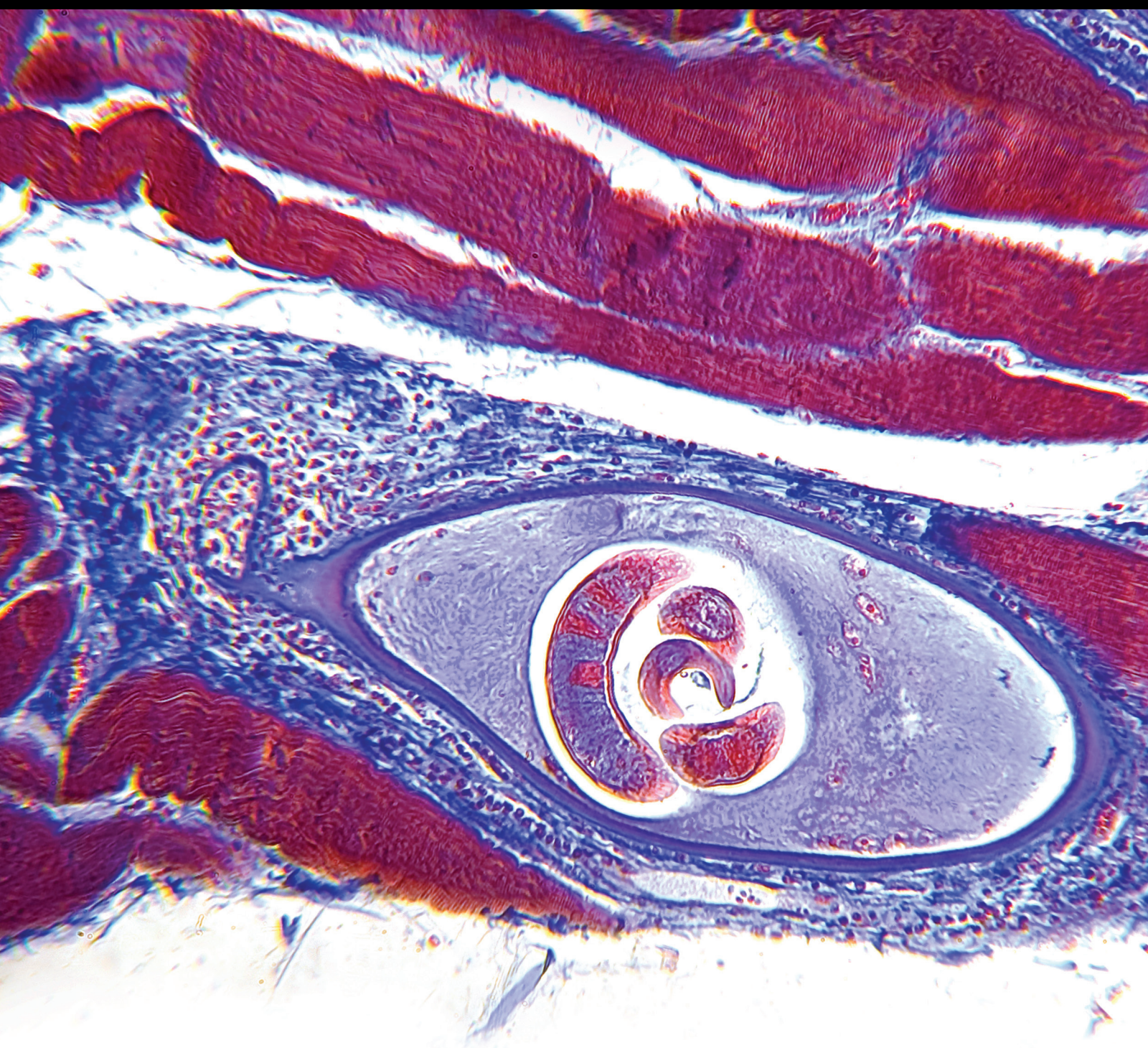
Gastroenterology Research and Practice

Advances in Therapeutic Endoscopy

Lead Guest Editor: James H. Tabibian
Guest Editors: Sooraj Tejaswi, Júlio P. Lima, and Mohit Girotra



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Editorial Board

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Editorial

Advances in Therapeutic Endoscopy

Sooraj Tejaswi,[1] **Mohit Girotra**,[2] **Júlio P. Lima**,[3] **and James H. Tabibian**[4,5]

[1]*Division of Gastroenterology & Hepatology, University of California, Davis, Sacramento, California, USA*
[2]*University of Miami Miller School of Medicine, Miami, Florida, USA*
[3]*Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil*
[4]*Division of Gastroenterology, Department of Medicine, Olive View-UCLA Medical Center, Sylmar, California, USA*
[5]*David Geffen School of Medicine, Los Angeles, California, USA*

Correspondence should be addressed to James H. Tabibian; jtabibian@dhs.lacounty.gov

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Advanced endoscopic techniques comprise an exciting and ever-evolving field in medicine, enabling minimally invasive interventions for the management of numerous benign and malignant diseases of the GI tract that historically were possible only with major surgery. This special issue covers many articles from across the globe, examining the role of such techniques in the management of pancreaticobiliary, foregut, and other diseases.

R. Berry et al. discuss the etiology, diagnosis, and management of hemobilia, a potentially life-threatening condition whose incidence has increased in light of the growing frequency of hepatopancreatobiliary procedures, including interventional radiologic and advanced endoscopic. The authors focus on the management of hemobilia from the perspective of an advanced endoscopist, while also providing an overview of the condition and the spectrum of available diagnostic and therapeutic modalities.

Several articles addressed the important topic of pancreatitis, from prevention to management of its sequelae. With regard to the former, administration of rectal indomethacin in the absence of contraindication has become a standard practice to decrease the risk of post-ERCP pancreatitis, especially for patients deemed to be at high risk. In the systematic review and meta-analysis by X. He et al., the authors show that rectal indomethacin is protective not only in high-risk patients, but also in those deemed to be average-risk patients. Interestingly, they also found that pre-ERCP administration of indomethacin was more protective. Studies such as these may help endoscopists who are undecided about the utility of rectal indomethacin in average-risk cases. A. Garber et al. review the mechanisms and management of acute pancreatitis, a major cause of morbidity and hospital admission. They discuss early supportive care, with an emphasis on early and adequate fluid resuscitation and nutrition and on endoscopic management of late complications. This is a timely review that reinforces the American Gastroenterology Association's 2018 guideline on the management of acute pancreatitis. Complementing this article, M. Jagielski et al. describe their experience with different techniques of endoscopic drainage of walled-off pancreatic necrosis (WOPN) and how the different methods have evolved over time.

Management of esophageal disorders, both benign and malignant, has become a staple of endoscopic practice and is discussed in this special issue. For example, Y.-W. Zhang et al. present the findings of a meta-analysis of randomized controlled trials (RCTs) which demonstrates the benefit of intralesional triamcinolone injection after endoscopic dilation in the management of benign esophageal strictures. Complementing this article and on the topic of postesophagectomy anastomotic leakage (a significant cause of mortality and morbidity), S. M. Noh et al. describe how endoscopic vacuum-assisted closure (E-VAC) can be an effective nonsurgical management technique in select cases.

Endoscopic submucosal dissection (ESD) is the topic of four articles included in this special issue, including two pertaining to esophageal ESD. P. Shi and X. Ding provide a succinct review of the various approaches, including

pharmacological treatments, esophageal stents, and tissue engineering/cell therapies, to prevent esophageal stricture formation after ESD. As an offshoot of (autologous) cell therapies, M. Uesato et al. describe the "log bridge" method of maximum mucosal preservation in near circumferential esophageal ESD cases; the authors found that this method was associated with quicker ESD site healing and a trend toward less esophageal stricture formation (a trend toward a lower need for subsequent endoscopic balloon dilation). Of the remaining two ESD-related articles, X. Feng et al. examined the efficacy and safety of endoscopic submucosal *tunnel* dissection (ESTD) for the resection of large (mean size 4.6 cm) superficial gastric lesions and compared it to a traditional ESD approach; the authors found excellent results with both, though ESTD was found to have the advantage of shorter resection (i.e., procedure) times. D. Kikuchi et al. investigated whether the treatment of an ESD site with autologous fibrin glue (prepared using autologous blood) alone or with polyglycolic acid (PGA) sheets could decrease the risk of delayed bleeding in patients receiving antithrombotic therapy; of the 20 patients included, none had delayed bleeding. These early results are promising and may suggest the need for a randomized study.

J. W. Choe et al. conducted a RCT comparing the conventionally used uncovered self-expanding metallic stent (SEMS) to a shape-modified partially covered SEMS for the management of gastric outlet obstruction (GOO). The study did not find a significant difference in patency or distal migration; thus, the appropriate stent shape and design (uncovered versus partially covered) for the management of GOO remains an unresolved question and is likely to be the subject of future studies, though it is probable that no single stent will be superior in all clinicoanatomical scenarios.

Finally, Y. Jiang et al. report on the comparable efficacy of cyanoacrylate injection vs. through-the-scope (TTS) clip placement for the management of a bleeding duodenal Dieulafoy lesion. The authors found both techniques to be safe and effective, suggesting that cyanoacrylate glue may be an additional tool for the endoscopist in addition to the more commonly used TTS clips.

We hope that the articles in this special issue will make for useful reading for an audience interested in advanced endoscopy and in the latest advances in endoscopic management of pancreaticobiliary and foregut diseases.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this Special Issue.

Sooraj Tejaswi
Mohit Girotra
Júlio P. Lima
James H. Tabibian

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Review Article

Efficacy and Safety of Endoscopic Intralesional Triamcinolone Injection for Benign Esophageal Strictures

Ya-Wu Zhang,[1,2,3] Feng-Xian Wei,[1,2,3] Xue-Ping Qi,[3] Zhao Liu,[4] Xiao-Dong Xu,[1,2,3] and You-Cheng Zhang[1,2,3]

[1]*Department of General Surgery, Lanzhou University Second Hospital, Lanzhou 730000, China*
[2]*Hepato-Biliary-Pancreatic Institute, Lanzhou University Second Hospital, Lanzhou 730000, China*
[3]*Lanzhou University Second Clinical Medical College, Lanzhou University, Lanzhou 730000, China*
[4]*The First Clinical Medical College of Lanzhou University, Lanzhou 730000, China*

Correspondence should be addressed to You-Cheng Zhang; zhangyouchengphd@163.com

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Objectives. To evaluate the efficacy and safety of endoscopic intralesional triamcinolone injection (ITI) for benign esophageal strictures combined with endoscopic dilation (ED). *Methods.* Online databases including MEDLINE, EMBASE, the Cochrane Library, and Web of Science were comprehensively searched for prospective randomized control trials (RCTs) between 1966 and March 2018. A meta-analysis was conducted according to the methods recommended by the Cochrane Collaboration. *Results.* Six RCTs consisting of 176 patients were selected. Meta-analysis results showed that additional ITI had a significant advantage in terms of stricture rate and required ED sessions. Surgery-related and non-surgery-related strictures showed similar results. Additional ITI was not associated with significantly increased risk of complications. *Conclusions.* Our meta-analysis showed that additional ITI therapy was supposed to be effective and safe for benign esophageal strictures as it reduced the stricture rate and required ED sessions. However, more RCTs are necessary to support these findings.

1. Introduction

Surgical anastomosis, radiation therapy, Schatzki's rings, esophageal webs, corrosive injury, peptic injury, photodynamic therapy [1, 2], and endoscopic surgery can always induce benign esophageal strictures [3–5]. These injuries can induce edema, and finally lead to stricture formation through stimulating the proliferation of fibrotic tissue and/or accumulation of collagen [6]. Aside from resolving the severity of the stricture, the intended therapy also focused on the improvement of quality of life and avoidance of related complications, as well as the prevention of recurrences. Currently, endoscopic dilation (ED) is the first procedure adopted in clinical practice and is regarded as safe and effective, and the preferred initial treatment option irrespective of etiology [2, 7–9]. However, the procedure sometimes required frequent repetition due to a high risk of recurrence, and this severely influenced the patient's quality of life. Thus, a new therapeutic method is warranted to meet clinical demand.

In previous studies, oral administration and intralesional injection of corticosteroids have been used to soften scars and keloids with promising results, as it has pharmacological effects of inflammatory response inhibition and fibrotic tissue reduction [10, 11]. Some studies also investigated the efficacy of intralesional steroid injections for benign gastrointestinal strictures and proposed to augment the effect of ED [12–14]. Since the esophagus was a narrow tubular organ with a very high incidence and recurrence of stricture, local triamcinolone injection for esophageal strictures was supposed to reduce stricture recurrence by several studies [13, 14].

However, current studies about this issue were limited by small sample size or inconsistent data. We performed a meta-analysis including all prospective randomized controlled trials (RCTs) investigating the clinical efficacy and

safety of intralesional triamcinolone injection (ITI) for benign esophageal strictures.

2. Methods

2.1. Inclusion Criteria. The following inclusion criteria were used to identify relevant studies: (1) Patients were individuals with benign esophageal strictures after surgery and/or corrosive injury. (2) Intervention was ITI in the treatment group, and comparison was saline injection (sham control) or no injection (blank control) in the control group. ED was performed conventionally mainly based on the demand of patients because of significant strictures (defined as failure of passing by an adult using a gastroscope of 8–9.8 mm diameter). (3) Outcome measures included stricture rate, ED sessions, dysphagia-free time, and treatment-related complications. Besides, clinical studies designed as RCTs were available without language limitation.

2.2. Search Strategy. Literature search was conducted in databases including MEDLINE (1966–Mar 2018), EMBASE (1978–Mar 2018), the Cochrane Library (1993–Mar 2018), and Web of Science (1985–Mar 2018). Search terms are as follows: (esophageal OR oesophagus OR esophagus) AND (stenoses OR stricture OR stenosis) AND (triamcinolone OR steroid OR corticosteroids injection). References of case reports, comparative studies, and reviews were also scanned to manually search relevant articles. Two reviewers independently reviewed the search results according to the inclusion criteria through screening the title and abstract. For potential studies, full-text papers were further evaluated independently for final inclusion. Disagreements between reviewers were resolved in consultation with a third reviewer (Zhang YC).

2.3. Data Extraction and Quality Assessment. Another two reviewers independently extracted the data including basic information, outcome measures, and methodological quality items. Any disagreements between the reviewers were resolved by discussion. Basic information included first author, publication year, sample size, average age of patients, intervention, comparison, dose of triamcinolone, diagnosis of patients, and follow-up periods. Outcomes included stricture rates, required dilation sessions, dysphagia-free time, and complications. Methodological quality items included randomization, allocation concealment, blinding, withdrawal and dropout, selective reporting result, and other biases. Quality assessment was performed independently by two reviewers according to the method and the tool of risk of bias recommended by the Cochrane Handbook [15].

2.4. Statistical Analysis. Review Manager (version 5.3, the Cochrane Collaboration, Copenhagen) was used to analyze data. For dichotomous outcomes, risk ratio (RR) with 95% confidence intervals (CI) was used. For continuous outcomes, standard mean difference (SMD) or mean difference (MD) were used. $P < 0.05$ was considered of statistical significance. The chi-square test was performed to assess the statistical heterogeneity across trials and I^2 value to assess the extent of inconsistency. When $I^2 > 50\%$, the random-effect model was used. If $I^2 \leqq 50\%$, the fixed-effect model was applied. Publication bias was explored using an inverted funnel plot.

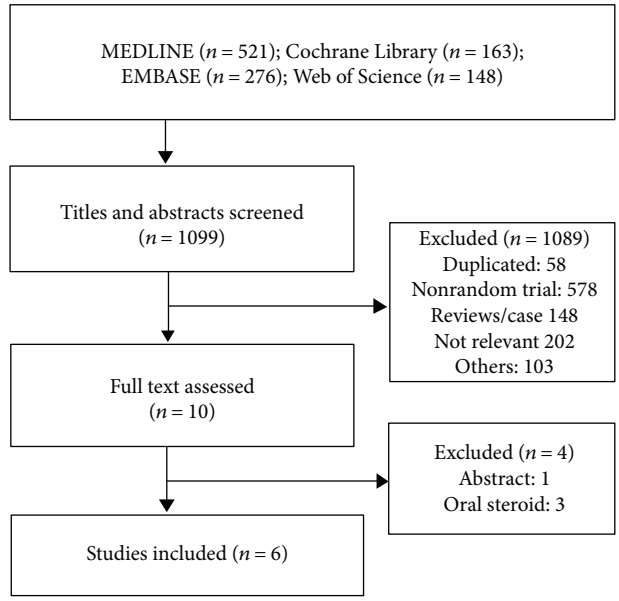

Figure 1: Flow chart of trial selection process.

3. Results

3.1. Literature Search Result and Study Characteristics. We identified 1099 citations from online databases and obtained 10 full texts of articles based on the titles, abstracts, and full-text evaluation. Finally, six studies enrolling 176 patients were included for quantitative analysis [16–21], as shown in Figure 1. Basic information of the included RCTs was listed in Table 1. The sample size ranged from 14 to 60 patients. Two trials adopted a sham control with saline injection [19, 21], and four trials adopted no injection. Five trials adopted bougie dilation, and only one trial adopted balloon dilation [18]. In the study of Ramage et al. [18], the patients received dilation 1-2 times in the past 18 months, which was reported comparable between the groups. The doses of intralesionally injected triamcinolone ranged at 20 mg, 32 mg, and 40 mg per patient, and one trial injected 5 mg of triamcinolone every 10 mm point around the stricture. The diagnosis included surgical injury in three trials, peptic and corrosive injury in two trials, and both surgical and corrosive injury in one trial. Quality assessment was shown in Figure 2, and the overall quality was moderate to high.

3.2. Stricture Rate. Five studies reported the stricture rate after steroid injection during follow-up [16–20]. Significant stricture was defined as failure of passing by an adult using a gastroscope of 8–9.8 mm diameter and the demand of a repeated dilation. Meta-analysis in a fixed-effect model showed that ITI significantly reduced the incidence of stricture compared with control, and stricture rates were 50% and 78% in the groups.

Subgroup analysis according to different stricture etiologies showed that the risks of surgery-related strictures and

Table 1: Characteristic of included randomized controlled trials.

Study	Country	Case (T/C, *n*)	Age (T/C, y)*	Intervention (T/C) T	Intervention (T/C) C	Dose	Diagnosis	Follow-up (months)
Takahashi et al. 2015 [16]	Brazil	7/7	39 (23–64)/ 46 (22–65)	ED + ITI	ED + saline injection	40 mg	Corrosive stenosis	12
Altintas et al. 2004 [17]	Turkey	10/11	49 (24–69)/ 45 (17–76)	ED + ITI	ED	32 mg	Corrosive, surgical, postradiotherapy	>6
Ramage et al. 2005 [18]	USA	15/15	66/67	ED + ITI	ED	20 mg	Corrosive esophageal stricture	>12
Hirdes et al. 2013 [19]	Netherlands	29/31	64 ± 9/62 ± 8	ED + ITI	ED + saline injection	20 mg	Anastomotic stricture	6
Pereira-Lima et al. 2015 [20]	Brazil	10/9	56 ± 8/52 ± 15	ED + ITI	ED	40 mg	Anastomotic stricture	6
Camargo et al. 2003 [21]	Japan	16/16	70 ± 10/71 ± 7	ED + ITI	ED	>30 mg	Endoscopic surgery stricture	>16

*Data were presented as mean ± standard deviation or median (range); T, treatment group; C, control group. ED, endoscopic dilation. ITI, intralesional triamcinolone injection.

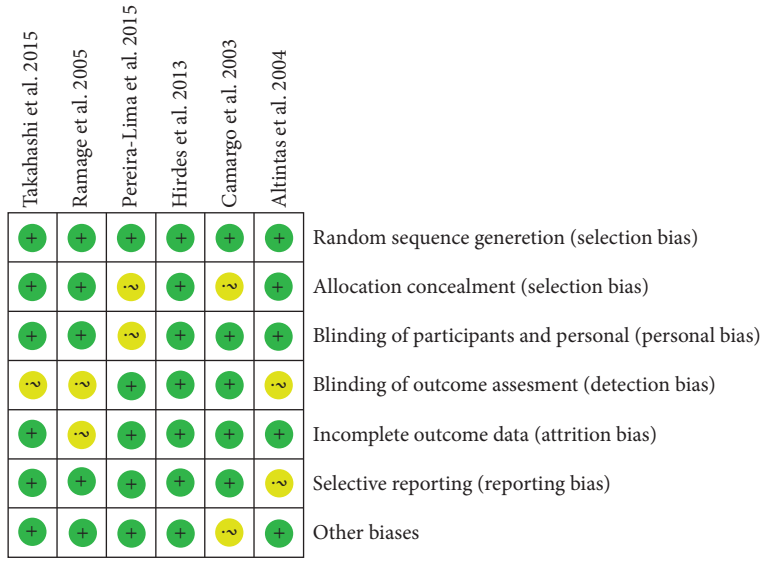

Figure 2: Summary of methodological quality of included studies.

non-surgery-related strictures were both reduced after ITI therapy, as shown in Figure 3.

3.3. Required ED Sessions. Four studies reported the number of required ED sessions during follow-up [16, 17, 19, 20]. Statistical heterogeneity was mild ($I^2 = 11\%$). Meta-analysis results showed that ITI significantly reduced the required ED sessions compared with the control.

Also, subgrouping according to different stricture etiologies showed that the number of required ED sessions was reduced after ITI therapy in the subgroup of surgery-related strictures. However, there was only one study including 21 patients in the subgroup of non-surgery-related strictures, and no significant difference was found, as shown in Figure 4.

3.4. Dysphagia-Free Time. Four studies reported the data of dysphagia-free time [16, 17, 19, 20]. There was a large heterogeneity across the trials ($I^2 = 88\%$), thus the random-effect model was used. No significant difference in dysphagia-free time was found between the groups.

After excluding the study causing the large heterogeneity [16], the I^2 value was reduced to 38% and fixed-effect model meta-analysis results of the remaining three studies showed that ITI significantly reduced the duration of dysphagia-free time compared with the control (Figure 5).

3.5. Complications. Injection-related complications were reported in two trials with a total of eight patients, and the others stated no related complications. Among them, two had perforations, one experienced bleeding, one had mucosal tearing, and four suffered from local infection. The adverse effects were similar between the patients treated with steroids and those without steroids. There was no statistically significant difference in the incidence of complications.

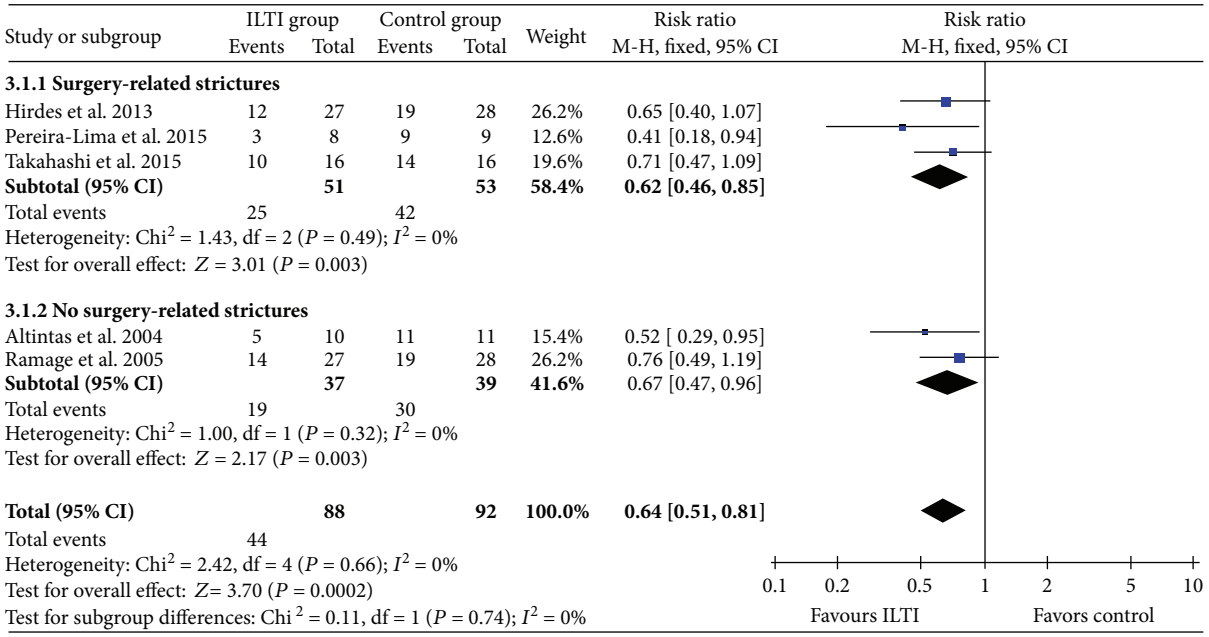

Figure 3: Forest plot of stricture rate between ITI and control.

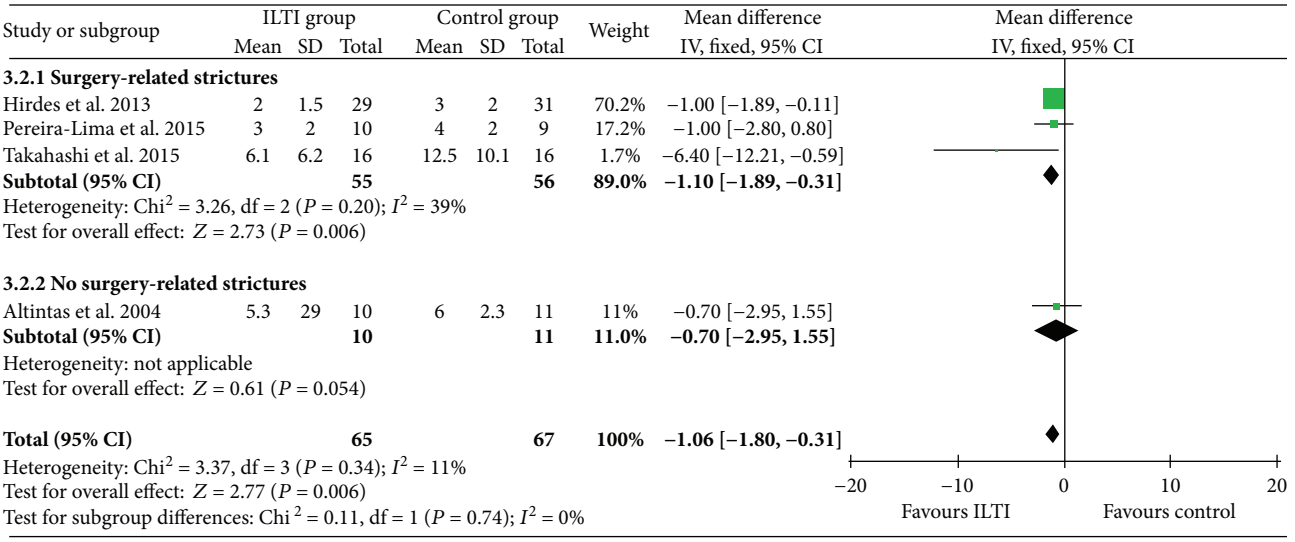

Figure 4: Forest plot of EBD sessions during follow-up between ITI and control.

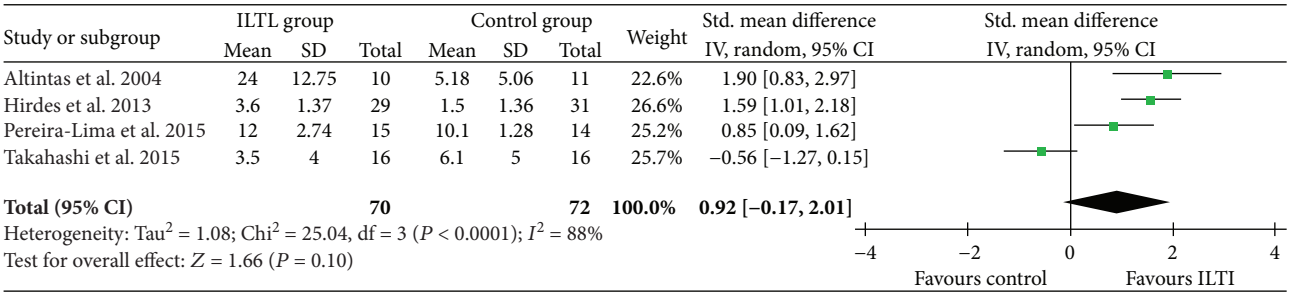

Figure 5: Forest plot of dysphagia-free time between ITI and control.

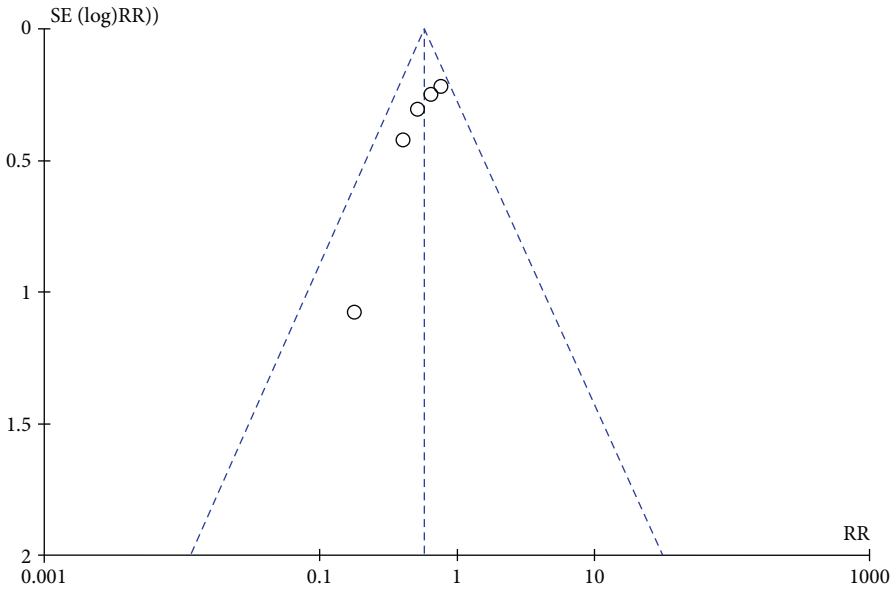

Figure 6: Inverted funnel plot of stricture rate.

3.6. Publication Bias. Due to the limited number of included studies, a publication bias test through an inverted funnel plot was only adopted for the outcome of the stricture rate. The shape was to some extent symmetrical, indicating a lower risk of publication bias (Figure 6).

4. Discussion

A benign esophageal stricture was diagnosed by clinical, radiological, and endoscopical features and biopsies [16, 22]. Therapeutic options for a benign stricture included ED, temporary stent placement, intralesional steroid injection, and incisional therapy. Among these methods, ED is the cornerstone treatment [1]. Esophageal dilation was performed using either through-the-scope balloons or wire-guided bougies. A defined esophageal diameter to be targeted by dilation is different from patients with different severities, but the majority of patients have considerable symptomatic improvement when a diameter of 15–18 mm has been reached [16–19]. However, most of the intractable strictures are often unsuccessful with a high incidence of recurrence, which then require repeated dilations [23, 24]. This would seriously influence the quality of life and also increase the risk of complication in these patients. As estimated by the current study, the recurrence rate of stricture in the control group of benign esophageal stricture in a 6- to 12-month follow-up period was as high as 78%.

Various investigators investigated the role of corticosteroid injection into the stricture for the prevention of recurrent and complex strictures. Holder et al. were the first to report the use of intralesional steroid injection (ISI) into benign esophageal strictures of dogs and children, and the therapy was used only occasionally during the 1970s and 1980s [25, 26]. Over the last decade, increasing interests were presented in the use of the therapy for refractory benign esophageal strictures [12, 13, 16, 18].

Some other large-scale comparative studies reported their primary results and findings as follows. Kochhar et al. reported 71 patients with benign esophageal stricture receiving ISI; all categories of stricture that required ED sessions were significantly decreased, while the luminal diameter was increased. Interestingly, it also indicated that the location, number, and length of the stricture did not influence the efficacy of treatment [13]. Lee et al. reported a study of 31 patients, where all of them were diagnosed by endoscopy and treated with ED and steroid injection in each of the four quadrants at the narrowest region of the stricture [12]. The results showed that ISI led to symptomatic improvement and less frequent dilation. Furthermore, no complications were encountered. However, Camargo et al. did not find an improvement in dilation frequency or dysphagia in 14 patients with corrosive strictures allocated to steroid injections [21]. A study that included 21 patients with strictures of various etiologies receiving preventive ED found an increase in dysphagia-free period and periodic dilation index, while no difference in required dilations [16]. So, for the difference across the studies, study design, kinds of etiology, and dose of steroid would be all potential factors that influenced the clinical outcomes.

The present meta-analysis of the high quality of RCTs only investigated the benign esophageal stricture of surgical and corrosive injuries, and the results showed that additional ITI was more helpful than ED alone for the management of the strictures, as it reduced the stricture rate and number of required ED sessions during follow-up. Subgroup analysis for etiology of surgery- or non-surgery-related strictures showed that ITI therapy seemed to achieve even better results for surgery-related strictures in all outcomes. Thus, it is supposed that when endoscopic ITI was applied with a conventional intention of ED, the outcomes of stricture control as well as patients' quality of life would be significantly improved. Regretfully, the meta-analysis indicated that the

dysphagia-free time might not be prolonged, as the dysphagia-free time was determined by the time when a patient felt dysphagia and came to visit the surgeons. Meanwhile, dysphagia is a very subjective complaint, and the tolerance levels across patients may be very different. Thus, such negative results would be caused by the situations and by the insufficient test power of the relatively small sample size.

Obviously, there were no life-threatening or serious complications that occurred in patients undergoing quadrant injection. Additionally, our study did not find a significant difference in reported injection-related complications such as perforation, bleeding, mucosal laceration, and local infection. However, it was reported that ISI may increase the risk of candidal esophagitis [18]. Due to the rare incidence of complications, as well as our relatively small sample size, the current conclusion should be considered carefully, and high-risk patients need to be evaluated thoroughly in clinical practice.

The limitation of this meta-analysis included the small sample size of participants, which might be insufficient to achieve very strong results in aspects of dysphagia-free time and complications. There are also some differences in the included studies: (1) Even though both surgical and corrosive strictures were benign, without clear resolution of the mechanism they still might have possible differences in pathogenesis and pathophysiology, and this gave rise to different prognoses and heterogeneities, although subgroup analysis was performed with no significant statistical difference. (2) The detailed ITI procedure was not completely the same, and this might also influence the outcomes, although the interventions in each trial were comparable. (3) Both bougie dilation and balloon dilation were used to conduct the dilation, which may also partly influence the treatment efficacy, which could be difficult to avoid in the follow-up periods after more than six months.

5. Conclusions

Additional ITI therapy was supposed to be effective and safe for the management of benign esophageal strictures as it reduced the stricture rate and required ED sessions. However, the relatively small sample size of participants was included especially in the evaluation of safety, and larger-scale RCTs are still needed to support the findings.

Abbreviations

ITI: Intralesional triamcinolone injection
ISI: Intralesional steroid injection
ED: Endoscopic dilation
RCTs: Randomized control trials
SMD: Standard mean difference
MD: Mean difference.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

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Review Article

Hemobilia: Perspective and Role of the Advanced Endoscopist

Rani Berry,[1] James Han,[2] Mohit Girotra,[3] and James H. Tabibian[4]

[1]*Department of Internal Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA*
[2]*Department of Internal Medicine, University of California, Irvine, CA, USA*
[3]*Division of Gastroenterology, University of Miami, Miller School of Medicine, Miami, FL, USA*
[4]*Division of Gastroenterology, Department of Medicine, Olive View-UCLA Medical Center, Sylmar, CA, USA*

Correspondence should be addressed to James H. Tabibian; jtabibian@dhs.lacounty.gov

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Hemobilia refers to bleeding from and/or into the biliary tract and is an uncommon cause of gastrointestinal hemorrhage. Hemobilia has been documented since the 1600s, but due to its relative rarity, it has only been more critically examined in recent decades. Most cases of hemobilia are iatrogenic and caused by procedures involving the liver, pancreas, bile ducts, and/or the hepatopancreatobiliary vasculature, with trauma and malignancy representing the two other major causes. A classic triad of right upper quadrant pain, jaundice, and overt upper gastrointestinal bleeding has been described, but this is present in only 25–30% of patients with hemobilia. Historically, the gold standard for diagnosis and treatment has been angiography and interventional radiologic intervention, respectively. However, the paradigm is shifting, at least in select cases, towards first-line reliance on noninvasive imaging (e.g., computed tomography) and therapeutic endoscopy, owing to advances in and the less invasive nature of both, while saving interventional radiological and/or surgical intervention for refractory or imminently life-threatening cases.

1. Introduction

1.1. Overview. Hemobilia, in the most elemental sense, refers to the admixture of blood in bile or to blood in the biliary tract. The most common causes of hemobilia are surgical and nonsurgical trauma, malignancy, and/or cholangiovenous (or arterobiliary) fistulae. Though hemobilia remains an uncommon cause of digestive tract bleeding, its incidence has gradually increased as the arsenal of advanced endoscopic and other minimally invasive hepatopancreatobiliary procedures has expanded. Likewise, with more hepatopancreatobiliary procedures comes the advent of new therapeutic endoscopic and interventional radiologic approaches to diagnose and treat hemobilia [1].

1.2. Historic Background. The first known report of hemobilia was from Francis Glisson (Figure 1) in 1654, who described the clinical presentation of a nobleman whom in the midst of a sword fight suffered a fatal blow to the right upper quadrant, leading to massive (upper) gastrointestinal bleeding and death 1 week later. Post mortem, the source of bleeding was found to be from a liver laceration, which in turn led to the landmark description of hemobilia. Antonie Portal was the first to publish a case of hemobilia identified antemortem, reporting suspected hemobilia that was later confirmed on autopsy in 1777. Portal drew important attention to the difficulty in identifying the pinpoint source of bleed, a problem still faced today [2]. One hundred years later, Quincke identified the clinical triad of right upper quadrant pain, jaundice, and upper gastrointestinal tract bleeding, known as Quincke's triad [3]. By the 1900s, there were many scattered case reports of biliary tract hemorrhage, though the term hemobilia was not actually coined until 1948 in a paper entitled, "Hemorrhage into the Biliary Tract Following Trauma: Traumatic Hemobilia" [4].

2. Epidemiology

Though uncommon, hemobilia is an important cause of upper gastrointestinal hemorrhage. Published data on the topic is mainly in the form of case reports and three large case series. In 1973, Sandblom reported a series reviewing 355

Figure 1: Francis Glisson, who recounted the first recorded case of hemobilia in his treatise *Anatomica Hepatis* [67].

cases and reporting 59 iatrogenic cases (16.6%) and 137 (38.6%) due to trauma [4]. Yoshida et al. published a series of 103 patients in 1987, of whom 41% of cases were iatrogenic and 19% were traumatic, thus reversing the incidence (compared to prior reports) to favor iatrogenic causes, citing increasing hepatobiliary interventional procedures as the primary contributing factor [5]. This sentiment was echoed later on by Green et al. in a series of 222 patients published in 2001, among whom 65% had an iatrogenic cause and only 6% had trauma (Figure 2) [6]. This is consistent with more recent reports indicating iatrogenic injury as the leading cause of hemobilia, accounting for over 50% of all cases.

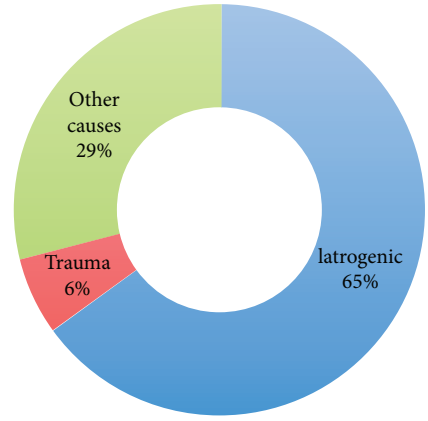

Figure 2: Common causes of hemobilia [6].

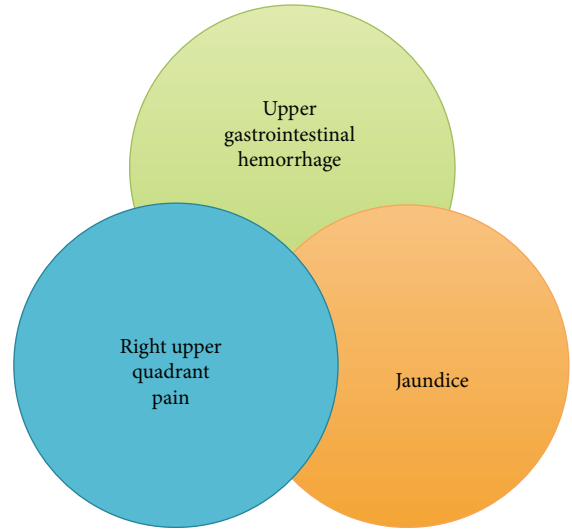

Figure 3: Quincke's triad of hemobilia. Notably, all three symptoms are only present in 22–35% of patients [6, 7].

3. Clinical Presentation and Pathophysiology

The classic presentation of hemobilia is formally known as Quincke's triad: jaundice, right upper quadrant abdominal pain, and upper gastrointestinal hemorrhage (Figure 3), but all three findings are only present in 22–35% of cases [6, 7]. The presentation of hemobilia often depends on the cause. For instance, patients with a percutaneous transhepatic biliary drain (PTBD) may present with bloody output from the biliary drain. The timing of presentation can also vary and possibly aid in diagnosis. Endoscopic retrograde cholangiopancreatography- (ERCP-) related hemobilia tends to present immediately or within a few days after the inciting biliary duct injury (e.g., sphincterotomy or biliary stricturoplasty) [8, 9]. In instances where the hepatic artery is ligated during surgery or interventional procedures, an environment for fistulization between a high-pressure arterial system and low-pressure biliary tract (i.e., arteriobilious fistula) is created. The difference in density between blood and bile causes the two to separate once joined within the biliary tree, and as the initial bleed stops, the blood that originally entered the biliary tract begins to clot, serving as a physical impediment to biliary outflow. These clots can cause symptomatic jaundice, biliary obstruction, and subsequent right upper quadrant pain. Clots also cause biliary stasis and hepatobiliary inflammation [8]. As clots travel through the hepatopancreatic ampulla, patients may preferentially complain of discomfort at the level of the right hypochondrium, extending to the epigastrum [8, 10]. Additionally, because of their similar echogenicity, clots can masquerade as biliary stones on imaging studies. Hemobilia can also emanate from venous blood flow, which in contrast tends to be of lower volume or self-limited (except in cases of portal hypertension, in which case it may be of larger volume and/or persistent).

