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FACULTÉ DE MÉDECINE

ASSESSMENT AND IMPLEMENTATION OF A NEW TECHNOLOGY FOR TREATMENT OF VARICEAL BLEEDING

Mostafa IBRAHIM

Service de Gastro-entérologie

Hôpital Erasme

Thèse présentée en vue de l'obtention du titre académique de Docteur en Sciences médicales

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SUMMARY, RÉSUMÉ, ABBREVIATIONS AND TABLE OF CONTENTS

SUMMARY

Acute variceal bleeding (AVB) is the most dramatic complication of portal hypertension. It occurs in one-third of cirrhotic patients with varices and causes 70% of all upper gastrointestinal (GI) bleeding episodes in cirrhotic patients resulting in major morbidity and mortality despite improvements in primary prophylaxis and management of acute bleeding episodes over the past three decades. The best strategies for management of AVB have been investigated in numerous clinical trials and this has led to multiple guidelines. Endoscopic management combined with pharmacotherapy is the ideal strategy to control variceal bleeding, but this can be challenging. Bleeding may be difficult to identify or may occur from sites that are difficult to approach. A trained multidisciplinary team consisting of endoscopists, hepatologists, and specialized nurses as well as interventional radiologists is required to administer the ideal treatment for AVB. However, this setup is not available everywhere. Early management of AVB is mandatory within 24 hours of admission and better outcomes are reported in those patients who receive endoscopic therapy within 12 hours. Although this is still controversial, it seems to be increasingly obvious that earlier hemostasis leads to better outcomes.

In practice, treatment for AVB is often delayed by a lack of expert endoscopists. Therefore, having a simple endoscopic hemostatic technique that does not require an experienced team could have a major impact on AVB management.

Hemospray powder (Hemospray, TC-325; Cook Medical Inc., Winston-Salem, NC, USA) is an FDA-approved organic powder made from a proprietary mineral blend. The material works in two different ways: as a mechanical barrier and by absorption. When in contact with the bleeding site, the powder forms a barrier over

the vessel wall, quickly stopping the bleeding. In addition, the absorbent powder increases the local concentration of clotting factors and enhances clot formation.

Previous studies described Hemospray as a simple and feasible new modality for obtaining rapid hemostasis of peptic ulcer bleeding during gastrointestinal endoscopy, either as primary treatment or as a salvage indication.

The work presented here evaluated the safety, feasibility, clinical efficacy, and potential outcome benefits of applying this hemostatic powder early in the management of AVB, as a potential new clinical indication. We have performed our research in three phases, starting with a safety study on AVB that originated from esophageal varices and two case reports on portal hypertension-related bleeding. This was followed by an efficacy study and then we confirmed our data in a randomized controlled study where we observed a potential impact on survival, opening the door to additional clinical investigations.

The aim of the research was to investigate the concept of treating portal hypertension-related AVB with early endoscopic hemostasis using a novel hemostatic powder which can be applied without the need for a skilled team.

We showed that this easy-to-perform technique, in a novel indication, is indeed safe and effective when added to the gold standard of care for AVB and can improve endoscopic and clinical hemostasis, providing easier elective treatment with less need for experienced teams. An effect on mortality was also observed in the randomized controlled study as a secondary outcome measure.

The next step is to design a study focused on survival, perhaps with a simplified design in which the spraying catheter can be used without the need for endoscopy or sedation. Another interesting future investigation will be to design a study that compares two groups with early powder application that are randomized within 24

to 48 hours either to elective endoscopic treatment or a transjugular intrahepatic portosystemic shunt (TIPS) procedure. This would allow us to learn whether this new therapeutic approach impacts the need for early TIPS placement in severe cases of AVB.

RÉSUMÉ

Les saignements variqueux aigus (AVB) sont la complication la plus dramatique de l'hypertension portale. Il survient chez un tiers des patients cirrhotiques et provoquent 70% de tous les épisodes de saignements gastro-intestinaux chez les patients cirrhotiques. Ils sont grevés d'une morbidité et d'une mortalité importantes malgré les améliorations apportées à la prophylaxie et à la gestion des saignements aigus au cours des trois dernières décennies.

