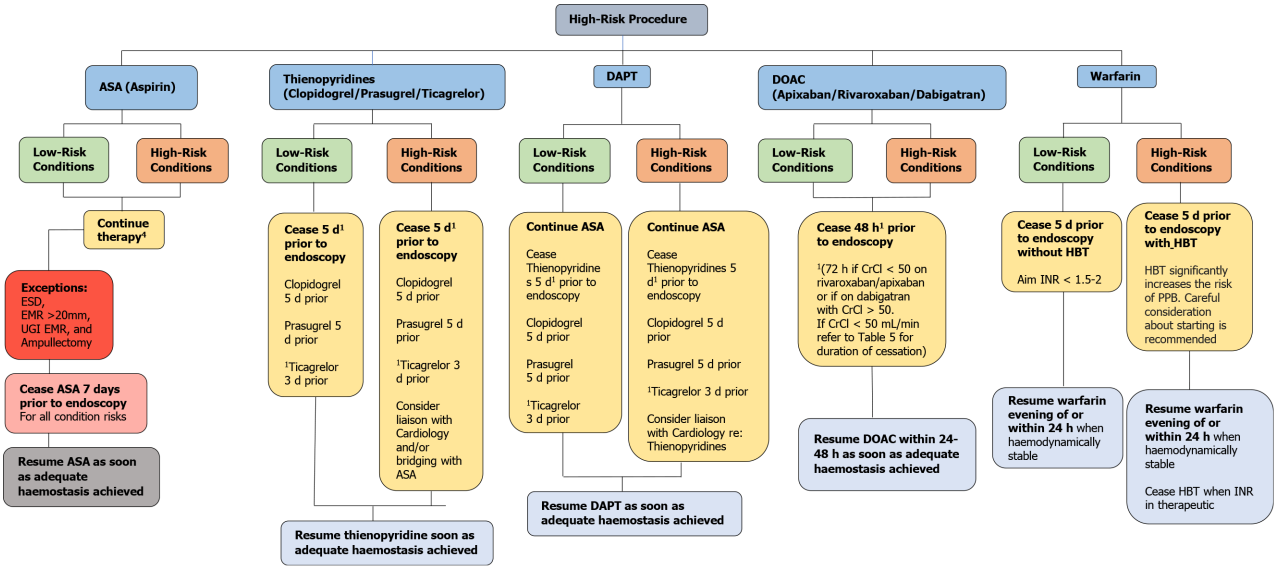
It is well established that anticoagulant and antiplatelet therapy is associated with an increased risk of PPB in endoscopic procedures. The reported risk will vary depending on endoscopic procedure and the study in which the data was published, but overall, the rate is similar over various publications and has been emphasised in this review. This variability may be explained by the different approaches taken by each study, the patient and geographical demographics, and the technical competency of the proceduralists.

There is no doubt temporary interruption of anticoagulant and antiplatelet therapy, compared to continuation therapy, reduces the risk of PPB in endoscopic procedures. However, this needs to be carefully considered against the risk of thromboembolic event and the potential serious irreversible consequences that comes with anticoagulant and antiplatelet interruption. Careful timing of anticoagulant and antiplatelet interruption to minimise the risk of PPB, while avoiding unnecessary increased risk of thromboembolic event, is of utmost importance. The aim of this review is to provide an evidence-based framework for safe clinical application of anticoagulant and antiplatelet management in the context of both low and high-risk endoscopic procedures for all endoscopists, as outlined in Figures 1 and 2.

This article has reviewed and considered the last 10 years of originally published literature and has found the evidence largely agrees with the current position statements and guidelines from the major gastroenterology societies in anticoagulant and antiplatelet agent management in endoscopic procedures. However, as highlighted earlier, there is emerging evidence that calls attention to some discrepancies in the current recommendations.

For example, current position statements and guidelines[2-4] advise warfarin should be bridged with HBT in all patients with high risk of thromboembolic event undergoing high-risk endoscopic procedures. Peri-endoscopic management with HBT is now becoming a controversial management decision with regards to its efficacy and safety. Numerous studies highlighted in this review have demonstrated that the use of HBT is associated with a two- to three-fold increased risk of PPB[7,41,142], while being non-superior in thromboembolic event prevention, compared to warfarin cessation without HBT[1,107,143,144]. This heightened risk of PPB associated with HBT has been shown in a range of endoscopic procedures, including EMR, ESD, polypectomy, EUS ± FNA and ERCP with sphincterotomy. However, this is still emerging evidence and further larger studies directly looking at the safety of HBT compared to warfarin cessation without HBT, specifically evaluating the risk of PPB and the efficacy in thromboembolic prevention, is still very much needed. We currently recommend that HBT use should be considered carefully in all patients undergoing an endoscopic procedure despite current guidelines from major gastroenterology societies still advising for HBT in patients undergoing high-risk endoscopic procedures.

In addition, current position statements and guidelines[2-4] considers CSP for polyps < 10 mm as a high-risk procedure and advises anticoagulant and antiplatelet therapy be ceased before the procedure. However, the risk of PPB on continued antiplatelet therapy of aspirin or thienopyridine (either as monotherapy or DAPT) in CSP for polyps < 10 mm has been reported to be overall low in small retrospective studies[111,113]. Even on continuation DAPT, the risk of PPB is only estimated to be around 2.4% as reported in a small RCT by Won *et al*[112]. Therefore, continuing antiplatelet therapy in CSP for polyps < 10 mm may be possible in some circumstances. There is also no significantly increased risk of PPB shown when



High-Risk Procedures	
- Polypectomy - ESD - EMR of polyps ≥ 2 cm - ERCP with sphincterotomy +/- balloon sphincteroplasty - Ampullectomy	- Therapy of varices - PEG / PEJ insertion - EUS with FNA - Dilatation of strictures - Cystgastrostomy - Tumour ablation - Balloon enteroscopy

Low-Risk Conditions	High-Risk Conditions[4]
- Mechanical aortic valve (without any risk factors[1]) - All bioprosthetic heart valves - VTE > 12 mo (with no other risk factors[1]) - Stable CAD - AF without valvular disease and CHA_2DS_2-VASc[2] < 2	- AF with mitral stenosis - Mechanical mitral valve - Mechanical aortic valve with one or more risk factors[1] - VTE < 3-12 mo - Thrombophilia - AF with CHA_2DS_2-VASc[2]≥2 - PCI – DES ≤ 12 mo or BMS ≤ 3 mo (with no other history of stent occlusion)[3] - Active malignancy

[1]AF, prior CVA or TIA, HTN, DM, CCF, age > 75
[2]CHA_2DS_2-VASc = CCF, HTN, age ≥ 75 (2 pts), DM, stroke (2 pts), vascular disease, age 65–74, female
[3]If ACS or PCI < 6 wk, ideally defer the procedure unless emergency procedure
[4]Medium-risk conditions (indicated in the APAGE-APSDE guideline only) have been considered as high-risk procedures

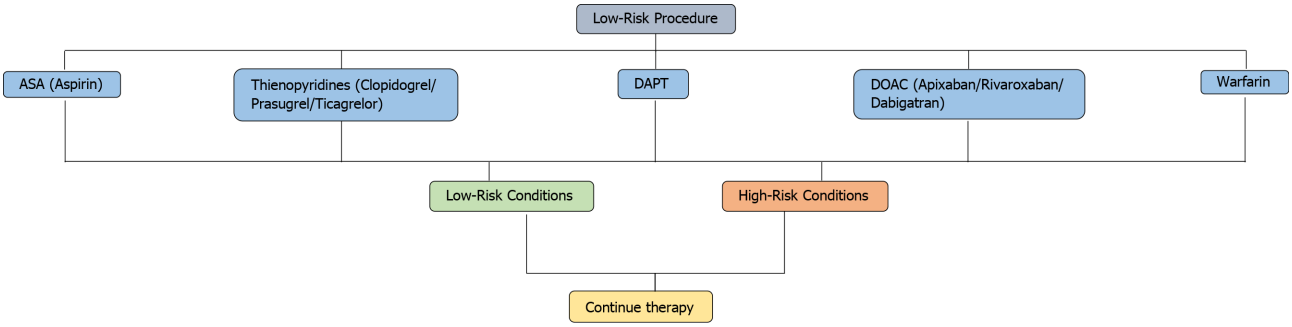
Figure 1 An evidence-based framework for safe clinical application of anticoagulant and antiplatelet management in the context of high-risk endoscopic procedures for all endoscopists. ASA: Acetylsalicylic acid; DAPT: Dual antiplatelet therapy; DOAC: Direct oral anticoagulant; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; UGI: Upper Gastrointestinal; CrCl: Creatinine clearance; HBT: Heparin bridging therapy; INR: International normalisation ratio; PPB: Post-procedural bleeding; ERCP: Endoscopic retrograde cholangiopancreatography; PEG: Percutaneous endoscopic gastrostomy; PEJ: Percutaneous endoscopic jejunostomy; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; VTE: Venous thromboembolism; CAD: Coronary artery disease; AF: Atrial fibrillation; PCI: Percutaneous coronary intervention; DES: Drug eluding stent; BMS: Bare metal stent; CVA: Cerebrovascular accident; TIA: Transient ischaemic attack; HTN: Hypertension; DM: Diabetes mellitus; CCF: Congestive cardiac failure; ACS: Acute coronary syndrome.

anticoagulant therapy (DOAC or warfarin) is continued in CSP for polyps < 10 mm[110,111,133]. However, this is still emerging evidence and has only been captured in a few retrospective studies and one small RCT. Further larger studies directly looking at the safety of continuation therapy is still needed. Furthermore, although the risk of PPB is not significantly increased, uninterrupted anticoagulant and antiplatelet therapy in CSP for polyps < 10 mm has shown to be associated with a significantly increased risk of immediate/intraprocedural bleeding, estimated at around 4.8%-17.8% when on DAPT[111,112], 11.9% when on a DOAC[111] and 5.7%-9.8% when on warfarin[111,133]. Given the current paucity of high-quality evidence and significant increased risk of immediate/intraprocedural bleeding, until more substantial evidence becomes available to verify the safety of continuation therapy, we recommend all anticoagulant and antiplatelet therapy be ceased before CSP for polyps < 10 mm, in accordance to the current position statements and guidelines.

CONCLUSION

This review largely agrees with the current position statements and guidelines from the major gastroenterology societies on the recommendations on anticoagulant and antiplatelet management in endoscopic procedures. Although, it has also highlighted some emerging discrepancies that requires further exploration in future guidelines, such as the two- to three-fold increased risk of PPB with HBT, and that anticoagulant and antiplatelet therapy may be safe to be continued in CSP for polyps < 10 mm.

In the meantime, we recommend strict endoscopic practice in accordance with the current major Gastroenterology guideline recommendations[2-4] be applied. Although in certain situations, anticoagulant and antiplatelet management may need to be



Low-Risk Procedures
- Diagnostic endoscopy with biopsy - ERCP with stenting without sphincterotomy - EUS without FNA - Diagnostic push or device assisted enteroscopy - Capsule endoscopy - Oesophageal, enteral, and colonic stenting - Argon plasma coagulation - Barrett's ablation

Low-Risk Conditions	High-Risk Conditions[4]
- Mechanical aortic valve (without any risk factors[1]) - All bioprosthetic heart valves - VTE > 12 mo (with no other risk factors[1]) - Stable CAD - AF without valvular disease and CHA_2DS_2-VASc[2] < 2	- AF with mitral stenosis - Mechanical mitral valve - Mechanical aortic valve with one or more risk factors[1] - VTE < 3-12 mo - Thrombophilia - AF with CHA_2DS_2-VASc[2] ≥ 2 - PCI – DES ≤ 12 mo or BMS ≤ 3 mo (with no other history of stent occlusion)[3] - Active malignancy
[1]AF, prior CVA or TIA, HTN, DM, CCF, age > 75	
[2]CHA_2DS_2-VASc = CCF, HTN, age ≥ 75 (2 pts), DM, stroke (2 pts), vascular disease, age 65-74, female	
[3]If ACS or PCI < 6 wk, ideally defer the procedure unless emergency procedure	
[4]Medium-risk conditions (indicated in the APAGE-APSDE guideline only) have been considered as high-risk procedures	

Figure 2 An evidence-based framework for safe clinical application of anticoagulant and antiplatelet management in the context of low-risk endoscopic procedures for all endoscopists. ASA: Acetylsalicylic acid; DAPT: Dual antiplatelet therapy; DOAC: Direct oral anticoagulant; ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; VTE: Venous thromboembolism; CAD: Coronary artery disease; AF: Atrial fibrillation; PCI: Percutaneous coronary intervention; DES: Drug eluding stent; BMS: Bare metal stent; CVA: Cerebrovascular accident; TIA: Transient ischaemic attack; HTN: Hypertension; DM: Diabetes mellitus; CCF: Congestive cardiac failure; ACS: Acute coronary syndrome.

considered on a case by case basis and tailored to the individual. Consultation with a cardiologist or haematologist is advised in these instances to ensure optimal patient safety.

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ORIGINAL ARTICLE

Basic Study

Peroral traction-assisted natural orifice trans-anal flexible endoscopic rectosigmoidectomy followed by intracorporeal colorectal anastomosis in a live porcine model

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Abstract

BACKGROUND

Compared to traditional open surgery, laparoscopic surgery has become a standard approach for colorectal cancer due to its great superiorities including less postoperative pain, a shorter hospital stay, and better quality of life. In 2007, Whiteford *et al* reported the first natural orifice trans-anal endoscopic surgery (NOTES) sigmoidectomy using transanal endoscopic microsurgery. To date, all cases of NOTES colorectal resection have included a hybrid laparoscopic approach with the use of established rigid platforms.

AIM

To introduce a novel technique of peroral external traction-assisted transanal NOTES rectosigmoidectomy followed by intracorporeal colorectal end-to-end anastomosis by using only currently available and flexible endoscopic instrumentation in a live porcine model.

METHODS

Three female pigs weighing 25-30 kg underwent NOTES rectosigmoid resection. After preoperative work-up and bowel preparation, general anesthesia combined with endotracheal intubation was achieved. One dual-channel therapeutic endoscope was used. Carbon dioxide insufflation was performed during the

Hospital (Approval No. 2014-ZQN-ZD-6).

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operation. The procedure of trans-anal NOTES rectosigmoidectomy included the following eight steps: (1) The rectosigmoid colon was tattooed with India ink by submucosal injection; (2) Creation of gastrostomy by directed submucosal tunneling; (3) Peroral external traction using endoloop ligation; (4) Creation of rectostomy on the anterior rectal wall by directed 3 cm submucosal tunneling; (5) Peroral external traction-assisted dissection of the left side of the colon; (6) Trans-anal rectosigmoid specimen transection, where an anvil was inserted into the proximal segment after purse-string suturing; (7) Intracorporeal colorectal end-to-end anastomosis using a circular stapler by a single stapling technique; and (8) Closure of gastrostomy using endoscopic clips. All animals were euthanized immediately after the procedure, abdominal exploration was performed, and the air-under-water leak test was carried out.

RESULTS

The procedure was completed in all three animals, with the operation time ranging from 193 min to 259 min. Neither major intraoperative complications nor hemodynamic instability occurred during the operation. The length of the resected specimen ranged from 7 cm to 13 cm. With the assistance of a trans-umbilical rigid grasper, intracorporeal colorectal, tension-free, end-to-end anastomosis was achieved in the three animals.

CONCLUSION

Peroral traction-assisted transanal NOTES rectosigmoidectomy followed by intracorporeal colorectal end-to-end anastomosis is technically feasible and reproducible in an animal model and is worthy of further improvements.

Key Words: Transanal; Natural orifice trans-anal endoscopic surgery; Rectosigmoidectomy; Intracorporeal anastomosis; External traction

Core Tip: A novel technique, natural orifice trans-anal endoscopic (NOTES) rectosigmoidectomy followed by intracorporeal colorectal end-to-end anastomosis, may be successfully performed in a live porcine model with the assistance of peroral external traction and the trans-umbilical rigid grasper.

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INTRODUCTION

Compared to traditional open surgery, laparoscopic surgery has become a standard approach for colorectal cancer due to its great superiorities including less postoperative pain, a shorter hospital stay, and better quality of life. Since the first report of its clinical application in 1991, an increasing number of minimally invasive surgical techniques, including single-incision laparoscopic surgery (SILS)[1], needlescopic surgery (NS)[2], and natural orifice transluminal endoscopic surgery (NOTES)[3], have been developed rapidly. Of these, only NOTES can provide an opportunity for incision-free abdominal surgery. Although NOTES-related techniques continue to evolve, they remain mainly confined to animal models due to technical constraints and instrument limitations. In 2007, Whiteford *et al*[4] reported the first NOTES sigmoidectomy using transanal endoscopic microsurgery. To date, all cases of NOTES colorectal resection have included a hybrid laparoscopic approach with the use of established rigid platforms. Our study aimed to introduce the novel technique of peroral external traction-assisted transanal NOTES sigmoidectomy followed by

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intracorporeal colorectal end-to-end anastomosis by using only currently available and flexible endoscopic instrumentation in a live swine model.

MATERIALS AND METHODS

Animal preparation

Three female pigs weighing 25-30 kg were used in this study. Preoperative work-up and bowel preparation comprised a 3-d liquid diet and a 1-d fast, followed by preoperative polyethylene glycol given orally. The induction of anesthesia was achieved by an intramuscular injection of 100 mg ketamine, 10 mg droperidol, and 1 mg atropine, and the maintenance of anesthesia was achieved by an intravenous drip of propofol at a dosage of 10 mL/h after endotracheal intubation. The heart rate and oxygen saturation of each animal were monitored during the operation. Animals were maintained in a supine Trendelenburg position to allow for optimal access and peritoneal exploration[5]. One dual-channel therapeutic endoscope (GIF-2TQ260M, Olympus) was used. Carbon dioxide insufflation was performed during the operation. This study was approved by the Institutional Animal Use and Care Committee of Beijing Pinggu Hospital and Fuzhou General Hospital of Nanjing Military Command (IACUC-2015-010).

Peroral traction-assisted transanal NOTES sigmoidectomy followed by intracorporeal colorectal end-to-end anastomosis under trans-gastric endoscopic guidance

The anterior wall of the rectosigmoid colon was tattooed with India ink by submucosal injection under trans-anal endoscopic vision (Figures 1 and 2).

Creation of gastrostomy by directed submucosal tunneling under trans-gastric endoscopic vision[5]: A 2-cm transversal mucosal incision was created near the gastroesophageal junction with a dual knife (KD650L; Olympus, Tokyo Japan), followed by the creation of a 3-5 cm longitudinal submucosal pelvis-directed tunnel. The tunnel ended with a seromuscular incision, and the exit site was selected at the anterior wall of the stomach.

Peroral external traction using endoloop ligation under trans-gastric endoscopic vision: An external endoloop knotted to a segment of dental floss was passed through by a twin grasper[6] *via* one of the accessory channels of the endoscope. Then, the dual-channel therapeutic endoscope was again advanced into the peritoneal cavity through the gastrostomy site. After abdominal exploration, the twin grasper was used to catch and pull the anterior wall of the rectosigmoid colon tattooed with India ink so that the endoloop might rope the part of the targeted colon. Once the endoloop was tightened followed by stretching of the floss, peroral external traction was achieved, allowing exposure of the sigmoid mesocolon and subsequent endoscopic dissection of the vessel and mesentery.

Creation of rectostomy on the anterior rectal wall 5 cm distal to the tattooed marker of the rectosigmoid colon by using directed short submucosal tunneling under trans-anal endoscopic vision: This was the same as the creation of gastrostomy.

Peroral external traction-assisted dissection of the left side of the colon under trans-anal endoscopic vision: With the help of peroral external traction, the sigmoid colon mesentery was mobilized off the retroperitoneum with a hook knife (model KD-620LR; Olympus). The inferior mesenteric vessels were successfully dissected using a Coagrasper (model FD-410LR; Olympus) and endoscopic clips (HX-600-135; Olympus), which was similar to the description issued by Park *et al*[7]. After being dissected for around ten cm in length, the mobilized rectosigmoid colonic segment was transected at the site of the tunnel entrance.