Hemobilia presents on serum laboratory tests as (iron deficiency) anemia and/or as hyperbilirubinemia and elevated alkaline phosphatase and/or aminotransaminases, as seen with other causes of bleeding. Clinically, hemobilia can present as hematemesis, melena, or hematochezia, with or without choluria, depending on the rate of bleeding and anatomical factors (e.g., postbilioenteric surgical anatomy).

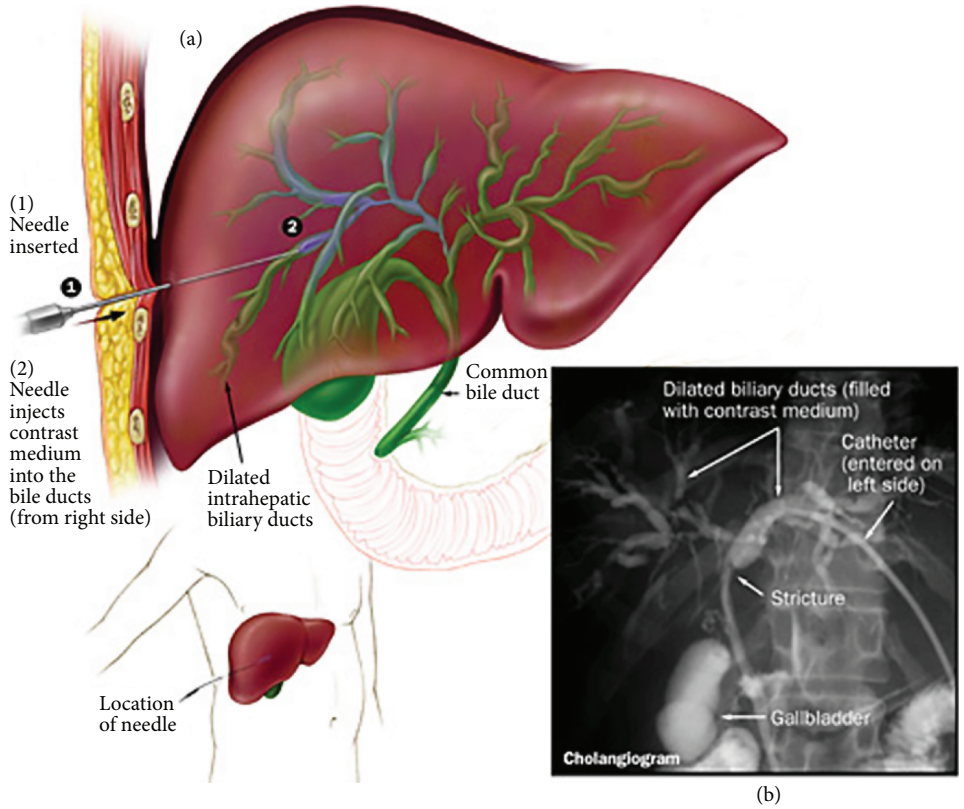

Figure 4: Percutaneous transhepatic cholangiography. This technique can be utilized to inject contrast directly into the biliary system and show, fluoroscopically, evidence of filling defects, which in the proper clinical context may be consistent with (clotted) hemobilia [68].

4. Causes of Hemobilia

The causes of hemobilia have evolved overtime, as alluded to earlier. Possible causes include iatrogenic, traumatic, neoplastic, inflammatory, infectious, and vascular. More recently, iatrogenic causes of hemobilia (though still relatively rare) have superseded other causes in most series/populations and can be categorized by procedural type.

4.1. Interventional Procedures

4.1.1. Percutaneous Hepatobiliary Interventions. Common causes of iatrogenic hemobilia include interventions including percutaneous and (to a lesser extent) transjugular liver biopsy, diagnostic percutaneous transhepatic cholangiography (PTC), (Figure 4), and percutaneous transhepatic cholangiography with biliary drain (PTBD) placement; percutaneous biliary therapies such as radiofrequency ablation can also cause hemobilia but collectively comprise a smaller proportion of cases due to their relative rarity [11].

(1) Percutaneous Liver Biopsy. The published literature shows some discrepancy in the risk of hemobilia due to liver biopsy; for example, a recent study by Zhou et al. found that "hemobilia accounts for 3% of all major percutaneous liver biopsy complications," whereas a larger retrospective study reported only 4 cases of hemobilia out of 68,276 liver biopsies (0.005% risk). The discrepancy between studies may suggest that either liver biopsies have become more risky overtime (e.g., due to detection and subsequent sampling of smaller or more central lesions), although another explanation could be that the difference is attributable to better detection and reporting of hemobilia over time, among other potential explanations [12, 13].

(2) Percutaneous Transhepatic Cholangiography with and without Biliary Drain. Percutaneous interventions run the risk of inadvertently nicking a vascular structure, resulting in hemobilia, with the risk being higher in the case of factors such as a nondilated biliary tree (i.e., a smaller target). Rivera et al. compared hemobilia caused by PTBD versus PTC and found that the risk of hemobilia is higher with PTBD (2.2%) versus the rate from PTC alone (0.7%) [14]. Thought varies as to the reason for this 3-fold increase in hemobilia with PTBD compared to PTC, but it is likely that at least some of this difference may be due to the greater size of the aperture made in the bile duct wall with PTBD and the presence of a foreign material remaining in the duct which can serve as cause of inflammation or erosion [8]. A retrospective cohort study had similar results, citing that the risk of hepatic artery injury was 2.6% with PTBD and 0.7% with PTC [15]. Less common interventional procedures which may result in hemobilia include ultrasound-guided radiofrequency ablation and transarterial chemoembolization as well as transjugular intrahepatic portosystemic shunt placement [16–20].

4.1.2. Endoscopic Hepatopancreatobiliary Interventions. The main endoscopic procedure associated with hemobilia is ERCP and, in particular, sphincterotomy. Though sphincterotomy-associated bleeding typically occurs at the level of cut papillary sphincter, as initially described by Sandblom, blood can occasionally flow into or reflux from the duodenum back into the biliary tree [4]. In general, the risk of hemobilia depends on the invasiveness of the maneuvers performed during ERCP (e.g., stricturoplasty and extraction of large stones) as well as patient-level variables such as coagulopathy or presence of malignant tissue. Additional risk factors for ERCP-related hemobilia which should be mentioned are variant anatomy, especially anomalous location of the ampulla, aggressive biliary balloon dilation or intraductal biopsying, vascular anomalies (e.g., associated with hereditary hemorrhagic telangiectasia), and transbiliary ductal drainage procedures (e.g., EUS-guided choledochoduodenostomy and hepaticogastrostomy) [8, 21–24].

4.2. Noniatrogenic Causes

4.2.1. Portal Biliopathy. Hemobilia can rarely occur due to portal biliopathy, with or without preceding biliary tract intervention. Portal biliopathy occurs as a result of hypertension of the peribiliary (e.g., choledochal) venous plexus, often in patients with portal vein thrombosis and ensuing portal cavernomas, and manifests radiographically or cholangiographically with multifocal biliary stenoses from tortuous venous structures encircling the bile duct. Hemobilia in this context often requires interventional radiologic or other endoscopic or nonendoscopic intervention as the bleeding is not from an abnormality of the biliary epithelium. Risk factors such as coagulopathy and biliary stenosis also increase the risk of ERCP-related hemobilia [25–27].

4.2.2. Chronic Ductal Obstruction. Obstruction of the hepatopancreatobiliary tract can potentially lead to inflammation, erosion, and fistulization with adjacent structures with resultant hemobilia [28]. As mentioned earlier, intrabiliary clots which form due to hemobilia are often mistaken as gallstones; however, even when gallstones are indeed present, there can still be concurrent hemobilia, especially in cases in which the stone erodes through the cystic artery or other vascular structures and cause bleeding, analogous to how a stone can erode and fistulize into the duodenum and cause outlet obstruction in Bouveret's syndrome [29]. It is worth mentioning here, although not classified as hemobilia, that hemosuccus pancreaticus (also referred to as Wirsungorrhagia) can occur via pathophysiologically similar mechanisms, for example, pancreatitis eroding into the splenic artery and causing bleeding into the main pancreatic duct [30, 31].

4.2.3. Malignancy. Arguably the most common natural cause of hemobilia is due to (primary or metastatic) hepatobiliary tumors [32]. The tumor tissue and vasculature both tend to be more friable leading to an increased risk of spontaneous hemorrhage [13]. As mentioned above, treatment of hepatobiliary tumors (e.g., with radiofrequency ablation) can also lead to hemobilia [29].

4.2.4. Infection. The most clinically significant cause of infectious hemobilia is "tropical hemobilia," a result of parasitic invasion of the biliary tract. Common instigators include the roundworm (*Ascaris lumbricoides*), the Chinese liver fluke (*Clonorchis sinensis*), and the sheep liver fluke (*Fasciola hepatica*). Echinococcal infections can indirectly cause hemobilia in that hydatid cysts may cause inflammation of perivascular tissue, weakening of vessel walls, and/or pseudoaneurysm formation with resultant bleeding into the biliary tract. Divided by region, China, Korea, and Vietnam carry the highest incidence of ascariasis and subsequently higher rates of hemobilia secondary to this infection [29].

4.3. Surgical Interventions. Though surgical intervention is now rarely needed in the treatment of hemobilia, it remains an important cause of hemobilia. Complications of both laparoscopic and laparotomic surgeries that are performed near the cystic and right hepatic artery are most prone to lacerating or otherwise manipulating nearby structures in a manner which can lead to hemobilia. Cholecystectomy, liver transplantation, and pancreaticoduodenectomy (Whipple procedure) are examples of surgeries which have been reported to cause hemobilia [29, 33].

5. Diagnosis

Hemobilia should be suspected in any patient with an unclear source of GI bleed, recent blunt force or penetrating trauma to the upper abdomen, or biliary instrumentation or manipulation, particularly in the context of contemporaneous signs or symptoms of biliary obstruction. The diagnosis of hemobilia requires radiographic or endoscopic findings such as direct visualization of blood emerging from the biliary tract or radiographic findings suggestive of intrabiliary hemorrhage (Figure 5).

5.1. Computed Tomography. Computed tomography (CT) of the abdomen (preferably angiography protocol) has become a first-choice diagnostic test for hemobilia due to its noninvasive nature, low radiation exposure compared to angiography, rapid results, and diagnostic performance characteristics. CT imaging has improved dramatically over the years such that even subtle salient abnormalities can be identified [30, 34, 35].

5.2. Upper Endoscopy and ERCP. Endoscopy is commonly used to evaluate upper gastrointestinal bleeding (with or without suspicion of hemobilia) and can, sometimes incidentally, find hemobilia as the cause/source of bleeding. Up to 60% of hemobilia cases can be diagnosed by endoscopy [35]. Depending on anatomical and other factors, a duodenoscope (i.e., side-viewing scope) may be needed to visualize the ampulla and assess clots or other evidence of bleeding. ERCP can be used to visualize the biliary tree or gallbladder and may offer therapeutic options in patients with hemobilia and/or associated biliary obstruction (Figure 6). Characteristic ERCP findings that suggest the presence of blood clots include amorphous, tubular, or cast-like filling defects; gallbladder filling defects, and otherwise unexplained common bile ductal dilation [36] (Figures 7 and 8).

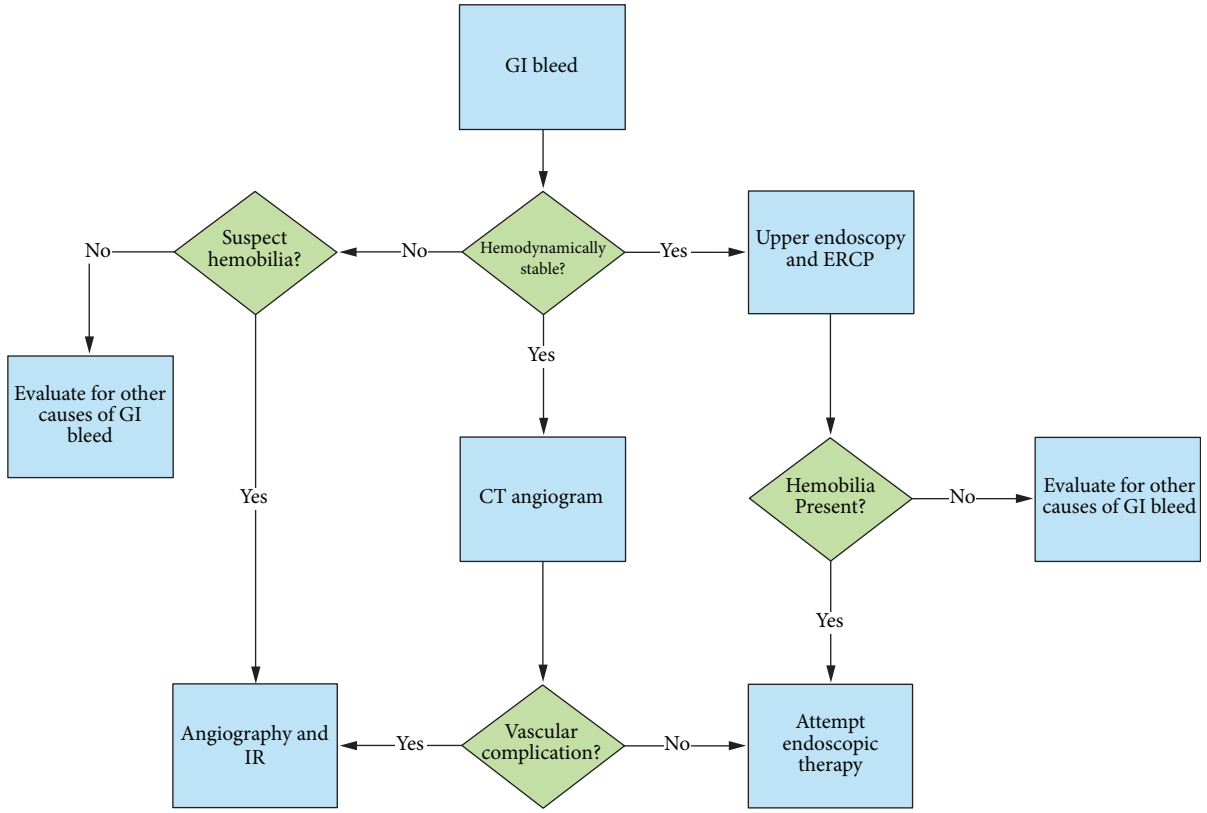

Figure 5: Proposed algorithm for the diagnosis of hemobilia. Vascular complications include hepatic artery aneurysms, pseudoaneurysms, and cholangiovenous or arterioductal fistulae.

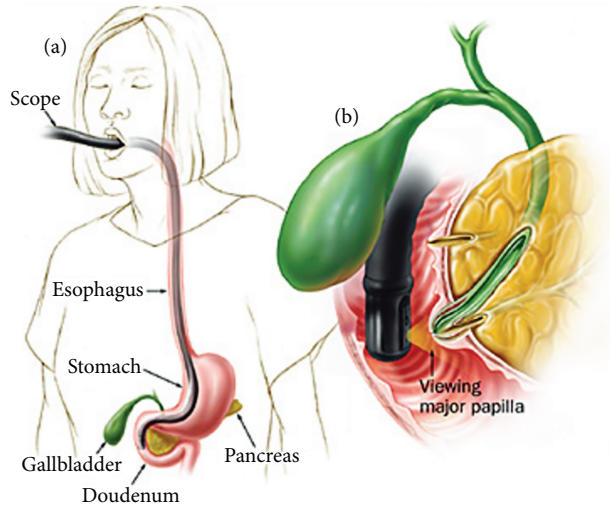

Figure 6: Endoscopic retrograde cholangiopancreatography (ERCP). (a) Schematic of duodenoscope trajectory to reach the major duodenal papilla. (b) Positioning and vantage point of duodenoscope viewing the major duodenal papilla [68].

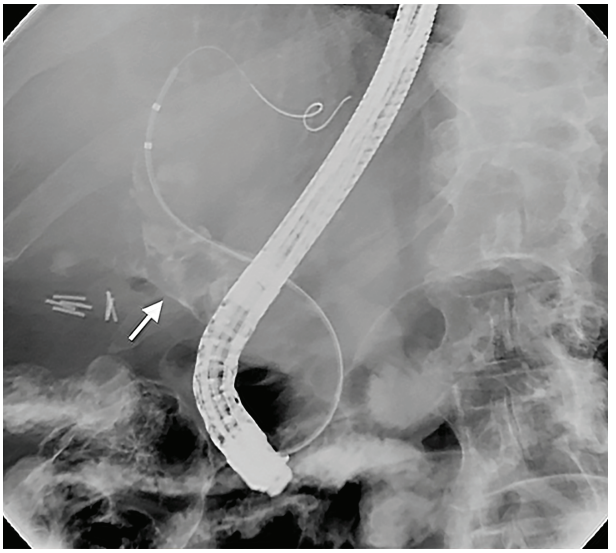

Figure 7: ERCP demonstrating radiolucent filling defects in a dilated CBD in a patient found to have hemobilia. This fluoroscopic image obtained during ERCP is from a patient with recent fine-needle aspiration (FNA) of a malignant-appearing pancreatic head mass one day prior. The radiolucent filling defects throughout the common hepatic duct and more proximal perihilar ducts in the context of recent FNA are consistent with hemobilia.

The presence of gallbladder filling defects does not necessary mean that the gallbladder is the source of bleeding, as blood can enter the gallbladder retrograde from the biliary ducts. If endoscopic ultrasound (EUS) is available, it may be used as an adjunctive noninvasive method to evaluate

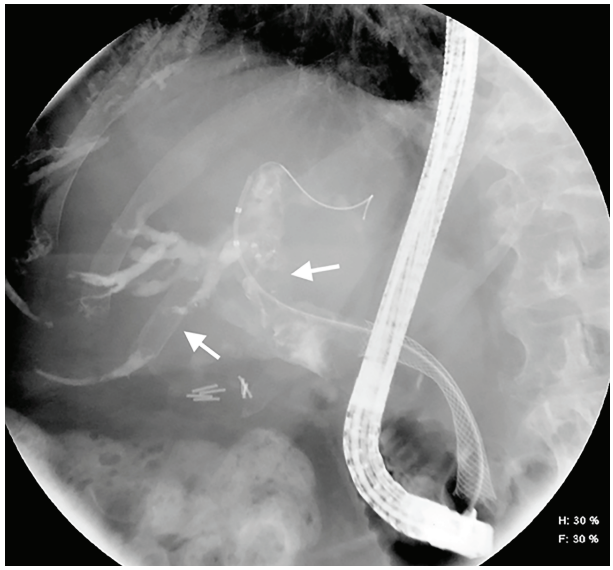

Figure 8: ERCP with therapeutic placement of self-expanding metallic stent (SEMS). A biliary SEMS has been placed during ERCP, which helps mitigate both bleeding and biliary obstruction (from large-volume hemobilia as well as the malignant pancreatic head mass).

vascular aneurysms and blood clots within the biliary ducts when ERCP findings are equivocal [36–38]. EUS can also be used to detect portal biliopathy-related bleeding (e.g., in the context of portal hypertension with intra- or paracholedochal varices [30].

5.3. Angiography. Although formal angiography is no longer used as first-line study, it remains the gold standard for both diagnosis and treatment of hemobilia in most settings. If the bleeding vessel has not already been identified on noninvasive imaging, the first angiographic study should be a celiac arteriogram with delayed phase imaging to visualize both the hepatic arteries and the portal vein. It is necessary to ensure that the portal vein is patent prior to hepatic artery embolization because the liver is supplied by both the hepatic artery and the portal vein; performing hepatic artery embolization when the portal vein is thrombosed or otherwise obstructed could potentially cause significant hepatic ischemia. This is especially important in patients who are liver transplant recipients as the transplanted liver does not receive as much blood from the portal vein as a native liver, thus making it more dependent on the hepatic artery for its blood supply. Patients with cirrhosis and hereditary hemorrhagic telangiectasia involving the liver are also at risk for hepatic ischemia for the same reason [39].

Any percutaneous drains should be removed over a guidewire (to maintain access) so as to disable the potential tamponade effect from the drain and allow for blood to flow and be visualized angiographically. Evaluation of the vasculature typically progresses in a stepwise fashion; if celiac arteriography does not reveal a clear source, then the catheter should be advanced and arteriographies of both the left and right hepatic arteries should be performed. If no branches of the celiac or hepatic arteries are identified as the source, then the superior mesenteric artery should be interrogated for potential accessory hepatic arteries. Contrast extravasation into the biliary tree, peripheral arterial truncation, arterial transection, pseudoaneurysms, and arterioportal fistula can all also suggest arterial injury [40].

5.4. Other Diagnostic Modalities. Lesser used methods include magnetic resonance cholangiopancreatography (MRCP), abdominal ultrasound (US), and surgical exploration. MRCP is a noninvasive alternative to ERCP but lacks the therapeutic options that ERCP offers and also requires more time for image acquisition. Abdominal US has been used to evaluate the presence of blood within the gallbladder, but its diagnostic effectiveness is limited due to its limited ability to visualize the biliary ducts, particular the distal CBD and in patients with truncal obesity. Surgical exploration is usually reserved as a final option in which other modalities are unable to identify or resolve the hemobilia [30].

6. Management

Management of hemobilia consists of two main objectives: (1) achieving hemostasis and (2) maintaining bile flow. The latter is important because the formation of blood clots within the biliary tract can cause complications such as obstructive jaundice, acute cholangitis, acute cholecystitis, and pancreatitis [8].

The approach to management depends on several factors, including the suspected source of bleeding (arterial versus venous bleeding), degree of hemodynamic instability, and etiology/cause (Figure 9). All patients should have a type and screen performed and be closely monitored for hemodynamic instability. Patients who present with minor hemobilia can potentially be addressed with conservative treatment, including intravenous fluids and correction of coagulopathy. Major hemobilia that causes significant hemoglobin drop or persistent bleeding typically requires endoscopic, radiologic, or, rarely, surgical intervention. Hemodynamically unstable patients should go directly to interventional radiology for hepatic angiogram and embolization or to surgery. Vasopressors may be necessary in cases of major hemobilia as part of resuscitative measures and as a bridge to therapeutic intervention.

6.1. Conservative Treatment. Minor hemobilia, which typically presents as blood-tinged output from a biliary drainage catheter, is often due to injury related to PTBD catheters and can often be treated conservatively. Exchanging a PTBD catheter with a larger sized one and adjusting its position such that the side holes of the tube are not in the same location as potential portal vein transgression sites can also help tamponade blood by increasing pressure on the walls of the bile ducts. Any underlying coagulopathies should be corrected as well. Minor hemobilia will often resolve with maturation of the surgically created tract. A tractogram or "tubogram", an imaging study where contrast is injected into the tract to visualize its course and patency, can be performed if bleeding persists or if there is impaired

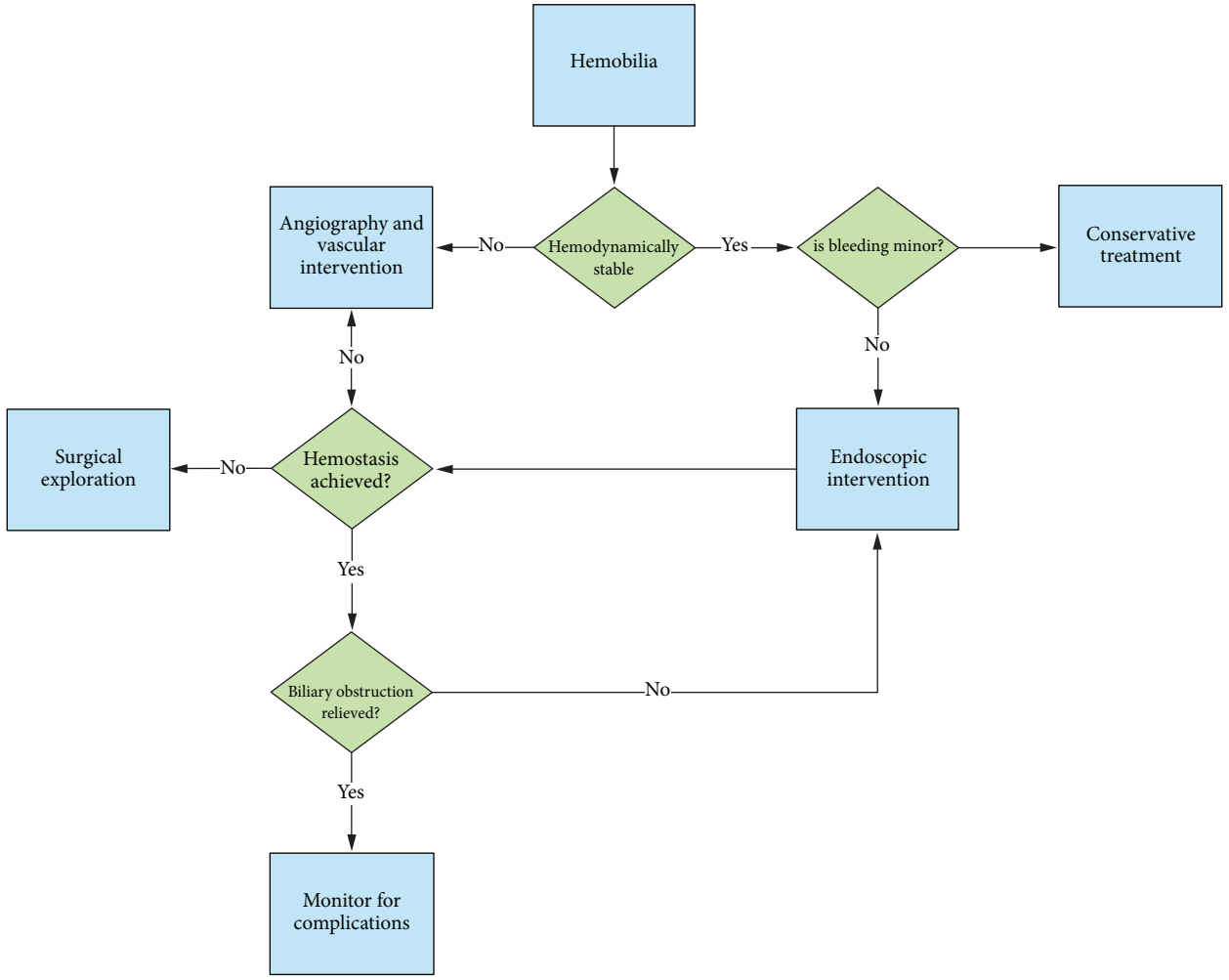

Figure 9: Proposed algorithm for management of hemobilia. Endoscopic intervention includes stenting, endonasal biliary drainage, and various techniques to achieve hemostasis at the ampulla.

drainage (e.g., due to obstruction from clot material). If hemobilia persists, options such as embolization of the existing percutaneous tract and creation of a new tract can be considered [39].

6.2. Advanced Endoscopic Techniques. For hemodynamically stable hemobilia without clear arterial sources of bleeding or significant vascular abnormalities on noninvasive imaging, upper endoscopy (with a duodenoscope or a clear endcap-outfitted gastroscope) and ERCP are typically the initial therapeutic procedure of choice because of its utility in concurrently managing both bleeding and biliary obstruction [41].

There are a wide variety of endoscopic techniques to achieve hemostasis; the choice of which to implement will depend on the cause (e.g., trauma), location (e.g., common hepatic duct), and source (e.g., paracholedochal vein) of hemobilia, for instance, postsphincterotomy hemobilia, which typically is a result of injury to the posterior branch of the superior pancreaticoduodenal artery (itself a branch of the gastroduodenal artery) during sphincterotomy. Management options for hemobilia in this context include spraying diluted epinephrine (1 : 10,000) over the area of hemorrhage, injection of epinephrine into the adjacent tissue, monopolar or bipolar coagulation, fibrin sealant injection, hemoclipping, balloon tamponading, and stent placement (Figure 10) [42–48]. These methods are most useful for postsphincterotomy hemobilia or in cases where the site of bleeding is distal, for example, located at the level of the papilla or ampulla. When hemobilia is from a more proximal (e.g., perihilar) bleeding source, the accessories and methods to treat the hemobilia tend to be different and include devices to extract intraductal clots, for example, extraction balloon catheters and retrieval baskets (Figures 10 and 11), followed by stent placement. One case report has also described the use of endobiliary radiofrequency ablation for hemorrhage secondary to malignant hemobilia [49].

6.2.1. Endoscopic Ultrasound-Guided Biliary Drainage Procedures (EUS-BD). ERCP-guided drainage using sphincterotomy, biliary stenting, and biliary drain placement is associated with over a 95% success rate and an adverse event rate of 5–10% [50]. The majority of complications arise to difficulties with biliary cannulation. In one study, biliary

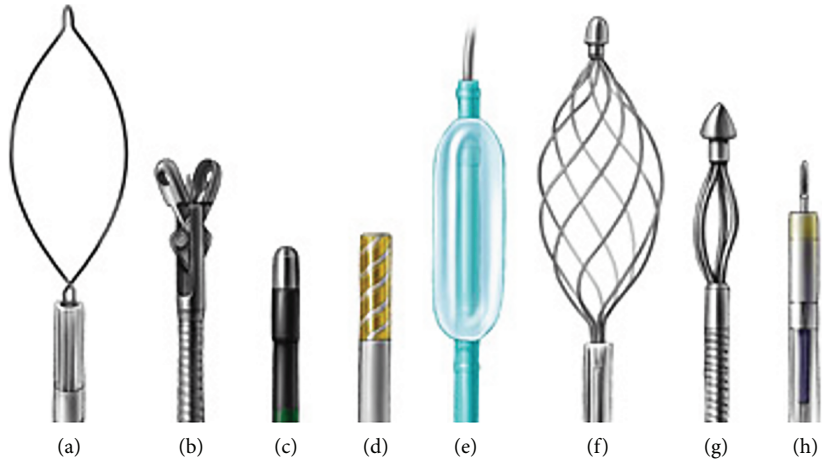

Figure 10: Accessory instruments relevant to hemobilia which may be used through a duodenoscope (or therapeutic gastroscope). (a) Snare, (b) biopsy forceps, (c) heater probe, (d) bipolar probe, (e) dilation balloon, (f) retrieval basket, (g) mechanical lithotriptor, and (h) sclerotherapy needle [68].

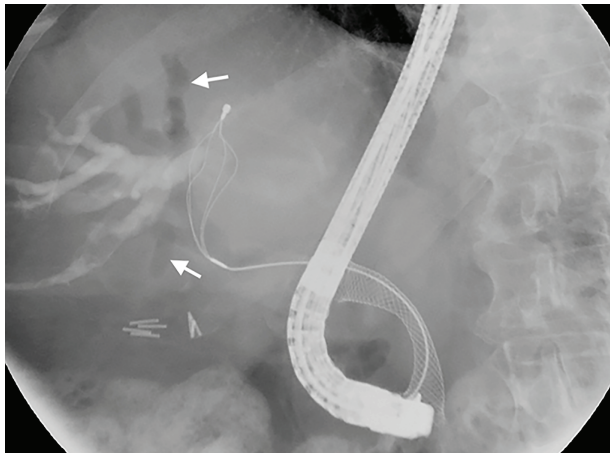

Figure 11: ERCP following several sweeps with flower basket demonstrating clearance of the hemobilia and resultant air cholangiogram. A self-expanding metallic stent is also noted in the biliary tree, which helps maintain luminal patency and flow. Arrows denote intraductal air, indicative of ductal patency (i.e., communication with the duodenum).

cannulation was rated as difficult in 15–22% of patients and not achievable in 7–13% of patients, mostly due to cancers of the pancreatic head causing obstruction [51]. Endoscopic drainage has similar rates of success and complications when compared to percutaneous drainage but is often preferred by patients due to its superior comfort [52].

When ERCP-guided drainage cannot be achieved, EUS-guided options for biliary drainage (EUS-BD) can be pursued as an alternative to percutaneous drainage. EUS-BD techniques include EUS-guided choledochoduodenostomy (EUS-CDS) and EUS-guided hepaticogastrostomy (EUS-HGS). When combined with stenting, these procedures are associated with a 90% success rate, and an adverse event rate of 8–25% [23, 24]. The procedure, however, is highly operator dependent and may require specialized training in EUS.

6.2.2. Biliary Stenting. The use of biliary stents merits additional discussion. Stents have been shown to achieve immediate hemostasis in certain cases and work by creating a tamponade effect on the bile wall while maintaining luminal patency and thus bile flow. It can act as salvage therapy when other methods fail and as a bridge to more permanent therapy through interventional radiology or surgery [53]. Both metal and plastic stents has been used successfully for hemobilia resulting from sphincterotomy, ductal dilation for biliary stenosis, fine-needle aspiration (e.g., pancreatic), bile duct biopsy, and malignancy, among other causes. Fully covered self-expanding metallic stents (FCSEMs) appear to have better tamponade and patency and have thus largely supplanted plastic stents when and where available [53–56]. Newer lumen-apposing biflanged FCSEMSs can be used to mitigate the risk of stent migration but at an increased risk of perforation during insertion [57].

Another type, the biodegradable biliary stent, has been proposed for use in hemobilia, but it has only been studied in patients with biliary strictures following hepaticojejunostomy procedures thus far (thereby potentially avoiding the need for cumbersome repeat ERCP); however, the long-term ductal patency after the use of biodegradable stents has not been studied yet [58]. Stenting can also be performed in conjunction with other methods; for example, balloon tamponade can be performed by inserting a biliary dilation balloon catheter into the common bile duct as a temporizing measure until blood flow has slowed adequately enough to permit stent placement as a more durable treatment [45]. In addition, endoscopic nasobiliary drainage can help treat hemobilia, though it is not commonly performed any longer (primarily due to the associated discomfort) and is mainly limited to postliver transplantation patients. An advantage to nasobiliary drainage is that it enables monitoring of bleeding, irrigation of the bile duct, and follow-up cholangiograms without a need for a repeat endoscopy; the same applies to percutaneous biliary drains [36, 59]. When drainage alone is inadequate, infusions of thrombolytic agents directly into the biliary tree via a drain have been described to dissolve

biliary blood clots, though this technique requires validation before it can be widely recommended [44].

6.3. Transcatheter Arterial Embolization. As the cause of hemobilia has shifted away from traumatic to iatrogenic over the years, radiologic intervention has become the gold standard for both diagnosis and management of persistent or hemodynamically unstable hemobilia. Angiography with transcatheter arterial embolization (TAE) should be considered as the initial therapy of choice if noninvasive imaging shows significant arterial extravasation, the presence of large arterial aneurysms or pseudoaneurysms, presence of arteriobiliary fistulae, and/or intrahepatic or extrahepatic vascular lesions. The success rate of TAE has been reported to be as high as 80% to 100% [60, 61]. TAE should be avoided, however, in patients with liver allografts, cirrhosis with concurrent shock, and portal vein thrombosis given that these patients have compromised collateral blood flow from the portal vein, as a result of which TAE can lead to ischemic liver injury [30]. Such patients may benefit from arterial stenting (as a tamponading measure) instead.

Once the bleeding site has been identified angiographically, superselection of the injured artery via threading of a microcatheter to the target area is performed, followed by embolization using coils. Coiling should be deployed in a distal-to-proximal fashion to ensure that no back bleeding occurs via intrahepatic arterial collaterals [39]. Pseudoaneurysms should be embolized with coils from the two ends to reduce the risk of enlarging the aneurysm. Alternatives to coils include embolization with Gelfoam, PVA particles, and liquid embolic agents such as n-BCA, Onyx, or thrombin. There have also been case reports of percutaneous injection of thrombin into pseudoaneurysms under ultrasound guidance [62]. The method of embolization depends on the anatomy of the hepatic arteries, presence of vasospasms, tortuosity of vessels, and operator/center experience. For instance, liquid embolic agents may be helpful in patients with tortuous vessels or when there are several smaller feed into an aneurysm but require experienced radiologists due to the risk of spilling the agent and causing embolization of nontarget arteries or the biliary ducts [63].

If selective embolization of the bleeding artery cannot be performed, nonselective embolization of the left or right hepatic artery may be performed. In patients who are hemodynamically unstable, embolization of the main hepatic artery can be performed if the patient is a poor surgical candidate, though recognizing the increased risk of liver necrosis [39]. It is currently not recommended to empirically embolize any hepatic arteries if no bleeding source is detected due to this very risk, even with patent portal veins. Furthermore, because the bile ducts are supplied primary by the hepatic arteries rather than the portal vein, there is a risk of biliary ischemia and resultant multifocal strictures [7].

Complications of TAE include hepatic abscesses, postembolization syndrome, hyperaminotransaminasemia, hepatic ischemia, and hepatic infarction or rarely failure [35]. A study of 72 patients who underwent TAE showed that 55 experienced hepatic ischemia evidenced by transiently elevated serum liver enzymes, while 3 experienced focal hepatic infarcts in the areas corresponding to the embolized arterial branches [61].

6.4. Vascular Stenting. An alternative to embolization, as alluded to earlier, is the placement of a covered stent across the site of vascular injury. Stenting has the advantage of preserving flow through the artery, which may be beneficial if not crucial in patients with liver transplants or compromised portal vein flow. The diameter of most hepatic vessels is similar to the size of coronary vessels, making coronary stents ideal for this application. Stent diameter should be slightly oversized by about 10–20% of the diameter of the target vessel and extend approximately 10 mm to either side/end of the site of injury to ensure proper tamponade. There are also new flow-directing stents that reduces flow across the stents into pseudoaneurysms while preserving laminar flow [64, 65].

6.5. Surgery. Surgical intervention is rarely necessary and usually reserved for failed endoscopic, endovascular, and/or percutaneous therapies. However, it is a first line if pseudoaneurysms are infected or if they are compressing other vascular structures. Surgery may also be indicated if cholecystitis is present, among other uncommon scenarios. Options for surgery include hepatic artery ligation, pseudoaneurysm excision, or hepatic segmentectomy/lobectomy with the potential for concurrent cholecystectomy if cholecystitis is present or the gallbladder neck is involved. Although surgery has a high success rate of up to >90%, it is also associated with a high mortality of up to 10% [7].

6.6. Managing Complications. Complications that arise from hemobilia should be managed as they would be in any other scenario. For example, cholecystitis should be treated with early cholecystectomy, as it carries a high mortality rate with rates of gallbladder perforation between 2–15% [66]. Acute pancreatitis is another complication that can occur due to obstruction of the ampulla or more proximal main pancreatic duct by blood clots and reverse flow of blood into the pancreatic ducts and should be managed medically and in some instances by ERCP. Biliary strictures can form following hepatic artery embolization because the vascular supply for the biliary tree comes mostly from the hepatic artery and these will generally require treatment with endoscopic or percutaneous balloon dilation [7].

7. Conclusion

Hemobilia is an unusual but important cause of GI bleeding and most commonly due to hepatopancreatobiliary tract procedures, regional trauma, and malignancy. CT angiography and endoscopy/ERCP have become common initial diagnostic testing modalities due to their versatility in excluding other causes of bleeding, low contrast requirement, and relative safety. Most cases of minor hemobilia can be treated conservatively or with minimally invasive endoscopic management. Major hemobilia which is refractory to conservative measures or leading to hemodynamic instability should be managed by interventional radiology in conjunction with endoscopy/ERCP. While TAE is a mainstay,

vascular stenting has gained traction as an alternative to arterial embolization due to the preservation of hepatic arterial blood supply. Surgery is typically reserved as a last resort due to its high mortality rate and invasive nature. Although the gold standard for management remains angiography, with new technologies and techniques such as advanced endoscopic procedures, endoscopy has become an attractive alternative for both the diagnosis and treatment of hemobilia.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Rani Berry, James Han, and James H. Tabibian acquired the images; Rani Berry and James Han drafted the manuscript; James H. Tabibian provided supervision and critical revision of the manuscript.

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Research Article

Rectal Indomethacin Is Protective against Pancreatitis after Endoscopic Retrograde Cholangiopancreatography: Systematic Review and Meta-Analysis

Xingkang He,[1,2,3] **Wenfang Zheng**,[1,2] **Yue Ding**,[1,2] **Xia Tang**,[2,4] **Jianmin Si**,[1,2] **and Lei-min Sun**[1,2]

[1]*Department of Gastroenterology, Sir Run Run Shaw Hospital, Zhejiang University Medical School, Hangzhou 310016, China*
[2]*Institute of Gastroenterology, Zhejiang University (IGZJU), Hangzhou 310016, China*
[3]*Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, 171 77, Stockholm, Sweden*
[4]*Sir Run Run Shaw Hospital, Zhejiang University Medical School, Hangzhou 310016, China*

Correspondence should be addressed to Jianmin Si; jianmin_si@zju.edu.cn and Lei-min Sun; sunlm@zju.edu.cn

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Background and Aim. Rectal indomethacin was reported to be effective for postendoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) prophylaxis. However, the preventive effect of indomethacin for average-risk patients remains unclear. Recently, some conflicting evidence was addressed by recent articles. We aimed to determine the protective role of indomethacin in PEP based on the latest available literature. *Methods*. A systematic literature search was conducted using PubMed, Embase, Web of Science, and the Cochrane Library to identify related articles published before October 2016. Studies that evaluated the administration of indomethacin in the prevention of PEP were included in the analysis. We adopted a random-effects model to calculate the overall relative risk (RR) and 95% confidence interval (CI). *Results*. Ten trials from an initial search were finally included in the meta-analysis. The administration of rectal indomethacin significantly reduced the incidence of PEP in consecutive ERCP population (RR, 0.63; 95% CI, 0.50–0.77). There was no significant heterogeneity across included studies ($I^2 = 14.2\%$, $P = 0.31$). Further subgroup analyses also revealed that rectal indomethacin could protect the individuals at high and average risks and reduced severity of PEP. Pre-ERCP administration of indomethacin seemed to be better than the post-ERCP given. There was no evidence of significant publication bias. *Conclusions*. Rectal administration of indomethacin is an effective approach to prevent the incidence of PEP in both high- and average-risk populations undergoing ERCP. However, more high-quality RCTs are needed to further investigate the optimal timing for the administration of indomethacin.