Le traitement endoscopique associé à la pharmacothérapie est la stratégie idéale pour contrôler les saignements variqueux, mais cela peut être complexe. Les saignements peuvent être difficiles à identifier ou provenir de sites d'accès difficile. La prise en charge endoscopique précoce de l'AVB est obligatoire dans les 24 heures suivant l'admission et de meilleurs résultats sont rapportés chez les patients traités par endoscopie dans les 12 heures.

Bien que cela reste controversé, il semble de plus en plus évident que l'hémostase plus précoce conduit à de meilleurs résultats. En pratique, le traitement de l'AVB est souvent retardé par un manque d'endoscopistes experts. Par conséquent, le recours à une technique hémostatique endoscopique simple ne nécessitant pas de personnel expérimenté pourrait avoir un impact majeur sur la gestion de l'ABV.

Hemospray est une poudre organique approuvée par la FDA composée d'un mélange de minéraux. Le matériau fonctionne de deux manières différentes : Il forme une barrière mécanique et provoque une dessiccation par absorption. En contact avec le site de saignement, la poudre forme une barrière sur la paroi du vaisseau qui arrête le saignement.

Le travail présenté ici a évalué la faisabilité, l'efficacité clinique et les avantages potentiels de l'application de cette poudre hémostatique à un stade précoce de la prise en charge de l'AVB, explorant une nouvelle indication clinique.

Nous avons effectué notre recherche en trois phases, en commençant par une étude évaluant la sécurité de ce traitement en cas d'AVB provenant de varices œsophagiennes et deux rapports de cas de contrôle de saignement dans des situations complexes.

Cette étude a été suivie d'une étude d'efficacité, puis nous avons confirmé nos données dans le cadre d'une étude randomisée dans laquelle nous avons observé un impact potentiel sur la survie, ouvrant la voie à des investigations cliniques supplémentaires.

Le but de la recherche était d'étudier le concept de traitement de l'AVB liée à l'hypertension portale avec une hémostase endoscopique précoce au moyen d'une nouvelle poudre hémostatique pouvant être appliquée sans recourir à une équipe qualifiée.

Nous avons montré que cette technique facile à utiliser, dans une indication nouvelle, est en effet sûre et efficace lorsqu'elle est ajoutée à la norme de soins de référence pour l'AVB, peut améliorer l'hémostase clinique et endoscopique et pourrait avoir un effet bénéfique sur la survie. Ce dernier point devra être évalué dans des études ultérieures focalisées sur la survie des patients

ABBREVIATIONS

ARFI	Acoustic Radiation Force Impulse Imaging
AVB	Acute Variceal Bleeding
AASLD	American Association for The Study of Liver Diseases
CE	Capsule Endoscopy
CSPH	Clinically Significant Portal Hypertension
CTP	Child Turcotte-Pugh Score
CT	Computed Tomography
EGD	Esophagogastroduodenoscopy
EVL	Endoscopic Variceal Ligation
EV	Esophageal Varices
EUS	Endoscopic Ultrasound
FDA	Food and Drug Administration
GOV	Gastroesophageal Varices
GV	Gastric Varices
GI	Gastrointestinal
GIT	Gastrointestinal Tract
HCC	Hepatocellular Carcinoma
HVPG	Hepatic Venous Pressure Gradient
HE	Hepatic Encephalopathy
INR	International Normalized Ratio
IL-8	Interleukin-8
IGV	Isolated Gastric Varices
MRI	Magnetic Resonance Imaging
MELD	Model for End-Stage Liver Disease

NASH	Nonalcoholic steatohepatitis
NSBB	Non-Selective Beta-Blocker
PH	Portal Hypertension
PHE	Portal Hypertensive Enteropathy
PHG	Portal Hypertensive Gastropathy
PPI	Proton Pump Inhibitor
RAAS	Renin–angiotensin–aldosterone system
RCT	Randomized controlled trial
SOC	Standard of Care
SWE	Shear Wave Elastography
TE	Transient Elastography
TNF-a	Tumor Necrosis Factor Alpha
TIPS	Transjugular Intrahepatic Portosystemic Shunt
TLR	Toll-Like Receptor
WHVP	Wedged Hepatic Vein Pressure

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INTRODUCTION

1. INTRODUCTION

1.1. CIRRHOSIS AND PORTAL HYPERTENSION

Portal hypertension is an inevitable and frequent pathological complication of chronic liver disease leading to the formation of portosystemic collateral vessels (1). The most clinically significant are those that occur in the wall of the stomach and esophagus. This pathology may result in a series of complications, such as intestinal bleeding, formation of ascites, encephalopathy, and development of a hyperdynamic circulation involving peripheral and splanchnic vessels (2) and may also be associated with multi-organ dysfunction (3).

