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Letter From the Guest Editor

Despite the availability advanced therapeutic modalities, gastrointestinal bleeding (GIB) remains a significant health concern worldwide not only because of its clinical manifestations but also due to associated hospitalizations and costs. Among all admissions for gastrointestinal bleeding, upper gastrointestinal bleeding (originating from esophagus, stomach and duodenum) accounts for about 50% and lower gastrointestinal bleeding (from colon and anorectum) represents 40% of the cases and remaining 10% is indeterminate bleeding (arising from the small intestine). Gastrointestinal bleeding is a condition that warrants a multifaceted assessment all the way from the diagnosis to the treatment including detection of the severity of bleeding, resuscitation of the patient, localization of the bleeding site, laboratory studies, hospitalization process, initial medical therapies, endoscopic treatments, imaging methods and surgical treatment approaches.

This special issue focuses on gastrointestinal bleeding which is covered under the headings of variceal and non-variceal upper GI bleeding, lower GI bleeding, occult and obscure bleeding, hemorrhage associated with polypectomy, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), post-ERCP bleeding and GI bleeding occurring in individuals taking direct oral anticoagulants as well as treatments for the respective conditions. Each topic has been reviewed in detail by academicians with extensive knowledge in their areas of interest. This allowed updating of all information through different perspectives. This special issue also features a case report and quality research articles which present experiences of the general surgery, interventional radiology and gastroenterology specialists on GI bleeding.

It is our pleasure to bring you this special issue on gastrointestinal bleeding with the hope, excitement and belief that it will make a valuable contribution to the current understanding of GIB among physicians working in this field.

Dr.Talat AYYILDIZ

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Review Article

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Diagnostic and therapeutic approaches for non-variceal upper gastrointestinal bleeding

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Abstract

Upper gastrointestinal bleeding (UGIB) is a common, life-threatening medical condition. Non-variceal causes account for more than 90% of bleeding episodes. Peptic ulcer disease is the most frequent cause of non-variceal UGIB. Patients present with hematemesis and/or melena but hematochezia might be present in patients with severe bleeding. Despite advances in diagnostic and therapeutic methods, mortality remains high in the elderly and patients with comorbidities. Endoscopy is the primary procedure that should be performed to identify the etiology of UGIB and for treatment purposes following adequate resuscitation of patients. Early endoscopy (within the first 24 hours) has considerably improved the clinical outcomes. A number of scoring systems are being used in patients with UGIB to identify the risk of complications, rebleeding risk, the need for interventional procedures and the risk of death. The most commonly used scoring tools are the Rockall score, Glasgow-Blatchford score and AIMS65 score. Primary treatment modalities include adequate resuscitation, intravenous fluid support, transfusion of red blood cell suspension, acid suppression therapy and administration of prokinetic agents. In general, angiography, computed tomography, technetium-99m-labeled red blood cell scintigraphy and capsule endoscopy may be used in patients whose bleeding cannot be detected endoscopically. Interventional radiological procedures should be initially performed for hemorrhages that cannot be stopped endoscopically and surgical options should be considered when interventional radiological procedures are out of reach or unsuccessful.

Keywords: upper gastrointestinal bleeding, endoscopy, scintigraphy, non-variceal bleeding

1. Introduction

Upper gastrointestinal bleeding (UGIB) is a common, life-threatening medical condition. UGIB is defined as bleeding originating from a source proximal to the ligament of Treitz including esophagus, stomach and duodenum. UGIB is broadly divided into two groups as variceal and non-variceal hemorrhages. Gastroduodenal ulcers are the leading cause of non-variceal UGIB (Hunt et al., 1995). Non-variceal causes account for more than 90% of bleeding episodes. Clinically, it may present with massive bleeding as well as slow, chronic bleeding. Despite the advances in diagnostic and therapeutic methods, bleeding-related mortality has not changed significantly in comparison to previous years because the mortality is still high in the elderly and the patient population with comorbidities (Wilcox and Clark, 1999; Hwang et al., 2012). In Western countries, the reported annual incidence of UGIB in adults ranges from 103 to 172 episodes per 100,000 population (Rockall, et al., 1995; Van Leerdam et al., 2003). Hospitalizations for UGIB have decreased by nearly 20% in the last decade due to reduction of peptic ulcer bleeding as a result of the use of anti-secretory drugs and decreased prevalence of *Helicobacter pylori* (Laine, et al., 2012). The mainstay of patient management is achieving hemodynamic stability, followed by performing endoscopy for the purposes of diagnosis and treatment. Early endoscopy within the first 24 hours have greatly improved clinical outcomes (Vergara, et al., 2014). In 80% of the cases, non-variceal UGIB stops spontaneously (Van Leerdam et al., 2003). At the same time, early risk stratification of patients is important for treatment planning including the timing of endoscopic treatment and Glasgow-Blatchford, Rockall and AIMS65 scores are commonly used for this purpose (Alzoubaidi, et al., 2019). In the case of persistent and recurrent bleeding, repeat upper endoscopy should be performed initially, followed by consideration of interventional radiology procedures such as trans arterial chemoembolization (TACE) and surgical treatment options (Gralnek et al., 2015).

2. Etiology of non-variceal upper gastrointestinal bleeding

The etiology of non-variceal UGIB most commonly involves peptic ulceration/inflammation (most prevalent, approximately 50%), vascular lesions, congestive gastropathy, malignant

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lesions and other causes (Mallory-Weiss tears, Cameron ulcers, anastomotic ulcers, post-procedural hemorrhages). The etiology cannot be determined in about 10% of the patients (Table 1) (Naseer et al., 2020).

Table 1. Causes of non-variceal gastrointestinal bleeding

Ulcer / Inflammation	Peptic ulcer disease Esophagitis, gastritis, duodenitis Anastomotic ulcers
Vascular Lesions	Gastric antral vascular ectasia (GAVE) Dieulafoy lesion Angiodysplasia Aorta-enteric fistula
Congestive Gastropathy	Portal hypertensive gastropathy
Malignancies	Gastric, esophageal tumors Metastatic tumors
Other	Mallory Weis tear Cameron ulcer

Peptic ulcer disease is defined as a lesion that penetrates into the muscularis mucosa layer of the gastric and duodenal mucosa and is the most common cause of UGIB. *Helicobacter pylori* infection, the use of non-steroidal anti-inflammatory drugs, physiological stress and increased gastric acid secretion are risk factors for bleeding (Hunt et al., 1995). Esophagitis is a frequent cause of UGIB and its risk factors include gastroesophageal reflux disease, the use of certain medications and infections (Da Costa et al., 2001; Guntipalli et al., 2014). Gastritis and duodenitis are inflammation-mediated mucosal injuries and although these are frequent endoscopic findings, they are less likely to cause hemorrhage and usually self-limiting (Guntipalli et al., 2014).

Vascular lesions of the gastrointestinal tract that may cause UGIB to include angiodysplasia, Dieulafoy's lesion and gastric antral vascular ectasia (GAVE). Angiodysplasia is the most common vascular abnormality of the gastrointestinal tract. In the upper GI tract, angiodysplasias are mostly found in the stomach, duodenum but rarely in the esophagus. Its pathogenesis has not been fully elucidated. Endoscopic diagnosis of angiodysplasia can sometimes be challenging because the lesions are small and may resemble fresh bleeding. Rarely, the diagnosis of angiodysplasia can be made by radiological or surgical modalities. Dieulafoy's lesion is a vascular abnormality consisting of dilated, aberrant submucosal vessels and an infrequent cause of UGIB. The majority of the lesions are located in the stomach. Dieulafoy's lesions exhibit an intermittent bleeding pattern and therefore, are identified at a low rate on initial endoscopic examination (Marangoni, et al., 2009). GAVE also known as 'watermelon stomach' is a rare but important cause of UGIB. Endoscopically, it is characterized by linear, diffuse erythematous stripes that radiate from the pylorus to the antrum, giving the appearance of watermelon streaks. The etiology of GAVE is not clear (Jabbari et al., 1984). Mallory-Weiss syndrome is marked by longitudinal superficial mucosal lacerations (Mallory-Weiss tears). Mallory-Weiss tears are often located in the gastroesophageal junction and may extend proximally to involve the stomach and duodenum. Excessive alcohol consumption is the most common cause. Risk factors include hiatal hernia, hyperemesis gravidarum and gastroesophageal reflux disease. Repeated acts that cause a sudden and severe increase in the intra-abdominal pressure such as retching and vomiting precipitate Mallory-Weiss syndrome. Longitudinal tears may progress and extend deep into submucosal arteries and veins, causing bleeding. Bleeding is often self-limiting and recurs infrequently (Kortas, et al., 2001; Rawla and Devasahayam, 2019). Gastrointestinal tumors, primary gastrointestinal tumors, metastatic tumors and locally invasive tumors may cause UGIB. Gastric tumors are the most common cause of UGIB (Kim and Choi, 2015). Unlike other non-variceal UGIB, the success rate of endoscopy is low in bleeding from gastrointestinal tumors and rebleeding after a short time occurs in about 80% of the cases. Surgical or radiological intervention may be required when the endoscopic procedure fails (Adler et al., 2004).

3. Diagnostic and therapeutic approaches for the management of bleeding

There have been considerable advances in the management of UGIB in recent years. However, advanced age and comorbid conditions are still risk factors for many patients (Lanas, 2010) The management of bleeding consists of 3 approaches: pre-endoscopy, endoscopy, and post-endoscopy. For treatment planning, it is important to question the presence of comorbidities (coronary artery disease, pulmonary disease, renal disease, heart failure, chronic liver disease). It allows identification of thresholds for transfusion of red blood cell suspension and intravenous fluid support. History of medication use (non-steroidal anti-inflammatory drugs, antiplatelet drugs, anticoagulants) is crucial in terms of the balance between bleeding control and cardiovascular risk as well as to determine whether the medication should be discontinued and when it should be resumed. Studies have shown that routine nasogastric intubation does not offer any clinically relevant benefit for patients. The presence of coffee ground material or fresh blood in the nasogastric content indicates UGIB (Lanas, 2010). A number of scoring systems are being used in patients with UGIB to identify the risk of complications, rebleeding risk, the need for interventional procedures and mortality risk. These scoring systems are categorized into three groups as those including endoscopic parameters, those with both clinical and endoscopic parameters and those with clinical parameters alone. It is recommended that these scoring tools be used in an early stage in patients presenting with UGIB (Barkun et al., 2010). The most widely used scoring systems are Forrest classification, Rockall score, Glasgow-Blatchford score and AIMS65 score.

3.1. Initial resuscitation

For a patient with a preliminary diagnosis of UGIB, the first thing to do is to assess the patient's airway, breathing and circulation. Oral intake of the patient is stopped. Adequate peripheral access should be achieved with two large-bore (18

gauge) catheters and a central venous catheter inserted when necessary. Blood pressure, oxygen saturation and heart rate should be monitored. Patients should be provided intravenous fluid support without delay. It is particularly important to ensure hemodynamic control and stabilization with intravenous fluid support prior to endoscopy; this way, the risk of treatment-related complications is reduced (Baradarian et al., 2004). No difference in mortality was observed in a meta-analysis comparing colloids and crystalloids for fluid resuscitation in critically ill patients (Perel and Roberts, 2012). The quantity of fluid to be administered is adjusted according to the hemodynamic state of the patient.

3.2. Anemia and thrombocytopenia

In patients with UGIB, red blood cell (RBC) transfusion is often required to maintain tissue perfusion. The decision for transfusion is made individually on a patient basis. Hemoglobin threshold for transfusion is a controversial topic. In hemodynamically unstable patients and patients with severe bleeding, transfusion up to higher thresholds is needed, as hemoglobin values will decrease even further with intensive fluid treatment. Reduced transfusion volume is associated with decreased mortality in hemorrhagic patients; this has led to the consideration of the negative effects of over transfusion on hemostasis (Crooks et al., 2011). Transfusion of red blood cell suspension is needed in patients with active hemorrhage regardless of hemoglobin level. The liberal transfusion strategy aims transfusion to patients with hemoglobin values below 9-10 g/L, whereas the restrictive transfusion strategy targets the patient population with hemoglobin values below 7-8 g/L. In a meta-analysis, patients treated with the restrictive strategy had lower rates of mortality and rebleeding in comparison to patients treated with the liberal strategy (Odutayo et al., 2017). If there is a concern for potential harm to the patient from ischemia (e.g., coronary artery disease) related to anemia, the hemoglobin value is kept above 9 g/L. In the presence of active ischemia, RBC transfusion should be given by keeping the hemoglobin value at 10 g/L. In patients with UGIB, transfusion of platelet suspension is warranted at a platelet count less than 50.000 cells/microliters. There is no evidence demonstrating the benefit of platelet transfusion suspension in patients receiving antiplatelet drugs; therefore, it should be decided on a patient basis.

3.3. Use of antiplatelet and anticoagulant medications

Increasing use of antiplatelet and anticoagulant drugs is a risk factor for UGIB and 44% of patients take these medications (Chang et al., 2015; Dunne et al., 2019). Anticoagulant and antiplatelet drugs are discontinued in UGIB patients when possible. However, potential harms from discontinuation of these drugs should be weighed against the risks of bleeding prior to stopping these therapies and the decision to discontinue or administer an antidote should be made individually for each patient by consulting the departments that started the patient on these medications.

Guidelines suggest an INR (International Normalized Ratio) value less than 2.5 before performing endoscopy (Acosta et al., 2016). Fresh frozen plasma is usually used in patients with a high INR value and prothrombin complex concentrate (PCC) is recommended to achieve a rapid INR reduction in patients with life-threatening bleeding (Maltz et al., 2000). Limited data are available for novel oral anticoagulants (NOACs) which have a short half-life of 5 to 17 hours. PCC may be used in severe bleeding (Veitch et al., 2016). There are no sufficient data on the use of idaricuzimab as an antidote for dabigatran and andexanet alfa (a recombinant modified Factor Xa) for Factor Xa inhibitors in patients with UGIB.

3.4. Acid suppression

Gastric acid suppression contributes to achieving hemostasis. The use of proton-pump inhibitors (PPIs) prior to endoscopy reduces the symptoms of severe bleeding and the need for endoscopic treatment. Patients are started on PPI treatment on the day of admission. Optimal dosage is not clear; studies showed that PPI treatment administered as an intravenous 80 mg bolus dose followed by continuous infusion at 8 mg/h for 72 hours reduced the rates of rebleeding and mortality compared to placebo and non-PPI treated groups (Laine and McQuaid, 2009). Some guidelines recommend intermittent use of high-dose intravenous or oral PPI (80 mg bolus, followed by 80 to 160 mg daily in divided doses) (Gralnek et al., 2015). Patients with peptic ulcer should receive a PPI once daily for 4 -8 weeks after a UGIB.

3.5. Prokinetic agents and tranexamic acid

Prokinetic agents such as erythromycin and metoclopramide improve the endoscopic visibility by accelerating gastric emptying when given prior to endoscopy and they may also reduce the need for a second-look endoscopy. Erythromycin, administered as a single dose at 20-120 minutes before endoscopy, has been shown to provide better endoscopic visibility, shorter duration of endoscopy and reduced need for second endoscopy (Frossard et al., 2002). Tranexamic acid is an antifibrinolytic agent; studies have shown that it has no benefit in the treatment of gastrointestinal bleeding and predisposes to venous thrombus (Roberts et al., 2020).

3.6. Risk Scores

In addition to bleeding, mortality has been shown to be associated with other clinical parameters (e.g., age, comorbidities, shock, endoscopic diagnosis, hemoglobin levels, ulcer diameter, need for transfusion), all of which can have an impact on the prognosis in patients with non-variceal UGIB (Nahon et al., 2012; Monteiro, et al., 2016). The Forrest classification is used to predict the rebleeding risk of patients based on endoscopic findings (Table 2). The most commonly used scoring tool is the Rockall score with both clinical and endoscopic components. Possible scores range from 0 to 11 points.

Table 2. Forrest classification

Forrest Score	Endoscopic Appearance	Risk of Rebleeding (%)
1a	Ulcer with active pulsating bleeding	90
1b	Ulcer with active non-pulsating bleeding	10-20
2a	Ulcer with a visible nonbleeding vessel	50
2b	Ulcer with an adherent clot	25-30
2c	Ulcer with hematin on ulcer base	7-10
3	Ulcer with a clean base without signs of recent bleeding	3-5

Endoscopic findings are not included in the calculation of clinical Rockall score and scoring is done with maximum seven points (Table 3) (Rockall, et al., 1996). The Glasgow-Blatchford score (GBS) consists of eight clinical and laboratory parameters. Scores range between 0 and 23 points. Higher scores indicate greater need for endoscopy. The major advantage of this scoring tool is its ability to identify low-risk patients who do not need to be admitted to hospital. A patient suspected of having an UGIB whose score is 0 can be safely followed on an outpatient basis (Table 4) (Blatchford, et al., 2000; Stanley et al., 2009).

Table 3. Rockall scoring system

Variable/ Score	0	1	2	3
Age	<60	60-79	80≥	
Shock	No shock	Blood pressure>100 Pulse≥100	Blood pressure<100 Pulse>100	
Comorbidity	None		Circulatory failure/coronary artery disease	Renal failure Liver failure Disseminated malignancy
Diagnosis	Mallory-Weiss syndrome/no pathology	All other diagnosis	Malignancy of the upper gastrointestinal tract	
Endoscopic signs of bleeding	None/dark spot		Blood/adherent clot/visible or spurting vessel	

Table 4. Glasgow-Blatchford scoring system

Variable	Score
Blood urea nitrogen (mmol/L)	
6.5-8	2
8-10	3
10-25	4
>25	6
Hemoglobin for men (g/L)	
120-130	1
100-120	3
<100	6
Hemoglobin for women (g/L)	
100-120	1
<100	6
Systolic blood pressure (mm/hg)	
100-109	1
90-99	2
<90	3
Pulse≥100	1
Other markers	
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

The AIMS65 score is an acronym of albumin, INR, alteration in mental status, systolic blood pressure and age. It is a clinical risk scoring tool and the score is calculated by assigning one point for each of the aforementioned components (for a total of five scores). The presence of two or more components indicates a higher risk of mortality (Table 5) (Saltzman et al., 2011).

Table 5. AIMS65 scoring system

Variable	Score
Albumin<3 g/dL	1
INR>1.5	1
Systolic Blood Pressure<90 mm/Hg	1
Altered Mental Status	1
Age>65 year	1

3.7. Endoscopy

Endoscopic examination is recommended for UGIB patients within the first 24 hours after admission for diagnostic and therapeutic purposes. This time interval is 12 hours in patients with impaired hemodynamic state and suspicion of variceal bleeding (Sung et al., 2011). Endoscopic treatment should be instituted following adequate resuscitation and hemodynamic stabilization. In patients with a higher risk of mortality and bleeding (GBS≥12), clinical outcomes were not different between those undergoing early endoscopy (within 6-24 hours) and those treated with emergency endoscopy (within 0-6 hours) (Lau et al., 2020). The diagnosis and treatment of UGIB are conducted by endoscopic examination. In general, angiography, computed tomography, technetium-99m-labeled red blood cell scintigraphy and capsule endoscopy may be used in patients whose bleeding cannot be detected endoscopically. The colonoscopic examination is planned to identify colon-related etiologies for patients in whom a bleeding focus cannot be demonstrated by endoscopy.

Epinephrine injections, argon plasma coagulation, heater probe and endoscopic clips are the methods used in endoscopic

treatment. In the case of failure of conventional treatments, over the scope clips, hemostatic powder, endoscopic suture, endoscopic band ligation, coagrasper or hemostatic forceps, endoscopic ultrasound-guided angiography, cryotherapy, radiofrequency ablation and endoscopic laser coagulation are newer treatment modalities that can be used in UGIB (Naseer et al., 2020). Firstly, repeat endoscopy should be done in a recurring UGIB episode. Interventional radiological procedures should be initially performed for hemorrhages that cannot be stopped endoscopically and surgical options should be considered when interventional radiological procedures are out of reach or unsuccessful. The transarterial chemoembolization (TACE) procedure is recommended for bleeding that persists after optimal endoscopic treatment (Gralnek et al., 2015).

4. Conclusion

Currently, non-variceal upper gastrointestinal bleeding is still a common condition. There have been considerable advances in the endoscopic treatment modalities in the last decade. It is important to determine the risk score of the patients in an early stage. Patients should be evaluated and managed thoroughly taking into account all aspects of their condition due to high numbers of patients with comorbidities, concomitant use of antiplatelet and anticoagulant drugs. Hemostatic powder, over the scope clips, endoscopy guided by Doppler probes are newly developed endoscopic techniques for use in patients in whom bleeding cannot be controlled with conventional endoscopic interventions.

Conflict of interest

All authors declare no conflict of interest regarding this manuscript.

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Treatment of variceal bleeding

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Abstract

Variceal bleeding is a gastrointestinal emergency that is one of the major causes of mortality in patients with cirrhosis. A rise in portal pressure (portal hypertension) occurs when there is resistance to outflow from the portal vein. Varices develop to decompress the hypertensive portal vein and return blood to the systemic circulation. A major cause of cirrhosis-related morbidity and mortality is the development of variceal hemorrhage, a direct consequence of portal hypertension. Prevention of bleeding of these variceal veins and treatment after bleeding is an important target. In this article, we will discuss variceal bleeding secondary to portal hypertension and its treatment based on current data.

Keywords: variceal bleeding, endoscopic band ligation, endoscopic sclerotherapy

1. Introduction

Cirrhosis is termed as the late stage of progressive hepatic fibrosis characterized by the disruption of the hepatic parenchymal structure and the formation of regenerative nodules. Many factors play a role in the etiology of cirrhosis (D'Amico et al., 2006). Currently, mortality is still high and causes significant labor loss. The prognosis of patients with cirrhosis is largely due to its complications. Treatment of cirrhosis is limited except liver transplantation. An important cause of the morbidity and mortality associated with cirrhosis is the development of variceal bleeding secondary to portal hypertension. The prognosis of patients with variceal bleeding depends on the bleeding or other complications are associated with underlying chronic liver disease and its management. The mortality rate due to active variceal bleeding is around 20 percent during each bleeding and re-bleeding is observed in 70 percent of patients within one year. Upper gastrointestinal bleeding unrelated to portal hypertension is also common in patients with portal hypertension (e.g., peptic ulcer disease).

2. Formation of varices

Portal vein pressure is determined by the product of the portal flow volume and the resistance to flow out of the portal vein. Portal hypertension (defined as hydrostatic pressure>5 mmHg) occurs from the obstruction of proximal portal venous outflow. Occlusion may occur in the presinusoidal (e.g., portal vein thrombosis, portal fibrosis), sinusoidal (e.g., cirrhosis) or postsinusoidal (e.g., veno-occlusive disease, Budd-Chiari syndrome) area. Cirrhosis in the form of obstruction in the sinusoidal region is the most common cause of portal hypertension. In these patients, portal vein pressure increased due to increased resistance to permeability in portal sinusoids and increased portal blood inflow due to splanchnic arteriolar vasodilation. An increase in portal pressure occurs when there is resistance in the outlet tract of the portal vein (portal hypertension). Variceal veins direct blood into the systemic circulation via portocaval shunts to open the hypertensive portal vein and drain the blood. These shunts are the gastroesophageal, paraumbilical, retroperitoneal, intestinal and hemorrhoidal regions. When the pressure gradient between the portal and hepatic veins rises above 12 mmHg, variceal veins begin to form. At low pressures, variceal veins do not occur, and they do not bleed (D'Amico et al., 2006; Chang et al., 2020; Egbe et al., 2020). Measuring the difference between portal-hepatic venous pressure gradient, wedge hepatic venous pressure (approximates sinusoidal and portal pressures in cirrhosis) and free hepatic venous pressure can be done by the hepatic venous catheterization method. Measuring by hepatic venous catheterization method does not estimate the size of varices but may be useful for monitoring the success of treatment aimed at lowering portal pressures.

2.1. Risk of variceal bleeding

The annual risk of variceal bleeding in patients with varices due to cirrhosis has been found to be five percent and 28

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percent for three years (Merli et al., 2003). Many clinical and physiological factors are used to predict the risk of variceal bleeding in patients with cirrhosis. These are:

• Location of varices

• Size of varices

• Appearance of varices

• Clinical characteristics of the patients

• Variceal pressure

2.2. Location of varices

Varices can theoretically be seen in the entire gastrointestinal system from mouth to rectum. But it is often found in portosystemic shunt sites in the esophagus, stomach, and rectum. Varices develop deep within the submucosa in the middle of the esophagus, but gradually become more superficial in the distal esophagus. Therefore, esophageal varices at the gastroesophageal junction have the thinnest supportive tissue layer and there is a high probability of rupture and bleeding (Sarin et al., 2014).

Gastric varices are usually classified according to their location associated with bleeding risks:

Gastroesophageal varices (GOV) type 1; These are variceal veins that directly continue from the small curvature of the stomach with the esophagus.

Gastroesophageal varices (GOV) type 2; These are variceal veins that directly continue with the esophagus from the great curvature of the stomach.

Isolated gastric varices (IGV) type 1; It is less common than GOVs. It is in the fundus of the stomach.

Isolated gastric varices (IGV) type 2; It is found in other locations in the stomach.

Gastroesophageal varices bleeding more frequently than isolated gastric varices, but when IGVs bleed, they bleed more massively. The bleeding incidence of IGV type 1 is high (78 percent). The most common bleeding type is GOV type 2 (Sarin et al., 1992).

2.3. Size of varices

The risk of variceal bleeding is related to the diameter (size) of the varices. The explanation for the relationship between variceal size and bleeding risk is derived from Laplace's law; Small increases in vessel radius cause large increases in wall tension. This causes the vessel to burst and bleed. The classification of esophageal varices' size is commonly as follows (Beppu et al.,1981);

• F1: Small, flat varices

• F2: Enlarged, tortuous varices occupying less than a third of the lumen

• F3: Large coil-shaped varices covering more than one third of the lumen

In general, F2 and F3 type varices should be treated. In addition, patients with decompensated cirrhosis should be treated even if their varices' size is small (Garcia-Tsao et al., 2017).

2.4. Appearance of varices

Various morphological features of varices observed on endoscopy are associated with an increased risk of bleeding (Kim et al., 1997).

• Cherry red spots

• Red velvet vein appearance

• Hematocystic spots are separate red spots on varices that resemble "blood bubbles"

• Diffuse erythema indicates the diffuse red color of varices

3. Clinical features of the patients

CHILD scoring is an indicator of liver dysfunction based on the presence of serum albumin concentration, bilirubin level, prothrombin time, acid, and encephalopathy. A higher score is associated with an increased likelihood of variceal bleeding. A previous history of variceal bleeding is an indicator of an increased risk of bleeding again. For example, only one third of all patients with cirrhosis experience variceal bleeding, while more than 70 percent experience recurrent variceal bleeding after the first bleeding. Bleeding recurs within six weeks in one third of patients with the first bleeding referred to as "early re-bleeding", and after six weeks in one third referred to as "late re-bleeding" (Tripathi et al., 2015). Among the risk factors for early recurrent bleeding are being over 60 years old, kidney failure and ascites (de Francis et al., 1992). The risk of early re-bleeding is greatest immediately after cessation of active bleeding (50 percent of such events occur within 48 hours) and decreases over time.

3.1. Variceal pressure

Although measurement of variceal pressure is not routinely performed, it can be accurately measured with a pressure sensitive endoscopic gauge. Variceal pressure may be an important determinant for variceal bleeding. The incidence of variceal bleeding with variceal pressure at different levels is as follows (Bosch et al.,1986);

• ≤13 mmHg - 0/25 (0 percent)

• > 13 and ≤14 mmHg - 1/11 (9 percent)

• > 14 and ≤15 mmHg - 2/12 (17 percent)

• > 15 and ≤16 mmHg - 7/14 (50 percent)

• > 16 mmHg - 18/25 (72 percent)

3.2. Risk classification

The calculation of an index that numerically measures the risk of variceal bleeding numerically in each patient with CHILD classification, variceal size and the presence of specific appearance can be used to evaluate the prognosis (Table 1) (North Italian Endoscopic Club for the Study and Treatment of

Esophageal Varices, 1988). The calculated risk is the highest in the first year after these risk factors are identified. As an example, a patient with CHILD class C cirrhosis and tense ascites and large variceal veins with red marks has an approximately 76 percent chance of developing variceal bleeding within one year. Such a patient is an open candidate for prophylactic treatment to prevent bleeding.

Table 1. Shows the percentage of bleeding within a year according to the characteristics of variceal veins

Percent of variceal bleeding in a year according to its characteristics									
Appearance of varices	CHILD CLASS A			CHILD CLASS B			CHILD CLASS C		
	F1	F2	F3	F1	F2	F3	F1	F2	F3
-	6	10	15	10	16	26	20	30	42
+	8	12	19	15	23	33	28	38	54
++	12	16	24	20	30	42	26	48	64
+++	16	23	34	28	40	52	44	60	76

End Stage Liver Disease (MELD) score was also found to predict mortality after acute variceal bleeding. MELD score above 19 is associated with a 20 percent mortality rate, and a MELD score below 19 is associated with a mortality rate of less than five percent. MELD scores have also been shown to predict gastric variceal bleeding (Soga et al., 2009).