Trans-anal rectosigmoid specimen transection: The mobilized rectosigmoid colon was exteriorized and transected trans-anally. A 25-mm circular stapler anvil (Medtronic) was inserted into the proximal segment after purse-string suturing, and the proximal bowel was then returned into the abdomen.

Intracorporeal end-to-end colorectal anastomosis using a circular stapler by a single stapling technique under trans-gastric endoscopic guidance: The dual-channel therapeutic endoscope was again advanced into the peritoneal cavity through the gastrostomy site. Pneumoperitoneum was reestablished, and then an endoloop was used to ligate the lateral rectostomy by endoscopy. After the stapler was inserted into the rectum and pricked the top wall of the rectum, a trans-umbilical rigid grasper was used to orient the proximal bowel properly and then guide the proximal stapler anvil

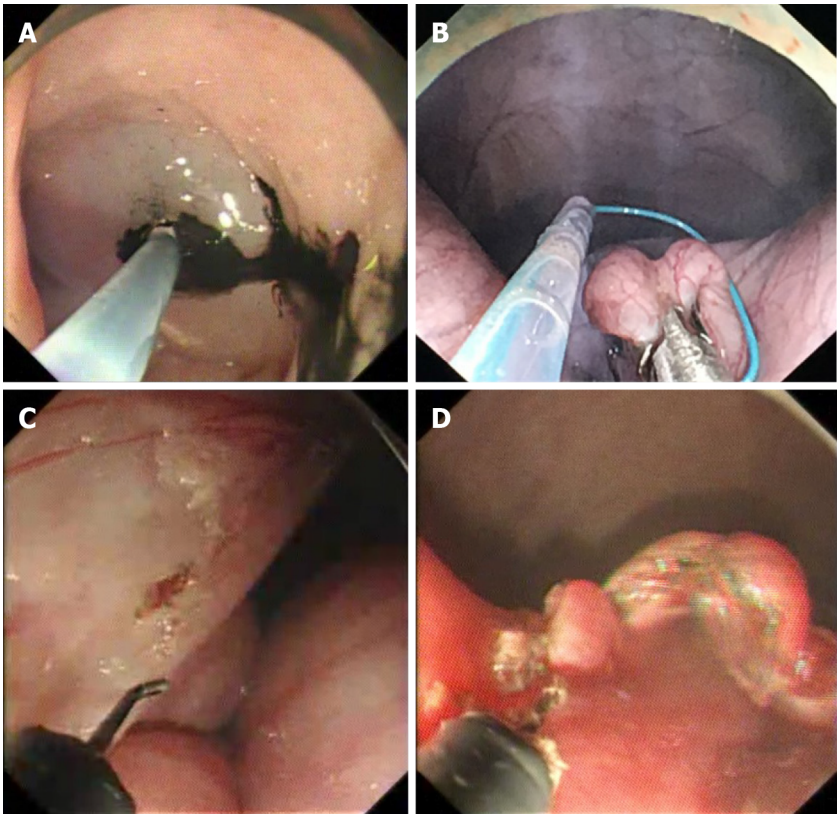

Figure 1 Peroral traction-assisted transanal natural orifice trans-anal endoscopic surgery sigmoidectomy followed by intracorporeal colorectal end-to-end anastomosis under trans-gastric endoscopic guidance. A: The anterior wall of the rectosigmoid colon was tattooed with India ink by submucosal injection; B: An endoloop was placed over the anti-mesenteric side of one colonic segment for traction; C: Dissection of the inferior mesenteric vessels; D: The mobilized rectosigmoid colon was exteriorized and transected trans-anally.

to mate with the stapler. Once apposed, the stapler was fired. The stapler was then removed, and the anastomotic tissue rings were immediately inspected for completeness by trans-anal endoscopy.

Closure of gastrostomy using endoscopic clips under trans-gastric endoscopic vision: The defect of the gastric tunnel entrance was closed with endoscopic clips.

After the procedure, all three animals were euthanized immediately, abdominal exploration was performed, and the air-under-water leak test was carried out[4]. The pelvis was filled with normal saline, and the rectum was insufflated to confirm whether the anastomosis was airtight.

Euthanasia and outcome measurements

The primary outcome of this study was the procedure success rate. The secondary outcomes were the total operative time, specimen length, completeness of colorectal anastomosis, and adverse event rate in the perioperative period. At necropsy, the anastomosis was tested for leaks using the air-under-water test.

Animal care and use statement

The animal protocol was designed to minimize pain or discomfort to the animals. All animals were euthanized by barbiturate overdose (intravenous injection, 150 mg/kg pentobarbital sodium) for autopsy.

RESULTS

The procedure was completed in all three animals, with the total operation time ranging from 193 min to 259 min (Table 1). Neither intraoperative complications nor hemodynamic instability occurred during the operation. Adequate anatomic exposure around the inferior mesenteric vessels was achieved by peroral external traction using endoloop ligation. Endoscopic dissection of the inferior mesenteric vessels was successful in all cases. The length of the resected specimen ranged from 7 cm to 13 cm,

Table 1 Results of the procedure

Animal No.	Rectosigmoidectomy	Specimen length (cm)	Duration (min)	Anastomosis completeness
1	Success	9	259	Complete
2	Success	13	217	Uncomplete
3	Success	7	193	Complete

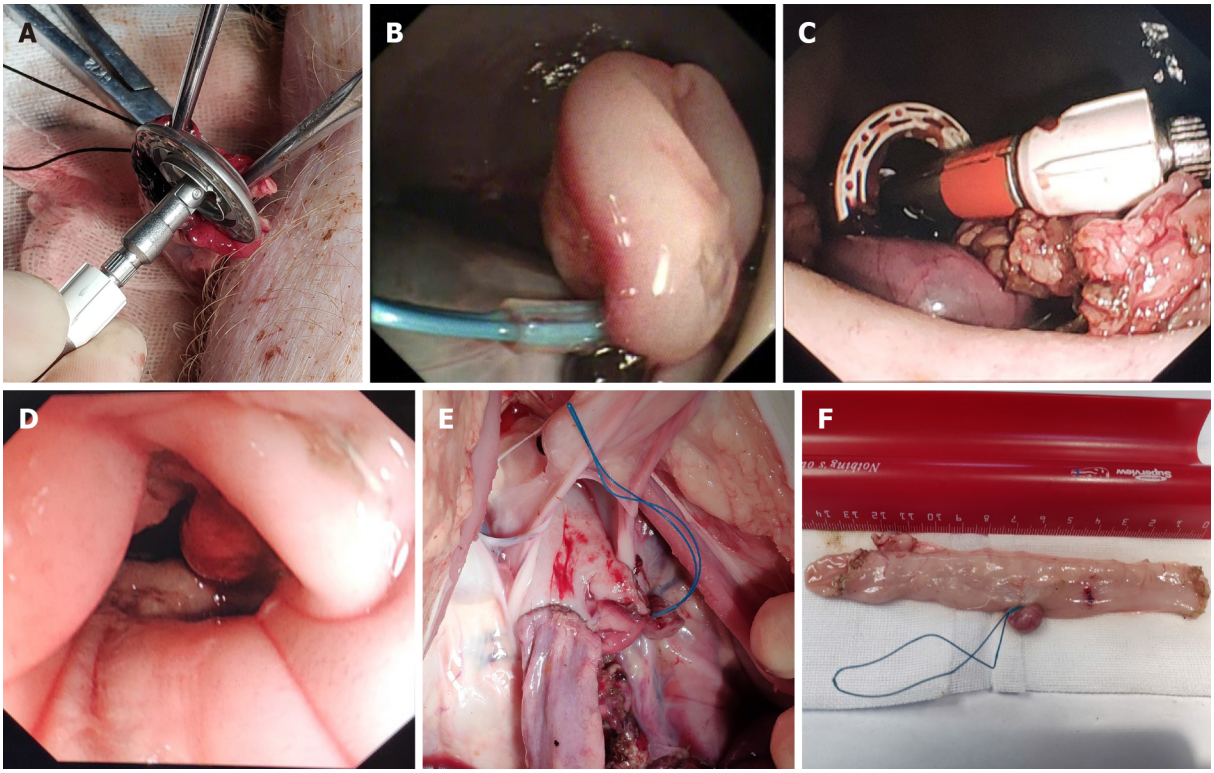

Figure 2 Peroral traction-assisted transanal natural orifice trans-anal endoscopic surgery sigmoidectomy followed by intracorporeal colorectal end-to-end anastomosis under trans-gastric endoscopic guidance. A: A purse-string suture was placed around the top of the open proximal colonic segment after a stapler anvil was inserted; B: An endoloop was used to ligate the lateral rectostomy by endoscopy; C: The anvil was used to approach the stapler with the assistance of a rigid grasper; D: Endoscopic observation of the colorectal anastomotic tissue ring; E: View *via* laparotomy of the lower abdomen and pelvis showing colorectal end-to-end anastomosis; F: The resected sigmoid colon specimen.

attached by the sigmoid mesentery.

With the assistance of a trans-umbilical rigid grasper, intracorporeal end-to-end colorectal anastomosis was achieved in all three animals. The anastomotic tissue ring in the second case was noted to be incomplete along the posterior rectal wall due to the insufficient occluding purse-string suturing of the proximal colonic segment. This may be a result of excessive resection of the sigmoid colon leading to retraction of the proximal segment, impairing sufficient purse-string suturing. The anastomotic defect was then reinforced with clips by tans-anal endoscopy.

At necropsy, there were no injuries to the adjacent organs. A properly oriented, tension-free colorectal end-to-end anastomosis was achieved in all three animals. Fortunately, the leak test was also negative in all animals regardless of whether anastomotic completeness was achieved.

DISCUSSION

To the best of our knowledge, this is the first study assessing the feasibility and safety of peroral external traction-assisted transanal NOTES sigmoidectomy followed by intracorporeal colorectal end-to-end anastomosis by using only currently available endoscopic flexible accessories except a rigid grasper in a live swine model.

In our study, endoscopic sigmoid mesocolon dissection, major vessel ligation, and

en bloc retrieval were feasible *via* the pure NOTES approach. As Park *et al*[7] stated, "The most important is that the operating field exposure through traction should be performed before dissection itself". Different from the description of Park *et al*[7], in our study, external traction of the sigmoid mesocolon was achieved through trans-oral introduction of an endoloop knotted to a segment of dental floss. Furthermore, our traction method could be used in the whole colon, while traction through the trans-anal introduction of a circular stapler was only available for the sigmoid colon[7]. Notably, the direction of traction was fixed both in our study and Park SJ's study. In the future, gastrointestinal endoscopic robots may enable real-time changes in traction direction by remote control[8].

The CO_2 pneumoperitoneum maintained by an endoscopic insufflator also permitted intra-abdominal visualization. Since it was difficult to monitor the intra-abdominal pressure during the procedure, endoscopic discontinuous suction was necessary.

In contrast to extracorporeal colorectal anastomosis published in previous reports[9-13], intracorporeal end-to-end anastomosis under trans-gastric endoscopic guidance was introduced in our study to achieve high colorectal anastomosis. According to the updated metaanalysis, compared to extracorporeal anastomosis, intracorporeal anastomosis may be associated with a shorter extraction site incision, faster bowel recovery, fewer perioperative complications, and lower rates of conversion to open surgery, anastomotic leakage, surgical site infection, and incisional hernia[14-18]. In our study, the most technically challenging and time-consuming step was to mate the proximal stapler anvil with the stapler inserted trans-anally. A trans-umbilical rigid grasper was used to achieve alignment.

Similar to gastrostomy, lateral rectostomy on the anterior rectal wall was achieved by using directed short submucosal tunneling for subsequent end-to-end anastomotic creation.

To date, gastric closure remains one of the major difficulties, and endoscopic clipping can only achieve mucosal apposition. For secure gastric closure, the creation of gastrostomy by directed submucosal tunneling was applied in this study so that we only needed to close the mucosal defect of the gastric tunnel entrance[19].

There were also several technical challenges in our study. First, due to the lack of a wide field of vision and the spatial orientation of laparoscopy, accurate endoscopic dissection is still technically demanding. It is difficult to precisely identify the beginning and endpoint of the colon segment to be dissected. Since virtual reality with three-dimensional reconstruction allows an enhanced understanding of crucial anatomical details, it would contribute to improving safety and accuracy in endoscopic surgery[20-23]. Second, although intracorporeal end-to-end anastomosis was achieved in this study, rigid instrumentation was still needed. Before clinical application of this technique, instrument development, including endoscopic anastomotic equipment, would be required[24-26]. Third, to determine whether the anastomotic method can achieve histological anastomosis, subsequent survival experiments should be carried out.

CONCLUSION

In conclusion, this novel technique for performing NOTES sigmoidectomy with the assistance of peroral external traction, followed by intracorporeal colorectal end-to-end anastomosis aided by a trans-umbilical rigid grasper, is safe and feasible in a live animal model and is worthy of further improvements.

ARTICLE HIGHLIGHTS

Research background

Since 1991, an increasing number of minimally invasive surgical techniques, including single-incision laparoscopic surgery (SILS), needlescopic surgery (NS), and natural orifice transluminal endoscopic surgery (NOTES), have been developed rapidly. To date, all cases of NOTES colorectal resection have included a hybrid laparoscopic approach with the use of established rigid platforms.

Research motivation

Our research aimed to improve NOTES-related techniques.

Research objectives

Our study aimed to introduce the novel technique of peroral external traction-assisted transanal NOTES sigmoidectomy followed by intracorporeal colorectal end-to-end anastomosis by using only currently available and flexible endoscopic instrumentation in a live swine model.

Research methods

Three female pigs weighing 25-30 kg underwent NOTES rectosigmoid resection. The procedure of trans-anal NOTES rectosigmoidectomy included the following eight steps: (1) The rectosigmoid colon was tattooed with India ink by submucosal injection; (2) Creation of gastrostomy by directed submucosal tunneling; (3) Peroral external traction using endoloop ligation; (4) Creation of rectostomy on the anterior rectal wall by directed 3 cm submucosal tunneling; (5) Peroral external traction-assisted dissection of the left side of the colon; (6) Trans-anal rectosigmoid specimen transection, where an anvil was inserted into the proximal segment after purse-string suturing; (7) Intracorporeal colorectal end-to-end anastomosis using a circular stapler with a single stapling technique; and (8) Closure of gastrostomy using endoscopic clips.

Research results

The procedure was completed in all three animals, with the operation time ranging from 193 min to 259 min. The length of the resected specimen ranged from 7 cm to 13 cm. With the assistance of a trans-umbilical rigid grasper, intracorporeal colorectal, tension-free, end-to-end anastomosis was achieved in the three animals.

Research conclusions

Peroral traction-assisted transanal NOTES rectosigmoidectomy followed by intracorporeal colorectal end-to-end anastomosis is technically feasible and reproducible in an animal model and is worthy of further improvements.

Research perspectives

The techniques of NOTES rectosigmoidectomy need to be improved for clinical application.

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ORIGINAL ARTICLE

Observational Study

Evaluation of the diagnostic and therapeutic utility of retrograde through-the-scope balloon enteroscopy and single-balloon enteroscopy

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Abstract

BACKGROUND

Retrograde single balloon enteroscopy (SBE) is a minimally invasive procedure which is less frequently performed compared with antegrade SBE. There are few studies on the retrograde through-the-scope enteroscopy (TTSE), a novel technique for evaluation of the small bowel.

AIM

To compare the clinical utility and safety of retrograde TTSE with retrograde SBE.

METHODS

Clinical data and complications of retrograde TTSE (2014-2018) and retrograde SBE (2011-2018) performed in a community hospital were reviewed and presented as mean ± SD or frequency (%) and compared using proper statistical tests. Technical success was defined as insertion of the enteroscope > 20 cm beyond ileocecal valve.

the final submitted manuscript.

Institutional review board statement: The study was approved by the Texas Tech University Health Sciences Center Institutional Review Board (Approval Number. E14078).

Conflict-of-interest statement: The authors have nothing to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at [marc.zuckerman@ttuhsc.edu]. Consent was not obtained but the presented data are anonymized and risk of identification is low.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

RESULTS

Data obtained from 54 retrograde SBE in 49 patients and 27 retrograde TTSE in 26 patients were studied. The most common indication for retrograde enteroscopy was iron deficiency anemia (41 patients) followed by gastrointestinal bleeding (37 patients), and chronic diarrhea (7 patients). The duration of retrograde SBE procedure (91.9 ± 34.2 min) was significantly longer compared with retrograde TTSE (70.5 ± 30.7 min) (P = 0.04). Technical success was comparable in TTSE [23/27 (85.2%)] and SBE [41/54 (75.9%) (P = 0.33)]. The mean depth of insertion beyond the ileocecal valve in retrograde SBE (92.5 ± 70.0 cm) tended to be longer compared with retrograde TTSE (64.6 ± 49.0 cm) (P = 0.08). No complication was observed in this study.

CONCLUSION

Both retrograde TTSE and retrograde SBE are feasible and safe. Retrograde TTSE takes a shorter time and has a comparable technical success with SBE. TTSE has a lower capacity of small bowel insertion.

Key Words: Enteroscopy; Small intestine; Gastrointestinal bleeding; Retrograde enteroscopy; Single balloon enteroscopy; Small intestinal endoscopy

Core Tip: Retrograde single balloon enteroscopy (SBE) and retrograde through–the-scope enteroscopy (TTSE) are minimally invasive procedures with limited data available about their value in the management of small intestinal pathologies. This study compared the clinical utility and safety of retrograde TTSE with retrograde SBE and found them to be feasible and safe with a shorter procedure time for retrograde TTSE and a comparable technical success with SBE.

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INTRODUCTION

The small bowel used to be inaccessible and out of reach by gastrointestinal endoscopists because of its depth, length and complex loops. For many decades, the only available diagnostic and therapeutic interventions for evaluation and management of small bowel disorders were radiographic imaging, laparotomy and intraoperative enteroscopy[1-3]. Video capsule endoscopy (VCE) revolutionized the evaluation of small bowel disorders due to its non-invasive nature and higher diagnostic yield compared with conventional imaging modalities, but remains a purely diagnostic modality without any interventional capability[4,5]. While current guidelines suggest VCE to be the first-line endoluminal intervention for suspected small bowel disorders[6], deep enteroscopy may be considered as the initial diagnostic procedure in select patients with a high level of suspicion of small-bowel angioectasias or in patients with surgically altered anatomy[7,8].

Balloon-assisted enteroscopy provides a minimally invasive diagnostic and therapeutic approach to the small bowel allowing real-time endoscopic assessment, tissue sampling and therapeutic interventions extending beyond the diagnostic capabilities of capsule endoscopy and radiographic imaging[9,10]. Single-balloon enteroscopy (SBE) is now available in many centers; however, the availability of double balloon enteroscopy and spiral enteroscopy is limited[11].

Diagnostic and therapeutic enteroscopy has two major routes, antegrade and retrograde enteroscopy. The technically easier route, antegrade SBE, is usually performed first for small bowel disorders of uncertain location. Retrograde SBE is

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more difficult and less commonly performed than antegrade, but can approach average insertion depths proximal to the ileocecal valve from 73 to 199 cm[11-13].

A new enteroscopy device has been designed to allow deep enteroscopy with a novel through–the-scope balloon [NaviAid (SMART Medical Systems Ltd, Ra'anana, Israel)][14,15]. This technique was introduced as a safe and effective way to perform deep enteroscopy by using a conventional colonoscope without the need for an enteroscope or an overtube. The ASGE guideline has not sufficiently elaborated on this newly introduced technique due to limited data regarding the use of this device for deep enteroscopy[16]. We conducted the current study to evaluate the clinical utility of retrograde TTSE and its impact on the diagnosis and management of small-bowel disorders and to compare both clinical and procedure characteristics of retrograde TTSE with retrograde SBE.