Approximately 60% of patients with portal hypertension have gastrointestinal varices at the time of diagnosis (4). A complex interplay among inflammatory stimuli, vaso-regulatory molecules, neurotransmitters, and ion channels maintains and drives the mechanisms of portal pressure. Thus, portal hypertension is both a cause and a part of a dynamic process triggered by chronic liver disease and systemic inflammation (5). In the advanced stage of liver disease, it is mainly fixed structural changes, such as fibrosis or the formation of regenerative nodules, that are responsible for developing and sustaining portal hypertension. In addition, dynamic factors involving the regulation of blood flow in different vascular beds play an influential role in the modulation of portal pressure and its associated

physiopathology. Systemic therapy is aimed at the modulation of these dynamic processes. These are most likely similar in end-stage liver disease, regardless of the etiology of hepatic damage. However, in the early stages of liver disease, the pathological sequence of events depends more on etiological factors, whether they are metabolic, infectious, or autoimmune.

1.1.1. Clinical Presentation

Patients with esophageal or gastric variceal bleeding present with hematemesis or melena or both. Chronic blood loss is a more frequent presentation of portal hypertensive gastropathy or gastrointestinal vascular ectasia. The classic presentation of patients with variceal bleeding is painless and recurrent hematemesis; the vomitus is described as dark red in color. Portal hypertension should be suspected in all patients with gastrointestinal tract (GIT) bleeding and peripheral stigmata of liver disease, namely, jaundice, spider telangiectasias, palmar erythema, Dupuytren's contractures, parotid enlargement, and testicular atrophy, loss of secondary sexual characteristics, ascites, and hepatic encephalopathy. Splenomegaly is also an important indicator of the presence of portal hypertension, and the presence of ascites makes the presence of esophageal varices even more likely (6). Laboratory studies frequently reveal evidence of hepatic dysfunction, including prolonged prothrombin time, hypoalbuminemia, and hyperbilirubinemia, as well as anemia. Hypersplenism may be present with thrombocytopenia and

leukopenia. Patients with severe bleeding may present with hypovolemic shock and renal insufficiency.

1.1.2. Staging and Diagnosis of Chronic Liver Disease and Portal Hypertension

For the purpose of staging chronic liver disease, a variety of different tools are available, including, in addition to physical examination, laboratory tests, imaging techniques, and hemodynamic measurements. Imaging techniques comprise endoscopy, ultrasound determination of liver stiffness, computed tomography (CT), and magnetic resonance imaging (MRI). Physical examination includes important parameters of the Child–Pugh classification (7). If the patient has no signs of jaundice, ascites, or encephalopathy, they are considered to be in a compensated stage of cirrhosis with a 10-year survival of above 50%, while clinical signs of decompensation may be associated with a mortality of more than 75% within the next 5 years (8).

Endoscopy is still the best standard method for diagnosing and staging varices in the upper gastrointestinal tract as well as for evaluating the risk of bleeding (9). While in any patient with suspected liver cirrhosis a standard examination previously included endoscopy, new guidelines recommend abstaining from early endoscopy in patients with liver stiffness <20 kPa and platelet count >150 G/L (10,

11). However, endoscopy retains its central role as the main test for the initiation of primary and secondary prophylaxis of variceal bleeding in patients with higher stiffness values or a lower platelet count. Also, it is still considered to be the central method for the assessment of variceal bleeding and achieving hemostasis (11). In addition, elastographic techniques enable estimation of the degree of liver fibrosis via transient elastography (TE), acoustic radiation force impulse imaging (ARFI), or shear wave elastography (SWE) (12, 13).