4. Treatment of variceal bleeding

The prognosis of patients with variceal bleeding depends on achieving hemostasis and avoiding complications associated with underlying chronic liver disease. Treatment of the underlying cause of liver disease reduces the severity of portal hypertension and variceal bleeding. This is most common in patients who quit alcohol and who have a sustained virological response after hepatitis C treatment. Treatment of acute variceal bleeding usually requires multidisciplinary care including gastroenterology, intensive care, and interventional radiology.

4.1. Goals of treatment

- Ensuring and maintaining hemodynamic stability
- Ensuring and maintaining adequate oxygenation
- Control of bleeding
- Prevention of complications

4.2. Basic treatment

General resuscitation and supportive measures are applied for patients with a history of variceal bleeding or gastrointestinal bleeding who may have varices (e.g., patients with cirrhosis). To ensure hemodynamic stability, appropriate vascular access is established, and fluid replacement is initiated. Oxygenation is provided with a nasal cannula. Endotracheal intubation may be considered in patients with hemodynamic instability as it will facilitate the endoscopic procedure. Whether endotracheal intubation is effective in preventing aspiration pneumonia is controversial. Typically, nasogastric tube placement followed by gastric lavage can be used to remove particulate matter, fresh blood, and clots from the stomach prior to endoscopy. Typically, a prokinetic agent (e.g., erythromycin) may be given prior to upper endoscopy to improve endoscopic imaging (Pateron et al., 2011). If hemoglobin is <7 g / dL, blood transfusion should be performed to keep hemoglobin between ≥7 g / dL and <9 g / dL. However, it should be aimed to keep hemoglobin at 9 g / dL for patients at high risk of mortality and morbidity, such as patients with comorbid disease such as unstable coronary artery disease or with ongoing active bleeding. Prophylactic antibiotic therapy is recommended in patients with cirrhosis presenting with gastrointestinal bleeding because antibiotic prophylaxis reduces the risk of death, infection, and bleeding (Chavez-Tapia et al., 2011). Typically, parenteral ceftriaxone therapy is administered (1 g intravenous daily for seven days). The patient is discharged with oral ciprofloxacin treatment. For hospitalized patients, prophylactic antibiotics reduce the risk of mortality, infection (e.g., spontaneous bacterial peritonitis, urinary tract infections) and bleeding.

5. Treatment

Current treatment options for acute variceal bleeding include medications (vasopressin, somatostatin, and analogs), endoscopy, transjugulary intrahepatic portosystemic shunt (TIPS) and surgical treatment.

5.1. Medical therapy

The first step to stop variceal bleeding is pharmacological treatment. Vasoactive drugs reduce portal blood flow and are used for the treatment of acute variceal bleeding. It includes vasopressin, somatostatin, and its analogs (terlipressin and octreotide). As a group, it has been shown that vasoactive drugs reduce mortality and develop hemostasis in patients with acute variceal bleeding (Wells et al., 2012). Pharmacological treatment should be initiated considering variceal bleeding in all patients with upper gastrointestinal bleeding in patients with varices or suspected portal hypertension (e.g., patients with cirrhosis). Pharmacological treatment should continue until it is determined that the source of bleeding is not from varices. Terlipressin should be considered first in pharmacological treatment. It is administered at an initial dose of 2 mg IV every four hours and can be titrated up to 1 mg IV every four hours after bleeding has been controlled. Pharmacological treatment typically continues for three to five days after the bleeding has ceased. Terlipressin is the most effective drug for mortality (Ioannou et al., 2003). When used in addition to sclerotherapy, treatment with somatostatin or octreotide infusions is superior to sclerotherapy alone or somatostatin alone for prevention of premature re-bleeding and possibly survival (D'Amico et al.,1998; Besson et al., 1995; Avgerinos et al., 1997). Combination therapy with somatostatin analogues and endoscopic variceal ligation has a higher five-day success rate compared to endoscopic variceal ligation alone. Ocreotide is only useful when combined with endoscopic therapy. However, no effect on mortality was shown (D'Amico et al., 2002).

5.2. Endoscopic therapy

It is the definitive treatment method for active variceal bleeding. Two types of endoscopic treatments are commonly used: endoscopic variceal ligation (EVL) and endoscopic sclerotherapy (ES). EVL is generally preferred as the first treatment. If the first treatment attempt with EVL fails, ES can be tried. The aim should be to perform an upper GIS endoscopy after fluid resuscitation and within 12 hours after admission to the hospital.

• EVL is like hemorrhoidal taping; It involves placing small elastic bands around the variceal veins.

• ES involves the injection of sclerosing solution into variceal veins. There are a number of sclerosing solutions available, all of which are effective. The volume and frequency of injections varies widely among endoscopists. 1-2 mL of 5 percent sodium morrhuate can be used per injection for a total of 12 to 20 mL per session. Other commonly used alternatives are polidocanol and cyanoacrylate excisions (Lux et al., 1997).

5.3. TIPS (Transjugulary intrahepatic portosystemic shunt) and surgery

If the bleeding cannot be controlled endoscopically, a second endoscopic procedure can be performed. Subsequently, treatment options include TIPS placement or surgical shunting. Hemostasis is achieved following TIPS placement in more than ninety percent of patients. In addition, early TIPS placement following endoscopic treatment may increase non-transplant survival in patients with advanced cirrhosis (Lv et al., 2019a; Conejo et al., 2018; Lv et al., 2019b). Absolute contraindications for TIPS placement include heart failure, polycystic liver disease, severe pulmonary hypertension, uncontrolled systemic infection, sepsis, and severe tricuspid regurgitation. Relative contraindications include hepatocellular carcinoma (especially if it is central), portal vein thrombosis, and severe coagulopathy or thrombocytopenia. Complications of TIPS placement include portosystemic encephalopathy, technical complications (e.g., cardiac arrhythmias, liver capsule injury) and TIPS stenosis.

5.4. Balloon tampon

It is an option to temporarily stop bleeding from esophageal or stomach varices, but is associated with serious complications, including esophageal rupture. Balloon tamponade appears to be less successful in patients who fail pharmacological therapy and patients with premature bleeding. Esophageal stent placement (Danis stent) has begun to be used as an alternative to balloon tamponade in patients with uncontrolled acute variceal bleeding, and the stent has been replaced by tamponade due to its lower risk of complications and the possibility of feeding while the stent can remain for a long time.

5.5. Surgical treatment

It is extremely effective at stopping bleeding and preventing re-bleeding but is associated with a mortality rate of up to 50 percent. It is generally not used because TIPS has a high success rate and lower complication rates. Despite hemostasis, many patients die of postoperative liver failure and surgical complications. Those with severe bleeding, tense ascites, coma, aspiration pneumonia, kidney failure or sepsis are particularly at risk of surgery. The ideal patient for surgical treatment is a person with well-preserved liver function who cannot pass the emerging endoscopic treatment and who does not have bleeding or complications from endoscopy (Rikkers et al., 1995).

Treatment for bleeding gastric varices is cyanoacrylate injection, if possible. However, it is not approved for the treatment of bleeding in gastric varices. If cyanoacrylate injection is not an option, TIPS is done. Varices can sometimes develop in areas other than the stomach and esophagus, and when they bleed, they become clinically important. These are called ectopic varices. Examples are duodenal, rectal, and peristomal varices (developing around the stoma in patients with colostomy). TIPS or surgery is the most appropriate treatment for patients with ectopic variceal bleeding. Endoscopic treatment is usually unsuccessful in ectopic varices.

5.6. Complications of variceal bleeding

Hemostasis is achieved with treatment in most patients with variceal bleeding; however, patients with cirrhosis are at risk of complications during hospitalization. Major complications include pneumonia, sepsis, chronic/acute liver failure, hepatic encephalopathy, and kidney failure. All complications are more common when the endoscopic procedure is performed as an emergency rather than elective.

5.7. Prophylaxis of variceal bleeding

In the presence of variceal veins, prophylaxis is applied to prevent bleeding. Prophylaxis of variceal bleeding is divided into two as primary and secondary prophylaxis.

5.8. Primary prophylaxis

Primary prophylaxis aims to prevent variceal bleeding in patients with esophageal varices without a history of bleeding. Pre-Primer prophylaxis refers to the measures to prevent the development of varices. In patients with such portal hypertension but without variceal veins, treatment of the underlying liver disease may help prevent the development of variceal veins. However, treatment with beta blockers is not recommended in patients without variceal veins (Groszmann et al., 2005). Measures to prevent bleeding in patients with a history of variceal bleeding are called secondary prophylaxis. We aim to achieve one of two results in primary prophylaxis;

• Reduction of portal hypertension (e.g., beta blockers, surgical portal decompression or transjugular intrahepatic shunts)

• Direct treatment of variceal veins (e.g., variceal ligation)

Endoscopic screening for esophageal varices should be performed in most of the patients with cirrhosis, so prophylactic treatment can be given in case of high risk of

bleeding varices. Scanning is typically done with an upper GIS endoscopy. Screening is repeated every two to three years in patients with compensated cirrhosis without varices. Screening is repeated every two years in patients with small variceal veins. Endoscopy is repeated every year in patients with decompensated cirrhosis or in the presence of endoscopic evidence of increased bleeding risk in variceal veins. At these periodic controls, patients with CHILD B or C disease, medium-large size variceal veins, and patients with red color changes in varices should receive primary prophylaxis. Patients with CHILD B or C disease or with red discoloration of varices can be treated with beta blockers, but if they cannot tolerate EVL can be applied. EVL is preferred primarily in patients with medium-large variceal veins (Li et al., 2011).

In general, for patients treated with non-selective beta-blockers, nadolol can be used starting with a dose of 40 mg per day (as it can be given once a day). Propranolol may also be preferred in this regard. The hemodynamic goal of treatment with a non-selective beta blocker is to reduce the hepatic venous pressure gradient (HVPG) to 10 percent or ≤12 mmHg. If HVPG cannot be used to monitor therapy, the beta blocker dose can be titrated by targeting a heart rate of about 55 to 60 beats per minute. Patients with decompensated cirrhosis (Child B or C) receiving beta blockers should be closely monitored for side effects. Beta blockers may need to be stopped if the patient becomes resistant to treatment, develops hepatic encephalopathy or spontaneous bacterial peritonitis. Approaches not recommended for primary prophylaxis include nitrates (alone or in combination with beta-blockers), shunt therapy, or sclerotherapy. In addition, combination therapy with beta blockers and EVL is not recommended for primary prophylaxis (de Franchis et al., 2010).

5.9. Secondary prophylaxis

Measures to prevent bleeding in patients with a history of variceal bleeding are called secondary prophylaxis (Shi et al., 2013). Patients recovering from the first episode of esophageal variceal bleeding experience a high rate of bleeding (up to 60 percent during the first year).

• Acute variceal bleeding: The acute bleeding episode consists of the time interval from admission to the hospital to the 120th hour (5th day).

• Variceal re-bleeding: Variceal bleeding describes the bleeding occurring≥120 hours after the first bleeding, provided that initial hemostasis can be achieved.

Liver transplantation is recommended for patients with a MELD score of 14 and a history of esophageal variceal bleeding because transplantation is the most effective long-term treatment for variceal bleeding and other complications of portal hypertension (Zhang et al., 2009). Patients are evaluated for interventions that prevent the progression of liver disease. So, treatment of the underlying disease is important. For patients with cirrhosis recovering from an attack of esophageal variceal bleeding, EVL is preferred to prevent re-bleeding rather than endoscopic sclerotherapy. EVL is performed one to two weeks after discharge from the hospital and then every two to four weeks until variceal veins disappear. A nonselective beta blocker is started on the 5th day after the first bleeding period. The duration of beta blocker therapy varies depending on the patient's course of disease, the development of side effects and the clinician's preference.

In patients who are contraindicated or intolerant to beta blockers, only EVL is recommended to prevent recurrent variceal bleeding. TIPS placement is the preferred long-term strategy for patients with cirrhosis who initially recover from variceal bleeding but later develop recurrent variceal bleeding despite EVL and / or beta blocker therapy (Propst et al., 1995; Westaby et al., 1992).

6. Conclusion

Among patients with cirrhosis, variceal veins occur at a rate of 5 to 15 percent per year, and variceal bleeding develops in one third of patients with varices. Variceal bleeding is a gastrointestinal emergency that is one of the main causes of death in patients with cirrhosis. The prognosis of patients with variceal bleeding depends on achieving hemostasis and avoiding complications associated with the underlying chronic liver disease. Treatment options available for acute variceal bleeding include medications (vasopressin, somatostatin, and analogs), endoscopy, TIPS and surgery. An important issue as well as intervention in variceal bleeding is the primary and secondary measures that will prevent bleeding after variceal formation and bleeding again after bleeding.

Conflict of interest

All authors declare no conflict of interest.

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Lower gastrointestinal bleeding

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Abstract

Bleeding from the lower part of the digestive system that appears as hematochezia (fresh blood, clot or cherry-colored stool) or melena (dark-colored tarry stool) is called lower gastrointestinal tract bleeding (lower GI bleeding) (or colonic bleeding). In the traditional definition, lower GI bleeding was generally classified as bleeding distal to the Treitz ligament (duodenojejunal junction) as the border. In the last decade, GI bleeding has adopted three categories in some recent publications: Upper, middle, and lower. According to this category, bleeding from a source between the Treitz ligament and the ileocecal valve is classified as middle GI bleeding, bleeding from the distal of the ileocecal valve is classified lower GI bleeding. Lower GI bleeding and hospitalization rates increase with aging. Currently, physicians managing lower GI bleeding have many different diagnostic and therapeutic options ranging from colonoscopy and flexible sigmoidoscopy to radiographic interventions such as scintigraphy or angiography. Lower GI bleeding often stops spontaneously and less common than upper GI bleeding. Even though no modality has emerged as the gold standard in the treatment of lower GI bleeding, colonoscopy has several advantages and is generally considered as the preferred initial test in most of the cases.

Keywords: bleeding, colonoscopy, hematochezia, sigmoidoscopy

1. Introduction

Bleeding from the lower part of the digestive system that appears as hematochezia (fresh blood, clot or cherry-colored stool) or melena (dark-colored tarry stool) is called lower gastrointestinal tract bleeding (lower GI bleeding) (or colonic bleeding) (Ghassemi and Jensen, 2013; Khan and Mandiga, 2020). In the traditional definition, lower GI bleeding was generally classified as bleeding distal to the Treitz ligament (duodenojejunal junction) as the border. In the last decade, GI bleeding has adopted three categories in some recent publications: Upper, middle, and lower. According to this category, bleeding from a source between the Treitz ligament and the ileocecal valve is classified as middle GI bleeding, bleeding from the distal of the ileocecal valve is classified lower GI bleeding (Kim et al., 2014). Lower GI bleeding and hospitalization rates increase with aging. Currently, physicians managing lower GI bleeding have many different diagnostic and therapeutic options ranging from colonoscopy and flexible sigmoidoscopy to radiographic interventions such as scintigraphy or angiography (Davila et al., 2005). Lower GI bleeding often stops spontaneously and less common than upper GI bleeding. Even though no modality has emerged as the gold standard in the treatment of lower GI bleeding, colonoscopy has several advantages and is generally considered as the preferred initial test in most of the cases (Lhewa and Strate, 2012).

2. Epidemiology

2.1. Incidence

Acute lower GI bleeding is one of the most prevalent gastrointestinal hospitalization indications. The incidence of hospitalization due to lower GI bleeding is estimated at 20 to 30 per 100,000 people per year (Longstreth, 1995). This ratio increases dramatically as the age progresses. However, in the same population, the incidence of hospitalization for acute upper gastrointestinal bleeding is 100 per 100,000 people annually (Longstreth, 1995).

2.2. Demographic information

In most studies, lower GI bleeding predominantly affects the elderly population, on average over 65 years of age (Velayos et al., 2004). Simultaneously along with advanced age distribution, it is also an important burden of comorbidities. Studies indicate that at least 70% of patients with lower GI bleeding have at least one comorbidity (Schmulewitz et al., 2003). Males were significantly more frequently affected than

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females in Longstreth 's population-based lower GI bleeding study (Longstreth, 1995).

2.3. Disease course

Most patients with lower GI bleeding have positive results despite older age and comorbidities (Lewis and Ndsg, 2008). Mortality rates range from 0% to 25% (Ghassemi and Jensen, 2013). The main cause of most deaths is not directly the uncontrolled bleeding, but the worsening of an underlying condition or due to a nosocomial complication. Increasing age, length of stay at hospital, and several comorbid conditions are independent predictors of all-cause mortality (Longstreth, 1995). Advances in endoscopic and radiological hemostasis techniques seem to reduce surgical intervention and recurrent bleeding rates (Oakland, 2019). Interventional radiology and surgery are at high risk for morbidity and mortality these patients. (Bregenzer et al., 2002).

3. Initial evaluation and treatment of acute lower gastrointestinal bleeding

3.1. Clinical history

Initial evaluation of the patient with suspected acute lower GI bleeding consists of medical history, obtaining vitals, thorough physical examination including rectal touch, and also nasogastric lavage if necessary and can be performed simultaneously with resuscitation (Strate and Gralnek, 2016b). Risk factors such as drugs that may cause colon ulcers or bleed, previous large bowel surgery, and symptoms to help identify the source of bleeding should be carefully questioned (Kim et al., 2014). Symptoms can help identify the source of the bleeding or be misleading. For example, bright red or cherry rectal bleeding may unexpectedly originate from the upper gastrointestinal tract at 15% (Ghassemi and Jensen, 2013).

3.2. Physical examination

In the first evaluation, physical examination should be done in detail and systemically. The patient's vital signs should be recorded, focusing on hypovolaemia symptoms such as orthostatic symptoms, postural complaints, pallor, palpitations, fatigue, chest pain, dyspnea, tachypnea, hypotension. The abdominal examination should be examined in terms of the surgical scar, organ growth, tenderness with palpation, and masses. The patient's stool should be examined to identify the color; however, the definition of the color of the stool varies widely between patients and physicians. Rectal examination should be performed both for investigating the probable anorectal disease also to confirm the stool color described by the patient. Whether the rectum is empty, stool, and possible blood contamination, gaita density and color of the finger on the rectal touch should be noted.

3.3. Laboratory

Standard total blood count, biochemistry panel, and coagulation tests should be studied from the blood samples of the subject with acute lower GI hemorrhage. Blood should be collected in a separate tube for blood group typing and cross-matching to prepare erythrocyte suspension in risky patients.

Hematocrit and hemoglobin values may not accurately reflect blood loss on hematological evaluation after the onset of bleeding, because it takes more than 24 to 72 hours for the vascular space to stabilize with extravascular fluid. Hemodilution also occurs in subsequent intravascular fluid administration and the result may be lower than its value.

Total leukocyte count does not increase much in lower GI bleeding than upper GI bleeding. It may increase according to the accompanying inflammatory condition with severe bleeding. Decreased thrombocyte levels may increase the severity of bleeding. In patients with upper GI bleeding, due to higher absorption of urea after blood proteins from the intestines that are broken down by gut bacteria, blood urea nitrogen level generally raises to a greater extent compared to the serum creatinine level, whereas this rate is not seen with lower GI bleeding.

Prothrombin time (PT) and INR levels may indicate if a subject has disruption in the extrinsic coagulation pathway. Increased values may be seen in chronic hepatic disease or due to warfarin, and may change the severity of bleeding and treatment approach

3.4. Clinical determination of the bleeding area

The duration, frequency, and colour of blood passing through the bowel can help distinguish the severity and probable location of bleeding. While melena mostly indicates an upper GI origin, it can also be present in the small intestine or proximal colon bleeding. Hematocesia usually means a colorectal or anal origin of hemorrhage if the patient is not hypotensive (rapid blood loss). The presence of hypovolemic findings may indicate severe upper GI bleeding with the rapid passage of blood through the digestive system. In addition to stool colour, various tools are available to distinguish whether the bleeding is from upper- or lower-part GI tract. This step is important because 2% to 15% of patients who are presumed to have lower GI bleeding will have upper GI bleeding.

3.5. Hospitalization

Cases with severe GI bleeding should be hospitalized and closely followed and treated in the hospital. Those presenting only with mild bleeding (self-limiting hematochezia or rare melena) and those who are hemodynamically stable, with normal blood tests and that can be certain about returning to the hospital in case of recurrence of symptoms may be followed up in an outpatient setting rather than directly in the hospital. These patients may be suitable candidates for elective outpatient clinic examination and endoscopy. If there is abundant red-coloured blood from the rectum and large amounts of hematochezia, unstable vital signs, or other serious illnesses that may worsen the underlying medical conditions, patients should be monitored at the intensive care unit, followed by treatment.

4. Diagnostic procedures and endoscopic imaging

4.1. Colonoscopy

New improvements in endoscopic technologies have made

colonoscopy the leading modality in lower GI bleeding in the last 30 years. Following a rapid bowel cleaning, emergency colonoscopy is the first procedure for almost all patients presenting with suspected acute lower GI bleeding. It has both diagnostic and therapeutic intervention. After bowel preparations such as polyethene glycol (PEG) cleaning, in most cases initial evaluation is required before colonoscopy, but in selected ones, anoscopy or flexible sigmoidoscopy can be performed without prior bowel cleansing or following only enema (Hassan et al., 2019; Niikura et al., 2018).

One of the most important issues in diagnostic colonoscopy for acute lower GI hemorrhage is to identify the stigmata of recent hemorrhage, including active bleeding, visible vessel without bleeding, and adherent clot.

The best time to do emergency bowel cleansing and colonoscopy is unknown. Emergency colonoscopy for lower GI bleeding is usually planned approximately 6-24 hours following the patient's admission to the hospital.

In theory, the earlier the endoscopic procedure is performed, the more likely it is to find a stigmatic lesion (e.g., bleeding diverticula, a polyp stalk) which may be available to endoscopic intervention. One prospective study revealed no difference between urgent (12 hours after admission) and elective (36 to 60 hours after admission) colonoscopy in terms of more bleeding, blood transfusion, hospital days, or hospital costs (Laine and Shah, 2010).

Appropriate medical resuscitation in these patients not only allows more secure endoscopy but also provides an improved diagnostic evaluation for volume-dependent lesions and provides more effective hemostasis due to correction of coagulopathy.

Patients who are hemodynamically stable, whose general condition is better able to tolerate colonoscopy without any finding of active bleeding, can usually undergo an emergency colonoscopy (within 24 hours) in the GI endoscopy department instead of the ICU.

4.2. Anoscopy

Anoscopy with a slotted tool may be beneficial for patients suspected of ongoing bleeding due to internal haemorrhoids or any other anorectal diseases (e.g., fissures, fistulas, proctitis). Emergency treatment with rubber band ligation is recommended for internal haemorrhoids (Oakland et al., 2019).

4.3. Flexible sigmoidoscopy

Flexible sigmoidoscopy is used to examine the rectum and left colon for the possible hemorrhage, and it may be in an enema, or even an unprepared colon (Papagrigoriadis et al., 2004). Even though it's not sufficient for the examination of the anal canal, flexible sigmoidoscopy itself can be successful in diagnosing nearly 9% of patients (Ferguson, 2005).

In cases that the distal colon may be cleaned sufficiently with enema, urgent flexible sigmoidoscopy may be performed depending on the aetiology of bleeding such as solitary rectal ulcer, inflammatory bowel disease, radiation proctitis, post-polypectomy procedure bleeding (in rectosigmoid flexure)) or internal hemorrhoids. Therapeutic hemostasis can be achieved via endoscopy (Asge Technology et al., 2009).

Conventionally, colonoscopic examination for lower GI bleeding was postponed due to the required adequate bowel preparation and hesitation of increased procedural risks (Caos et al., 1986).

4.4. Computed tomography and computed tomography colonography

Using computed tomography (CT) in patients with acute bleeding has been extremely attractive due to its rapid and widespread availability and comprehensive evaluation capability. Multidetector CT (MDCT) is able to detect lesions in the colon which may be the origin of the hemorrhage (diverticula, colitis, masses, or varicose veins) (Wells et al., 2018). If there are hematochezia and abdominal pain available, CT is often performed. Fluoroscopic angiography and CT angiography are both useful in cases which do not respond well to resuscitation or who are unlikely to achieve appropriate bowel cleansing and have ongoing bleeding.

CTA has the advantage of ability to pinpoint the source of arterial and/or venous GI bleeding and identify the etiology that may cause the bleeding to guide subsequent treatment (Mortimer et al., 2011). Among the handicaps of CTA are reduced sensitivity compared to radionuclide imaging, relatively high radiation exposure, and development of iv contrast-induced renal damage. Due to the short scanning time, false-negative results may be seen if the patient is not bleeding during the imaging process.

4.5. Radionuclide imaging

Gastrointestinal bleeding study is a non-invasive diagnostic radionuclide imaging study to examine patients with an obvious suspicion of GI bleeding, particularly involving the middle and lower GI tracts (Dam et al., 2014). It is performed with erythrocytes with technetium-99m (99mTc-RBC) and helps to interpret the bleeding status (active or intermittent), also the gross localization, and quantitation (Dam et al., 2014). Radionuclide imaging in lower GI bleeding implies injecting 99mTc-RBC intravenously and obtaining serial scintigraphy to identify focal collections of radiolabeled material. This radionuclide imaging is reported to identify blood loss as low as 0.04 mL / min. In this examination, it was reported that the overall positive diagnosis rate was approximately 45%. Additionally, it detected with an accuracy of 78% to localize the actual bleeding site (Dam et al., 2014). False-positive results most probably occur if the passage of blood in the lumen is fast, so that the radiolabeled blood is identified in the lower GI tract even if the blood has exited the upper GI tract (Khan and Mandiga, 2020).

4.6. Angiography

Mesenteric angiography is most likely to identify a bleeding area during the arterial blood loss is minimum 0.5 mL/min to

identify extravasation in the intestine (Rasuli et al., 2014). One of the benefits of this procedure is that when the bleeding site is identified, therapeutic interventions are available with the same method. Mesenteric angiography is usually planned following positive technetium 99mTc-RBC scintigraphy or following positive CT in conditions of intermittent bleeding. The rate at which angiography detects an active bleeding site has been shown to depend on the bleeding rate, with the required bleeding rate of minimum 0.5 mL/min (Strate, 2005; Yoon et al., 2006). With technological improvements in super selective embolization of distal artery branches in interventional angiography, it has become an effective method for controlling upper GI bleeding quickly and safely (Hreinsson et al., 2016; Lv and Gu, 2019). However, significant complications may be seen in 3% of cases. These may be due to contrast agent reactions, hematoma formation, bowel ischemia, acute kidney injury, femoral artery thrombosis, and transient ischemic attacks (Wortman et al., 2017).

4.7. Barium enema

The role of double-contrast barium enema (DCBE) is decreasing in examination of lower GI bleeding (Farrell and Friedman, 2005). Emergency DCBE is not beneficial in subjects with lower GI hemorrhage. This imaging technique is not usually diagnostic due to its inability to show vascular lesions and can be misguiding when only diverticula are present (Iwamoto et al., 2008).

4.8. Surgery

Surgical treatment for lower GI hemorrhage is rarely required in subjects as majority of these cases are self-limiting or easily managed with medical or endoscopic treatment modalities (Ghassemi and Jensen, 2013). Surgical intervention may be needed when diffuse bleeding that cannot be stopped by medical therapy (such as ischemic colitis or bleeding due to inflammatory bowel disease), absent or ineffective angiography in the unstable cases, ongoing bleeding despite repeated endoscopic and/or angiographic interventions in the stable cases, or definite resection-managed etiology such as the neoplasm (Whitehurst, 2018; Yi et al., 2012). Conventional surgical indications include hemodynamic instability despite giving six units of blood, bleeding that persists for more than 72 hours, or re-bleeding 24 hours after admission.

5. Causes and management

Lower GI bleeding may present as an acute and mortal event or as chronic bleeding that can present as iron deficiency anemia, positive fecal occult blood test, or intermittent hematochezia (Barnert and Messmann, 2009). In cases where lower GI bleeding does not stop spontaneously, urgent intervention is required to determine the origin of the bleeding and to stop the bleeding. Colonoscopy allows detection of stigmata of recent hemorrhage (SRH) (visible vessels, adhering clot and/or spots) and provides information on location of the lesions and risk stratification, although active bleeding may not be always visible during colonoscopy (Aoki et al., 2019). A bleeding lesion can generally be diagnosed accurately when there is ongoing bleeding, a visible vessel, or a clot (Strate and Gralnek, 2016a).

5.1. Diverticular bleeding

The pseudo diverticulosis of the colon is defined as the mucosal and submucosal layers that penetrate through the intramural blood vessels from the weak points of the muscle layer (Wedel et al., 2015). Histologically, diverticula of the colon are in fact pseudo diverticulosis as they do not include all layers of the colon wall (Maykel and Opelka, 2004). Diverticula are typically seen as the colonic tissue is pushed out due to intraluminal pressure at spots of entry of the small arteries (vasa recta) (Schieffer et al., 2018). These spots of the vasa recta are places that are relatively weak so that the mucosa and submucosa may herniate when intraluminal pressure is raised (Wedel et al., 2015). Diverticula vary in size from a few millimeters to several centimeters and are mostly in the left colon (Brian West, 2006).

Most colonic diverticula remain asymptomatic and uncomplicated. Diverticular disease is the fifth most critical gastrointestinal condition in terms of healthcare costs in Western countries and its incidence increases with advanced age as being up to 60 % in people over 70 years (Violi et al., 2018).