1. Introduction

Post-ERCP pancreatitis (PEP) is a serious adverse event after ERCP, with a reported incidence of 9.7% in unselected patients [1]. Several risk factors were identified for PEP, such as "suspected sphincter of Oddi dysfunction" and "female gender" [2]. Given a huge economic and clinical burden, effective approaches for post-ERCP pancreatitis prophylaxis remain a major priority for research.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are reported to be effective in PEP prophylaxis so far [3]. Several prospective RCTs and meta-analysis have well demonstrated that the rectal administration of indomethacin significantly decreased the rate of PEP [4–6]. Based on the above evidence, the European Society for Gastrointestinal Endoscopy (ESGE) guideline (2014) recommended the administration of 100 mg of rectal indomethacin for PEP prophylaxis in patients undergoing ERCP with no contraindication [3]. Subsequently, the Japanese Society of Hepato-Biliary-Pancreatic Surgery (2015) [7] also published similar guidelines. Indomethacin, therefore, as an effective pharmacologic prophylaxis, seemed to be appealing. In this context, some conflicting findings

emerged recently. A recent prospective, double-blind, controlled trial conducted by Levenick et al. [8] in the USA showed that the reduction in PEP using indomethacin was not as significant as previously reported in multiple RCTs [4, 5, 9]. In fact, even more cases of pancreatitis occurred in the indomethacin group compared with the placebo group. Subsequently, a high-quality meta-analysis also concluded that there is no prophylaxis for the prevention of PEP among average-risk patients [10]. These findings raised the question of whether the administration of rectal indomethacin should be recommended in average-risk patients. However, a recent RCT with a large number of patients was performed in China and concluded that rectal indomethacin should be administrated across patients without contraindication prior to ERCP [11].

Therefore, the benefit of rectal indomethacin needs to be well demonstrated in the majority of patients (average-risk) undergoing ERCP in practice. Confronted with the above conflicting results, we performed a meta-analysis to assess the role of rectal indomethacin for PEP prophylaxis in average-risk individuals.

2. Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

2.1. Literature Search. A comprehensive electric search was conducted across PubMed, Embase, and the Cochrane Library for relevant articles with no language limitations from database inception to October 2016. The following Medical Subject Heading (MeSH) terms and text words were adopted in the research: ('indomethacin') AND ('cholangiopancreatography endoscopic retrograde' OR 'pancreatitis' OR 'post-ERCP pancreatitis'). References of the included articles and reviews were also manually scrutinized.

2.2. Eligibility Criteria. The included criteria were based on the patients, intervention, comparator, outcomes, and study design (PICOS) criteria and were as follows[13]: (1) population: adults undergoing endoscopic retrograde cholangiopancreatography (ERCP); (2) intervention: assessment of rectal indomethacin prior to or post ERCP; (3) comparator: indomethacin exposure compared with placebo exposure or unexposed; (4) outcomes: risk of PEP, presented as relative risks (RR) with 95% confidence intervals (CI); and (5) study design: randomized controlled trial (RCT). Reviews, case reports, abstracts, and letters were excluded. Based on the above "PICOS" criteria, two reviewers (HXK and ZWF) independently scanned all titles and abstracts of articles after an initial search and removed apparently irrelevant studies. Afterward, we reviewed the full texts of the remaining articles in order to identify relevant studies for inclusion. When there were multiple publications from the same population, the most comprehensive article was included. Any discrepancies in the processes were discussed and resolved by agreement.

2.3. Definition of Patients and Outcomes. According to previous studies, the definition of PEP was referred by

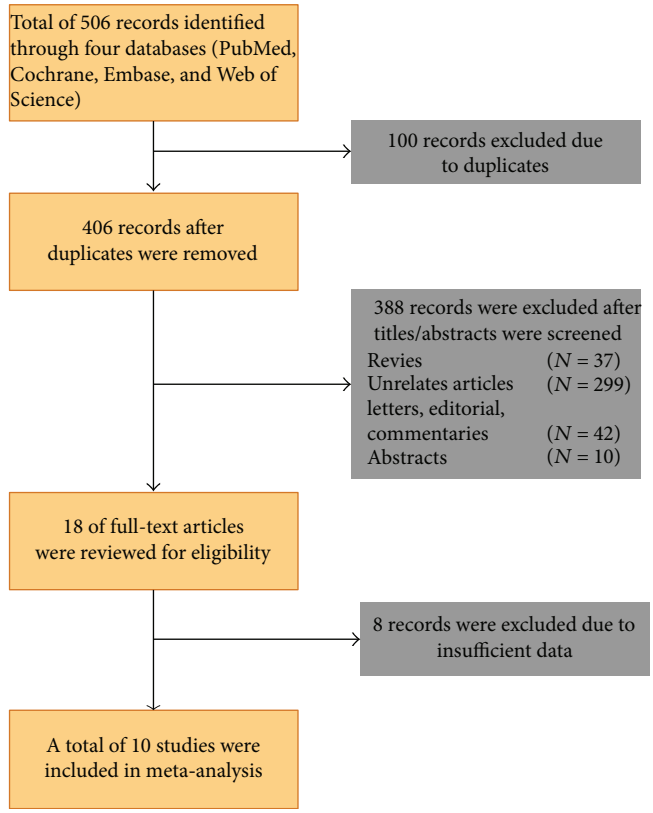

Figure 1: Flow diagram of included and excluded trials in this meta-analysis.

previous studies [5, 8, 9, 11, 14]. The severity was classified according to "the length of hospitalization and the degree of intervention required" [15]. The criteria to identify high- or average-risk individuals were based on the study by Elmunzer et al. [4]. Detailed information is summarized in Supplementary Data (available here) [4].

2.4. Data Extraction and Quality Assessment. Two authors (HXK and ZWF) independently extracted the related information from eligible articles regarding the author, year, study design, location, number of patients, intervention, and definition of PEP. The methodological quality of eligible studies was evaluated by two reviews using the Cochrane Collaboration's tool [16] independently. The tool included seven items for assessment, and each item was graded as low bias, high bias, or unclear. The discrepancy in data extraction and assessment was resolved by the third author (SLM).

2.5. Statistical Analysis. We adopted a random-effects model to calculate the overall estimate relative risk of PEP in relation to rectal indomethacin exposure with 95% confidence intervals (CI) considering the expected heterogeneity between studies. The heterogeneity among individual studies was assessed qualitatively by the Cochran Q statistic, with $P < 0.1$ indicating some heterogeneity [17]. The degree of heterogeneity was evaluated by I^2, and an $I^2 > 30\%$ suggests that there is moderate to high heterogeneity between included studies [17]. Furthermore, we carried out subgroup analyses stratified by selected population, the timing of

Table 1: Characteristics of included studies in the meta-analysis.

Study	Year	Country	Type of trial	Patients (T/C)	Intervention	Definition of PEP
Sotoudehmanesh et al. [14]	2007	Iran	Double-blind randomized trial	245/245	100 mg rectal indomethacin versus inert suppository; before ERCP	Serum amylase more than 3 times the upper limit of normal associated with epigastric pain, back pain, and epigastric tenderness
Montaño Loza et al. [21]	2007	Mexico	Randomized controlled trial	75/75	100 mg rectal indomethacin versus rectal glycerine; before ERCP	Amylase level 3 times the upper limit of normal and epigastric pain or throughout the abdomen radiating to back associated with nausea or vomiting
Döbrönte et al. [19]	2012	Hungary	Prospective randomized clinical trial	130/98	100 mg rectal indomethacin versus inert placebo; before ERCP	Amylase level 3 times the upper limit of normal and epigastric pain or throughout the abdomen radiating to back associated with nausea or vomiting
Elmunzer et al. [4]	2012	American	Multicentre, randomized, placebo-controlled, double-blind clinical trial	295/307	2 ∗ 50 mg rectal indomethacin versus placebo suppository; after ERCP	Amylase level 3 times the upper limit of normal and epigastric pain or throughout the abdomen radiating to back associated with nausea or vomiting
Döbrönte et al. [18]	2014	Hungary	Multicentre prospective, randomized, controlled trial	347/318	100 mg, rectal indomethacin versus placebo suppository; before ERCP	Amylase level 3 times the upper limit of normal and epigastric pain or throughout the abdomen radiating to back associated with nausea or vomiting
Patai et al. [5]	2015	Hungary	Prospective, placebo-controlled, double-blind trial	270/269	100 mg rectal indomethacin versus placebo suppository; before ERCP	Abdominal pain, extended hospitalization 2–3 days, elevation of amylase 3 times the upper limit of normal in 24 hours
Andrade-Dávila et al. [9]	2015	Mexico	Prospective randomized controlled trial	82/84	100 mg rectal indomethacin versus glycerine; after ERCP	New or increased abdominal pain consistent with pancreatitis, elevated amylase or lipase greater than three times the normal upper limit until 24 hours after the procedure, and hospitalization (or prolongation of existing hospitalization) for at least 2 nights
Levenick et al. [8]	2016	America	Prospective, double-blind, placebo-controlled trial	223/226	100 mg rectal indomethacin versus placebo suppository; during the ERCP	New upper abdominal pain, an elevated lipase greater than three times the upper limit of the normal 24 hours after the onset of pain, and hospitalization for at least two nights
Hosseini et al. [20]	2016	Iran	Randomized controlled trial	100/105	100 mg rectal indomethacin versus glycerine; before ERCP	New onset or worsened abdominal pain, increase in serum amylase at least 3 times above the upper limit of normal measured 24 h after the procedure, and need for more than one night of hospitalization
Luo et al. [11]	2016	China	Multicentre, single-blinded, randomized controlled trial	1297/1303	100 mg rectal indomethacin versus no treatment; before ERCP	New onset of upper abdominal pain associated with an elevated serum amylase of at least three times the upper limit of normal range at 24 h after the procedure and admission to a hospital for at least 2 nights

ERCP: endoscopic retrograde cholangiopancreatography; T/C: treatment/control.

administration, the severity of pancreatitis, and different regions. Sensitivity analyses were conducted by excluding each individual study in turn in order to ensure the robustness and consistency of overall results. The funnel plot asymmetry and Egger's test were performed to evaluate the potential publication bias. All statistical analyses were used by the Review Manager (RevMan) V.5.0 software and Stata version 13 (StataCorp, Texas, USA).

3. Results

3.1. Study Characteristics. The initial search strategy yielded 506 studies, and ten studies [4, 5, 8, 9, 11, 14, 18–21] were finally included. Figure 1 depicts the detailed selection and identification process. The characteristics of each individual study are summarized in Table 1. Overall, there was a total of 6094 patients undergoing ERCP, with 459 patients

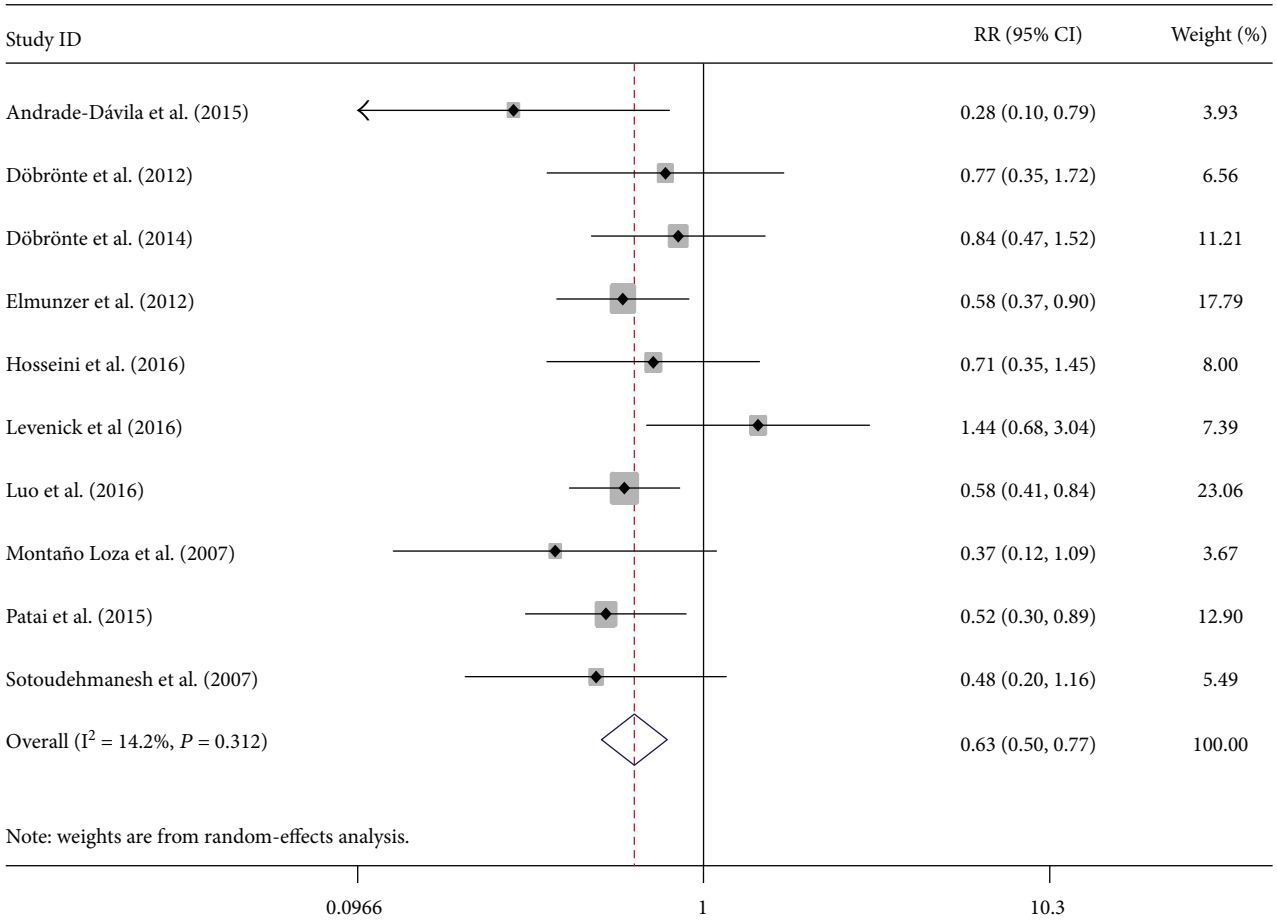

Figure 2: Forest plot for the overall relative risk of post-ERCP pancreatitis with rectal indomethacin.

presenting with PEP. All trials adopted 100 mg rectal indomethacin suppository, whereas nine studies used placebo suppository as controls, and one study did not receive placebo. All trials adopted a similar definition of post-ERCP pancreatitis to include patients. The overall methodological quality of RCTs was generally moderate to high according to the Cochrane Collaboration's tool, and detailed information is shown in Supplementary Figures S1 and S2.

3.2. Overall Analyses of Rectal Indomethacin for PEP Prevention. A total ten of RCTs evaluated the prophylactic effect of rectal indomethacin on the prevention of PEP, with the incidence ranging from 4.83% to 13.66% [14, 20]. The relative risk (RR) of individual studies ranged from 0.28 to 1.44, and the cumulative meta-analysis by publication year showed that the rectal administration of indomethacin before or after ERCP was associated with a reduced risk of PEP in the overall population (RR = 0.63; 95% CI, 0.50–0.77) (Figure 2). Furthermore, we also performed a cumulative meta-analysis by publication year and number of included patients. The overall results gradually became stable and tended toward becoming significant with the increase in published year and larger samples (Supplementary Figures S3 and S4). The relatively low heterogeneity (I^2 = 14.2%, P = 0.31) was observed across included studies. Furthermore, sensitivity analyses by removing each study also supported the robustness of the overall outcomes in the meta-analysis. The funnel plot (Supplementary Figure S5) and Egger's test (P = 0.59) suggested no evidence of substantial publication bias in our analysis. No trial reported a higher incidence of adverse events associated with the administration of rectal indomethacin, suggesting the safeness of indomethacin.

3.3. Subgroup Analysis

3.3.1. High-Risk versus Average-Risk Patients. Three studies selected high-risk population, and seven studies chose average-risk patients as the targeted population. The overall rates of PEP in high- and average-risk populations were 14.1% and 6.0%, respectively. The administration of indomethacin significantly reduced the risk of PEP among high-risk patients (RR, 0.49; 95% CI, 0.35–0.71), as well as across average-risk population (RR, 0.69; 95% CI, 0.55–0.86) (Figure 3(a)). No heterogeneity for average-risk and high-risk patients was noted. Furthermore, our sensitivity analyses also showed that the overall results were not changed by a single study.

3.3.2. Pre-ERCP versus Post-ERCP Administration of Indomethacin. Most of the studies (7/10) administered

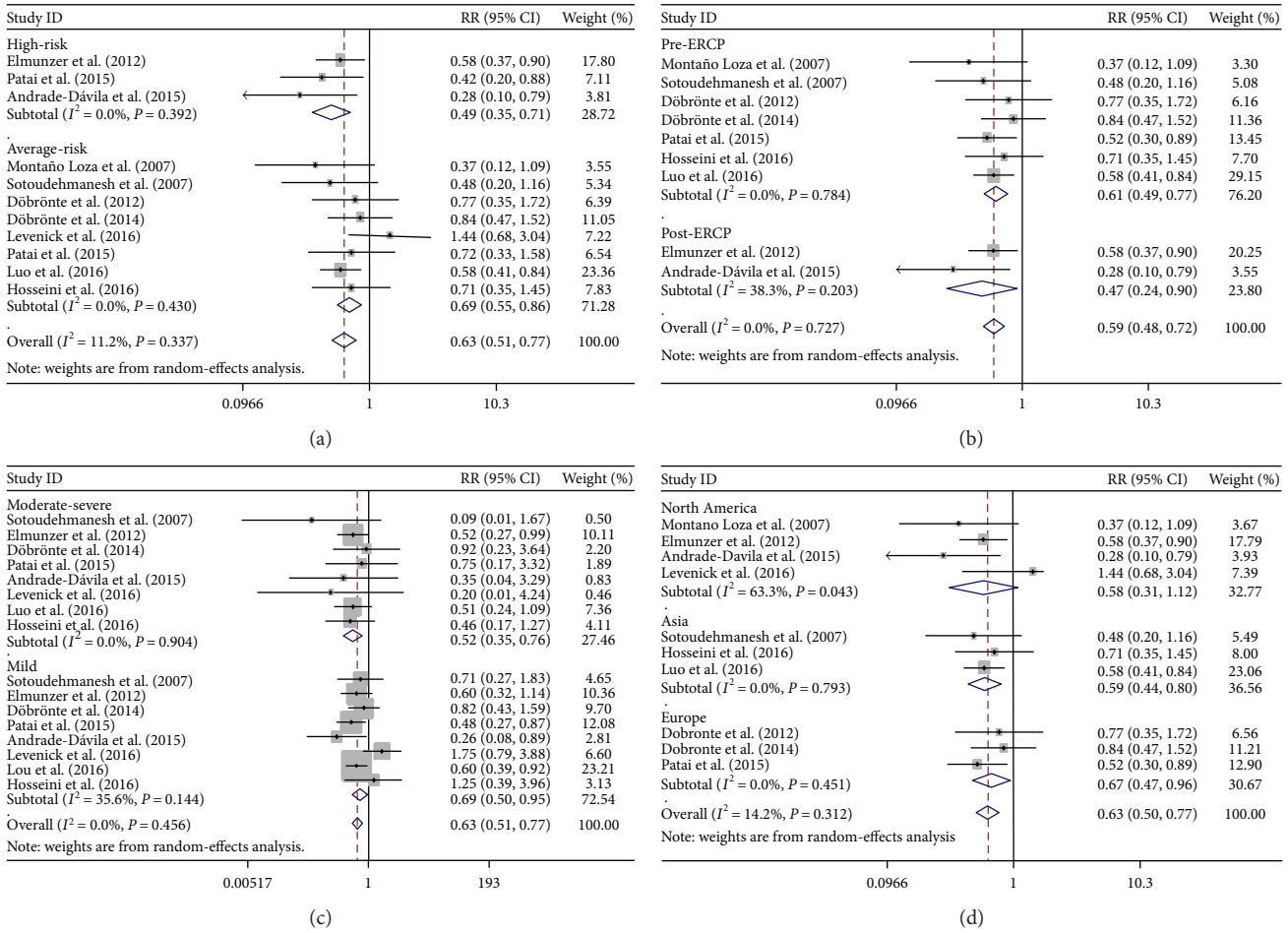

FIGURE 3: Forest plots of subgroup analysis stratified by (a) high-risk and average-risk patients, (b) pre-ERCP and post-ERCP administration, (c) mild and moderate-severe post-ERCP pancreatitis, and (d) patients from different regions.

indomethacin rectally prior to ERCP, two studies after ERCP, and one administered during ERCP. The pooled relative risks for pre- and post-ERCP administration were 0.61 (95% CI, 0.49–0.77) and 0.47 (95% CI, 0.24–0.90), respectively (Figure 3(b)). A low degree of heterogeneity (I^2 = 38.3%, P = 0.20) was noted among studies for post-ERCP while no heterogeneity existed in studies for pre-ERCP (I^2 = 0%, P = 0.78).

3.3.3. Mild PEP versus Moderate-Severe PEP. Six Pooled studies showed that indomethacin administration significantly decreased the risk of mild and moderate-severe PEP (RR, 0.52, 95% CI, 0.35–0.76; RR = 0.69, 95% CI, 0.50–0.95, resp.) (Figure 3(c)). A relatively low heterogeneity (I^2 = 35.6%, P = 0.14) was observed across studies for mild PEP.

3.3.4. Different Regions of Medical Centers. Among the included studies, three studies were performed in Asia (2/3 in Iran, 1/3 in China), three in Europe (3/3 in Hungary), and four in North America (2/4 in the United States, 2/4 in Mexico). The estimated pooled relative risks of PEP for Asia, Europe, and North America were 0.59 (95% CI, 0.44–0.80), 0.67 (95% CI, 0.47–0.96), and 0.58 (95% CI, 0.31–1.12), respectively. A high degree of heterogeneity (I^2 = 63.3%, P = 0.043) was noted among patients from North America.

4. Discussion

This exhaustive meta-analysis revealed a significant reduction of PEP risk (RR = 0.48, 95%, 0.26–0.87) in patients with rectal indomethacin. From 2006 to 2016, the cumulative meta-analysis by publication year showed that the overall result gradually became stable and tended toward becoming significant. In a subgroup analysis, the beneficial effect consistently favoured the administration of rectal indomethacin across most of the predefined variables. The prophylactic effect of rectal indomethacin was consistent across the average-risk and high-risk patients, and the administration of indomethacin before or after ERCP reduced the risk of mild and moderate-severe PEP. These results support the recommendation by ESGE and Japanese guidelines that individuals undergoing ERCP with no contraindications ought to be administrated indomethacin rectally to prevent post-ERCP pancreatitis [3, 7]. No increased risk of NSAID-associated adverse event was associated with the administration of indomethacin, indicating the safeness of rectal indomethacin.

Considering PEP as a serious adverse event, several pharmacologic agents were adopted for PEP prophylaxis, such as NSAIDs [22]. Several high-quality RCTs have demonstrated

the effective prophylaxis of diclofenac and indomethacin for PEP, although the magnitude of benefits varied [3, 23]. In this context, it seemed that the rectal administration of NSAIDs is a sort of "panacea" for PEP prophylaxis [24]. However, discordant results from recent published RCTs and meta-analysis potentially challenge current evidence [8, 10]. The results of this trial showed that not only the effect of indomethacin for PEP was nonsignificant but also an opposite trend (higher incidence of pancreatitis in the indomethacin group than in the placebo group) was observed, although it is not significant. Levenick et al. [8] concluded that indomethacin may not prevent against PEP in ordinary population. However, we should interpret the conclusion with caution because the early termination of trial may lead to a type II statistical error [25]. Subsequently, a meta-analysis conducted by Inamdar et al. also showed that rectal indomethacin reduced the incidence of PEP in the high-risk patients, rather than in the average-risk [10] patients, which refuted the current guideline and previous meta-analysis. After that, two published RCTs also addressed this issue and supported the benefits of indomethacin in PEP prophylaxis.

Our findings are consistent with previous meta-analyses on this topic [6, 26, 27], although these are in contrast to a recent meta-analysis [10]. The advantage of the current study consists of the inclusion of enough high-quality RCTs, especially for some RCTs that have not been included in the previous studies. Relative low heterogeneity also reflects the similarity of included studies, which might further enhance the validity of results. Being different from the prior meta-analyses, our study is unique in performing cumulative meta-analyses and detailed subgroup analyses. However, this meta-analysis also has several limitations that merit further consideration. The final results and interpretations might be limited by the quantity and quality of included studies. Firstly, the significant heterogeneity across studies in North America could not be fully explained. Therefore, further trials should be conducted in the United States in order to examine the effect of indomethacin. Secondly, we were unable to identify clearly the optimal timing of administration due to lack of adequate RCT data. Finally, it was difficult to rule out the possibility of publication bias due to chance because of the limited number of included articles.

In summary, we demonstrated that rectal indomethacin significantly decreased PEP risk among high- or average-risk population undergoing ERCP and provided strong evidence for current guidelines in clinical practice. Considering its ease of administration, cost-effectiveness, and safety, indomethacin seemed to be an ideal and appealing pharmacological prophylaxis for PEP. However, optimal timing and its benefit in average-risk patients following ERCP needs to be confirmed in further larger prospective studies.

Abbreviations

ERCP: Endoscopic retrograde cholangiopancreatography
PEP: Postendoscopic retrograde cholangiopancreatography pancreatitis
RR: Relative risk
CI: Confidence interval
RCT: Randomized controlled trial
ESGE: European Society for Gastrointestinal Endoscopy
NSAIDs: Nonsteroidal anti-inflammatory drugs.

Conflicts of Interest

The authors have no potential conflicts of interest to declare.

Authors' Contributions

Lei-min Sun, Jianmin Si, and Xingkang He had the concept for the systematic review; Lei-min Sun, Xingkang He, and Wenfang Zheng designed and conducted the search strategy to identify included studies; Xingkang He, Yue Ding, and Lei-min Sun conducted the data extraction; Xingkang He, Wenfang Zheng, and Lei-min Sun conducted the statistical analysis; Xingkang He and Lei-min Sun wrote the first draft of the manuscript; and Xia Tang contributed great work to the revision of manuscript. All authors edited and critically revised the final version of the manuscript.

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Supplementary Materials

Supplementary Data: major and minor criteria for patients with high risk of post-ERCP pancreatitis. Supplementary Figure S1: quality assessments for included randomized control trials in the meta-analysis. Supplementary Figure S2: overall quality assessments for included randomized control trials in the meta-analysis. Supplementary Figure S3: cumulative meta-analysis of indomethacin for post-ERCP pancreatitis prevention by publication year. Supplementary Figure S4: cumulative meta-analysis of indomethacin for post-ERCP pancreatitis prevention by the number of patients. Supplementary Figure S5: funnel plot of all studies included in the present meta-analysis for the assessment of possible publication bias. *(Supplementary Materials)*

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Research Article

Comparison on the Efficacy between Partially Covered Self-Expandable Metal Stent with Funnel-Shaped Enlarged Head versus Uncovered Self-Expandable Metal Stent for Palliation of Gastric Outlet Obstruction

Jung Wan Choe, Jong Jin Hyun, Dong-won Lee, Sang Jun Suh, Seung Young Kim, Sung Woo Jung, Young Kul Jung, Ja Seol Koo, Hyung Joon Yim, and Sang Woo Lee

Department of Internal Medicine, Korea University Ansan Hospital, Ansan, Republic of Korea

Correspondence should be addressed to Jong Jin Hyun; sean4h@korea.ac.kr

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Background. Shape modification has been one of the methods adopted to improve stent patency but has not always translated into positive outcome. The aim of this study was to compare the efficacy of shape-modified partially covered self-expandable metal stent (SEMS) that has enlarged head versus uncovered SEMS for palliation of gastric outlet obstruction (GOO). *Methods*. A total of 48 patients underwent insertion of either enlarged-head SEMS ($n = 24$) or uncovered SEMS (uSEMS) ($n = 24$) for palliation of GOO from July 2009 to July 2016. Patients with inoperable or advanced malignancy were included. Technical feasibility and clinical outcomes were compared. *Results*. Technical success rate was 100% (24/24) and 95.8% (23/24) for enlarged-head SEMS group and uSEMS group, respectively. Clinical success rate was 87.5% (21/24) and 87.0% (20/23) for enlarged-head SEMS group and uSEMS group, respectively. The gastric outlet obstruction scoring system score significantly improved in both groups ($p < 0.001$ for both). Mean survival was similar between the groups: enlarged-head SEMS group, 99.3 days (range, 19–358 days) versus uSEMS group, 82.1 days (range, 11–231 days) ($p = 0.418$). The mean stent patency also showed no difference between the groups: enlarged-head SEMS group, 87.1 days (range, 8–358 days) versus uSEMS group, 60.4 days (range, 2–231 days) ($p = 0.204$). With enlarged-head SEMS, distal migration did not occur, but proximal migration was observed in four cases. *Conclusions*. Distal migration was prevented by shaping the SEMS to have an enlarged head, but improvement in stent patency could not be observed.

1. Introduction

Gastric outlet obstruction (GOO) is a complication that can occur in gastric, duodenal, pancreatobiliary, and other malignancies. Placement of self-expandable metal stent (SEMS) has emerged as a good alternative to a bypass operation in relieving GOO symptoms for palliation in patients with inoperable and advanced malignancy or those refusing surgery. According to a systemic review, the overall clinical success rate of SEMS for GOO palliation is high, ranging from 84% to 93%, with a technical success rate ranging from 93% to 97% [1–3]. The less invasive endoscopic treatment yields lower morbidity and mortality, shorter hospital stay, and earlier symptom relief compared to surgery [4]. SEMS can be largely divided into covered SEMS and uncovered SEMS (uSEMS). Many studies have focused on which of the two SEMS showed better patency [5, 6]. Covered SEMS has risk of stent migration, whereas uSEMS is associated with increased chance of restenosis due to tumor ingrowth. Despite different limitations of each stent type, they showed similar patency rates [7]. As a result, there have been various trials to test different methodologies for decreasing migration in covered SEMS, including modifying the design of the stent, increasing the diameter of the stent, or using endoscopic clips to fix the stent in the desired location [8–10]. If the proximal portion of the SEMS is enlarged so as to take

on a funnel shape and covering material is applied at the midportion that is in contact with the tumor, both the migration and tumor ingrowth could be expected to be minimized. This study aimed at evaluating the technical and clinical efficacies of partially covered SEMS with enlarged head compared to uSEMS for palliation of GOO.

2. Materials and Methods

2.1. Patients. A total of 48 patients with malignant GOO underwent endoscopic SEMS placement at Korea University Ansan Hospital from July 2009 to July 2016. Inclusion criteria were as follows: (1) inoperable malignancy or refusal to undergo surgery, (2) absence of additional stricture in the small bowel and colon, and (3) capability to undergo upper endoscopy. Baseline characteristics including demographics, cancer type and stage, site of GOO, general condition (BMI and ECOG performance status), and severity of obstruction presented by the GOO scoring system (GOOSS) were identified. The GOOSS score is an objective evaluation of the efficacy and patency of SEMS in clinical practice [11]. Data were collected by retrospectively reviewing the electronic medical records of patients. This study was approved by the internal review board committee of Korea University Ansan Hospital (AS16173).

2.2. Stent Placement. SEMSs were inserted using the standard through-the-scope placement technique with either GIF 2T-240 (Olympus Optical, Tokyo, Japan) or duodenoscope (TJF-240 or TJF-260V; Olympus Optical, Tokyo, Japan). From July 2009 to July 2012, uSEMSs were primarily used, and from August 2012 to July 2016, partially covered SEMS with enlarged head was used in the majority cases after its introduction. The length and degree of obstruction were assessed by injecting contrast agent through the stricture and by using a hydrophilic guide wire with radiopaque centimeter markers that was passed through the stricture. When the guide wire was correctly positioned distal to the stricture, the delivery device loaded with the stent was advanced over the guidewire. A stent that was at least a few centimeters longer than the stricture on both sides was chosen to guarantee a disease-free margin and to extend well around curves. Finally, the stent was deployed under continuous fluoroscopic control. Two types of duodenal SEMSs, that is, partially covered SEMS with enlarged head and uSEMS, were used. The partially covered SEMS with enlarged head used in this study (HANAROSTENT® Pylorus/Duodenum Kim's Flare, M.I. Tech, Seoul, Korea) is preloaded into a 10.2 Fr (OD 3.4 mm) delivery sheath. When deployed, it has a funnel-shaped enlarged head in the proximal end intended to prevent distal migration by being fitted at the pylorus or proximal end of the duodenal stricture (Figure 1). The midportion of this stent is covered with a membrane to prevent tumor ingrowth. Both the proximal end (2 cm) and distal end (0.5 ~ 1 cm) of the stent are uncovered. The funnel-shaped enlarged head at the proximal end is 40 mm in diameter that tapers to 20 mm over the length of 2 cm. As for the uSEMSs, the following SEMSs with delivery sheath diameter of 10 Fr (OD 3.33 mm) were used: BONASTENT M-duodenal stent (Standard Sci-Tech, Seoul, Korea), Niti-S D-type pyloric/duodenal stent (Taewoong Medical, Seoul, Korea), and Wallflex duodenal stents (Boston Scientific Corp., Natick, MA). All endoscopic procedures were performed by experienced endoscopists (JJH, SWJ, and SYK) with patients consciously sedated with midazolam (0.05 mg/kg body weight; 1 mg if age > 70 or ASA class III-IV) and meperidine (50 mg; 25 mg if age > 70).

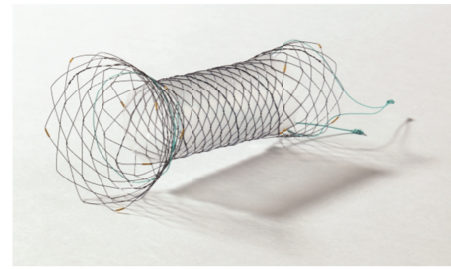

Figure 1: The proximal portion of this partially covered stent takes on a funnel shape in order to prevent distal migration. The midportion is covered with a membrane to prevent tumor ingrowth, whereas both the proximal portion and distal end are uncovered.

2.3. Outcome Measures and Definitions. The primary end points were technical and clinical success. Technical success was defined as successful stent placement at the site of the stricture. Clinical success was defined as relief of GOO symptom or improvement of the GOOSS score 1 week after stent insertion. The secondary end points were duration of stent patency (from the time of stent insertion to the time of stent failure or death) and early (within 1 week) or late (after 1 week) intervention-related complications. Stent failure was defined as stent migration, restenosis due to tumor ingrowth/overgrowth, or any other conditions that caused GOO. Whenever GOO was suspected, CT and upper endoscopy were performed. Patients who had not experienced recurrent obstructive symptoms owing to stent dysfunction were censored at the date of the last follow-up or upon death.

2.4. Statistical Analysis. Statistical analyses were performed using IBM SPSS Statistics version 20.0 (IBM, Armonk, NY, USA). Data are expressed as means ± standard deviation (SD) or n (%). Categorical variables were compared using the χ^2 tests or Fisher's exact tests, and continuous variables were compared using the independent two-tailed t-tests. Analyses of pooled data using univariate and multivariate logistic regression models were conducted to define the independent predictive factors for stent patency. Cumulative stent patency and patient survival were analyzed using the Kaplan–Meier method and were compared by using the log-rank test. Two-sided p values < 0.05 were considered to indicate statistical significance.

3. Results

3.1. Patient Characteristics. A total of 48 patients with GOO caused by malignant tumors who underwent endoscopic SEMS placement at Korea University Ansan Hospital

between July 2009 and July 2016 were included. Partially covered SEMS with enlarged head was inserted in 24 patients (enlarged-head group) and uSEMS was inserted in the remaining 24 patients (uSEMS group). The demographic and clinical characteristics of the patients are summarized in Table 1. There were no statistically significant differences between the two groups with regard to age, sex, tumor characteristics, site of obstruction, and length of stenosis, albeit the length of stenosis tended to be longer in the uSEMS group (2.91 ± 1.12 cm versus 2.38 ± 0.71 cm, $p = 0.06$). General conditions represented by BMI and ECOG performance status were also similar between the two groups. The GOOSS scores between the two groups showed no significant differences at baseline before stent placement.

3.2. Clinical Outcomes. The overall technical success rate was 97.9% (47/48): 100% (24/24) in the enlarged-head group and 95.8% (23/24) in the uSEMS group. The reason for unsuccessful stent placement in 1 patient from the uSEMS group was difficulty in approaching the stricture segment and passing the guidewire. Among patients who achieved technical success, the clinical success rates of partially covered SEMS with enlarged-head placement and uSEMS placement were 87.5% (21/24) and 87.0% (20/23), respectively ($p = 1.00$). Among 6 patients that failed to achieve clinical success (i.e., improvement in the GOOSS score), 1 patient underwent gastrojejunostomy because the inserted uSEMS did not adequately expand. There were no differences in primary outcomes. The median procedure time, length of stent, chemotherapy after stent placement, oral intake status after stent placement, and median GOOSS score before and after stent placement were not different between the two groups (Table 2). However, when the mean score before stenting was compared with the score after stent placement, improvement was seen for all types of SEMS (Figure 2(a)) in both groups (Figure 2(b)).

3.3. Overall Stent Patency and Survival. The median stent patency time was 87.1 days for the enlarged-head group compared to 60.4 days for uSEMS group. Although the stent patency tended to be longer for the enlarged-head group, it was not statistically significant ($p = 0.204$). The median survival duration was 99.3 days for the enlarge-head group compared with 82.1 days for the uSEMS group, again without statistical significance ($p = 0.418$) (Table 2). The cumulative stent patency and patient survival were analyzed using the Kaplan–Meier method. The stent patency rate and survival rate of enlarged-head group seemed to be slightly superior to those of uSEMS group, but there were no statistically significant differences (Figure 3).

3.4. Complications. No acute complications, including perforations or aspiration pneumonia, were noted in patients after stent insertion, except for one patient with an inadequate expansion of the uSEMS. There were no stent insertion-related deaths. As for the late complications in the enlarged-head group, fracturing of the funnel (Figure 4) occurred in 2 cases, and tumor ingrowth through the uncovered portion of the SEMS, that is, funnel, occurred in 2 cases. In the uSEMS group, tumor ingrowth occurred in 8 patients. Distal migration of SEMS did not occur in the enlarged-head group, but proximal migration was observed in 4 cases. Proximal migration was observed in 1 patient from the uSEMS group during chemotherapy after stent insertion. All proximally migrated SEMSs fully migrated into the stomach and were endoscopically removed by rat-tooth forceps.

3.5. Predictive Factors for Stent Patency. Using univariate and multivariate logistic regression analysis, all possible factors considered to have influence on the stent patency were analyzed. In the univariate analysis, chemotherapy after stent insertion was identified as an independent predictor of stent patency. However, in the multiple regression analysis, none of the variables proved to be significant (Table 3).

4. Discussion

In this retrospective study, we showed the efficacy of the partially covered SEMS with enlarged head compared to uSEMS for palliation of GOO. The clinical and technical success rates with this modified SEMS in the management of GOO were 87.5% and 100%, respectively, which were in accordance with the SEMS success rate mentioned in the literatures [7]. Although distal migration was prevented by shaping the partially covered SEMS to have an enlarged head and tumor ingrowth occurred less frequently compared to uSEMS, there was no difference in the stent patency between the two types of SEMS.

Many studies have been focused on determining which type of SEMS showed better patency, covered SEMS or uSEMS [5–7]. Stent migration rarely occurs with uSEMS, but tumor ingrowth is a problem. Tumor ingrowth can be minimized with covered SEMS, but migration, particularly distal migration due to peristalsis, poses a problem. Perhaps due to the advantages and disadvantages of each stent, one type of SEMS had not been shown to be superior over the other with systematic review demonstrating similar patency rates [7]. Until now, much efforts had been put into to overcome the drawbacks of each type of SEMS as follows. Regarding the uSEMS, three methods have been applied to enhance the stent patency. First, uSEMS had been combined with chemotherapy, which would retain the mechanical advantages of the SEMS and the chemical advantages of chemotherapy [12, 13]. In our study, poststent chemotherapy showed a possible protective effect against stent dysfunction. This result is comparable to results of other studies [12–14]. The challenge to this approach is that systemic chemotherapy cannot be uniformly applied, considering that the subjects are in relatively immune-compromised state and have poor performance status due to existing malignancy. Moreover, large prospective series found a significant association between the use of chemotherapy and increased incidence in stent migration [13]. Nevertheless, it would be worth mentioning that there is a risk of bias when performing analysis in this kind of situation where competing risks are present as clearly pointed out by Hamada et al. [15]. Second, simultaneous double placement of a covered

Table 1: Demographic and clinical characteristics of the 48 included patients.