MATERIALS AND METHODS

Subjects

We collected data from consecutive adult patients (> 18 years old) who underwent retrograde balloon-assisted enteroscopy procedures at the University Medical Center in El Paso, a general hospital along the United States-Mexico border. The retrograde SBE studies were performed in the period from September 2011 to December 2018. The TTSE device was introduced after June 2014 and procedures were reviewed to December 2018. After June 2014, every other case was done with alternating retrograde enteroscopy methods depending on equipment availability. There were no preset criteria to prefer one technique over the other. This resulted in an approximately one to one allocation assignment. Double-balloon enteroscopy or the spiral-assisted enteroscopy system were not available at this institution. The study was approved by the Texas Tech University Health Sciences Center Institutional Review Board.

Procedure

Patient demographics, clinical characteristics, endoscopy procedure data and complications were reviewed. The electronic medical record was used to obtain information about patient demographics and clinical characteristics, use of prior VCE and documented adverse effects, enteroscopy procedure data (routes, duration of procedures, depth of insertion for successful endoscopy cases, diagnostic yield, findings, and interventions) and complications. The indications for enteroscopy included iron deficiency anemia, overt gastrointestinal bleeding, abdominal pain, chronic diarrhea, familial adenomatous polyposis screening, and previous abnormal imaging. Depth of insertion was estimated on withdrawal by counting in 10 cm intervals as the endoscope was slowly withdrawn.

All enteroscopy procedures were performed by an experienced gastroenterologist (Zuckerman MJ). Single balloon enteroscopy was done with the Olympus SIF-Q180 enteroscope (Olympus, Melville, NY, United States) (Figure 1A), the balloon overtube system and the inflation/deflation external device. The through-the-scope (NaviAid) balloon system (SMART Medical Systems Ltd.) consisted of a single-use catheter-based inflatable balloon inserted through the instrument channel of a standard adult colonoscope (Olympus CF-180 or CF-190) (Figure 1B) and the external inflation/deflation system[10]. Depth of insertion was estimated on withdrawal by counting 10 cm intervals as the endoscope was slowly withdrawn, similar to the technique previously described by Efthymiou *et al*[17] and utilized by Christian *et al*[18]. Technical success was defined as insertion of the endoscope greater than 20 cm beyond the ileocecal valve[18]. Procedure time was defined as the time from insertion to the time of complete withdrawal. All patients were monitored for complications. All patients were monitored for complications including uncontrolled bleeding (defined as need for blood transfusion), gastrointestinal perforation, infection, abdominal pain, fever, nausea and vomiting throughout the procedures and for 24 h afterward.

Statistical analysis

Continuous variables were described using mean and standard deviation while categorical variables were described using frequencies and percentages. Baseline characteristics were compared between groups using either Student's *t*-test or Wilcoxon sum rank test, for continuous data and Fisher's exact test for categorical data. Furthermore, primary and secondary outcomes between groups were also compared using Student's *t*-test or Wilcoxon rank sum test or Fisher's exact test depending on the type and distribution of outcome. One way analysis of variance was

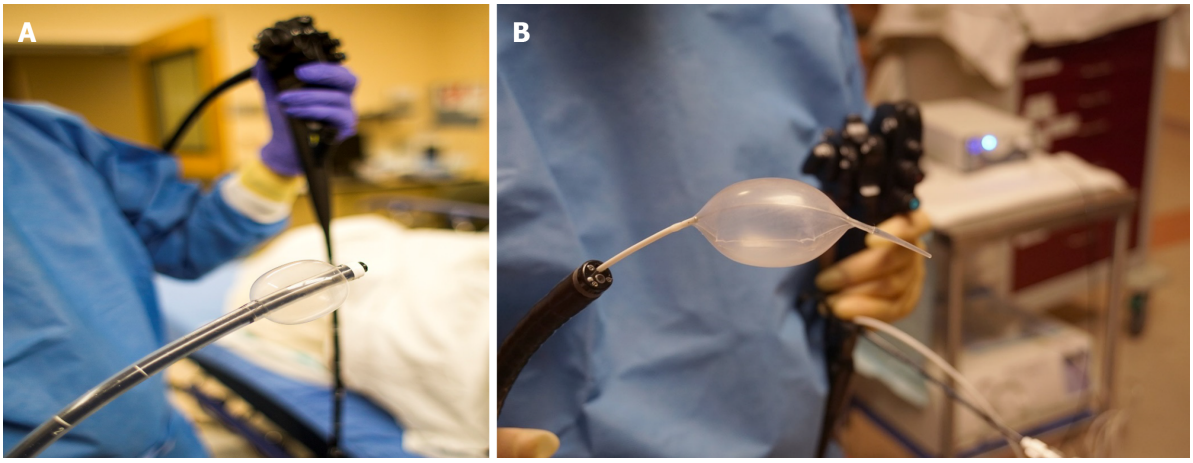

Figure 1 Enteroscopy. A: Single Balloon; and B: Through–the-scope balloon system.

used to compare the differences in the durations over the time periods while two way analysis of variance was used to compare the differences in the durations between two groups accounting for time period differences as well. Correlations were assessed using linear regression model.

RESULTS

A total of 81 retrograde enteroscopy procedures were performed in 75 patients during the study period. Overall, 54 retrograde SBE in 49 patients and 27 retrograde TTSE in 26 patients were performed. From 81 procedures, 74 was under general anesthesia, 6 under monitored anesthesia care and one under moderate sedation. There were no statistically significant differences in age, body mass index (BMI), gender, ethnicity, and history of abdominal surgery between the retrograde SBE and retrograde TTSE groups (Table 1). The main indications for both groups were iron deficiency anemia in 41 (50.6%), overt gastrointestinal bleeding in 37 (45.7%), abdominal pain in 17(21.0%), chronic diarrhea in 7 (8.6%), and FAP screening in 2 (2.5%). There were no differences in distribution of indications between two groups (Table 1). Thirty-nine patients and 19 patients underwent VCE before SBE and TTSE, respectively. The positive findings (35/39 and 17/19) were higher on VCE, but lower on both types of enteroscopy (15/54, 6/27) (Table 2). Other patients had abnormal imaging studies (CT abdomen, CT enterography, small bowel series) suggesting a distal small bowel lesion and would have gone straight to retrograde enteroscopy without VCE.

Retrograde enteroscopy was successful (> 20 cm beyond ileocecal valve) in 23/27 (85.2%) with TTS compared with 41/54 (75.9%) retrograde SBEs (P = 0.33). No specific trend was observed for the failure rate by time. Terminal ileal intubation was not achieved in 9/81 procedures [8 (14.8%) retrograde SBE and 1 (3.7%) TTSE]. The mean duration of procedures was longer in retrograde SBE (91.9 ± 34.2 min) compared with retrograde TTSE (70.5 ± 30.7 min) (P = 0.04). The mean depth of insertion beyond the ileocecal valve was not statistically different in retrograde SBE (92.5 ± 70.0 cm) compared with retrograde TTSE (64.6 ± 49.0 cm), but there was a trend for TTSE to have shorter depth of insertion (P = 0.08) (Table 3). There was no correlation between the depth of insertion and the duration of the procedure in retrograde SBE (linear regression R^2 = 0.01; P = 0.56) and retrograde TTSE (linear regression R^2 = 0.11; P = 0.23) groups. Analyzing the depth of endoscope insertion in successful procedures in consecutive time periods did not indicate any significant change from 2011 to 2018 (Figure 2).

Positive findings were detected in 21 (32.8%) of all retrograde enteroscopies, including angioectasia in 8, erosion or ulcers in 7, foreign body in 3, polyps in 2, strictures in 2, mass/gastrointestinal stromal tumor in 1, congestion/nonspecific inflammation in 1, and blood in the lumen in 1. Intervention was performed in 16/81 (19.8%) procedures or 16/21 (76.2%) of procedures with findings. Some findings did not require intervention. Small intestinal sampling was performed in 4 patients. The hemostasis procedures consisted of argon plasma coagulation (APC) in 7, hemoclip in 1, both APC and hemoclip in 1. There were no complications, such as uncontrolled

Table 1 Patient demographics and clinical characteristics

	Enteroscope device			
	Entire cohort	Retrograde SBE[1]	Retrograde TTSE[2]	
Number of patients	75	49	26	
	Mean (standard deviation)	Mean (standard deviation)	Mean (standard deviation)	*P* value
Age (yr)[3]	61.2 (17.6)	62.6 (16.5)	58.4 (19.6)	0.33
Body mass index[3]	29.0 (6.1)	28.7 (6.3)	29.6 (5.9)	0.55
Gender, *n* (%)				0.63
Female	43 (57.3)	27 (55.1)	16 (61.5)	
Male	32 (42.7)	22 (44.9)	10 (38.5)	
Ethnicity, *n* (%)				0.91
Hispanic	27 (36.0)	18 (36.7)	9 (34.6)	
Other non-hispanic	10 (13.3)	7 (14.3)	3 (11.5)	
White	38 (50.7)	24 (49.0)	14 (53.9)	
Indication[3]				0.63
Iron deficiency anemia, *n* (%)	41 (50.6)	28 (51.9)	13 (48.2)	
Overt GI bleeding	37 (45.7)	23 (42.6)	14 (51.9)	
Abdominal pain	17 (21.1)	7 (13.0)	10 (37.0)	
Diarrhea	7 (8.6)	4 (7.4)	3 (11.1)	
FAP screening	2 (2.5)	2 (3.7)	0 (0)	

[1]Single balloon enteroscopy.
[2]Through the scope.
[3]Some patients have 2 indications. GI: Gastrointestinal; FAP: Familial adenomatous polyposis; SBE: Single balloon enteroscopy; TTSE: Through–the-scope enteroscopy.

Table 2 Prior video capsule endoscopy

	Entire cohort	Retrograde SBE[1]	Retrograde TTSE[2]	
Number of procedures	81	54	27	
Prior video capsule, *n* (%)				1.00
No	23 (28.4)	15 (27.8)	8 (29.6)	
Yes	58 (71.6)	39 (72.2)	19 (70.4)	
Video capsule positive finding, *n* (%)				0.30
No	6 (10.3)	4 (10.3)	2 (7.4)	
Yes	52 (89.7)	35 (89.7)	17 (92.6)	

[1]Single balloon enteroscopy.
[2]Through the scope enteroscopy. SBE: Single balloon enteroscopy; TTSE: Through–the-scope enteroscopy.

bleeding, gastrointestinal perforation, infection, abdominal pain, fever, nausea and vomiting, reported and all of the patients tolerated the procedure.

DISCUSSION

In this study, we evaluated and compared the clinical utility and procedure

Table 3 Procedure data including routes, diagnostic yield, findings, and interventions

	Enteroscope device			
	Entire cohort	Retrograde SBE[1]	Retrograde TTSE[2]	
Number of procedures	81	54	27	
	Mean (SD)	Mean (SD)	Mean (SD)	*P*value[3]
Duration of procedure	86.2 (34.2)	91.9 (34.2)	70.5 (30.7)	0.04
Depth of the scope insertion	82.1 (64.1)	92.5 (70.0)	64.6 (49.0)	0.08
Successful procedure with diagnostic yield, *n* (%)	*n* = 64	*n* = 41	*n* = 23	0.39
Normal	43 (67.2)	26 (63.4)	17 (73.9)	
Positive finding	21 (32.8)	15 (36.6)	6 (26.1)	
Intervention performed, *n* (%)				0.38
No	65 (80.3)	45 (83.3)	20 (74.1)	
Yes	16 (19.8)	9 (16.7)	7 (25.9)	
Failed (2011-2018), *n* (%)	17 (21.0)	13 (24.1)	4 (14.8)	0.33
Terminal ileum not intubated	9 (11.1)	8 (14.8)	1 (3.7)	
Insertion < 20 cm	8 (9.9)	5 (9.3)	3 (11.1)	
Years	Failed/procedure	Failed/procedure	Failed/procedure	
2011-2012	5/14	5/14	-	
2013-2014	4/27	4/22	0/5	
2015-2016	6/26	3/11	3/15	
2017-2018	2/14	1/7	1/7	

[1]Single balloon enteroscopy.
[2]Through the scope enteroscopy.
[3]Compares retrograde single balloon enteroscopy and retrograde through–the-scope enteroscopy.

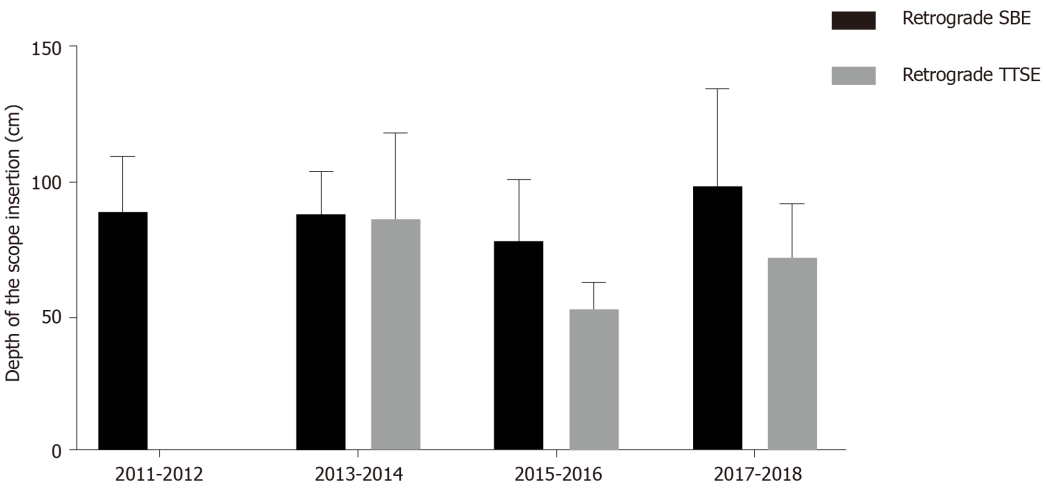

Figure 2 Depth of endoscope insertion beyond the ileocecal junction based on the endoscopic technique (bars represent mean ± SEM; two-way ANOVA; F (2, 45) = 0.1851; *P* = 0.83). SBE: Single balloon enteroscopy; TTSE: Through–the-scope enteroscopy.

characteristics of retrograde SBE and retrograde TTSE. We found that both interventions were safe with comparable diagnostic yield. Our study had an overall positive findings of 21/81 procedures (25.9%). The major findings included angioectasia 27 (33.3%) and erosions or ulcers 18 (22.2%). Interventions were performed in 20 (24.7%) procedures with most of them being hemostasis procedures.

Previous studies reported similar distributions with vascular lesions as the most common endoscopic findings. Our study had a lower diagnostic yield compared with others reporting 41%-65% and variable intervention rate for SBE ranging from 7%-54%[7,12-15]. The discrepancy between the higher yield on capsule endoscopy than on retrograde enteroscopy could be attributed to two factors. Not all procedures were successful and most importantly, retrograde enteroscopy depth of insertion may not have been sufficient to reach the abnormality seen on capsule endoscopy. Additionally, due to the time elapsed between capsule endoscopy and enteroscopy and the nature of some of the abnormalities seen, they may have no longer been present. Based on a new study, urgent enteroscopy might be associated with higher diagnostic and therapeutic yield with a lower small bowel rebleeding[19].

Small bowel enteroscopy is an effective diagnostic and therapeutic intervention for management of small bowel diseases, especially in patients with overt or occult gastrointestinal bleeding and chronic diarrhea[6,20]. DBE is a well-tolerated and safe procedure with a high diagnostic yield[9], but is somewhat laborious, requires a substantial operator learning curve, and requires relatively long procedure times[21-23]. On the other hand, SBE is a relatively newer procedure than DBE with shorter procedure time and comparable diagnostic yield, but with less probability to achieve total enteroscopy using both antegrade and retrograde routes. Retrograde SBE is technically more difficult compared with antegrade SBE[12,13]. Recently, a novel through–the-scope balloon system (NaviAid) was introduced as an enteroscopy device to allow deep enteroscopy insertion using standard colonoscopes[14,15,20]. Data on retrograde TTSE are very limited. According to a letter published in 2013, Rubin and Goeppinger[24] used the NaviAid balloon device in 6 patients for the diagnosis of ileal Crohn's disease. In all patients, TTSE permitted retrograde intubation of extra 15 to 60 cm of the ileum, which clarified disease activity in all patients, without any reported adverse events. Subsequently, Kumbhari *et al*[14] published a letter indicating they had successfully performed retrograde enteroscopy using TTS in 24 patients, 3 for the diagnosis and management of suspected ileal Crohn's disease. Initial concerns about the use of this device included advancing the balloon in a blind fashion through potentially inflamed ileal mucosa; however, complications in this setting have not been reported[14]. In 2015, a multicenter study was published that included reporting retrograde TTSE in 33 cases with an average depth of insertion of 89 cm (range: 20-150 cm) beyond the ileocecal valve and overall diagnostic yield of 44% with no procedure-related adverse events. The average advancement time for the enteroscopy cases was 15.5 min in this study[15]. In this multicenter study[15], there were no adverse events reported, including no mucosal injury or perforation and it has been used in patients with small bowel diverticula. We did not encounter adverse events in our study with either modality, but there is a possibility that since the TTSE balloon is inflated without direct vision, there could be a problem when there is a stricture or diverticulum in the proximal segment, despite the soft flexible nature of the balloon catheter and controlled inflation-deflation system.

In a large retrospective study of 136 retrograde SBE procedures conducted with an overtube endoscope system, Christian found a mean depth of insertion of 68.3 cm and mean time to completion of 41.7 min[18]. In another study of 36 patients who underwent retrograde SBE using a single-balloon technique, median procedure time was 54 min, with a mean insertion depth of 68 cm beyond the ileocecal valve. The technical success rate was 86%. The diagnostic and therapeutic yields were 61% and 25%, respectively[25].

Several factors may affect the success rate of retrograde enteroscopy, procedure time, and depth of insertion, including endoscopist experience, patient anatomy, the severity of symptoms/complaints as well as patient setting (inpatient *vs* outpatient). Shorter procedure time which we observed in this study would increase technical feasibility and cost-effectiveness of retrograde TTSE. Previous studies report a range of retrograde SBE procedure time of 48-78 min and a range of depth of insertion from 73-199 cm[12,18,26,27]. Our overall failure rate of 21% is similar to the 10%-30% failure rate reported by others[18,26,27].

Depth of insertion in our study tended to be longer with SBE. This was assessed using the visualization estimation method on withdrawal described by Efthymiou *et al*[17] and utilized in the large study of retrograde SBE by Christian *et al*[18]. There is no agreed upon accurate method for measurement of insertion depth. Another method proposed is the fold-counting method on withdrawal, which May *et al*[27] found to correlate in their study with the visual estimate method. The first validated method for measuring insertion depth was the Erlangen method used with double-balloon enteroscopy by estimating the net advancement of the enteroscope at each cycle of overtube advancement, after training with the model. This technique may be more

difficult to use in measuring the insertion depth in SBE than in double-balloon enteroscopy. However, depth of insertion always involves an estimate by the endoscopist[27]. Furthermore, we used the same technique developed for SBE to estimate depth of insertion using the TTSE system to provide consistency between results.

Our study had some limitations including nonrandomized design (patients were not randomized to be done with either TTSE or SBE), modest sample size, and lack of a gold standard for measurement of depth of insertion as discussed above. The post-study statistical power was 12% for the success rate and 10% for the diagnostic yield. Although the sample size was relatively modest in our study for success rate and diagnostic yield, the clinical difference in outcomes was within ± 10% indicating a comparable performance of two procedures for the success rate and diagnostic yield outcomes. This reflects that it is unlikely to observe significant differences in these outcomes even after substantially inflating the sample size for this study. The current sample size was sufficient to detect a statistically significant difference for the duration of procedures with 80% power at a 5% level of significance using an unpaired *t*-test. Other limitations of this study were the procedure which was performed by only one operator and the retrospective design. On the other hand, this is one of the few studies looking at efficacy and safety of retrograde TTSE and has the advantage of looking at this in the context of a center also doing retrograde SBE.

CONCLUSION

Both retrograde TTSE and SBE are feasible and safe. We demonstrate that the TTSE balloon system has comparable technical success and reduces enteroscopy time compared with SBE, but has a lower capacity of small bowel insertion. Larger prospective randomized studies are needed to further assess the diagnostic and therapeutic potential of the TTSE system and its role relative to other modalities available for evaluation of the small bowel.