Of the many different causes of lower GI bleeding, diverticular bleeding remains the most common reason (Laine et al., 2012). Diverticular bleeding of the colon usually presents as brisk hematochezia accounting for 30% to 50% of massive rectal hemorrhage cases (Rustagi and McCarty, 2014). The site of bleeding in a diverticulum may be bleeding from the veins in the diverticulum neck or base. Definitive diverticular hemorrhage, the site of the hemorrhage was the base in 52% and the neck in 48% of diverticula (Mohammed Ilyas and Szilagy, 2018). According to colonoscopy, CT angiography or surgical findings, diverticular bleeding should be classified carefully and rapidly (Mohammed Ilyas and Szilagy, 2018). Advanced age, tobacco and/or alcohol consumption, use of several medications (nonsteroidal anti-inflammatory medications (NSAIDs), aspirin, antithrombic drugs), and presence of bilateral diverticulosis and atherosclerosis-related diseases such as hypertension, diabetes mellitus, ischemic heart disease, and obesity have been proposed as possible risk factors for colonic diverticular bleeding. In addition, it has been suggested to increase the risk of prolonged recurrent hemorrhage (Rustagi and McCarty, 2014).

Diverticular hemorrhage generally manifests as painless, intermittent, and large volume lower GI hemorrhage. Although the nature or the color of the hemorrhage differs according to the severity of the hemorrhage, it can be seen in right-sided diverticular bleeding, clinically dark, burgundy blood, or bleeding resembling melena. Diverticular bleeding spontaneously ceases in 70-80% of cases with the rebleeding rate reported to range between 22% to 38% (Mohammed Ilyas

and Szilagy, 2018).

About one-third of patients with true diverticular hemorrhage (presumptive or definitive) during urgent colonoscopy following adequate cleansing have an SRH bleeding, such as ongoing bleeding, a visible vessel, an adherent clot, or a flat spot in a single diverticulum (Jensen, 2018).

Immediately after the appearance of SRH, the accepted standard management for diverticular hemorrhage is endoscopic intervention, which is endoscopic band ligation (EBL), injection therapy, clipping, endoscopic detachable snare ligation therapy (EDSL), or thermal contact. (Bloomfeld et al., 2001; Jensen et al., 2000; Kishino et al., 2020).

The hemostatic powder as topical sprays (hemospray, EndoClot, Ankaferd) is not a preffered hemostatic treatment modality for diverticular hemorrhage.

The over-the-scope clip (OTSC) system (Ovesco Endoscopy AG, Tübingen, Germany) is developed for a full-thickness tight closure by using the saw-like teeth of a shark and can treat a GI perforation or post-surgery leakage or fistula (Kato, 2019).

After the endoscopically identification and treatment of diverticulum bleeding is achieved, a permanent submucosal tattoo should be made throughout the lesion. Because it makes it easy to locate the colonoscopy in case of repetition or surgery for recurrent bleeding.

Arterial embolization is recommended for massive colon diverticular bleeding that is difficult to achieve with colonoscopy and in persistent or recurrent colon diverticular bleeding where it is difficult to determine the bleeding site. (Nagata et al., 2019). Surgical intervention for diverticular hemorrhage is rarely needed that cannot otherwise be stopped or if the bleeding vessel cannot be located, laparotomy and total colectomy can be recommended (Wilkins et al., 2009).

5.2. Colitis bleeding

The term colitis indicates any form of inflammation of the colon. Causes of severe lower GI hemorrhage may include ischemic colitis, inflammatory bowel disease, or infectious colitis. Ischemic colitis is cause of ischemic damage in the gastrointestinal tract, the following most common cause of inpatient hematosis, and the third most common colonic cause of severe hematochezia (Dimitrijevic et al., 2008; Washington and Carmichael, 2012). The blood supply of the colon is abundant. It is where anastomoses between the upper and lower mesenteric arteries are most prone to ischemia as there is less vascularia normally supplied by 10-35% of cardiac output, and ischemia may be seen when blood supply reduces by more than 50% (Salsano et al., 2018).

Ischemic colitis may present as a wide spectrum of injury and clinical severity ranging from mild reversible mucosal injury to life-threatening, irreversible, transmural involvement (Chavalitdhamrong et al., 2011). Risk factors related to ischemic colitis have been suggested to include advanced age, shock, cardiovascular surgery, cardiac failure, chronic obstructive lung disease, ileostomy, colorectal malignancy, abdominal surgery, constipation, use of laxative, oral contraceptive and/or use of an H2 receptor blockers (Cubiella Fernandez et al., 2010). Most of the patients (75-85 percent) have self-limited ischemic colitis and generally respond to medical treatment (Green and Tendler, 2005; Tadros et al., 2013). As with other ulcers, focal ischemic ulcers with bleeding marks, which can be seen as a result of endoscopic epinephrine injection and hemoclip, can also be seen (Chavalitdhamrong et al., 2011). Rapid recognition and surgical intervention are critical in gangrenous colitis and bleeding that cannot be stopped endoscopically. Inflammatory colitis encompasses chronic inflammatory bowel disease which accounts for up to 6-30% of all patients with lower GI bleeding (Frost et al., 2017). Inflammatory bowel disease that involves the colon does not usually cause critical acute lower GI hemorrhage. Most of those cases had Crohn's disease, and majority of them responded well to medical treatment.

Infectious colitis should be excluded in all patients with severe lower GI hemorrhage and colitis. Infections such as *Campylobacter jejuni, Salmonella, Shigella, enterohemorrhagic Escherichia coli* (O157: H7), *Cytomegalovirus* or *Clostridioides difficile* can cause lower GI bleeding. Other causes of lower GI bleedings include opportunistic infections associated with HIV, such as lymphoma and Kaposi sarcoma (Navaneethan and Giannella, 2011). Substantial blood loss is unusual except in cases with severe bleeding diathesis. Stool cultures and flexible sigmoidoscopy or colonoscopy may be useful for diagnosis. Medical management is the main treatment; preference of antibiotics depends on the causative organism. Endoscopic intervention usually has no benefit in infectious colitis.

5.3. Post-polypectomy bleeding

Polypectomy via colonoscopy has become a valuable modality for eliminating the precursors of colorectal malignancies. However, complications such as bleeding, perforation and pain may occur. The most prevalent complication after following the procedure is bleeding, which is reported to range from 1% to 6% and that can be instantly or delayed (Kim and Lim, 2011). Early bleeding occurs instantly after resection and delayed bleeding occurs in a few hours to a few days after the procedure in approximately 2% of all patients (Kim, 2011). Polyp size (large), thick stalk, shape (pedunculated), use of anticoagulants, use of aspirin or another NSAIDs, and location (right Hemi-colon) stood for important risk factors for the development of delayed bleeding following colonoscopic polypectomy (Kim et al., 2013; Kwon et al., 2015). In cases with severe bleeding in whom an SRH is found in the ulceration, a doppler endoscopic probe can be used to determine underlying arterial blood flow and the need for endoscopic hemostasis include endoscopic clips, direct thermal

therapy, performed with bipolar cautery, snare tip, or thermal probes with or without epinephrine injection (Gutta and Gromski, 2020; Ma and Bourke, 2016).

5.4. Colon neoplasia bleeding

Colon polyps and cancer may manifest as acute lower GI bleeding. Hematochezia is a symptom that should be considered carefully. Colonic neoplasia was the eighth most prevalent cause of severe hematochezia. Studies pointed out that 7-10% of patients with chronic overt rectal bleeding did actually have colorectal cancer (Carlo et al., 2006). Typically, microcytic iron deficiency anemia consistent with gradual GI blood loss before overt hemorrhage occurs (Jensen and Machicado, 1988). Acute lower GI bleeding due to colorectal neoplasia generally is a consequence of superficial ulcerations of an advanced tumor (Committee et al., 2014). Epinephrine may be injected intralesionally to slow ongoing bleeding during colonoscopy, and hemoclips may be applied to treat SRH on ulcerated lesions that are unresectable endoscopically (Raju et al., 2007) Hemostatic powder may have a palliative role. Surgical intervention is generally needed to avoid rebleeding from a large, ulcerated sessile lesion (Anderloni et al., 2014).

5.5. Radiation proctitis bleeding

Radiation proctitis generally results in mild chronic hematochezia but rarely may cause acute severe lower GI hemorrhage. Radiation therapy may result in acute and chronic injury of the normal colorectal mucosa when aimed to treat pelvic tumors—gynecologic, prostatic, bladder, or rectal (Kennedy and Heise, 2007). Tenesmus, diarrhea, abdominal cramping, and, infrequently, hemorrhage may be seen for a few weeks in approximately 75% of cases who have received a radiation dose of 4000 cGy (Do et al., 2011). Chronic radiation effects arise 6-18 months following the end of radiotherapy and present as fresh red blood in the stool. Most of the cases are diagnosed following colonoscopy or sigmoidoscopy indicating pallor, friability, and telangiectasias (Do et al., 2011).

Treatment involves avoidance of aspirin and other NSAIDs, a high-fiber diet, and iron replacement therapy if the subject has iron deficiency anemia. For noninvasive management of chronic radiation proctitis, oral, rectal or gaseous drugs or agents are used initially. These agents consist of anti-inflammatory drugs (steroids or various 5-aminosalicylic acid (5-ASA) preparations, sucralfate, short-chain fatty acids, misoprostol, hyperbaric oxygen treatment, 4% formalin, metronidazole, and antioxidant agents. Various endoscopic ablation therapies including the Nd: YAG and argon lasers are available for the management of chronic proctitis-related hemorrhage resulting from local telangiectasias.

5.6. Angioectasia

Colonic angioectasia are the most prevalent vascular lesion in the gastrointestinal tract in the elderly and is one of the most frequent causes of chronic or recurrent lower gastrointestinal hemorrhage (Diggs et al., 2011). Estimated prevalence differ from 2% to 50% in studies of colonoscopy performed for various indications (Diggs et al., 2011). Colonic angioectasia is suggested to be a consequence of chronic, intermittent, low-grade occlusion of submucosal vessels. Endoscopic procedures are performed for both diagnostic and therapeutic purposes of vascular malformations. In a significant number of patients, the patient's age, comorbidities, clinical severity of anemia and blood loss, as well as size, location, and accompanying lesions prevent this therapeutic approach (Garcia-Compean et al., 2019; Gifford et al., 2012). There are many endoscopic treatment methods involving different techniques, all of which aim the eradication of the mucosal abnormality. Nevertheless, recurrent hemorrhage following endoscopic procedure is not rare; frequently requiring more than one intervention (Garcia-Compean et al., 2019). with several methods which, are argon plasma coagulation, monopolar electrocoagulation, and bipolar electrocoagulation as well as photocoagulation with Nd: YAG and argon. The laser has been available for a long time (Garcia-Compean et al., 2019). Embolization with high selective angiography has a successful hemostatic efficacy, increasing from 80% to 90%. Hormonal drugs (a mixture of estrogen and progestogens), somatostatin analogs (octreotide and lanreotide), and thalidomide are not currently suitable for clinical use as effective prophylactic therapy. However, the most effective rescue treatment is surgical intervention (Gifford et al., 2012).

5.7. Internal hemorrhoid bleeding

Hemorrhoids are common and are estimated to affect 4% to 38% of the adult population (Krebs et al., 2020). An important proportion of people who have hemorrhoids may have complaints such as bleeding, pain, and itching (Lohsiriwat, 2012). The most common presentation of hemorrhoids is rectal bleeding during defecation without pain that may be associated with prolapsing anal tissue (Aigner et al., 2009). In hemorrhoid bleeding, the blood does not mix with the stool, it covers the outer surface of the stool or may be noticed during cleaning following defecation. The blood is usually bright red since the hemorrhoid plexus has direct arteriovenous communication (Aigner et al., 2009). typically, bleeding is mild, intermittent, and self-limited but, rarely, severe transfusion-requiring bleeding may occur due to hemorrhoids (Krebs et al., 2020). Hemorrhoids are seldom life threatening. Usually, these patients are treated to improve the quality of life. (Riss et al., 2011).

A careful history and detailed physical examination, including digital rectal examination and anoscopy, are essential for the diagnosis of hemorrhoids (Lohsiriwat, 2013). If bright red blood is not clearly visible in the anal canal, flexible sigmoidoscopy or colonoscopy should be planned after colonic cleansing preparation for every patient with rectal bleeding, especially those with colorectal cancer risk (Lohsiriwat, 2013).

The management of internal hemorrhoids begins with

medical approach involving fiber supplementation, stool softeners, lubricant rectal suppositories (with or without glucocorticoids), and warm sitz baths (Hollingshead and Phillips, 2016). Anoscopic intervention may also be used and involves injection sclerotherapy (5% phenol almond oil, aluminum potassium sulfate- tannic acid), rubber band ligation, cryosurgery, manual anal dilatation (Lord's procedure), the harmonic ultrasonic scalpel hemorrhoidectomy, infra-red photocoagulation, radiofrequency ablation, MPEC, and direct current electrocoagulation (Agbo, 2011; Tomiki et al., 2015). When recurrent mild hemorrhoidal bleeding and severe bleeding fail with a rubber band or some other endoscopic treatment, surgery is ultimately required (Agbo, 2011).

5.8. Anal fissures bleeding

An anal fissure defines a linear tear or ulcer of the lining mucosa of anus (Nelson et al., 2012). Anal fissures are one of the most prevalent perianal conditions presenting with bleeding, itching, and pain of varying severity (Gupta, 2005). The hematochezia is usually mild and is noticed with cleansing; infrequently, moderate to severe hematochezia may be seen. Treatment aims to heal the anal fissure, rather than using specific hemostasis techniques. Management of anal fissures begins with conservative treatment involving stool softeners, fiber supplementation, sitz baths, and topical lidocaine gel for pain relief (Gardner et al., 2020). Surgical treatment is preferred in chronic fissures. (Gardner et al., 2020).

5.9. Rectal variceal bleeding

Rectal varices are one of the portosystemic shunts that may be seen due to portal hypertension (Al Khalloufi and Laiyemo, 2015). Endoscopy is the main modality for diagnosing rectal varicose veins. They are seen as blue-tinted submucosal elevations located near the anus (Philips et al., 2016; Tajiri et al., 2010) The management of variceal rectal bleeding is like esophageal varices (Garcia-Tsao et al., 2007). Treatment of bleeding rectal varices mainly involves prophylactic antibiotic, vasoactive drugs such as vasopressin, terlipressin or octreotide, while endoscopic therapies (endoscopic injection sclerotherapy, endoscopic band ligation, cyanoacrylate injection), interventional radiology (transjugular intrahepatic portosystemic shunt placement, balloon-occluded retrograde transvenous obliteration). (Al Khalloufi and Laiyemo, 2015). Surgery may be considered for the management of rectal varices especially when endoscopic intervention has failed with sclerotherapy, band ligation, or a portosystemic shunt (Al Khalloufi and Laiyemo, 2015).

5.10. Rectal dieulafoy lesions bleeding

Dieulafoy's lesion, also known as "caliber persistent artery", is a rare cause of gastrointestinal hemorrhage (Jeon and Kim, 2015). It accounts for approximately 6% of gastrointestinal nonvariceal hemorrhages, and 1% to 2% of all acute gastrointestinal hemorrhages (Wang et al., 2017). Dieulafoy lesions bleeding in the rectum, can be treated successfully with endoscopic hemostasis such as regional injection therapy, thermal coagulation, mechanical therapy (hemostatic clipping, band ligation, OTSC, EUS-guided treatment) (Jeon and Kim, 2015; Wang et al., 2017).

5.11. Rectal ulcers bleeding

Acute Hemorrhagic Rectal Ulcer Syndrome (AHRUS) is defined as acute onset, painless, and massive bleeding from rectal ulcer(s) in subjects with serious underlying conditions (Tseng et al., 2004). The lesions typically lie 3- 10 cm superior to the dentate line, and lead to venous congestion, poor blood flow, and edema in the mucosal lining of the rectum, and ischemic changes causing ulceration (Komai et al., 2018). As elderly population and the survival of critically ill patients increase, the incidence of "acute hemorrhagic rectal ulcer syndrome" recently has been increasing in the whole world (Maneerattanaporn et al., 2012).

Clinical features of AHRUS patients include rectal hemorrhage, profuse mucus discharge, prolonged excessive straining, perineal and abdominal pain, feeling of incomplete emptying after defecation, constipation (Tseng et al., 2004). Most of the AHRU cases (88%) could be treated with endoscopy. Urgent endoscopy may be beneficial in the early diagnosis and proper management of AHRU patients because their prognosis relies on the accurate diagnosis and management of underlying diseases (Jung et al., 2017). The treatment of AHRU includes gauze tamponade, cauterization, pure ethanol injection, transanal suture ligation, visceral angiography, and, OTSC is recommended with hemoclips in the treatment of stigmatized large, hard ulcers.

Conflict of interest

None.

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None.

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Review Article

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Management of the gastrointestinal system bleeding caused by direct-acting oral anticoagulants

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Abstract

Arterial and venous thromboembolism is a common and serious clinical condition where anticoagulation is administered for its treatment and prophylaxis. Anticoagulants prevent the formation of new thrombi and thus the extension of the existing thrombus. Direct-acting oral anticoagulants (DOAC) include dabigatran, which is a thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban, which are anti-Xa agents. These are administered in the secondary prophylaxis and treatment of various diseases of thrombus. Although it is specified that they reduce the risk of bleeding due to all causes, many important studies have also reported that they increase the risk of gastrointestinal system (GIS) bleeding. Therefore, similar to Vitamin K antagonists (VKA), their use is contraindicated in active bleeding, active ulcers, hemorrhagic angiodysplasia, and recurrent bleeding requiring recurrent transfusion. However, these contraindications are mostly transient. We aimed to analyse the risk, prophylaxis and management of the active GIS bleeding in patients taking DOAC in this article

Keywords: direct-acting oral anticoagulants, gastrointestinal system bleeding, venous thromboembolism

1. Introduction

Arterial and venous thromboembolism is a common and serious clinical condition where anticoagulation is administered for its treatment and prophylaxis. Anticoagulants prevent the formation of new thrombi and thus the extension of the existing thrombus. Anticoagulant drugs can be broadly classified as standard (unfractionated) heparin (SH), low molecular weight heparin (LMWH), parenteral direct thrombin inhibitors, fondaparinux, danaparoid, Vitamin K antagonists (VKA) and direct-acting oral anticoagulants (DOACs). Although new generation direct-acting oral anticoagulant agents are not proven to be significantly superior to Vitamin K Antagonists (VKA) in terms of efficacy, they have recently become more preferred, especially because they do not require regular laboratory monitoring.

Direct-acting oral anticoagulants include dabigatran, which is a thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban, which are anti-Xa agents. These are administered in the secondary prophylaxis and treatment of venous thromboembolism (VTE) and pulmonary embolism (PE), in the prophylaxis of VTE that may develop after major elective orthopedic surgery, in reducing stroke and systemic embolism that may occur in non-valvular atrial fibrillation, whereas its use in acute coronary syndrome is still controversial.

Although it is specified that direct-acting oral anticoagulants are as effective as heparin therapy and reduce the risk of bleeding due to all causes, many important studies have also reported that they increase the risk of gastrointestinal system (GIS) bleeding (Cohen et al.,2015; Deutsch et al., 2017)

2. General characteristics of direct-acting oral anticoagulants

Drugs in this group act rapidly and their effectiveness starts between 30 minutes and four hours (Tmax 1.5-4 hours). Their oral bioavailability is variable. Dabigatran is a substrate of P-gp in the cell membrane. After oral intake, it causes P-gp re-secretion in the intestines and may interfere with drugs that inhibit or stimulate the P-gp transporter. FXa inhibitors, on the other hand, can interfere with drugs that affect this mechanism as they are metabolized by the CYP 3A4 system. They are known to interact most commonly with azole agents, rifampicin, and some antiviral agents, whereas it is not known whether they are pharmacologically related to proton pump inhibitors (PPIs).

Although it is advantageous due to its rapid onset of action, oral administration, minimal interference with foods and drugs, not requiring laboratory follow-up, being safer in terms of

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intracranial bleeding, it has such disadvantages as loss of effectiveness when the dose is skipped, limited effectiveness in renal dysfunction, failure to discern patient-compliance to drug and its high-price. The most fundamental difference between thrombin inhibitors and factor Xa inhibitors is the renal excretion of the drug. Dabigatran elimination is predominantly from the kidneys, while the kidneys are less involved in the elimination of Factor Xa inhibitors.

When evaluated in terms of the gastrointestinal system, similar to VKA, its use is contraindicated in active bleeding, active ulcers, hemorrhagic angiodysplasia, and recurrent bleeding requiring recurrent transfusion. However, these contraindications are mostly transient. Other contraindications include potential bleeding GIS lesions that cannot be reached by endoscopic or surgical treatment and Child-C cirrhosis. It is known that the risk of bleeding increases in those with a history of GIS bleeding, but this is not an absolute contraindication (Deutsch et al., 2017).

2.1. Dabigatran

It prevents fibrin formation from fibrinogen by directly inhibiting free and bound thrombin (FIIa). It is a pro-drug with a bioavailability of 6.5%. It has no interaction with food. Tmax is 0.5-2 hours and $t_{1/2\ is}$ 12-14 hours (longer in the presence of renal failure). Its metabolization is very low and the excretion is from the kidney with a rate of 85%. Dialysis can be applied in case of overdose. The average dose is administered as 150 mg or 110 mg b.i.d. When glomerular filtration rate (GFR) is 30-50 ml/min, it is administered as a low dose of 110 mg b.i.d.

2.2. Rivaroxaban

Its bioavailability is 80-100% below 15 mg, while it is 66% when fasted and 100% when fed with 15 mg and above. Tmax is 2-4 hours, and $t_{1/2\ is}$ 5-9 hours in young patients, whereas 11-13 hours in elderly patients. It has high metabolism and excretion is 1/3 fecal and 66% renal. The average dose is administered as 20 mg qd in AF patients, 15 mg b.i.d (21 days) in DVT-PE patients, and 20 mg qd afterward. If GFR is 15-30 ml/min, 15 mg qd should be administered.

2.3. Apixaban

Its bioavailability is 50% and it has no interaction with food. Tmax is 3-4 hours, and $t_{1/2}$ is 12 hours. Its metabolism is high and its excretion is 50% fecal and 27% renal. Dialysis can very rarely be useful in overdose or intoxication. The average dose is 5 mg b.i.d or 2.5 mg b.i.d, and 2.5 mg b.i.d should be preferred for those with a GFR of 15-30 ml/min.

2.4. Edoxaban

Its bioavailability is 62% and it has no interaction with food. Tmax is 1.5 hours and $t_{1/2}$ is 10-14 hours. It has low metabolism with 60% fecal and 35% renal excretion. Dialysis can very rarely be useful in overdose or intoxication also. The average dose is 60 mg q.d, and 30 mg q.d should be preferred for those with GFR 15-50 ml/min.

Drug dose should be reduced taking into consideration the bleeding risk of patients (old-age, low weight, or renal insufficiency). DOACs are contraindicated in hepatic insufficiency as it affects coagulation and significantly increases the risk of active bleeding. Based on their pharmacokinetics, DOACs should never be used in combination with other anticoagulants (unfractionated heparin, LMWH).

The effectiveness of DOACs that do not normally require follow-up should be evaluated in some specific situations such as life-threatening bleeding. Routine coagulation testing has no significant role in this. Only the presence of normal activated partial thromboplastin time can be considered as a finding that dabigatran affect is in desired therapeutic range. Also normality of Prothrombin time (PT) suggests that drug levels are normal in patients receiving anti-Xa treatment. Measuring thrombin time (TT) for dabigatran and anti-Xa activity for others is helpful. Normal TT indicates that dabigatran is not used at an effective dose. TT prolongation is detected in cases higher than the treatment dose. Diluted TT, Ecarin chromogenic test (ECA) and Ekarin coagulation time (ECT) can be performed in these cases (Deutsch et al., 2017).

3. Gastrointestinal system bleeding risk with direct-acting oral anticoagulants

Gastrointestinal system bleeding is an important adverse event associated with the use of anticoagulants, and discontinuation of anticoagulation during bleeding can lead to thromboembolic events. Unlike non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA), anticoagulants are not ulcerogenic drugs. Little pathophysiological evidence is available for anticoagulants in the development of GIS bleeding. The annual risk of GIS bleeding in patients taking anticoagulant therapy is assumed to be 1.5-5%. This risk increases in the presence of comorbidities and multiple drug use, as well as the administration of antithrombotics and NSAIDs in the elderly **(**Sharma et al., 2015). When comparing DOACs with VKA, studies are reporting an increase of 25% in the risk of GIS bleeding, whereas some studies have not shown an elevated risk (Ruff et al., 2014; Miller et al., 2012; Chai-Adisalisopha et al., 2014; Sherwood et al., 2015; Tamayo et al. 2015; Camm et al., 2016; Abraham et al., 2015; Youn et al., 2018).

In comparative studies of all DOACs with VKA, although the risk of GIS bleeding was similar, dabigatran and rivaroxaban were reported to have a higher risk in terms of GIS bleeding compared to VKA (Burnett et al., 2016). However, Chan et al., in their study, stated that the low dose of dabigatran (2x110 mg) did not increase the risk of major GIS bleeding compared to VKA (Chan et al., 2016)**.** Besides, in another study, it was reported that rivaroxaban caused non-critical GIS bleeding at a higher rate (Chan et al., 2016).

4. Gastrointestinal System Bleeding Prophylaxis in Patients Taking Direct-Acting Oral Anticoagulants

Patients considered to have an elevated risk of bleeding should be consulted with cardiology or neurology for a temporary

reduction in their drug doses. Since there is an increased risk of bleeding in combination with NSAIDs, ASA, and other antithrombotic drugs, these drugs should be avoided whenever possible. PPI can be added to the treatment if there is a history of ulcer or GIS bleeding. During concomitant use of anticoagulants and acid suppressants, the treatment should be personalized and a decision should be made based on a risk-benefit assessment (Bang et al., 2020).

Although Helicobacter Pylori (HP) eradication is not yet recommended before DOAC treatment, it is still a controversial issue. Bleeding parameters, complete blood count, and serum creatinine values should be monitored annually and dose adjustment and follow-up should be done when necessary (Chan et al., 2015).

5. Active GIS bleeding management in patients taking direct-acting oral anticoagulants

In GIS bleeding occurring during the use of Direct-Acting Oral Anticoagulants, treatment must be interrupted, the last date of the drug use should be queried and renal function and basal coagulation testing should be performed. In case of minor bleeding, the next dose should be skipped or treatment should be interrupted.

In case of moderate to severe bleeding, it is required to perform supportive therapy, mechanical compression (where practical), fluid and blood infusions, and activated charcoal should be administered if dabigatran has just been taken. In the presence of major bleeding, hemodynamic stability must first be achieved. Transfusion of erythrocyte suspension is recommended in cases where Hb <7/dl or <9 g/dl in the presence of severe comorbidity. Fluid replacement should be applied, and if there is hypothermia or acidosis, it should be corrected as it may worsen the coagulopathy. If necessary, cryoprecipitate replacement can be applied so that the fibrinogen is above 100 mg/dL.

If hemodynamically stable and/or adequately responding to resuscitation, it is recommended to observe the patient closely and postpone the endoscopy for 12-24 hours. This ensures the maintenance of drug clearance and normal hemostatic functions. The theoretical advantage of this approach is that endoscopic treatment can be performed more easily and safely in a patient who has not been fully anticoagulated. Otherwise, emergency endoscopy may be appropriate for active bleeding in patients with permanent or intermittent hemodynamic instability. In this case, the use of nonspecific pro-hemostatic agents may be considered to accelerate the reversal of anticoagulation activity.

Initiation of activated recombinant factor VII or prothrombin concentrate, administration of activated charcoal and hemodialysis in those taking dabigatran, and the use of a monoclonal antibody called idarucizumab as an antidote in life-threatening bleeding are practiced. It binds to dabigatran and removes the anticoagulant effect within minutes. In case of bleeding in those who take DOACs, if the drug is taken within the last 2-4 hours, activated charcoal, Four-factor prothrombin complex concentrate (4F-PCC) or activated prothrombin complex concentrate (aPCC) 50 IU/kg iv can be applied. For those who take dabigatran, 5 g of idarucizumab can be administered and it should be kept in mind that hemodialysis can also be administered for these patients. Studies on PER977 (Ciraparantag), which binds direct and indirect inhibitors of water-soluble synthetic FXa and thrombin, are still ongoing.

Emergency endoscopy indications are not different from those taking non-DOAC anticoagulants. It is recommended that endoscopy be performed within the first 24 hours from the onset of bleeding. The short half-life of DOACs provides an important advantage for emergency endoscopy approaches. Since normal coagulation characteristics are achieved in the period of 4 half-lives after discontinuation of DOACs, the last DOAC administration should be questioned carefully and the period of possible bleeding risk should be calculated.

Alternative treatments may be considered in life-threatening bleeding, in cases that cannot be controlled by endoscopy with a recent history of DOAC intake. Nonspecific procoagulant drugs, aPCC, or PCC or tranexamic acid can be administered (Bennet et al., 2014). Factor Eight Inhibitor Bypassing Activity (FEIBA) is an aPCC and is the primary agent that should be selected. A total of 30-50 IU/kg should be administered intravenously, with a maximum flow rate of 2 IU/kg/min (Marlu et al., 2012; Dager et al., 2013).