Determination of liver stiffness has recently become a tool for screening of fibrosis and portal hypertension in patients with liver disease. Fibrosis leads to an increased stiffness of the liver. In organs with higher stiffness, shear waves travel at a higher speed through tissues. By delivering pulses, shear waves can be induced in order to evaluate their speed as an indirect measure of fibrosis. There are different systems using mechanical 50 Hz pulses (TE), a focused ultrasound pulse to deform internal tissue (AFRI and SWE), or a two-dimensional gradient-recalled-echo sequence analyzed by certain algorithms.

Transient elastography (TE) is a stand-alone technique based on shear wave speed measurement, and is not integrated into ultrasound devices. Values below 5.2–9.5 kPa (TE) or 1.22–1.63 m/s (ARFI) can rule out liver fibrosis, whereas higher values can provide false positive results with respect to cirrhosis assessment due to obstructive cholestasis, liver congestion, or severe liver inflammation (14). SWE

has shown slightly better sensitivity and specificity for liver fibrosis and portal hypertension compared to TE (15). Nevertheless, it is important to take testing conditions, such as fasting state, into consideration (16). By combining liver and spleen SWE, portal hypertension can be excluded with a very high probability on the one hand or assessed with regard to its clinical significance on the other (17). These various systems have pros and cons. TE is available in many centers and is well-validated but may have a high failure rate in obese patients or ascitic patients. AFRI provides ultrasound guidance for the region of interest but is less well validated, and increased body weight may also be a problem. MR elastography allows one to include a large sampling volume, but it is affected by iron deposition, high body mass index, and massive ascites (18).

Ultrasound allows a more sensitive and specific assessment of ascites than clinical examination together with assessment of size, surface, and echotexture of the liver.

Like ultrasound, computed tomography and MRI are applicable for the diagnosis of hepatocellular carcinoma (HCC). This is essential, because liver fibrosis and cirrhosis are precancerous conditions. However, MRI has the broadest potential for staging liver disease with respect to morphology, including the biliary system, tissue texture, perfusion, formation of collaterals, and function of hepatic cells, but is not always available (19).

1.1.3. Hepatic Venous Pressure Gradient Assessment

Assessment of the hepatic venous pressure gradient (HVPG) is one of the most critical evaluations in chronic liver disease. It was first introduced in the 1950s (20) and was subsequently modified by Groszmann *et al*.(21), becoming the gold standard for indirect assessment of the degree of portal hypertension. The HVPG value is closely related to portal vein pressure, especially in alcoholic liver disease, which, in turn, shows a significant correlation to the pressure in esophageal varices (22). Measurement of the HVPG adds prognostic evidence to laboratory and clinical evaluations in advanced liver disease (23, 24).

Portal hypertension is defined as HVPG>5 mm Hg, but the risk of developing gastroesophageal varices (GEV) and the clinical complications of decompensated cirrhosis (e.g. ascites, variceal bleeding and overt hepatic encephalopathy [HE]) are only evident when HPVG reaches ≥10 mm Hg (25). Hence, HVPG ≥10 mm Hg is called clinically significant portal hypertension (CSPH).

Patients with compensated liver cirrhosis and an HVPG value less than 10mmHg have a lower risk of developing varices or decompensation of liver function (26). It is generally accepted that esophageal varices do not bleed if HVPG remains below 12 mmHg and that a reduction of HVPG by more than 20%, regardless of the baseline value, significantly reduces the risk of bleeding from varices. Thus,

measurement of HVPG has repeatedly been proposed as a tool for tailoring the treatment of variceal bleeding (23). There is also a good correlation between liver stiffness, as assessed by TE, and HVPG (27). Values below 14 kPa exclude CSPH (HVPG ≥10 mmHg) with high sensitivity and specificity (28).

1.1.4. MELD and Child–Pugh Classification

Since the introduction of the Child–Turcotte classification and its modification according to Pugh *et al*.(29), it has been repeatedly shown that, in patients with liver cirrhosis, laboratory results reflecting hepatocyte function allow prediction of survival rates. Thus, serum levels of bilirubin, albumin, or coagulation factors have been used for decades to stage chronic liver disease. They are part of the model for end-stage liver disease (MELD) system (30) as well as of the Child–Pugh classification (29).