Characteristics	Enlarged-head group ($n = 24$)	uSEMS group ($n = 24$)	p value
Age, years	70.5 ± 10.4	73.0 ± 11.9	0.447
Sex, male	11 (45.8)	12 (50.0)	0.781
Tumor characteristics			0.420
Pancreatic cancer	10 (41.6)	10 (41.7)	
Cholangiocarcinoma	7 (29.2)	3 (12.5)	
Duodenal cancer	1 (4.2)	0 (0.0)	
Gastric cancer	2 (8.3)	7 (29.2)	
Gallbladder cancer	4 (16.7)	3 (12.5)	
Ampulla of Vater cancer	0 (0.0)	1 (4.1)	
Site of obstruction			0.457
Pylorus	5 (20.8)	6 (25.0)	
First part of duodenum	13 (54.2)	8 (33.3)	
Second part of duodenum	5 (20.8)	7 (29.2)	
Third part of duodenum	1 (4.2)	3 (12.5)	
Length of stenosis	2.38 ± 0.71	2.91 ± 1.12	0.06
General condition			
BMI, kg/m^2	20.54 ± 3.47	20.13 ± 3.44	0.686
ECOG performance status	2 (2–4)	2 (2-3)	0.519
Severity of obstruction			
GOOSS score			0.512
0 no oral intake	5 (20.8)	5 (20.8)	
1 liquids only	12 (50.0)	16 (66.7)	
2 soft solid	7 (29.2)	3 (12.5)	
3 low-residue or normal diet	0 (0.0)	0 (0.0)	

Values are n (%) or mean ± SD or median (range). SEMS: self-expandable metallic stent; BMI: body mass index; GOOSS: gastric outlet obstruction scoring system.

Table 2: Clinical outcomes of 47 patients who achieved technical success.

	Enlarged-head group ($n = 24$)	uSEMS group ($n = 23$)	p value
Clinical success	21/24 (87.5)	20/23 (87.2)	1.00
Short-term outcomes			
Median procedure time (min)	13 (5–40)	14 (5–30)	0.901
Length of stent	9.08 ± 1.50	8.65 ± 2.30	0.46
Chemotherapy after stent placement	3/24 (12.5)	6/23 (26.1)	0.286
Oral intake status after stent placement			0.197
Liquid	3 (12.5)	4 (17.4)	
Soft solid	7 (29.2)	12 (52.2)	
Low-residual or full diet	14 (58.3)	6 (26.1)	
Median GOOSS			
Prestent placement	1 (0–2)	1 (0–2)	0.505
Poststent placement	3 (1–3)	2 (1–3)	0.200
Long-term outcomes			
Recurrent symptoms	9 (37.5)	8 (34.8)	1.00
Stent patency, days	87.1 (8–358)	60.4 (2–231)	0.204
Survival duration, days	99.3 (19–358)	82.1 (11–231)	0.418
Tumor ingrowth	2 (8.3)	8 (34.8)	0.036
Stent migration	4 (16.7)	1 (4.34)	0.348

Values are n (%) or mean ± SD or median (range). SEMS: self-expandable metallic stent; GOOSS: gastric outlet obstruction scoring system.

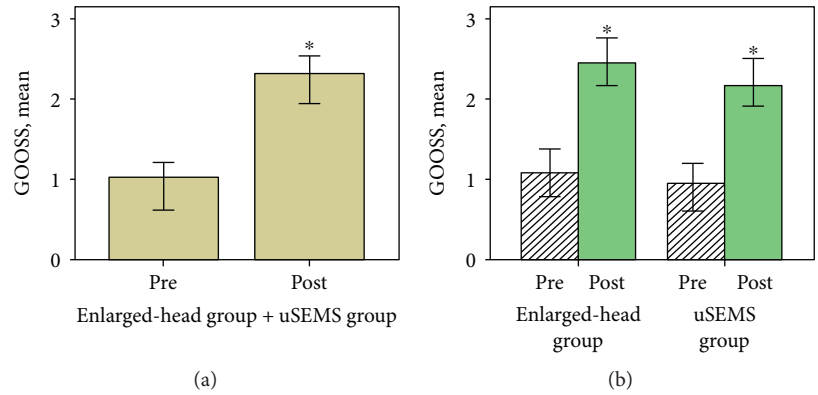

Figure 2: Comparison of mean GOOSS score before and after stent insertion. (a) GOOSS score significantly improved in 47 patients in whom the stent has been successfully placed. (b) When the result is analyzed according to the group, both the enlarged-head group ($n = 24$) and uSEMS group ($n = 23$) showed significantly higher GOOSS score after stent placement. GOOSS: gastric outlet obstruction scoring system; uSEMS: uncovered self-expandable metallic stent. $^*p$ value < 0.001.

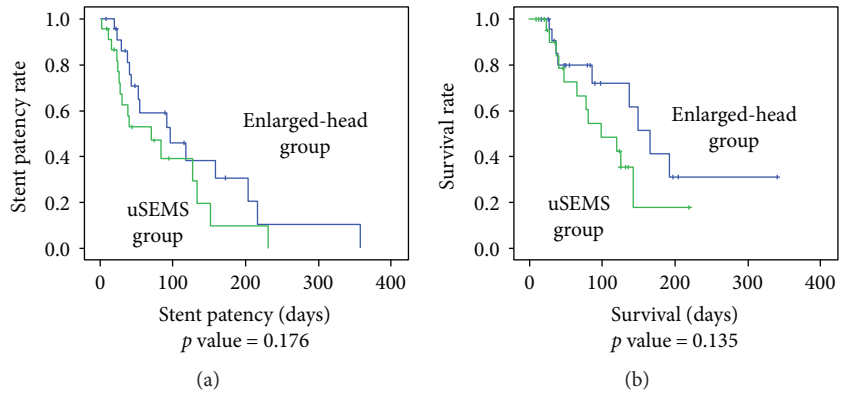

Figure 3: Cumulative stent patency and survival rate. Both the (a) stent patency rate and (b) survival rate seem to be slightly better in the enlarged-head group; there was no statistical significance. uSEMS: uncovered self-expandable metallic stent.

SEMS and a uSEMS during the same session had been attempted to decrease both the migration and obstruction [16, 17]. However, the problems of longer procedure time, higher costs, and a lower-than-expected efficacy remain to be solved. Furthermore, a double-layered SEMS, consisting of an outer uncovered stent designed to reduce migration and an inner covered stent to suppress tumor ingrowth, is already on the market [12]. With this SEMS, procedure time can be saved by not having to go through the procedure twice, and the cost is similar to other duodenal SEMS. However, the currently available data shows no definite advantage of double-layered SEMS over a covered SEMS with regard to patency rate. As for covered SEMS, there have been several efforts to reduce the tendency for migration by modifying the design of the stent or mechanical fixation. As a part of this effort, the central portion of a covered SEMS was given a bumpy and wavy external appearance to provide mechanical resistance [9]. However, the migration rate of this new SEMS was still higher than that of uSEMS, albeit not statistically significant [9]. In another attempt to overcome stent migration, SEMS was anchored using endoscopic clips that grasped an adequate amount of the adjacent healthy tissue with one of the wires of the metal stent at its proximal end [8]. However, this technique did not show the desired control over stent migration. Another SEMS technique employed by van den Berg et al. was making a partially covered SEMS with a big cup [10]. This study was prematurely terminated because migration occurred in 50% (3/6) of cases at a relatively early stage. In our study however, the rate of proximal migration was 16.7% (4/24), which would be much lower compared to the study by van den Berg et al. Although the efficacy of the SEMS with a big cup could not be fully evaluated due to the small sample size in their study, high rate of proximal stent migration could clearly be perceived as an obstacle that had to be overcome with this type of design modification. Recently, Shi et al. designed a "tailored" partially covered SEMS and compared it with conventional uSEMS [18]. Two shapes of "tailored" SEMS were used in this study; the proximal end of one stent was cup shaped (53.3 ± 5.5 mm in diameter and 15 to 20 mm in length) and the other was funnel shaped (33.6 ± 3.6 mm in diameter and 25 to 30 mm in length). These "tailored" partially covered SEMS reduced tumor ingrowth/outgrowth but did not prevent migration of stent or increase survival. The overall outcomes of their study were similar with those of our study. However, whereas the "tailored" partially covered SEMS had to be placed fluoroscopically since it needed larger

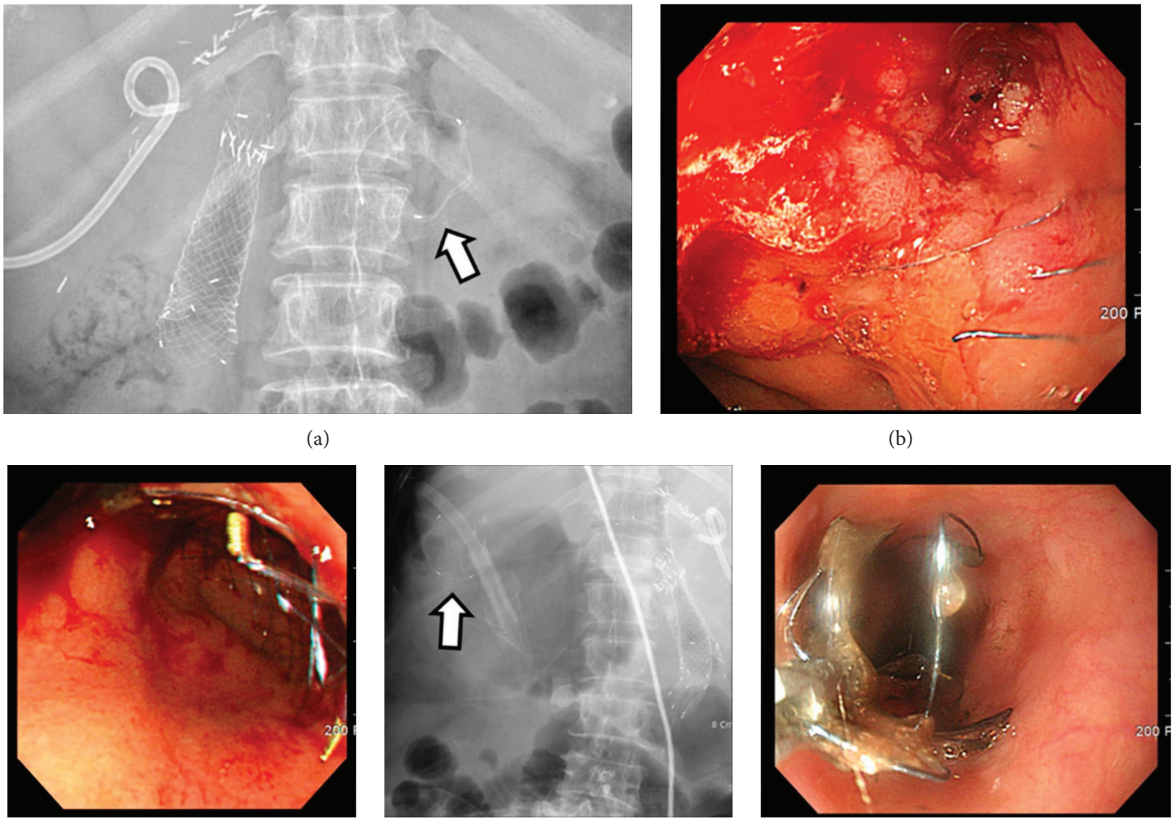

FIGURE 4: Fracturing of the funnel portion of partially covered SEMS with enlarged head. Detached part of the fractured stent (arrow) is seen on plain abdominal X-ray (a). Fractured proximal end of the stent is observed along with prominent tumor ingrowth (b). The endoscopic view (c) and fluoroscopic view (d) after 2nd partially covered SEMS with enlarged-head placement show that it has been properly deployed over the 1st SEMS. The ring-shaped detached part of the fractured SEMS (arrow) (d) is being removed by rat-tooth forceps (e).

than 6 mm delivery system, all the partially covered SEMSs with enlarged head in the current study were placed using through-the-scope method under direct endoscopic visualization. Through-the-scope method ensured technical ease and proved to be less time-consuming (mean procedure time, 15.8 min versus 56 min) [19]. Takahara et al. also conducted a study with a partially covered SEMS with a large-bore flare proximal end, a concept similar to that of the present study [20]. Although this SEMS proved to be safe and effective for the palliation of malignant GOO, stent migration could not be overcome with a migration rate of 23%. However, it is noteworthy that all migrations in their study were distal. This is in contrast with the direction of migration observed in our study where proximal and not distal migration was the problem. Therefore, the size (40 mm) and radial force of the funned-shaped enlarged head used in our study seem to be more ideal in preventing distal migration compared to the 25 mm-sized proximal flare with low radial force used in their study.

As expected, tumor ingrowth occurred less frequently in the enlarged-head group and distal migration was prevented. Thus, the partially covered SEMS with enlarged head could be considered a promising stent option for durable palliation of symptomatic GOO if higher proximal migration rate compared to the uSEMS could be overcome. One of the most plausible mechanisms of proximal migration with covered SEMS could be explained by the soap bar effect which was described by Adam et al. [21]. According to his description, peristalsis combined with the conical shape of the stent within a relatively short stricture and the smooth surface of the covered stent that is in contact with the tumor would have resulted in upward forces to push the stent in a proximal direction. Therefore, lowering the axial force would help reduce the proximal migration due to soap bar effect. Another improvement that can be made with the partially covered SEMS with enlarged head in prolonging the stent patency would be to further decrease tumor ingrowth which occurred in 2 patients. The location of the tumor ingrowth was at the funnel portion that was not covered by the covering material. This could have occurred because the part where the uncovered funnel portion meets the covered portion of the SEMS and becomes anchored is where the obstruction by the tumor begins. Therefore, in order to increase stent patency, the SEMS could be modified to have part of the funnel covered with the covering material.

This study has some limitations. First, it was a retrospective study with a small number of cases during a long study period at a single center, albeit a tertiary referral center. Second, several uSEMSs from a different manufacturer were used. Thus, the axial force and the radial force would not

Table 3: Univariate and multivariate logistic regression analysis for the stent patency.

Stent patency	OR (95% C.I.)	p value
Univariate analysis		
Chemotherapy after stent insertion	1.937 (0.131 ~ 2.540)	0.032
Survival	0.722 (0.215 ~ 2.427)	0.599
Clinical success	4.833 (0.779 ~ 30.005)	0.091
Stent type		
Enlarged head	Reference	
Uncovered	1.371 (0.408 ~ 4.614)	0.610
Obstruction site		
Pylorus	Reference	
First part of duodenum	1.429 (0.303 ~ 6.737)	0.229
Second part of duodenum	0.800 (0.149 ~ 4.297)	0.795
Third part of duodenum	1.143 (0.077 ~ 16.947)	0.923
Stricture length	1.138 (0.595 ~ 2.174)	0.696
Stent length	0.761 (0.542 ~ 1.068)	0.114
Cancer etiology		
Cholangiocarcinoma	Reference	
Pancreatic cancer	2.800 (0.562 ~ 13.952)	0.209
Stomach cancer	8.000 (0.711 ~ 90.001)	0.092
Multivariate analysis		
Clinical success	4.833 (0.779 ~ 30.005)	0.091

have been uniform and may have affected the clinical success, complications, and stent patency in the uncovered SEMS group. However, since no significant differences in terms of outcomes among the manufacturers of the uSEMS have been demonstrated in a systematic review, the influence of having used SEMS from various manufacturers could have been minimal [22]. Third, lack of specific information on the impact of possible confounding factors for stent patency, such as chemotherapy response and histologic differentiation of tumors, could not be analyzed for being a retrospective study. Fourth, determining the exact cause of stent dysfunction was not always possible because enrolled patients tended to die of complications from malignancy rather than GOO. Regular endoscopic surveillance or upper GI series study would be helpful in determining the cause but would not be a very realistic approach in terminal cancer patients.

In conclusion, although distal migration was prevented by shaping the SEMS to have an enlarged head, there was no difference in the stent patency between the two types of SEMS. Therefore, choice of SEMS type should be left at the discretion of the physician depending on the characteristics and site of the stricture until further progress is made with SEMS.

Disclosure

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors and thus has no financial ties to disclose.

Conflicts of Interest

The authors have no conflicts of interest for this article.

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Research Article

Preserving the Mucosa to the Maximum Possible Extent for Endoscopic Submucosal Dissection of Subcircumferential Superficial Esophageal Carcinoma

Masaya Uesato,[1] **Kentarou Murakami**,[1] **Yoshihiro Nabeya**,[2] **Kazunori Fugo**,[3] **and Hisahiro Matsubara**[1]

[1]*Department of Frontier Surgery, Chiba University Graduate School of Medicine, Chiba-shi, Chiba 260-8670, Japan*
[2]*Division of Gastroenterological Surgery, Chiba Cancer Center, Chiba 260-8717, Japan*
[3]*Department of Molecular Pathology, Chiba University Graduate School of Medicine, Chiba-shi, Chiba 260-8670, Japan*

Correspondence should be addressed to Masaya Uesato; uesato@faculty.chiba-u.jp

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Aim. To show our unique strategy of endoscopic submucosal dissection (ESD) for esophageal squamous cell carcinoma larger than the subcircumference. *Methods*. From April 2011, we used a mucosal preservation method called the log bridge (LB) method for the lesion larger than the subcircumference. The patients in whom the circumference of the mucosal defect was 5/6 to <1 were classified into the LB group; those who underwent whole circumferential ESD were classified into the non-LB group. The data were collected retrospectively and were compared between the two groups. *Results*. Eighteen patients into the LB group and 7 into the non-LB group were classified. The median number of endoscopic balloon dilation sessions after ESD in the LB group tended to be lower than that in the non-LB group. The mean period until complete epithelialization after ESD was significantly shorter in the LB group. The rates of curative resection were 100% (7/7) in the non-LB group and 61.1% (11/18) in the LB group. However, there was no local recurrence in either group for approximately two years. *Conclusion*. In cases involving subcircumferential esophageal lesions, the LB method is useful for achieving rapid healing and might be related to a reduced degree of esophageal stricture.

1. Introduction

Endoscopic submucosal dissection (ESD) is a useful and minimally invasive procedure that is used in the management of early esophageal cancer. It also enables the en bloc resection of large lesions [1, 2]. Moreover, ESD facilitates the accurate histopathological assessment of specimens resected en bloc with tumor-free horizontal/vertical margins, thereby resulting in the prevention of residual disease and local recurrence [3, 4]. However, extensive resection results in esophageal stricture or slow healing. The frequency of stricture after ESD for esophageal cancer in high-risk patients (a mucosal defect of >3/4 of the circumference) is approximately 70–90% [5–7]. However, the intraregional injection of steroids or the oral administration of prednisolone may be able to prevent stricture after ESD [8, 9]. Our institution administers multiple intraregional steroid injections (mISI) in the first session (just after ESD) and every two weeks to effectively suppress inflammation. Among the patients who underwent ESD without ISI at our institution from December 2002 to March 2011, the rate of stricture after ESD in patients with a wound of <1/2 the circumference was 0% (0/98 patients), while the rate in patients with a lesion covering < 1/2 the circumference was 7.62% (8/105 patients) (data not shown). Thus, the method of preserving the mucosa, the so-called log bridge (LB) method, which systematically preserves the mucosa to the maximum possible extent, is performed for subcircumferential superficial esophageal squamous cell carcinoma. The aim of this retrospective study is to prove the usefulness of the LB method in promoting rapid healing and preventing stricture after ESD.

2. Materials and Methods

2.1. Patients. A total of 104 patients were treated with ESD plus ISI for esophageal carcinoma at the Chiba University Graduate School of Medicine from April 2011 to February 2018. The LB method was attempted for lesions larger than the subcircumference. As a result, the patients in whom the mucosa was preserved and the circumference of the mucosal defect was 5/6 to <1 were classified into the LB group; those who underwent whole circumferential ESD were classified into the non-LB group. Patients in whom the esophageal carcinoma was located in the cervical or abdominal esophagus, where stenosis is likely to occur, were excluded. Data from these patients were collected retrospectively. The management of wound healing and the pathological evaluation of the resected specimen were examined in the two groups.

2.2. ESD with the Log Bridge (LB) Method. Preoperative upper gastrointestinal endoscopy was performed, and the patients in whom a B2 or B3 vessel pattern [10, 11] was recognized around the lesion on magnified narrow band imaging were excluded from the analysis (Figures 1(a) and 1(b)). ESD was performed under general anesthesia. Marking was performed around the boundary of the lesion using a Flush knife. A sufficient amount of glycerol solution was inserted into the submucosal layer of the mucosa that was to be preserved (Figure 1(c)). The first incision was made immediately above the markings on both sides (Figure 1(d)). Trimming was not performed at this time. After making a small incision on the distal side, we connected the incision from the proximal side to the surrounding lesion. A hemoclip with a thread was attached to the proximal side of the specimen, and the thread was pulled out of the mouth. The dissection of the submucosal layer was performed while applying tension to the specimen. The LB method enables the mucosa to be precisely preserved (Figure 1(e)).

2.3. Multiple Intraregional Steroid Injection (mISI). If a mucosal defect covered more than 2/3 of the circumference, mISI was applied. Triamcinolone acetonide (Kenacort, 40 mg/1 mL; Bristol-Myers Squibb, Tokyo, Japan) was diluted 1 : 19 with saline to make a 2 mg/mL solution. A 26-gauge needle was used to inject 2.0 mL (10 injections) of the solution into the residual submucosal tissue of the ulcer bed. If the longer axis of the ulcer bed was >5 cm, then 2.0 mL (20 injections) of the solution was injected. It was easy to inject when the bevel of the needle faced the ulcer bed. The first intraregional steroid injection (ISI) procedure performed just after ESD. ISI was repeated approximately every two weeks until epithelization reached >3/4 of the circumference.

2.4. Endoscopic Balloon Dilation (EBD). Follow-up endoscopy was performed every two weeks. If an endoscope of 9.2 mm in diameter could not pass through the esophagus, EBD was performed using a controlled radial expansion balloon (Boston Scientific, Marlborough, MA, USA). The size of the dilators that was used for the initial procedure ranged from 12 to 15 mm, according to the degree of the stricture.

2.5. Statistical Analyses. Fisher's exact test and the Mann–Whitney U test were used to evaluate the differences between the groups. The statistical analyses were conducted using the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA). P values of less than 0.05 were considered to indicate statistical significance.

3. Results

Eighteen patients and 7 patients were classified into the LB and non-LB groups, respectively. There was no significant difference in the gender or age of the two groups (Table 1). Other comparisons are shown in Table 2. The difference between the median lesion size and the median resected specimen size in the non-LB group was 8.0 mm. On the other hand, the difference in the LB group was only 4.0 mm. The median total triamcinolone dose in the non-LB group was approximately 2.0 times than that in the LB group (non-LB group/LB group: 220.0 mg/106.0; $P = 0.008$).

The ratio of patients with EBD after ESD did not differ between the groups to a statistically significant extent (LB group versus non-LB group: 6/18 patients (33.3%) versus 4/7 (57.1%); $P = 0.490$). However, in the LB group, the median number of endoscopic balloon dilation sessions after ESD tended to be lower than that in the non-LB group (LB group versus non-LB group: 1 versus 2; $P = 0.122$). The median period until complete epithelialization after ESD was significantly shorter in the LB group (LB group versus non-LB group: 51.0 days versus 105 days; $P = 0.012$). The horizontal margins in all 7 patients of the non-LB group were negative. On the other hand, in the LB group, 3 patients (3/18; 16.7%) had unclear margins and 4 patients (4/18; 22.2%) had positive margins. However, there was no local recurrence for approximately two years in either group.

4. Discussion

In the present study, the LB method was useful for promoting rapid healing after ESD in patients with subcircumferential esophageal cancer. mISI and the LB method might be useful for preventing esophageal stricture after ESD.

The ESD procedure is widely performed for the treatment of superficial esophageal cancer in Japan; there is no limitation in lesion size if the tumor depth is within the epithelium or the mucosa of the lamina propria [1–4]. However, it is said that the risk of esophageal stricture increases if a mucosal defect covers more than 3/4 of the circumference, especially in full circumference ESD [5–7, 12]. Various approaches, including steroid injection [6, 8], oral steroid administration [9], polyglycolic acid sheet [13, 14], cell sheet [15], collagen patch [16], and stent placement [17, 18], are used for the prevention of the esophageal stricture after ESD. We have previously performed insurance-adapted mISI and are of the opinion that it is safe and effective. However, in our institution, the rate of stricture after ESD in cases in which the wound covered less than half the circumference was 0%; the rate in cases in which the lesion covered less than half the circumference was 7.62%. We assumed that this created too large of a margin around the lesion. Thus, the LB

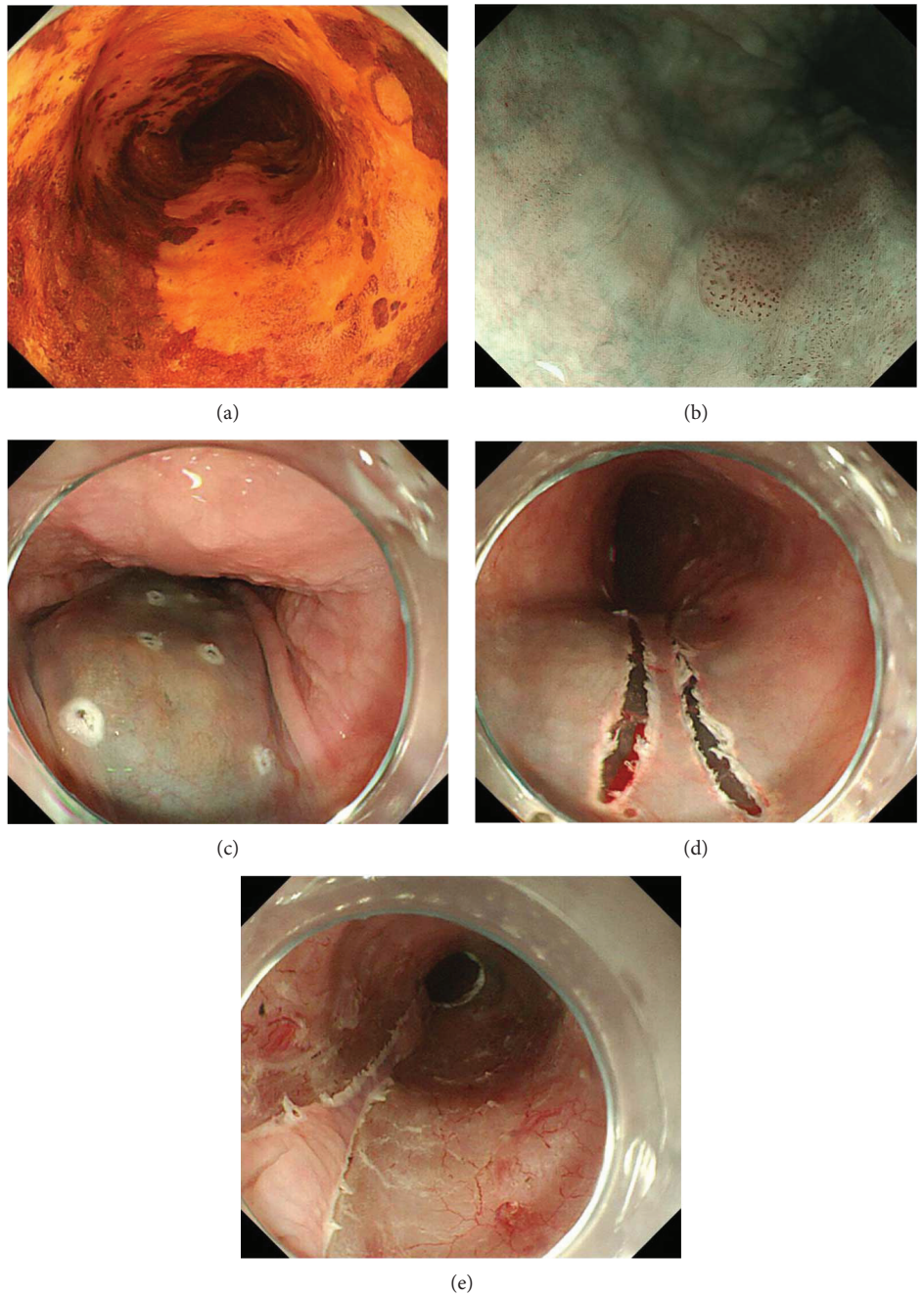

Figure 1: (a) The appearance of subcircumferential superficial esophageal cancer on endoscopy with iodine staining. (b) A B2 or B3 vessel pattern [10, 11] was not recognized around the lesion on magnified narrow band imaging. (c) The boundary of the lesion was marked with a Flush knife. A sufficient volume of glycerol solution was injected into the submucosal layer of the mucosa that was to be preserved. (d) The first incision was made immediately above the markings on both sides of the lesion. (e) There is little damage to the remnant mucosa. The LB method allows for the precise preservation of the mucosa.

method, which preserves the mucosa to the maximum possible extent, was performed to treat subcircumferential esophageal cancer. The stricture, wound healing, and the results of a pathological examination were compared between the LB group and the non-LB group (in which whole circumference ESD was performed).

With regard to esophageal stricture after whole circumference ESD, the number of patients who required EBD and the number of EBD sessions that were required at our institutions were lower in comparison to other reports [19, 20]. Thus, our mISI method might be effective. At present, there are no standards regarding the number of local injections and the total steroid dose. In our institution, ISI was first performed just after ESD. ISI was repeated approximately every two weeks until the epithelization reached >3/4 of the circumference. The total steroid dose administered to the non-LB group was approximately 2.0 times than that administered to the LB group. The total dose of triamcinolone was greater in

Table 1: The patients' characteristics.

	Non-LB group	LB group	*P* value
Circumference of mucosal defect	1	5/6 < < 1	
Number of patients	7	18	
Male/female	5/2	14/4	0.775※
Age median (years) [range]	72.0 [55–80]	74.0 [49–85]	0.442※※
Tumor location	Ut 2, Mt 4, Lt 1	Ut 4, Mt 11, Lt 3	0.782※※

Ut: upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus; ※Fisher's exact test; ※※Mann–Whitney *U* test.

Table 2: The patients' characteristics and the details of management after ESD.

	Non-LB group	LB group	*P* value
Number of patients	7	18	
Median procedure time (min) [range]	156.0 [110–210]	140.0 [60–340]	0.544※※
Median lesion size (mm) [range]	59.5 [52–85]	56.0 [42–82]	0.412※※
Median resected specimen size (mm) [range]	67.5 [59–105]	60.0 [47–87]	0.363※※
pHM x (%)	0 (0)	3 (16.7)	0.724※
pHM1 (%)	0 (0)	4 (22.2)	0.558※
Local recurrence (%)	0 (0)	0 (0)	
Median observation period (days) [range]	806 [184–2512]	763 [42–1834]	0.288※※
Median post-ESD period until complete epithelization (days) [range]	105 [48–132]	51.0 [25–76]	0.012※※
Number of EBD patients (%)	4 (57.1)	6 (33.3)	0.490※
Median number of EBD sessions (number) [range]	2 [2–9]	1 [1–8]	0.122※※
Median total Triamcinolone dose (mg) [range]	220 [152–312]	106 [40–216]	0.008※※
Median injection sessions (number) [range]	5.0 [2–10]	2.3 [1–4]	0.025※※

※Fisher's exact test; ※※Mann–Whitney *U* test.

comparison to that administered in other facilities [6, 8, 20], which probably had a good effect on the prevention of stricture. We hypothesize that our mISI method had a preventive effect against stricture after whole circumferential ESD. However, in order to investigate this hypothesis, it would be necessary to compare our mISI group to a group of patients undergoing whole circumferential ESD in whom the steroid dose was restricted. Moreover, the ratio of patients with EBD after ESD did not differ between our two groups to a statistically significant extent. If the number of patients increases, it might prove the preventive effect of the LB method against stricture.

On the other hand, the period until complete epithelization in the LB group was significantly shorter than that in the non-LB group. Epithelialization after ESD occurs from the margin of the normal mucosa. Thus, it is easy to imagine that the LB group, in which much of the mucosa is preserved, will heal earlier than the non-LB group. However, the administration of steroids might prolong epithelialization. The possibility that healing was significantly delayed in the non-LB group cannot be denied. However, it is thought that the amount of steroid used in non-LB method was necessary to prevent esophageal stricture after ESD. Moreover, the LB method was considered to contribute to shortening the period until complete epithelization under the condition of steroid administration, which minimized the occurrence of stricture after ESD.

The pathological evaluation of resected specimens revealed that the rate of curative resection was 100% (7/7) in the non-LB group and 61.1% (11/18) in the LB group. No residual lesions were on follow-up endoscopy for approximately two years. Based on these results, the procedures in all of the cases in the LB group might finally be considered to be clinically curative. However, follow-up endoscopy should be carefully performed every 3–6 months in cases in which resection is noncurative and additional treatments, such as mucosal resection or argon plasma coagulation should always be prepared.

We experienced one case in which a patient underwent whole circumferential ESD for a whole circumferential lesion and in whom additional chemoradiotherapy was considered to be necessary. The esophageal ulceration had still not completely healed at 4 months after ESD. He could not wait until such ulceration had completely healed. Therefore, he received chemoradiotherapy which thus led to the onset of severe stricture due to radiation. Thus, whole circumferential ESD plus local steroid injection may delay the start of additional chemoradiotherapy. In other words, whole circumferential ESD can be tolerated when the possibility of additional treatment is low or when surgery for additional treatment is desired. However, if additional chemoradiotherapy is desired, the esophageal ESD should be limited to lesions down to the subcircumference (within the indication of the LB method).

This study is associated with several limitations. It was a retrospective study that was performed in a single institution. Therefore, the number of patients was small. In addition, there was a significant difference in the steroid doses that were administered to the two groups.

In conclusion, the LB method plus mISI is useful for promoting rapid healing after ESD in cases of subcircumferential superficial esophageal cancer and might have a preventive effect against esophageal stricture.

Abbreviations

ESD: Endoscopic submucosal dissection
mISI: Multiple intraregional steroid injection
LB: Log bridge
EBD: Endoscopic balloon dilation.

Consent

Patients were not required to give their informed consent for the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment with their written consent.

Conflicts of Interest

The authors declare no conflicts of interest in association with the present study.

Authors' Contributions

Masaya Uesato designed and performed the research and wrote the paper. Kentarou Murakami provided clinical advice. Kazunori Fugo diagnosed the pathology of the resected specimens. Yoshihiro Nabeya and Hisahiro Matsubara supervised the report.

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Research Article

Endoscopic Vacuum-Assisted Closure Therapy in Patients with Anastomotic Leakage after Esophagectomy: A Single-Center Experience

Soo Min Noh,[1] Ji Yong Ahn,[2] Jeong Hoon Lee,[2] Hwoon-Yong Jung,[2] Zeead AlGhamdi,[3] Hyeong Ryul Kim,[3] and Yong-Hee Kim[3]

[1]*Department of Internal Medicine, Asan Digestive Disease Research Institute, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*
[2]*Department of Gastroenterology, Asan Digestive Disease Research Institute, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*
[3]*Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*

Correspondence should be addressed to Ji Yong Ahn; ji110@hanmail.net

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Aim. To study the efficacy of E-VAC therapy for patients with anastomotic leakage after esophagectomy. *Methods*. Between January 2013 and April 2017, 12 patients underwent E-VAC therapy for the management of postoperative leakage. Their clinical features and endoscopic procedure details, therapy results, adverse events, and survival were investigated. *Results*. All 12 patients were male and the median age was 57 years (interquartile range 51.5–62.8 years). The reasons for esophageal surgery were esophageal cancer (83.3%), gastrointestinal stromal tumor (8.3%), and esophageal diverticulum (8.3%). Prior to E-VAC therapy, 6 patients had undergone failed primary surgical repair and the median duration from esophagectomy to leakage discovery was 13.5 days (IQR 6–207 days). The median duration of E-VAC therapy was 25 days (IQR 13.5–34.8 days) and the average sponge exchange rate was 2.7 times during the treatment period. After E-VAC therapy, 8 patients (66.7%) had complete leakage closure, 3 (25%) had a decreased leakage size, and 1 (8.3%) was unchanged. The three patients with a decreased leakage size after E-VAC therapy were treated with endoscopic and conservative management without further surgery. *Conclusion*. With proper patient selection, E-VAC therapy is a feasible and safe method for the treatment of anastomotic leakage after esophagectomy.

1. Introduction

Anastomotic leakages occur at a rate of about 8% to 13% after esophageal surgery [1–4]. Because postoperative esophageal leakages are life-threatening events, the purpose of treatment is to prevent the leakage from affecting the perforation area and thereby protect gastrointestinal tract functions and ensure proper nutrition. Although surgical management is considered the primary treatment, it is often difficult to perform given the potential morbidity risks associated with reoperation. As alternatives, many patients have been treated with various endoscopic techniques [5–7]. However, no uniform endoscopic method exists for correcting postoperative anastomotic leakage. Among the many endoscopic methods tried, endoscopic vacuum-assisted closure (E-VAC) therapy is reported to be a good method for the treatment of postoperative esophageal leakage [8–14]. However, patient and method characteristics varied slightly among the clinical centers and sufficient data from a large number of patients have not been reported because these cases are rare in most hospitals.

We therefore analyzed in this study the efficacy and safety of E-VAC therapy in patients with anastomotic leakage after esophageal surgery performed in a single tertiary center.

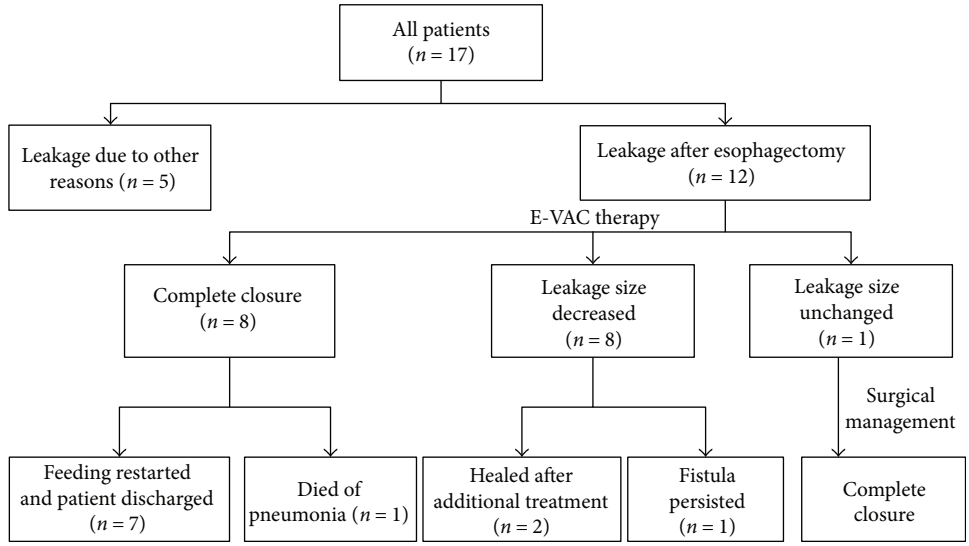


Figure 1: Flow chart of case enrollment.

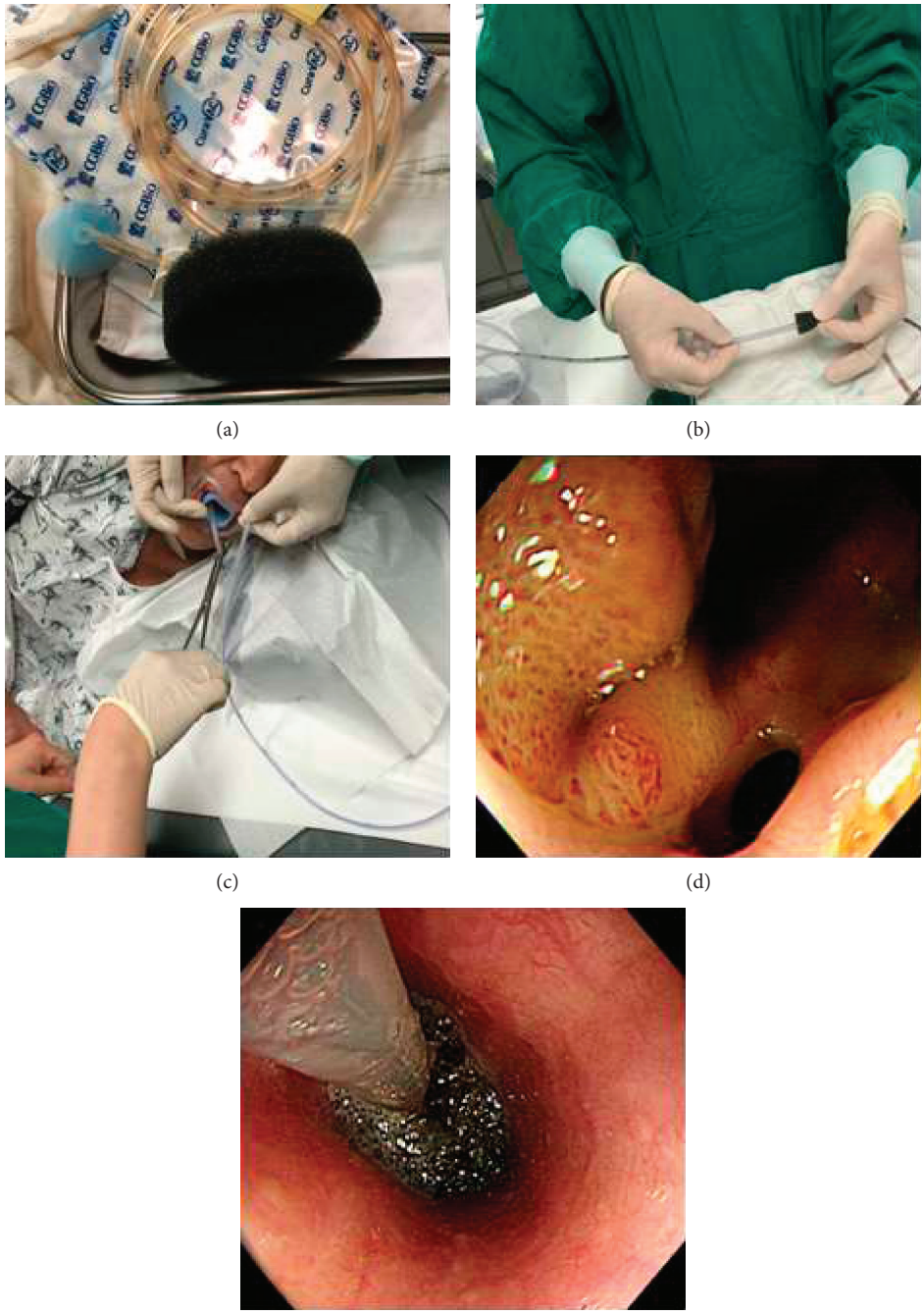
2. Patients and Methods

2.1. Patients. Between January 2013 and April 2017, 17 patients underwent E-VAC therapy at Asan Medical Center, Seoul, Korea. Among the 17 patients, 12 patients underwent E-VAC therapy after esophagectomy. The other 5 patients who underwent E-VAC therapy for reasons other than post esophagectomy leakage were excluded (Figure 1). We retrospectively studied these patients and reviewed their clinicopathological features, radiologic studies, endoscopy reports, and clinical course. Outcome data included clinical success, evidence of need for an additional endoscopic procedure with or without surgery, and procedure-related complications. This study was approved by the Institutional Review Board of Asan Medical Center (IRB number: 2017-0736).