Specific antibodies are being developed against DOACs. Idarucizumab is a human monoclonal antibody fragment (Fab) developed for dabigatran, while andexate alpha is a recombinant factor Xa molecule produced for rivaroxaban, apixaban and edoxaban, which does not affect hemostasis. Idarucizumab was approved by the FDA in 2015. It is used in situations such as the perioperative management of an emergency surgical procedure with life-threatening bleeding or a high risk of bleeding that cannot be delayed for up to 8 hours. The recommended dose of idarucizumab is two consecutive infusions of 2.5 g each administered at a maximum interval of 15 minutes (lasting for 5-10 minutes) or as a bolus. Dabigatran plasma concentration should be measured before administration of idarucizumab and, if re-bleeding occurs, 12-18 hours after this bleeding. In such cases, an additional 5 g of idarucizumab infusion can be administered if there is a concentration above 30 ng/ml. Hemostasis tests are normalized within minutes at a rate of 88-98% in patients (Pollack et al., 2015). Idarucizumab does not require dose adjustment in renal failure.

Andexanet alfa shows a rapid onset of action (within 2-5 minutes) by restoring thrombin formation and normal clotting in patients treated with rivaroxaban, apixaban, and edoxaban. The first bolus followed by a two-hour infusion and andexanet reduces anti-factor Xa activity by 79% with effective hemostasis. Andexanet (recombinant Factor Xa) was approved

by the FDA in 2018 and is effective on FXa inhibitors and does not require renal dosage adjustment (Siegal et al., 2015; Connoly et al., 2016). With the introduction of these antidotes, it is believed that the management of bleeding complications in patients treated with DOACs will be easier.

For non-life-threatening bleeding in the absence of kidney or liver failure, temporary discontinuation of DOAC is likely sufficient. There is no evidence for the use of vitamin K or fresh frozen plasma (FFP) to reverse the effects of DOACs. Hemodialysis can be used to rapidly and effectively reduce the plasma concentration of dabigatran (65% at 2-4 hours) and is considered the most effective strategy for in-patients with renal insufficiency with dabigatran-associated bleeding; however, it is not effective for other DOACs (i.e.; rivaroxaban, apixaban, and edoxaban) that bind to plasma proteins at higher rates than dabigatran. No direct data is available about when to continue DOACs following gastrointestinal bleeding. When DOACs are discontinued, the risk of thrombosis is stated to be 4.8% for 30 days and 6.8% for 90 days (Kyaw and Chan, 2018).

Data on the resumption of DOACs after gastrointestinal bleeding are lacking. The principles adopted for VKAs may be extrapolated to DOACs, but caution should be exercised because, unlike warfarin, DOACs cause anticoagulation within a few hours. In one study, it was shown that resumption of anticoagulation within seven days of the admission of an index GIS bleeding did not affect the 90-day hospital readmission rates for recurrent GIS bleeding, and it was stated that it may be reasonable to continue DOAC treatment within seven days (Valanejad et al., 2020).

The time of resumption of anticoagulant therapy is controversial in patients with clinically significant GIS bleeding and no source of bleeding detected on endoscopy. The decision should be made based on estimates of the risks of re-bleeding and thrombosis in these patients. Also, in patients in whom the endoscopist is not fully confident in achieving hemostasis, there cannot be a definitive recommendation to continue anticoagulant therapy. In such cases, it is recommended that another endoscopist evaluate the patient as a second opinion (Radaelli et al., 2015).

Patients taking DOACs and who have undergone endoscopic procedures should be followed-up for 6 hours due to the risk of bleeding. In some studies, it is stated that if hemostasis is achieved, the drug can be resumed at 12-24 hours after the procedure, even if there is high risk. Later initiation of the drug may be considered in procedures that may have delayed bleeding, such as endoscopic mucosal resection or endoscopic submucosal dissection. Based on the decision of the endoscopist, it is recommended to resume treatment 48-72 hours after endoscopic procedures, which are considered to have a high risk of bleeding (Tien et al., 2020). Also, it should be kept in mind that discontinuing the drug for more than 48 hours increases the risk of thrombosis.

6. Conclusion

Physicians gain more experience in the management of DOAC treatment where side effects of gastrointestinal bleeding are more frequently encountered, before, during, and after the endoscopy procedure. However, better information should be obtained about these clinical conditions, which can sometimes be life-threatening, to ensure minimization of morbidity and mortality

Conflict of interest

All authors declare no conflict of interest regarding this manuscript.

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Review Article

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Management of patients with occult gastrointestinal bleeding

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Abstract

The majority of cases of occult bleeding are found in the course of colorectal cancer screening or during the evaluation of iron deficiency anemia. In up to half of all patients with occult GI bleeding, the source will not be found on initial endoscopic evaluation. Occult gastrointestinal bleeding is an issue with difficulties in diagnosis and treatment. It may come to the clinic as asymptomatic, detected in routine screenings or as iron deficiency of unknown etiology. In recent years, there have been great advances in the diagnosis and treatment. Capsule endoscopy and enteroscopy have provided these advances. However, the problem is not fully resolved. Additional developments are needed in this regard. In this review, the management of patients with occult gastrointestinal bleeding is explained in the light of the latest literature findings.

Keywords: occult, bleeding, gastrointestinal, management

1. Introduction

Iron deficiency anemia and gastrointestinal (GI) bleeding are common sources of referral to Gastroenterologists. Gastrointestinal bleeding (GIB) may be overt, obscure or occult. Overt bleeding is blood loss that is visible to the patient or clinician which manifests as hematemesis, melena or hematochezia. Obscure GIB is defined as persistent or recurrent bleeding for which no definitive source has been identified by an initial evaluation. Obscure GIB may be occult, if not visible or overt if it manifests with a continued passage of visible blood.

In most large series, the cause of bleeding is not found on EGD and colonoscopy in 5% of hospitalized patients with overt GI bleeding. In 75% of these patients, a bleeding site is located in the small intestine. Occult gastrointestinal bleeding refers to the initial presentation of a positive fecal occult blood test result and/or iron deficiency anemia when there is no evidence of visible blood loss to the patient or physician. The management of suspected bleeding consists of a judicious search for the cause of bleeding, which should be guided by the clinical history, physical findings, and the results of any previous evaluations and treatment with the appropriate method (Perencevich and Saltzman, 2020).

2. Fecal occult blood tests

There are two types of fecal occult blood tests generally used, which are immunochemical and guaiac-based stool tests.

2.1. Fecal immunochemical test (FIT) for blood

FIT directly measures hemoglobin in the stool. FIT is performed on a small sample of stool that the patient provides in a special container and does not require restrictions to medications or diet prior to providing the sample. FIT is made quantitatively using standardized automated analyzers and has the potential to produce more consistent results, with a higher PPV (Park et al., 2012; Huang et al., 2014; Doubeni, 2020). It should be done within 24 hours of collection, because FIT sensitivity declines with delayed testing due to degradation of hemoglobin.

FIT requires only one sample rather than three days of samples as for guaiac-based fecal occult blood testing (gFOBT). FIT is more sensitive than gFOBT for colonic lesions (Young et al., 2015; Robertson et al., 2017). In addition, a positive FIT has high specificity for lower gastrointestinal bleeding. FIT appears to be less sensitive for detection of right-sided than of left-sided colonic lesions (Wong et al., 2015). Fecal immunohistochemical testing detects only human globin and therefore does not detect upper GI bleeding due to digestion of globin. However, FIT can be positive in excessive upper gastrointestinal bleeding.

2.2. Guaiac-based fecal occult blood test (gFOBT)

Guaiac testing identifies hemoglobin by turning guaiac reagent-impregnated paper blue as the result of a peroxidase

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reaction. Guaiac testing of stool samples can identify hemoglobin that may be present due to bleeding from a colon lesion or for other reasons. gFOBT screening should only be performed using a highly sensitive guaiac reagent, such as Hemoccult SENSA, which has higher sensitivity than Hemoccult, Hemoccult-II, or Hemoccult-R, although it has lower specificity (Levin et al., 2008; Bibbins-Domingo et al, 2016).

A restrictive diet during gFOBT testing may not be necessary, although eliminating red meat for three days is recommended by the manufacturer (Pignone et al., 2001). Vitamin C intake should be restricted to <250 mg per day for at least three days prior to sampling. Large doses of vitamin C may cause false-negative tests (Jaffe et al., 1975). Stool for gFOBT should not be obtained during digital rectal examination (DRE). DRE may induce microtrauma and cause a false-positive result. But there are contradictory results in some studies. In the laboratory, gFOBT samples should not be rehydrated prior to processing (Duffy et al., 2011). Hydration increases test sensitivity but leads to an increased number of false-positive results. Positive results may also occur with upper gastrointestinal bleeding.

3. Causes of occult GI bleeding

The differential diagnosis for occult GI bleeding is broad (Table 1 and Table 2). More common causes include colon cancer, esophagitis, peptic ulcers, gastritis, inflammatory bowel disease, vascular ectasias, portal hypertensive gastropathy, gastric antral vascular ectasias, and small bowel tumors (e.g., GI stromal cell tumor, lymphoma, carcinoid, adenocarcinoma, or polyp). Less common causes, such as gastroesophageal cancers, hemosuccus pancreaticus, hemobilia, endometriosis, and infections also need to be considered.

In persons younger than age 40, bleeding is more likely to be caused by a tumor, Meckel diverticulum, or Crohn disease. Angioectasias or an NSAID-induced ulcer are common causes in persons 40 years of age and older. Non-GI sources of blood loss, such as hemoptysis and epistaxis, can also cause a positive fecal occult blood test.

A positive fecal occult blood test should not be attributed to GI lesions that are infrequently associated with occult bleeding (e.g., esophageal varices and colonic diverticula). Patients with bleeding colonic diverticular disease present with overt, rather than occult, bleeding. In a patient with known esophagogastric varices or colonic diverticula, a positive test for occult blood or otherwise unexplained iron deficiency anemia should not preclude a diagnostic evaluation. Colonic diverticula commonly occur in the age bracket with the highest incidence of colon cancer.

Positive fecal occult blood tests in patients using antiplatelet agents and anticoagulants should not be assumed as false-positive. These patients should be evaluated (Sawhney et al., 2010).

The presence of fecal occult blood should not be attributed to alcohol ingestion alone unless coexistent pathology has been excluded.

The medical history and physical examination can help focus the differential diagnosis. Aortic valve stenosis (Heyde's syndrome), chronic kidney failure and some rheumatologic diseases may have bleeding due to angiodysplasia. Epistaxis and telangiectasias in the oral-nasal mucosa may indicate hereditary hemorrhagic telangiectasia. Hyperpigmented macules on the lips and oral mucosa (melanosis) suggest Peutz-Jeghers syndrome.

4. Evaluation of a positive fecal occult blood test

The evaluation of a patient with a positive fecal occult blood is presented in Fig. 1. (Perencevich and Saltzman, 2020). The prevalence of lesions in the upper GI tract is greater than or equal to that of colonic lesions. There may be both upper and lower GI lesions in some patients. Patients without iron deficiency anemia can be evaluated with colonoscopy, with or without upper endoscopy. Patients with iron deficiency anemia require a more extensive evaluation, including upper endoscopy and colonoscopy.

If upper endoscopy and colonoscopy do not reveal a source of the bleeding, the next step is evaluation of the small bowel. Repeat examinations probably have greatest value in patients with occult bleeding with iron deficiency anemia, or overt bleeding with melena or maroon blood per rectum. Repeat upper endoscopy or colonoscopy should be the first step in the evaluation if either examination was suboptimal when initially performed.

Obscure bleeding lesions (Fig. 2) that are commonly missed in the upper gastrointestinal tract include Cameron ulcers or erosions in a large hiatus hernia, peptic ulcers on the medial aspect of the junction of the bulb and second part of the duodenum, Dieulafoy lesions, gastric antral vascular ectasia (GAVE), and angioectasia. A side-viewing duodenoscope may be of value in examining the medial aspect of the second part of the duodenum and periampullary area. Some of the lesions that may be missed in the colon include colon cancer, angioectasia, diverticula, and inflammatory bowel disease (Raju et al., 2007; Bull-Henry and Al-Kawas, 2013; Vlachogiannakos et al., 2011).

While hemorrhoidal bleeding can lead to bleeding and anemia, but bleeding leading to iron deficiency anemia should not be attributed to hemorrhoids unless significant bleeding from hemorrhoids is reported by the patient, bleeding seen during an endoscopic evaluation, and other sources have been excluded.

Table 1. Causes of occult gastrointestinal bleeding (Perencevich and Saltzman, 2020)

Inflammmatory/ Mechanical trauma	Mass lesions any site)	Vascular	Infectious	Miscellaneous
• Reflux esophagitis • Cameron lesions • Erosive gastritis • Gastric ulcer • Duodenal ulcer • Celiac sprue • Whipple disease • Meckel diverticulum with ulceration • Idiopathic cecal ulcer • Crohn disease • Ulcerative colitis	• Carcinoma • Large polyps	• Vascular ectasia(s) • Portal hypertensive gastropathy • Portal hypertensive enteropathy and colopathy • Gastric antral vascular ectasia • Hemangiomas • Blue rubber bleb nevus syndrome	• Hookworm • Strongyloidiasis • Ascariasis • Tuvberculous enterocolitis • Amebiasis	• Long-distance running • Factitious • Hemoptysis • Epistaxis • Oropharyngeal

Table 2. Causes of small bowel bleeding (Perencevich and Saltzman, 2020)

Common causes		Rare causes
Under age 40 years	Over age 40 years	
• Inflammmatory bowel disease • Meckel diverticulum • Dieulafoy lesions • Neoplasia • Polyposis syndrome	• NSAID ulcers • Angioectasia • Dieulafoy lesions • Neoplasia	• Henoch-Schonlein purpura • Small bowel varices and/or portal hypertensive enteropathy • Amyloidosis • Blue rubber bleb nevus syndrom • Pseudoxanthoma elasticum • Osler-Weber-Rendu syndrome • Kaposi sarcoma with AIDS • Plummer-Vinson syndrome • Ehkers-Danlos syndrome • Inherited polyposis syndromes (FAP, Peutz-Jeghers) • Malignant atrophic papulosis • Hemobilia • Aortoenteric fistula • Hemosuccus pancreaticus

FAP: familial adenomatous polyposis; NSAID: Nonsteroidal anti-inflammatory drug

A patient with a positive fecal occult blood test and no anemia should undergo a colonoscopy. If the patient has upper GI symptoms, an upper endoscopy should also be performed. If initial testing is negative and there are no signs of ongoing blood loss, further evaluation of these patients is not recommended.

A patient with a positive fecal occult blood test and iron deficiency anemia should undergo upper endoscopy and colonoscopy. If complete endoscopy and colonoscopy with adequate visualization do not reveal the source of the bleeding, small bowel evaluation is recommended. Wireless capsule endoscopy is of choice in the majority of patients. CT enterography, and magnetic resonance (MR) enterography are the alternatives of capsule endoscopy with similar or less sensitivity.

As bleeding continues deep small bowel enteroscopy is suggested. If there is any source and bleeding is going on additional testing like angiography, CT angiography, scintigraphy, Meckel's scan, or laparoscopy/laparotomy with intraoperative enteroscopy are recommended.

Capsule endoscopy is equally or more sensitive than other methods for the diagnosis of small bowel sources of blood loss. Capsule endoscopy is contraindicated in some patients, including those with partial or intermittent small bowel obstruction, women who are pregnant, and patients who are unable to swallow the capsule. The diagnostic yield of capsule endoscopy in patients with overt bleeding appears to be highest when it is performed as close as possible to the bleeding episode. Testing with a fecal immunochemical test (FIT) for occult blood may help with the timing of capsule endoscopy in patients with suspected small bowel bleeding.

Enteroscopy involves the passage of an adult or pediatric colonoscope or a special enteroscope beyond the ligament of Treitz. Several methods of enteroscopy have been described such as push, intraoperative, and deep small bowel enteroscopy like single balloon, double balloon, and spiral enteroscopy. In patients with a negative capsule endoscopy and computed tomographic (CT) enterography with ongoing bleeding, the next step in the evaluation is typically deep small bowel enteroscopy. All of the deep enteroscopy techniques allow for

both evaluation and therapeutic intervention in the small bowel. Capsule-directed deep enteroscopy may be associated with better long-term outcomes because of fewer complications and decreased utilization of endoscopic resources.

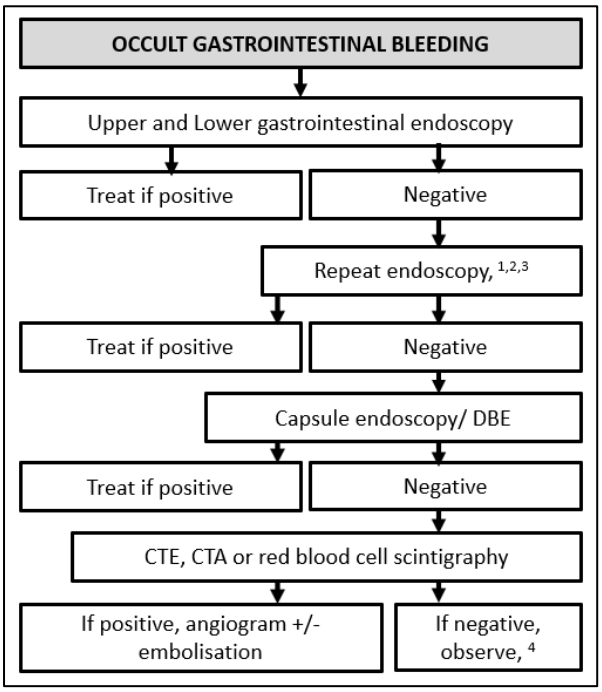

Fig. 1. Evaluation of occult gastrointestinal bleeding (Perencevich and Saltzman, 2020; Murphy et al., 2019) DBE; double balloon enteroscopy, CTE; computerised tomography enteroscopy. 1- If the initial endoscopy was inadequate, 2- If there are risk factors for hemobilia or hemosuccus pancreaticus, evaluate with side-viewing duodenoscope, 3- If there are risk factors for aortoenteric fistula, push enteroscopy, CT angiography, 4-Iron replacement if there is iron deficiency anemia

Intraoperative enteroscopy is an option if deep small bowel or push enteroscopy does not reveal a bleeding source, if there is massive bleeding with hemodynamic instability, or if there are contraindications to deep small bowel enteroscopy, such as dense abdominal adhesions. Intraoperative enteroscopy involves the insertion of an endoscope orally, rectally or through an enterotomy site during surgery. In general, intraoperative enteroscopy is avoided unless there is no known target established by endoscopy or imaging.

A radionuclide bleeding scan detects bleeding that is occurring at a minimum rate of 0.1 to 0.5 mL/minute. It is of little or no value in patients with gastrointestinal bleeding who appear clinically to have a low rate of blood loss (such as those with occult blood only) since the rate of bleeding is likely to be too slow to be detected. This technique only localize bleeding to an area of the abdomen. If a bleeding source is identified, additional interventions (such as angiography) are required.

A Meckel's scan consists of the intravenous administration of 99mTc pertechnetate, which has an affinity for gastric mucosa. The test does not detect active bleeding. Meckel's scan may reveal a potential bleeding source and is particularly appropriate in children and young adults.

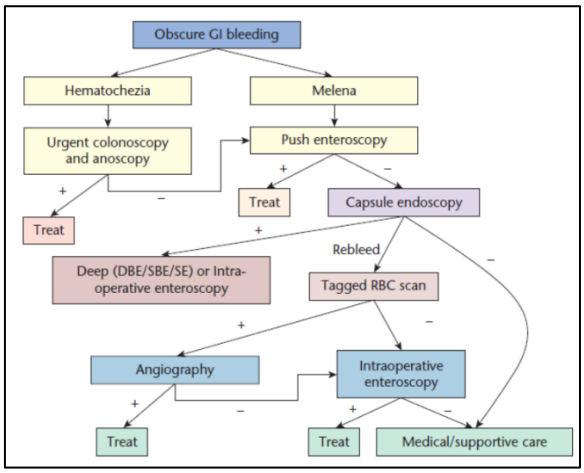

Fig. 2. Management of obscure gastrointestinal bleeding (Ghassemi et al., 2012). DBE; Double balloon enteroscopy, SBE; Single balloon enteroscopy, SE; spiral enteroscopy, RBC; red blood cell

5. Evaluation of ısolated ıron deficiency anemia:

Patients with unexplained iron deficiency anemia but a negative fecal occult blood test should be evaluated for a GI source of blood loss (Fig. 1.). Patients with isolated iron deficiency anemia should be evaluated for celiac disease if an alternative source of blood loss is not identified. If patients have symptoms suggesting either an upper or lower GI source, it is reasonable to start the evaluation with an upper endoscopy or colonoscopy, respectively (Rockey, 2010). For patients who are asymptomatic, a colonoscopy is often the first test obtained, but in patients with anemia, we suggest to start the evaluation with both an upper endoscopy and a colonoscopy. If both upper endoscopy and colonoscopy are negative, additional testing such as wireless capsule endoscopy should be pursued.

The optimal approach to iron deficiency anemia in women who continue to menstruate is uncertain. In one series, a clinically important lesion was detected in 23 of 186 premenopausal women (12 percent) who underwent endoscopy (Bini et al., 1998). Endoscopic evaluation should be obtained if a fecal occult blood test is positive, if the iron deficiency anemia is out of proportion to menstrual blood loss, if the patient has abdominal symptoms, or if the patient has a family history of GI malignancy in a first-degree relative, particularly if the patient is older than 40 years of age.

6. Treatment of occult gastrointestinal bleeding:

6.1. Medical management

Either intravenous or oral iron supplementation may be used in occult GI bleeding to maintain hemoglobin levels. In more acute or overt bleeding, red cell transfusion should be used where necessary (Murphy et al., 2019). GI bleeding will occur in 1–3% of patients taking anticoagulant therapy (Guerrouij et al., 2011). Holding these agents does not appear to lower the risk of recurrent bleeding, interestingly (Koh et al., 2013; Arakawa et al., 2009). Meta-analysis from 2014 shows benefit from the use of somatostatin analogs in patients with angiodysplasia but not hormonal therapy (Jackson and Gerson 2014). Thalidomide has been used successfully to treat patients with refractory GI bleeding. It is an angiogenesis

inhibitor and is therefore most effective in treating patients with vascular etiology, such as angiodysplasia and AVMs (Ge et al., 2011).

Tranexamic acid has been shown to reduce mortality in bleeding trauma patients (Crash-2 Collaborators, 2011). A systematic review has found that it can reduce the probability of receiving a blood transfusion in up to 33% of acute GI bleed patients (Roberts et al., 2012).

6.2. Interventional radiology and endoscopy

If a bleeding lesion is noted on angiography, success rates have been reported in 60–90% of cases. The advent of newer techniques and superselective embolization has further improved success rates and decreased the risk of bowel infarction (Patel et al., 2001; Schenker et al., 2001). Angiodysplastic lesions are treated typically with Argon Plasma Coagulation to good initial effect but rebleeding rates are high.

6.3. Surgery

Diagnostic laparoscopy or laparotomy may be considered in small bowel GI bleeding where no other modality has demonstrated a source. Furthermore, it may be utilized when a bleeding point has been identified but is not amenable to endoscopic/radiological therapy or mandates resection e.g., Meckel's diverticulum or mass lesion (Murphy et al., 2019).

Conflict of interest

None.

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ERCP-related bleeding

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Abstract

Clinically significant bleeding is an uncommon complication of diagnostic endoscopic retrograde cholangiopancreatography. But the endoscopists needs to be skilled at prevention and management. Post ERCP bleeding is most often seen following sphincterotomy. The overall risk of bleeding in patients undergoing sphincterotomy is approximately 1-2 percent. Most bleeding episodes are mild to moderate in severity. The risk of bleeding can be minimized by identifying patients at risk, correcting coagulation abnormalities and careful technique by skilled endoscopists in high-volume centers. Post-sphincterotomy bleeding often stops spontaneously and is rarely life-threatening, except in patients with a bleeding diathesis. Most clinically relevant bleedings can be managed with medical treatment and/or endoscopic therapy, which should be performed without delay in patients who have immediate bleeding. Endoscopic therapy options include epinephrine injection, hemostatic clips, thermal therapy and placement of full covered self-expandable metal stents. Angiography or surgery is usually reserved for patients with refractory bleeding and is rarely required.

Keywords: ERCP, ERCP adverse event, ERCP Bleeding, Post ERCP haemorrhage

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) remains the standard and invaluable procedure for diagnosis, evaluation, and management of pancreaticobiliary disorders. Over time, the role of ERCP has evolved from a diagnostic to therapeutic intervention because of improvements in other imaging modalities. While this expansion has improved treatment modalities for biliary pathology, complications and adverse events following ERCP continue to persist and may have a significant impact on patients' morbidity and rarely mortality (Talukdar, 2016).

Diagnostic ERCP alone or with associated pancreaticobiliary instrumentation and therapy may cause a variety of complications and adverse events, including pancreatitis, hemorrhage, cholecystitis, infection, intestinal perforation and cardiopulmonary events. These adverse events ranges from full recovery after an additional few days of hospitalization to severe and devastating outcomes such as permanent disability or death. Adverse events, along with increased morbidity, may also cause significant concern for the endoscopist and exposure to medical malpractice claims. Though ERCP is considered to be safe and effective, it carries the highest risk of procedure-related complications among all endoscopic procedures. Despite advances in endoscopic technology, better operator experience and research-driven safety protocols, the incidence of ERCP-related complications and mortality remains relatively constant. Several distinct studies reported a relatively consistent frequency of ERCP complications and mortality rates over a decade between 10–12% and 0.4–1.4%, respectively (Siiki et al., 2012; Kapral et al., 2012; Glomsaker et al., 2013)

Bleeding is one of the most feared complications of therapeutic biliary endoscopy. Although it has become a relatively rare complication of ERCP due to advances in equipment and skills, it is still a problem. It is critical for the endoscopist to understand how to avoid and treat adverse events. This chapter will focus on bleeding-related adverse events, including risk factors, prevention, and management.

The most common cause of ERCP-related bleeding is endoscopic biliary and/or pancreatic sphincterotomy, which has been reported in as few as 0.1% but up to 2% of cases (Chandrasekhara et al., 2017). The true incidence is unknown, and variable rates are described due to retrospective study design, lack of standardized definitions and insufficient data on relevant patient and physician factors. Bleeding seen endoscopically during sphincterotomy is often reported as an adverse event, but itself does not represent an adverse outcome to the patient unless there is clinically significant blood loss or a change in management.

2. Classification and grading

A more recent statement by the American Society for Gastrointestinal Endoscopy (ASGE) defines bleeding as

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hematemesis and/or melena or a hemoglobin drop >2 g following a procedure (Cotton et al., 2010). Bleeding after ERCP is classified as either immediate (intraprocedural or immediately after) or delayed (hours to weeks post-procedure with late being any time after 14 days). Delayed bleeding occurs from hours up to several weeks after endoscopic sphincterotomy and/or endoscopically interventions. Furthermore, bleeding can be classified as clinically significant (mild, moderate, and severe) or insignificant, based on the presence or absence of overt GI bleeding and/or change in hemoglobin level or the requirement for a secondary intervention such as endoscopy or blood transfusion.

The initial grading system proposed by Cotton et al. defined the severity of ERCP-related adverse events according to the number of transfused units and requirement for angiographic or surgical interventions (Cotton et al., 1991). Hospital admission and level of acuity are also critical descriptors. An adverse event that requires an unplanned hospital admission or prolongation of hospital stay for <3 nights is graded mild in severity compared to severe if requiring >10 nights or >1 night in ICU. Bleeding that requires transfusion or a repeat endoscopy is graded as moderate severity (Cotton et al., 2010). The traditional and new ERCP-related bleeding severity grading scores suggested by Cotton et al. are collectively shown in Table 1.

Table 1. Severity grading of the post ERCP bleeding

Severity grading		
Mild	Moderate	Severe
Either of the following: • Clinical (not just endoscopic) evidence of bleeding • Hemoglobin drop <3 gr/dL and no need for transfusion • Abortion of procedure • Unplanned admission <4 nights	Any one of the following: • Need for transfusion (<4 units) • Repeat endoscopy or *interventional radiology • Unplanned admission 4 -10 nights • ICU admission 1 night • Intervention for integument injuries	Any one of the following: • Transfusion >5 units • Unplanned admission >10 nights • ICU admission > 1 night • Need for surgery • Permanent disability

ICU, intensive care unit. *Radiology angiography intervention is classified as moderate severity grading in the new Cotton's grading system (Cotton et al., 2010). However, this was considered a serious situation according to the traditional severity grading system (Cotton et al., 1991)

3. Risk factors

The risk factors for ERCP-related bleeding can be categorized as patient-related, technique related and operator related factors. When evaluating a patient with post-ERCP bleeding, it is important to define the patient profile, including medical comorbidities, anatomical variants and medications.