The MELD score consists of serum levels of bilirubin and creatinine and prothrombin time determined as an international normalized ratio (INR). It was initially developed to determine the prognostic factors for patients receiving a transjugular intrahepatic portosystemic shunt (TIPS) (30, 31). It is now used to assess organ allocation prior to liver transplantation. It is easily calculated and has been prospectively validated in different cohorts, and contains no clinical parameters based on subjective assessment.

Although MELD is slightly superior to the Child–Pugh model in the prediction of survival, the addition of parameters such as sodium (32), hepatic encephalopathy (33), and sarcopenia (34) to MELD has been reported to further improve prognosis. Impairment of kidney function, such as sodium handling, occurs early in patients with liver disease, and an increase in serum creatinine of ≥0.3 mg/dL is an independent marker for unfavorable patient outcome (35).

Many of these parameters are factors considered by staging systems for liver cirrhosis specifically designed to distinguish between compensated and decompensated stages of the disease (36). The different factors mentioned above, such as the degree of fibrosis, HVPG, ongoing etiology, and Child–Pugh scoring, are somewhat interrelated. Thus, HVPG increases with the degree of cirrhosis or the degree of decompensation as assessed by the Child–Pugh score (37, 38). In contrast, the correlation can be weak, and the prognostic value of HVPG is partly independent of the Child-Pugh system (39). Therefore, there is always the question of how to coordinate different parameters or scores into an appropriate and simple bedside system. Jaundice and ascites are considered markers of poor prognosis. In this situation, bleeding, infections, overt encephalopathy, and deterioration of kidney function denote a high risk of death. Determination of HVPG and/or of liver stiffness may improve long-term prognosis in patients with compensated cirrhosis (36), and HVPG alone is an independent prognostic marker in

decompensated cirrhotic patients with variceal bleeding (21, 39, 40). In the future, we will likely develop more sophisticated systems (36, 41) that will improve prognosis and therapy.

1.1.5 Management of Portal Hypertension

1.1.5.1 Decrease of Portal Pressure by Shunt Procedures

The most effective therapy for reducing portal hypertension is the one that decreases intrahepatic resistance and bypasses blood flow into the inferior vena cava by portacaval, meso-caval, or proximal splenorenal shunts. Previous studies back to 1960 (42-44) assessed the efficacy of a surgical open shunt procedure for prevention of bleeding from varices. Long-term follow-up studies have been published as recently as 2012 and 2014 (45, 46). Although open surgical shunts may demonstrate good outcomes for secondary prevention of variceal bleeding in young patients with severe portal hypertension, recurrent bleeding, and good liver function, this surgery is less often performed due to the availability of less invasive procedures and also, as a consequence, because of decreasing surgical experience. By contrast, TIPS is considered less invasive and has become an established treatment approach in portal hypertension and its complications.

1.1.5.1 Transjugular Intrahepatic Portosystemic Shunting (TIPS)

In most patients with high portal pressure, TIPS placement reduces portal pressure by more than 50%, as assessed by HVPG. The degree of reduction depends on the diameter of the stent (24). TIPS can prevent variceal rebleeding in almost all patients. Many studies have shown that TIPS is superior to ligation of varices with or without the addition of beta-blockers (47). Currently, the combination of band ligation and administration of beta-blockers is still considered to be the standard prophylaxis against rebleeding (48) because TIPS patients with decompensated cirrhosis are suboptimal candidates for shunt insertion, as they have a relatively high risk of liver and mental dysfunction. Therefore, TIPS implantation is used as a potential rescue operation for the treatment of rebleeding of varices or for refractory ascites. According to randomized clinical trials, about 20% of patients receiving local endoscopic rebleeding secondary prophylaxis must be switched to TIPS implantation because of treatment failure or refractory ascites (49, 50). Thus, in patients with variceal bleeding and ascites, early placement of a small lumen TIPS should be considered as early treatment and will avoid progressive complications. Although TIPS is currently the most effective method for reducing portal hypertension and preventing bleeding in patients with liver cirrhosis, it does not improve survival rates compared to patients receiving a non-shunt approach

(47). This also holds true for the most recent trials comparing non-selective beta-blockers (NSBB), with or without ligation, to TIPS with covered stents (49, 51).