ARTICLE HIGHLIGHTS

Research background

A new device has been introduced and designed to allow deep enteroscopy with a through-the-scope balloon which can be used for the more difficult retrograde approach.

Research motivation

To compare safety, feasibility and outcomes of retrograde enteroscopy performed by the novel through- the-scope enteroscopy (TTSE) and traditional single balloon enteroscopy (SBE) techniques.

Research objectives

To describe how retrograde enteroscopy with the novel TTSE differs from the traditional SBE and to provide an in-depth overview of both techniques with detailed description of clinical findings, success rate and outcomes.

Research methods

We performed a retrospective cohort study comparing clinical data and complications of retrograde TTSE and retrograde SBE in a community hospital. Technical success was considered as insertion of the enteroscope > 20 cm beyond the ileocecal valve.

Research results

Retrograde enteroscopy was safe and feasible using both systems. TTSE had comparable technical success, and reduced enteroscopy time compared with SBE, but with a lower capacity of small bowel insertion.

Research conclusions

TTSE is a promising method for retrograde examination of the small bowel in adults.

Research perspectives

Prospective multicenter studies to understand whether the findings of this study can be observed in other centers with different levels of experience and to compare the learning curve of TTSE *vs* SBE by different endoscopists.

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SYSTEMATIC REVIEWS

Nonsteroidal anti-inflammatory drug effectivity in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: A systematic review and meta-analysis

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Abstract

BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP) is the primary therapeutic procedure for the treatment of diseases affecting the biliary tree and pancreatic duct. Although the therapeutic success rate of ERCP is high, the procedure can cause complications, such as acute pancreatitis [post-ERCP pancreatitis (PEP)], bleeding and perforation.

AIM

To assess the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) in preventing PEP during follow-up.

METHODS

Databases such as MEDLINE, EMBASE and Cochrane Central Library were searched. Only randomized controlled trials (RCTs) comparing the efficacy of NSAIDs and placebo for the prevention of PEP were included. Outcomes evaluated included the incidence of PEP, severity of pancreatitis, route of administration, types, dose, and timing of administration of NSAIDs.

RESULTS

Twenty-six RCTs were considered eligible with a total of 8143 patients analyzed. Overall, 4020 patients used NSAIDs before ERCP and 4123 did not use NSAIDs (control group). Ultimately, 298 cases of post-ERCP acute pancreatitis were diagnosed in the NSAID group and 484 cases in the placebo group. The risk of PEP was lower in the NSAID group risk difference (RD): -0.04; 95% confidence interval (CI): -0.07 to - 0.03; number needed to treat (NNT), 25; $P < 0.05$. NSAID use effectively prevented mild pancreatitis compared to placebo use (2.5% *vs* 4.1%; 95%CI: -0.05 to -0.01; NNT, 33; $P < 0.05$), but information on moderate PEP and severe PEP could not be fully elucidated. Only rectal administration reduced the incidence of PEP with RD: -0.06; 95%CI: -0.08 to -0.04; NNT, 17; $P < 0.05$). Furthermore, only the use of diclofenac or indomethacin was effective in preventing PEP, at a dose of 100 mg, which must be administered before performing ERCP.

CONCLUSION

Rectal administration of diclofenac and indomethacin significantly reduced the risk of developing mild PEP. Additional RCTs are needed to compare the efficacy between NSAID routes of administration in preventing PEP.

Key Words: Pancreatitis; Endoscopic retrograde cholangiopancreatography; Diclofenac; Indomethacin; Rectal

Core Tip: The present systematic review and meta-analysis shows that the use of non-steroidal anti-inflammatory drugs reduced the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). This review is the first to be carried out in Latin America with a large number of randomized controlled trials. The present study shows that rectal administration of diclofenac and indomethacin before endoscopic retrograde cholangiopancreatography can reduce the incidence of mild PEP in high, medium and low risk patients.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a useful tool in the treatment of biliopancreatic duct diseases with high technical and clinical success rates. The most common post-ERCP adverse events (AEs) are acute pancreatitis (AP), bleeding, perforation, and cholangitis[1]. AP is the most common, with an incidence between 3.5% and 9.7% and mortality ranging from 0.1% to 0.7%[2].

Mild AP is defined as the absence of organ failure and/or local and systemic complications, moderate AP as the presence of transient organ failure or local or systemic complications, and severe AP as the presence of persistent organ failure with or without complications. Persistent organ failure has a risk of mortality between 36% and 50% within the first phase[3]. Post-ERCP pancreatitis (PEP) is mild in 4%, moderate in 1.8% to 2.8%, and severe in 0.3% to 0.5%[4,5].

Risk factors associated with PEP are divided into patient- and procedure-related factors. Patient-related factors include sphincter of Oddi dysfunction (SOD), female gender, history of AP, and history of PEP, whereas procedure-related factors include difficult catheterization, passage of a guidewire in the main pancreatic duct (MPD) ≥ 1 time, and pancreatic injection ≥ 1 time[2]. The search for methods to prevent the

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occurrence of PEP is important to increase patient safety and reduce the incidence rate.

Studies have described preventive measures to avoid the occurrence of PEP, such as the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and pancreatic stent implantation. Theoretically, the use of NSAIDs that inhibit cyclooxygenase 2 (COX-2) improves the acute inflammatory effects of AP and reduces its systemic sequelae[6]. NSAIDs that inhibit phospholipase A2 (indomethacin and diclofenac) play a role in the early phase of the inflammatory cascade in AP. Research on the use of NSAIDs to prevent PEP started in the 1980s[7]. Randomized trials in animals have shown that indomethacin has a low mortality rate[7]. Its properties prevent papillary edema, at least theoretically decreasing the occurrence of PEP.

This systematic review and meta-analysis was performed to determine the effectiveness of NSAIDs in preventing PEP. The objective was to analyze the appropriate dose, route, time of administration, and the best NSAIDs to reduce the incidence of PEP.

MATERIALS AND METHODS

Protocol and registration

This systematic review and meta-analysis was carried out in accordance with the recommendations of the *Cochrane* manual, following the items in the preferred reporting items for systematic reviews and meta-analyses (PRISMA)[8]. The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database, under registration number 42016049582, and approved by the ethics committee of the Moriah Hospital, São Paulo, Brazil.

Eligibility criteria and search procedure

The eligibility criteria were organized according to the international standards for patient, intervention, comparison, and outcome. "Patient" (P) was those submitted to ERCP, "intervention" (I) was administration of different types of NSAIDs described in the literature, "comparison" (C) was the administration of placebo or other similar drugs to NSAIDs, and "outcome" (O) was the main outcome of PEP. The research was carried out using different databases or virtual libraries, among which were MEDLINE/PubMed, Embase, and central Cochrane library. The dates used were from the beginning of our study in July 2016 to December 2019.

The key words used in the MEDLINE research were ERCP, NSAIDs, pancreatitis, diclofenac, and indomethacin. For other databases, we used simpler terms, such as ERCP, pancreatitis, and NSAID. All types of studies that assessed the reduction in the incidence of PEP were researched. In this systematic review and meta-analysis, we included only randomized clinical trials (RCTs) that studied the incidence of PEP with the use of NSAIDs.

We excluded meta-analyses, prospective nonrandomized, retrospective studies, case series, pancreatic stent studies, NSAID *vs* NSAID, drugs that were not in the NSAID group, and abstracts and papers that were requested by the author without response. There was no restriction on the language and date of publication.

We included patients of any gender > 18 years old who underwent ERCP for the first time and with signed informed consent. We excluded those with previous sphincterotomy, periampullary tumor, signs of evident AP, chronic pancreatitis, allergies to NSAIDs, and active and healing gastric and duodenal ulcers.

The main outcome was the reduction in the overall incidence of PEP with the use of NSAIDs. We evaluated the reduction in incidence in relation to the severity of PEP (mild, moderate, and severe), types of NSAIDs (diclofenac, indomethacin, valdecoxib, ketoprofen, naproxen, and celecoxib), different routes of administration [rectal (R), oral (O), intramuscular (IM), and intravenous (IV)], and dose and time of administration (before, during, after, and before/after ERCP).

Evaluation of eligibility criteria and study selection

Two reviewers selected RCTs independently and by group analysis. Any disagreement was resolved by the reviewers and group members after consensus. The study selection process was described in the PRISMA flowchart[8]. This systematic review and meta-analysis was organized in relation to the critical assessment instruments according to the type of design of the JADAD scale[9]. Each study was classified according to the risk of bias, randomization, allocation, blinding, losses, prognostic factors, results, and patient number needed to treat (NNT).

Data analysis

Data were extracted based on the information on treatment intention. For all outcomes, risk difference (RD) was considered for analysis with a 95% confidence interval and statistical significance of $P < 0.05$. The difference between the outcomes of the analysis of each subgroup was calculated through RD together with dichotomous variables.

The analysis was performed with the statistical software RevMan 5.3 using the Mantel–Haenszel (MH) test with *fixed effect* (FE). Heterogeneity was considered by I^2, with a cutoff of 50%. When a value ≥ 50% was found, sensitivity analysis was performed to try to identify a study with a higher probability of publication bias ("outlier"), through graphic expression of the "funnel plot" with the model or FE.

The sensitivity study aimed to identify the publication bias that justifies heterogeneity through the Egger funnel plot test. Once the publication biases were identified, which maintained heterogeneity ≥ 50%, it was decided to work with RD and randomized effect (RE) and work or interpret within the present systematic review and meta-analysis with a substantial or true heterogeneity.

RESULTS

Selection of studies

The evaluated articles are presented in the PRISMA flowchart and include 26 RCTs, 142 article were excluded (Figure 1). The 26 RCTs selected[6,7,10-33] were considered eligible and included a total of 8143 patients. The intervention group (NSAID) included 4020 patients and the comparison group (control) included 4123 patients (placebo and other substances).

Study characteristics

We organized the studies after the consensus of two independent reviewers and after the group's consensus. Table 1 shows the included studies in alphabetical order, year, country of publication, route of administration, dose, and type of NSAIDs. Of the 26 RCTs, diclofenac was used in 12[10-21], indomethacin in 10[7,22-30], COX-2 inhibitors in 2[6,31], and other NSAIDs in 2[32,33]. Table 2 shows the included studies in alphabetical order, type of substance used (comparison) and number (*n*), and time of NSAID administration.

Description of articles

In assessing the risk of bias, all articles had adequate randomization, allocation, and blinding. The losses did not reach 20%. The JADAD score was above 3, which was satisfactory for inclusion in all studies. The description of each article is shown in Table 3. The time to diagnosis of PEP described in the RCTs ranged from 24 to 72 h and patients met at least two of Banks' three diagnostic criteria: History of abdominal pain, nausea, or vomiting, increase in serum amylase, and images compatible with AP.

PEP frequency

The overall incidence of PEP and a forest plot can be seen in Figure 2 and 3. In total there were 298 and 484 episodes of PEP in the intervention (4020) and comparison group (4123), respectively. RD was 95%CI -0.04 (-0.07, -0.03), $P < 0.05$, and NNT = 25.

PEP severity

Fourteen articles evaluated the incidence rate of mild PEP. A total of 2600 and 2569 patients were allocated to the intervention and comparison groups, respectively. There were 136 and 203 episodes of mild AP in the intervention (2600) and comparison group (2569), respectively. RD was 95%CI 0.03 (-0.05, -0.01), $P < 0.05$, and NNT = 33. Eleven articles evaluated the incidence of moderate PEP. A total of 2134 and 2150 patients were allocated to the intervention and comparison groups, respectively. Moderate PEP was observed in 54 and 203 patients in the intervention and comparison group, respectively. RD was 95%CI -0.01 (-0.02, 0.00) and $P > 0.05$. Seven articles reported the incidence of severe PEP. A total of 1740 and 1747 patients were allocated to the intervention and comparison groups, respectively. Severe PEP was observed in 16 and 23 patients in the intervention and comparison group, respectively. RD was 95%CI -0.00 (-0.01, 0.00) and $P > 0.05$. The forest plot shows the severity of PEP (Figure 4 and 5).

Table 1 Characteristics of the 26 randomized controlled trials, including administration route, dose, and type of non-steroidal anti-inflammatory drug

Ref.	Year	Country	Route	Dose	NSAID type
Andrade *et al*[24], 2015	2015	México	R	100 mg	Indomethacin
Bhatia *et al*[6], 2011	2011	India	IV	20 mg	Valdecoxib
Cheon *et al*[10], 2007	2007	United States	O	50 mg	Diclofenac
Döbrönte *et al*[7], 2014	2014	Hungary	R	100 mg	Indomethacin
Elmunzer *et al*[25], 2012	2012	United States	R	100 mg	Indomethacin
Hauser *et al*[11], 2016	2016	Croatia	R	100 mg	Diclofenac
Ishiwatari *et al*[12], 2016	2016	Japan	O	100 mg	Diclofenac
Kato *et al*[31], 2017	2017	Japan	O	400 mg	Celecoxib
Kato *et al*[13], 2019	2019	Japan	R	25/50 mg	Diclofenac
Khoshbaten *et al*[14], 2008	2008	Iran	R	50 mg	Diclofenac
Leerhøy *et al*[15], 2016	2016	Denmark	R	100 mg	Diclofenac
Levenick *et al*[26], 2016	2016	United States	R	100 mg	Indomethacin
Li *et al*[27], 2019	2019	China	R	100 mg	Indomethacin
Lua *et al*[16], 2015	2015	Malaysia	R	100 mg	Diclofenac
Mansour *et al*[32], 2016	2016	Iran	R	500 mg	Naproxen
Masjedizadeh *et al*[26], 2017	2017	Iran	R	50 mg	Indomethacin
Montaño *et al*[23], 2007	2007	México	R	100 mg	Indomethacin
Hosseini *et al*[28], 2016	2016	Iran	R	100 mg	Indomethacin
Murray *et al*[17], 2003	2003	Scotland	R	100 mg	Diclofenac
Otsuka *et al*[18], 2012	2012	Japan	R	50 mg	Diclofenac
Park *et al*[21], 2014	2014	South Korea	IM	100 mg	Diclofenac
Patai *et al*[29], 2015	2015	Hungary	R	100 mg	Indomethacin
Quadros *et al*[33], 2016	2016	Brazil	IV	100 mg	Ketoprofen
Senol *et al*[19], 2009	2009	United States	IV	50 mg	Diclofenac
Sotoudehmanesh *et al*[30], 2007	2007	Iran	R	100 mg	Indomethacin
Uçar *et al*[20], 2016	2016	Turkey	IM and IV	75/100 mg	Diclofenac

NSAIDs: Non-steroidal anti-inflammatory drugs; R: Rectal; IV: Intravenous; O: Oral; IM: Intramuscular.

Administration route

Nineteen articles described the rectal route for administering NSAIDs. A total of 3000 and 3017 patients were allocated to the intervention and comparison groups, respectively. PEP was observed in 208 and 388 patients in the intervention and comparison group, respectively. RD was 95%CI -0.06 (-0.08, -0.03), $P < 0.05$, and NNT = 17. In three articles, the IV route was described and the number of patients allocated to the intervention and comparison groups was 391 and 420 patients, respectively. PEP was observed in 20 and 24 patients in the intervention and comparison group, respectively. RD was 95%CI -0.00 (-0.04, 0.03) and $P > 0.05$. In three articles, the oral route of administration was described and the number of patients allocated to the intervention and comparison groups was 223 and 401 patients, respectively. PEP was observed in 47 and 49 patients in the intervention and comparison group, respectively. RD was 95%CI -0.00 (-0.05, 0.04) and $P > 0.05$. In two articles, the IM route was described, with 223 and 195 patients allocated to the intervention and comparison groups, respectively. PEP was observed in 23 and 23 patients in the intervention group and comparison group, respectively. RD was 95%CI -0.03 (-0.13, 0.07) and $P > 0.05$. The forest plot describes the different routes of administration (Figure 6 and 7).

Table 2 Characteristics of 26 randomized controlled trials, including comparison group (number), administration time (before, during, after, and before/after endoscopic retrograde cholangiopancreatography)

Ref.	Comparison (*n*)	Administration time (after, before, and during)	*n*	Intervention
Andrade *et al*[24], 2015	Glycerin (84)	Before ERCP	166	82
Bhatia *et al*[6], 2011	Glyceryl trinitrate (127)	Before ERCP	254	127
Cheon *et al*[10], 2007	Placebo SN (102)	Before and after ERCP	207	105
Döbrönte *et al*[7], 2014	Placebo SN (318)	After ERCP	665	347
Elmunzer *et al*[25], 2012	Placebo SN (307)	After ERCP	602	295
Hauser *et al*[11], 2016	Ceftazidime (143)	Before ERCP	272	129
Ishiwatari *et al*[12]., 2016	Placebo SN (214)	Before and after ERCP	430	216
Kato *et al*[31], 2017	Saline solution (85)	Before ERCP	170	85
Kato *et al*[13]., 2019	None (152)	Before ERCP	303	151
Khoshbaten *et al*[14], 2008	Placebo SN (50)	Before ERCP	100	50
Leerhøy *et al*[15], 2016	None (394)	After ERCP	772	378
Levenick *et al*[26], 2016	Placebo SN (226)	During ERCP	449	223
Li *et al*[27], 2019	Glycerin (50)	Before ERCP	100	50
Lua *et al*[16], 2015	None (75)	After ERCP	144	69
Mansour *et al*[32], 2016	Placebo SN (162)	Before ERCP	324	162
Masjedizadeh *et al*[26], 2017	Placebo lactated Ringer's solution (124)	Before ERCP	186	62
Montaño *et al*[23], 2007	Glycerin (75)	Before ERCP	150	75
Hosseini *et al*[28], 2016	Saline solution (205)	Before ERCP	406	201
Murray *et al*[17], 2003	Placebo SN (110)	After ERCP	220	110
Otsuka *et al*[18], 2012	Saline solution (53)	Before ERCP	104	51
Park *et al*[21], 2014	Saline solution (170)	After ERCP	343	173
Patai *et al*[29], 2015	Placebo SN (269)	Before ERCP	539	270
Quadros *et al*[33], 2016	Saline solution (253)	After ERCP	477	224
Senol *et al*[19], 2009	Placebo SN (40)	After ERCP	80	40
Sotoudehmanesh *et al*[30], 2007	Placebo SN (245)	After ERCP	490	245
Uçar *et al*[20], 2016	None (50)	Before ERCP	150	100
Total	-	-	8103	4020

n = total number of patients, and number of patient intervention. ERCP: Endoscopic retrograde cholangiopancreatography.