2.2. Diagnostic Method and Definitions. In the present study, radiological examinations to identify anastomotic leakage were routinely performed before food intake resumed. Leakage diagnosis was based on clinical presentation and radiological findings. Clinical diagnosis of anastomotic leakage was defined as physical findings suggesting pneumonia or as changes in content within the chest drain. Radiologic findings indicative of a leakage were defined as extraluminal extravasation of contrast on postoperative fluoroscopy or the presence of an infiltration around the anastomosis site and/or fistula tract formation on computed tomography (CT). Clinical success was defined as leakage closure confirmed by radiographic or endoscopic evaluation.

2.3. Leakage Management. There are no standard guidelines for the treatment of leakages after esophagectomy. The treatment methods varied among the patients in the current study according to the leakage size, timing of the diagnosis, and patient comorbidities. The attending surgeon decided whether to perform surgery or another medical treatment, including endoscopic procedures. In some cases, the surgery was performed first if primary repair was feasible. E-VAC therapy was then performed after consultation with an expert endoscopist when it was judged that the esophagoduodenoscopic assessment indicated the need for E-VAC therapy. During endoscopy, the distance from the incisors, defect diameter, and cavity shape were evaluated. All endoscopic interventions were performed by two expert endoscopists (JHL and JYA). During the E-VAC, all patients were treated with conservative treatment, which included nil by mouth, systemic antibiotics, total parental nutrition, and/or adequate external drainage.

2.4. The E-VAC Therapy Method. We used a single-channel gastroscope (GIF-H260 or GIF-H290; Olympus, Tokyo, Japan), nasogastric tube, and standard VAC kit (CuraVAC®; CGBio Inc., Hwaseong, Korea). The VAC kit comprises a medical-grade polyurethane sponge, adhesive drapes for sealing, and connector tubing inside a sterile pouch (Figure 2(a)). The procedure was performed under conscious sedation with intravenous administration of midazolam. We prepared a nasogastric tube and an appropriately sized piece of polyurethane sponge (Figure 2(b)). The size of the sponge is made to fit the size and the location of the cavity. Due to the size limitation of passing through the upper esophageal sphincter, most of them were made in sizes ranging from 2.0×2.0 cm to 3.0×3.0 cm. A nasogastric tube was inserted and retrieved through the mouth to attach the sponge (Figure 2(c)). A piece of sponge is cut to the appropriate size and positioned at the tip of the L-tube. Then, the sponge is sutured onto the L-tube tip using silk to connect and secure it. After the leakage site was identified (Figure 2(d)), the nasogastric tube with the polyurethane sponge was inserted into the esophagus and an endoscopic examination was performed to help in the correct placement of the tube and sponge with the use of a pair of forceps (Figure 2(e)). Usually, the intracavitary insertion of the drainage tube has been preferred if the sponge can fill the cavity properly. However, if the placement of the sponge in the cavity was difficult due to the small size or difficult location, it was placed in the esophageal lumen



(a) (b) (c) (d) (e)

Figure 2: Steps in the endoscopic vacuum-assisted closure procedure. (a) The vacuum-assisted closure kit (CuraVAC; CGBio, Hwaseong, Korea) comprises a polyurethane sponge, adhesive drapes, and connector tubing. (b) A nasogastric tube with a polyurethane sponge head. The form and size of the sponge is similar to those of the anastomotic leakage. (c) A pulled-out nasogastric tube is connected to a polyurethane sponge. (d) Anastomotic leakage was noted on endoscopy (GIF-H290; Olympus, Tokyo, Japan). (e) The nasogastric tube embedded with a polyurethane sponge was placed in the anastomotic leakage area.

adjacent to the defect. After inserting the sponge into the leak site, a suction of 80–125 mmHg was applied to remove the fluid which prevents reepithelization. If the suction works successfully, negative pressure is applied and it helps if the sponge can be fixed to the cavity to some extent. Then, the final nasogastric tube position on the nose is marked and care is taken so that it is not moved.

The change in the cavity was monitored and the sponge was endoscopically exchanged every 1 or 2 weeks if needed. If the leak appeared to be sealed on endoscopic examination, we removed the sponge and fluoroscopy was conducted to confirm complete closure of the leakage (Figure 3). If confirmed, the patient was allowed to sip water, before gradually advancing to a soft or regular diet. However, if the leakage

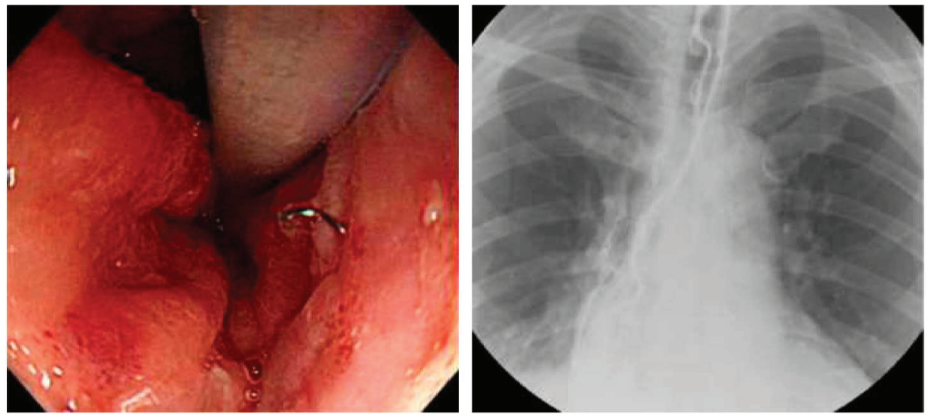


Figure 3: Endoscopic image and esophagography showing complete closure of the leakage after completion of the E-VAC therapy.

Table 1: Baseline characteristics of the study patients ($n = 12$).

Variable	No. of patients
Male	12 (100%)
Median age (years)	57.0 (51.5–62.75)
Etiology	
Esophageal cancer	10 (83.3%)
GIST	1 (8.3%)
Esophageal diverticulum	1 (8.3%)
Methods of primary surgery	
Open Ivor Lewis esophagectomy	7 (58.3%)
Robotic-assisted Ivor Lewis esophagectomy	4 (33.3%)
Robotic esophageal diverticulectomy	1 (8.3%)

Data are presented as a median value (interquartile range) or number (%). GIST, gastrointestinal stromal tumor.

Table 2: Anastomotic leakage diagnosis.

Variable	No. of patients
Median duration from esophagectomy to leakage (days)	11 (6.3–205.3)
Presence of symptoms	9 (75%)
Diagnostic modality	
Fluoroscopy	8 (66.7%)
Chest CT	3 (25%)
Other[a]	1 (8.3%)

Data are presented as a median value (interquartile range) or number (%). CT, computed tomography. [a]By high clinical suspicion.

persisted despite E-VAC therapy, clinicians discussed the case and decided whether to add treatment such as injection of fibrin glue (Beriplast; Aventis Behring Ltd., Marburg, Germany) or endoscopic clipping (Long Clip; Olympus Optical Co., Ltd.) or to continue with conservative management.

3. Results

3.1. Clinical Characteristics of the Study Patients. All 12 study patients were men, with a median age of 57 years (interquartile range (IQR) 51.5–62.8 years). The reasons for esophageal surgery were esophageal cancer (83.3%), gastrointestinal stromal tumor (GIST) (8.3%), and esophageal diverticulum (8.3%). Seven patients (58.3%) underwent open Ivor Lewis esophagectomy, four (33.3%) underwent robotic-assisted Ivor Lewis esophagectomy, and one (8.3%) underwent robotic esophageal diverticulectomy (Table 1).

3.2. Anastomotic Leakage Diagnosis. The median duration from esophagectomy to leakage discovery was 11 days (IQR 6.3–205.3 days). Nine patients (75%) reported symptoms at the time of diagnosis, and the other three patients were diagnosed by routine fluoroscopy. Leakages were diagnosed with fluoroscopy in 8 of the 12 patients, chest CT was used in three patients, and one patient who complained of dyspnea with increased contents within the chest tube was diagnosed without imaging. Three of the patients had previously been treated for anastomotic leakage immediately after the esophagectomy but the closed leakage opened again (Table 2).

3.3. Clinical Success of the E-VAC Therapy. The E-VAC therapy was initiated at a median of 11 days (IQR 5–54 days) after leakage diagnosis. Six patients (50%) had undergone failed primary surgical repair prior to E-VAC therapy, with persistence of the anastomotic leakage. In eight patients (66.7%), leakages were completely closed after E-VAC therapy with a median of five endoscopic interventions (IQR 2–8; four sponge insertions plus final sponge removal) and the median duration from the start of E-VAC therapy to final sponge removal was 28.5 days (IQR 15.0–34.8 days).

In three of the four remaining patients, the leakage size decreased after E-VAC therapy. In two of these patients, the leakage improved with further endoscopic management and conservative treatment. One patient had been treated with additional endoscopic clipping, but the fistula persisted. The remaining patient who had no response to E-VAC therapy was healed through surgical treatment. Details are given in Table 3 and Figure 1.

3.4. E-VAC Therapy-Related Complications and Death. The median follow-up duration was 12.9 months (IQR 1.2–18.6

Table 3: Characteristics of the 12 study patients who underwent E-VAC therapy.

Patient	Etiology	Premanagement prior to E-VAC therapy	Opening size (cm)	Placement of E-VAC	E-VAC therapy duration (days)	Sponge exchanges *(n)*	E-VAC therapy result	Clinical outcome	Complication
1	Esophageal cancer	Failed primary closure	2	Intracavitary	27	1	Complete closure	Discharged	Anastomotic site stricture
2	Esophageal cancer	None	1	Intraluminal	43	6	Complete closure	Discharged	None
3	Esophageal cancer	Failed primary closure	0.5	Intraluminal	31	3	Complete closure	Discharged	None
4	Esophageal cancer	None	1	Intraluminal	5	0	Complete closure	Discharged	None
5	GIST	None	1	Intraluminal	13	1	Complete closure	Discharged	None
6	Esophageal cancer	Succeeded in primary closure but leakage opened again	1	Intraluminal	36	6	Complete closure	Discharged	None
7	Esophageal diverticulum	None	1.5	Intraluminal	30	4	Complete closure	Discharged	None
8	Esophageal cancer	Failed primary closure	0.5	Intraluminal	21	3	Complete closure	Died of pneumonia	Anastomotic site bleeding
9	Esophageal cancer	Failed repeated primary closures	1, 1*	Intraluminal	62	5	Size decreased	Healed after further supportive tx.	None
10	Esophageal cancer	None	1.5	Intraluminal	15	1	Size decreased	Healed after supportive tx. & fibrin glue injection	None
11	Esophageal cancer	None	2.5	Intracavitary	23	2	Size decreased	Fistula persisted despite additional endoscopic clipping	None
12	Esophageal cancer	Failed primary closure	2.5, 1.5*	Intracavitary	10	0	No change	Healed after surgical management	None

GIST, gastrointestinal stromal tumor; tx., treatment. *Two fistulas.

Table 4: E-VAC therapy clinical success rates reported in previous case series.

Study	No. of treated patients	Complete closure rate (%)
Kuehn et al. [8] (2012)	3	2/3 (67)
Weidenhagen et al. [9] (2010)	6	5/6 (83)
Ahrens et al. [10] (2010)	5	5/5 (100)
Bludau et al. [11] (2014)	5	5/5 (100)
Ooi et al. [13] (2016)	2	2/2 (100)
Wedemeyer et al. [15] (2008)	8	7/8 (88)
Schorsch et al. [17] (2013)	12	11/12 (92)

months). There were no serious procedure-related complications and two patients had procedure-related complications that could be managed by additional medical treatment. In one patient, a symptomatic esophageal stricture was diagnosed and successfully treated with fluoroscopically guided balloon dilatation after 5 months of E-VAC therapy. In another patient, E-VAC therapy was stopped after 21 days due to bleeding at the anastomosis site. The bleeding was successfully treated with sponge removal and follow-up fluoroscopy revealed no more leakage of contrast media at the esophagocolonic anastomotic site. Although the leakage was closed, the patient died of persistent aspiration pneumonia 2 weeks later.

4. Discussion

In our present series of 12 patients who underwent E-VAC therapy for anastomotic leakage after esophagectomy, the clinical success rate was 66.7% (8/12) and 91.7% (11/12) of these cases showed a decreased leakage size, avoiding the need for additional surgery. The E-VAC therapy failed in one patient (8.3%) whose leakage was closed after surgical management. General anesthesia was not required and all procedures were performed safely using intravenous administration of midazolam. No major procedure-related complications were detected; the two patients who had an esophageal stricture and bleeding at anastomotic sites improved after proper management. These results suggest that, with careful case selection, E-VAC therapy can be an appropriate therapeutic option for the management of postoperative leakage that avoids further surgical intervention.

As an alternative treatment for anastomotic leakage after esophagectomy, E-VAC therapy was first introduced in 2008 by Wedemeyer et al. [15]. Compared with other endoscopic treatments, E-VAC therapy promotes healing of the anastomotic leakage by increasing vascular perfusion and enhancing the formation of granulation tissue [16]. According to previous data on 41 patients with postoperative leakage from the esophagus [8–11, 13, 15, 17], E-VAC therapy showed clinical success rates of between 66.7% and 100% (overall 90.2% (37/41)). The results of other studies are summarized in Table 4.

We found that the clinical success rate was considerably lower than that of other previous reports. In our study, six patients had already undergone failed primary closure before E-VAC therapy and other endoscopic management options were either impossible or deemed unfit. Thus, except for one patient, we chose E-VAC therapy as a treatment until it was changed because it was judged ineffective. Therefore, it is likely that we were offering E-VAC therapy to less well patients with more complex problems than in other series. Under difficult conditions, in 11 patients, additional surgical management could be avoided through E-VAC therapy and conservative treatment. Because surgical intervention for postoperative leakage is associated with a high risk of mortality and morbidity, E-VAC therapy was feasible in almost all patients.

There were no differences in leakage detection time after esophagectomy (176.0 ± 370.1 days versus 105.5 ± 187.8 days), duration from time of leakage diagnosis to E-VAC therapy (39.4 ± 60.6 days versus 42.5 ± 73.7 days), and duration of E-VAC therapy (25.8 ± 12.3 days versus 27.5 ± 23.6 days) between the successful and unsuccessful groups. According to other studies, failure is more likely in the case of chronic, larger, and/or loculated cavities [13]. Hence, these earlier reports recommended the evaluation of the cavity characteristics and determination of whether E-VAC therapy was indicated. Although, in our present study, there were no differences in patient characteristics between those who underwent successful or unsuccessful E-VAC therapy, we think that E-VAC therapy is less effective in a large leakage which cannot be covered by a swallow-to-mouth-sized sponge, in an opening which has lots of secretion such as the esophagobronchial fistula, and in a location where peristalsis exists. Therefore, the best-suited indication of E-VAC therapy is a less than 4 cm sized sealed-off leak lesion which is located on a relatively fixed site such as an anastomosis site. Further analysis with a larger number of patients in a multicenter setting should be performed to more precisely determine the clinical outcomes and indications for E-VAC therapy in patients with leakage after esophagectomy.

One of the limitations of E-VAC therapy is the need for repeated endoscopic procedures. Our current case studies required fewer sponge changes than reported for other patient series but there was no difference in the treatment period. Therefore, we recommend endoscopic sponge exchange at proper intervals according to patient comfort.

Our current study had limitations associated with its small number of subjects and retrospective design. In addition, our comparison between the successful and unsuccessful groups was limited. Nevertheless, we expect that our findings will provide an impetus for a future meta-analysis of the use of endoscopic therapy in the management of postoperative anastomotic leakage.

In conclusion, E-VAC therapy is a technically feasible and safe treatment option in patients with anastomotic leakage after esophagectomy. With proper implementation of additional supportive treatments, E-VAC therapy will be able to replace surgical management in carefully selected patients. Future studies involving a greater number of patients are needed to evaluate the efficacy of E-VAC therapy.

Disclosure

With the help of the Korean Society for Thoracic & Cardiovascular Surgery and the Korean Association of Internal Medicine, the authors were able to announce their study in part in conferences last fall. Since then, the authors have been able to complete the paper by modifying it a bit more.

Conflicts of Interest

The authors have no competing interests.

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Research Article

The Development of Endoscopic Techniques for Treatment of Walled-Off Pancreatic Necrosis: A Single-Center Experience

Mateusz Jagielski, Marian Smoczyński, Anna Jabłońska, and Krystian Adrych

Department of Gastroenterology and Hepatology, Medical University of Gdańsk, Gdańsk, Poland

Correspondence should be addressed to Mateusz Jagielski; matjagiel@gmail.com

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Background. Endotherapy is a common method of treatment in patients with symptomatic walled-off pancreatic necrosis (WOPN). The aim of this study is to indicate the potential therapeutic possibilities created by the combination of several new endoscopic techniques and the evaluation of their efficacy in the treatment of WOPN. *Methods.* The retrospective analysis of results and complications in the group of 101 patients, who underwent endoscopic treatment of symptomatic WOPN between years 2011 and 2015. *Results.* Endoscopic treatment was started in 101 patients (71 men, 30 women; mean age 50.97 years) with symptomatic WOPN. Single transluminal gateway technique (SGT) was used in 93/101 (92.08%) patients. SGT in combination with multiple transluminal gateway technique (MTGT) was exploited in 4/93 (4.30%) patients, while in combination with single transluminal gateway transcystic multiple drainage (SGTMD) in 22/93 (23.66%) patients. Transpapillary access was used in 11/101 (10.89%) patients. 20/101 (19.80%) patients underwent percutaneous drainage. Fluoroscopy-guided endoscopic necrosectomy was performed in 19/101 (18.81%) patients. The combinations of endoscopic techniques depended on the extent of necrosis. Procedure-related complications occurred in 16/101 (15.84%) patients. The mortality rate was 0.99% (1/101 patient). Therapeutic success was achieved in 99/101 (98.02%) patients. The long-term success of endoscopic treatment was achieved in 97/101 (96.04%) patients with symptomatic WOPN. *Conclusions.* Application of new endoscopic techniques in the treatment of the patients with symptomatic WOPN significantly improves the efficiency of endotherapy with an acceptable amount of complications.

1. Introduction

Walled-off pancreatic necrosis (WOPN) is diagnosed in 15% of patients with severe acute pancreatitis [1]. The most common form of necrotizing pancreatitis is mixed necrosis (parenchymal and peripancreatic) which affects 75%–80% of patients [2]. The less common is peripheral (peripancreatic 20%) and central (pancreatic 5%) types of necrosis [2]. Better results of the conservative treatment of acute pancreatitis allow to delay interventional therapy until the resolution of organ failure, demarcation and liquefaction of necrosis, and hence the formation of WOPN that usually takes place at least four weeks after the onset of symptoms [3–5]. Conservative treatment in the early phase of acute necrotizing pancreatitis and the delay of necrosectomy to the late stage of the disease significantly reduces mortality in this group of patients [6]. Interventional treatment is necessary for patients with clinical symptoms (including infection of necrosis) resulting from the presence of necrotic collection [1, 3].

Transmural endoscopic drainage is a common method of treatment for patients with symptomatic WOPN [1, 3, 7]. Single transluminal gateway technique (SGT) is based on the complete removal of necrotic tissues through a single fistula created between the cavity of necrotic collection and the lumen of the gastrointestinal tract (stomach or duodenum) [7, 8]. The described technique is particularly efficient in the case of unilocular necrotic collections. WOPN in most of the patients takes the form of a multilocular space divided by septa.

Decompression of necrotic collections during interventional treatment results in the formation of separated necrotic

areas that are in fact separate cavities (undrained areas) communicating with one another via narrow canals [9]. In such cases, a single access to necrotic collection is insufficient, and as additional access to necrosis is necessary [1, 3], a percutaneous drainage is usually performed [10, 11]. The use of other endoscopic techniques, like the creation of another transmural tract, endoscopic necrosectomy, or active transpapillary drainage, is also possible [7, 9, 12–14]. One method of treatment of WOPN—transpapillary drainage—is rarely described in the current literature and is still considered to be controversial [14].

The combination of several minimally invasive methods of treatment, allowing multiple access to necrotic collection, is an optimal strategy for the treatment of WOPN [1, 3, 10, 11]. Widening of the access to necrotic areas provides better draining conditions and increases the efficiency of treatment [1, 3, 7]. The method of access to WOPN should depend not only on the location of necrosis but also on the experience of the medical center.

Endoscopic drainage of walled-off pancreatic necrosis has been performed in our center since 2001 [7, 15]. Conventional transmural drainage (CTD) was performed between 2001 and 2011 [7]. Since 2011, the fistulas between the lumen of the gastrointestinal tract and the cavity of necrotic collection have been performed with endoscopic ultrasonography (EUS) guidance (EUS-guided drainage) [15]. The evolution and development of endoscopic therapy of WOPN in our medical center have led us to perform this retrospective analysis of efficiency and safety of the methods used.

This paper presents our own experience in the endoscopic treatment of walled-off pancreatic necrosis and indicates the potential therapeutic possibilities created by the combination of several new endoscopic techniques and evaluation of their efficacy in the treatment of WOPN.

2. Methods

The study was approved by the Ethics Committee of our Medical University. All patients gave their informed consent for endoscopic procedures.

2.1. Qualification to Study. The qualification to endoscopic treatment was based on the clinical picture and the results of imaging studies, mostly contrast-enhanced computed tomography (CECT). The walled-off pancreatic necrosis was diagnosed on the basis of the revised Atlanta classification from 2012 [4, 5]. The presence of necrotic tissues in an EUS image and morphology of an aspirate from the collection (dark brown color and fragments of necrotic tissues) confirmed the diagnosis of WOPN.

2.2. Exclusion Criteria. Excluded from the study were patients with WOPN who had no symptoms connected with the presence of pancreatic fluid collection (11 patients). We also excluded patients with symptomatic WOPN in whom EUS showed that the WOPN wall was located more than 15 mm from the gastrointestinal tract wall and endoscopic retrograde pancreatography (ERP) revealed no communication between the main pancreatic duct and the collection cavity (14 patients). Moreover, patients who were qualified to endoscopic drainage on the basis of a clinical picture and CECT image in whom EUS revealed no necrotic tissues ("solid debris") and morphology of aspirate (clear, serous) suggested pancreatic pseudocyst were also excluded (8 patients).

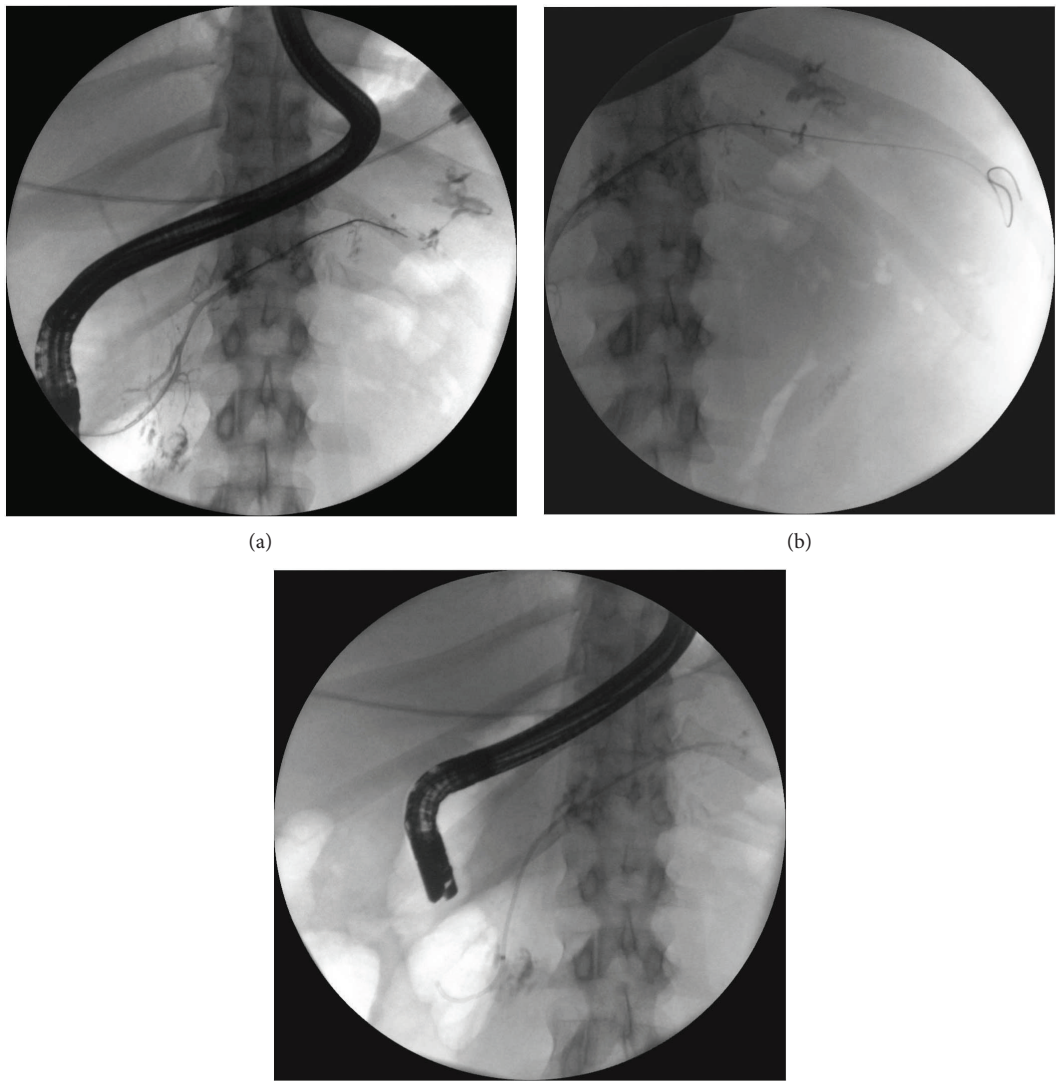
2.3. Study Group. The study group comprised 101 patients with symptomatic walled-off pancreatic necrosis who underwent endoscopic therapy in our department over a 5-year period from 2011 to 2015.

2.4. Choice of Endoscopic Treatment Technique. In all patients, an attempt of transmural drainage was made. In the case of patients with symptomatic WOPN, transmural drainage was not performed if the distance between the collection wall and the gastrointestinal wall exceeded 15 mm in EUS. Among patients who did not undergo transmural drainage, those in whom ERP revealed the leak of contrast medium into the necrotic collection were qualified to transpapillary drainage. Furthermore, when transmural drainage did not lead to complete regression of WOPN, in some patients with communication of the main pancreatic duct with collection cavity observed during ERP additional transpapillary, drainage was used. Endoscopic necrosectomy under fluoroscopic guidance was performed when the following criteria were fulfilled: lack of clinical effect or infection of necrotic collection despite the active drainage as well as a large number of necrotic tissues in a fluoroscopic and endosonographic image.

During the early period of the study (years 2011–2013) in the case of ineffective endoscopic drainage and spreading of necrosis outside the lesser omental sac, additional percutaneous drainage was performed. During the later phase of the study (years 2013–2015), if drainage through a single transmural access (single transluminal gateway technique (SGT)) was ineffective, another transmural tract was created (multiple transluminal gateway technique (MTGT)) when there was no communication between the necrotic collection subcavities or multiple access through a single transmural fistula (single transluminal gateway transcystic multiple drainage (SGTMD)) was used, which involved obtaining an additional access to extensive necrotic areas through a single transmural tract.

2.5. Procedures. Endoscopic procedures were performed with the use of duodenoscope Pentax ED3490TK and echoendoscope Pentax EG3870UTK. The procedure was performed with deep sedation. In all patients, endoscopic drainage was performed by one endoscopist. All patients received antibiotics before the procedure (ciprofloxacin or ceftriaxone with metronidazole). Routinely, antibiotic treatment was continued for two weeks. An aspirate from the collection was sent for amylase activity and microbial culture, and appropriate culture-directed modification of antibiotics was made.

2.6. Transmural Drainage (Single Transluminal Gateway Technique (SGT)). In all patients, an attempt to perform transmural drainage was made. The place of the transmural tract was chosen with EUS guidance. Gastrostomy



(a) (b) (c)

Figure 1: Endoscopic retrograde pancreatography done in the patient with WOPN. Partial disruptions of the main pancreatic duct in the body of pancreas are well visible as well as the complete disruption of MPD in the pancreatic tail (a). The guidewire inserted through the complete disruption of main pancreatic is located in the lumen of WOPN (b). Transpapillary 5Fr 12 cm pancreatic stent was used to bridge the disruption of the pancreatic duct (c).

(or duodenostomy) was created with the use of Giovannini cystostome (Cystotome CST-10, Wilson-Cook). The fistula formed between the gastrointestinal lumen and necrotic cavity was sequentially dilated with an 8 mm or 20 mm balloon dilator (Boston Scientific). A 7Fr or 8Fr nasocystic drain (Balton or Wilson-Cook) and double-pigtail stents 7Fr or 8.5Fr (ZSO-10-5, Wilson-Cook or Mar Flow) were deployed within the necrotic cavity through the transmural tract.

2.7. Endoscopic Retrograde Pancreatography (ERP). When the main pancreatic duct leak was observed, sphincterotomy was performed with an Olympus FlowCut KD-301Q0725 sphincterotome and pancreatic stent was placed (passive transpapillary drainage) to bridge the leak—5Fr, 7Fr, 8.5Fr, or 10Fr (Geenen, Zimmon Pancreatic Stent, Wilson-Cook Medical Inc. or Mar Flow) (Figures 1(a)–1(c)). The stent was then replaced with a new one after 6, 12, and 24 months or until the pancreatic duct leak was no longer demonstrated.

2.8. Active Transpapillary Drainage. In patients with active transpapillary drainage after sphincterotomy was performed during ERP, the main pancreatic duct was mechanically dilated with bougie dilator 7Fr, 8.5Fr, or 10Fr (Wilson-Cook). Sequentially, a nasocystic drain (7Fr or 8Fr, Balton or Wilson-Cook) and pancreatic stent (5–10Fr, Geenen, Zimmon Pancreatic Stent, Wilson-Cook Medical Inc. or Mar Flow) were placed through the duodenal papilla. The distal tip of nasocystic drain was deployed within the necrotic cavity.

2.9. Multiple Transluminal Gateway Technique (MTGT). In patients qualified to the creation of another transmural tract

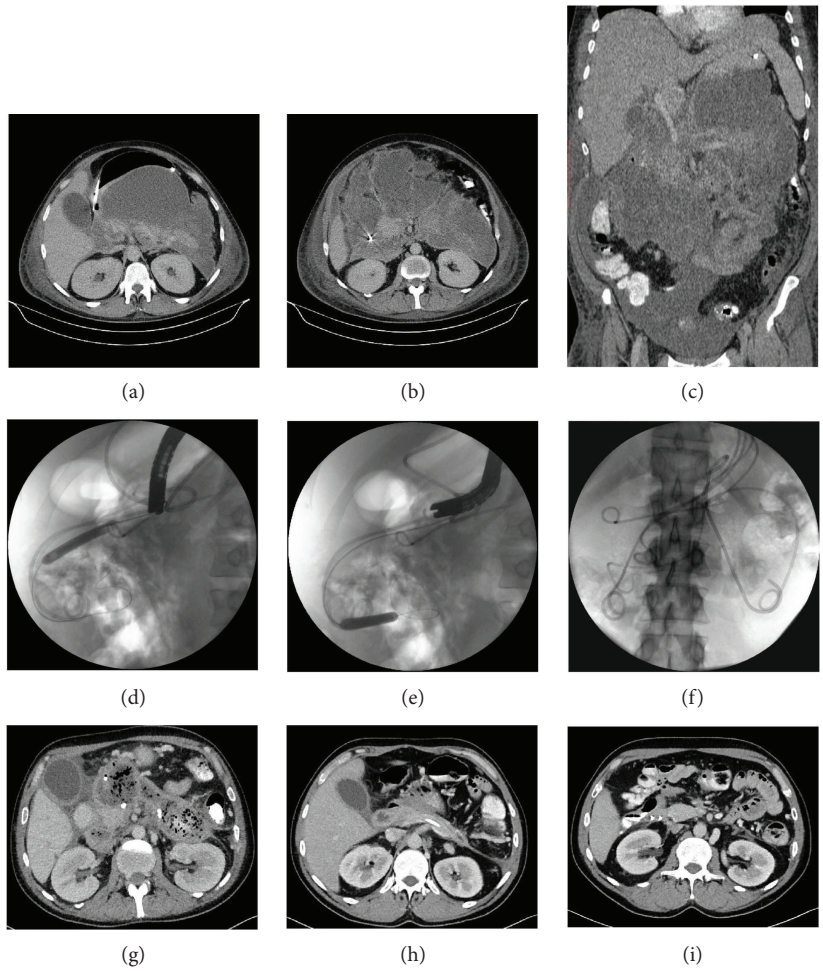


Figure 2: The patient with an extensive walled-off pancreatic necrosis visible in contrast-enhanced computed tomography (a, b, c). SGTMD technique was exploited for treatment (d, e, f, g). CECT performed after the end of endoscopic treatment stated complete regression of WOPN (h, i).

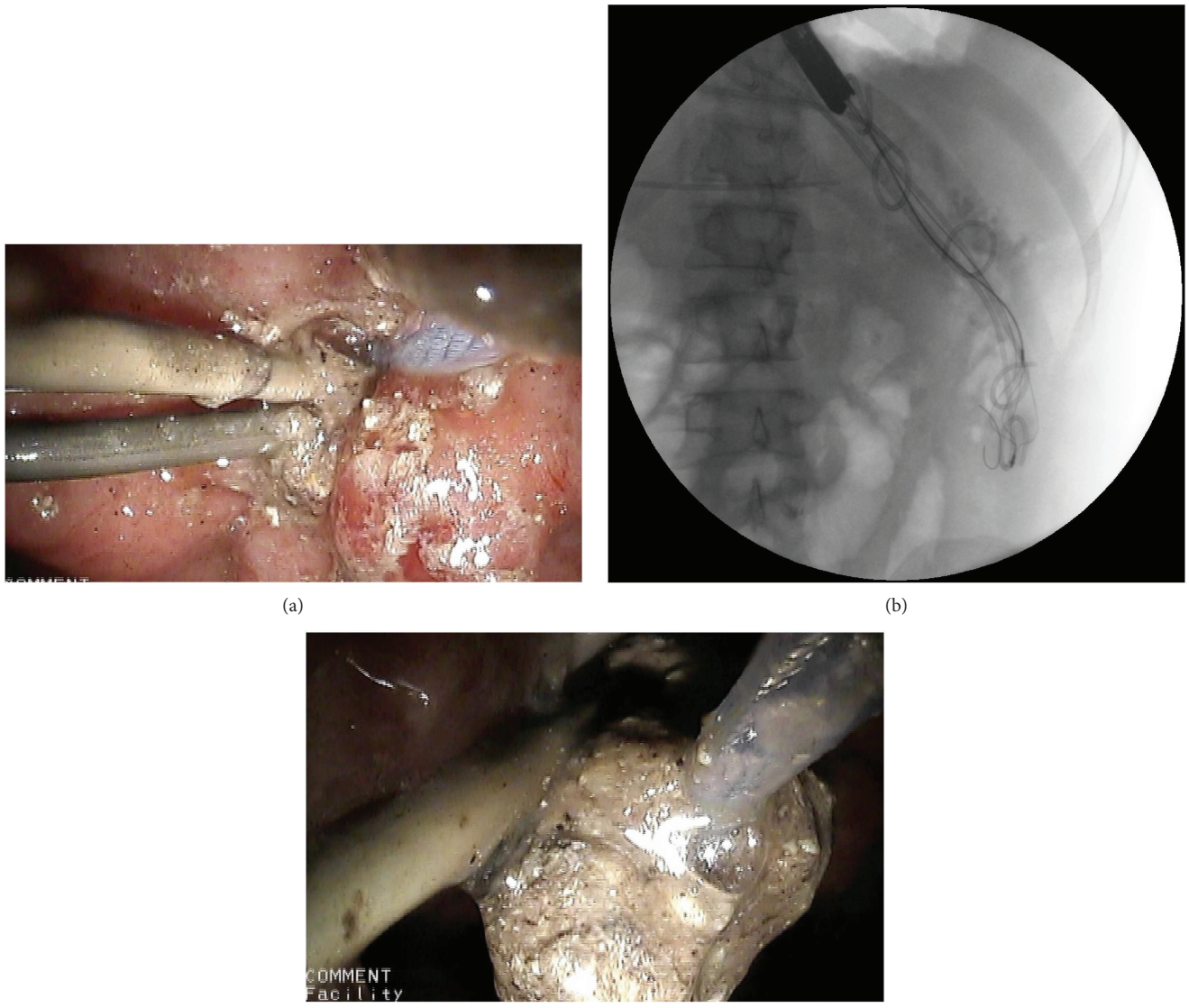
between the necrotic cavity and the gastrointestinal lumen, the site of fistulotomy was also chosen with EUS guidance. Enterostomy was performed with Giovannini cystostome (Cystotome CST-10, Wilson-Cook). The fistula was dilated with an 8 mm or 20 mm balloon dilator (Boston Scientific). A 7Fr or 8Fr nasocystic drain (Balton or Wilson-Cook) and double-pigtail stents 7Fr or 8.5Fr (ZSO-10-5, Wilson-Cook or Mar Flow) were placed in the necrotic cavity through the transmural tract.

2.10. Single Transluminal Gateway Transcystic Multiple Drainage (SGTMD). In patients qualified to SGTMD (Figures 2(a)–2(i)), subsequent endoscopic procedures were performed and a guidewire was introduced in the subcavities with fluoroscopy guidance through the transmural tract created between the necrotic collection and the gastrointestinal lumen. The canals between necrotic subcavities were dilated with an 8 mm balloon dilator (Boston Scientific) under fluoroscopy guidance (Figures 2(d) and 2(e)). Afterwards, another 7Fr or 8Fr nasocystic drain (Balton or Wilson-Cook) or double-pigtail stents 7Fr or 8.5Fr (ZSO-10-5, Wilson-Cook or Mar Flow) were introduced through those canals and their distal ends were deployed within necrotic subcavities (Figures 2(f) and 2(g)).

2.11. Fluoroscopy-Guided Endoscopic Necrosectomy. At the beginning of endoscopic necrosectomy procedure, a nasocystic drain was removed. Subsequently, a Dormia basket (FG-V422PR, Olympus) was introduced through the fistula in the necrotic area adjacent to the previously placed transmural stent. Necrotic tissues were removed with the Dormia basket through the transmural tract with fluoroscopy guidance (Figures 3(a)–3(c)). This action was repeated many times during each procedure of necrosectomy. At the end of procedure, another nasocystic drain was deployed.

2.12. Drainage System. The nasocystic drains were flushed with saline solution (60–200 mL) every 2 hours within the first 48 hours and then every 4 hours. When there was a clinical suspicion of WOPN infection, the use of antibiotics was prolonged and another microbial culture with antibiogram of necrotic collection contents was performed.

2.13. Assessment of Therapeutic Effect. The effect of drainage was monitored every 7 days, mainly with the use of



(a) (b) (c)

Figure 3: Endoscopic necrosectomy under fluoroscopic guidance. The Dormia basket is positioned in the lumen of necrotic collection (a, b). Numerous fragments of necrotic tissues were thereafter removed from the necrotic cavity during endoscopic necrosectomy (c).

conventional ultrasonography. Contrast-enhanced CT was performed to confirm complete regression of the collection. Active drainage/debridement was finished after the resolution of clinical symptoms and complete regression of the collection or the decrease of the collection's diameter to less than 40 mm.

2.14. Definition of Therapeutic Success and Recurrence of the Collection. Therapeutic success was defined as the lack of symptoms and complete regression of the collection or the dimension of the collection less than 40 mm during a three-month follow-up since the end of active drainage. Recurrence of the collection was determined as the collection size > 40 mm or relapse of symptoms during a follow-up. Long-term success was defined as the lack of symptoms and complete regression of the collection or the dimension of the collection less than 40 mm during a follow-up.

2.15. Statistical Analysis. All the statistical calculations were performed with the use of data analysis software system StatSoft Inc. (2011) STATISTICA version 10.0 (licensed for the Medical University of Gdansk). Quantitative variables were characterized by arithmetic means, standard deviation, and minimal and maximal values (range), whereas qualitative data were presented by the means of numbers and percentage.

3. Results

3.1. Patients' Characteristics. Patients' characteristics are presented in Table 1.

Endoscopic treatment was started in 101 patients with symptomatic WOPN. The etiology of acute pancreatitis was alcoholic in 61 patients and nonalcoholic in 40 (23: gallstones, 6: iatrogenic, 2: hypertriglyceridemia, and 9: idiopathic).