A landmark prospective study by Freeman et al. described the rate of adverse events after endoscopic biliary sphincterotomy according to the patient, procedure, and endoscopic technique. Clinically significant bleeding occurred in 2% (n = 48) of 2453 patients included in this study and was mild at 0.6%, moderate at 0.9% and severe at 0.5%. Multivariable analysis identified 5 independent risk factors for post-ERCP bleeding (PEB), including three patient-related factors: the presence of coagulopathy, active cholangitis before the procedure and initiation of anticoagulant therapy within three days after ERCP. Endoscopist's mean case volume (<1 per week) was the only operator-related factor and the fifth risk factor was the occurrence of any observed bleeding during the procedure (Freeman et al., 1996). Risk factors for PEB in multivariate analyses are shown in Table 2 (Srinivasan and Fre, 2019).

3.1. Patient- related factors

The role of anticoagulants and antiplatelets in post-ERCP bleeding has been a topic of interest as the use of antithrombotic therapy, as well as dual antiplatelet agents (APA) and acetylsalicylic acid (ASA) increases the risk of bleeding. Current guidelines suggest withholding APAs (not ASA) before ERCP. In Patients who start on anticoagulation within 3 days after ERCP due to any coagulopathies have an increased the risk of PEB. ASA or NSAIDs in the periprocedural period is safe and does not increase the risk of bleeding after ERCP. Current guidelines suggest that low doses of aspirin or NSAIDs may be continued safely in the peri-endoscopic period.

Table 2. Risk factors for PEB in most studies analyses

Definite (Significant by multivariate analyses)	Maybe (Significant by univariate analyses)	No (Not significant by multivariate analyses)
• Coagulopathy • Anticoagulation <3 days after ES • Cholangitis before ERCP • Bleeding during ES • Lower ERCP case volume	• Cirrhosis • Dilated CBD • CBD stone • Periampullary diverticulum • Precut sphincterotomy	• Aspirin or NSAID • Ampullary tumor • Longer length • sphincterotomy • Extension of prior ES

CBD, Common bile duct; ES, endoscopic sphincterotomy; NSAID, nonsteroidal anti-inflammatory drug.

Although the risk of bleeding associated with the use of a thienopyridine (ticlopidine, clopidogrel, and prasugrel) has not been well studied, it is recommended that these medications be discontinued at least five to seven days before high-risk endoscopic procedures (e.g., ERCP with sphincterotomy) with patients continued or switched to aspirin monotherapy until the thienopyridine can be safely resumed (Freeman et al., 1996; Acosta et al., 2016; Chandrasekhara et al., 2017). A recent South Korean study demonstrated at the timing of restarting anticoagulation and its impact on PEB in patients on warfarin

bridged with heparin therapy around the time of their procedure. They found no difference in PEB with resumption time; however, there was an increased risk of thromboembolic events in the late resumption group (Paik et al., 2018). The precise role of the newer direct-acting, non-vitamin K oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) on risk of bleeding requires further investigation.

Cirrhosis, renal disease and dialysis for end-stage renal disease (particularly year-long hemodialysis), were confirmed as risk factors for ERCP-related bleeding in a meta-analysis and retrospective studies (Mashiana et al., 2018; Nakaji et al., 2018; Leal et al., 2019).

3.2. Techniques and endoscopist related factors

The role of precut is controversial: in two meta-analyses early precut sphincterotomy in difficult biliary access did not increase the rate of post-ERCP bleeding compared with persistent cannulation attempts (Sundaralingam et al., 2015; Tang et al., 2018). However, contrary to these meta-analyses, precut sphincterotomy has been associated with an increased incidence of bleeding in former multi-center studies (Loperfido et al., 1998; Masci et al., 2001).

PEB was less frequent with endoscopic sphincterotomy associated with balloon dilation vs. endoscopic sphincterotomy alone for difficult biliary stones (de Clemente et al., 2018). A recent meta-analysis reported that bleeding risk depend on the extent of the endoscopic sphincterotomy (Hwang et al., 2013).

As an endoscopic sphincterotomy technique, the papillae should be incised in the 10 – 11 o'clock region, because this includes only 10% of all papillary arteries (Mirjalili and Stringer, 2011). Theoretically, it can be thought that bleeding may be less with this method. The type of current used during endoscopic sphincterotomy seems to affect the risk of ERCP related bleeding. Blended current, as opposed to pure-cut current, is recommended as it significantly reduces the incidence of bleeding without increasing the risk of post ERCP pancreatitis (Rey et al., 2010). Endocut may be preferred because it causes less bleeding compared to other blended current modes (Li et al., 2019). Endoscopist's case volume may also be another risk factor. One study reported that case volume <1 per week was an operator-related risk factor for post-ERCP bleeding (Freeman et al., 1996). Important factors that were not associated with bleeding included length of sphincterotomy incision, extension of prior sphincterotomy, the presence of a periampullary diverticulum or tumor and the use of aspirin or other NSAIDs within three days prior to procedure.

4. Prevention of post-ERCP bleeding

The risk of PEB can be minimized by identifying patients at risk, taking measures to correct coagulopathy, and using careful technique. The major method to reduce the risk of PEB is to avoid unnecessary sphincterotomy especially in patients with 1 or more risk factors. Prevention of PEB mandates careful patient assessment for risk factors and their correction whenever possible. An elective procedure provides the luxury of pre-procedure planning and preparations. Unfortunately, there may not be enough time to maintain optimum conditions in urgent procedures.

4.1. Identifying patients at risk

As a general rule, sphincterotomy is a high risk for bleeding in patients with advanced liver disease, kidney diseases, hemodialysis, and hemostasis disorders such as hemophilia and von Willebrand disease. Therefore, necessary corrections should be made as much as possible in these patients if sphincterotomy is required. Post ERCP observation should be extended in patients with portal hypertension or cirrhosis, renal disease and, dialysis for end-stage renal disease (particularly year-long haemodialysis). Bleeding rates after ampullectomy range from two to 18 percent (Kang et al., 2017). For this reason, caution is recommended in patients with papillary tumours that will undergo ampullectomy. This is probably a risk factor for bleeding based on pathophysiological and technical concerns and clinical experience (Bickerstaff et al., 1990).

4.2. Optimizing coagulation abnormalities

The general approach is to obtain a pre-ERCP coagulation screening (complete blood count and prothrombin time / international normalized ratio [INR]), particularly if an intervention (such as sphincterotomy, ampullectomy) is anticipated. A platelet count exceeding 50,000 to 80,000 / micro–L and an INR <1.5 are generally found to be safe (Sherman et al., 1992; Sherlock and Dooley J, 1993; Henning et al.,1994; Freeman et al., 1996; Prat et al., 1996). The guidelines from the ASGE recommend coagulation studies only in selected patients with active bleeding, a known or suspected bleeding disorder (including a history of abnormal bleeding), an increased risk of bleeding due to medication use (e.g., use of anticoagulants, prolonged antibiotic use), prolonged biliary obstruction, malnutrition or other conditions associated with acquired coagulopathies (Pasha et al., 2014). However, some endoscopists restrict pre-ERCP coagulation screening to patients with elevated bilirubin, who are receiving an anticoagulant or who have a history of a bleeding diathesis (Egan et al., 2014.). If a patient has coagulopathy, this should be corrected and platelet count and INR should be maintained at >50,000/ micro–L and less than 1.5, respectively. If the ERCP procedure is not emergent, one could wait until correction of coagulopathy. Otherwise, emergent reversal of anticoagulation can be achieved with fresh frozen plasma.

Clotting defects in cirrhotic patients can be corrected with fresh-frozen plasma, vitamin K or platelet transfusion before ERCP (Boujaoudé et al., 1994; Prat et al., 1996). Patients with known platelet dysfunction such as patients on hemodialysis should receive appropriate preventive measures, which may include infusion of desmopressin (DDAVP) (Sidawy et al., 2008). Consultation with an expert in coagulation disorders is recommended before performing endoscopic procedures in patients with disorders of hemostasis.

ASA, other NSAIDs and antiplatelet drugs (i.e., ticlopidine, clopidogrel, and prasugrel) have the potential to increase the risk of bleeding. The management of antiplatelet therapy can be individualized depending on weighing the procedural risk for bleeding with the risk of cardiovascular or thromboembolic events. Several professional societies recommend discontinuing clopidogrel and prasugrel before endoscopic sphincterotomy (5-7 days), while aspirin can be continued except ampullectomy (Boustière et al., 2011; Veitch AM et al., 2016).

For patients on warfarin therapy, British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend that warfarin should be discontinued for five days to allow the INR to reduce to <1.5 to perform endoscopic sphincterotomy and high-risk procedure (Veitch AM et al., 2016). Patients at high risk of thromboembolic events (mechanical valves, atrial fibrillation with a history of CVA, or a CHADSVASC of >2) can be bridged with heparin in the periprocedural period. After the procedure, clopidogrel and warfarin may be started by 48 h post procedure depending on the perceived risk of bleeding and thrombosis. The novel direct oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban, Edoxaban) should be stopped >2 half-lives before the procedure, which depends on the specific agent and the patient's renal function. The optimal timing for restarting antithrombotic therapy after ERCP intervention will depend on the perceived risk of post-procedural bleeding and thrombosis. Detailed advice on the management of anticoagulants and antiplatelet agents in the context of ERCP is available in the BSG/ ESGE Guidelines. (Dumonceau et al., 2020).

4.3. Endoscopic techniques

One of the important bleeding prevention approaches is the technique of sphincterotomy because sphincterotomy is the main cause of PEB. Papilla cutting length, sphincterotome type, electrocautery current mode, selection of balloon dilatation against sphincterotomy in the extraction of gallstones, submucosal injection is some of the endoscopic methods affecting the chances of PEB occurrence. The experience of the endoscopist and the volume of the center are directly related to the risk of ERCP related bleeding. The risk of PEB increases with sphincterotomy performed by relatively inexperienced endoscopists or when the volume of the endoscopy unit is low. Improvement in endoscopic methods may explain the slight decrease in the sphincterotomy-induced bleeding rate observed over time (Lee et al., 2020).

PEB can be prevented or restricted by proper orientation of the guidewire, avoidance of "zipper or Y type" cuts and unnecessarily long cuts, and judicious use of the electrocautery current (Ratani et al., 1999). The papillae should be incised in the 10-11 o'clock region. Optimal electrocautery settings are uncertain because of a trade-off in the risk of pancreatitis versus bleeding. Pure-cut electrocautery current is associated with an increase in the frequency of localized bleeding, which may temporarily obscure the view and interfere with the procedure (Ratani et al., 1999). Blended current is recommended as it significantly reduces the incidence of bleeding without increasing the risk of post ERCP pancreatitis (Rey et al., 2010). The use of combined current sphincterotomy technic (pure-cut and blended current in sequence, starting with pure cut and completing the sphincterotomy with the blended current) did not reduce the rate of clinically significant post-sphincterotomy bleeding in comparative studies (Stefanidis et al., 2003). Our practise is to use ENDO CUT mode (ERBE, Germany).

Endoscopic balloon dilatation (EBD) for the treatment of bile duct stones in patients with hemostatic disorder may reduce the risk of PEB compared to standard sphincterotomy. In particular, the technique of combining small (1/3) sphincterotomy with balloon dilatation is safe and may alleviate the risk of perforation and bleeding (Mok et al. 2017)

The rationale for using closed or partially closed sphincterotome is to provide a more controlled cut and avoid the "zipper" cut. Although this seems theoretically logical, the use of a partially closed sphincterotome was not associated with lower PEB compared to the results with a closed sphincterotome (Katsinelos et al., 2010).

Prophylactic submucosal injections have also been investigated to prevent bleeding after sphincterotomy. In a randomized prospective study, prophylactic submucosal injection of hypertonic saline-epinephrine has been shown to be effective in preventing PEB (Matsushita et al., 2010). Additional studies are needed to determine whether this technique will be routinely applied to patients with increased bleeding.

5. Management of post-ERCP bleeding

PEB often stops spontaneously and is rarely life-threatening. But PEB may become a big problem in patients with bleeding diathesis or hemostatic disorders. Most clinically significant bleeding can be managed with like any other cause of gastrointestinal bleeding such as medical treatment and endoscopic therapy, which should be performed without delay in patients who have immediate bleeding. The importance of resuscitation and medical treatment should not be ignored in all gastrointestinal bleeding cases. The first and major life saving steps include adequate intravenous replacement (fluid and/or blood products) and hemodynamic resuscitation and medical stabilization. Endoscopic therapy, pharmacologic treatment, angiographic treatment, and surgery are medical options for the current treatment of PEB. Angiography or surgery is rarely required for patients with refractory bleeding.

5.1. Endoscopic therapy

Several endoscopic techniques, such as injection therapy, mechanical methods, and thermal methods, are used to control bleeding. It is critical and particularly important to avoid any trauma in the pancreatic orifice located below the lower rim of

the sphincterotomy when performing one of the endoscopic haemostasis procedures. Accidental but well-intentioned endoscopic intervention in this area can cause acute pancreatitis.

5.2. Injection therapies

The most used and generally effective endoscopic intervention is injection therapy with diluted epinephrine (1:10,000) through a sclerotherapy needle into and around the sphincterotomy site (Boujaoudé et al., 1994; Vásconez et al., 1998). The volume of injectate varies between studies but usually is 0.5 ml to 4 ml. It is effective on controlling bleeding by volume tamponade and local vasoconstriction. The technique is easy to learn and does not damage to tissues. However, diluted epinephrine does not cause vascular thrombosis. Injection of sclerosing agents in combination with epinephrine has also been described, but extreme caution should be exercised when injecting sclerosing agents due to the risk of inflammatory or necrotic effects (Chester and Hurley, 1990). The effect of endoscopic haemostasis with epinephrine and/or alcohol injection therapy was illustrated effective and safe in a study of 1304 patients with 10 percent bleeding (Kim et al., 1999). Societal guidelines emphasize that epinephrine should always be combined with a second endoscopic therapy such as a mechanic or thermal method (high-grade recommendation). This recommendation can be applied to other GIS bleeding except for PEB because, as demonstrated in a retrospective study, epinephrine injection was as effective as epinephrine injection combined with thermal therapy for the management of delayed PEB (respectively; haemostasis 96 % vs 100% and re-bleeding 16% vs 12%) (Tsou et al., 2009). Therefore, injection therapies are the first-line treatment option, and if injection therapy fails, the second option may be other techniques or combinations.

The injection of fibrin sealant, a two-component adhesive consisting of human fibrin and thrombin with the addition of coagulation factor XIII, has also been successfully used to stop PEB in the case of rebleeding after injection therapy with epinephrine. The injection of a fibrin sealant has potential advantages over sclerosants. But, difficulty of preparation and injection, high cost, potential risk of transmission of infection, and possible occlusion of the pancreatic orifice are several drawbacks of fibrin sealant. So, before injection biliary and pancreatic outflow should be secured by placing pancreatic and biliary stents (Born et al., 2000). Injection of saline also causes local tamponade, which can be effective in achieving transient haemostasis. However, it is associated with higher recurrent bleeding rates compared with other standard therapies. It can be used to temporarily stop bleeding so that the endoscopist will have the chance to observe the bleeding area clearly while planning an intervention for permanently stopping the bleeding.

5.3. Thermal methods

Thermal coagulation with contact (heater or bipolar) or non-contact (argon plasma coagulation) probes achieves acute hemostasis and prevents recurrent bleeding by coagulation of the underlying artery in the bleeding area. The application of electrocautery current is more difficult than injection therapy because of the side view angle and elevator of duodenoscopy. But can be attempted with the sphincterotome wire or with an electrocautery, heater probe or argon plasma coagulation probe if a visible vessel or a specific bleeding point can be identified. If brisk bleeding occurs during the sphincterotomy procedure, electrocoagulation can be successfully completed without the need for another probe to change directly with the sphincterotome wire. The basic principles of electrocoagulation are the same as those used in other GIS bleeding. However, if thermal coagulation is required around the pancreatic orifice, the pancreatic stent should be placed first to prevent the development of potentially acute pancreatitis.

5.4. Mechanical methods

Hemoclip

Endoscopic clips are a mechanical clamping method that has many potential therapeutic applications. While currently available clips are relatively easy to use, they require specific practice on the part of both the endoscopist and the assistant. When first-line therapy epinephrine injection or thermal methods fail or bleeding recurs hemostasis can be achieved by precise placement of one or more hemoclips at the bleeding site (Katsinelos et al., 2005). Accurate targeting with good position, best viewing angle and application direction is required for success. However, in case of active bleeding, it may be difficult to apply the clips with side-viewing duodenoscope. The duodenoscope elevator often makes clip delivery challenging because the plastic sheath often becomes kinked while passing through the elevator. This disadvantage can be facilitated by using a forward-view endoscope with a cover (Kubiliun et al., 2015). If necessary, the prophylactic pancreatic stent should be inserted first. In two studies (67 patients with persistent PEB), clips provided hemostasis in 90%–100% of the cases (Liu et al., 2015; Chon and Kim, 2017). A novel duodenoscopy-friendly hemoclips designed for delivery using the duodenoscope may also be used. Also, it is necessary to avoid around the pancreatic orifice with the associated risk of pancreatitis during the application of hemoclip.

Balloon tamponade

The balloon tamponade of the sphincterotomy site can be obtained with a standard stone removal balloon catheter (Freeman et al., 1996). However, this technique is practical for active intraprocedural bleeding that occurs during sphincterotomy. The balloon is inflated maximally, creates a tampon, and temporarily stops bleeding. Meanwhile, temporary control of bleeding improves visualization of the bleeding site and may allow plan and successfully implement other treatment methods. It is not usually a permanent bleeding stop treatment method and the effectiveness of this method has not been well studied.

Fully covered self-expandable metal stent

Over the past decade, fully covered self-expandable metal stents (FCSEMs) have been used for refractory PEB with excellent clinical outcomes (Itoi et al., 2011; Canena et al., 2013). FCSEMSs also can be used to tamponade bleedings originating from deep within the ampulla or mid/distal common bile duct and can prevent the development of hemobilia. FCSEMs may be a particularly effective last-opportunity second-line method before resorting to embolization or surgery where primary endoscopic intervention has failed in PEB. A retrospective CEASE study included 67 patients with PEB found that, after the failure of primary endoscopic interventions, placement of a fully covered SEMS (n=23) significantly reduced the bleeding rate at 72 hours and resulted in less of a decrease in hemoglobin level than that of conventional methods (0.66 g/dL vs. 1.98 g/dL, $P < 0.001$) (Cochrane and Schlepp, 2016). There is no consensus among experts on the optimal stent diameter and the timing of stent removal. Stent migration also remains a concern. FCSEMSs are relatively expensive devices and need a repeat procedure for stent removal usually within 4–8 weeks to avoid adverse events related to long term indwelling stent.

5.5. Hemostatic nanopowder and hemostatic agents

A nanopowder that promotes hemostasis (Hemospray) has been developed that becomes cohesive and adhesive when it meets moisture, forming a stable mechanical barrier at the site of bleeding. It also has been shown to enhance clot formation and shorten coagulation time (Holster et al., 2015). The powder is delivered through a catheter and sprayed onto the bleeding site under endoscopic guidance. It is easy to apply, does not require an en face view of the ulcer, and does not require direct tissue contact. This treatment modality is available in Canada and Europe and was FDA approved in the United States in 2018. In a case of severe PEB, hemostasis was achieved through the application of 4 g of the hemostatic agent, with no evidence of secondary biliary obstruction (Appleby et al., 2015). The use of hemostatic nanopowder should be considered as a possible alternative to standard endoscopic therapy in cases where the position, site or size of the bleeding site makes conventional endoscopic therapy difficult.

Ankaferd Blood Stopper (ABS) (Ankaferd Sağlık ürünleri, A.Ş., İstanbul, Turkey), which is a commercial form of a traditional herbal medicine that has been used historically in Anatolia as a hemostatic agent for centuries, consists of a standardized mixture of five plants. ABS is locally active on the bleeding surface which is applied to the bleeding site and interacts with plasma proteins and acts by formation of an encapsulated protein network and stimulation of erythrocyte aggregation (Goker et al., 2008). Like the hemostatic nanopowder, it does not require injecting; spraying over the bleeding site is sufficient for hemostasis. Beyazit et al. reported that 3 mL of ABS was successfully applied and hemostasis was achieved in a 43-year-old woman with intraprocedural bleeding from the sphincterotomy site where electrocoagulation and injection therapy failed (Beyazit et al., 2010). Hemostatic powder, fibrin glue and other herbal hemostatic agents are possible rescue therapies, but the reported experience in the literature is extremely limited to just a few case reports and thus they cannot be routinely recommended.

Pharmacologic treatment

In the management of patients with disorders of hemostasis or coagulopathies who are undergoing ERCP, the disease severity, the procedure-related bleeding risk, and the timing of the procedure should be considered. The bleeding risk also depends on the patient's underlying disorder and the availability of interventions to enhance hemostasis (e.g., factor replacement for hemophilia, platelet transfusions for thrombocytopenia). Use of recombinant human factor VIIa as a preventive measure has also been reported in a patient with inherited factor VII deficiency who successfully underwent ERCP with sphincterotomy without bleeding (Abdulsamad et al., 2017). Infusion of terlipressin in four patients (Tyagi et al., 2009) and infusion of nitro-glycerine in another case report (Sharma 2010) were effective in controlling hemobilia during therapeutic ERCP in patients with portal biliopathy. In hemodialysis patients, the administration of desmopressin (DDAVP) infusion is an option to improve platelet dysfunction.

Angiographic treatment

In some cases, massive bleeding occurs during sphincterotomy and obscures the endoscopic field, which makes subsequent hemostatic procedures technically difficult and may result in the failure of the several endoscopic hemostatic methods. In these situations, bleeding needs to be stopped by radiologic or surgical intervention. Celiac or superior mesenteric angiography with transcatheter infusion of vasopressin or embolization of the bleeding artery can be effective but is uncommonly performed as underscored by the paucity of data on this approach. Arterial embolization is technically difficult and may cause infarction of abdominal organs. Therefore, it is necessary to target the right artery and make selective or super selective embolization as much as possible. Yamaguchi et al. reported that the papillary artery originates from the communicating artery which connects the posterior superior pancreaticoduodenal artery (PSPDA) and the anterior superior pancreaticoduodenal artery (ASPDA) (74%), or directly from the posterior pancreaticoduodenal artery as a vasa recta type (26%) among 73 papillary arteries. Furthermore, no papillary artery arises from the anterior pancreaticoduodenal artery, so the vessels targeted for vascular interventional treatments should be carefully and specifically selected (Yamaguchi et al., 2001). Studies have shown a reduction in the risk of bowel infarction due to technical improvements and increased experience of advanced interventional radiologists. Angiographic interventions successfully control bleeding in 83% to 100% of patients in reported series and should be considered before surgery (So et al., 2012; Dunne et al., 2013).

Angiographic embolization also can be used for treatment of hemobilia originating from the locations proximal to the hilum and for distal bleedings that are refractory to FCSEMs placement.

Surgery

As mentioned above, the need for surgery has decreased during the past two decades because of success with several endoscopic methods. The most performed rescue operation involves conversion of the sphincterotomy into a sutured sphincteroplasty and oversewing the bleeding artery at the apex of the sphincterotomy. If anatomic changes make direct access to the ampulla through the duodenal wall impossible, a Fogarty catheter can be inserted into the common bile duct (either through the cystic duct or a choledochotomy) permitting balloon tamponade of the bleeding point (Bardaxoglou et al., 1994). In older series, surgery was associated with postoperative mortality rates as high as 50 percent, largely because many of the patients were too ill for surgery (Goodall, 1985). The infusion of a topical gelatin matrix-thrombin hemostatic agent into the distal portion of the common bile duct during urgent surgical exploration was effective in a patient with life-threatening PEB (Dimitroulis et al., 2012). Further experience is needed to confirm the efficacy of this topical hemostatic agent in cases of PEB. There have been no head-to-head trials comparing clipping, cautery or metal stents for PEB, so various approaches can be utilized. Injection therapies and thermal methods are the first line option in daily practice. If the location of the suspected bleeding site allows the placement of hemostatic clips, it may be the second option to control bleeding when the first interventions fail. Balloon tamponade and injection of saline around the papilla ensure temporary control of bleeding, improves visualization of the bleeding site, and may allow plan and successful implementation other treatment methods. These approaches utilize the fundamental tools traditionally applied in other luminal causes of gastrointestinal bleeding. Caution should be taken to avoid thermal injury or clip placement over the pancreatic orifice, especially if the bleeding site is on the right-hand wall of the sphincterotomy incision. The placement of a FCSEMs is probably best reserved as a salvage therapy when traditional endoscopic methods fail. Hemostatic powder, fibrin glue and another herbal hemostatic agent cannot be routinely recommended. Pharmacological agents can be used in chronic systemic diseases, disorders of hemostasis or coagulopathies. In rare cases, angiography or surgery is required for refractory bleeding.

Conflict of interest

None.

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None.

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Review Article

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Management of bleeding in advanced endoscopic procedures

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Abstract

Endoscopic mucosal resection and endoscopic submucosal dissection are used for the treatment of early gastrointestinal tract cancers. Bleeding is one of the most common complications encountered when performing these procedures. It is more common in gastric cases than in esophageal and colorectal cases. It is important to take measures before, during and after the procedure to mitigate the risk of bleeding. Patient history should be carefully questioned for bleeding tendency, the use of medications which may potentiate bleeding and the presence of a condition known to increase the risk of bleeding. In the case of bleeding during the procedure, a knife, coagrasper, hot biopsy forceps or hemoclip may be used. Although bleeding is a common complication in advanced endoscopic procedures, it can be easily managed in experienced hands and effective intervention methods.

Keywords: endoscopic mucosal resection, endoscopic submucosal dissection, bleeding, gastrointestinal tract

1. Introduction

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are advance endoscopic procedures used for the treatment of early gastrointestinal tract cancers. EMR has been in use for many years due to its convenience, short duration of procedure and low cost. However, inability to perform en bloc resection in large lesions, limitations of histological evaluation and the high probability of cancer recurrence prompted research efforts for alternative modalities, culminating in the development of ESD applications. These newer modalities allowed removal of early stage lesions of the gastrointestinal tract in one piece and thus, reduced the need for surgery. Advances in endoscopic devices led to detection of an increased number of early stage gastrointestinal tract lesions and improved detection of lesions led to increased use of EMR and ESD procedures. However, these advanced procedures were also lead to an increase in the number of patients with complications. Therefore, it is crucial to have a good knowledge of potential complications before performing advanced endoscopic procedures and care should be taken to avoid complications during the procedure and to recognize them early and treat effectively.

Bleeding is one of the most common complications encountered when performing advanced endoscopic procedures. Post-EMR bleeding has been reported at a rate of 1.2% in esophageal lesions, 0.1-5.3% in gastric lesions and 2.3-3.5% in colon lesions (Tomizawa et al., 2013; Ono et al., 2016; Fukami, 2019). ESD procedures have been associated with bleeding rates of 0-0.7% in esophageal lesions, 0-15.6% in gastric lesions and 0.4-5.7% in colon lesions (Kataoka et al., 2016; Ono et al., 2016; Fukami, 2019).

Bleeding is classified into two categories including immediate (intra-procedural) bleeding and delayed (post-procedural) bleeding. Delayed bleeding may occur within 30 days after the procedure. While it is quite easy to recognize bleeding during the procedure, delayed bleeding is considered when there is substantial bleeding or the diminution of 2 g/dL in hemoglobin value (Tajiri and Kitano, 2004). It is important to take measures before, during and after the procedure. Patient history should be carefully questioned for bleeding tendency, the use of medications which may potentiate bleeding and the presence of a condition known to increase the risk of bleeding. The blood type should be determined prior to the procedure in patients at risk for bleeding. The knives used for the procedure, the type of vascular intervention and the procedure technique may affect the development of hemorrhage. It is recommended that the endoscopist performing ESD be experienced in the control of bleeding events (Yamamoto et al., 2009). Such expertise would greatly contribute to successful completion of procedure in patients with bleeding.

At the time of the procedure, the patient should be assessed as a whole and supported with parenteral fluids if excessive blood loss is anticipated in extended procedures. In advanced endoscopic procedures, early management of bleeding prevents falling in blood values and ensures a safe and high-quality procedure (Oda et al., 2005; Toyonaga, 2006). Since

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the bleeding is managed in a short time, bleeding that is severe enough to require replacement does not occurring such patients. While it is recommended to cut small submucosal vessels with a knife in the coagulation mode in order to avoid impairment of the endoscopic view due to bleeding, coagulation of the blood vessel with a coagrasper followed by dissection is recommended for large submucosal vessels. The cut-off vessel thickness for coagrasper was reported as 1 mm in some studies and 2 mm in others. Figures 1, 2, and 3 show submucosal area and submucosal vessels visualized during ESD.