However, several reports suggest that early TIPS insertion is beneficial in high-risk patients, mainly those with active bleeding, decompensated liver cirrhosis, and HVPG >20 mmHg (37, 52). However, this strategy still needs to be proven in general clinical practice. Currently, early TIPS insertion for acute variceal hemorrhage is not always available or is not widely used in daily clinical practice (53). The positive benefit of TIPS insertion for the secondary prophylaxis of bleeding in patients with cirrhosis decreases with increasing temporal distance to the index bleeding event in both acute (54) and elective (49) situations.

In conclusion, TIPS has become a standard procedure in the prevention and treatment of gastrointestinal bleeding and ascites in patients with cirrhosis. However, patient selection is key and, in cases where an early procedure is indicated, the availability of centers that perform the procedure remains an issue.

1.1.5.2 Modification of Portal Pressure using Non-Specific Drugs

Interruption of etiology (alcohol intake, active chronic viral infection, metabolic syndrome) is an important step in managing portal hypertension, mainly with respect to the progression of liver disease but also with respect to the immediate use of portal pressure lowering medications.

In the following sections, we refer to medical treatments that are not curative but may have beneficial adjuvant effects.

1.1.5.2.1 Non-Selective Beta-Blockers (NSBBs)

NSBBs were introduced four decades ago by a French team with the theory that portal tributary blood flow is increased in cirrhotic liver with portal hypertension and that NSBBs decrease portal flow and pressure by reducing cardiac output and causing splanchnic vasodilation (55). Further studies have reported the important role of NSBBs in the treatment of portal hypertension, mainly for the prevention of initial bleeding and recurrent bleeding and in combination with endoscopic ligation (48, 56).

A recent clinical trial suggested that cirrhotic patients with a hemodynamic response to NSBBs have high survival rates compared to those who fail to respond (57).

The choice of NSBB type for patients with liver cirrhosis has become an issue since it has been shown that carvedilol induces a better hemodynamic response (51) in patients with cirrhosis, as determined by HVPG drop, than nadolol or propranolol. It also prevents the progression of small esophageal varices (58). All of these findings must be considered with caution until enough large randomized trials with predefined endpoints have been performed.

1.2. ACUTE VARICEAL BLEEDING

Acute variceal bleeding is a major complication in patients with portal hypertension. It is associated with a high mortality rate in patients with decompensated liver cirrhosis accompanied by ascites or hepatic encephalopathy (59). It is estimated that every year, new varices develop or the pre-existing varices worsen in 7% of patients (26), bleeding occurs in 70% of cases, and mortality during the first episode is estimated to be 15%–20% (61).

Variceal bleeding accounts for 70% of all upper gastro-intestinal bleeding in patients with portal hypertension, and arises from esophageal varices (EVs), gastric varices (GVs), or ectopic varices. However, the remaining 30% is due to other causes, such as portal hypertensive gastropathy, Mallory Weiss lesions, and ulcers (62, 63).

The risk factors for variceal bleeding include varix size, red color sign on the surface of the varix, alcohol consumption, and the degree of deterioration of liver function (64). The 6-week mortality rate due to variceal bleeding is 15% to 20% and, in patients with severe decompensated liver cirrhosis (Child Turcotte-Pugh grade C), the mortality rate increases to 30% (65). Therefore, in patients with acute variceal bleeding, the timing of endoscopic hemostasis and prevention of rebleeding are of great importance. The treatment goals for acute variceal bleeding are 1) correction of hypovolemia, 2) rapid achievement of hemostasis, 3) prevention of early

rebleeding, 4) prevention and early treatment of complications related to bleeding, and 5) prevention of deterioration of liver function (66). The acute bleeding episode is represented by an interval of 120 h (5 days) from time zero. Evidence of any bleeding after 120 h is the first rebleeding episode (67).