Table 1: Characteristics of the patients with WOPN who underwent endoscopic treatment.

	All patients ($n = 101$)
Age, mean (range)	50.97 (21–85)
Sex, *n*, men (%)	71 (70.3%)
Etiology, *n* (%)	
Alcoholic	61 (60.4%)
Nonalcoholic	40 (39.6%)
WOPN size (cm), mean (range)	12.4 (5.0–36.3)
WOPN type, *n* (%)	
Pancreatic parenchymal necrosis alone	23 (22.77%)
Peripancreatic necrosis alone	10 (9.90%)
Both pancreatic and peripancreatic necroses	68 (67.33%)
Time from the acute bout of pancreatitis (weeks), mean (range)	19.17 (3–80)
Main indication to start endotherapy, *n* (%)	
Infected necrosis	31 (30.69%)
Abdominal pain	96 (95.05%)
Gastrointestinal obstruction	40 (39.60%)
Jaundice	8 (7.92%)
Weight loss	38 (37.62%)

Two of 101 patients (1.98%) did not complete endotherapy. One patient was referred to surgical treatment because of gastrointestinal perforation during endotherapy. During the operation, perforation was repaired and surgical drainage of WOPN was performed. Another patient died during endoscopic treatment because of splenic artery pseudoaneurysm hemorrhage.

3.2. Infection of Walled-Off Pancreatic Necrosis. The WOPN infection was diagnosed on the basis of positive microbial culture in 31/101 (30.69%) patients. The most common pathogens cultured in the necrotic contents were *Escherichia coli*, *Enterococcus faecalis*, and *Staphylococcus epidermidis*. In 12/101 (11.88%) patients, sepsis with positive blood culture was observed during endotherapy.

3.3. Access Route to Necrotic Collection. The access routes to necrotic collection and endoscopic management techniques applied to our patients are presented in Figure 4.

Transmural access was used in 93/101 (92.08%) patients (gastric: 86, duodenal: 7). In 8 patients, the transmural route was not performed, because the distance between the gastrointestinal lumen and the necrotic cavity exceeded 15 mm. Transpapillary access was used in 11 patients. Twenty patients underwent percutaneous drainage.

3.4. Endoscopic Retrograde Pancreatography (ERP). ERP was performed in 89 patients in order to diagnose and treat a main pancreatic duct leak. In 79/89 (88.76%) patients, the main pancreatic duct leak required transpapillary pancreatic stent placement. A partial rupture of the main pancreatic duct was diagnosed in 51/79 (64.56%) patients, and a complete rupture in 28/79 (35.44%) patients.

3.5. Duration and Effectiveness of Therapy. Therapeutic success was achieved in 99/101 (98.02%) patients. The mean duration period of active drainage of WOPN was 23 (4–173) days. The mean number of procedures was 4.35 (1–27).

3.6. Complications of Treatment. Procedure-related complications occurred in 16/101 (15.84%) patients. One patient required surgical treatment of endotherapy complications. The most common complication—gastrointestinal bleeding—was observed in 9/101 (8.91%) patients. Because of gastrointestinal bleeding, seven patients were required packed red blood cell transfusions, one underwent endovascular embolization of the hepatoduodenal artery pseudoaneurysm, and one patient died because of splenic artery pseudoaneurysm hemorrhage. Transmural stent migration into the WOPN cavity was stated in 3/101 (2.97%) patients. In all cases, the stent was retrieved endoscopically with the Dormia basket. Gastrointestinal perforation was diagnosed in 2/101 (1.98%) patients. One of them required surgical management, and the other one was treated conservatively.

3.7. Mortality. The mortality rate was 0.99% (1/101 patient). The cause of death was splenic artery pseudoaneurysm bleeding.

3.8. Long-Term Success. The mean follow-up period was 32 (15–74) months. During the follow-up, the recurrence of WOPN was observed in 9/101 (8.91%) patients. In two patients, the recurrence was managed surgically and in seven endoscopically. The long-term success of endoscopic treatment was achieved in 97/101 (96.04%) patients with symptomatic WOPN.

4. Discussion

For the last two decades, we have observed the development of endoscopic management of WOPN. Baron et al. were the first who presented the results of treatment with the use of single transmural access in patients with WOPN [8]. Therapeutic success was achieved in 9 of 11 patients (81.82%) [8]. In our study, the SGT was efficient in 37 of 93 patients (39.79%). The use of another endoscopic technique or additional route of access to the necrotic collection was necessary in 54 remaining patients (54/93 (58.06%)).

The first reports concerning transmural drainage of pancreatic necrosis presented the creation of fistulas between the gastrointestinal lumen and the necrotic collection cavity that were measuring 10–12 mm in diameter [8]. With the development of this method, the diameter of the fistula was enlarged even up to 20 mm, which allowed the insertion of fiberscope into the area of necrosis and the performance of endoscopic necrosectomy [13]. The implementation of endoscopic necrosectomy is considered to be the next step that improved the efficiency of endotherapy. Seifert et al. proved the beneficial effect of endoscopic necrosectomy in 75 of 93 (81%) patients with WOPN [16]. Complications were observed in 24 of 93 (26%) of patients, and the mortality rate was 7.5% [16]. In a multicenter study, Gardner et al. reached the therapeutic success in 95 of 104 (91%) patients who underwent endoscopic necrosectomy [17]. Comparable

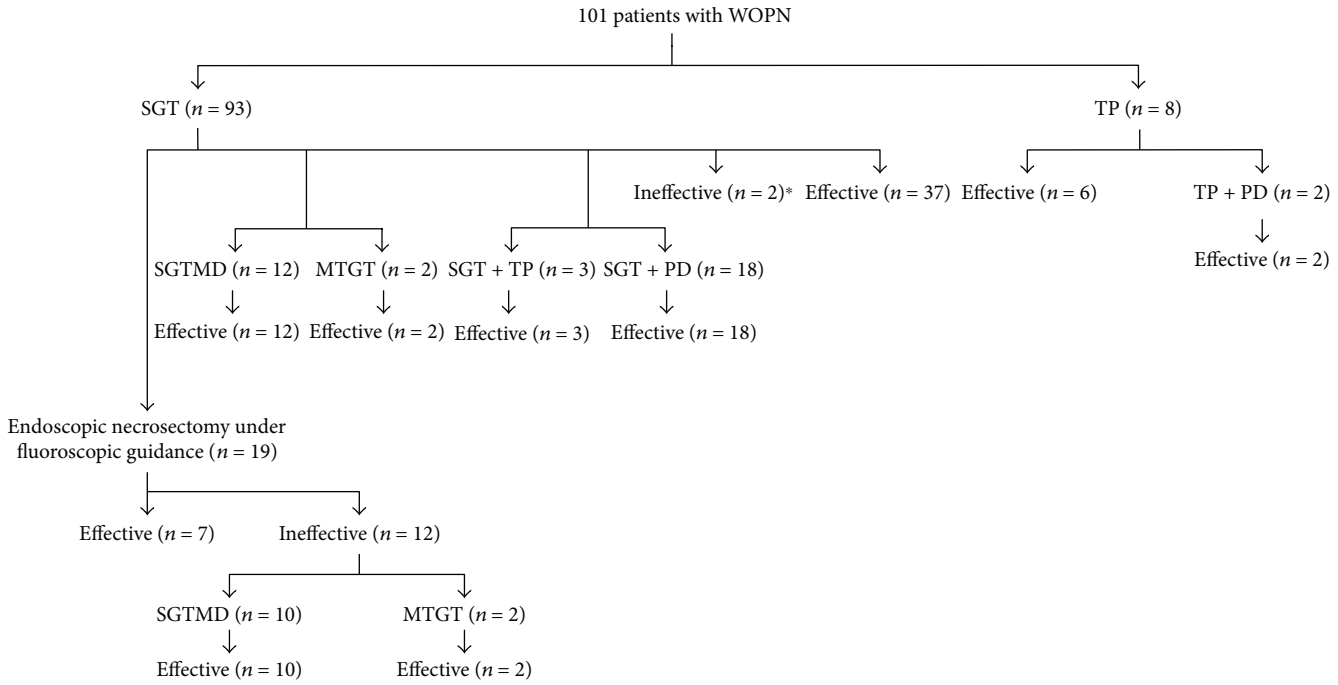


Figure 4: The access routes to necrotic collection and the results of treatment with the use of endoscopic techniques in patients with WOPN. PD: percutaneous drainage; TP: active transpapillary drainage; SGT: single transluminal gateway techniques; MTGT: multiple transluminal gateway techniques; SGTMD: single transluminal gateway transcystic multiple drainage; Effective: therapeutic success; Ineffective: without therapeutic success. *Two did not complete endotherapy: one patient was referred to surgical treatment, and another one patient died during endoscopic treatment.

results of treatment (with the efficiency of 86%) were described by Rische et al. [18]. Gardner et al. reported the complication rate of 14% and the mortality rate of 5.8% [17]. By comparison, in the study conducted by Rische et al., the complications occurred in 13% of patients and no lethal complications were observed [18]. All patients from the above studies underwent endoscopic necrosectomy. In our work, the indications for endoscopic necrosectomy under fluoroscopic guidance during transmural drainage were stated in 19 (18.81%) patients. A good therapeutic effect was achieved in all of the 19 patients; however, some of them required another access to necrotic areas with the use of other minimally invasive methods of treatment. The complications of endoscopic necrosectomy occurred in 4 of 19 (21.05%) patients. No lethal complications were observed.

Serious complications of air embolism were encountered in some studies that were connected with the inflation of gas into the necrotic collection to enable visualization of its cavity [16, 17, 19]. Seifert et al. reported two cases of air embolism (2.08%) in patients who underwent endoscopic necrosectomy (one case of fatal pulmonary embolism and one patient with cerebral infarction after air embolism via a persistent foramen ovale) [16]. Application of carbon dioxide [20] instead of room air [16, 17, 19] for endoscopic insufflations during endoscopic necrosectomy reduces the risk of the occurrence of air embolism [20]. In our study, we presented an endoscopic necrosectomy technique that is based on the removal of necrotic tissues under fluoroscopic guidance without the need to introduce fiberscope into the necrotic collection cavity and without its inflation with gas [21], which also eliminates the risk of air embolism. Furthermore, our method of necrosectomy [21] is less traumatic compared to the one described by many authors [16–20].

The reports describing the use of transpapillary drainage as the only way of access to pancreatic necrosis are rare in the literature [14]. Transpapillary drainage is much more often combined with the transmural or percutaneous route as multiplied access to the necrotic cavity [3, 7]. In our study, a transpapillary drainage was performed in eight patients with WOPN, in whom there was no chance to create a transmural fistula and the necrotic collection was communicating with the main pancreatic duct. Transpapillary drainage as the only route of access to necrosis was efficient in 6 of 8 (75%) patients. Two of 8 (25%) patients required additional percutaneous access.

The use of percutaneous access during the endoscopic treatment of WOPN decreases the number of both endoscopic and radiological procedures, shortens the duration of hospital stay, and increases the efficiency of treatment in patients with pancreatic necrosis [10, 11]. During the early stage of our study in the case of ineffective transmural drainage (lack of complete regression of WOPN), a transpapillary (3/93 patients (3.23%)) or percutaneous (18/93 patients (19.35%)) drainage was performed as another access route, which improved drainage conditions and increased the effectiveness of therapy. Therefore, percutaneous drainage can be used as both single and additional routes of access to necrotic collection in the management of WOPN. In a systematic

review of eleven studies, including 384 patients, percutaneous drainage appeared to be effective as the only method of treatment in more than half of patients (55.7%) [22]. In our study, percutaneous drainage was not used as the only access to WOPN.

With the development of endoscopic techniques of treatment, both the diameter and the number of fistulas were increased. In 2011, Varadarajulu et al. have first described multiple transluminal gateway technique based on the creation of multiple transmural tracts between the gastrointestinal lumen and the WOPN cavity [12]. The authors proved that the use of several (2-3) routes of access to pancreatic necrosis (MTGT) is a more effective method of treatment than single transluminal gateway technique [12]. Varadarajulu et al. achieved therapeutic success in 11/12 (91.7%) patients who underwent MTGT in comparison to 25/48 (52.1%) patients treated with SGT [12]. Three years later, Mukai et al. presented the technique that enables access to extensive necrotic areas through a single fistula (SGTMD) without the need to create an additional transmural route [9]. Mukai et al. observed a good therapeutic effect in all of 5 patients (100%). In the same report, the authors showed therapeutic success in all of 9 patients (100%) with WOPN that were treated with the use of MTGT [9].

The presented evolution of endoscopic techniques has significantly increased the efficiency of transmural drainage. In our center, the development of endoscopic methods allowed us to replace percutaneous drainage in patients with ineffective single transmural drainage with MTGT in 4/93 (4.3%) patients or SGTMD in 22/93 (23.66%) patients depending on the extent of necrosis. The use of these techniques in combination with endoscopic necrosectomy improved the effectiveness of WOPN treatment up to 100%.

In 2015, Mukai et al. published a report that showed a good therapeutic effect of various endoscopic techniques in 86/89 (96.6%) patients with WOPN and their complication rate was 12.4% (11/89 patients) [23]. In our study, the treatment success was achieved in 99/101 (98.02%) patients with a complication rate of 15.84% (16/101).

Endoscopic treatment is an alternative for other minimally invasive techniques for the treatment of WOPN, especially for percutaneous drainage. Presented results of endoscopic treatment of patients with WOPN provoke the discussion about the therapeutic strategy in this group of patients. On the basis of our own experience shown in this publication, it seems that the use of percutaneous drainage and other minimally invasive techniques with percutaneous access as the first stage of treatment could be effectively replaced with endoscopic transmural drainage. In a large group of patients with WOPN, endotherapy can remain the only method of treatment. Our study proved that SGT was an effective method of management in half (50.54%) of patients with symptomatic WOPN. In the case of extensive necrotic areas adjacent to the gastrointestinal tract, the creation of additional transmural access is efficient (MTGT). When the excessive distance between the gastrointestinal wall and the necrotic collection hinders the formation of another transmural tract, a good therapeutic effect can be achieved by additional drainage of extensive necrosis through a single fistula (SGTMD). In a selected group of patients, endoscopic necrosectomy combined with active transmural drainage improves the results of treatment. Transpapillary drainage remains an effective method of treatment in patients without transmural access to necrotic collection that is communicating with the main pancreatic duct.

The choice of an access route to WOPN should depend on the extent of necrosis and the experience of a medical center [1, 3, 19]. Comparing the results of treatment presented in this report with the publication originating from our center concerning 112 patients with WOPN who underwent conventional drainage [7], we conclude that with the increase of experience in the field of drainage procedures there is an improvement in the efficiency and safety of therapy.

The main limitations of our study are lack of randomization, retrospective character, relatively short follow-up, and highly selected group of patients from a single center. Although our report presents the experience of one center, we consider the fact that all endoscopic procedures were conducted by one endoscopist to be its advantage, which allows a reliable comparison of the endoscopic treatment results over the years. Recently, there have been many publications confirming the efficiency of self-expandable metal stents (SEMS) in the transmural drainage of pancreatic fluid collections [24, 25]. In our study, plastic transmural stents were used for all patients. The use of SEMS in our work could have reduced the duration of treatment and the number of endoscopic procedures.

Summing up, our report presents the evolution of various endoscopic techniques and their use in the management of WOPN. In our center, the development of transmural endoscopic methods of treatment has significantly reduced the use of other minimally invasive techniques, particularly percutaneous drainage. We have shown that the endoscopic treatment of patients with WOPN is an effective method with an acceptable number of complications.

The application of new endoscopic techniques in the treatment of the patients with symptomatic WOPN significantly improves the efficiency of endotherapy with an acceptable amount of complications. The development of endoscopic methods of treatment for WOPN has significantly reduced the use of other minimally invasive techniques.

Conflicts of Interest

Mateusz Jagielski, Marian Smoczyński, Anna Jabłońska, and Krystian Adrych have no conflicts of interest or financial ties to disclose.

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Clinical Study

A Retrospective Analysis of Cyanoacrylate Injection versus Hemoclip Placement for Bleeding Dieulafoy's Lesion in Duodenum

Yu Jiang,[1] Julong Hu,[1] Ping Li,[1] Wen Jiang,[2] Wenyan Liang,[3] and Hongshan Wei[1]

[1]*Department of Gastroenterology, Beijing Ditan Hospital, Capital Medical University, No. 8 Jingshun East St., Chaoyang District, Beijing 100015, China*
[2]*The Endoscopy Center, Huangshan Shoukang Hospital, Meilin Rd. Economic & Technological Development Zone, Huangshan, Anhui Province 245000, China*
[3]*Department of Gastroenterology, Huairou Hospital, Qingchun Rd., Huairou, Beijing 101400, China*

Correspondence should be addressed to Hongshan Wei; drwei@ccmu.edu.cn

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Background. Duodenal Dieulafoy's lesion (DL) is a rare disease that may lead to lethal hemorrhage in the upper gastrointestinal tract. The best technique for endoscopic intervention still remains unclear. In the present study, we performed a retrospective analysis of cyanoacrylate injection versus hemoclip placement for treating bleeding DLs. *Materials and Methods*. We retrospectively analyzed eighteen patients from three medical centers between October 2008 and February 2016; six patients received cyanoacrylate injection, while hemoclips were placed in 12 patients during the upper gastrointestinal endoscopy. *Results*. All patients received first endoscopic examination and/or endotherapy within 12 hours of admission to hospital. No difference was observed in the primary hemostasis rate or the recurrent hemorrhage rate between the cyanoacrylate injection (CI) group and the hemoclip placement (HP) group, except that in one patient from the HP group melena was found three days after the first endotherapy. This patient received cyanoacrylate injection once again. *Conclusion*. Both cyanoacrylate injection and hemoclip placement are effective in treating duodenal DL, and neither of them causes significant side effects.

1. Introduction

First described in 1898 by Dieulafoy, DL was identified in two patients with fatal upper gastrointestinal hemorrhage without ulceration. The incidence of this disease is rare; nonetheless, it can result in serious gastrointestinal bleeding [1]. In most patients, it is presented as melena, hematemesis, and hematochezia, and it accounts for 1–5.8% cases of acute upper GI bleeding [2]. With the advances in endoscopic techniques, the mortality of DL patients has been reduced from 80% to 8%, and surgical intervention is only considered in cases of failed endotherapy [3].

At the beginning of this century, the first perspective randomized-controlled study demonstrated that hemoclip and band ligation are equally effective compared to injection therapy for DL bleeding [4]. The overall hemostasis rate in hemoclip therapy has been shown to be up to 95% [5], but the ratio of emergent surgery is still above 5%, according to a recent multicenter report [6]. Furthermore, currently, there are no cohort studies on the effectiveness of cyanoacrylate injection for the treatment of duodenal DLs, since most of DLs are located in a proximal stomach. The best technique for endoscopic intervention in DL is still not clear [3]. In the present study, we performed a retrospective analysis of cyanoacrylate injection versus hemoclip placement for treating bleeding DLs in the duodenum.

2. Patients and Methods

2.1. Study Design. The present study was a retrospective cohort analysis. The study protocol was approved by the Ethics Board of Beijing Ditan Hospital, Capital Medical

University. Between October 2008 and February 2016, a total of 18 DL patients from three medical centers were enrolled in the study. All the patients received endoscopy within 12 hours of hospitalization and were diagnosed with duodenal DLs. The last follow-up was 3 months after the endoscopy treatment.

2.2. Patients. The diagnosis of duodenal DL was based on recently reported criteria [7, 8] including (i) active arterial spurting or bleeding from minute defect (<3 mm); (ii) a protruding vessel within nearly normal mucosa; and (iii) a fresh, densely adherent clot within the normal-appearing mucosa. The patients' age, sex, blood pressure, hemoglobin, prothrombin time (PT), concurrent disease, location, the type of bleeding stigmata, and final outcomes were analyzed. Primary outcomes, including the primary hemostasis rate and rebleeding rate, were compared between the two groups. The secondary outcomes such as the number of endoscopic sessions, need for emergent surgery or transcatheter arterial embolization, bleeding-related deaths, transfusion requirements, hospitalization period, and survival time information were also retrospectively compared between the two groups.

2.3. Endoscopic Therapy. Data were collected according to following criteria: (i) endoscopic treatments were performed by gastroenterologists with at least 3 years of endoscopic experience; (ii) patients received endoscopic examination within 12 hours of hospitalization; (iii) duodenal DL diagnosis was confirmed by endoscopy; (iv) after being diagnosed, the patient received either cyanoacrylate injection (CI group) or hemoclip placement (HP group); and (v) 3–10 days after the endoscopic treatment, patients received the first endoscopic follow-up, and after 1–3 months, they received the second endoscopic follow-up. For evaluating the efficacy of endoscopy, primary hemostasis and recurrent bleeding were determined based on previous reports [8]. The following apparatus/materials were used for endotherapy: GIF-260J or GIF-260 (Olympus, Japan); Sclerotherapy Needle and Interject™ Injection Therapy Needle Catheter (Boston Scientific, USA); Resolution™ Clip Hemoclip (Boston Scientific, USA); and N-butyl-2-cyanoacrylate 0.5 mL (Braun, German).

2.4. Statistical Analysis. GraphPad Prism 5.01 software was used for the statistical analysis. For comparing the differences in qualitative data between the two groups, chi-squared test or Fisher's exact test was performed. Student's *t*-test was used for comparing the mean differences between the two groups. $P < 0.05$ was considered statistically significant.

3. Results

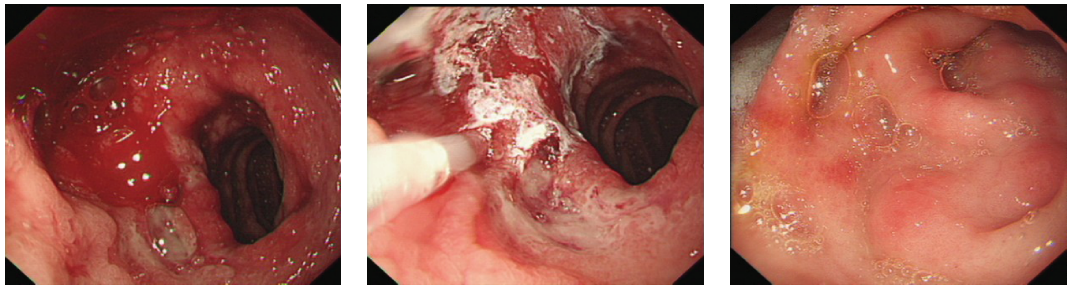
3.1. Demographic Data. A total of 18 duodenal DL patients from three medical centers met the inclusion criteria. Patient's demographic data are shown in Table 1. The major manifestation was melena (61.11%), hematochezia (22.22%), and hematemesis and melena (16.67%). Comorbidities of duodenal DL were observed in 12 patients (66.67%), including hypertension in 2 patients (11.11%), diabetes mellitus in 3 patients (16.67%), hepatic cirrhosis in 4 patients (22.22%), fat liver in 2 patients (11.11%), cholelithiasis in 1 patient (5.56%), arteriosclerosis in 3 patients (16.67%), and hyperlipoidemia in 2 patients (11.11%). The compensated shock was observed in three patients (16.67%). No significant difference was observed between the two groups with regard to age, sex, hemoglobin and PLT levels, and comorbidities (Table 1).

Table 1: Clinical characteristics of patients in the cyanoacrylate injection and hemoclip placement groups.

	CI ($n = 6$)	HP ($n = 12$)	P value
Age (years)	51.50 ± 7.29	44.58 ± 12.14	0.221
Blood pressure (mmHg)	109.8 ± 32.73	104.3 ± 14.37	0.616
Hemoglobin level (g/dL)	86.43 ± 30.15	88.30 ± 37.21	0.917
Platelet	177.0 ± 52.21	213.8 ± 104.9	0.434
Prothrombin time	13.93 ± 2.34	13.25 ± 2.45	0.579
Concurrent disease	4	8	1.00
Endoscopic characteristic			1.00
Active hemorrhage	2	8	
Protruding vessel without active hemorrhage	3	3	
Blood clot	1	1	
Location			0.344
Duodenum			
Duodenal bulb	3	9	
Descendant duodenum	3	3	

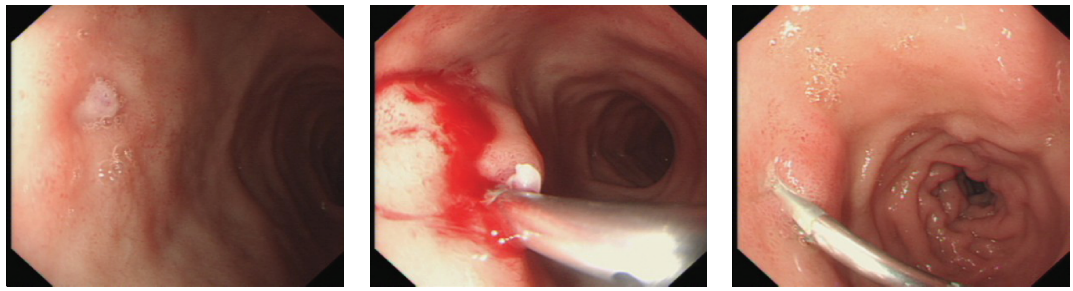
3.2. Endotherapy. All endotherapies at three medical centers were performed with standard upper endoscopes by experienced gastroenterologists. Based on the present data, the use of hemoclips or cyanoacrylate injection usually depends on the preference of endoscopists; two patients with active bleeding received cyanoacrylate injection in the CI group (Table 1, Figure 1). In the HP group, there were 12 patients (Figure 2), and totally, 16 hemoclips were used; 8 patients had active bleeding, 3 patients had a protruding vessel, and one patient had a clot (Table 1, Figure 2). In addition to 6 patients from the CI group, 4.5 mL (0.5 mL × 9) was used in total. None of the patients needed surgery or any other additional treatment. There were no marked side effects after our endoscopic treatment, except that one patient in the CI group developed mild ulcer at the injection site and completely recovered after rabeprazole therapy.

3.3. Hemostasis Rate and Rebleeding Rate. All patients received first endoscopic examination and/or endotherapy within 12 hours after being admitted into these medical centers. To observe the effects of CI and HP to duodenal DL, we compared primary hemostasis and recurrent hemorrhage between the two groups. As shown in Table 2, no differences were observed between the CI and the HP groups in primary hemostasis or recurrent hemorrhage, except for 1 patient from the HP group, who had melena reoccur three days after the first endotherapy; thus, cyanoacrylate injection was



(a) (b) (c)

Figure 1: A male (58 years old) duodenal DL patient received cyanoacrylate injection during upper endoscopy. (a) An active bleeding was observed on the descending part of the duodenum. (b) Cyanoacrylate injection. (c) One month after endotherapy.



(a) (b) (c)

Figure 2: A male (28 years old) duodenal DL patient received hemoclip placement during upper endoscopy. (a) A protruding vessel 1 month post endoscopy, without active hemorrhage on the superior part of the duodenum. (b) Hemoclip placement. (c) 10 days after endotherapy.

Table 2: Clinical outcomes of cyanoacrylate injection and hemoclip placement on Dieulafoy's lesions.

	CI ($n = 6$)	HP ($n = 12$)	P value
Primary hemostasis	6	11	1.00
Recurrent hemorrhage	0	1	
Transfusion (mL)	$N = 2$, total 4 IU	$N = 1$, total 1 IU	
Hospital stay (days)	9.833 ± 1.11	9.333 ± 1.45	0.824

performed once again. The clinical outcome was summarized in Table 2.

4. Discussion

Before the 1980s, a surgical approach was the only definitive treatment for DL patients failed by drugs, and the effectiveness of angiographic embolization was usually disappointing [9]. During that time, a surgical operation was considered the only life-saving option [10]. In the late 1980s, endoscopic electrocoagulation was first used for controlling hemorrhage in DL patients, and a selective arterial embolization was the alternative treatment used for failed endoscopic therapy [11]. After that, other endoscopic therapies have been used in clinical DL treatment as well, including epinephrine injection, heater probe technique, bipolar electrocoagulation, and Nd:YAG laser photocoagulation [12]. During the late 1990s, clipping and ethanol injection or sclerotherapy was introduced into the treatment of DL bleeding [13, 14]. However, subsequent retrospective analysis has suggested that endoscopic thermal coagulation should be the first choice of initial treatment for DL hemorrhage [15]. Hemoclip [16, 17] and band ligation [18] have also gradually become commonly used therapies for DL treatment [19, 20].

Since most of DLs are located in the stomach [21, 22], there are almost no reports on the methods of duodenal DL treatment before the 1990s. In 1990, Goldenberg et al. have reported that a patient with duodenal DL was successfully treated with endoscopic injection of epinephrine and electrocoagulation [23]. Several years later, Hokama et al. have combined endoscopic clipping and ethanol injection in treating duodenal DL [24]. At the beginning of this century, endoscopic band ligation also became widely used for treating duodenal DL [25]. Nevertheless, further controlled studies are needed to evaluate the different methods or combined therapies. Recently, the first clinical controlled study about endotherapy of duodenal DL treatment has been published [26], showing that endoscopic band ligation and hemoclip placement are equally effective in duodenal DL treatment.

Cyanoacrylate injection has been used to treat hemorrhage of esophageal varices since the late 1970s [27]. This technique is a standard method to control varix bleeding in cirrhotic patients worldwide [28, 29]. However, there has been no clinical evaluation of its effectiveness in treating

duodenal DL, except for a recent case report [30]. In the present study, we retrospectively analyzed the effectiveness of cyanoacrylate injection versus hemoclip placement in duodenal DL treatment. Based on our observation, there was no difference in effectiveness between the CI and the HP groups. In all of our cases, hemorrhage was completely controlled after cyanoacrylate injection. Moreover, no noticeable side effects were observed in either group. It seems that 0.5 mL cyanoacrylate (usual dosage per patient) was more expensive than one hemoclip.

The major limitation of the present retrospective study was patient grouping. Only six patients received cyanoacrylate injection, and eight patients with active bleeding received hemoclip placement. It seems that the patient grouping (with or without active bleeding) may lead to a selection bias. As a new method, cyanoacrylate injection was mainly used to control active hemorrhage, such as varix bleeding. More importantly, compared with other endoscopic hemostatic methods in a recent meta-analysis report, cyanoacrylate injection is associated with increased likelihood of hemostasis of active bleeding [31]. Moreover, according to a recent study, there is no difference in the hemostasis rate in acute nonvariceal upper gastrointestinal bleeding between cyanoacrylate injection and hemoclip placement [32]. In the present study, the data indicated that the patient grouping did not lead to significant clinical bias in the hemostasis rate.

In conclusion, both CI and HP are effective approaches for treating duodenal DL. CI has a higher hemostasis rate without significant side effects. Further large sample size and prospective randomized trials are necessary to evaluate the efficacy and safety of duodenal DL treatments.

Abbreviations

DL: Dieulafoy's lesion.

Conflicts of Interest

Drs. Yu Jiang, Julong Hu, Ping Li, Wen Jiang, Wenyan Liang, and Hongshan Wei have no conflicts of interest or financial ties to disclose.

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Review Article

Mechanisms and Management of Acute Pancreatitis

Ari Garber,[1] Catherine Frakes,[2] Zubin Arora,[1] and Prabhleen Chahal[1]

[1]*Department of Gastroenterology and Hepatology, Digestive Disease Institute, Cleveland Clinic Foundation, Cleveland, OH, USA*
[2]*Department of Internal Medicine, Medicine Institute, Cleveland Clinic Foundation, Cleveland, OH, USA*

Correspondence should be addressed to Prabhleen Chahal; chahalp@ccf.org

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Acute pancreatitis represents a disorder characterized by acute necroinflammatory changes of the pancreas and is histologically characterized by acinar cell destruction. Diagnosed clinically with the Revised Atlanta Criteria, and with alcohol and cholelithiasis/choledocholithiasis as the two most prominent antecedents, acute pancreatitis ranks first amongst gastrointestinal diagnoses requiring admission and 21st amongst all diagnoses requiring hospitalization with estimated costs approximating 2.6 billion dollars annually. Complications arising from acute pancreatitis follow a progression from pancreatic/peripancreatic fluid collections to pseudocysts and from pancreatic/peripancreatic necrosis to walled-off necrosis that typically occur over the course of a 4-week interval. Treatment relies heavily on fluid resuscitation and nutrition with advanced endoscopic techniques and cholecystectomy utilized in the setting of gallstone pancreatitis. When necessity dictates a drainage procedure (persistent abdominal pain, gastric or duodenal outlet obstruction, biliary obstruction, and infection), an endoscopic ultrasound with advanced endoscopic techniques and technology rather than surgical intervention is increasingly being utilized to manage symptomatic pseudocysts and walled-off pancreatic necrosis by performing a cystogastrostomy.

1. Introduction

Acute pancreatitis (AP), simply defined, represents a disorder characterized by acute necroinflammatory changes of the pancreas. The purpose of this review is to explore the historical, epidemiologic, histologic, and pathologic mechanisms underpinning the disease and the current evidenced-based management algorithms.

2. Historical Perspective

From the Greek roots "pan" (all) and "kreas" (flesh or meat), the term "pancreas" was first coined by Ruphos of Ephesus (c. 100 CE), to describe an organ that had no cartilage or bone. Despite its early roots, it was not until much later that the first clinical description of acute pancreatitis by Nicholaes Tulp (1593–1674), a Dutch anatomist, was published [1]. However, amidst much speculation of causality, the first systematic assessment of acute pancreatitis was authored by Reginald Fitz (1843–1913) in his entitled review "Acute Pancreatitis: A Consideration of Hemorrhage, Hemorrhagic, Suppurative, and Gangrenous Pancreatitis, and of Disseminated Fat Necrosis," highlighting alcohol, gallstones, and other etiologic factors. Claude Bernard (1813–1878) is credited as one of the early pioneers of pancreatic physiology, identifying pancreatic juice's capability of converting starch into sugar and emulsifying lipids into their constituents. Further classification, prognostication, and understanding of the pathogenic mechanisms have led to the burgeoning field of pancreatology, and the management of this complex pancreatic disease is the subject of this review.

3. Epidemiology

Acute pancreatitis is the number one gastrointestinal diagnosis prompting inpatient admission and ranks 21st on the list of all diagnoses requiring hospitalization. The incidence of acute pancreatitis ranges from 13 to 45/100,000 with equal affinity for each gender (though with differing etiologies) [2]. Acute pancreatitis secondary to alcohol is more common in men, whereas gallstone pancreatitis is more common in women and appears to affect African Americans disproportionately for unclear reasons. In 2009, the Healthcare Cost and Utilization Project National Inpatient Sample identified 274,119 individuals discharged from the hospital with acute

pancreatitis, representing a 30% increase from 2000 and necessitating a median length of stay of 4 days. Acute pancreatitis contributed to, and/or was responsible for, 8653 deaths in 2009, representing an underlying cause of death rate of 1 per 100,000 and ranking it as the 14th leading cause of gastrointestinal death with a cost of 2.6 billion dollars in inpatient expenses [3].

4. Embryology, Anatomy, Histology

Embryologically, the pancreas is an endodermal structure that is the product of the fusion of the ventral and dorsal pancreas at approximately 8 weeks' gestation. The celiac artery (via the superior pancreaticoduodenal artery) and the superior mesenteric artery (via the inferior pancreaticoduodenal artery) provide the arterial blood supply to the pancreas. Venous drainage of the pancreas occurs through the splenic and superior mesenteric veins, which drain into the portal vein.

The functional pancreas itself is divided into endocrine and exocrine components. The exocrine pancreas (comprised of acinar cells and ductal tissue) represents approximately 85% of pancreatic tissue and is responsible for zymogen and bicarbonate secretion into the duodenum [4]. The endocrine pancreas (comprised of the islets of Langerhans, itself comprised of alpha, beta, and delta cells) is responsible for hormonal secretion (glucagon, insulin, and somatostatin, resp.) into the general circulation.

Acinar cell destruction is the histologic hallmark of acute pancreatitis, a consequence of autodigestion secondary to zymogen activation. It is believed that premature activation of trypsin is the inciting event leading to the inflammatory cascade culminating in acute pancreatitis [5].

Histologically, three patterns of acute pancreatitis have been recognized. Type 1 necrosis (the predominant histologic form) refers to necrosis principally affecting perilobular, interlobular, or peripancreatic fatty tissue. Type 2 necrosis shows a predominant ductal involvement of necrosis. Type 3 necrosis involves only the acinar cell itself [6].

5. Diagnosis

The Revised Atlanta Criteria of 2012 (updated from 1992) requires two of three conditions be met to diagnose acute pancreatitis: (1) abdominal pain consistent with acute pancreatitis (i.e., epigastric abdominal pain with possible radiation to the back), (2) lipase or amylase ≥ 3 times the upper limit of normal, and or (3) characteristic imaging features of acute pancreatitis as noted on CT, MRI, or ultrasound [7]. However, imaging of the pancreas is recommended only in patients whom the diagnosis is unclear, for those who fail to improve within the first 48–72 hours, or to assess for complications (described below) [8]. Onset (time zero) refers to the timing of when abdominal pain began, not hospital admission.

Acute pancreatitis is further classified into two separate categories: interstitial edematous (Figure 1, where the pancreas shows evidence of diffuse enlargement and enhancement due to inflammatory edema without evidence of necrosis) and necrotizing (Figure 2, where cell death of the pancreatic and or peripancreatic tissue is observed). The latter occurs in approximately 5–10% of cases of acute pancreatitis [7]. Necrotizing pancreatitis is further subclassified into sterile or infected.

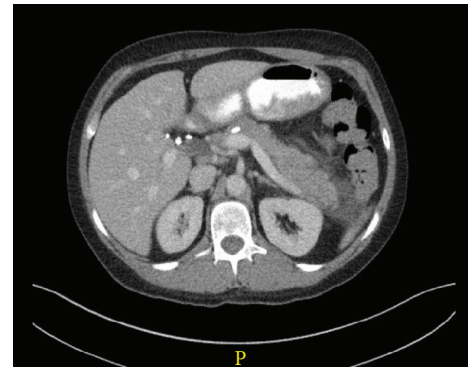

Figure 1

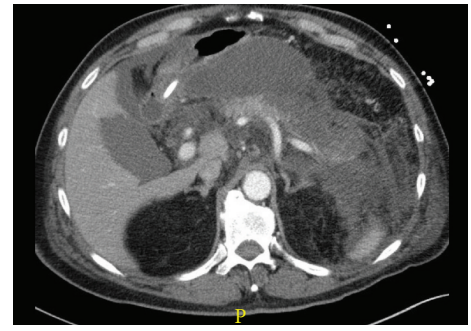

Figure 2

6. Etiology

The two most common causes of acute pancreatitis are cholelithiasis/choledocholithiasis and alcohol (definitions vary as does duration with consumption between 50 and 80 grams or 4–7 drinks/day) with frequency estimates of 40% and 30%, respectively. The other etiologies are hypertriglyceridemia (typically >1000 mg/dL), medications, trauma, infections, iatrogenesis (surgical or post-ERCP), genes, anatomy (pancreatic divisum, sphincter of Oddi dysfunction which remain controversial), and autoimmunity [9]. What follows is a discussion of a few of these important etiologies.

Medications thought to induce acute pancreatitis have been classified on the level of evidence to support the association. Class I medications are defined as those where recurrence of acute pancreatitis was confirmed upon rechallenging. Class I is further subdivided into 1a (other causes of pancreatitis ruled out) and 1b (alternative etiologies not ruled out). Class II medications do not meet strict criteria for class 1 but exhibit a consistent latency period in a preponderance of reported cases. Class III and IV medications refer to those in which two or one published case report of medication-induced pancreatitis has been reported, respectively. Some common Class 1a and 1b medications include amiodarone, all-*trans*-retinoic acid (ATRA), 6-MP/azathioprine, dexamethasone, enalapril, furosemide, hydrocortisone, isoniazid,

losartan, mesalamine, metronidazole, methyldopa, omeprazole, pravastatin, simvastatin, trimethoprim-sulfamethoxazole, tetracycline, and valproic acid [10].

Mutations, upregulation, and genetic variants in several genes have been implicated in acute pancreatitis, namely, the trypsinogen gene (PRSS1) and trypsin inhibitor (SPINK1), cystic fibrosis transmembrane regulator (CFTR) variants, and endothelial ion/water channel CLDN2 risk allele [5].

The exact pathologic mechanism by which gallstones cause pancreatitis remains unclear though it is hypothesized that either choledocholiths (typically stones < 5 mm) impinge on the adjacent pancreatic duct or lodge in the ampulla causing increased pressure, reflux of pancreaticobiliary secretions, and acinar cell secretion into the interstitium leading to the inflammatory cascade [11].

Post-ERCP pancreatitis estimates range from 1.6% to 15.7%, and a meta-analysis of 21 studies found an incidence of approximately 3.5% [12, 13]. Freeman identified young age, biliary sphincter balloon dilation in intact papilla, pancreatic duct contrast injection, normal bilirubin, precut sphincterotomy or pancreatic sphincterotomy, and suspected sphincter of Oddi dysfunction as risk factors for post-ERCP pancreatitis [14].

Autoimmune pancreatitis is a predominantly lymphocytic inflammatory process that results in eventual organ fibrosis and dysfunction. While many diagnostic criteria have been promulgated, the modified Japan Pancreas Society Criteria require a combination of typical imaging (CT, MRCP, or ERCP) and either serology (IgG4 or IgG totals, etc.) or pancreaticobiliary/extraintestinal findings (sialadenitis, nephritis, or IgG4 pneumonitis) for diagnosis [15].

7. Complications

Two known local complications of pancreatitis are pseudocysts and walled-off necrosis. Both are walled-off encapsulated collections that usually mature 4 weeks after the initial acute pancreatitis episode. The difference lies in the fact that a pseudocyst has a homogenous fluid density whereas walled-off necrosis describes both fluid and nonfluid heterogeneous components which represent necrotic debris with or without loculation [7]. Pseudocysts are the product of pancreatic/peripancreatic fluid collections, whereas walled-off necrosis is the product of initial pancreatic/peripancreatic necrosis.