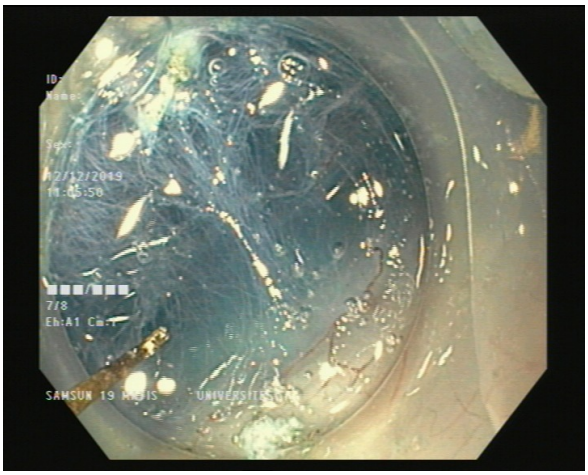

Fig. 1. The appearance of submucosal area during ESD

In the case of bleeding during the procedure, a knife, coagrasper, hot biopsy forceps or hemoclip may be used. The operation modes to be used to manage bleeding in advanced endoscopic procedures should be adjusted according to the instructions for use of the cautery device taking into account the site of bleeding, and knife or coagrasper used. Prior to performing coagulation with a knife, coagrasper or hot biopsy forceps, visualization of the focus of the bleeding and intervention to that site provides effective bleeding control and also decreases the risk of perforation. For this purpose, the endoscopes used for advanced endoscopic procedures have a water-jet canal which provides a clear view of the focus by flushing the bleeding site. Uncontrolled minor bleeding may impair the clarity of endoscopic view, resulting in increased complications. For lesions requiring the use of a hemoclip, care should be exercised to ensure that the site is dissected and clipping does not interfere with continuation of the procedure. Otherwise, there may be a possibility of residue in the clipped area (Takizawa, 2015).

There are some endoscopists who advocate addition of diluted adrenaline into the solutions used for mucosal elevation since it reduces the risk of intra-procedural bleeding. However, others claim that since adrenaline reduces bleeding during the procedure, the focus of bleeding may be overlooked and bleeding starts again after the hemostatic effect of epinephrine is lost. In ESD procedures, bleeding is more common in gastric cases than in esophageal and colorectal cases (Takizawa, 2015). As submucosal arteries located in the proximal and middle sections of the stomach have a larger diameter, bleeding occurs more commonly in ESDs of these sites (Toyonaga, 2006). The frequency of bleeding increases with greater lesion size (Toyonaga, 2006). However, delayed bleeding is more common in ESDs of distal stomach compared to proximal and middle sections (Oda et al., 2005). The lesion size (Okada et al., 2011), advanced patient age and longer procedure time have been shown to be associated with a higher risk of bleeding. Blood transfusion is rarely needed (Takizawa, 2015). Although it has been reported that a follow-up gastroscopy on the day after gastric ESD decreases the likelihood of delayed bleeding (Goto et al., 2010), it is not widely accepted for routine use. Nasogastric intubation was suggested to be useful in the early detection of bleeding (Takizawa, 2015).

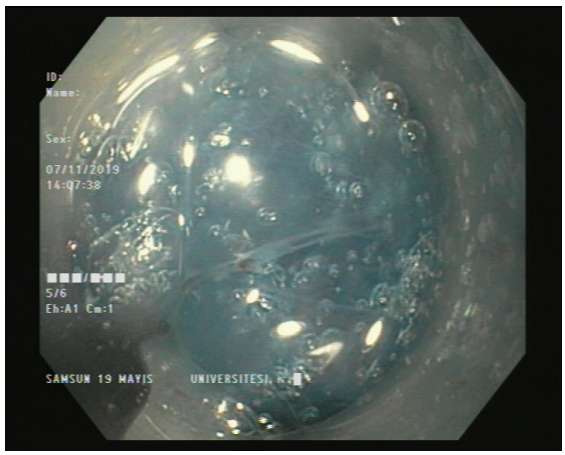

Fig. 2. The appearance of small submucosal vessels during ESD

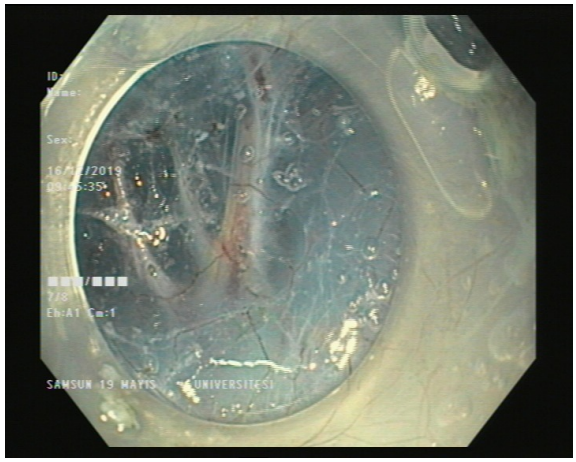

Fig. 3. The appearance of large submucosal vessels during ESD

Active bleeding should be suspected in a patient with hematemesis and/or hematochezia /melena and vital findings of the patient should be assessed rapidly along with hemoglobin/ hematocrit monitoring and the site of ESD site should be inspected endoscopically. In general, the use of APC is not recommended in post-ESD bleeding due to difficulty in controlling the coagulated region. Approaches to bleeding vary in relation to the time from ESD. While coagulation with a coagrasper and hemoclip use are recommended for early bleeding because of the softness of post-ESD ulcer, injection treatment is advised for bleeding that develops after the formation of granulation tissue (Oda et al., 2013).

H2 receptor blockers or proton-pump inhibitors (PPI) have been demonstrated to be effective in ESD ulcers although data on their superiority are variable (Yamaguchi et al., 2005; Uedo, 2007). Additionally, administration of a proton-pump inhibitor before the procedure was reported to reduce the severity of pain. At our clinic, patients undergoing ESD are given PPIs via intravenous route one hour before the procedure and ESD ulcer is coated with sucralfate after the procedure. Liquid foods are initiated the next day and PPI therapy is given twice daily within the first month and once daily for the following two months. These patients also receive eradication therapy for *Helicobacter pylori* if it is present.

Another consideration for bleeding in advanced endoscopic procedures involves patients receiving antiplatelet and anticoagulant therapies. EMR and ESD are endoscopic procedures that carry a high risk of bleeding. Therefore, such patients should be evaluated in terms of the risk of thromboembolism before the procedure and the doses of their medications should be adjusted before, during and after the procedure through consultation with the physician treating the patient. Current guidelines recommend discontinuation of other antiplatelet drugs for a specified period before the procedure and the use of aspirin or cilostazol if antiplatelet therapy is mandatory. For patients taking warfarin as oral anticoagulation therapy, normalization of prothrombin time or switch to a direct oral anticoagulant may be advised. However, direct oral anticoagulants also need to be discontinued before the procedure depending on their duration of action. The treatment may be resumed after confirmation of hemostasis endoscopically after the procedure (Tanaka, 2020).

2. Conclusion

In conclusion, although bleeding is a common complication in advanced endoscopic procedures, it can be easily managed in experienced hands and effective intervention methods.

Conflict of interest

None.

Acknowledgments

None.

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Research Article

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Transarterial embolization of acute gastrointestinal bleeding

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Abstract

Transarterial embolization (TAE) is a minimally invasive treatment method developed alternative to surgery for acute gastrointestinal bleeding (AGIB). The aim of this study was to evaluate the efficacy and outcome of TAE in AGIB patients. The data of 30 patients who underwent TAE with complaint of AGIB between January 2007- May 2020 was collected retrospectively. The etiology of hemorrhage, localization and type of lesion, embolizing agent used, and postprocedural complications were recorded. Lesions were classified as pseudoaneurysm (PA), extravasation, pathological tumor vascularity and vasospasm. A total of 22 patients, 5 females, were included in the study. The most common underlying cause was tumors (n=15, 50%). The most common lesion detected on angiograms was pathological tumor vascularity. Embolizing agents used were N-butyl-2-cyanoacrylate in five patients, coils in three patients, polyvinyl alcohol particles in six patients and microsphere in seven patients. The technical success rate was 90.9%, and two patients developed rebleeding in the early postprocedural period. TAE is a safe, effective and minimally invasive method in emergency treatment of patients with AGIB.

Keywords: transarterial embolization, acute gastrointestinal bleeding, embolic agents

1. Introduction

Acute gastrointestinal bleeding (AGIB) is a life-threatening severe emergency condition (Manning-Dimmitt et al., 2005). Massive bleeding can lead to hemodynamic instability, hemorrhagic shock, and even death, so the lesion that causes bleeding needs to be detected and treated quickly (Peynircioğlu et al., 2011; Chan et al., 2015). Arterial angiography was used for the first time in 1963 by Nusbaum in the diagnosis of AGIB (Nusbaum et al., 1969). Rösch et al. developed transarterial embolization (TAE) in the treatment of AGIB in 1972 (Rösch et al., 1972). Rapid development in interventional radiological techniques and materials has enabled AGIB to be treated quickly and effectively with angiographic methods. In patients whom bleeding can't be stopped with conservative or endoscopic treatment, TAE is a minimally invasive treatment alternative to surgery (Walker et al., 2012; Loffroy, 2013).

In this study, we aimed to investigate retrospectively the arteriographic findings and the effectiveness of the treatment in cases that we performed TAE due to AGIB in our interventional radiology unit.

2. Materials and methods

Patients who underwent angiography with the diagnosis of AGIB between January 2007 and June 2020 in the interventional department of our hospital were retrospectively screened. The institutional Ethical Committee of the Ondokuz Mayıs University has approved this retrospective study, and the procedures were in accordance with the ethical standards.

Etiology of gastrointestinal bleeding, localization of haemorrhage, embolic agents used and postoperative complications were recorded. Pathologic vascular findings on digital subtraction angiography (DSA) were grouped as extravasation, pseudoaneurysm (PA), pathological tumor vascularity and vasospasm. Cessation of bleeding on postembolization angiograms and hemodynamic stability were described as technical success. Patients were evaluated for recurrence of haemorrhage within the 30-day postprocedural period.

2.1. Embolization procedure

Written informed consent was obtained from all patients before the procedure. Following the monitorization of patient, a 5F introducer sheath was placed into common femoral artery. Celiac trunk, superior mesenteric artery (SMA) and inferior mesenteric artery (IMA) were catheterized by 5F Simmons-2 (Terumo, Tokyo, Japan) or Cobra (Cook, Bloomington, IN) catheter selectively. A 3F microcatheter (Renegade, Boston

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Scientific, USA) or Echelon 10 microcatheter (ev3 Endovascular, Plymouth, MN, USA) were used for embolization according to the detected lesion and the nature of the embolizing agent to be used. All embolization procedures were done under fluoroscopy in order to prevent off- target embolization. N-butyl-2-cyanoacrylate (Histoacryl; B. Braun Melsungen AG, Melsungen, Germany), polyvinyl alcohol (PVA) particles (Contour; Boston Scientific, Cork, Irland) (Contour SE®, Boston Scientific, Nattick, MA, US ve BeadBlock®, Biocompatibles, Farnham, United Kingdom), microsphere (Embosphere Microspheres®, BioSphere Medical, Rockland, MA) and detachable coils (GDC coils; Boston Scientific) were used as embolizing agents. Cyanoacrylate was used in combination with ionized oil (Lipiodol Ultra Fluide; Guerbet, Roissy, France) for both visibility and embolizing effect (the ratio of cyanoacrylate /iodized oil was 1:2, 1:3 or 1:8). Results for the quantitative variables were expressed as the mean and standard deviation (SD), and the results for the categorical variables were shown in terms of frequencies and percentages.

3. Results

Thirty patients with AGIB were included in the study. Five of them were female and the mean age was 56.5±16.3 (aged between 20-81). There was no hemorrhagic lesion detected by DSA in seven patients. Twenty-three lesions were detected and embolized.

When patients were evaluated according to the etiology of bleeding; it was due to gastroduodenal ulcer in seven patients, gastric carcinoma in eight patients, iatrogenic bleeding in three patients, pancreatic cancer in two patients, secondary to other tumors in five patients, diverticulitis in three patients, pancreatitis in one patient and amyloid-related bleeding in one patient. We identified 8 pseudoaneurysm, 10 tumor vascularity, five contrast extravasation and seven vasospasms (Table 1).

Table 1. GIS bleeding etiology and angiography findings

Cause (n)	Contrast extravazation	Pseudoaneurysm	Tumor vascularity	Vasospazm
Gastric or duedonal ulcer (4)	2	1		2
Gastric carsinom (5)		2	4	
Tumor bleeding (7)		3	6	3
Iatrogenic (3)	1	1		1
Diverticulite (1)	1			
Pankreatit (1)		1		1
Amyloid angiopathy (1)	1			

Eight gastroduodenal artery, five left gastric artery, six SMA branches, one splenic artery, one right gastric artery, one left gastroepiploic artery and one inferior pancreaticoduodenal artery were embolized. Embolization could not be performed in one patient because catheterization could not be achieved secondary to tortiosity and vasospasm although angiography revealed a bleeding focus in the right gastric artery. In one patient, front-back door technique was used to cut the retrograde flow and both the inferior pancreaticoduonal artery and the left gastric artery were embolized. Cyanoacrylate was used (the ratio of cyanoacrylate /iodized oil was 1:2, 1:3 or 1:8) in five patients, coil in three patients, PVA (in sizes of 500-700 microns) in six patients, and microsphere in eight patients as embolizing agents (Table 2). TAE technical success was 90.9% and recurrent bleeding occurred only in two patients. None of the patients experienced intestinal ischemia or duodenal stenosis during the postprocedural period

Table 2. Clinical, angiographic characteristics of patients undergoing trans arterial embolization for AGIB

Characteristics	Value
Patients, n	30
Age (years)	56.5±16.3 (20-81)
Male, n (%)	25 (83.3)
Digital substraction angiography, n	
DSA positive patients, n (%)	23 (76.6%)
DSA negative patients, n (%)	7 (232.3%)
Localization (n=23)	
Gastroduedonal artery, n (%)	8 (34.8%)
Left gastric artery, n (%)	5 (21.7%)
Superior mesenteric artery branchs, n (%)	6 (26%)
Splenic artery, n (%)	1 (4.3%)
Left gastroepiploic artery, n (%)	1 (4.3%)
Right gastric artery, n (%)	1 (4.3%)
Inferior pancreaticoduedonal artery, n (%)	1(4.3%)
Embolization agents (n=22)	
Microspheric embolizing agent, n (%)	8 (36.3%)
Cyanoacrylate, n (%)	5 (21.7%)
PVA, n (%)	6 (527.2%)
Coil, n (%)	3(13.6%)
Successfull treatment frequency (n=22)	
Cessation of bleeding, n (%)	20 (90.9%)
Rebleeding, n (%)	2 (9.09%)

4. Discussion

Annual incidence of AGIB is 20 to 150 per 100,000 population and upper gastrointestinal bleeding is about four to six times more common than lower gastrointestinal bleeding (Manning-Dimmitt et al., 2005; Arber et al., 1994). Mortality rates in AGIB range between 3.6 and 19% and increase up to 40% in case of massive bleeding (Frattaroli et al., 2009).

AGIB often develops secondary to gastric-duodenal ulcer, diverticulitis, Mallory-Weiss syndrome, erosive gastritis, duodenitis, reflux esophagitis, pancreatitis, chronic inflammatory bowel disease, angiodysplasia, tumors of the gastrointestinal tract, iatrogenic and trauma (Manning-Dimmitt et al., 2005; Hreinsson et al., 2013; Barnert et al., 2009). Although the most common cause of AGIB is ulcers, it is noteworthy that tumoral etiology is more common in patients scheduled for endovascular treatment (Shi et al., 2017). Similarly, in our study, AGIB patients with tumoral causes were more common. Ulcers, on the other hand, took the second place in etiology (Fig 1).

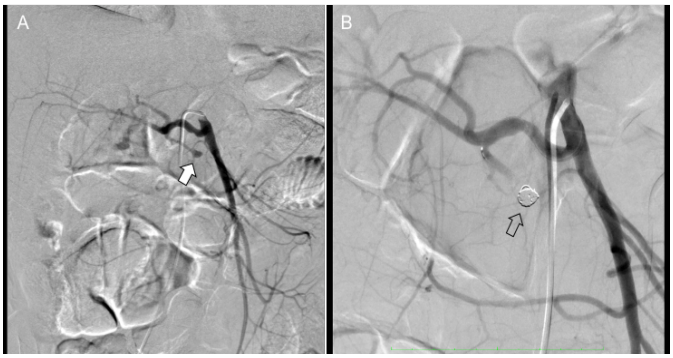

Fig. 1. CTA of a 47-year-old man who presented with massive hematochezia due to duodenal ulcer. Selective hepatic artery angiography showed a PA arising from the gastroduodenal artery (A). After the lesion was super selectively catheterized, the PA embolized with coil (B)

This situation was related to the treatment of bleeding caused by ulcers frequently with endoscopic interventions. Hemorrhage of peripancreatic arteries caused by pancreatitis or pancreatic tumor is a rare cause of AGIB. In two of our cases, bleeding was secondary to erosion caused by the pancreatic mass in the gastroduodenal artery and in 1 case, it was due to erosion caused by pancreatitis in the splenic artery and posterior of the stomach. All three cases were successfully treated with the endovascular method. The sensitivity of arteriography is approximately 90% for upper gastrointestinal bleeding and 86% for lower gastrointestinal bleeding, respectively (Lee et al., 2004). DSA enables detection of bleeding in patients with blood loss rates of 0.5-1 mL/min (Nusbaum et al., 1969). Direct angiographic findings of active GI bleeding are contrast media extravasation and pseudoaneurysm (Walker et al., 2012). In our study, 18 of 22 patients underwent embolization based on direct angiography findings. Intermittent course of AGIB can lead to negative angiographic results (Sos et al., 1978; Eriksson et al., 2006).

In cases where direct findings can't be detected, vasospasm and irregularity in the suspected area are considered as indirect findings. In a study with embolization series of 75 patients by Aina et al. (2001) empirical embolization was performed based on angiography findings in 61.3% of patients and endoscopy findings in 38.7%. It was reported that blind embolization could be performed in case of clinical necessity because there was no difference in bleeding recurrence between both groups. Padia et al. (2009) reported that arterial embolization was equally effective in patients with or without contrast extravasation in their study comparing embolization results in 36 patients with extravasation in angiography due to bleeding in the upper gastrointestinal tract and 72 patients without extravasation. In four of our cases, empirical embolization was performed based on endoscopy findings and vasospasm although there was no lesion in direct angiography and there was no bleeding in the follow-up.

In a meta-analysis performed by Loffroy and Guiu, the technical success rate of TAE was reported as 93% and rebleeding rate as 25% in upper GIB (Loffroy et al., 2009). The technical success rate of TAE in lower GIB was reported as 82% and rebleeding rate as 12% in the meta-analysis conducted by Weldon et al. (2008). In our study, the success rate of TAE due to AGIB was 90.9% and rebleeding rate was 9.09% and these rates were compatible with the literature. In the study of Loffler et al. (2009) investigating the causes of early rebleeding in AGIB patients who could not be treated endoscopically, coagulation disorders and the use of coils as the only embolic agent were reported to be the independent predictors of rebleeding. Aina et al. (2001) also determined that the presence of a coagulation disorder and the use of coils as the only embolic agent were associated with early rebleeding after an embolization procedure.

In our study, rebleeding that developed after gastroduedonal artery embolization in a patient with AGIB secondary to gastric ulcer may be related to the use of only coils in embolization and the absence of front-back door embolization. In another patient who experienced rebleeding, we think that both previous hemicolectomy surgery and the presence of acute myeloblastic leukemia as a comorbidity caused bleeding again.

Various embolizing agents have been used for embolization including gelatin spongostan, PVA, cyanoacrylate, onyx, coil and combinations of these (Loffroy et al., 2015; Širvinskas et al., 2017; Shi et al., 2017). The effect of embolic agent type on clinical results is controversial and there is no consensus on the selection of embolic agent in the literature. Particular agents such as PVA and microsphere are recommended for tumor embolization's using flow dynamics. Larger (> 500 μm) particles should be preferred to reduce the risk of ischemia (Lang, 1992). In a study which the treatment results of acute nonvariceal upper gastrointestinal bleeding with cyanoacrylate were retrospectively evaluated, bleeding was ended in 14 of 16 patients and it was reported that cyanoacrylate was an effective embolizing agent (Lee et al., 2007).

In a similar study by Jae et al., it was demonstrated that cyanoacrylate was a very effective and safe agent, especially when it was not possible to advance the microcatheter to the bleeding site and in the presence of coagulopathy (Jae et al., 2007). Low risk of intestinal ischemia is an important advantage of the coils due to the preservation of the distal arterial bed (Padia et al., 2009). In our study, the most common etiological cause was malignancy and PVA, microspher or cyanoacrylate were preferred for the embolization of the tumor vascular bed (Fig. 2). Coil was used as an embolizing agent in three patients with pseudoaneurysm on the background of gastroduodenal ulcer. In addition to acute ischemia that may develop after embolization, duodenal stenosis secondary to avascular necrosis caused by severe hypoxia in the long-term period is another important complication (Walsh et al., 1999; Whitaker and Gregson, 1993).

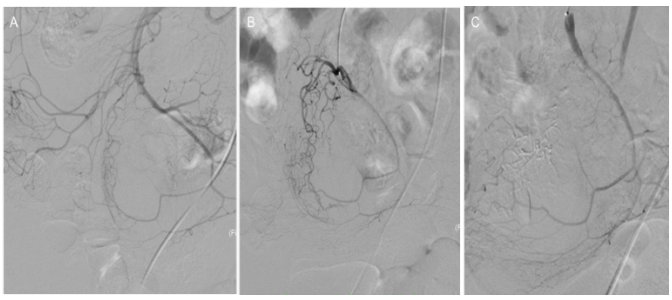

Fig. 2. A 56-year-old woman presented with persistent melena. Angiography of the superior mesenteric artery shows the feeding arteries of the liposarcoma (A). A super selective microcatheter is placed in the right ileocolic artery for embolization (B). Microsphere was injected under continuous fluoroscopy. Angiography after TAE shows disappearance of the tumor enhancement (C)

In a study evaluating the long-term outcomes and complications of TAE in duedonal ulcer bleeding, duodenal stenosis developed in seven (25%) of 28 patients when cyanoacrylate was mostly used, eight months to seven years after embolization of terminal vessels (Lang, 1992). In our series, duodenal stenosis was not detected in any patient who underwent gastroduedonal artery embolization. This may be due to the short follow-up period, as well as not using cyanoacrylate in gastroduodenal artery embolizations. Also, none of the patients had intestinal infarction or off-target embolization in our study.

AGIB requires a multidisciplinary approach that gastroenterologists, surgeons, and interventional radiologists should act together. TAE is an effective, reliable and minimally invasive treatment method in AGIB treatment. In order to increase the success rate of the procedure and avoid possible complications, interventional radiologists should have sufficient information about the flow dynamics in the targeted artery, the properties of the embolic agents and the mechanism of occlusion.

Conflict of interest

None.

Acknowledgments

None.

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A practical alternative for salvage therapy in gastrointestinal bleeding: Ankaferd blood stopper

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Abstract

Upper and lower gastrointestinal bleeding is a common medical condition routinely encountered in clinical practice. Endoscopic procedures still constitute the basis of the treatment for hemostasis and the prevention of rebleeding. A variety of endoscopic treatment modalities including hemostatic clipping, argon plasma coagulation, sclerotherapy, heater probe and hemosprays are used alone or in combination. However, these conventional endoscopic therapies are often challenging, so new topical hemostatic agents have been introduced to allow for easier and more effective hemostasis in recent years. In this study, we shared our experience with Ankaferd blood stopper, which is becoming an effective alternative hemostatic medicine for gastrointestinal bleedings, in 64 patients who applied to our clinic with upper or lower gastrointestinal bleeding between January 2019 and April 2020.

Keywords: ankaferd blood stopper, bleeding, endoscopy, gastrointestinal tract

1. Introduction

Gastrointestinal bleeding (GIB) is a very common condition in gastroenterology clinical practice with an incidence of about 61-78 cases per 100.000 population in upper gastrointestinal bleeding (UGIB) (Al et al., 2009) and 33-87 cases per 100.000 population in lower gastrointestinal bleeding (LGIB) (Augustin et al., 2009). In studies, mortality rates are reported as 7-10% for non-variceal UGIB (Barkun et al., 2019), 20% for variceal UGIB (Barkun et al., 2003), and 2.5-3.9% for LGIB (Bilgili et al., 2009). Currently established standard medical and endoscopic therapeutic options are still essential for the management of GIB. Hemostatic approaches including hemoclips, argon plasma coagulation (APC), sclerotherapy, heater probe and hemosprays may serve as an adjuvant and/or primary theraphy in endoscopic interventions. Each of these treatment modalities has both advantages and disadvantages, therefore the treatment choice should be specific to the patient.

In addition, the success of the procedure is closely related to the skill and experience of the endoscopist, the type of the bleeding source, the available equipment, the patient's clinical condition and costs. Despite all advances in endoscopic and clinical management, mortality rates are still high for GIBs. Hence, there is an ongoing intensive search for novel techniques or treatments. In recent years, new topical hemostatic agents have been introduced to allow for easier and more effective hemostasis.

Ankaferd Blood Stopper (ABS) is a novel topical hemostatic agent which is a mixture of plants including *Thymus vulgaris*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Alpinia officinarum* and *Urtica dioica* (Farrell and Friedman, 2005). Although the exact mechanism is still unknown, it achieves its basic hemostatic effect through erythroid aggregation by forming an encapsulated protein network (Goker et al., 2008). The aim of our study is to share our experience with ABS which is not widely used in gastroenterology clinical practice.

2. Materials and methods

The records of 9512 patients who underwent endoscopic procedures between January 2019 and April 2020 in our clinic were retrospectively reviewed. A total of 64 patients who applied with UGIB or LGIB and in whom Ankaferd was used for the treatment of bleeding were included in the study. Demographic data of the patients, symptoms at admission, additional risk factors, comorbid diseases, concomitant medications, laboratory tests at the time of admission, causes of bleeding, treatment methods applied, complications and early or late re-bleeding after the procedure were recorded.

SPSS 25 package program (IBM, Statistical Package for Social Sciences) was used for statistical analysis of the data. The results were expressed using the mean±standard deviation, number and percentages depending on whether the data were parametric or not. Kolmogorov Smirnov and Shapiro-Wilk

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tests were used to evaluate the compliance of the quantitative data to the normal distribution. For the comparison of more than two groups, first Fisher exact test and then Bonferronni Correction were used. Values of $p<0.05$ were considered statistically significant for all tests.

3. Results

A total of 64 patients, 22 (34.4%) female and 42 (65.6%) male, participated in the study. The mean age was 54.32±16.72 years for female patients and 54.3±15.82 years for male patients. Fifty (78.1%) of the patients applied with UGIB, 14 (21.9%) with LGIB, and all patients had an endoscopic procedure within the first 24 hours after admission to the hospital. While the number of male patients with UGIB was higher than female patients, the number of male and female patients with LGIB was equal.

The mean age of patients with LGIB was significantly higher than those with UGIB ($p<0.001$). There was no significant difference in terms of smoking status and nonsteroidal anti-inflamatory drugs (NSAID) or anticoagulant drug use according to the bleeding locations. Metastatic cancer was observed in most patients with LGIB (57.1%), whereas it was much lower in patients with UGIB (14%). As expected, LGIB was more common in those with diverticulosis ($p=0.007$). Demographic characteristics, additional risk factors and comorbid diseases of the patients according to the location of GIB are given in Table 1.

Table 1. Demographic characteristics, additional risk factors and comorbid diseases of the patients according to the location of GIB

Characteristics		Lower GI Bleeding n (%)	Upper GI Bleeding n (%)	p
Gender	Female	7(50.0)	15(30.0)	0.142
	Male	7(50.0)	35(70.0)	
Age (years)		69.29±10.3	50.06 ±14.7	0.001
Smoking	No	9 (64.3)	28 (56.0)	0.804
	Yes	5 (35.7)	22 (44.0)	
NSAID	No	11 (78.6)	32 (64.0)	0.245
	Yes	3 (21.4)	18 (36.0)	
Anticoagulant Drugs	No	10 (71.4)	36 (72.0)	0.605
	Yes	4 (28.6)	14 (28.0)	
CVD	No	10 (71.4)	40 (80.0)	0.362
	Yes	4 (28.6)	10 (20.0)	
Heart failure	No	14 (100)	49 (98.0)	0.781
	Yes	0 (0)	1 (2.0)	
Metastatic cancer	No	6 (42.9)	43 (86.0)	0.002
	Yes	8 (57.1)	7 (14.0)	
CLiD	No	12 (85.7)	46 (92.0)	0.392
	Yes	2 (14.3)	4 (18.0)	
CKD	No	13 (92.9)	49 (98.0)	0.392
	Yes	1 (7.1)	1 (2.0)	
CLuD	No	13 (92.9)	49 (98.0)	0.392
	Yes	1 (7.1)	1 (2.0)	
Diverticulosis	No	10 (71.4)	49 (98.0)	0.007
	Yes	4 (28.6)	1 (2.0)	

GI: Gastrointestinal, BMI: Body mass index, NSAID: Nonsteroidal anti-inflammatory drugs, CVD: Cardiovascular disease, CLiD: Chronic liver disease, CKD: Chronic kidney disease, CLuD: Chronic lung disease

Forty-nine (98%) of the patients with UGIB had melena, 21 (42%) had syncope, 9 (18%) had hematemesis, whereas all of the patients with LGIB had hematochezia and 3 (21.4%) of those had also syncope. The distribution of symptoms at admission and laboratory results according to the bleeding location of the patients are given in Table 2. When the patients were evaluated according to the etiology of bleeding, the most frequent cause was peptic ulcer in patients with UGIB and malignancies in patients with LGIB. The causes of UGIB and LGIB are given in Table 3.