1.2.1. Epidemiology of AVB

Gastroesophageal varices (GOVs) are a common complication of chronic liver disease and affect up to 50% of patients with liver cirrhosis (68, 69). The development of varices correlates with the severity of liver disease and, therefore, varices are more commonly seen in Child Turcotte-Pugh (CTP) class C patients (85%) than CTP class A patients (40%) (69, 70). The annual incidence ranges from 5% to 15% in patients with cirrhosis (71). Also, development of varices is seen with a hepatic venous pressure gradient (HVPG) more than 10 mmHg (68, 71). Esophageal varices (EV) are most frequently seen in the distal 2 to 5 cm of the esophagus (72). Gastric varices are classified into four types, depending on their location and relation to esophageal varices. In GOV-1, esophageal varices extend along the lesser curvature of the stomach, and this is the most common type of GV (70%). In GOV-2, esophageal varices extend into the greater curvature (21% of gastric varices) (73, 74). Isolated gastric varices (IGVs) are less commonly seen and are divided into type 1 IGVs, which occur in the fundus only (7%), and type 2 IGVs, which are seen anywhere in the stomach or in the duodenum (2%) (74, 75).

Gastric varices are observed in about 15% to 20% of patients with portal hypertension and they are responsible for 10% to 30% of cases of variceal hemorrhage. However, they are associated with higher re-bleeding rates, transfusion requirements, and mortality rates (74, 76).

As previously mentioned, AVB is the most common serious cause of upper gastrointestinal bleeding in cirrhosis (66, 74, 77). Several factors increase the risk of bleeding, but the most important is the wall tension of the varix which is correlated to the diameter and pressure of the vascular wall. Over two years, the risk of bleeding in varices less than 5 mm in diameter is 7%, and this increases to 30% if the diameter is greater than 5 mm (78). Despite advances in treatment, mortality rates during initial hospitalization are as high as 30%. Mortality rates are highest during the first few days of bleeding and decrease slowly over the successive six weeks (78).

1.2.2. Physiopathology of AVB

Portal hypertension (defined as hydrostatic pressure >5 mmHg) results initially from obstruction to portal venous outflow. Obstruction may occur at a presinusoidal (portal vein thrombosis, portal fibrosis, nodular regenerative hyperplasia, or infiltrative lesions), sinusoidal (cirrhosis), or post-sinusoidal (veno-occlusive disease, Budd-Chiari syndrome) level. The increase of portal venous pressure is

measured as the difference in pressure gradient between the portal vein and the inferior vena cava (79). This results from changes in portal resistance, along with changes in portal flow. In portal hypertension, porto-systemic collateral decompresses portal circulation and progresses to esophageal varices (79).

In liver cirrhosis, sinusoidal portal pressure is mainly determined by the hepatic vein pressure gradient (HVPG), which is defined as the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (21, 80).

1.2.3. Location of Varices

The most common sites for development of varices are the distal esophagus, stomach, and rectum. However, varices may develop at any level of the gastrointestinal tract between the esophagus and rectum. Varices develop deeply within the submucosa in the mid-esophagus but become progressively more superficial in the distal esophagus. Thus, esophageal varices at the gastroesophageal junction have the thinnest layer of supporting tissue and are most likely to rupture and bleed. Esophageal varices develop from the deep venous plexus to the lumen of the esophagus (81). The last five centimeters of the esophagus is the inclination area of the rupture and, as the varices increase in size, the rupture is larger and more severe (82). Analysis of data from eight endoscopic studies with a total of 3,000

patients with cirrhosis indicated that the incidence of varices is 58.7% (83-85). The incidence increased in 10 years from 8% to 58.7% (86). Extended varices from the esophagus to gastric fornix and the greater curvature have an increased risk of bleeding, especially in patients with Child B and Child C cirrhosis (87).

1.2.4. Size of Varices

The risk of variceal bleeding is independently proportional to the diameter or size of the varix. The explanation for the relationship between variceal size and risk of bleeding is derived from Laplace's law which is defined as (Wall tension (T) = [Transmural pressure (P varices -P lumen) × variceal radius (R)] / [Variceal wall thickness (WT)])