Organ failure in acute pancreatitis is defined by the modified Marshall score, which assesses the degree of dysfunction in three organ systems (cardiovascular, renal, and pulmonary). Each organ system is scored on a scale of 0–4, and any organ that is scored as 2 or above meets criteria for organ failure. The cardiovascular, pulmonary, and renal systems receive a score greater than 2 when the following are identified (resp.): systolic blood pressure is <90 mmHg and not responsive to fluids, PaO_2/FiO_2 ratio of 201–300, and serum creatinine 1.9–3.6 mg/dL. [16].

8. Severity

Mortality in the setting of acute pancreatitis has been estimated at 5%, though when stratified into interstitial versus necrotizing (3% versus 17%), and in the necrotizing subset, infected versus sterile (30% versus 12%), the range is quite variable [17]. Several models have been promulgated to predict the initial severity of the acute pancreatitis episode with the most common indices described below.

The well-recognized Ranson criteria is one of the earliest predictive models, but is difficult to utilize in clinical practice. It requires 5 parameters on admission and 6 parameters after 48 hours of hospitalization. A meta-analysis of 110 studies showed that it was a poor predictor of severity, with a high false positive rate [18].

The Acute Physiology and Chronic Health Examination (APACHE) II score comprises 12 physiologic measures (Glasgow coma scale, leukocyte count, hematocrit, creatinine, potassium, sodium, pH/HCO_3, respiratory rate, arterial-alveolar gradient, heart rate, mean arterial pressure, and temperature) and extra points for age and chronic diagnoses. Scores less than 8 on admission and at 72 hours portend a mortality less than 4% with risk increasing to 11–18% with scores > 8 [17].

The systemic inflammatory response syndrome (SIRS criteria), a scoring system that assigns a point to the presence of various thresholds in temperature, respiratory rate, leukocyte count, and heart rate (and considered present when two or more criteria are met), has been used to predict pancreatitis severity, with SIRS presence on the day of admission indicating increased risk of severe disease [19].

The bedside index of severity in acute pancreatitis (BISAP) score uses a one point scoring system with each component of the indexes: BUN > 25 mg/dL, altered mental status, SIRS (as described above), age > 60, and the presence of pleural effusions with mortality ranging from <1% (BISAP = 0) to 22% (BISAP = 5) [20].

9. Treatment

The management of acute pancreatitis depends on the severity of disease and the concomitant complications that may arise. Our discussion begins with uncomplicated disease and then expands to more complex clinical scenarios.

9.1. Fluid Resuscitation. The disease process leads to acinar cell injury and the consequent proinflammatory cytokine cascade leads to microvascular permeability, interstitial edema, vasoconstriction, and eventual decreased capillary perfusion in animal models. Pancreatitis also causes hypovolemia by inducing poor oral intake, insensible losses, third-spacing of fluids, and emesis. Therefore, fluid resuscitation has become the cornerstone of conservative treatment [21]. In the absence of cardiac, pulmonary, or renal contraindications, various recommendations on the initial fluid resuscitation regimen have varied from 250–500 cc/hr with or without bolus to achieve hemodynamic stability, targeting a mean arterial pressure > 60 or simply targeting a urine output > 0.5 cc/kg/hr [22–25]. While no specific targets are currently recommended, hemodilution (decreased hematocrit), reduced uremia (indicating adequate kidney perfusion), and normalization or maintenance of normal creatinine have

been proposed. A practical, evidence-based approach to fluid resuscitation is needed [26–28].

With respect to timing, early resuscitation has been shown to decrease the risk of SIRS, ICU admission, organ failure, and length of stay. Even though the exact duration of aggressive hydration remains unclear, the first 24 hours appear to be paramount [29, 30]. In addition, the type of fluid may make a difference as well. In a randomized controlled study performed by Wu and colleagues comparing the effectiveness of normal saline and lactated ringers in acute pancreatitis, the authors found a significant reduction in SIRS and CRP levels in those who received lactated ringers [28]. These findings, in conjunction with possible nonanion gap metabolic acidosis with normal saline make lactated Ringer's solution preferable. Thus, we utilize a total infusion of 2500–4000 mL in the first 24 hours while reassessing noninvasive clinical targets and biochemical targets every 6–8 hours.

9.2. Nutrition. Current data supports early resumption of a low-fat solid diet with mild acute pancreatitis. While it does not lead to a shorter length of hospital stay or decreased 30-day readmission rate, a randomized trial evaluating the tolerance of a low fat solid meal versus a liquid diet showed no increased adverse events (pain/nausea necessitating cessation) and led to increased caloric intake [31]. Moreover, it appears that it is safe to initiate oral intake in mild acute pancreatitis on admission and that one does not have to wait for the pancreas to "cool down" per se [32]. Randomized controlled trial data of enteral versus parenteral nutrition in severe pancreatitis has shown a decreased incidence of pancreatic infectious complications such as infected necrosis, abscess, and multiorgan failure [32]. Enteral nutrition prevents bacterial translocation by maintaining the intestinal barrier. The benefit of initiating enteral nutrition does not appear to extend beyond 48 hours of admission, as no reduction in mortality, infectious complications, or multiorgan failure was recognized when initiated beyond that point [33].

The benefit of nasogastric versus nasojejunal feeds was evaluated in a randomized trial of 78 patients which showed that nasogastric feeding was not inferior to nasojejunal feeding with no difference in secondary endpoints such as pain, intestinal permeability (measured by lactulose/mannitol excretion), and endotoxemia (as measured by immunoglobulin core G and M endotoxins) [34]. Thus, we utilize nasojejunal feeds in those unable to tolerate oral feeding.

9.3. Role of Endoscopic Retrograde Cholangiopancreatography (ERCP). The role of ERCP in patients with AP is generally reserved for acute biliary pancreatitis secondary to choledocholithiasis. While many scoring systems and algorithms have been developed, the proposed strategy to assign risk of choledocholithiasis proposed by the American Society for Gastrointestinal Endoscopy is the most widely used. It stratifies predictors of choledocholithiasis into very strong (observed on US, cholangitis or total bilirubin > 4 mg/dL), strong (CBD > 6 mm with gallbladder in situ or total bilirubin between 1.8 and 4 mg/dL), and moderate (abnormal AST/ALT or alkaline phosphatase, clinical gallstone pancreatitis, or age > 55). When a patient has one very strong predictor or two strong predictors, the risk of choledocholithiasis is high. All other predictors are considered intermediate and no qualifying predictors is considered low risk [35, 36].

In patients with mild biliary pancreatitis with improving signs and symptoms, ERCP preceding cholecystectomy has limited value and may be harmful. In these cases, magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) can be used for diagnostic purposes [8].

Rectally administered indomethacin has been shown in a multicenter, randomized, placebo-controlled, double-blind clinical trial of 602 high risk patients to reduce the risk of postprocedural pancreatitis and the severity of pancreatitis in those who subsequently developed symptoms [37]. However, in a similar study of 449 predominantly average risk patients undergoing ERCP, no clinical benefit was observed and the study was stopped due to futility [38]. Thus, rectally administered indomethacin could be considered in high risk patients prior to ERCP, as it is easy to utilize, inexpensive, and safe.

9.4. Antibiotics. Antibiotic prophylaxis in the absence of suspected or confirmed infection is not recommended. Apart from imipenem, no decrease in pancreatic infection risk or mortality has been observed with prophylactic antibiotic use [39]. Further randomized trials utilizing prophylactic antibiotics have failed to show benefit [8]. In the setting of confirmed or suspected pancreatic infection (infected pseudocyst or necrosis), prompt use of regimens known to penetrate pancreatic necrosis are recommended (quinolones and metronidazole, or carbapenems).

9.5. Cholecystectomy. Cholecystectomy should be performed on initial hospitalization in patients with acute biliary pancreatitis. Systematic review of 9 studies involving 998 patients with mild biliary pancreatitis showed that early cholecystectomy in the setting of gallstone pancreatitis (i.e., during the index admission) reduced the incidence of recurrent admissions for repeat biliary-related events including pancreatitis, cholecystitis, and biliary colic. Early cholecystectomy was not associated with increased adverse events including mortality nor conversion from a laparoscopic procedure to an open procedure [40].

9.6. Management of Persistent Fluid Collections or Infected Necrosis. We intervene upon pancreatic fluid collection or infected necrosis only when there are significant symptoms present, including persistent abdominal pain, gastric outlet obstruction, fluid leakage due to disconnected pancreatic duct, and infection [41]. It is crucial to classify fluid collections as either pseudocyst or walled-off pancreatic necrosis because of the differences in prognosis and treatment. CT imaging can underestimate the existence of necrotic debris; therefore, MRI (Figure 3) and endoscopic ultrasound (EUS) (Figure 4) are better for assessment [41]. The management has changed from what historically was a surgical intervention to now less invasive approaches. The approach to managing these complications is discussed below.

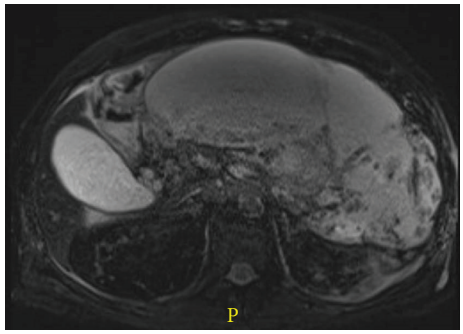

Figure 3

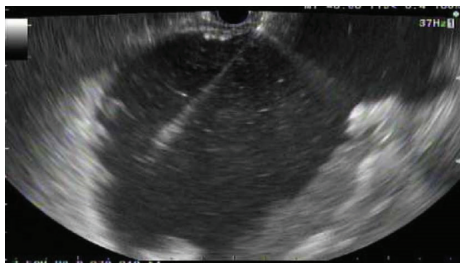

Figure 4

9.7. Open Surgical Drainage. Open necrosectomy is performed via laparotomy through a subcostal incision, where blunt removal of all necrotic tissue is done [42]. Early conservative management with late surgical intervention is superior to early necrosectomy [43]. Surgery is delayed preferably four weeks after onset of disease, as this is thought to allow for time for the acute necrotic collection to mature and demarcate, hereby facilitating necrosectomy [44]. In a recent randomized control trial, open necrosectomy had a high rate of complications or death (69%) [43]. Those undergoing open necrosectomy also had a higher rate of long-term complications, including incisional hernias (24%), new onset diabetes (38%), and use of pancreatic enzymes (33%). Therefore, therapy has shifted toward a minimally invasive "step-up" approach. This approach starts with more conservative techniques (percutaneous, laparoscopic, and endoscopic) first and then reserving surgery for cases of salvage therapy [43].

9.8. Minimally Invasive Techniques. There are several different types of noninvasive techniques to drain and debride persistent fluid collections or infected pancreatic necrosis, including image-guided percutaneous drainage, laparoscopy, and retroperitoneoscopy [45].

Using ultrasound or CT guidance, percutaneous drain placement allows for external access to the area of necrosis to be obtained [46]. A considerable number of patients can be treated with percutaneous drain (PCD) alone without the need for surgical necrosectomy [47]. The PANTER trial found that 35% of their patient population undergoing drainage did not need further surgery [43]. A systematic review by van Baal et al. showed that percutaneous drainage alone was successful in 56% of cases [47]. In the patients who did need surgery, drain placement delayed operative management for several weeks, by allowing for sepsis control [48]. Complications of percutaneous drain placement are pancreaticocutaneous and pancreaticoenteric fistulas (most common), as well as procedure-related complications (i.e., bleeding, colonic perforation, abdominal pain, pneumothorax, or catheter dislodgment) [47].

Transperitoneal laparoscopy is generally not supported because of the technical difficulty and risk of contamination of the peritoneal cavity [45].

Video-assisted retroperitoneal debridement (VARD) is an endoscopic necrosectomy performed over a dilated percutaneous drain tract. A 5 cm subcostal incision is made in the left flank, the necrosis is initially moved with grasping forceps, and the videoscope is inserted. Residual necrosis is removed with laparoscopic grasping forceps [49]. The PANTER trial assigned patients with pancreatic necrosis to either primary open necrosectomy or a step-up approach, where PCD drain was placed initially followed by minimally invasive retroperitoneal necrosectomy when needed. It showed that a minimally invasive step-up approach was associated with lower rate of major complications and death when compared to open necrosectomy [43].

9.9. Endoscopic Techniques in the Management of Persistent Fluid Collections or Infected Necrosis. Over the last two decades, endoscopic ultrasound- (EUS-) guided intervention of PFCs and infected necrosis has significantly evolved. There are multiple techniques for the drainage of PFCs including lumen-apposing metal stents (LAMS), direct endoscopic necrosectomy (DEN), and a double-pigtail plastic stent [41]. The TENSION trial is currently underway and will compare the surgical step-up approach versus an endoscopic step-up approach [50].

While there are no absolute size guidelines as to when to intervene, encapsulated areas less than 3 cm do not allow placement of a stent for drainage [51]. The necessity for a mature wall around a pseudocyst or walled-off pancreatic necrosis is imperative, as endoscopic cystogastrostomy can lead to free perforation in its absence. It is recommended that the luminal wall and the target cyst or walled-off necrosis lie within 10 mm of the gastrointestinal lumen as evaluated on an endoscopic ultrasound. This ensures technical success and allows the practitioner to assess for pseudoaneurysms and other vascular structures prior to intervention [51, 52]. Pseudocyst contents tend to be fluid and therefore one to two 7–10 Fr pigtail stents are often sufficient for drainage (unless multiple pseudocysts necessitate otherwise). On the other hand, walled-off necrosis often requires multiple stents (given the debris) or a large-caliber fully covered metal stent or lumen-opposing stents such as the Axios™ stent (Figure 5) [53]. Some centers manage WOPN with a hybrid technique involving percutaneous large caliber drain placement for irrigation and endoscopic cystogastrostomy creation working an egress route for irrigation and lavage. Given complications with surgical management approaching 24% with mortality rates reported around 5.8%, minimally invasive endoscopic techniques are considered optimal when expertise is readily available [54].

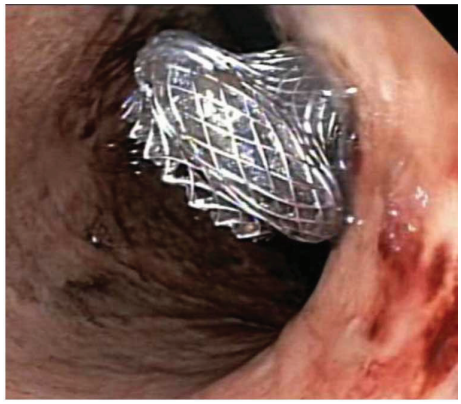

Figure 5

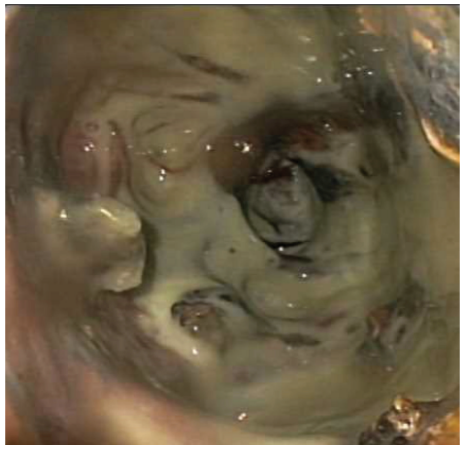

Figure 6

The technique of direct endoscopic necrosectomy (DEN) involves utilization of an endoscopic ultrasound to visualize the fluid collection with the subsequent fistulous tract made large enough to allow for the passage of the endoscope for debridement and visualization of walled-off pancreatic necrosis (Figure 6). Mechanical cleaning and removal of necrotic debris is then performed [55]. A retrospective analysis has shown that direct endoscopic debridement is feasible with initial success rates of 80% of patients and long-term clinical efficacy in 68% [56]. This endoscopic procedure was shown in one recent RCT to reduce the proinflammatory response (measured with IL-6 levels) and risk of procedure-related complication, in comparison to surgical necrosectomy [57]. Thus, minimally invasive management of complications of AP is presently the standard of care.

10. Conclusion

Acute pancreatitis remains a frequent cause of hospital admission necessitating a multipronged approach for the diagnosis and management. While its antecedents remain multifactorial, as are the number of scoring systems that define severity, treatment is predominantly geared toward supportive care with advanced endoscopic adjuncts (in the setting of choledocholithiasis, symptomatic pseudocysts, or walled-off pancreatic necrosis) and early surgical intervention (i.e., cholecystectomy in the setting of an index admission for gallstone pancreatitis) utilized when clinically indicated.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Clinical Study

Endoscopic Submucosal Tunnel Dissection for Large Gastric Neoplastic Lesions: A Case-Matched Controlled Study

Xiuxue Feng, Enqiang Linghu, Ningli Chai, Zhongsheng Lu, Xiangdong Wang, Ping Tang, Jiangyun Meng, Hong Du, and Hongbin Wang

Department of Gastroenterology, Chinese PLA General Hospital, Beijing 100853, China

Correspondence should be addressed to Enqiang Linghu; linghuenqiang@vip.sina.com

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Aim. To evaluate the efficacy and safety of endoscopic submucosal tunnel dissection (ESTD) for resection of large superficial gastric lesions (SGLs). *Methods.* The clinicopathological records of patients performed with ESTD or endoscopic submucosal dissection (ESD) for SGLs between January 2012 and January 2014 were retrospectively reviewed. 7 cases undergoing ESTD were enrolled to form the ESTD group. The cases were individually matched at a 1 : 1 ratio to other patients performed with ESD according to lesion location, ulcer or scar findings, resected specimen area, operation time and operators, and the matched cases constituting the ESD group. The treatment outcomes were compared between the two groups. *Results.* The mean specimen size was 46 mm. 10 lesions were located in the cardia and 4 lesions in the lesser curvature of the lower gastric body. En bloc resection was achieved for all lesions. The mean ESTD resection time was 69 minutes as against 87.7 minutes for the ESD ($P = 0.01$). The mean resection speed was faster for ESTD than for ESD (18.86 mm^2/min versus 13.76 mm^2/min, $P = 0.03$). There were no significant differences regarding the safety and curability during the endoscopic follow-up (mean 27 months). *Conclusions.* ESTD is effective and safe for the removal of SGLs and appears to be an optimal option for patients with large SGLs at suitable sites.

1. Introduction

The widespread use of gastroscopy and equipment innovations in endoscopic technology has increased the detection rate of superficial gastric lesions (SGLs) [1, 2]. Progress has improved the resectability of endoscopic techniques, thereby sparing patients from potentially major ablative surgery [3]. Meantime, as the acceptance of expanded indications of endoscopic resection, endoscopists have to face an increasing number of patients with large SGLs. Endoscopic submucosal dissection (ESD) has been established as one standard treatment for SGLs, providing a higher en bloc resection rate and more accurate pathological evaluation than endoscopic mucosal resection (EMR) [1, 2, 4]. Although ESD enables en bloc resection regardless of the lesion size, conventional ESD is time-consuming and poses high risk for large lesions. The main influencing factor in ESD operation for large lesions is poor visualization of the submucosal layer due to contraction or curling of the resected mucosa [5–17]. Therefore, how to lift the submucosal layer and dissect large lesions under direct vision becomes a very challenging problem.

Several traction methods for ESD have been investigated to overcome the problem, such as percutaneous traction [5], clip with line [6–8], clip-and-snare [9], external grasping forceps [10], internal traction [11, 12], suture-pulley [13], magnetic anchor [14], double-channel endoscope [15], double-endoscope [16], and robot-assisted method [17]. However, those traction methods need extra devices or equipment and may be invasive or difficult to control the pulley strength and direction or inconvenient to be operated. Therefore, ESD techniques remain to be further improved to establish the most ideal method for large lesions.

With the advent of the submucosal tunneling technique, endoscopic application has been expanded. In this technique, one submucosal tunnel is created to provide a working space for endoscopic interventions, including resection of gastrointestinal neoplastic lesions [3, 18–21] and submucosal tumors

[22, 23], myotomy for achalasia [24] and gastroparesis [25], and even to permit safer access to the peritoneal and thoracic cavity for related diagnosis and treatment [26, 27]. Endoscopic submucosal tunnel dissection (ESTD) secures a stable and good view for the dissection through the submucosal tunnel, which facilitates the lateral mucosal stretching, easy insufflation with air, and maintaining the effect of submucosal injection. Previous studies have shown that ESTD is quick and effective in the resection of large esophageal neoplastic lesions [19]. In porcine models, ESTD was proven to be feasible and safe for SGLs and provides a better quality histologic specimen than ESD [3]. Additionally, Choi et al. [18] reported that ESTD was feasible for two cases of ulcerative early gastric cancer. Based on the experience of ESTD for large esophageal neoplastic lesions and upper gastrointestinal submucosal tumors, we attempted ESTD to improve the efficacy and safety of ESD for large SGLs from 2012. The aim of this study was to evaluate the efficacy and safety of ESTD compared with conventional ESD for large SGLs based on a case-matched controlled analysis.

2. Methods

2.1. Patients. The study was reviewed and approved by the institutional review board of Chinese PLA General Hospital. The medical and endoscopic records of patients performed ESD with or without tunneling method in our institute for SGLs between January 2012 and January 2014 were retrospectively reviewed. To achieve accurate operation time, the patients with more than one lesions resected simultaneously were excluded. There were 8 cases who underwent ESD with the tunneling method, but one was excluded because of one submucosal tumor resected simultaneously in the same location. Then, the other 7 cases were enrolled to form the ESTD group. The cases were individually matched at a 1 : 1 ratio to other patients undergoing conventional ESD according to lesion location, ulcer or scar findings, resected specimen area ($\pm 100\,mm^2$), operation time (± 6 months) and operators, and the matched ones constituting the ESD group. When more than one control patient was matched, the patient with the date of endoscopic operation closest to the corresponding operation was selected. All of the patients signed the informed consent prior to the endoscopic therapy.

2.2. ESD and ESTD Procedures. All of the procedures in this study were performed under general anesthesia by 2 experienced operators, who had completed more than 100 ESD cases before January 2012. Magnified narrow-band imaging (M-NBI) and chromoendoscopy (using indigo carmine) were used to determine lesion area before the operation. The endoscopic equipment and accessories used in the operation included a single-accessory channel endoscope (GIF-Q260J; Olympus, Tokyo, Japan) with a transparent cap (D-201-11804; Olympus) attached to the front, a high-frequency generator (ICC-200; ERBE Elektromedizin, Tübingen, Germany), an argon plasma coagulation unit (APC 300; ERBE) for marking, an injection needle (INJ1-A1; Medwork, Höchstadt, Germany), a dual knife (KD-650L; Olympus) for cutting or circumferential incision or dissection, an insulated-tip (IT) knife (KD-611L; Olympus) or a hook knife (KD-620LR; Olympus) for circumferential incision or dissection or bilateral resection, and hot biopsy forceps (FD-410LR; Olympus) for hemostasis. Carbon dioxide insufflation was used during all the procedures. Normal saline with 0.1% methylene blue and 0.5% epinephrine was injected into the submucosal layer to elevate the lesion.

The ESD procedure was previously described in detail [8], namely, marking, submucosal injection, circumferential incision, and dissection. The comprehensive ESTD procedure was recorded in our published book [28], and the ESTD standard procedure was briefly presented as marking, submucosal injection, anal incision, oral incision, tunnel creation, and bilateral resection. For the lesions in the lower curve of the gastric body, the tunnel was created in retroflex approach from the anal to oral side. The two different procedures are shown in Figures 1 and 2. After complete removal of the lesion, the artificial ulcer was reassessed and visible vessels were routinely coagulated with hemostatic forceps or argon plasma coagulation. The resected specimen was immediately pinned flat to a rubber plate for measurement and imaging and then fixed into formalin for subsequent histopathological evaluation. Then, the specimen was sliced at 2 mm intervals. Each slice was processed for histopathological assessment of histological type, invasion depth, horizontal and vertical margins, and lymphovascular invasion.

2.3. Postoperative Treatment. After the operation, the patients were observed closely for complications, such as bleeding, perforation, and infection, and were given immediate treatment when necessary. In the absence of any complications, water intake was permitted on the second day, and the diet of the patients was changed gradually from clear liquid diet to semiliquid diet from the third day. Proton pump inhibitors were prescribed for 2 months and antibiotics for at least 3 days.

2.4. Outcomes and Definitions. To evaluate the safety and efficacy of ESTD, the following outcomes were analyzed between the two groups: resection time, size and area of the resected specimen, resection speed, en bloc resection rate, complete resection rate, recurrence rate, and rates of complications, including the muscularis propria (MP) damage, perforation, and postprocedural bleeding. The follow-up data were also analyzed to assess the curability of ESTD.

The macroscopic types and the depth of invasion were classified according to the Paris endoscopic classification of superficial neoplastic lesions [29]. The resection time was defined as the time from the start of cutting to the completion of the resection, including handling the ulcer. The resected specimen was measured directly after resection and imaged; the picture stored in the endoscopic database. The specimen size was defined as the maximum diameter. The specimen area was calculated as follows: area (mm^2) = major axis (mm) × minor axis (mm) × 3.14/4. The resection speed (mm^2/min) was calculated as the area of the resected specimen (mm^2) divided by the resection time (minutes). En bloc resection meant removal of the lesion in one piece. Complete resection was defined as the lesion was removed

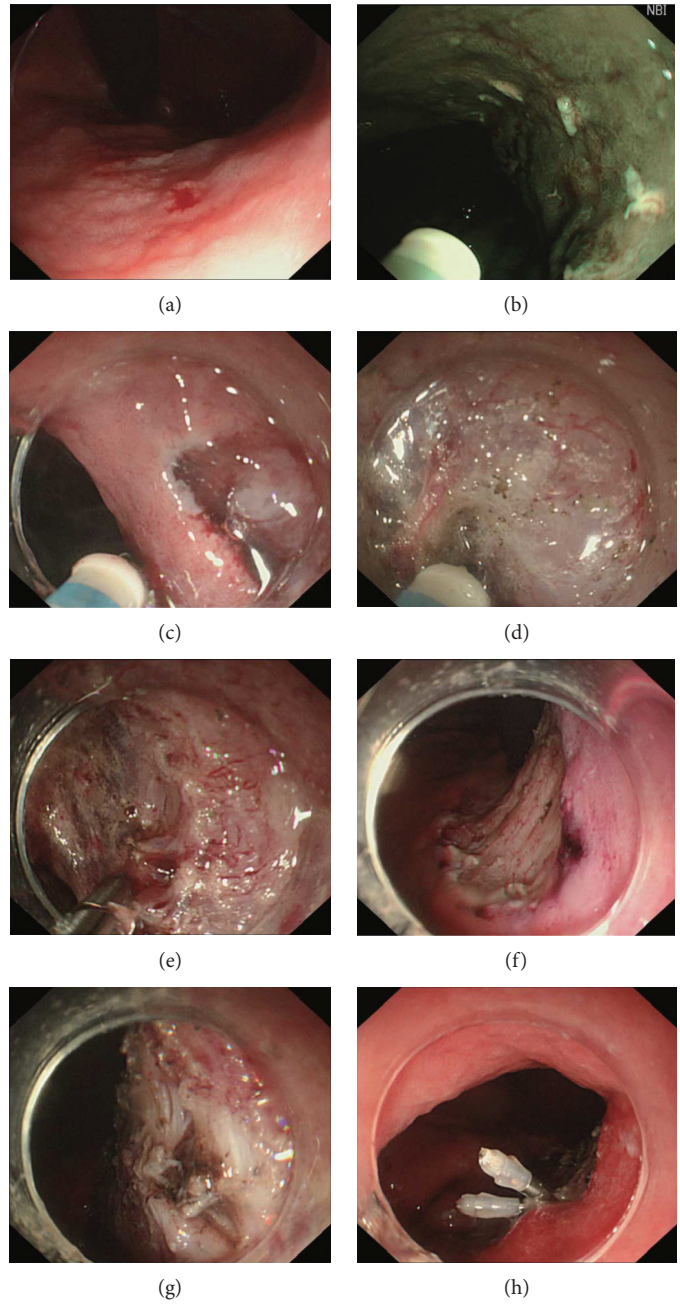


Figure 1: ESD procedure. (a) Lesion under light endoscopy. (b) Marking the margin. (c) Circumferential incision. (d) Submucosal dissection. (e) Hemostasis with hot biopsy forceps. (f) The artificial ulcer after complete removal of the lesion. (g) The muscularis propria damage. (h) The damage was closed with clips to prevent perforation.

as one piece with pathologically negative margins. Curative resection was considered when the lesion met the absolute and expanded indications [30]. After removal of the primary lesion, local recurrence was diagnosed when a similar or worse lesion was detected at the primary resection site after at least two negative follow-ups of endoscopic examination. A new lesion detected at a location different from the primary resected lesion within 12 months was defined as synchronous recurrence, and a new lesion detected at more than 12 months was regarded as metachronous recurrence [31]. MP damage meant the coagulation change of MP observed from the artificial ulcer after the procedure. Perforation was diagnosed if the extramural organ or tissue was visualized under endoscopy or if free air was observed on abdominal radiography or computed tomography [8]. Postprocedural bleeding was diagnosed when two of the four following parameters were satisfied after the procedure: (i) hematemesis, melena, or dizziness; (ii) a blood pressure decrease of >20 mmHg or a pulse rate increase of >20 times/min; (iii) decrease in the hemoglobin level of at least 2 g/dL; and (iv) endoscopic confirmation of bleeding from the artificial ulcer by presenting active bleeding, exposed vessels and/or fresh

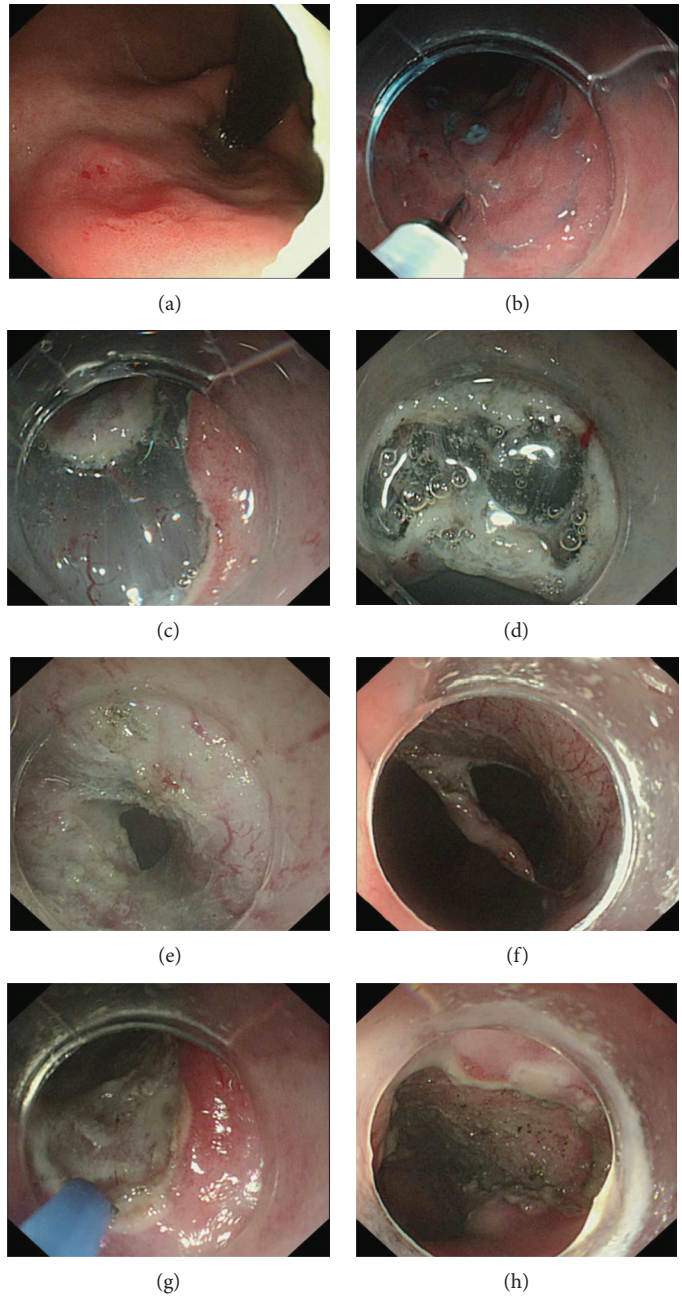


Figure 2: ESTD procedure. (a) Lesion under light endoscopy. (b) Marking the margin followed by submucosal injection. (c) Anal incision. (d) Oral incision. (e) One tunnel was established from oral to anal incision through submucosal dissection. (f) Bilateral resection. (g) Visible vessels were preventatively coagulated with APC. (h) The artificial ulcer after en bloc resection of the lesion.

clots that were not seen immediately after the operation or an evident increase in clots in the stomach compared observations during the operation [32].

2.5. Statistical Analysis. Quantitative data were presented as mean ± standard deviation (SD). Comparisons between the two groups were assessed using the paired sample *t*-tests for continuous variables and the chi-square or Fisher's exact test for categorical variables. The Wilcoxon signed-rank test was used when equal variances were not assumed. $P < 0.05$ was considered significant for all tests.

3. Results

The detailed baseline characteristics and treatment outcomes of the lesions in the ESTD and ESD groups are shown in Table 1. The mean specimen size was 46 mm (range 40–60 mm). 10 lesions were located in the cardia (6 mainly in lesser curvature and 4 mainly in the posterior wall) and 4 lesions in the lesser curvature of the lower gastric body. En bloc resection was achieved for all lesions. No differences in the baseline characteristics of the patients and lesions were found between the groups ($P > 0.05$), including all of the

Table 1: Baseline characteristics and treatment outcomes of the SGLs.

	ESTD ($n = 7$)	ESD ($n = 7$)	P value
Baseline characteristics			
Age (years)	63.3 ± 5.53	61.1 ± 6.96	0.59
Gender (male/female)	6/1	4/3	0.31
Lesion location			1.00
LC or PW of the cardia	5	5	
LC of lower gastric body	2	2	
Macroscopic type of lesions			0.61
0 – Is/0 – IIa/0 – IIa + IIc/0 – IIc	0/1/4/2	1/2/3/1	
Presence of ulcer/scar of lesions	0	0	1.00
Treatment outcomes			
Resection time (min)	69.0 ± 25.88	87.71 ± 28.61	0.01*
Specimen area (mm^2)	1181.99 ± 388.08	1166.29 ± 370.09	0.31
Resection speed (mm^2/min)	18.86 ± 7.13	13.76 ± 3.25	0.03*
En bloc resection	7	7	1.00
Complications			1.00
MP damage	0	1	
Perforation	0	0	
Postprocedural bleeding	0	0	
Pathology type			0.63
Precancerous lesion/cancer	3/4	2/5	
Complete resection	6	7	0.50
Curative resection	6	6	1.00
Endoscopic follow-up (months)	27.14 ± 16.31	27.57 ± 20.98	0.94
Recurrence	1	1	1.00

LC: lesser curvature; PW: posterior wall; MP: muscularis propria. Quantitative data are presented as mean ± standard deviation. *$P < 0.05$.

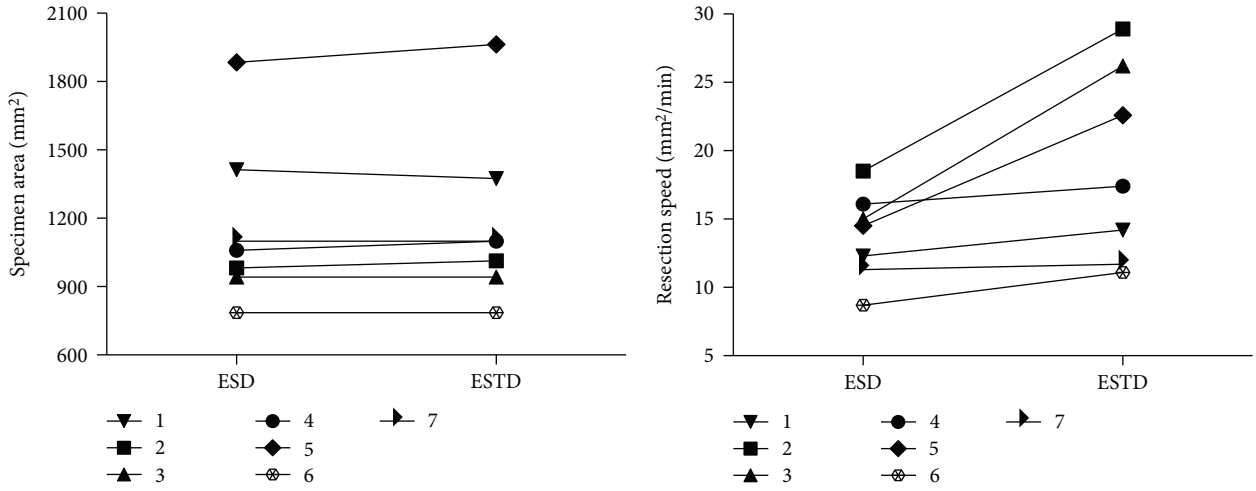
matched factors. As shown in Figure 3(a), the mean specimen area in the two group was similar (1166.29 mm^2 in ESD versus 1181.99 mm^2 in ESTD, $P > 0.05$). The mean ESTD resection time was 69 minutes as against 87.7 minutes for the ESD ($P = 0.0.01$). The mean resection speed was faster for ESTD than for ESD (18.86 mm^2/min versus 13.76 mm^2/min, $P = 0.03$), and the differences of resection speed were shown in Figure 3(b). No complications were observed in the ESTD group, but one case with MP damage was found in the ESD group and the damage was closed with two clips.

Histopathological evaluation of the resected specimens revealed 3 dysplasia, 4 cancers in the ESTD group, 1 hyperplastic polyp, 1 dysplasia, and 5 cancers in the ESD group. Among the cancers, 5 curative cancers (2 in the ESTD group, 3 in the ESD group) were intramucosal well-differentiated cancer with negative margins and vascular invasion. The other 4 noncurative cancers are presented in Table 2. One cancer in the ESTD group presented positive vertical margin, but no residual cancer tissue from the resected specimen was found after supplemental surgery.

The mean follow-up period of endoscopy examination was 27.1 months (range 3–52 months) for the ESTD group and 27.6 months (range 5–54 months) for the ESD group. One poorly to moderately differentiated intramucosal adenocarcinoma based on the pathological results from the surgical specimen was found at 15 months after ESTD for one curative cancer at the same location, but the 3-month and 6-month endoscopic follow-ups showed negative results. In the ESD group, one intramucosal adenocarcinoma presented local recurrence at 54 months of follow-up with negative results during 4 assessments over 42 months of follow-up and then surgery was performed.

4. Discussion

To the best of our knowledge, this report is the first clinical study to compare the safety and efficacy of ESTD and ESD for SGLs. A case-matched controlled study was performed to minimize the differences in the patient and lesion covariates. After comparison between the two groups, ESTD was demonstrated to be faster for large SGLs than ESD. No complications were observed in the ESTD group, but one case presented MP damaged during the ESD operation. Therefore, ESTD provided a higher resection speed without increasing risk than ESD for large SGLs, which could be explained by the following advantages of ESTD. (1) The submucosal tunnel established in ESTD facilitated the lateral mucosa stretching to maintain a clear view for the operation, which could effectively avoid obstruction from the infolding of the resected mucosa after circumferential incision in conventional ESD [11]. The good visibility contributed to



(a) Specimen area between the two groups

(b) Resection speed between the two groups

Figure 3: Graph representing the changes of the paired cases. (a) The specimen areas are similar between the two groups. (b) Compared with ESD, ESTD presents faster resection speed in all pairs.

Table 2: The characteristics of noncurative cancers in this study.

Case number	1	2	3	4
Age (years)	69	61	69	62
Gender	Male	Male	Female	Female
Location	Cardial LC	Cardial LC	LC of LGB	Cardial LC
Specimen size (mm)	50	40	50	50
Procedure	ESTD	ESTD	ESD	ESD
Pathology				
Ulcer findings	None	None	None	None
Differentiation	tub2 > por	tub1	sig	tub1
Positive margin	None	VM (+)	None	None
Vascular invasion	Ly (+) v (+)	None	None	None
Depth	sm1	sm2	sm1	sm2
Supplemental therapy	None	Surgery*	None	None
Total follow-up (months)	52 (alive)	51 (alive)	54 (alive)	40 (alive)
Endoscopic follow-up (months)	52	36	48	25
Recurrence	None	None	None	None

LGB: lower gastric body; Ly: lymphatic infiltration; v: venous infiltration; VM: vertical margin involvement; m: intramucosal cancer; sm1: invasion depth < 500 μm from the lower margin of the muscularis mucosa; sm2: invasion depth ≥ 500 μm; tub1: well-differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma; por: poorly differentiated adenocarcinoma; sig: signet ring cell carcinoma. *There was no residual cancer tissue found from the resected specimen after supplemental surgery.

reducing the rates of complications and to saving time while addressing the events. In our study, just one case presented muscular damage, and the safe advantage of ESTD was not obvious. However, Huang et al. [21] demonstrated that ESTD had a lower rate of muscular injury than ESD (28.9% versus 52.6%, $P < 0.05$) in 115 patients analysis. (2) In the ESD procedure, additional submucosal injection tended to dissipate easily after circumferential incision [20]. However, the submucosal tunnel during ESTD allowed submucosal injection solutions to be mainly retained in the submucosa and thus reduced the amount and time of injection [19]. (3) The transparent cap in the front of the endoscopy and CO2 insufflation contributed to blunt dissection in the tunnel [19]. (4) ESTD enabled easier dissection close to the muscularis propria and allowed complete resection of the submucosa. This advantage had been warranted by one prospective, randomized, and comparative experimental animal study, which revealed that ESTD enabled deeper dissection than ESD according to the submucosal thickness of resected specimen [3]. This advantage also makes complete resection of lesions with ulcers or fibrosis possible [18]. (5) After the tunnel was established, the bilateral

resection took advantage of traction of both sides and gravity from the high to low locations to help shorten the operation time.