Types of NSAIDs

Diclofenac was used to prevent PEP in 15 articles. A total of 1709 and 1792 patients were allocated to the intervention and comparison groups, respectively. In the intervention and comparison group, PEP was observed in 150 and 229 patients, respectively. RD was 95%CI -0.04 (-0.08, -0.01), $P < 0.05$, and NNT = 25. Indomethacin was described in seven articles. A total of 1713 and 1704 patients were allocated to the intervention and comparison groups, respectively. In the intervention and comparison group, PEP was observed in 109 and 197 patients, respectively. RD was 95%CI -0.06 (-0.09, -0.02), $P < 0.05$, and NNT = 17. Two articles described the use of COX-2 inhibitors in the prevention of PEP. A total of 212 patients were allocated to the intervention and 212 to the comparison group. In the intervention and comparison groups, PEP was observed in 22 and 25 patients, respectively. RD was 95%CI -0.01 (-0.07, 0.05) and $P > 0.05$. Naproxen (1) and ketoprofen (1) have been described in the prevention of PEP. In the global analysis of both NSAIDs, 386 and 415 patients were allocated to the

Table 3 Description of 26 randomized controlled trials in relation to allocation, losses, blinding, prognosis, and JADAD

Ref.	Randomization	Allocation	Blinding	Losses	Prognosis	AIT	JADAD
Andrade *et al*[24], 2015	Yes	Yes	No	No	Homogeneous	Yes	3
Bhatia *et al*[6], 2011	Yes	Yes	No	No	Homogeneous	No	3
Cheon *et al*[10], 2007	Yes	Yes	Yes	Yes	Homogeneous	No	5
Döbrönte *et al*[7], 2014	Yes	No	No	Yes	Homogeneous	No	3
Elmunzer *et al*[25], 2012	Yes	Yes	Yes	No	Homogeneous	Yes	5
Hauser *et al*[11], 2016	Yes	Yes	Yes	No	Homogeneous	Yes	5
Ishiwatari *et al*[12], 2016	Yes	Yes	Yes	Yes	Homogeneous	No	3
Kato *et al*[31], 2017	Yes	Yes	Yes	No	Homogeneous	Yes	4
Kato *et al*[13], 2019	Yes	Yes	Yes	Yes	Homogeneous	No	5
Khoshbaten *et al*[14], 2008	Yes	Yes	Yes	No	Homogeneous	No	5
Leerhøy *et al*[15], 2016	Yes	No	No	No	Homogeneous	No	3
Levenick *et al*[26], 2016	Yes	Yes	Yes	No	Homogeneous	Yes	5
Li *et al*[27], 2019	Yes	Yes	Yes	Yes	Homogeneous	No	5
Lua *et al*[16], 2015	Yes	Yes	No	Yes	Homogeneous	Yes	3
Mansour *et al*[32], 2016	Yes	Yes	Yes	No	Homogeneous	Yes	4
Masjedizadeh *et al*[26], 2017	Yes	No	Yes	No	Homogeneous	Yes	4
Montaño *et al*[23], 2007	Yes	No	Yes	No	Homogeneous	No	3
Hosseini *et al*[28], 2016	Yes	Yes	Yes	No	Homogeneous	No	3
Murray *et al*[17], 2003	Yes	Yes	Yes	No	Homogeneous	No	3
Otsuka *et al*[18], 2012	Yes	No	No	No	Homogeneous	Yes	3
Park *et al*[21], 2014	Yes	Yes	Yes	No	Homogeneous	No	3
Patai *et al*[29], 2015	Yes	Yes	Yes	Yes	Homogeneous	Yes	5
Quadros *et al*[33], 2016	Yes	Yes	Yes	No	Homogeneous	Yes	5
Senol *et al*[19], 2009	Yes	No	No	No	Homogeneous	No	3
Sotoudehmanesh *et al*[30], 2007	Yes	Yes	Yes	No	Homogeneous	Yes	4
Uçar *et al*[20], 2016	Yes	No	No	Yes	Homogeneous	No	3

AIT: Analysis of intervention and treatment.

intervention and comparison group, respectively. In the intervention and comparison groups, 17 and 33 patients had PEP, respectively. RD was 95%CI -0.04 (-0.18, 0.09) and $P > 0.05$. Figure 8 and 9 shows the forest plot of the incidence of PEP using different types of NSAIDs.

Timing of NSAID administration

Thirteen articles described the use of NSAIDs before ERCP to prevent PEP. A total of 1513 and 1585 patients were allocated to the intervention and comparison groups, respectively. PEP was observed in 115 and 229 patients in the intervention and comparison groups, respectively. RD was 95%CI -0.07 (-0.11, -0.03), $P < 0.05$, and NNT = 14.

Ten articles described the use of NSAID after ERCP to prevent PEP. A total of 1963 and 1996 patients were allocated to the intervention and comparison groups, respectively. PEP was observed in 130 and 208 patients in the intervention and comparison groups, respectively. RD was 95%CI -0.04 (-0.07, -0.01), $P < 0.05$, and NNT = 25. Two articles described the use of NSAID before and after ERCP to prevent PEP. A total of 321 and 316 patients were allocated to the intervention and comparison groups, respectively. PEP was observed in 37 and 36 patients in the intervention and comparison groups, respectively. RD was 95%CI 0.00 (-0.05, -0.05) and $P > 0.05$. Only

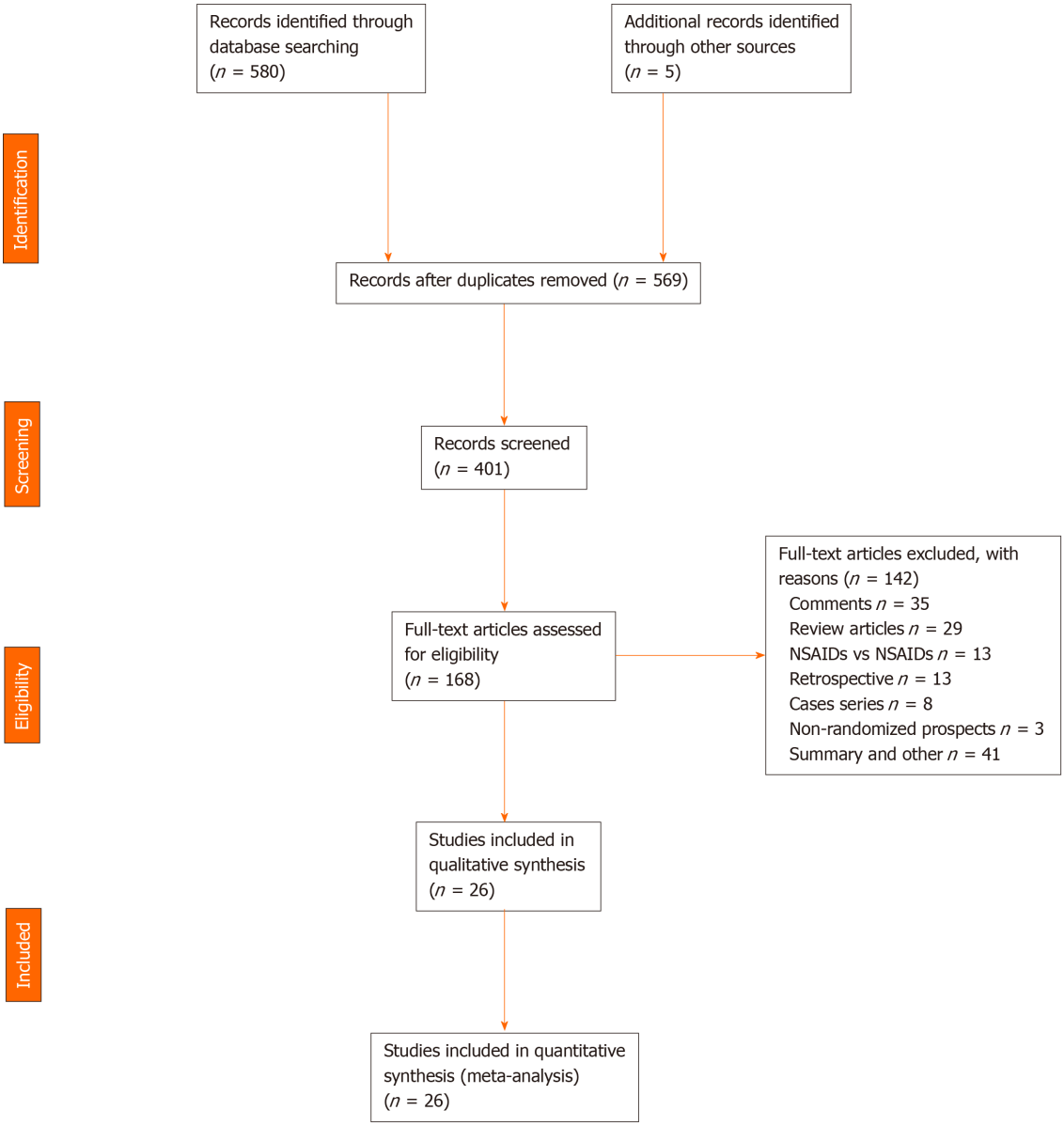

Figure 1 Inclusion of 26 randomized controlled trials in the PRISMA flowchart. NSAIDs: Non-steroidal anti-inflammatory drugs.

one article described the use of NSAIDs during ERCP to prevent PEP. A total of 223 and 226 patients were allocated to the intervention and comparison groups, respectively. PEP was observed in 16 and 11 patients in the intervention and comparison groups, respectively. In this work, detailed statistical analysis was not possible. The forest plot in Figure 10 and 11 shows the incidence of PEP in relation to the timing of NSAID administration.

DISCUSSION

The use of NSAIDs and their impact on the prevention of PEP has been described in numerous RCTs. Although the number of RCTs is small and no convincing results have been presented, the major international societies of endoscopy and gastroenterology recommend its use in daily clinical practice, but make it clear that it is up to the endoscopist to decide whether or not to use it.

The European Society of Gastrointestinal Endoscopy (ESGE) recommends the use of diclofenac or indomethacin at a dose of 100 mg before ERCP in all patients whether they are at high, medium, or low risk for PEP and when there are no contraindications[2]. Japan Gastroenterological Endoscopy Society advocates a similar policy for the intrarectal administration of NSAIDs in all cases of ERCP when there are no contraindications[34]. The American Society for Gastrointestinal Endoscopy[35]

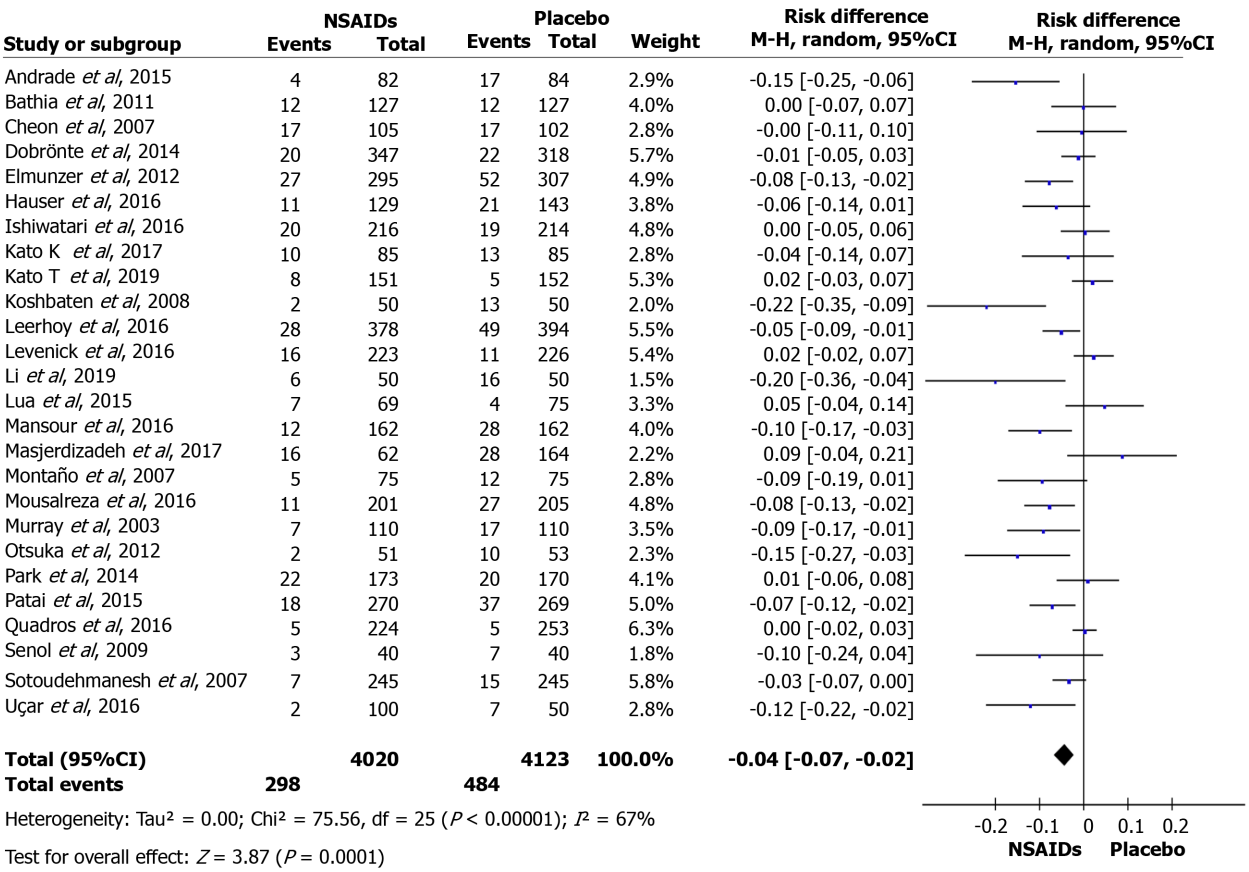

Figure 2 *Forest plot* of the global incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis. NSAIDs: Non-steroidal anti-inflammatory drugs; CI: Confidence interval.

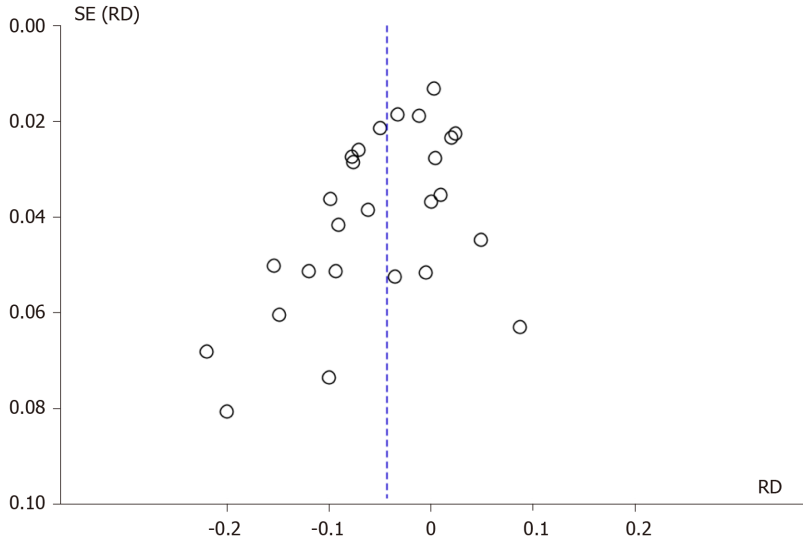

Figure 3 *Funnel plot* of the global incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis. SE: Standard error; RD: Risk difference.

recommends the administration of indomethacin in medium- and high-risk patients.

The Brazilian Society of Digestive Endoscopy does not define an effective method to prevent PEP. In Brazil, there are books dedicated to the subject that recommend the use of indomethacin as a method of preventing PEP[36]. A systematic Brazilian review showed a statistical significance with the use of indomethacin and diclofenac after analyzing 21 studies[37].

Unlike systematic reviews already published on NSAID use to reduce the risk of

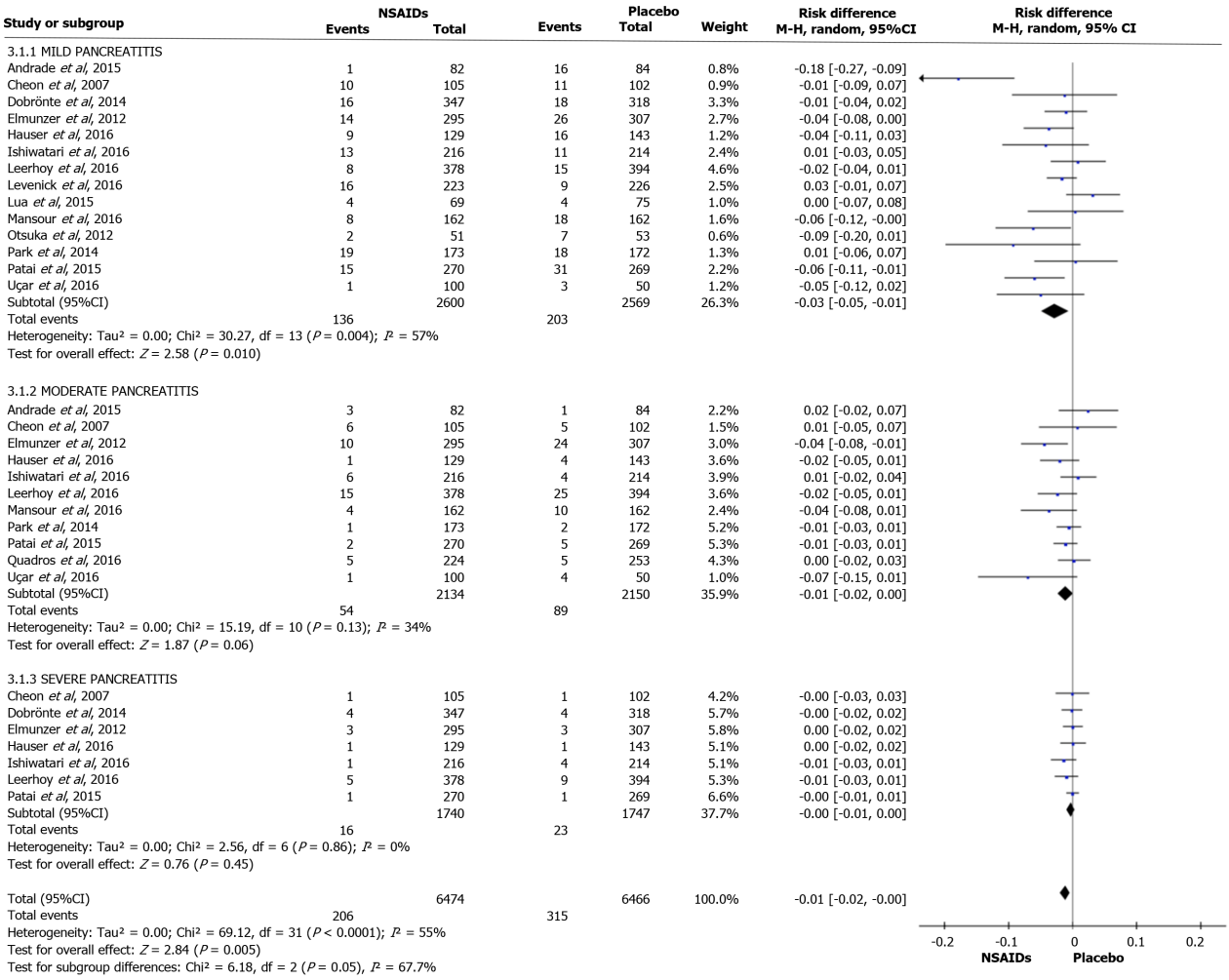

Figure 4 *Forest plot* of the incidence according to post-endoscopic retrograde cholangiopancreatography pancreatitis severity. NSAIDs: Non-steroidal anti-inflammatory drugs; CI: Confidence interval.

PEP, the current study included only RCTs, with a more robust methodology, in which an analysis was carried out in relation to the prevention of PEP and its incidence. This analysis according to the severity of AP episode, type of NSAID, dose, and time and route of administration showed a more detailed perception of important details, which contributed to a more robust conclusion.

The analysis of 26 RCTs showed a significant reduction in the risk of PEP with the use of NSAIDs in both high and low risk patients. However, this study revealed that AEs prevented by the use of NSAIDs mainly involved mild AP. This study showed the efficacy of rectal indomethacin (100 mg) or diclofenac (100 mg) before ERCP, with statistical significance and lower NNT compared to post-ERCP administration.

Due to the small number of RCTs published in the literature, it was not possible to identify whether another route of administration (oral, IV, and IM), another type of NSAID, another time of administration, and doses lower or greater than 100 mg are effective in preventing PEP. Thus, further large multicenter RCTs comparing other NSAIDs, other routes, and times and doses of administration are required to obtain robust conclusions. However, decisions on NSAIDs may be influenced by cost, as indomethacin is more expensive than diclofenac. A cost comparison of the types of NSAIDs to decrease the incidence of PEP should be conducted, in order to obtain more data on this issue. To our knowledge, this is the first meta-analysis on the prevention of PEP using NSAIDs, which includes all types of NSAIDs described in the literature, such as diclofenac, indomethacin, naproxen, valdecoxib, celecoxib, and ketoprofen.