Table 2. Symptoms at admission and laboratory results according to the bleeding location

		Lower GI Bleeding n (%)	Upper GI Bleeding n (%)
Syncope	No	11 (78,6)	29 (58,0)
	Yes	3 (21,4)	21 (42,0)
Hematemesis	No	14 (100,0)	41 (82,0)
	Yes	0 (0,0)	9 (18,0)
Melena	No	14 (100,0)	1 (2,0)
	Yes	0 (0)	49 (98,0)
Hematochezia	No	0 (0)	50 (100)
	Yes	14 (100)	0 (0)
Blood pressure	>100 mmHg	3 (21,4)	21 (42,0)
	<100 mmHg	11 (78,6)	29 (58,0)
Pulse	> 100bpm	2 (14,3)	21 (42,0)
	< 100bpm	12 (85,7)	29 (58,0)
Hemoglobin	>10	13 (92,9)	37 (74,0)
	<10	1 (7,1)	13 (26,0)
Hematocrit	>35	13 (92,9)	36 (72,0)
	<35	1 (7,1)	14 (28,0)
INR	<1.2	2 (14,3)	6 (12,0)
	>1.2	12 (85,7)	44 (88,0)

GI: Gastrointestinal; INR: International normalized ratio

The ABS method was preferred for bleeding control in all instances because the bleeding could not be stopped completely with standard endoscopic hemostasis methods or these procedures could not be performed technically. ABS solution was applied to the bleeding area by spraying 5-10 cc with endoscopic sclerotherapy needle. ABS was used as the sole method of hemostasis since other methods could not be used in 10 (20%) of 50 patients with UGIB and in 1 (7.1%) of 14 patients with LGIB. Five out of 10 patients with UGIB had esophageal variceal bleeding, which was primarily managed with ABS. In 3 of these patients, ABS was preferred because the esophageal mucosa was highly sclerotic due to multiple variceal ligations, and in two patients the bleeding area could not be visualized due to massive bleeding. Until their control endoscopy, no recurrent bleeding was observed in patients whom only topical ABS was applied. In the control endoscopies performed after 24 hours, no bleeding residue was observed in the esophagus and stomach lumen that would prevent the endoscopic view. Nipple was detected on the sclerosed varicose veins in both patients and sclerotherapy was applied with N-butyl-2-cyanoacrylate (Histoacryl). ABS was

used alone in only one of the patients with LGIB, who was followed-up with diagnosis of hemophilia, since other endoscopic procedures would increase bleeding. The bleeding in the form of leakage from the edge of the rectal ulcer was successfully stopped after ABS application.

Table 3. The causes of upper and lower GI bleeding

Causes of UGIB	Number (%) n= 50	Causes of LGIB	Number (%) n= 14
Duodenal ulcer	22 (44)	Colon Cancer	8 (57,1)
Gastric Cancer	8 (16)	Post polypectomy	2 (14,2)
Gastric Ulcer	10 (20)	Post ESD	1 (7,1)
Mallory Weiss tears	2 (4)	Rectum Ulcer	2 (14,2)
Variceal bleeding	5 (10)	Hemorrhoidal bleeding	1 (7,1)
Post sphincterotomy	2 (4)		
GAVE	1 (2)		

UGIB: Upper gastrointestinal bleeding, LGIB: Lower gastrointestinal bleeding, GAVE: Gastric antral vascular ectasia, ESD: Endoscopic submucosal dissection

The patients were evaluated in terms of early and late re-bleeding after ABS application. Recurrent bleeding within the first 24 hours from the same location was considered as early re-bleeding. Recurrent bleeding within the first month was considered as late re-bleeding. Early re-bleeding was not observed in any of the patients. Late re-bleeding occurred in only 1 (1.5%) of 64 patients who had stomach cancer. No mortality was observed in any of the patients after ABS application during the study.

4. Discussion

There are numerous studies about the application of ABS for bleeding control in dental and surgical procedures and in hemorrhages due to gastroenterological and hematological disorders. (Strate and Gralnek, 2016) All these studies have demonstrated that ABS is highly safe and an effective alternative method in the treatment of bleeding. Endoscopic therapy in clinical practice has some drawbacks that limit its efficacy. For instance, despite being highly effective in achieving hemostasis in acute UGIB, in 5%-10% of patients this bleeding will not be initially controlled or they will experience a recurrence (Gralnek et al. 2008). In patients with severe acute bleeding, hemorrhagic diathesis and bleeding due to gastrointestinal tract cancers, endoscopic therapy can be challenging, often requiring a high level of technical expertise. Therefore, new topical hemostatic agents in the control of GI bleedings refractory to conventional antihemorrhagic measures seem promising. The reason for using ABS in all patients included in our study was that the hemostasis could not be achieved with standard endoscopic methods. It was an important finding that bleeding was primarily managed with ABS in all. ABS, technically, seems to be a practical treatment alternative with its easy applicability. Therefore, its ease of use reduces the need for highly skilled expertise compared to other endoscopic techniques.

Our study is one of the studies involving the highest number of patients in whom ABS is used for the control of GI bleeding. It is also remarkable that only one patient had re-bleeding and no patient was died due to bleeding in one month follow-up considering the fact that the mortality rate due to GIB is 2.5%-20% despite current treatments. Variceal bleeding still carries a significant mortality of 7%-15%, as well. Endoscopic interventions are very difficult to perform, especially in patients who have recurrent band ligations, due to fibrosis in the esophageal mucosa at the ligation site. In our study, it was observed that ABS was applied to five patients for variceal bleeding at their admission and hemostasis was successfully achieved in all. This is very important regarding the high mortality rates in variceal bleeding. Another finding that should be taken into account is that there was no obstacle in the lumen of two patients in early endoscopic re-evaluation and intervention, after application of ABS due to massive bleeding with poor visualization.

ABS is a medicinal product that can be applied endoscopically like Hemospray which is also used as a topical hemostatic agent in the management of GI bleeding. ABS and Hemospray may be helpful in the control of bleeding alone or in combination with other endoscopic techniques. They are effective options in various clinical situations such as salvage therapy, massive bleeding with poor visualization and bleeding from luminal malignancies due to their ease of use, noncontact/nontraumatic application and ability to cover large bleeding areas. (Chen and Barkun, 2015). The liquid form of ABS is superior to the powder form of Hemospray cause it can be applied with standard endoscopic equipments and the treatment cost is cheaper. Further controlled studies are needed to establish ABS as an effective and safe treatment option in the management of all types of GI bleeding

Conflict of interest

None.

Acknowledgments

No competing financial interests exist.

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A comparison of propofol with ketofol for sedation quality and side effects in patients undergoing colonoscopy

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Abstract

Colonoscopy is an endoscopic method and ıt is better to perform this procedure under sedoanalgesia in order to eliminate patients' anxiety, the colic-like pain and discomfort that occur during the procedure. The aim of this study was to compare the effects of propofol and propofol+ketamine (ketofol) on sedation and side effects in patients undergoing colonoscopy. 50 patients with ASA I-II that are between the ages of 18-65. The patients in the propofol group and Ketofol group were given 0.1mL/kg of drug and/or combination of drugs. The vital parameters, injection pain, spontaneous time of opening eyes, the time of Modified Aldrete Score (MAS) ≥ 9 and the amount of medication used during the procedure and in the recovery, room were recorded. There was no significant difference between the two groups during the procedure and in the recovery room ($p<0.05$). It was shown that the ketamine reduces the amount of propofol by 50% and propofol induced injection pain. Ketofol had no positive effects on hemodynamic and respiratory parameters. We assert that the ratio of combinations will vary depending on the necessary sedation level and analgesic need of the procedure to be performed and depending on the frequency of the administration of additional doses. Although ketofol is being used in different procedures and different age groups in the recent years, there is still need for studies conducted with different drug dosages of this combination.

Keywords: colonoscopy, ketofol, hemodynamics, sedoanalgesia

1. Introduction

Outpatient procedures are generally performed on same-day anesthesia patients. It is better to perform this procedure under sedoanalgesia in order to eliminate patients' anxiety and colic-like pain and uncomfort that occur during the procedure (Seip et al., 2010). For this reason, short-acting drugs and drugs without any side-effects should be preferred. As there is not one drug that provide all these effects, the aim is to combine this with other drugs to increase its effects and reduce high dose induced side effects. When short-acting propofol that provides fast and full recovery is used in high dosage to provide the suitable conditions for the performance in order to avoid analgesic effect, it leads to complications such as hypotension, respiratory depression and loss of protective reflexes (Akcaboy et al., 2006). To reduce the complications at high dosages, several sedative and analgesics can be used either on their own or as a combination.

Ketamine is a different drug from other anesthetic agents as it has an analgesic characteristic while not having a depressant effect on the cardiovascular and respiratory systems. Its main effect is seen by separating the connection between talamus and the lymbic system. Thus, it provides "dissociative anesthesia." Using propofol and ketamine together, not only the hypotensive effect of propofol is prevented by sympathomimetic and analgesic effect of ketamine, but also inhibits the ketamine induced nausia, vomiting and psychotomimetic effects during recovery by the antiemetic and strong hypnotic effect of propofol. The combination of propofol and ketamine is called ketofol. These two drugs provide an ideal anesthetic approach with their synergistic effects.

Due to the fact that outpatient procedures are becoming common, anesthesia in outpatient procedures are becoming more important in order to improve the quality of the procedure and the patient comfort in procedures that cause pain and anxiety in patients. Outpatient anesthesia is needed in colonoscopy as well like in several other procedures. The colon is dilated with air during the procedure for a clear evaluation. As patients feel pain during dilation, this procedure becomes too difficult to tolerate for patients most of the time. In several ketofol conducted studies, ketofol is used in painful or invasive

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procedures in emergency rooms in adults and children. However, there are few studies conducted on patients where semi-noninvasive procedures such as colonoscopy are performed. In this study, we aim to study the effects of ketofol on the quality of sedation and side effects in patients undergoing colonoscopy.

2. Materials and methods

After receiving an Ethical Review Board approval from Ondokuz Mayis University School of Medicine (OMU KAEK 2013/301), the study was conducted between January 2013 and February 2014 within the scope of outpatient anesthesia applications in the Gastroenterology Clinic in our hospital. All the patients were informed about the study prior to the colonoscopy and were asked to sign a consent form.

Fifty patients with ASA I-II that are between the ages of 18-65 undergoing an elective colonoscopy were included in this study. Patients who rejected to participate in the study, who is allergic to any of the drugs used in the study, patients with uncontrolled hypertension, severe renal, liver, cardiovascular and respiratory disorders, patients with epilepsy, patients with intracranial space-occupying lesion, pregnant patients, patients with severe neuropsychiatric disorders and patients with BMI>30 were not included in the study. A power analysis with a reference of 50% reduction of the total propofol dosage, was completed to determine the sample size of our study based on the study conducted by Mourad et al. (2004) on ketofol. The number of participants for each group was determined to be 25 with effect size of 99% and power of 99%.

2.1. Grouping

Randomization was completed by having patients draw closed envelopes that were prepared prior in accordance with the patient number in each group. The patients were distributed into two groups: Group P (Propofol) and Group K (Ketofol), of 25 randomly.

2.2. Procedure

The patients were asked not to eat for at least six hours. After taking patients into the procedure room, a 20-22 G intravenous cannula was inserted either from the dorsum of the hand or front arm and an infusion of 0.9% physiological saline solution was started with a speed of 1-2mL/kg/hour. Supplemental O_2 (4-6 L/minute) via a nasal cannula was administered during the procedure. A 0.02 mg/kg midazolam was given intravenously 15 minutes prior to the procedure to all patients. Colonoscopy and sedoanalgesia procedures were performed by the same gastroenterologist and anesthesiologist.

2.3. Preparation of drug syringes

Preparation of ketofol: 100 mg ketamine (2 ml from a 50 mg/mL ketamine) (Ketalar, Pfizer) and 100 mg propofol (10 mL from 1% Propofol lipuro) (Propofol Lipuro 1%, Fresenius Kabi) were drawn into a 20 mL syringe. The total volume was completed to 20 mL. Thus, a combination of 5 mg/mL propofol + 5 mg/mL ketamine was obtained (mix with a 1/1 ratio). This combination was given to patients in Group K. Preparation of Propofol: A 10 mg/mL propofol was prepared by drawing from a 1% propofol lipuro into a 20 mL syringe and given to patients in Group P. The study protocol was conducted as a double-blind manner. Patients were monitored for heart rate (HR), systolic, diastolic, and mean blood pressure (SBP, DBP and MBP respectively), respiratory rate (RR), and peripheral oxygen saturation (SpO_2) when they were at the colonoscopy table. Afterwards, patients were given the prepared drugs of 0.1 mL/kg intravenously. The colonoscopy procedure started after the reactions for verbal stimulations and the cornea reflex is lost. A ≥ 4 of sedation level was targeted according to the Ramsay Sedation Scale (RSS) during the procedure. When RSS was lower than 4, additional dosages of 0.05 mL/kg of the prepared drug were given. The pain during the injection was evaluated according to the “four-point injection pain scale” (0: no pain,1: light pain (only a response of having pain to the without any movement), 2: mild pain (a verbal response of pain with movement or expression pain spontaneously without being asked), 3: Severe pain (severe verbal response or behavioral response such as facial expressions or moving arm). A score of 2 or 3 was considered as having pain while a score of 0 or 1 was no pain.

Heart rate, SBP, DPB and, MBP, RR, and SpO2 were identified, and basal values were taken before the procedure. After the colonoscopy started, the values at 1, 5, 10, 15, 20, 30 minutes and at the end of the procedure were recorded. An MBP level of 20% more from the baseline value for one minute during the procedure was accepted as hypertension. In the case of hypertension, at first light anesthesia symptoms (opening eyes, moving) were evaluated. If the anesthesia is light, 0.05 mL/kg additional drug combination were given. If the hypertension continued, a 50-100 µg perlinganit was applied intravenously and the patient was monitored for another minute. An MBP level being 20% less than the baseline value was considered as hypotension. In the case of a hypotension, 5 mg of ephedrine was applied intravenously, and the patient was monitored for another minute. When needed, an additional dose of ephedrine was given. A HR of <45 beat/min was evaluated as bradycardia. In the case of a bradycardia, a 0.5 mg of atropine was applied intravenously. When the HR was >100 beat/min, light anesthesia symptoms were reconsidered, and a drug combination of 0.05 mL/kg was applied intravenously. When it was determined that the anesthesia is not light, a 5-10 mg esmolol was applied intravenously. The patient was monitored for one minute and an additional dosage of esmolol was repeated if needed.

The duration of anesthesia is identified as the time between the first propofol or ketofol dosage administration and the patient’s opening eyes spontaneously. The duration of colonoscopy is identified as the time between the insertion and removal of the colonoscope. And both durations were recorded as well as the total drug dosages.

After the colonoscopy procedure, spontaneous eye-opening

times, and the time for Modified Aldrete Scale (MAS) to become ≥ 9 were recorded. Satisfaction of the patient, the person who performed the colonoscopy and the anesthesiologist were evaluated on a scale of 1-10; 1: being not satisfied, and 10: very satisfied. The patients were given oxygen with a mask at the end of the procedure and were monitored for one hour in the recovery room equipped with emergency equipments. The HR, SBP, DBP and MBP, SpO2 and RR were recorded on the 5, 10, 20, 30 and 60 minutes after the procedure. The complications that occurred (hypertension, hypotension, bradycardia, bronchospasm, allergic rash, nausea-vomiting, coughing, dizziness, diplopia, agitation, desaturation, apnea, airway obstruction, laryngospasm, aspiration) were recorded.

The statistical analysis of the obtained data was completed with SPSS for Windows 15.0 statistical package program. As the data were evaluated, constant variables were stated as average ± standard deviation and the frequency data were stated as numerically (5). A "Shapiro-Wilk" test was completed in all statistical analysis to check normal distribution of measured variables. Categorical data were compared by Chi-square test. Differences between numeric variables were tested with Mann–Whitney U test. Friedman test was used in comparing the repeated measures within the group as there were parameters that did not fit the normal distribution in the HR, SBP, DBP and MBP values. A Spearman's Correlation test was conducted to determine the correlation between data. A p value of less than 0.05 was statistically significant.

3. Results

Study groups were similar in terms of demographic data, duration of colonoscopy and anesthesia (Table 1). When the injection pain during induction was compared, there was no pain in the patients given ketofol while there was pain in 19 patients who were given propofol ($p<0.05$). There was no significant difference between the groups in HR, SBP, DBP, MBP and RR during and after the procedure ($p>0.05$) (Figures 1 and 2). The SpO_2 level did not fall below 94% during and after the procedure in any of the patients.

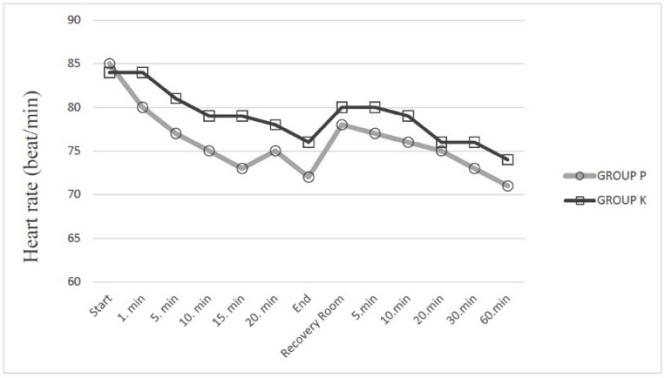

Fig. 1. Heart rates of the groups

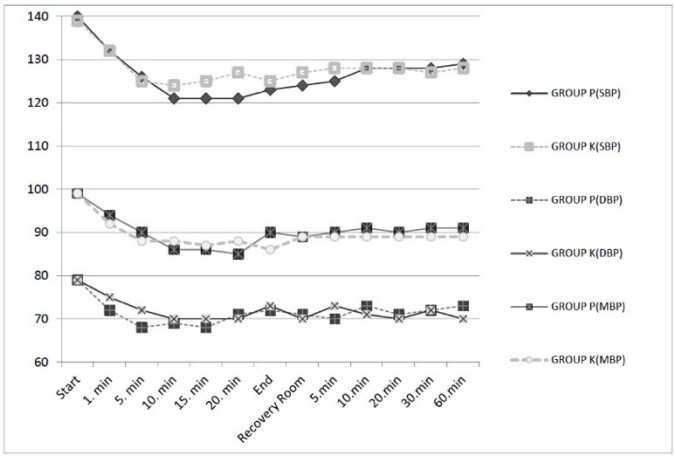

Fig. 2. Systolic, diastolic, and mean blood pressures of the groups

Table 1. Demographic data of groups, and duration of anesthesia and colonoscopy (mean±SD)

	Group P	Group K
Age (year)	49.9 ± 12.4	48.5 ± 12.7
Gender	20 (80%) / 5 (20%)	19 (76%) / 6 (24%)
Height (cm)	160.1 ± 6.9	164.4 ± 8.7
Weight (kg)	70.6 ± 15.2	74.6 ± 11.8
ASA (I/II) n	10 (40%) / 15 (60%)	13 (52%) / 12 (48%)
Duration of anesthesia (min)	24.7 ± 6.5	22.8 ± 5.7
Duration of colonoscopy (min)	22 ± 6.2	21 ± 5.5

In Group P 101.7±32.2 mg propofol was used while 50.55±11.4 mg propofol and 50.55±11.4 mg ketamine was used in Group K (Table 2). There was not a significant difference between the groups in spontaneous eye-opening times and the time for MAS being ≥ 9 ($p>0.05$) (Table 2).

Table 2. Administered drug amounts in Group P and Group K, and the times of spontaneous opening eyes and MAS ≥9 (mean±SD)

	Group P	Group K
Propofol Amount (mg)	101.7±32.2	50.5±11.4
Ketamine Amount (mg)	-	50.5±11.4
Time to reaching MAS ≥ 9 (min)	3.8±2.8	3.1±3.7
Spontaneous opening eye time (min)	3.2±2.0	2.3±2.8

No hypotension hypertension, bradycardia, tachycardia, bronchospasm, allergic rash, coughing, nausea-vomiting, agitation, desaturation, apnea, partial and full airway obstruction, apnea, or aspiration were seen in any patients in the recovery room. All the patients in both groups had dizziness in the early stages of monitoring in the recovery room, however, the dizziness regressed spontaneously within 30 minutes without a need for medical intervention.

There was not a significant difference between the groups in the satisfaction of the person that performed the colonoscopy, the patient, and the anesthesiologist ($p>0.05$) (Table 3).

Table 3. Satisfaction of patient, anesthesiologist, and the doctor performing colonoscopy

	Group P	Group K	p
Patient satisfaction	8.3±0.8	8.4±0.5	0.853
Anesthesiologist satisfaction	7.6±0.8	7.6±1.0	0.919
Satisfaction of the doctor performing colonoscopy	7.6±0.8	7.8±0.8	0.407

4. Discussion

Use of propofol and ketamine combination, called ketofol, for sedation in invasive procedures have become a popular approach in recent years. Ketofol is used frequently in outpatient procedures, particularly in the emergency room and for pediatric patients. Its sedation quality is good, it provides hemodynamic stability, minimizes the side effects of profol, therefore, it's emphasized that it can be uses in children and adults safely (Andolfatto and Willman, 2010; Shah et al., 2011; Willman and Andolfatto, 2007). The purpose in colonoscopy is to provide sedation along with analgesia. For this purpose, ketofol is used in different dosage and combination ratios (Akcaboy et al., 2006; Seip et al., 2010).

The analgesic effect of ketamine should also be mentioned. Ketamine in the ketofol combination is used at lower dosages than the dosages that would create anesthesia. Ketamine at the lower plasma level provides preemptive analgesic effect by inhibiting nociceptive central sensitization (Kwok et al., 2004). In the literature, comparative studies of propofol and ketofol do not address the injection pain of propofol. In our study, the patients who were induced with ketofol solution did not show any injection pain. Also, combining ketamine with propofol and the use at a subdissociative dosage reduce the need of anticholinergic premedication (Friedberg, 1993; Messenger et al., 2008). In our study, no hypersalivation that would require anticholinergic pre-medication was observed.

Although there are many studies supporting this fact, we did not see any significant effects of ketofol in sedation quality, hemodynamic stability, and side-effect profiles. Comparison of the use of propofol and ketamine together in invasive procedures to solely propofol use would theoretically suggest a cardiovascular stability, however, no benefit was shown in a systematic review (Slavik and Zed, 2007).

Ketamine is combined with propofol to reduce the side-effect incidence due to propofol. It is thought that combining propofol with low dosage of ketamine rather than high dose ketamine would provide a synergistic effect in sedation. Smischney et al. (2012) showed that ketofol prepared in a syringe with the ratio of 2:1 in the entubation of critical patients provide a better hemodynamic stability during the first 10 minutes after induction. Akın et al. (2005) and Frey et al. (1999) stated that ketofol reduces respiratory depression while increasing the sedation quality. Although there are several other studies supporting this statement, we did not see a benefit of ketamine addition to propofol in terms of sedation quality, hemodynamic stability, and side effect profiles in our study. Although it is thought that the use of propofol and ketamine together would provide cardiovascular stability compared to use of propofol only, this was not demonstrated in a systematic review(Slavik and Zed, 2007).

David and Shipp (2011) demonstrated that addition of ketamine at a subdissociative dosage to propofol does not reduce the respiratory depression rate and decreases the amount of propofol used while providing a better sedation level and satisfaction. Dereli et al. (2011) compared the effects of different sedation protocols in patients undergoing colonoscopy and showed that the addition of ketamine, fentanyl or remifentanil to propofol provided similar hemodynamic and sedation conditions while they did not find any significant difference in patient satisfaction. Khajavi et al. (2013) compared the ketofol and propofol+fentanil combination to provide conscious sedation and analgesia in colonoscopy and found that the patient satisfaction was higher in the ketofol group while they did not find any significant differences between the hemodynamic parameters, side-effects, and recovery times.

Aydogmus et al. (2015) showed that the addition of ketamine in different dosages to propofol in patients undergoing colonoscopy did not increase patient satisfaction. In this study, although there was a significant difference in the satisfaction of the person performing the colonoscopy in ketofol group, the necessity of ketamine addition into propofol is debatable.

Many studies emphasize on the hypotensive effect of propofol in ketofol which is reduced by ketamine, that ketamine's nausea-vomiting effect is reduced by propofol, and the differences of sedation quality, many randomized clinical studies support the opposite where they argue that it is not necessary to use ketamine with propofol, that there may be ketamine induced recovery agitations, and that using ketamine and propofol together is not necessary (Green et al., 2011). Effect of ketofol for providing a better hemodynamic stability compared to propofol is not very important and propofol induced hypotension is almost always temporary in healthy individuals and it constrains itself (Miner et al., 2015). In studies conducted by David and Shipp (2011) and Shah et al. (2011), procedural success and safety were mentioned and there were no significant difference between the two groups in respiratory side effects. As a result, the necessity of this combination is still questionable. Green et al. (2011) argue that ketamine and propofol can have a synergistic effect, however, this synergistic effect is not needed. They also state that ketofol's more positive effects compared to other agents that are used solely should be demonstrated before recommending ketofol. Considering the similarity of results for both group in the same review, it is difficult to explain the different results on doctor and nurse satisfaction and it is thought that there might be some bias. If the desired sedation is deep, then it can be provided very fast and safely by propofol only. If the desire

is dissociation, this can be achieved by ketamine fastly with dissociative dosages (Shah et al., 2011). Propofol is short-termed, and it would not create any problems even in long cases with repeated dosages. However, repeated dosages of ketofol can cause unpleasant pharmacokinetic effects due to ketamine's accumulative characteristic.

Although it is mentioned that ketofol provides a better hemodynamic stability and creates a better side-effect profile, there are no major complications or side-effect profile seen in studies conducted with only propofol. This may be due to the short duration of procedures, administration of low dose drugs, and the need for additional dose being less and therefore, not observing cumulative effects. Similarly in our study, no significant difference was found between patient and doctor satisfaction, and no significant clinical effect was found on the reduced propofol dosage due to ketamine addition. Similar values were obtained in terms of hemodynamics in both groups.

There are the studies showing the positive effects of propofol and ketamine combination on hemodynamics (Green et al., 2011; Mourad et al., 2004), there are also studies demonstrating that this combination does not have a clinical importance (Aouad et al., 2008; Badrinath et al., 2000; David and Shipp, 2011; Green et al., 2011; Loh and Dalen, 2007). Although the amount of propofol administered in the propofol group was twice as much the amount used in the ketofol group, there was no difference in hemodynamics. Additionally, although spontaneous eye-opening times of patients and time for sending the patients to the ward were shorter in the ketofol administered group, there was no statistical significance between groups. In other words, double dosage of propofol administration did not prolong the recovery time of patients.

Theoretically, ketofol may protect sedation efficacy while reduce the cardiovascular and respiratory adverse effects thought the dose reduction and because of their synergistic effects. The benefit of ketamine reducing the propofol dose has not been fully demonstrated. There is no significant difference in hemodynamic and respiratory parameters in both groups. This may be due to the small number of groups and patients in the groups. The combination of these drugs reduces their disadvantages and provide a better result. There are publications that support this as well as publications that support no clinical difference. No significant difference was seen in our study. Whether ketofol is useful is uncertain.

Sedation depth was titrated according to Ramsay Sedation Scale (RSS), respiratory and hemodynamic parameters (HR, SBP, DBP, SpO_2) verbal stimulations and cornea reflex was lost and not by using any special monitoring like bispectrl index (BİS) and End-tidal CO_2 monitoring.

Optimal dose and combination not yet found and the required dose probably depend on the planned sedation depth. It is recommended that the amount of ketamine in the mixture is as low as possible. Because the combination of subdissociative ketamine dose and propofol is seen with low side effects and high advantage in clinical applications. A low dose ketamine cause nausea, vomiting and hallucinogenic effects are less seen, as the analgesic effect it provides will be less, and it will not help us understand how much analgesic need is required for the procedure.

Overall, addition of ketamine into propofol with a 1:1 ratio only ameliorated the injection pain of propofol in adult patients who underwent colonoscopy. Additionally, it didn't affect the spontaneous eye-opening time and the time to reach a MAS ≥ 9. It didn't have have positive effect on the hemodynamic and respiratory parameters either. However, there were no side effects. There was no significant difference between the patient and doctor satisfaction. Although ketofol is being used in different procedures and different age groups in the recent years, there is still need for studies conducted with different drug dosages of this combination. We believe that the combination ratios would vary depending on the sedation level needed, analgesia, procedure times and the frequency of additional dosage.

Conflict of interest

None.

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Can asymptomatic Crohn's Disease be diagnosed in patients with iron deficiency anemia by CT-enterography?

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Abstract

It is difficult to diagnose Crohn's disease in the asymptomatic period. The aim of this study is to evaluate the diagnostic utility of CT enterorrhaphy (CTE) in the diagnosis of asymptomatic Crohn's disease (CD) with small intestine involment in patients with iron deficiency anemia (IDA). 250 patients who underwent CTE examination between 2017 and 2018 were retrospectively scanned. Forty-five patients who had endoscopic examinations and diagnosed with IDA were included in the study. While one or more pathological findings to explain IDA were observed in 31 (68%) patients with endoscopic examinations, findings that could be explained as CD sequelae were observed in four (8.8%) patients. No lesions were observed by CTE in 10 (22.2%) patients. Diagnosis is difficult in mild forms of Crohn's disease or in periods of remission. In this period, CTE can contribute to the diagnosis as it can also show extraluminal findings.