There were no differences in the rates of complete, curative resection, and recurrence between the two groups, which were mainly related to the diagnosis before the operation rather than the operation itself. One gastric cancer in the ESTD group presented positive vertical margins after pathological evaluation. Then, surgery was supplemented, but no residual cancer was found in the resected specimen. One reason was that the residual cancer was missed because not all of the surgical specimen was assessed; the other reason was that the burning effect on the margin might prevent accurate pathological assessment after ESTD. During follow-up, 2 local recurrent cancers were found at 15 months and 54 months. However, the corresponding primary cancers of those recurrent cancers were curative cancers rather than noncurative cancer without supplementary treatment. Because of the limited number of the cases, the risk factors of recurrence after ESD were not analyzed in this study. Previous studies had demonstrated that the risk factors included tumor size (>30 mm) and location (upper third of the stomach) [33, 34], which were also demonstrated in this study because of all the primary cancers located at the cardia with size ranging from 50 to 60 mm. Therefore, close endoscopic follow-up after endoscopic resection was necessary for the patients with those risk factors.

Various traction methods have been devised to provide adequate tension and good visibility during the ESD procedure to improve its efficacy and safety, but as described in the review by Imaeda et al. [2], these methods have their own advantages and disadvantages due to their inherent characteristics. In this study, the novel ESTD technique was used to improve the ESD procedure without extra devices or equipment and any additional invasiveness. Recently, Miura et al. [35] reported pocket-creation method (PCM) for gastric neoplasms. The pocket can recognized the tunnel in ESTD, and these two methods have the same principles. In the procedures in ESTD, one anal incision is created before the tunnel creation, which is different from PCM. In our experience, the anal incision can serve as the endpoint of the tunnel creation and prevent excessive mucosal separation. The advantage and optimum indications of these two methods need to be further investigated.

However, there are limitations for ESTD as well. First, skilled and experienced operators are needed to perform the procedure. The creation of a submucosal tunnel is more difficult than that in the esophagus because of the gastric anatomical and physiological features, such as the large and nonstraight lumen, unfixed position, and high flexibility [23, 36]. Therefore, the operators need experience gained from ESD and other tunnel techniques to ensure the success and safety of the procedure. Second, the lesion location is a limiting factor. The cardia, lesser curvature of the gastric corpus, and greater curvature of the gastric antrum are the optimal locations to establish the submucosal tunnel based on our experience with the use of the tunnel technique in the stomach for SGLs, submucosal tumors, and gastroparesis, which also reported in previous studies [23, 36]. Although there were no lesions in the gastric antrum in this study, Choi et al. [29] reported the feasibility of ESTD for ulcerative early gastric cancer in the gastric antrum. Creating a submucosal tunnel in the other parts of the stomach is relatively difficult, time-consuming, and unsafe now. Third, ESTD is not superior to ESD for any size lesions. We assume that the tunnel section was semicircular with a minimum radius of 10 mm; therefore, the lesions with widths $\geq$30 mm (width $= 2 \times \pi \times 10/2$) are suitable for ESTD. However, the optimal cutoff points of lesion length and width between ESD and ESTD should be further investigated from more cases.

This study has several limitations. First, this study is one retrospective study with a limited case number in a single institution. The operators in this study have extensive experience with ESD for gastric lesions and endoscopic submucosal tunneling technique for superficial esophageal neoplasms and submucosal tumors in the esophagus and stomach. Therefore, the study results may not be generalizable. Second, the patients with SGLs performed with conventional ESD were chosen for the control group and whether ESTD was superior to other traction methods was not assessed. To provide more reliable evidence for the benefit of ESTD, we are conducting a large, multi-institutional, and prospective study.

In conclusion, this preliminary study has shown that ESTD technique is effective and safe for resecting large SGLs at suitable sites. Further prospective studies are needed to confirm the advantages of ESTD for large and ulcerative SGLs.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Acknowledgments

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Review Article

Progress on the Prevention of Esophageal Stricture after Endoscopic Submucosal Dissection

Peina Shi[1] **and Xiaoyun Ding**[2]

[1]*Medical School, Ningbo University, Ningbo, Zhejiang, China*
[2]*Gastroenterology Department, Ningbo First Hospital, Ningbo, Zhejiang, China*

Correspondence should be addressed to Xiaoyun Ding; dyyyding@126.com

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Endoscopic submucosal dissection (ESD) has been widely accepted as an effective, minimally invasive treatment for superficial esophageal cancers. However, esophageal stricture often occurs in patients with large mucosal defects after ESD. In this review, we discuss various approaches recently researched to prevent esophageal strictures after ESD. These approaches can be classified as pharmacological treatments, esophageal stent treatments, and tissue engineering approaches. Most of the preventive approaches still have their limitations and require further research. With the improvement of current therapies, ESD can be more widely utilized as a minimally invasive treatment with minimal complications.

1. Introduction

Currently, endoscopic submucosal dissection (ESD) has been widely accepted as an effective, minimally invasive treatment for superficial esophageal cancers, including esophageal squamous cell carcinoma and Barrett's adenocarcinoma [1–3]. Compared to endoscopic mucosal resection (EMR), ESD has substantially higher en bloc and curative resection rates, lower local recurrence rates, and more precise histopathologic assessment [4, 5]. However, esophageal stricture often occurs inevitably in patients who have large mucosal defects after ESD. Esophageal strictures cause nausea, vomiting, and varying degrees of dysphagia and may influence patients' vocalization, severely decreasing the patient's quality of life. Patients with esophageal strictures require multiple endoscopic balloon dilations (EBDs) or dilations with a bougie over a long period [6]. Multiple sessions of endoscopic dilation are painful and increase the risk of esophageal perforation [7, 8]. Therefore, various kinds of approaches to prevent esophageal strictures after ESD are necessary and useful.

Esophageal stricture after ESD can be structurally divided into two categories: (1) a simple stricture, meaning that the stricture is short, focal, and not angulated and has a diameter that will allow the endoscope to pass, and (2) a complex stricture, meaning that the stricture is long (>2 cm), irregular, and angulated or has a severely narrow diameter [9]. In clinical research, esophageal stricture after ESD often refers to the complex stricture, and the patient has a feeling of dysphagia or the stricture prevents the passage of a standard 9.2–10 mm diameter endoscope. Two main mechanisms can explain the esophageal stricture after ESD: (1) the loss of the esophageal epithelium, which means the loss of a barrier against saliva, gastric acid, microorganisms, and so on, and (2) inflammation, fibrosis, and scar formation in the process of wound healing [10]. The rate of stricture occurrence after near-circumference or whole-circumference ESD was reported to be 88–100% [2, 9, 11, 12]. Esophageal stents, extracellular matrix scaffolds, and cell-based therapy have been researched to address this problem. The severe inflammation is due to the stimulation of several physical and chemical factors, as well as to the after-effects of the heat damage caused by the use of a high-frequency wave snare [13]. This inflammation results in ulceration of the deep layer of the esophagus. Myofiber atrophy and fibrosis reactions gradually appear during the period of the wound

recovery, which finally results in esophageal stricture [13, 14]. Steroids and some antifibrotic drugs have been reported to mitigate these types of reactions.

2. Pharmacological Treatment

2.1. Endoscopic Intralesional Injection of Steroid Therapy. Steroids can inhibit inflammation and fibrosis. The endoscopic intralesional injection of triamcinolone acetonide (TA) has been used for the treatment of benign and malignant esophageal strictures [15, 16]. Hashimoto et al. found that the endoscopic injection of TA after ESD in 41 patients with mucosal defects of three-quarters of the esophageal circumference was safe and effective to prevent esophageal stricture [17]. Twenty-one patients in the treatment group had an endoscopic injection of TA on the 3rd, 7th, and 10th days after ESD with a dose of 16–62 mg of TA for each treatment. The incidence of stricture in the treatment group (19.0%) was apparently lower than that in the control group without TA injection (75.0%), and the number of extra EBD procedures to treat the stricture decreased. Hanaoka et al. also reported a prospective study in 30 patients who had a single injection of 100 mg TA immediately after ESD [18]. The stricture rate was 10%, which is lower than that in the historical control group of 29 patients without TA injection (66%). However, Takahashi et al. showed that in patients with a circumferential mucosal defect of more than three-quarters of the circumference of the esophagus, it was difficult to prevent refractory stricture, despite the patients receiving TA injection after ESD [19]. The stricture rate was not significantly different, from 87.5% in the control group to 62.5% in the study group. Additionally, the perforation rate during dilatation procedures was 1.0% in the study group but 0.5% in the control group. Hanaoka et al. confirmed that a tumor extent greater than 75% of the esophageal circumference was an independent risk factor for complex stricture [20]. Nagami et al. reported in a retrospective matched case-control study of 602 patients that a single injection of TA after ESD effectively reduced the esophageal stricture rate and the number of EBD sessions [21]. However, the efficacy reduced in patients with entire circumferential mucosal defects. Steroid treatment concerns include the possibility of periesophageal abscess after steroid treatment and the increased risk of delayed perforation in the extra EBD procedures [22, 23].

2.2. Steroid Gel Therapy. An improper endoscopic intralesional injection carries the risk of bleeding and myofiber atrophy because TA must be injected in the submucosa. Therefore, Mori et al. changed the application method of TA by a prospective study [24]. Twenty patients received a 17.5 mL TA gel treatment applied to the ulcer floor and 5 minutes of balloon dilatation to permeate the steroid on the 5th, 8th, 12th, and 15th days after ESD. The control group accepted TA injection and balloon dilatation after ESD. The stricture rate had no significant difference between the two groups. The TA gel application is safe and effective to prevent esophageal stricture after ESD, but visibly, it has too many operation procedures.

2.3. Oral Administration of Steroid Therapy. The oral administration of steroids has also been widely researched to prevent esophageal stricture due to their anti-inflammatory effects. Yamaguchi et al. reported the effectiveness for stricture prevention in the study of 41 patients who underwent more than three-quarters of circumference circular ESD [25]. Twenty-one patients in the study group received oral prednisolone starting on the third day after ESD. The dose of prednisolone was 30 mg/d for the first two weeks, 25 mg/d for the next two weeks, and then was gradually decreased to 5 mg/d each week over the next four weeks until termination, eight weeks after ESD. The stricture rate in the study group (5.3%) was lower than that in the control group (31.8%). The control group performed preemptive EBD twice a week for 8 weeks after ESD. Isomoto et al. reported similar conclusions in patients with complete, circular ESD [26]. Sato et al. evaluated a retrospective cohort study and found that early administration of oral prednisolone combined with EBD is an effective method to prevent esophageal stricture after ESD and early steroid administration is better than late administration or no steroid therapy [27]. However, it is possible for some systemic problems to appear after long-time oral steroid therapy, such as peptic ulcers, immune suppression, metabolic disturbances, and psychiatric symptoms. Kataoka et al. shortened the period of steroid use in their research [28]. Seventeen patients in the study group underwent prednisolone treatment from the third day after ESD, at a dose of 30 mg/d during the first one week. Then, the dose was gradually decreased to 10 mg/d every week for the next two weeks until termination, three weeks after ESD. The patients in the two groups showed no significant differences, but the incidence of esophageal stricture was lower in the study group than in the ESD-alone group (17.6% versus 68.7%, resp.). Recent studies showed that oral administration of steroids has little adverse events or serious complications. However, there is a study that reported a nocardiosis infection in an elderly patient who received oral steroid treatment after ESD [29].

2.4. Antifibrotic Drug Therapy. Some antifibrotic drugs have been studied in the prevention of esophageal stricture. Antifibrotic drugs inhibit the proliferation of fibrous scars. 5-Fluorouracil (5-FU) is an antineoplastic drug. 5-FU combined with TA was researched in regard to the reduction of strictures that occur after subepiglottic surgery [30]. Mizutani et al. reported that 5-FU can be used as an antiscarring agent [31]. In their research, 5-FU was combined with liposome and mixed with atelocollagen, for sustained release. It was effective in preventing esophageal strictures after ESD in a canine model, by reducing submucosal fibrosis.

Tranilast is an antiallergic drug that can inhibit the release of transforming growth factor-beta (TGF-β1), prostaglandin-E_2 (PGE2), and interleukin-1 (IL-1), which reduces collagen synthesis and fibrosis [32]. Tranilast was used to treat keloids and hypertrophic scars in an animal study [33]. Uno et al. reported a pilot study that demonstrated the availability and safety of oral tranilast with EBD to prevent esophageal strictures after ESD [34].

N-acetylcysteine is an antioxidant that inhibits TGF-β1. However, the use of N-acetylcysteine failed to reduce the formation of esophageal fibrogenesis after circumferential ESD in a pig model [35].

Botulinum toxin type A (BXT-A) is a neurotoxin that inhibits the deposition of collagen fibers and improves hypertrophic scars [36]. Wen et al. proved that BTX-A can reduce esophageal strictures in patients who underwent more than two-thirds of circumference circular ESD [37]. The endoscopic intralesional injection of BTX-A after ESD can reduce stricture rates to 6.1%, compared with 32.4% in the control group.

3. Esophageal Stent Treatment

3.1. Esophageal Self-Expandable Stents. Metallic esophageal stents function to expand the esophagus. Metallic esophageal stents were initially researched for the interventional treatment of esophageal fistulas and esophageal strictures caused by malignant esophageal neoplasms [38, 39]. The application of metallic esophageal stents in benign esophageal strictures is controversial, due to common adverse reactions such as bleeding, esophageal perforation, stent migration, or stricture recurrence [39, 40]. Comparatively speaking, temporary self-expandable metallic stents are more suitable to be used in the treatment of benign esophageal strictures [41, 42]. A positive aspect of these stents is that they can be removed easily; however, a negative aspect is the high recurrence rate after stent removal [40, 43]. Several studies reported that elderly patients with refractory cicatricial strictures after ESD had temporary self-expandable metal stents placed, which resulted in successful esophageal treatment without complications (i.e., fever, chest pain, or stricture recurrence) [44, 45]. The efficacy of circumferential esophageal stents for the prevention of stricture formation after ESD has been reported by Wen et al. [46]. In their randomized controlled trial, 22 patients with a circumferential mucosal defect of more than three-quarters of the esophageal circumference were included. The study group had esophageal stents for 8 weeks and had a significantly lower stricture rate (18.2%) than the no-stent group (72.7%). The complication of stent migration into the stomach still occurred, which markedly reduced the expansion effect of the stents and required a repeat endoscopy operation to reposition the stent. The long-term stricture-preventing effects after the removal of the stents were unknown.

3.2. Biodegradable Stents. Some researchers attempted to use biodegradable stents to treat benign esophageal strictures [47]. Compared to metallic or plastic stents, biodegradable stents have the advantages that they do not need to be removed and have sufficient radial force to expand esophagus [44, 48]. Poly-L-lactic acid (PLLA) is one kind of biodegradable stent that was reported to prevent restricture in two patients after near-circumference ESD [49]. Lua et al. reported on biodegradable stents made of carboxymethyl cellulose (CMC) [50]. Seven patients with mucosal defects of three-quarters of the esophageal circumference had endoscopic placement of CMC stents after ESD. This research had no control group. The stricture rates were approximately 57%. Compared to the other research, the preventing efficacy of CMC esophageal stents appears to be limited.

Polyglycolic acid (PGA) sheets have been used in implantation surgeries to reinforce sutures [51]. In recent years, PGA sheets have been used to repair mucosal defects, prevent scar contracture, and alleviate postoperative pain [52–54]. The combination of PGA sheets and fibrin glue as an endoscopic tissue shielding method has been used in the colon and duodenum, with few postoperative adverse events [50, 55]. Iizuka et al. demonstrated the potential of PGA and fibrin glue for the prevention of stricture after ESD [56]. Fifteen patients with defects greater than half of the circumference after ESD were included in the study, and 6 weeks later, the esophageal stricture rate was 7.7%. The small PGA sheets (15×7 mm) were placed on an artificial ulcer without overlapping, and fibrin glue was sprayed to affix the PGA. Limitations of this method include that the small sheets take a long time to place and are easy to drop. Thus, Ono et al. reported a novel technique called "the clip and pull method", using a whole PGA sheet to shield an artificial ulcer [57]. This method was used in eight patients with a circumferential mucosal defect of more than three-quarters after ESD [58]. The stricture rate was 37.5%, and the number of EBD sessions was 0.8 ± 1.2. Additionally, Kataoka et al. reported a case of an elderly patient that did not suffer dysphagia after circumferential ESD, by the treatment of the steroid injection, shielding the ulcer with PGA and fibrin glue [59]. The combination therapy of intralesional steroid injection and PGA sheets also showed positive effects on ten patients after near-circumference ESD [60]. Although further research is needed to confirm these findings, the results from these studies increase the interest in the combination therapy of PGA sheets and other treatments.

4. Tissue Engineering Approaches

4.1. Extracellular Matrix Scaffold Therapy. Extracellular matrix (ECM) scaffolds can support the growth of epithelial cells, are compatible with perivascular stem cells, and promote wound recovery and esophageal structure remodeling [61–63]. The ECM scaffolds derived from the small intestinal submucosa or urinary bladder submucosa were reported to achieve reconstruction of the esophagus in a dog model [64]. Then, Badylak et al. reported that the ECM scaffolds can minimize stricture and promote esophageal remodeling in five male patients after endoscopic inner-layer circumferential resection [65]. The actual esophageal remodeling mechanisms in patients were unclear, but the study showed that cryptic peptides formed in scaffold degradation maybe the potential factor. Nieponice et al. researched a dog model to evaluate the potential of urinary bladder ECM tubular scaffolds for the prevention of esophageal stricture [66]. Five dogs had endoscopic ECM scaffold placement after circumferential esophageal EMR, while another five dogs only had circumferential esophageal EMR. As a result, histological assessment of the ECM treatment group showed a continuous, intact, regenerate esophageal mucosa with

Table 1: Treatments for the prevention of esophageal stricture after endoscopic submucosal dissection.

Group		Mechanisms	Advantages	Disadvantages and limitations
Pharmacological treatment	Steroid	Anti-inflammatory, antifibrotic formation, antiscar formation	Effective in many small comparative clinical studies	Hard to prevent stricture in patients with circumferential esophageal mucosal defects, systematic side effects (peptic ulcers, immune suppression metabolic disturbances, and psychiatric symptoms), and delayed wound healing
	Antifibrotic drug	Inhibit the proliferation of fibrous scars	Antifibrotic effect	No randomized controlled trials or systematic reviews with sufficient evidence
Esophageal stent treatment	Esophageal self-expandable stents	Expand the esophagus	Persistently expand the esophagus, easily to be removed at any time	Adverse reactions (bleeding, chest pain, esophageal perforation, and stent migration), high recurrence after stent removal, and long-term effects were unknown
	Biodegradable stents	Expand the esophagus	Expand the esophagus, no need to remove	No randomized controlled trials or systematic reviews with sufficient evidence
Tissue engineering approaches	Extracellular matrix scaffold	Support the growth of epithelial cells, promote esophageal structure remodeling	Support tissue, enhance mucosal healing and structure remodeling	Potential safety problem, no randomized controlled trials, or systematic reviews with sufficient evidence
	Cell-based therapy	Promote reepithelialization and scarless wound healing	Reepithelialization, enhancement of mucosal healing and structure remodeling, great potential for development	Complicated technique, high cost, large-sample controlled trial, and long-term follow-up research are needed

no inflammation or necrosis, while histology of the control group showed an immature epithelial layer with inflammation and severe scarring. A surgical adhesive was used in this study to prevent scaffold migration, but the influence of this adhesive on esophageal mucosal remodeling was unclear. Additionally, the efficacy of the ECM scaffold was controversial. Schomisch et al. reported an unsuccessful study on the prevention of stricture formation using three ECM scaffolds: the small-intestine submucosa, acellular dermal matrix, and urinary bladder matrix [67]. The major influencing factors of the study included the preparation technique of the scaffold and the use of a self-expanding stent rather than the use of surgical adhesive to attach the scaffold. Future biological ECM research may focus on novel materials and proper techniques to promote the recovery of the esophagus.

4.2. Cell-Based Therapy. Cell transplantation is applied to esophageal mucosal defects, inducing early reepithelization and promoting scarless wound healing. The efficacy of implantation of autologous keratinocytes or adipose stromal cells was proven in several animal model studies [68–70]. However, the long-term efficacy of the direct injection of the cells was unknown. The cells that migrated after injections were difficult to trace for prolonged periods. Additionally, the real mechanism of the reepithelization is still uncertain.

A new approach using endoscopic transplantation of cultured autologous cell sheets overcame the limitations of cell migration and low viability rates of transplanted cells. The cell sheets are fabricated on a temperature-responsive culture surface and can be easily harvested. The sheets can be transplanted to the target sites without the use of sutures or adhesives [71]. The transplantation of cell sheets after ESD can contribute to early epithelium regeneration and mild fibrosis. However, much of this area of research was performed in animal models. Kanai et al. proved that the epidermal cell sheets can reduce the symptom of dysphagia in patients who underwent circumferential ESD [72]. Perrod et al. reported that adipose tissue-derived stromal cell sheets can reduce the stricture rate after ESD [73, 74]. In animal and clinical research, cultured autologous oral epithelial cell sheets can suitably cover ulcer areas and effectively reduce the degree of stricture [75–78]. Ohki et al. demonstrated that transplantation of autologous oral epithelial cell sheets can safely and effectively prevent esophageal stricturing and promote epithelial healing after ESD without the need for additional treatments for complications [76, 78]. The growth factors, cytokines, and the source of regenerated epithelia may be related to the early reconstruction of the esophageal surface [75]. In further studies, more clinical evaluation and long-term follow-up should be performed to ensure the safety and reproducibility of the cell sheet technique. The high cost of fabrication and rapid adhesion warrants further research of methods to facilitate the transplantation of the cell sheets. In addition, some methods demonstrate the potential of cell-based therapy for the prevention of postoperative strictures. Mizushima et al. showed that the application of conditioned medium obtained from mesenchymal stem cells, combined with the injection of steroids, can significantly decrease inflammation and fibrosis of the animal esophagus after ESD [79].

5. Conclusion

In brief, we reviewed recent publications on the prevention of esophageal stricture after ESD, all of which inevitably have their own limitations and cannot be widely accepted in clinical application (Table 1). The steroid therapies have been effective in many clinical trials but cannot completely prevent stricture in some high-risk patients. The reduced efficacy of these therapies to prevent stricture after near-circumference or whole-circumference ESD is an ongoing problem. Thus, a sufficient evaluation before endoscopic surgery and a prolonged assessment after preventive therapy are essential to current comprehensive treatment. The combination of different therapies should be evaluated in future studies.

In recent years, many innovative therapies have shown appreciable feasibility, but they still require controlled clinical research to confirm effectiveness. Some single case reports lack consensus, needing more evidence to sufficiently confirm safety. After the improvement of current therapies, ESD can be more widely utilized as a minimally invasive treatment with minimal complications.

Conflicts of Interest

The authors declare no conflict of interests.

Authors' Contributions

All authors equally contributed to this paper.

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Clinical Study

Feasibility of Autologous Fibrin Glue and Polyglycolic Acid Sheets to Prevent Delayed Bleeding after Endoscopic Submucosal Dissection of Gastric Neoplasms in Patients Receiving Antithrombotic Therapy

Daisuke Kikuchi,[1] **Toshiro Iizuka**,[1] **Kosuke Nomura**,[1] **Yasutaka Kuribayashi**,[1] **Masami Tanaka**,[1] **Satoshi Yamashita**,[1] **Tsukasa Furuhata**,[1] **Akira Matsui**,[1] **Toshifumi Mitani**,[1] **Shigeyoshi Makino**,[2] **and Shu Hoteya**[1]

[1]*Department of Gastroenterology, Toranomon Hospital, Minato-ku, Tokyo, Japan*
[2]*Department of Transfusion Medicine, Toranomon Hospital, Minato-ku, Tokyo, Japan*

Correspondence should be addressed to Daisuke Kikuchi; dkiku1230@gmail.com

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Background/Aims. Delayed bleeding is one of the most serious complications following gastric endoscopic submucosal dissection (ESD) under antithrombotic therapy. As a safety measure, for patients receiving antithrombotic therapy, we covered the ESD ulcer with autologous fibrin glue (prepared using autologous blood) alone or with polyglycolic acid (PGA) sheets. *Methods*. From July 2014 to November 2015, 20 patients with gastric neoplasms who were receiving antithrombotic therapy were enrolled in this study. After ESD, the ESD ulcers were covered with autologous fibrin glue alone or with PGA sheets. We prospectively evaluated the feasibility of this safety measure. *Results*. In total, 22 lesions in 20 patients were resected en bloc by ESD. The mean specimen size and tumor size were 31.5 ± 9.5 mm and 14.0 ± 8.8 mm, respectively. There were no cases of delayed bleeding or adverse events in this study. Attachment of autologous fibrin glue was observed in 81.8% (18/22) and 68.2% (15/22) of lesions at endoscopy performed 1 day and 7 days after ESD, respectively. *Conclusion*. No patient in this study had delayed bleeding or adverse events. This suggests that this measure may facilitate the safety of gastric ESD in patients receiving antithrombotic therapy. This trial is registered with UMIN000019386.

1. Introduction

Endoscopic submucosal dissection (ESD) is a standard treatment for early gastric cancer. ESD can be performed safely, but some procedural problems still need to be addressed. For example, intraoperative and postoperative bleeding is a serious problem in ESD for gastrointestinal (GI) lesions. However, owing to technological advances in endoscopic devices and techniques, factors associated with intraoperative blood are being addressed, reducing the number of patients who cannot be treated because of intraoperative bleeding and those requiring transfusion [1, 2]. In contrast, postoperative bleeding remains a problem [3, 4]. Because of the frequent preventive and therapeutic use of antithrombotic drugs in patients with a history of myocardial infarction or stroke, it is important to develop new safety measures for patients receiving antithrombotic therapy [5, 6].

We have developed a new safety measure for gastric ESD in patients receiving antithrombotic therapy, who have an increased risk of postoperative bleeding, whereby autologous blood is collected from the patient before gastric ESD to develop an autologous fibrin glue that is used in combination with polyglycolic acid (PGA) sheets to cover the post-ESD

ulcer. In this prospective study, we investigated the feasibility of this safety measure.

2. Methods

Patients with early gastric cancer or adenoma as the indication for ESD and who met the study eligibility criteria were enrolled in this study and underwent autologous blood collection. The inclusion criteria were age ≥ 20 years, gastric neoplasm as the indication for ESD, and concomitant antithrombotic therapy. The following exclusion criteria were applied: anemia (hemoglobin ≤ 11 g/dL), fever or other symptoms suggesting active infection, severe dehydration, sensitivity to bovine blood products, concomitant treatment with antiplasmin agents or aprotinin, and unsuitability for enrollment based on the opinion of their managing physician. The study was approved by the institutional review board at Toranomon Hospital in July 2014 (UMIN000019386). Written informed consent was obtained from all study participants.

2.1. Autologous Blood Collection. At least 7 days before the patient underwent ESD, 400 mL of blood was collected from the cubital fossa using an 18-gauge needle. Autologous fibrinogen was prepared manually immediately after blood collection. Autologous blood was stored in a freezer or refrigerator until the managing physician determined that the patient was no longer at risk of delayed bleeding.

2.2. Endoscopic Submucosal Dissection (Figure 1). All patients in the study underwent conventional ESD. The decision regarding continuation, discontinuation, or switching to alternative antithrombotic therapy was made by the managing physician. ESD was performed ≥7 days after the autologous blood collection. After ESD, the blood vessels in the ulcer bed were coagulated using hemostatic forceps (Pentax Medical, Tokyo, Japan). After hemostasis was confirmed, autologous fibrinogen and bovine thrombin solution (200 units/mL, prepared using fine granules for oral administration) were sprayed simultaneously onto the ulcer bed to form a layer of fibrin glue to cover the ESD ulcer. After using this protocol in 5 patients, we felt that the adhesiveness of the fibrin glue to the ulcer bed needed to be strengthened, so we revised our protocol to include the use of PGA sheets (Neoveil®; Gunze Ltd., Osaka, Japan). For this reason, the enrollment in the study was stopped between September and December 2014, and the revised protocol was applied from patient 6 onward. A PGA sheet was cut to the size of the ulcer bed and applied using biopsy forceps. After fixing the sheet at the ulcer margins using clips (Olympus Co., Tokyo, Japan), the autologous fibrinogen and bovine thrombin solution were sprayed simultaneously to bond the PGA sheet to the ulcer bed. Clips were used only for the fixation of the PGA sheet to the ESD ulcer. Post-ESD diet, proton pump inhibitor, and antithrombotic therapy were administered/performed according to the conventional protocol at our hospital. Endoscopy was repeated 1 day, 7 days, and 8 weeks after ESD to evaluate the amount of autologous fibrin glue remaining (both in those treated with fibrin glue alone and in those treated with fibrin glue and PGA sheets) and healing of the ulcer. At the time of endoscopy, blood vessels requiring hemostasis, if any, were cauterized using hemostatic forceps. The managing physician decided whether transfusion was needed in the event of GI bleeding or anemia.

2.3. Sample Size. A sample size of 20 was estimated to be necessary for a study investigating the ability of autologous fibrin glue and PGA sheets to prevent bleeding after gastric ESD in patients receiving antithrombotic therapy.

2.4. Study Endpoints. The primary endpoint of the study was the incidence of delayed bleeding, which was defined as hematemesis, melena, other bleeding-related symptoms, or anemia (defined as a decrease in hemoglobin of ≥2 g/dL compared with the preoperative level) that warranted emergency endoscopy for hemostasis. Secondary endpoints were the incidence of adverse events, such as allergic reactions and fever related to the autologous fibrin glue, the incidence of post-ESD allogeneic or autologous transfusion, the amount of autologous fibrin glue remaining at 1 and 7 days after ESD, and the ulcer cure rate at 8 weeks after ESD. The effect of the autologous fibrin glue on hemostasis was evaluated in patients who required a hemostatic procedure to the post-ESD ulcer bed. Endoscopic hemostasis for visible vessels or oozing without the clinical criterion of bleeding on second-look endoscopy was not included in delayed bleeding.

3. Results

ESD was performed for 22 lesions in 20 patients (17 men, 3 women) enrolled between July 2014 and December 2015, with a 3-month gap in recruitment during the revision of the protocol between September and December 2014. The patient demographic and clinical data are shown in Table 1. The mean age was 75.5 ± 5.9 years. Four of the 22 lesions were in the U region, 10 in the M region, and 8 in the L region. On pathologic examination, the lesions were identified as adenoma ($n = 7$), mucosal carcinoma ($n = 11$), and submucosal carcinoma ($n = 4$). The mean maximum tumor diameter was 14.0 ± 8.8 mm, and the mean diameter of the resected specimens was 31.5 ± 9.5 mm.

The most frequent indication for antithrombotic therapy was cerebrovascular disease (11 patients), followed by coronary artery disease and arrhythmia in 4 patients each. Sixteen patients were being treated with one antithrombotic agent and 4 were receiving multiple antithrombotic agents. More specifically, 14 patients were on antiplatelet therapy, 4 were on anticoagulation therapy, and 2 were receiving a combination of an antiplatelet agent and an anticoagulant. Detailed data of the antithrombotic therapy in this study are shown in Table 2. In terms of antiplatelet therapy, aspirin was used in 7 cases. Second to aspirin, cilostazol and clopidogrel were used in 4 cases each. On the other hand, in anticoagulant therapy, warfarin was used in 4 cases. Heparin alternative therapy was performed perioperatively in 4 of the 6 patients who received anticoagulation therapy. Antithrombotic therapy was discontinued during ESD in one patient but

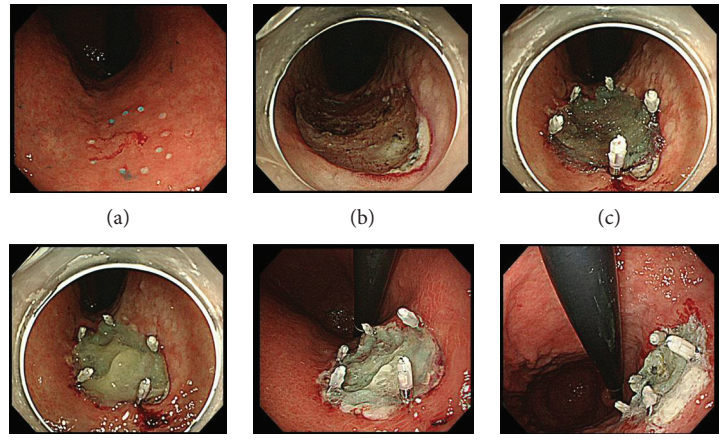

Figure 1: (a) Endoscopic view of the lesion. The lesion is located at the lesser curvature of the lower gastric body. (b) ESD ulcer. Visible blood vessels were coagulated using hemostasis forceps. (c) Polyglycolic acid (PGA) sheet was applied using biopsy forceps and fixed using clips. (d) Autologous fibrinogen and bovine thrombin solution were sprayed simultaneously to bond the PGA sheet. (e) Endoscopic view of ESD ulcer 1 day after ESD. (f) Endoscopic view of ESD ulcer 7 days after ESD. This patient was discharged from our hospital without any symptom of bleeding.

Table 1: Patient characteristics.

Patients (lesions), *n*	20 (22)
Mean age, years ± SD	75.5 ± 5.9
Sex (male/female)	17/3
Indication for antithrombotic therapy (CVD/CAD/arrhythmia/others)	11/4/4/1
Lesion location (U/M/L)	4/10/8
Mean diameter of resected specimen, mm ± SD	31.5 ± 9.5
Mean diameter of the tumor, mm ± SD	14.0 ± 8.8
Pathologic diagnosis (adenoma/mucosal cancer/ submucosal cancer)	7/12/3

Data are presented as the number or mean and standard deviation as appropriate. CAD: coronary artery disease; CVD: cerebrovascular disease; L: lower; M: middle; SD: standard deviation; U: upper.

Table 2: Antithrombotic therapy in this study.

Type of antithrombotic therapy	Drug name	Number of cases
Antiplatelet therapy	Aspirin	7
	Cilostazol	4
	Clopidogrel sulfate	4
	Others	2
Anticoagulant therapy	Warfarin potassium	4
	Dabigatran etexilate	1
	Apixaban	1

was continued in the remaining patients. No adverse events or complications such as perforation, severe intraoperative bleeding, or pneumonia were observed. Sixteen patients were able to resume a normal diet on the day after ESD. The mean postoperative hospital stay was 8.1 ± 1.0 days.

The outcomes of this study are shown in Table 3. No patient in the study had delayed bleeding after ESD. However, one patient required cauterization using hemostatic forceps for bleeding during second-look endoscopy performed 7 days after ESD. In this case, hemostatic procedure was performed for oozing during second-look endoscopy without any bleeding symptom such as melena or hematemesis. According to the protocol, we did not judge this case as delayed bleeding. The autologous fibrin glue and PGA sheets did not significantly affect hemostatic procedures and were not associated with any allergic reactions or adverse events. In this study, attachment of the fibrin glue alone or fibrin glue with PGA sheet to the ulcer bed was observed in 81.8% (18/22) and 68.2% (15/22) of lesions at endoscopy performed 1 day and 7 days after ESD, respectively. After revision of the protocol, the respective proportions were 94.1% (16/17) and 82.4% (14/17). Over 80% (81.8%, 18/22) of the post-ESD ulcers had formed scars 8 weeks after ESD. None of the patients needed an autologous or allogenic blood transfusion.

4. Discussion

Technological advances in endoscopy, especially the transition from endoscopic mucosal resection to ESD, mean that it is now possible to perform en bloc resection of GI tumors regardless of their location and size and whether or not ulceration is present [7]. ESD is now the standard treatment for early gastric cancer with no risk of lymph node metastasis [8]. The advantages of en bloc resection include no risk of residual or recurrent tumor and an accurate pathologic diagnosis; however, the high incidence of adverse events

Table 3: Study outcomes.

Patients (lesions), *n*	20 (22)
Delayed bleeding rate, % (*n*)	0 (0)
Perforations, % (*n*)	0 (0)
Severe intraoperative bleeding episodes, % (*n*)	0 (0)
Allergic reactions, % (*n*)	0 (0)
Fever, ≥38°C, % (*n*)	0 (0)
Attachment rate of fibrin glue alone or with PGA sheets on POD1, % (*n*)	81.8 (18/22)
Attachment rate of fibrin glue alone or with PGA sheets on POD7, % (*n*)	68.2 (15/22)
Scar formation rate 8 weeks after ESD, % (*n*)	81.8 (18/22)
Mean duration of fasting after ESD, days ± SD	1.3 ± 0.7
Mean length of stay after ESD, days ± SD	8.3 ± 1.0

ESD: endoscopic submucosal dissection; POD: postoperative day; SD: standard deviation.

and complications, particularly perforation and bleeding, remains a problem in patients undergoing ESD [9, 10]. Compared with esophageal and colorectal ESD, gastric ESD has a particularly high incidence of postoperative bleeding, which can be severe. Further, no appropriate preventive measures have been established nor any consensus has been reached, despite various attempts to prevent postoperative bleeding, such as the use of a proton pump inhibitor, endoscopic suturing, or PGA sheets and fibrin glue [11–16].

The Japan Gastroenterological Endoscopy Society has recently revised its guidelines for the management of patients undergoing GI endoscopy under antithrombotic therapy [17]. The earlier guidelines recommended that invasive procedures should be undertaken only after discontinuation of antithrombotic therapy. However, the new guidelines acknowledge the increased risk of thrombosis on cessation of antithrombotic therapy and allow invasive procedures in patients continuously undergoing antithrombotic therapy after adequate assessment and obtaining appropriate informed consent. Following this revision, more gastric ESD procedures have been performed routinely in Japanese patients receiving antithrombotic therapy, and concern has been growing about the corresponding increase in cases of postoperative bleeding. The risk factors for postoperative bleeding in patients undergoing gastric ESD include tumor size and location and, more importantly, antithrombotic therapy [18, 19]. Although the new guidelines allow ESD to be performed in patients undergoing antithrombotic therapy, we believe that further measures are needed to improve the safety of gastric ESD in these patients.

PGA sheets and fibrin glue have been used to cover post-ESD ulcers at various sites in the GI tract, including the esophagus, stomach, duodenum, and colon [20–23]. This novel safety strategy has a range of uses, including preventing stricture in esophageal ESD, minimizing the risk of bleeding in gastric ESD, and avoiding perforation in duodenal and colorectal ESD. Many studies have reported the benefits of this strategy, but none to date have utilized a randomized multicenter study design.

Our safety measure has three important advantages. First, bleeding can be prevented by covering post-ESD ulcers with PGA sheets and autologous fibrin glue. Tsuji et al. reported a significant reduction in postoperative bleeding using this method to cover gastric ESD ulcers, but their fibrin glue was prepared from a nonautologous source. Because nonautologous fibrin glue may contain human parvovirus B19, hepatitis virus, or prion protein, autologous fibrin glue may be a safer alternative to avoid the risk of these infections. Second, because autologous blood is collected preoperatively, allogenic blood transfusion can be avoided in the event of postoperative bleeding. Third, unlike fibrin glue made from nonautologous blood products, autologous fibrin glue contains coagulation factor X, fibronectin, and other adhesive glycoproteins that can improve wound status rapidly, thereby decreasing the risk of infection. In our study, over 80% of post-ESD ulcers converted to scars within 8 weeks of ESD [24–26]. The possibility that the time frame of conversion is shorter when these ulcers are covered by fibrin glue warrants further investigation.

There are a few limitations to this study. First, appropriate training and adequate experience are needed to apply PGA sheets to post-ESD ulcers, so less experienced endoscopists cannot perform the procedure. For this reason, the protocol used in our first 5 patients consisted simply of spraying autologous fibrin glue on the ulcer bed [27]. However, the fibrin glue alone remained until the next day in 2 patients. Therefore, we revised our protocol to incorporate the application of PGA sheets from our sixth patient onward. After revision of the protocol, the proportions of PGA sheets and autologous fibrin glue that remained on the first postoperative day and 7 days after ESD were 94.1% (16/17) and 82.4% (14/17), respectively, suggesting that PGA sheets are essential when applying fibrin glue to a post-ESD ulcer and that a simpler method needs to be developed. In the present study, only 50% (3/6) of the PGA sheets and autologous fibrin glue remained in the L region because of the intense peristalsis. In contrast, 100% (11/11) of the PGA sheets and autologous fibrin remained in the U/M region, suggesting that the adhesiveness of this combination differs by anatomic site. Nevertheless, the results of this noncomparative study suggest that our protocol is technically feasible. Moreover, the absence of adverse events and complications related to ESD procedures suggests that this protocol is safe. However, the feasibility of our protocol needs to be verified in a prospective comparative study in the future. When developing the protocol, we decided that antithrombotic therapy could be continued or discontinued during ESD, but it was discontinued preoperatively in only one patient, mainly because the managing physicians considered that their patients would not have increased risk of delayed bleeding when their antithrombotic therapy was discontinued. Moreover, our patients were receiving various antithrombotic therapies, ranging from antiplatelet monotherapy to polytherapy with concurrent heparin. Therefore, the feasibility of our protocol needs to be confirmed in a study with more consistent management of antithrombotic therapy. We observed no adverse events that could be attributable to

bovine thrombin, but this does not necessarily exclude the possibility of an allergic reaction in some patients. Because it is now possible to produce autologous thrombin for use in clinical settings, we plan to perform a study using fibrin glue prepared under full autologous conditions [28, 24]. Finally, the problem of medical expenses must be mentioned. It is necessary to evaluate that the prevention for delayed bleeding using this method contributes to the repression of medical expenses in future.

In conclusion, the use of autologous fibrin glue and PGA sheets to cover post-ESD ulcers prevented delayed bleeding in patients undergoing gastric ESD while receiving antithrombotic therapy. Our findings suggest that this measure will improve the safety of gastric ESD performed concurrently with antithrombotic therapy in the future.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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