COX-2 inhibitors, regardless of the initial trigger (the injured pancreatic acinar cell), quickly lead to a pro-inflammatory cascade with a short therapeutic intervention window for some types of interventions. COX enzymes play an important pro-inflammatory role in AP. The isoform of COX-2 is overexpressed in AP, while the expression of COX-1 remains constant. Pharmacological inhibition of COX-2 improves

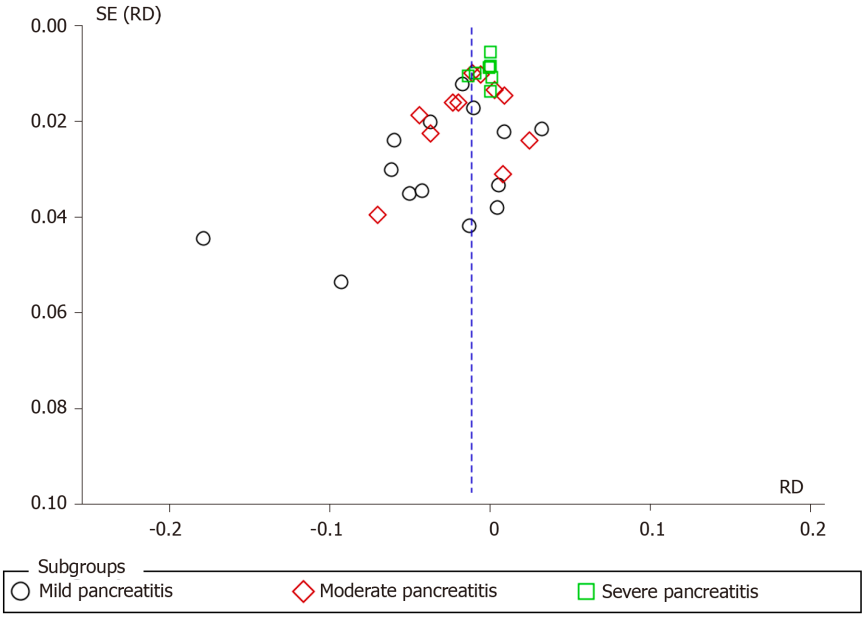

Figure 5 *Funnel plot* of the incidence according to post-endoscopic retrograde cholangiopancreatography pancreatitis severity. SE: Standard error; RD: Risk difference.

the severity of the acute effects on AP and its systemic and ischemic sequelae. COX-2 inhibitors may show some benefit in AP[6].

Diclofenac and indomethacin, by inhibiting phospholipase A2, play a role in the early phase of the inflammatory cascade in AP. Phospholipase A2 inhibition results in the suppression of several important classes of pro-inflammatory lipids (prostaglandins, leukotrienes, and platelet-activating factor). NSAIDs further inhibit neutrophil-endothelial cell binding. Of the NSAIDs studied in animals, indomethacin showed a lower mortality rate[7]. However, the effectiveness of other NSAIDs should be investigated.

It is important to emphasize that the results of this meta-analysis may have been influenced by heterogeneity > 50%, in relation to the weight of each RCT included in this study. When we refer to the weight of each study, we refer to the number of patients in each of them which was observed within the forest plot with a minimum weight of 1.5%[26] and a maximum weight of 6.3%[34]. These weights influence the time interpreted in the RevMan 5.3 software.

As mentioned by the ESGE, different demographic factors influence the development of PEP, such as patients with suspected SOD, females, previous AP, previous PEP, difficult cannulation, guidewire passage and MPD contrast, children, fine bile duct, absence of chronic pancreatitis, normal serum bilirubin, end-stage renal disease, previous sphincterotomy, pancreatic sphincterotomy, balloon sphincteroplasty, and failure to remove bile duct stones[38]. For these reasons, PEP prevention is important to increase patient safety.

This study emphasized how each RCT reached the diagnosis of AP, with each of the authors defining an episode of AP as the presence of abdominal pain 24 to 72 h after ERCP, increased pancreatic enzymes, and an image compatible with inflammatory alteration of the pancreatic gland (6.8, 11-34). The recent ESGE guideline suggests testing serum amylase and/or lipase 2 to 6 h after ERCP in patients with post-ERCP abdominal pain who should be discharged on the same day of ERCP. Patients with serum amylase and lipase values below 1.5 to 4 times the normal limit can be discharged without concern for PEP development[2]. Another limitation of the study was that not all RCTs stratified the severity of AP in order to be able to adequately interpret at what level of severity the use of NSAIDs may be most beneficial.

Of the 26 RCTs, 521 episodes of AP were assessed for severity. In 339, the AP episode was mild, representing 65% of stratified patients (339/521). Thus, our results demonstrated that the use of NSAIDs prevents the development of mild PEP. Finally, this systematic review focused solely and exclusively on PEP and its severity, but it is important to note that other AEs can occur post-ERCP which were not included in this review.

Thus, in relation to the subgroups examined, the rectal route adequately reduced

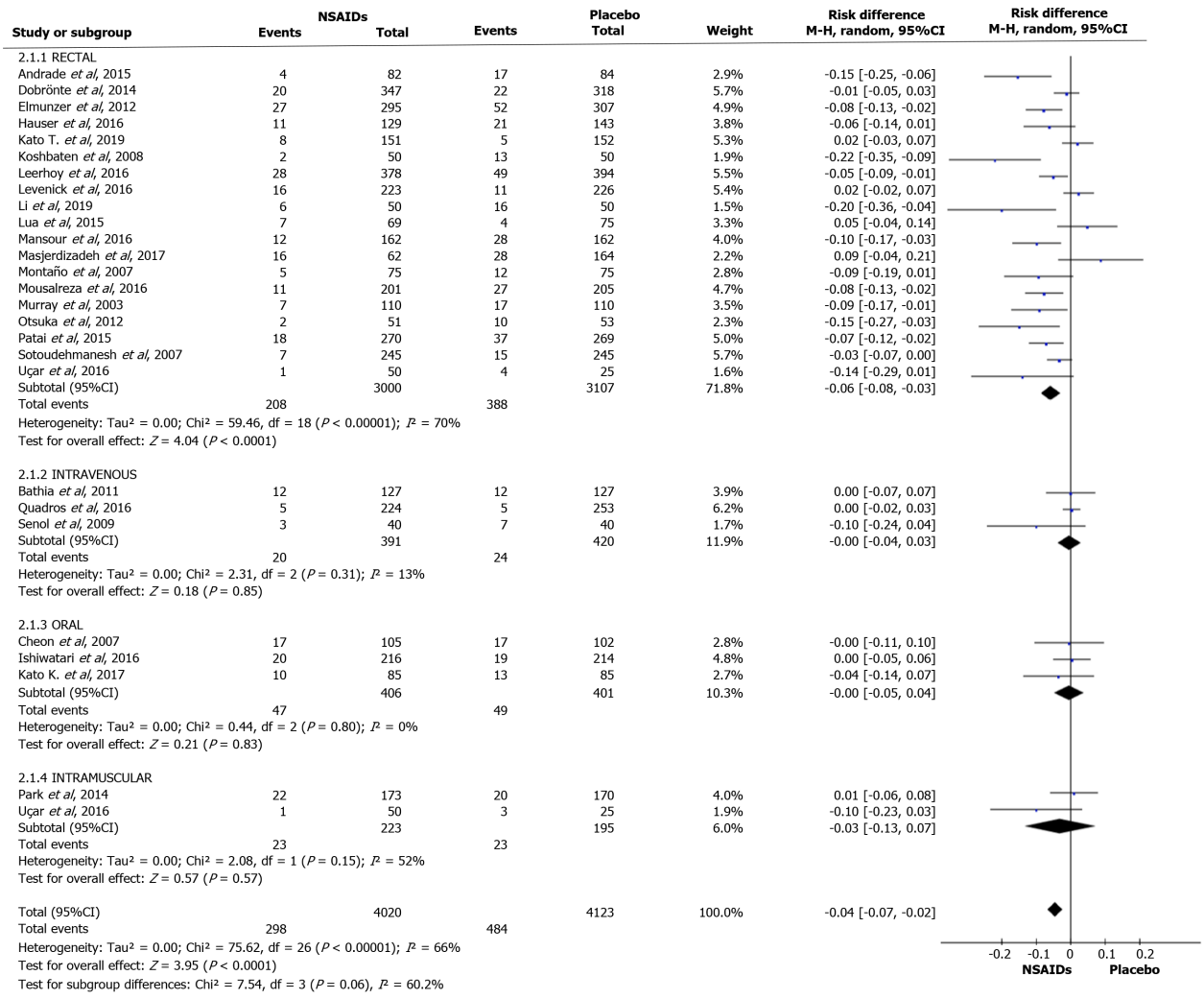

Figure 6 *Forest plot* of the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis according to different routes of administration. NSAIDs: Non-steroidal anti-inflammatory drugs; CI: Confidence interval.

the incidence of PEP. The use of NSAIDs was shown to be better in mild AP episodes. Both diclofenac and indomethacin were effective in preventing PEP. The best time to administer NSAIDs is before ERCP and the most appropriate dose that achieved the best results was 100 mg.

Other RCTs are needed to resolve some remaining doubts, such as: Would other NSAIDs be more effective? Would the IV route be better? Could smaller doses of more potent NSAIDs be more effective in preventing PEP?

CONCLUSION

It is concluded that rectal administration of 100 mg diclofenac or 100 mg indomethacin before ERCP prevents the occurrence of mild episodes of PEP.

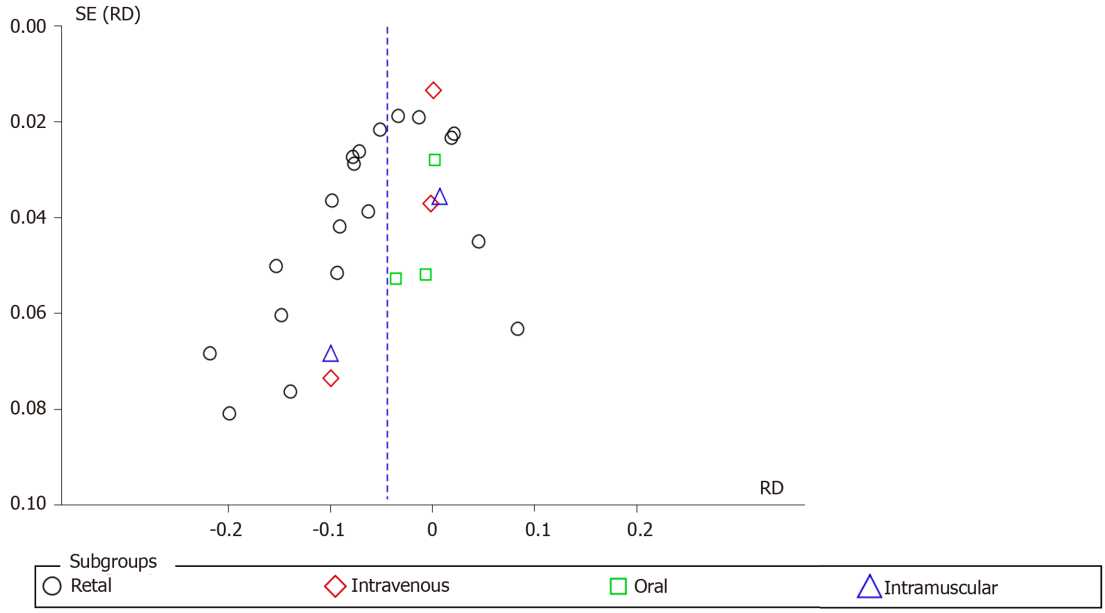

Figure 7 *Funnel plot* of the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis according to different routes of administration. SE: Standard error; RD: Risk difference.

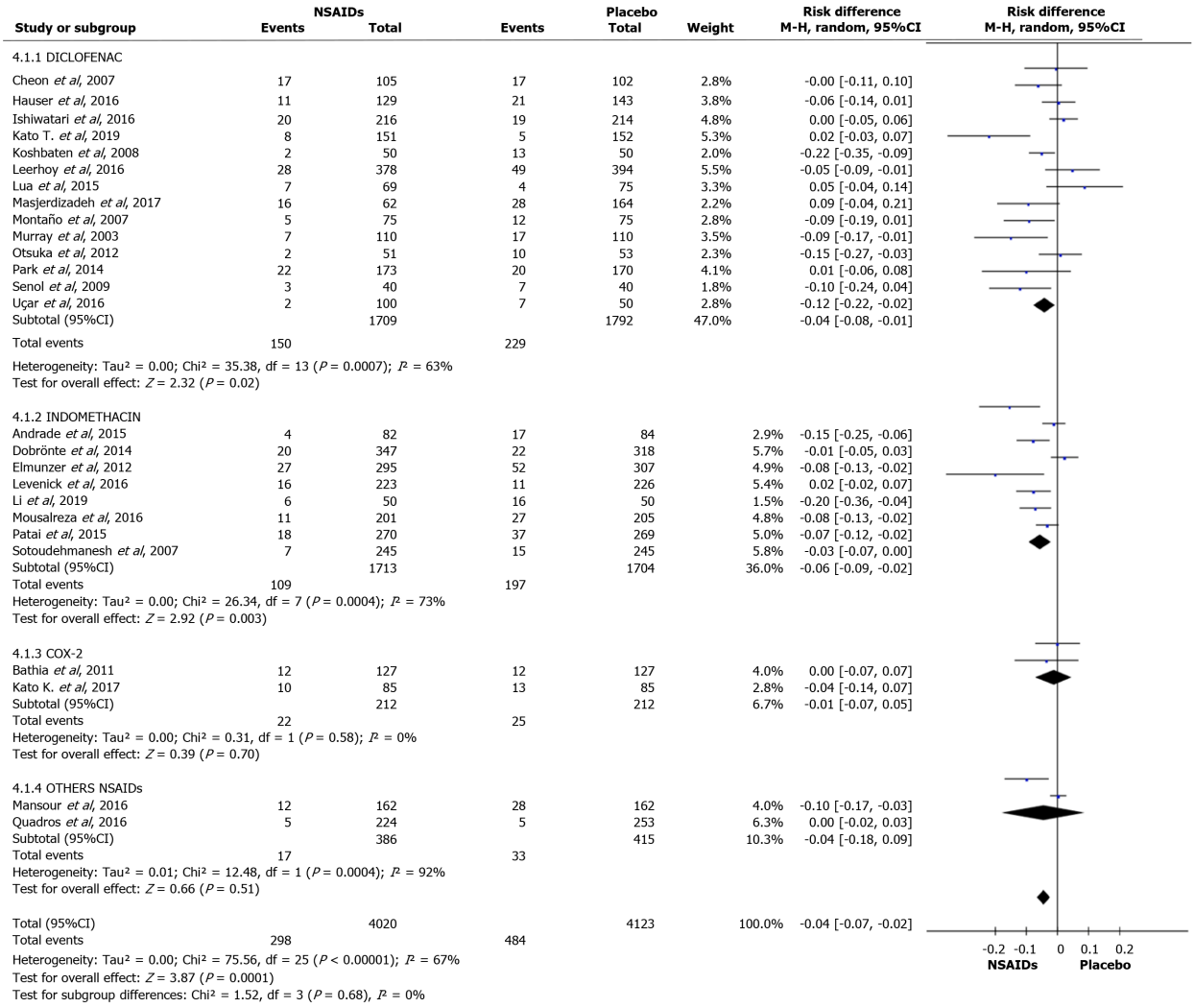

Figure 8 *Forest plot* showing the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis with different types of non-steroidal anti-inflammatory drugs. NSAIDs: Non-steroidal anti-inflammatory drugs; CI: Confidence interval.

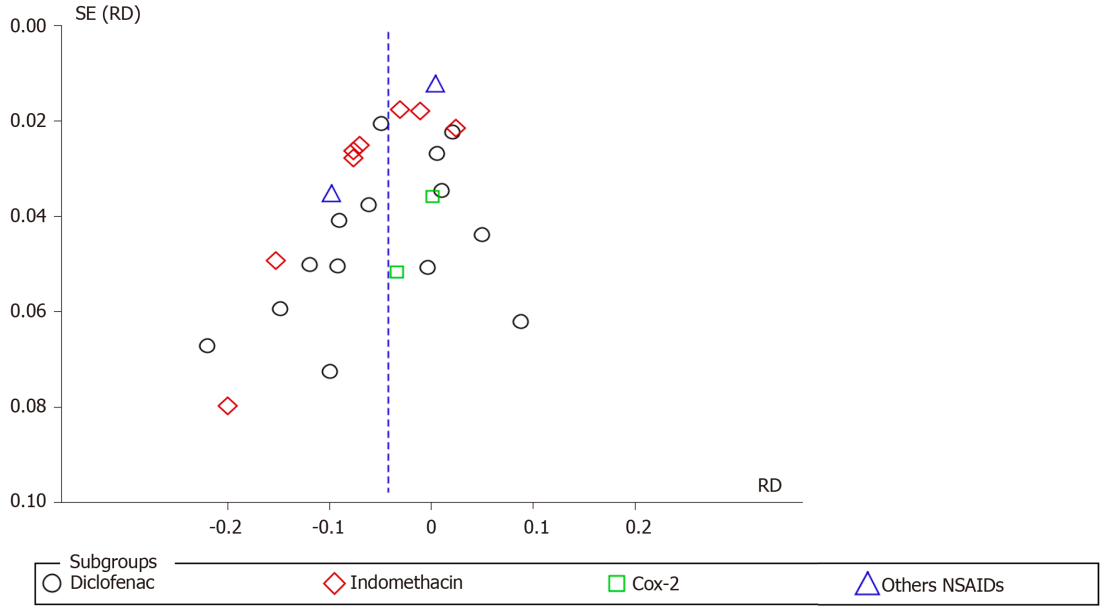

Figure 9 *Funnel plot* showing the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis with different types of non-steroidal anti-inflammatory drugs. SE: Standard error; RD: Risk difference; NSAIDs: Non-steroidal anti-inflammatory drugs.

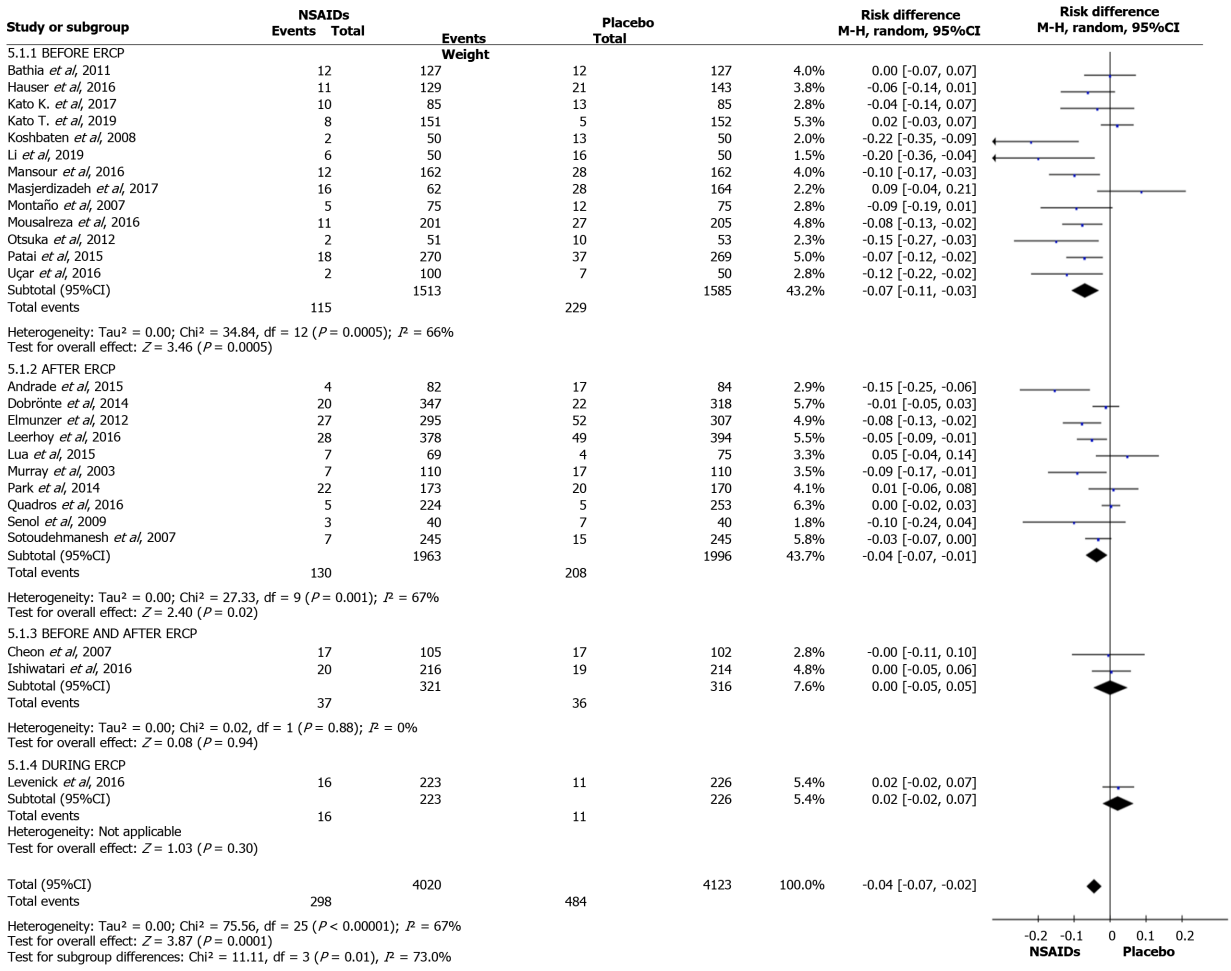

Figure 10 *Forest plot* showing the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in relation to the timing of non-steroidal anti-inflammatory drug administration. NSAIDs: Non-steroidal anti-inflammatory drugs; CI: Confidence interval.