Keywords: crohn's disease, iron deficiency anemia, CT enterography

1. Introduction

Crohn's disease (CD) is an inflammatory disease of the digestive system that may affect any segment of the gastrointestinal tract from mouth to anus with focal, asymmetrical and transmural involvement. There are no pathognomonic clinical, serological, endoscopic and microscopic findings in CD. The main findings of CD are the presence of intestinal inflammation that does not persist endoscopically and radiologically, and granulomas (but not necessarily) in the biopsy material. Anemia is defined by the World Health Organization as the level of hemoglobin for adults is less than 13 g/dl for men and 12 g/dl for women (Beutler and Waalen, 2006). Anemia is a global public health problem affecting both developing and developed countries at all ages (Cappellini and Motta, 2015). IDA is the most common type of anemia. Gastrointestinal losses are the most common cause of IDA in adult men and postmenopausal women (Hardwick and Armstrong, 1997). The frequency of IDA in this patient group ranges from 2 to 5% (Looker et al., 1997). In this study, our aim is to evaluate the diagnostic utility of CT enterography (CTE) in the diagnosis of asymptomatic CD with small intestine involvement in patients with IDA.

2. Materials and methods

Two hundred fifty patients who underwent CTE examination in the radiology department of our hospital between 2017 and 2018 were retrospectively scanned. Patients who were previously diagnosed with CD, those with a history of abdominal surgery and those without endoscopic examinations were excluded from the study. Hb, Htc, MCV, MCHC, ferritin, Neutrophil, sedimentation and CRP parameters of 81 patients who were examined with the diagnosis of IDA were evaluated. Forty-five patients diagnosed with IDA and whose endoscopic examinations were available were included in the study.

3. Results

There was a pathology to explain IDA with endoscopic examinations in 31 (68%) patients. 10 (22.2%) patients did not have any lesions in CTE while four (8.8%) patients had findings that could be explained as CD sequelae. These findings were as follows: Strictures and adhesions in the mesentery of the left upper quadrant and at the level of cecum, appendix and distal ileum, incomplete rotation in the intestines in one patient; diffuse symmetrical edematous wall thickness in prepyloric antrum in one patient; diffuse symmetrical thickening of the terminal ileum wall in one patient; diffuse symmetrical thickening and minimal enhancement in terminal ileum in one patient. The demographic characteristics, laboratory findings and CTE findings of the patients are shown in Table 1.

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Table 1. Demographic characteristics, laboratory findings and CTE findings of patients with CD sequelae findings

No	Age	Gender	Hb g/dL	Hct %	Ferritin ng/mL	ESR mm/h	CRP mg/dL	Neutrophil x109/L (SI)	CTE Findings
1	48	M	11.6	36.5	22.5	12	0.26	4.26	Strictures and adhesions in the mesentery of the left upper quadrant and at the level of cecum, appendix and distal ileum, incomplete rotation in the intestines
2	77	M	11.5	35.2	17.5	18	0.44	2.44	Diffuse symmetrical edematous wall thickness in prepiloric antrum
3	22	M	11.6	33.9	10	33.8	0.3	3.60	Diffuse symmetrical thickening of the terminal ileum wall
4	38	F	10.0	31.9	6.08	39	0.33	5.77	Diffuse symmetrical thickening and minimal enhancement in terminal ileum

Hb: Hemoglobin; Hct: Hematocrit; ESR: Erithrocyte sedimentation rate, CRP: C-reactive protein

4. Discussion

Endoscopic and radiological techniques are used to differentiate small intestine pathologies. The small intestines are not radiologically well-visualized due to their localization, length and tightly placed locations on each other, nor do they allow for a complete and optimal endoscopic exploration. Due to the technical difficulties of endoscopic methods in examining small intestine pathologies, high cost of examination and difficulties in reaching the examination, radiological examinations such as CT and MRI are taking more place in clinical practice day by day. With multidetector CT devices developed in recent years, images with a thin section thickness of less than 1 millimeter are obtained during a single breath hold. Multiplanar reformatted images created with this method allow for a more detailed evaluation and characterization of small intestine pathologies and play an important role in revealing extraluminal complications and extraenteric anomalies (Bodily et al., 2006; Macari et al., 2007; Maglinte et al., 2006). In CTE method, in addition to the routine abdominal CT examination performed after intravenous contrast agent injection, small intestine distension is provided with an appropriate amount of neutral contrast agent given orally before the examination to allow optimal evaluation of the lumen and wall (Booya et al., 2006). The main current indications for CTE are suspected gastrointestinal bleeding, CD and small intestine neoplasms. In cases where adequate bowel distension can be achieved, wall thickness of 3 mm and above is defined as "increase in wall thickness" (Macari et al., 2007). The contrast pattern observed after intravenous contrast agent injection, the length of the involvement, the degree of thickening, whether the thickening is symmetrical, the localization of the lesion in small intestine (proximal or distal), the depth of involvement in the intestinal wall (mucosal, submucosal or serosal), mesentery and vascular pathologies can be evaluated with CT enterography (Berther et al., 2008).

Despite the common view that there is involvement in the form of 'skip areas' in CD, the inflammatory and spreading pattern in the bowels is completely individual (Bruining and Loftus, 2006). The form of inflammation in CD can be in the form of superficial lesions, as well as fibrous structures that penetrate the intestinal wall, mesenteric inflammatory masses, or fistulas accompanied by abscesses that surround the intestines. Serological studies are becoming more specific for CD, but yet, they do not have sufficient positive predictive value to confirm the disease (Griffiths., 2013). The diagnosis of CD is made by the history, physical examination, laboratory tests and advanced diagnostic tests (endoscopy, biopsy, cross-sectional imaging) with differentiation from other inflammatory enteropathies. The course of the disease is variable. While some patients have a continuous, active and progressive disease course, approximately 20 percent of patients experience long-term remission after the first attack (Solberg et al., 2007). The diagnostic efficacy of CTE for CD during active disease is over 90% (Siddiki et al., 2009). Luminal pathology may not be seen in endoscopic examinations performed after the period of active disease in CD. CTE, which can detect sequelae due to fibrosis and inflammatory changes, especially in the ulcers descending below the mucosa, may contribute to the diagnosis. CD most commonly involves the terminal ileum and cecum (Satsangi et al., 2006). It is noteworthy that in our study, 3 of 4 patients with pathology in CTE had sequelae changes in this region that could be considered significant in terms of CD, whereas there was no evidence of inflammation in the terminal ileum mucosa evaluated endoscopically. Although there was no evidence of mucosal inflammation in the prepyloric antrum region in endoscopy of one patient, findings that could be interpreted as sequel changes for CD were observed. However, since this region is also a risky region for peptic ulcer disease, it would be more appropriate to interpret these changes in favor of peptic ulcer sequelae. The negative aspects of CTE in terms of its contribution to the diagnosis of CD are that it is a radiation-based examination with necessity of optimizing the shooting technique, has indirect and nonspecific findings and does not allow histopathological sampling. However, even in

symptomatic patients in CD, the tests that are used for diagnosis are insufficient in approximately 10% of the patients (Siddiki et al., 2009). In the remission periods and mild forms of CD, which is generally asymptomatic, the advantage of CTE to show extraluminal findings and sequelae changes may provide additional findings. Larger studies involving more patients are needed in this regard.

Conflict of interest

All authors declare no conflict of interest regarding this manuscript.

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Clinical characteristics of patients with *Clostridium difficile* infection and its relationship with fecal occult blood test

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Abstract

Clostridium difficile infection (CDI) is an important health problem with severe morbidity and mortality. In our study, 266 adult patients admitted to the hospital between the years 2005 and 2020, and were diagnosed with CDI were included. The relationship between CDI and fecal occult blood test (FOBT) was examined, and it was aimed to determine the clinical characteristics of CDI patients and risk factors for mortality and recurrence in these patients. FOBT was found to be positive in 42.8% of our CDI patients who underwent FOBT. Pseudomembranous enterocolitis (PME) developed in 2.2% and toxic megacolon developed in 0.8% of our patients. It was found that 10.2% of the CDI patients died within 30 days and 5.2% of the CDI patients had a recurrence. In our study, a significant relationship was found between mortality and advanced age, FOBT negativity, presence of hospitalization history. In addition, a significant relationship was found between recurrence and FOBT positivity, presence of PME. We believe that the data documented in this study are important because these data reveal both the clinical characteristics of CDI patients and its relationship with FOBT.

Keywords: clostridium difficile infection, fecal occult blood test, pseudomembranous enterocolitis, toxic megacolon

1. Introduction

Clostridium difficile (C. difficile) is a fecal-orally transmitted, gram-positive, spore- forming anaerobic bacillus that can be found in the stools of healthy individuals. *Clostridium difficile* infection (CDI) is the most common cause of nosocomial diarrhea and has recently become an important clinical problem. The overall clinical picture caused by *C. difficile* is spread across a wide range of spectrum; from asymptomatic colonization to mild diarrhea, pseudomembranous enterocolitis (PME), paralytic ileus, toxic megacolon, and mortality (Gerding et al., 1995).

Use of antiacids, recent antibiotic use (clindamycin, cephalosporin, fluoroquinolone group), advanced age, tube feeding, inflammatory bowel disease and immunosuppression are risk factors for CDI. There are tests such as fecal glutamate dehydrogenase antigen, fecal *C. difficile* toxin A-B, stool culture, nucleic acid amplification methods to detect the presence of CDI. The most commonly used method is to investigate the presence of fecal *C. difficile* toxin A-B by ELISA method. Metronidazole, vancomycin, fidaxomycin, probiotics and fecal implantation can be used in the treatment (Yolken et al., 1982; Bignardi, 1998; Bartlett and Gerding, 2008; Kılıç, 2013).

Fecal occult blood test (FOBT) is a widely used test to screen for malignancy in the gastrointestinal system (GIS) and to detect bleeding in the GIS (Feldman et al., 2016). FOBT can also be detected positive in ischemic, inflammatory and infectious bowel diseases. In this study, the relationship between CDI and FOBT was examined. It was aimed to determine the clinical characteristics of CDI patients and also to determine the risk factors for mortality and recurrence in these patients

2. Materials and methods

This is a retrospective, single-center study conducted at Ondokuz Mayıs University Hospital in Turkey. Our study included 266 adult patients who were admitted to Ondokuz Mayıs University Hospital between the years 2005 and 2020, and diagnosed with the CDI by detecting fecal *C. difficile* toxin A-B by immunochromatographic card test method (Certest Biotec). Patient information was reached using the Nucleus medical information system database. The gender (female-male) and age (>65 and ≤ 65) of the patients were recorded. By reaching the endoscopy (rectosigmoidoscopy or colonoscopy) results of the patients, the presence of PME (yellow-white plaques and membranes that are seen endoscopically) was investigated. By analyzing the clinical characteristics and laboratory findings of the patients, the presence of toxic megacolon (detection of transverse colon diameter> 6 cm by radiological methods and accompanying fever, leukocytosis,

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signs and symptoms of acute abdomen syndrome) was investigated. Hospitalization rates of patients within 14 days before the CDI detection were recorded. The recurrence and 30-day mortality rates of the patients were analyzed. The number and results of the FOBTs which performed by fluorescent immunoassay method (Boditech ichroma) between 2005 and 2020 were reached.

The research data were uploaded and evaluated using IBM SPSS 25 (IBM Statistical Package for Social Sciences). Descriptive statistics of categorical variables are presented as numbers and percentages. For a comparison of categorical variables, using cross tables, Pearson chi-square test, Yates continuity correction or Fisher's exact test were applied. Sub-group ratio test and Bonferonni correction were used for significant results. Statistical significance levels were accepted as $p < 0.05$, $p < 0.01$ and $p < 0.001$.

3. Results

Between the years 2005 and 2020, 16642 FOBTs were performed in adult patients, and 2330 (14%) FOBT positivity were detected. While 113 of 266 patients (42.5%) with CDI who participated in the study were female, 153 of them (57.5%) were male.

While 213 of the patients (80.1%) were equal to or less than 65 years old, 53 of them (19.9%) were older than 65. 91 of the female patients (80.5%) were under or equal to 65 and 122 of the men patients (79.7%) were under or equal to 65. No statistically significant difference was found between age groups according to gender ($p = 0.873$). Descriptive statistics regarding the patients' FOBT results, lower GIS endoscopy findings, presence of PME, presence of toxic megacolon, 30-day mortality, hospitalization within 14 days before CDI detection and presence of recurrence are given in Table 1. According to this; FOBT was not examined in 86 CDI patients (32.3%). FOBT was found to be positive in 77 of CDI patients (42.8%) who were examined. Lower GIS endoscopy was performed in 63 patients (23.7%) and PME was detected in six of these patients (9.5%).

Table 1. Clinical and endoscopic features in patients with *C. difficile* infection

Variables		n (%)
FOBT	Positive	77 (42.8)
	Negative	103 (57.2)
Lower GIS Endoscopy	Performed	63 (23.7)
	Not Done	203 (76.3)
PME	Yes	6 (9.5)
	No	57 (90.5)
Toxic Megacolon	Yes	2 (0.8)
	No	264 (99.2)
Mortality	Yes	27 (10.2)
	No	239 (89.8)
Hospitalization History	Yes	97 (78.8)
	No	26 (21.2)
Recurrence	Yes	14 (5.3)
	No	252 (94.7)

FOBT fecal occult blood test, PME pseudomembranous enterocolitis, GIS gastrointestinal system. Variables are expressed as numbers

Toxic megacolon developed in two patients (0.8%). There were 27 patients (10.2%) who died within 30 days. The hospitalizations of 143 patients (53.8%) were unknown. It was observed that 97 of the patients (78.8%) whose condition was known had a hospitalization history within 14 days before CDI detection.

Table 2. Variables associated with mortality in patients with *C. difficile* infection

		Mortality	No Mortality	p
Gender	Female	10 (8.8)	103 (91.2)	0.690
	Male	17 (11.1)	136 (88.9)	
Age	<=65	17 (8.0)	196 (92.0)	0.036*
	>65	10 (18.9)	43 (81.1)	
FOBT	Positive	7 (9.1)	70 (90.9)	0.045*
	Negative	16 (15.5)	87 (84.5)	
Hospitalization	Yes	24 (24.7)	73 (75.3)	<0.001*
	No	1 (3.8)	25 (96.2)	

FOBT, fecal occult blood test; variables are expressed as numbers (% columns) *p <0.05 or p <0.001

The relationship of the variables with the mortality is given in Table 2. A significant relationship was found between the 30-day mortality and the age, FOBT results, hospitalizations of the patients.

The 30-day mortality rate in the patients was 10.2%. While 8% of patients aged 65 and under were mortal, this rate was 18.9% for patients over 65 years old ($p = 0.036$). While 9.1% of patients with positive FOBT result were mortal, this rate was 15.5% in FOBT negative patients ($p = 0.045$). While 24.7% of patients who had a history of hospitalization within 14 days before CDI detection ended with mortality, this rate was 3.8% in patients without a history of hospitalization ($p < 0.001$). In other words, mortality was found to be significantly higher in patients with advanced age, FOBT negativity and a history of hospitalization. The relation of variables with recurrence is given in Table 3. Accordingly, the recurrence rate was found to be 5.2%. A statistically significant relationship was found between recurrence and FOBT positivity, presence of PME. Recurrence developed in 11.7% of the patients with positive FOBT result, while this rate was 2.9% in FOBT negative patients ($p = 0.011$). While 33.3% of the patients with PME have recurrence, this rate was 15.8% in patients without PME ($p < 0.001$).

4. Discussion

C. difficile infection is a serious health problem with an increasing prevalence around the world, causing serious morbidity and mortality. Its clinical picture can vary widely, from asymptomatic carriage to sepsis and mortality (Gerding et al., 1995). FOBT is an inexpensive and easily accessible test that can be used in GIS malignancies, GIS bleeding, inflammatory and infective bowel pathologies (Feldman et al., 2016). In our center, 16642 FOBTs were applied to adult patients between the years 2005 and 2020. 2330 FOBT results (14%) were positive. Between the years 2005 and 2020, the number of patients with *C. difficile* toxin A-B positive was 266.

FOBT was examined in 180 of CDI patients and 77 of them were found to be positive. As a result, CDI was detected in 77 of 2330 patients who were positive for FOBT. In other words, CDI was detected in 3.3% of FOBT positive patients. There is no study investigating the relationship between CDI and FOBT in the Turkish and English literature, so our findings could not be compared.

Determination of mortality rate and factors affecting mortality in CDI is decisive for the prognosis. In the study conducted in Canada, one-year mortality in CDI was found to be 37%; in another study, the 180-day mortality was found to be 5.7% (Pépin et al., 2005; Dubberke et al., 2008). In the study conducted by Shorr et al., involving an elderly patient population, it was reported that 30-day mortality was 10% and one-year mortality was 19% (Shorr et al., 2016). In the study conducted by Nanwa et al., it was reported that one-year mortality was determined as 13% (Nanwa et al., 2017). In the study conducted in Asian pacific countries, 60-day mortality in CDI patients was found to be 5.2% (Collins et al., 2020). In the study conducted in Taiwan, 30-day mortality was found to be 23.4%; and the presence of malignancy, high glucose level, 1.5-fold increase in serum creatinine were determined as independent risk factors affecting mortality (Chiang et al., 2019). Chopra et al. found that, the presence of a history of malignancy or organ transplant, a history of hospitalization in the last 60 days, long-term antibiotherapy, presence of nasogastric tube or parenteral nutrition and rectal enema were found as risk factors determining the 30-day mortality (Chopra et al., 2016). In our study, the 30-day mortality rate of the CDI patients was found to be 10.2%. A significant relationship was found between 30-day mortality and the age, FOBT results, hospitalizations of the patients. Patients with advanced age (> 65), negative FOBT result and a history of hospitalization in the last 14 days before CDI detection had a more mortal prognosis. Although our data are similar to the literature, there is no study in the literature investigating the relationship between FOBT and mortality in CDI. Not knowing the comorbid diseases of the patients and the drugs they used is seen as the deficiency of the study in interpreting this result. Unlike other studies mentioned above, our study concluded that advanced age affects mortality.

PME is a clinical picture characterized by leukocytosis, diarrhea, high fever and abdominal pain, in which pseudomembranes that can settle in the bowel, most frequently in the rectosigmoid region, as a result of inflammation caused by *C. difficile* toxins in the intestinal mucosa. Pseudomembranes appear as small, yellowish-white raised plaques or nodules (Tedesco et al., 1974). Toxic megacolon is a rare clinical picture of CDI that causes dilatation in the intestinal segments and systemic toxicity with severe morbidity and mortality. In one study, four of 207 patients with a diagnosis of CDI (1.9%) had PME (Musher et al., 2005). In the study conducted in Asia-Pacific countries, the incidence of toxic megacolon in CDI patients was found to be 0.2% (Collins et al., 2020), while this rate was found to be 0.4% and 3% in other studies (Berman et al., 2008; Earhart, 2008). In our study, it was observed that six patients (2.2%) developed PME and two patients (0.8%) developed toxic megacolon. In this sense, our data are similar to the literature.

CDI patients are known to have a recurrence rate of 20–35% (Neemann and Freifeld, 2017). In the study conducted in Asia Pacific countries, the recurrence rate in CDI patients was found to be 9.1%. Continuing to use antibiotics, using antacids and advanced age are known as risk factors for the development of recurrent CDI (Kılıç, 2013; Collins et al., 2020). The recurrence rate in our study was found to be 5.2%. Unlike the literature, no significant relationship was found between age and the development of recurrence. A statistically significant relationship was found between recurrence and FOBT positivity, presence of PME.

In conclusion; both the frequency and the severity of CDI have recently increased all over the world and it has become an important health problem. There are well-defined risk factors for the disease and it is important for clinicians to evaluate patients based on these risk factors. We believe that the data documented in this study are important because these data reveal both the clinical characteristics of patients with CDI in our region and their relationship with FOBT, which is a common test. Our findings need to be supported by new studies to be planned with a large patient population

Conflict of interest

All authors declare no conflict of interest regarding this manuscript.

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Case Report

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A case of Meckel's diverticulum with life-threatening recurrent gastrointestinal bleeding in an adult

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Abstract

Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal system. It results from the incomplete closure of the omphalomesenteric canal in intrauterine life. It is mostly diagnosed in childhood with intestinal obstruction and bleeding. It is uncommon and often clinically silent in adults. Also, it is difficult to diagnose the patients with symptomatic Meckel's diverticulum. We report a 28-year-old male who presented with life-threatening recurrent lower gastrointestinal (GI) bleeding and was operated with the diagnosis of Meckel's diverticulum with duodenal ulcer.

Keywords: congenital anomaly, Meckel's diverticulum, recurrent gastrointestinal bleeding

1. Introduction

Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract (Sagar et al., 2006). It results from the incomplete closure of the omphalomesenteric canal in intrauterine life. The incidence in the general population has been estimated to be about 2 percent (Lüdtke et al., 1989). It occurs more frequently in men than in women. It is a true diverticulum so it contains all normal layers of the intestinal wall and results from the incomplete closure of the omphalomesenteric canal (DeBartolo and Van Heerden, 1976). It is mostly diagnosed in childhood with intestinal obstruction and bleeding. It is uncommon and often clinically silent in adults. Also, it is difficult to diagnose the patients with symptomatic Meckel's diverticulum. We report a 28-year-old male who presented with life-threatening recurrent lower gastrointestinal (GI) bleeding and was operated with the diagnosis of Meckel's diverticulum with duodenal ulcer.

2. Case report

A 28-year-old male patient, with no medical or surgical history, presented to the emergency department with complaint of hematochezia for three days. According to the history of the patient, the bleeding started suddenly three days ago and gradually increased. He had bright red, jelly-like stool with an amount of approximately 200 ml, four or three times in the last 24 hours. He had also fatigue, dizziness and cold sweating. On physical examination, the patient was afebrile (36.4°C) with a pulse rate of 105 beats per minute, respiratory rate of 22 breaths per minute, blood pressure of 130/70 mm Hg on lying and 110/60 mmHg on standing. The sclera of both eyes was pale, abdominal examination was normal and bright red bloody contamination was observed on rectal examination. The patient's reference laboratory values were as follows: Hemoglobin: 7.4 g/dl, Platelet: 177.000/Ul, Hematocrit: 33.7%, MCV: 72fL, Wbc: 8300 / Ul, Creatine: 1.31 mg / dl, AST: 26 U / l, ALT: 14 U / l, Na: 141 mEq / L, K: 4.2 mEq / L, Ca: 9.6 mg / dl and INR: 1.2.

During the follow-up of the patient, two more abundant bloody stools occurred and one unit of erythrocyte suspension was given. Upper GI endoscopy and colonoscopy examination was performed. In the upper GI endoscopy of the patient, there was no remaining or fresh blood in the stomach, Forest 2c ulcer was observed in the bulb and was intervened with Argon plasma coagulation. On colonoscopy, fresh blood was seen in the terminal ileum and all colon segments. No active bleeding focus was observed.

Since it was thought that the current clinical status of the patient could not be explained by the ulcer in the bulb, CT angiography was performed to detect the bleeding focus. At the umbilical level, posterior to the distal ileal segment, a tubular structure with mucosal thickening, intraluminal air, and blind ending (approximately 45 mm in length and 15 mm in thickness) was seen and interpreted as Meckel's diverticulum (Figure 1). Since the bleeding continued during follow-up, the patient was consulted to the general surgery department, and partial small bowel resection and end-to-end anastomosis were

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performed. The pathology of the small intestine resection material was compatible with Meckel's diverticulum containing ectopic gastric mucosa (Figure 2).

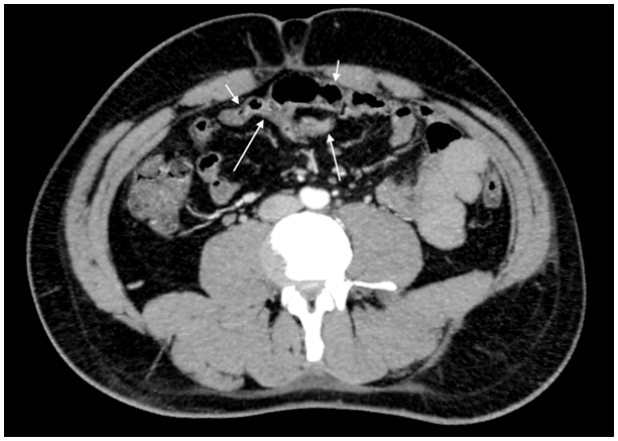

Fig. 1. Meckel's diverticulum seen at the umbilical level on CT angiography

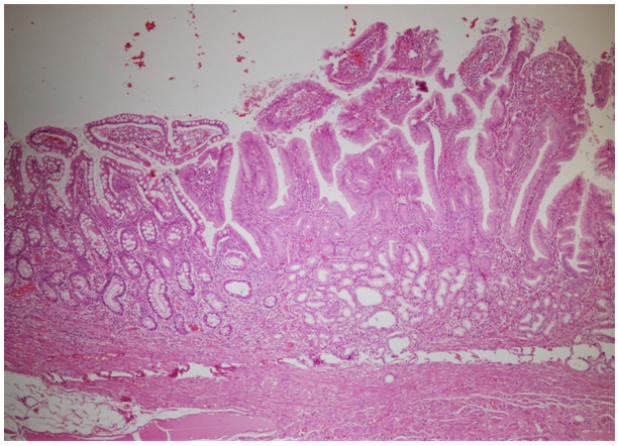

Fig. 2. Normal small intestinal mucosa (left side) followed by gastric mucosa (right side) (H&E stain, x400 magnification)

3. Discussion

Meckel's diverticulum is often clinically silent in adults compared to children, but complications are more serious. The most common clinical finding is gastrointestinal system bleeding, as in our patient (Park et al., 2005). In addition to bleeding, it may also present with other clinical findings such as obstruction, invagination, diverticulitis, and perforation. It usually contains intestinal mucosa, but may contain gastric, colon, duodenal and pancreatic tissue. As in our patient, bleeding in Meckel's diverticulum containing gastric tissue usually develops on the basis of peptic ulcers due to acid secreted from the ectopic gastric mucosa. Bleeding due to Meckel's diverticulum may be overt or occult (Slívová et al., 2018). Some risk factors have been defined for Meckel's diverticulum to be symptomatic. These risk factors are; age under 50, male gender, diverticulum larger than 2 cm and those contained histologically abnormal tissue. All of these risk factors were present in our patient (Park et al., 2005).

There are no specific laboratory and physical examination findings for the bleeding due to Meckel's diverticulum. In the approach to bleeding, the priority is endoscopic evaluation likewise for all gastrointestinal system bleeding. In patients presenting with bleeding due to Meckel's diverticulum, there is usually no pathology in endoscopic evaluation. Because of this, other imaging methods such as CT Angiography and scintigraphy are referred (Enge and Frimann-Dahl, 1964). Duodenal ulcer was detected in our patient, which could explain the bleeding. However, further examination was required because the patient had hematemesis rather than melena, fresh blood was seen in the terminal ileum in colonoscopy, and the duodenal ulcer did not bleed during the endoscopic procedure.

CT angiography is an important diagnostic method to show low amount of bleeding up to 0.3 ml / min, but it is not preferred in special patient groups such as pregnant women, kidney failure patients and those who have contrast allergy due to the need for iv contrast medium. Scintigraphy is based on the principle of the uptake of Tc-99m pertechnetate by the gastric mucosa (Lin et al., 2002). It has 51-92% positive results in lower gastrointestinal system bleeding and can detect bleeding between 0.1-0.3 ml/min. The positive predictive value of scintigraphy in adults is low (60%). There are promising studies on other methods, especially double balloon enteroscopy. Retrospective studies involving large populations have demonstrated that double balloon enteroscopy has higher diagnostic accuracy than scintigraphy. In addition, it allows treatment in some cases although it is limited (Geng et al., 2017). However, its disadvantages are that it is technically difficult, it is not available in most endoscopy centers, and optimal imaging cannot be obtained due to blood and bleeding residues accumulated in the lumen during bleeding.

In patients presenting with bleeding due to Meckel's diverticulum, the first treatment approach is to start proton pump inhibitors. Proton pump inhibitors do not reduce the diagnostic sensitivity of scintigraphy. Our patient continued to bleed under PPI treatment because of the duodenal ulcer (Bandi et al., 2017). Surgery is the next treatment approach for persistent gastrointestinal system bleeding despite proton pump inhibitor therapy. Surgical options are diverticulectomy or segmental resection (Clark et al., 2008). Segmental resection is generally preferred in lesions larger than 2 cm, as in our patient (Hosn et al., 2014).

In conclusion, Meckel's diverticulum is a rare condition in the adult population. However, it should be kept in mind as a differential diagnosis for every patient presenting with lower GI bleeding and whose bleeding etiology cannot be detected in endoscopic examination, so additional radiological and scintigraphic examinations should be performed for diagnosis.

Conflict of interest

All authors declare no conflict of interest regarding this manuscript.

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No competing financial interests exist.

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