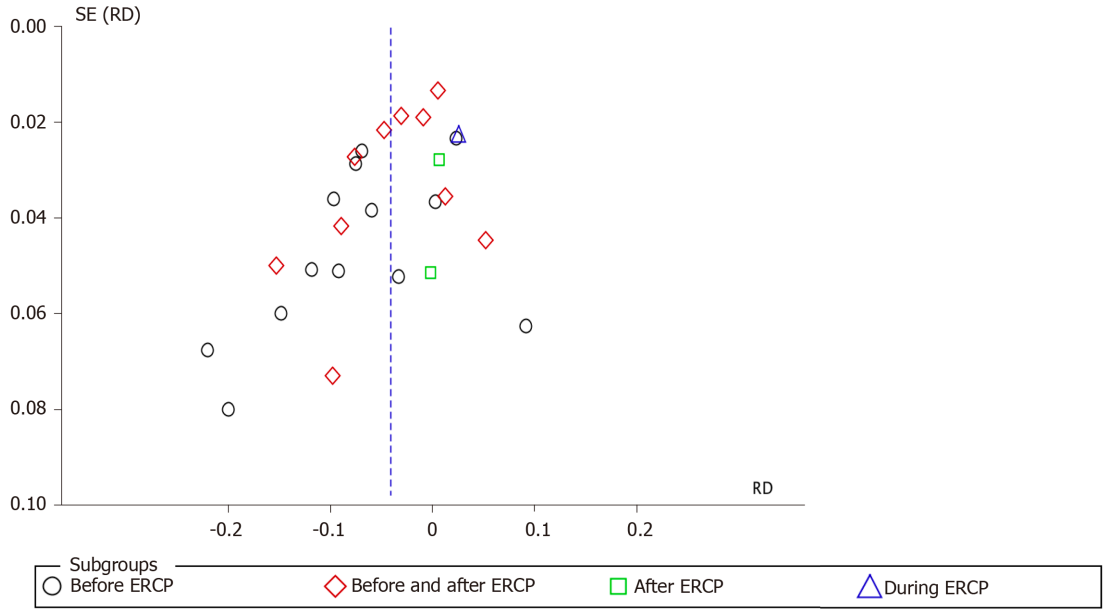

Figure 11 ***Funnel plot*** **showing the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in relation to the timing of non-steroidal anti-inflammatory drug administration.** SE: Standard error; RD: Risk difference; ERCP: Endoscopic retrograde cholangiopancreatography.

ARTICLE HIGHLIGHTS

Research background

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most widely performed therapeutic procedures for bile duct access. However, important complications can occur such as: Post-ERCP pancreatitis (PEP), bleeding, puncture and cholangitis. PEP is considered the main complication after the procedure. Large societies such as ASGE, European Society of Gastrointestinal Endoscopy and Japan Gastroenterological Endoscopy Society describe it as a very important complication and methods must be used to prevent and reduce this pathology. Various methods such as using non-steroidal anti-inflammatory drugs (NSAIDs), prostheses, somatostatin and others have been used, but NSAIDs showed a higher rate of effectiveness.

Research motivation

In many studies, NSAIDs have demonstrated good results, but there are also conflicting results. As there is still controversy as to whether the use of NSAIDs would help in reducing PEP, our group carried out the present study including all the randomized controlled trials (RCTs) described in the literature and the results showed that NSAIDs can help in the prevention of PEP.

Research objectives

Our main objective was to determine the effectiveness of NSAIDs *vs* "Placebo" as a method of choice or first-line therapy to reduce PEP, using the most recent RCTs. All NSAIDs mentioned in the literature, their route of administration and when they should be administered were investigated. In addition, we hope that this research will have important implications within the medical community.

Research methods

We performed this meta-analysis according to the PRISMA guidelines. Virtual databases were searched up to December 2019 to identify RCTs without date or language restrictions. Following selection of the studies, they were organized according to the PICO criteria and the design followed the JADAD scale. Statistical analysis of the data was performed using RevMan 5.3 software. The main endpoint evaluated in this study was the reduction in the incidence of PEP. Subgroup analyses were also performed and included the severity of pancreatitis, route of administration, time of administration and the types of NSAIDs administered. The results were

evaluated with the Higgins test method, using a risk difference with a random effect with a significance of $P < 0.05$, 95% confidence interval (CI) and interpreted as true heterogeneity.

Research results

Twenty-six high quality RCTs examining the use of NSAIDs *vs* Placebo for the reduction of PEP were included, involving a total of 8143 patients. 4020 patients used NSAIDs before ERCP and 4123 did not use NSAIDs (control group). A total of 298 cases of acute pancreatitis after ERCP were diagnosed in the NSAID group and 484 cases in the placebo group. The risk of PEP was lower (risk difference (RD)) in the NSAID group: -0.04; 95%CI: -0.07 to -0.02; number needed to treat (NNT), 25; $P < 0.05$. The use of NSAIDs effectively prevented mild pancreatitis compared to the use of placebo (2.5% *vs* 4.1%; 95%CI: -0.05 to -0.01; NNT, 33; $P < 0.05$), but data on moderate and severe PEP could not be fully elucidated. Only rectal administration reduced the incidence of PEP with the RD: -0.06 95%CI, -0.08 to -0.04; NNT, 17; $P < 0.05$.

Research conclusions

In conclusion, the use of NSAIDs does reduce the incidence of PEP. In particular, NSAIDs reduce the incidence of mild acute pancreatitis. The most effective drugs were diclofenac and indomethacin. The best route of administration was rectal and the best time for NSAIDs administration was before ERCP.

Research perspectives

It is hoped that these findings will help clinicians decide on the best treatment to prevent PEP.

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CASE REPORT

Endoscopic ultrasound-guided gallbladder drainage in pancreatic cancer and cholangitis: A case report

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Abstract

BACKGROUND

Head pancreatic cancers often present with clinical challenges requiring biliary drainage for chemotherapy or palliative scope. If usual endoscopic modalities fail or if percutaneous approach is not feasible, endoscopic ultrasound (EUS) guided biliary drainage can be considered. Here we describe and discuss an interesting clinical case in which EUS-guided gallbladder drainage (EUS-GBD) was chosen to treat acute severe cholangitis in a patient with advanced pancreatic cancer.

CASE SUMMARY

An 84-year-old female with a previous EUS-biopsy proven diagnosis of head pancreatic cancer presented with clinical signs of acute cholangitis. In September 2018 she had positioned a biliary and duodenal stent to relieve jaundice and an initial duodenal substenosis. In the emergency ward, an abdominal computed tomography scan showed proximal biliary stent occlusion due to neoplastic progression, but endoscopic retrograde cholangiopancreatography was impossible because of worsening duodenal stenosis and the absence of a chance to reach the Vater's papilla area. EUS-guided choledocoduodenostomy was not technically feasible but because the cystic duct was free of neoplastic infiltration, an EUS-GBD using an Axios™ stent was successfully performed. The patient started to feed after 48 h and was discharged 1 wk later. No other hospitalizations due to cholangitis or symptoms of Axios™ stent occlusion/dysfunction were observed up until her death 6 mo later due to underlying disease.

CONCLUSION
This case demonstrated how different EUS therapeutic approaches could have a key role to treat critical and seemingly unsolvable situations and that they could play a more fundamental role in the next future.

Key Words: Gallbladder drainage; Endoscopy ultrasound; Pancreatic cancer; Cholangitis; Case report; Axios stent

Core Tip: The present case explored the feasibility, safety and efficacy of an endoscopic ultrasound-guided gallbladder drainage to decompress the biliary tree and treat severe cholangitis in a patient with advanced pancreatic cancer. Endoscopic ultrasound-guided gallbladder drainage could be effective to drain the biliary tree if the cystic duct is free from neoplastic tissue. Using the new lumen-apposing self-expandable metallic stent, the procedure could be technically and clinically feasible, safe and an effective alternative to conventional endoscopic retrograde cholangiopancreatography or percutaneous drainage.

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INTRODUCTION

Malignant neoplasms of the pancreatic head often present with clinical challenges requiring biliary drainage before upfront chemotherapy or palliative treatment[1]. When endoscopic retrograde cholangiopancreatography (ERCP) fails due to anatomical or technical difficulties, the use of endoscopic ultrasound (EUS)-guided biliary drainage could be more appropriate than the percutaneous approach[2]. Moreover, some authors have proposed EUS-guided gallbladder drainage (EUS-GBD) as another alternative to drain the biliary tree if the cystic duct is not entrapped by neoplastic tissue[3,4]. Gallbladder drainage has been simplified by the development of dedicated enhanced lumen-apposing self-expandable metallic stents that create a stable fistula between the gallbladder and the lumen of the stomach or the duodenum. This approach has been recently reported to be more effective than percutaneous drainage to treat high-risk surgical patients with acute cholecystitis[5]. We herein report a case of a patient with a known pancreatic head cancer already previously treated with endoscopic stenting who required urgent biliary decompression through cholecystoduodenostomy for severe acute cholangitis.

CASE PRESENTATION

Chief complaints

An 84-year-old female presented to our Emergency Unit with fever (max 39.5 C), jaundice and leukocytosis.

History of present illness

The clinical data suggested a diagnosis of acute cholangitis due to the occlusion of a biliary metal stent positioned previously.

History of past illness

In September 2018, the patient had a diagnosis of an EUS biopsy proven unresectable pancreatic head cancer with biliary, and a duodenal stent was placed to relieve jaundice and symptomatic duodenal substenosis.

approved the final version of the article, including the authorship list.

Informed consent statement: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published, and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Personal and family history

She had a familial history of colorectal cancer (her sister).

Physical examination

On presentation her vital signs were temperature of 39.5 °C, pulse of 115 bpm, respiratory rate of 17 rpm, blood pressure of 80/50 mmHg and oxygen saturation of 92%. On general physical examination she looked pale and dehydrated. Abdominal examination revealed nondistended, tender abdomen in the right hypochondrium with a reduction of bowel sounds. The cardiovascular, pulmonary and neurological examination were unremarkable.

Laboratory examinations

Complete blood count analysis revealed a huge increase of the white blood cells (24754 cells/mL) and a significant increase of liver cytolysis and cholestasis enzymes: Aspartate aminotransferase 123 U/L, alanine aminotransferase 234 U/L and gamma-glutamyltransferase 431 U/L.

Imaging examinations

Abdominal computed tomography scan showed proximal biliary stent occlusion due to neoplastic progression with presence of stones above it. An ERCP was attempted, but access to the biliary tree was impossible because of worsening duodenal stenosis with complete incorporation of the metallic duodenal stent.

MULTIDISCIPLINARY EXPERT CONSULTATION

In an effort to avoid placement of a percutaneous drainage and due to the presence of new metastatic hepatic lesions, a multidisciplinary team discussed the case and decided to propose a further EUS evaluation with the aim of performing an alternative drainage procedure.

FINAL DIAGNOSIS

Acute cholangitis due to biliary metallic stent occlusion in advanced pancreatic cancer with duodenal infiltration and stenosis.

TREATMENT

Because of the absence of a suitable sonographic window above the biliary obstruction, EUS-guided choledocoduodenostomy was not technically feasible. On the other hand, the cystic duct appeared to be free of neoplastic infiltration, thus we decided to perform an EUS-GBD using an Axios™ stent plus electrocautery enhanced delivery system. The gallbladder was best visualized from the duodenum and penetrated with EC-Axios by applying cautery. A 10 mm × 10 mm Axios™ stent (Figure 1 and Video 1) was placed under EUS guidance from the duodenal bulb through the stent wire meshes into the gallbladder.

OUTCOME AND FOLLOW-UP

The procedure was technically successful without short- and long-term adverse events (Figure 2) and with a dramatic decrease in bilirubin concentration (2.7 mg/dL) and progressive normalization of inflammatory indexes. The patient started to feed after 48 h and was discharged 1 wk later after full antibiotic treatment was completed. No other hospitalizations due to cholangitis or symptoms of the Axios™ stent occlusion/dysfunction were observed before the patient died due to her underlying disease 6 mo later.

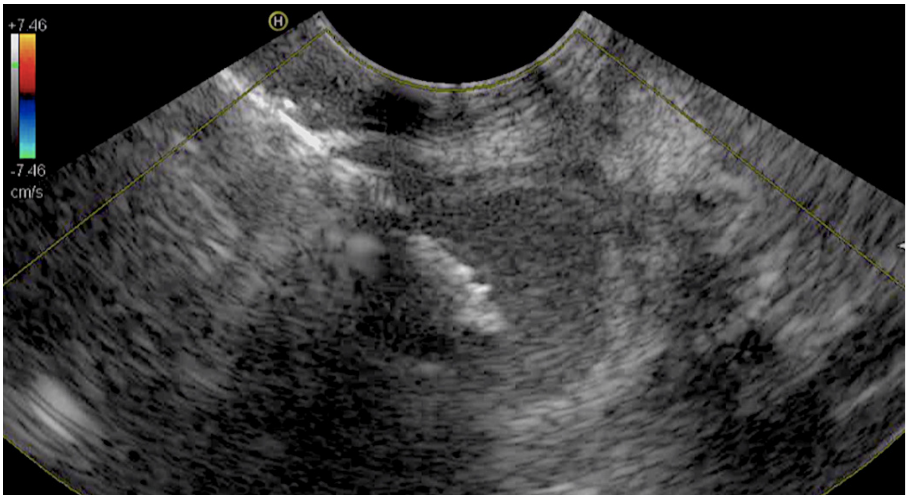

Figure 1 Endoscopic ultrasound guided wound of the gallbladder through the duodenal bulb.

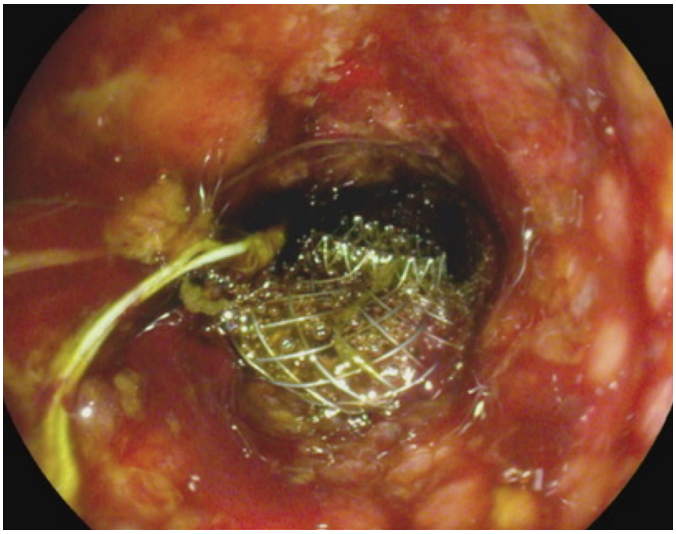

Figure 2 Endoscopic view of gallbladder drainage.

DISCUSSION

ERCP is the gold standard to treat obstructive jaundice due to malignant distal biliary obstruction[6]. However, ERCP can fail or be impossible in cases of duodenal stenosis, no access to Vater's papilla zone or altered postsurgical anatomy. In these cases, EUS-guided biliary drainage techniques, such as EUS-guided rendezvous, EUS-guided choledochoduodenostomy and EUS-guided hepaticogastrostomy are all recognized alternative modalities that have a better outcome than percutaneous drainage[7,8].

Recently, several studies demonstrated that EUS-GBD is useful to treat acute cholecystitis in patients unfit for surgery because of its similarity to percutaneous transhepatic gallbladder in terms of efficacy and safety[9]. Thus, when ERCP and EUS-biliary drainage cannot be performed for technical reasons, EUS-GBD may be a suitable alternative given that the gallbladder is a large organ with better accessibility by EUS from the gastric antrum or duodenal bulb[10].

The key factor to perform an effective EUS-GBD in this clinical scenario was lack of involvement of the cystic duct by the tumor. In our case, we performed EUS-GBD as a rescue procedure to treat severe acute cholangitis in a patient with advanced pancreatic neoplasia, in whom previous biliary and duodenal stenting were done. Before performing drainage, careful visualization of the pancreatic mass and lack of involvement of the cystic duct were done, followed by the drainage procedure that was technically and clinically successful as demonstrated by the rapid decrease of the patient's inflammatory indexes, disappearance of the septic status and normalization of the bilirubin. The persistent clinical success was demonstrated by the absence of

further episodes of jaundice or cholangitis.

CONCLUSION

In conclusion, our report showed that EUS-GBD could be a useful option to obtain an effective biliary drainage in patients in which conventional ERCP or EUS-guided choledocoduodenostomy could not be performed or were unsuccessful.

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CASE REPORT

Preemptive endoluminal vacuum therapy after pancreaticoduodenectomy: A case report

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Abstract

BACKGROUND

Pancreaticoduodenectomy is a technically demanding operation, with reported morbidity rates of approximately 40%–50%. A novel idea is to use endoscopic vacuum therapy (EVT) in a preemptive setting to prevent anastomotic leakage and pancreatic fistulas. In a recent case series, EVT was proven to be effective in preventing leaks in patients with anastomotic ischemia. There have been no previous reports on preemptive EVT after pancreaticoduodenectomy.

CASE SUMMARY

We describe the case of a 71-year-old woman with hypertension and diabetes who was admitted to the emergency room with jaundice, choluria, fecal acholia,

conflicts of interest.

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abdominal pain, and fever. Admission examinations revealed leukocytosis and hyperbilirubinemia (total: 13 mg/dL; conjugated: 12.1 mg/dL). Abdominal ultrasound showed cholelithiasis and dilation of the common bile duct. Magnetic resonance imaging demonstrated a stenotic area, and a biopsy confirmed cholangiocarcinoma. Considering the high risk of leaks after pancreaticoduodenectomy, preemptive endoluminal vacuum therapy was performed. The system comprised a nasogastric tube, gauze, and an antimicrobial incise drape. The negative pressure was 125 mmHg, and no adverse events occurred. The patient was discharged on postoperative day 5 without any symptoms.

CONCLUSION
Preemptive endoluminal vacuum therapy may be a safe and feasible technique to reduce leaks after pancreaticoduodenectomy.

Key Words: Preemptive; Endoluminal; Vacuum; Pancreaticoduodenectomy; Case report

Core Tip: Leaks and fistulas represent a high cost burden to health systems worldwide, with high morbidity and mortality rates in affected patients. Preventing these transmural defects remains challenging. Despite the progress in surgical techniques, pancreaticoduodenectomy still has a high risk of adverse events, including leaks and pancreatic fistulas. Here, we present a feasible technique to reduce these complications of pancreaticoduodenectomy. To the best of our knowledge, this is the first report of preemptive endoluminal vacuum therapy after pancreaticoduodenectomy.

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INTRODUCTION

Pancreaticoduodenectomy is a technically demanding operation, with reported morbidity rates of approximately 40%-50%[1,2]. Gastroparesis and bleeding are the most frequent complications, while pancreatic fistula, which can cause intra-abdominal abscess, sepsis, and occasionally death, is the most serious[3]. Patients may require another operation, representing a therapeutic challenge that directly impacts mortality, morbidity, and cost to health systems worldwide[4,5]. Several techniques, such as pancreatic duct occlusion, pancreatogastric anastomosis, Wirsung-jejunal duct-to-mucosa anastomosis, and drainage to the pancreatic duct, have been developed to prevent complications[6-8].

In recent years, endoscopic procedures have begun to fill the large gap between medical and surgical treatments aimed at avoiding fistulas and leaks[9-12]. There have been no previous reports of preemptive endoscopic vacuum therapy (EVT) after pancreaticoduodenectomy.

CASE PRESENTATION

Chief complaints

A 71-year-old woman was admitted to the emergency room with jaundice, choluria, fecal acholia, abdominal pain, and fever.

History of present illness

The patient had a 6-day history of worsening abdominal pain and fever 2 d before admission at the emergency unit.

History of past illness

She had a medical history of hypertension and type 2 diabetes mellitus, controlled with oral agents.

Personal and family history

She had not undergone any prior abdominal surgery.

Physical examination

Physical examination revealed fever (38.5°C), jaundice, and tenderness in the upper abdomen.

Laboratory examinations

Laboratory tests revealed elevated serum bilirubin levels (total: 13 mg/dL; conjugated: 12.1 mg/dL), leukocytosis (white blood cells: 16500/μL), and reduced serum albumin levels (2.1 g/dL). Carbohydrate antigen 19-9 and carcinoembryonic antigen levels were within normal limits.

Imaging examinations

Abdominal ultrasonography showed cholelithiasis and intrahepatic and extrahepatic dilatations. Magnetic resonance imaging (MRI) demonstrated a circumferential tumor of the middle bile duct with upstream biliary dilatation, cholangitis, and cholelithiasis (Figure 1). The pancreas and caliber of the duct of Wirsung were normal. Endoscopic retrograde cholangiopancreatography (ERCP) was performed, although drainage was unsuccessful because the guidewire could not be passed across the lesion.

FINAL DIAGNOSIS

The patient was diagnosed with moderately differentiated biliary adenocarcinoma pT4pN0pM0 (stage group IIIB).

TREATMENT

Considering the success of ERCP, we opted for percutaneous drainage. The patient had a history of weight loss, reduced serum albumin levels (2.1 g/dL), and lower oral food intake. Therefore, enteral nutrition was initiated through a nasoenteral feeding tube and high-protein oral supplementation.

Pancreaticoduodenectomy (Figure 2) was performed on hospital day 14, after tumor staging and perioperative nutrition. A laparoscopic approach was attempted, although the procedure was converted to open pancreaticoduodenectomy because of bleeding from a branch of the portal vein. A harmonic power clamp was applied to a pancreatic section, showing a thin duct of Wirsung. End-to-side duct-to-mucosa pancreaticojejunostomy and choledochal-jejunal anastomosis were performed with Caprofyl. The surgical procedure lasted 10 h, requiring blood transfusion (4 units of red blood cells). The patient was admitted to the intensive care unit, where she remained for 1 d.

Preemptive endoluminal vacuum therapy was provided during surgery. The system implemented the Dr. Flaubert Sena technique[12] (Figure 3), using a nasogastric tube, antimicrobial incise drape, and gauze. The negative pressure was constant at 125 mmHg. The nasoenteral feeding tube was placed through the alimentary limb (Figure 4), and enteral feeding was initiated 12 h postoperatively. The endoscopic vacuum system was removed on postoperative day 3, without adverse events or symptoms.

The peripancreatic abdominal drain was removed on postoperative day 5, and the amylases were measured. The patient was discharged 5 d after pancreaticoduodenectomy.

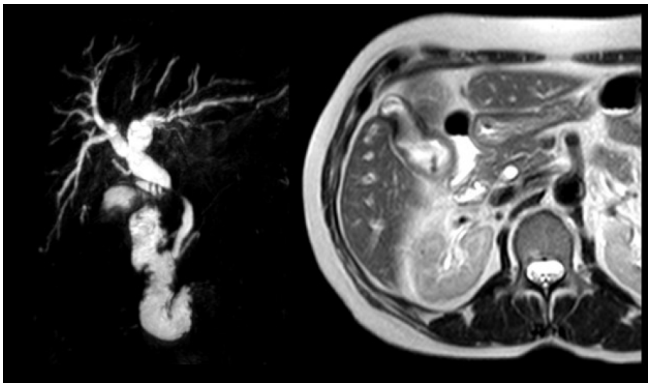

Figure 1 Magnetic Resonance Cholangiopancreatography demonstrated a circumferential tumor of the middle bile duct with upstream biliary dilatation, cholangitis and cholelithiasis. Magnetic Resonance Imaging showing gallbladder invasion.

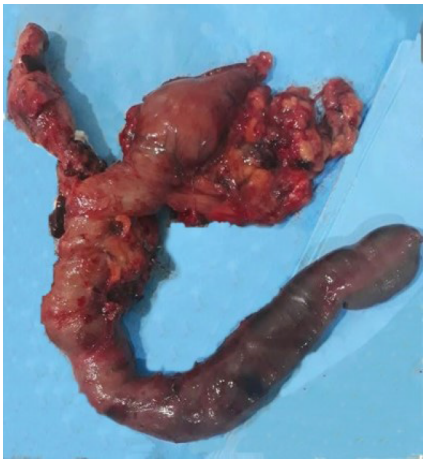

Figure 2 Surgical specimen following pancreaticoduodenectomy.

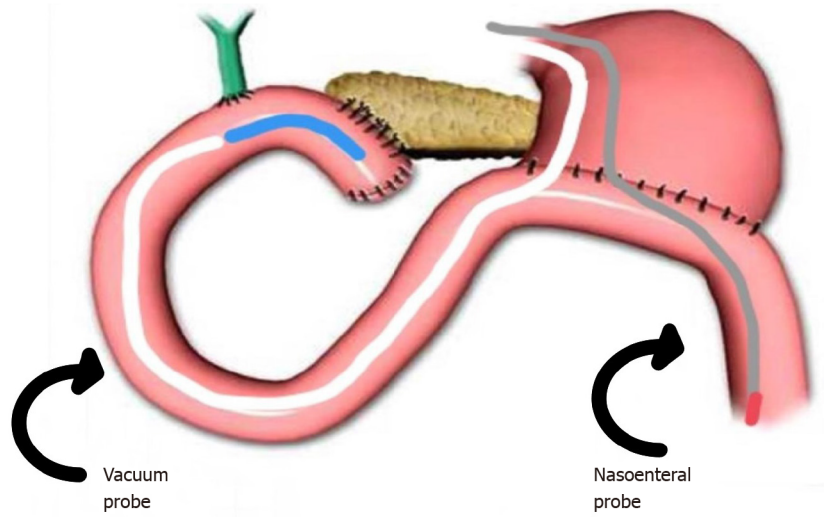

Figure 3 Endoscopic vacuum system.

OUTCOME AND FOLLOW-UP

At the time of drafting this manuscript, the patient was being followed up in the outpatient clinic and had developed no complications related to the procedure. The Oncology Group opted for no adjuvant therapy.

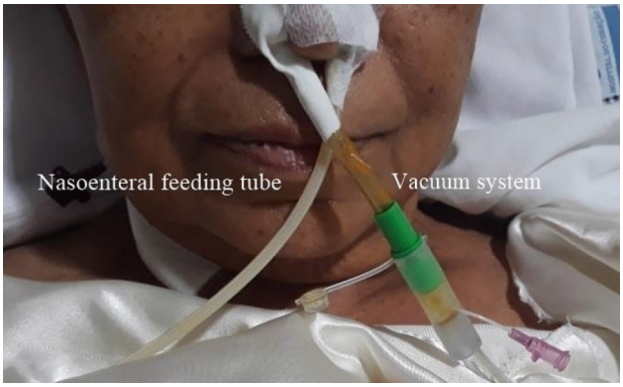

Figure 4 Endoscopic vacuum system placed through the right nostril and the nasoenteral feeding tube placed through the left nostril.

DISCUSSION

Pancreaticoduodenectomy is a technically demanding operation, with morbidity rates of approximately 40%–50%. The mortality rate is around 2.6%, and 37%–43% of deaths are directly linked to pancreatic fistulas[1,2,13,14]. However, the prevention of this complication remains challenging, being related to non-modifiable factors (patient's age, comorbidities, pancreatic texture, and pancreatic duct size) and modifiable variables (anastomosis technique, somatostatin analogs, bleeding, and massive blood transfusions)[6,8,14]. These variables influence the development of leaks and pancreatic fistulas.

Although cavity drainage is unlikely to influence the rate of these adverse events, we proposed the use of an endoscopic vacuum system to prevent pancreatic fistulas[9,15,16]. The system is feasible and effective for the treatment of transmural defects[12]. Tools for building the system include a nasogastric tube (14 Fr), gauze, an antimicrobial incise drape, and a nylon suture. The first step is to make several holes in the nasogastric tube and cut the antimicrobial incise drape to match the size of the fenestrated portion. Subsequently, using an 18-G needle, several holes are made in the antimicrobial incise drape. The next step is wrapping the fenestrated portion of the nasogastric tube using gauze and then with an antimicrobial incise drape. Finally, a 2.0 nylon suture is used to fix the gauze and antimicrobial incise drape at the nasogastric tube (Figure 5). Polyvinyl alcohol foam and polyurethane foam are alternatives for making the system. However, gauze is just as safe and effective as these materials, and is less expensive.

Similar to the therapeutic vacuum, the endoscopic preemptive vacuum may also promote continuous exudate evacuation, reduction of inflammatory edema, improvement of blood supply, and lymphatic drainage. The negative pressure also promotes microdeformation and macrodeformation, leading to angiogenic factors that increase local healing.

Liu *et al*[17] proposed that the increased pressure in anastomosis associated with pancreatic enzymes (proteases and phosphatases) could lead to increased leakage in non-hermetic anastomoses due to self-digestion of the anastomosis, and a negative pressure could prevent this process. Therefore, we believe that the endoscopic vacuum system decreases pressure in the biliopancreatic limb and reduces contact between the anastomosis and pancreatic juice. Thus, the preemptive vacuum can prevent leaks and pancreatic fistulas.

In a systematic review of 60739 patients, Sergio Pedrazzoli[7] supported this theory, stating that for fluid flow from one lumen to another, there must be a pressure differential between the means to overcome gravity and peristaltic activity. However, at present, these pressures are not documented. Furthermore, the use of endoluminal drains would favor the removal of biliopancreatic secretions and could be used for the infusion of protease inhibitors.

With regard to complications, a recent systematic review with a meta-analysis published by do Monte Junior *et al*[18] demonstrated bleeding, stricture, and difficulty in removal as the main adverse events. Difficulty in removing the system only occurred in one patient. Considering that the preemptive vacuum therapy system remains in the anastomosis for no longer than 3 d, and the novel system has no sponge, the risk of those complications is small, although they may still exist. Neumann *et al*[19] performed preemptive vacuum therapy for the treatment of anastomotic ischemia after esophageal resection. Using a continuous suction of 125

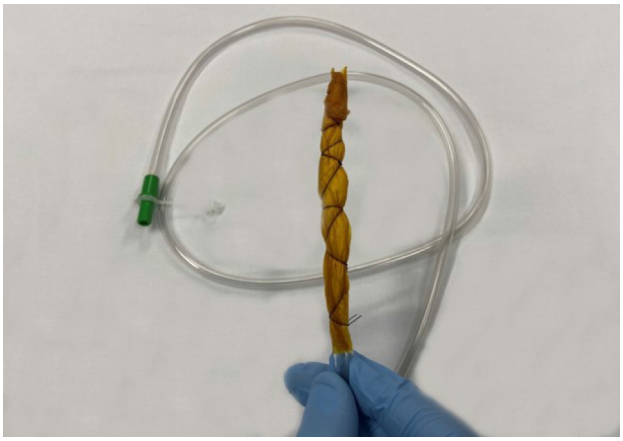

Figure 5 Modified endoscopic vacuum system (distal part).

mmHg, complete mucosal recovery was achieved in 75% of cases. Thus, ischemia caused by this regimen of negative pressure is improbable.

To diagnose pancreatic fistulas, we used the criteria of the International Pancreatic Fistula Study Group modified in 2016[20]. Our patient had several risk factors for the development of this complication, such as age, malignancy, fat-substituted pancreas, pancreatic duct size < 3 mm, intraoperative transfusion, and preoperative malnutrition. Nevertheless, there were no complications during her evolution[21]. An early oral diet was initiated on postoperative day 2 when peristaltic movements returned.

Various techniques are used to minimize the risk of anastomosis dehiscence, including the application of a fibrin sealant or a fibrin glue-coated collagen patch. The first advantage of preemptive vacuum therapy is that it allows enteral feeding while reducing the risk of leak and fistulas. Compared with the modified vacuum system, a preemptive vacuum is a feasible and cost-effective method for preventing those circumstances. Aside from this, recent studies demonstrated that fibrin sealant patches had no significant effect on the rate of postoperative pancreatic fistula[22,23].

CONCLUSION

Preemptive endoluminal vacuum therapy might be a safe and feasible technique to reduce leaks after pancreaticoduodenectomy.

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CASE REPORT

Curling ulcer in the setting of severe sunburn: A case report

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Author contributions: Schosheim A, Tobin M and Chawla A contributed equally to this work. Schosheim A, Tobin M, and Chawla A conceptualized and drafted the initial manuscript, and reviewed and revised the manuscript along with also critically reviewing the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Informed consent statement: Informed verbal consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: There are no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Abstract

BACKGROUND

While sunburns are very common, especially in pediatrics, curling ulcers secondary to sunburns are a very rare entity that has not been noted in the literature in over fifty years. This case is the first addition to the literature since the originally documented case.

CASE SUMMARY

A previously healthy 17 year old male presents to the emergency room with lethargy, shortness of breath on exertion, dark stools and nausea. His fatigue started to become significantly worse four days prior to admission. Approximately two weeks prior to admission, the patient was on a beach vacation with his family at which time he suffered severe sunburns. He had developed crampy epigastric abdominal pain, which was followed by dark, loose stools. On exam, he is non-toxic appearing, but with pallor and peeling skin on his face and chest with epigastric tenderness. Infectious stool studies were all negative including *Helicobacter pylori*. He denies use of any non-steroidal anti-inflammatory drugs and also denies alcohol or recreational drug use. While admitted he is found to be significantly anemic with his hemoglobin as low as 6.3 requiring two units of packed red blood cells. Endoscopy revealed several severe and deep ulcerations in the antrum and body of the stomach indicative of stress or curling ulcers.

CONCLUSION

While the incidence of stress ulcers is not known, it is most common with severe acute illness, most commonly presenting as upper gastrointestinal (GI) bleeding. It is essential to be aware of the risk of curling ulcers secondary to severe sunburns as patients with stress ulcer GI bleeding have increased morbidity and mortality compared to those who do not have GI bleed.

Key Words: Curling ulcer; Sunburn; Stress ulcer; Pediatrics; Gastroenterology; Gastrointestinal bleed; Case report

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Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

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Core Tip: While sunburns are very common, especially in pediatrics, curling ulcers secondary to sunburns are a very rare entity that has not been noted in the literature in over fifty years. Although a very rare consequence of sunburn, it is essential to be aware of the risk of curling ulcers secondary to severe sunburns as patients with stress ulcer gastrointestinal bleeding have increased morbidity and mortality compared to those who do not have gastrointestinal bleed.

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INTRODUCTION

Stress ulcers are a well-known clinical entity with various findings ranging from asymptomatic superficial lesions and occult gastrointestinal (GI) bleed to overt clinically significant GI bleeding. It is thought that this is typically due to gastric and sometimes esophageal or duodenal mucosal barrier is disruption[1]. When the etiology of the stress ulcer is a burn, they are characterized as curling ulcers. Most cases of curling ulcers in the current literature are secondary to severe systemic burns and although rare, there was one previous case report of curling ulcer secondary to sunburn[2].

CASE PRESENTATION

Chief complaints

A previously healthy 17 year old male presented to Stony Brook University Hospital from an outside hospital with lethargy, shortness of breath on exertion, dark stools and nausea.

History of present illness

The patient's fatigue had become significantly worse for four days prior to admission. Approximately two weeks prior to admission, the patient was on a beach vacation with his family at which time he suffered severe sunburns. He had developed crampy epigastric abdominal pain that was followed by dark, loose stools.

History of past illness

He has no significant past medical history.

Personal and family history

He and his family have no significant history.

Physical examination

On physical exam, he was pale and tired-appearing with epigastric tenderness.

Laboratory examinations

Infectious stool studies were all negative including *Helicobacter pylori*. His complete blood count revealed that he was significantly anemic with a hemoglobin of 6.3 and his complete metabolic panel was within normal limits.

Imaging examinations

No imaging was performed.

Further hospital course

Endoscopy was performed and revealed severe, deep ulcerations in the antrum and body of the stomach (Figure 1).

FINAL DIAGNOSIS

Curling ulcers in the antrum.

TREATMENT

The patient was treated with high dose proton-pump inhibitor and carafate along with iron and folate supplementation.

OUTCOME AND FOLLOW-UP

With time, the patient's symptoms and blood work improved. Five months after his original admission, endoscopy was performed and all previous areas of ulceration had completely resolved.

DISCUSSION

While the incidence of stress ulcers is not known, it typically occurs with severe acute illness, most commonly presenting as upper GI bleeding. Although stress ulcers can lead to perforation, it is very rare with less than 1% incidence[3]. An impaired mucosal barrier where the mucosal glycoprotein breaks down due to increased concentrations of refluxed bile salts or uremic toxins in the setting of critical illness may be the possible pathologic changes that lead to ulceration. Increased secretion of gastric acid secondary to higher secretion of gastrin during stress is likely as well[4].

CONCLUSION

Curling ulcers secondary to sunburns are a previously described phenomenon, but it is a rare entity that has not been noted in the literature in over fifty years[2]. It is essential to be aware of the risk of curling ulcers secondary to severe sunburns as patients with stress ulcer GI bleeding have increased morbidity and mortality when compared to those without GI bleed.

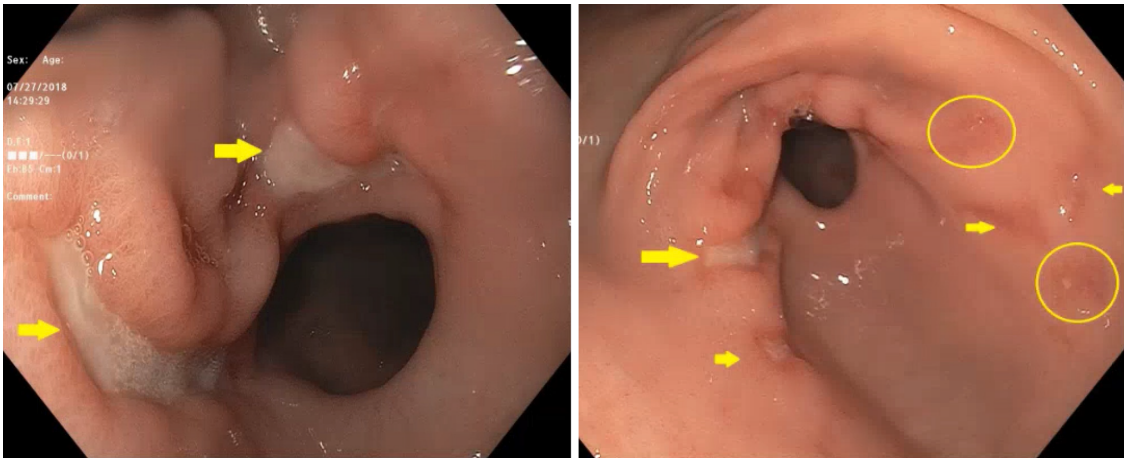

Figure 1 Deep ulcerations in the antrum of the stomach.

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