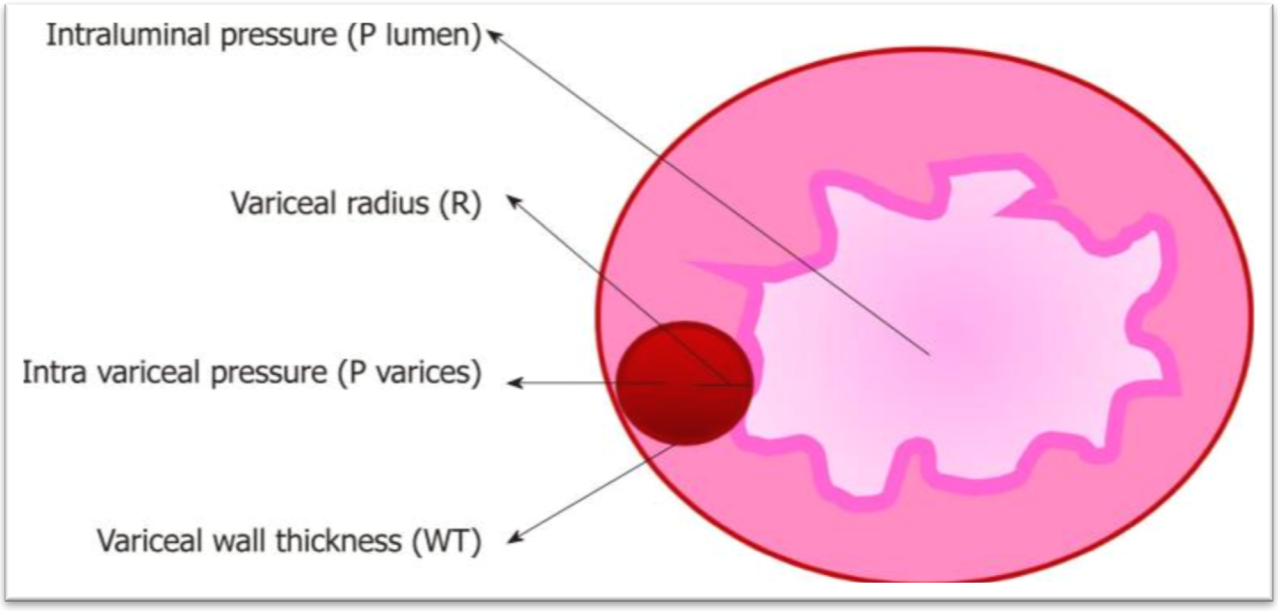

Figure 1 : Mechanism of variceal bleeding. P: Pressure; R: Radius; WT: Wall thickness.

There are several ways in which esophageal variceal size is classified using subjective evaluation. A commonly employed system of classification (9, 88) includes the following:

- F1: Small, straight varices
- F2: Enlarged, tortuous varices that occupy less than one-third of the lumen
- F3: Large, coil-shaped varices that occupy more than one-third of the lumen

An increased hepatic venous pressure gradient over 12mm Hg enhances development of esophageal varices and there is a risk of gastroduodenal bleeding

(1, 89, 90). At pressures over 16mm Hg, survival decreases. Variceal rupture occurs most frequently at 2 years after confirmation of the diagnosis of liver cirrhosis (91, 92). The severity of bleeding produced by variceal vein tears is dependent on hemodynamic factors and hemostatic disorders due to cirrhosis (94-96).

It is well known that mortality during the first episode is estimated to 15%–20%, but this is higher in severe patients (Child Pugh C), at around 30%, whereas it is very low in patients with compensated cirrhosis (Child Pugh A) [3]. The main predictors of bleeding in clinical practice are: large versus small varices, red wale marks, Child Pugh C versus Child Pugh A–B (97). Bleeding may be severe due to the deficient synthesis of coagulation factors and decreased platelet counts caused by hypersplenism (96).

1.2.5. Role of Endoscopy in the Diagnosis and Grading of Varices

Varices can be detected using various diagnostic and imaging techniques such as ultrasound, CT, and MRI. However, they are less precise than endoscopy.

1.2.5.1. Esophagogastroduodenoscopy (EGD)

EGD is considered to be the gold standard for the diagnosis of gastroesophageal varices (98). Direct imaging is needed to determine the size and presence of high-risk stigmata of bleeding, in order to decide if prophylactic variceal banding is warranted. Examination for EV is best done during withdrawal of the scope, with

the esophagus maximally insufflated with air/CO_2 and the stomach completely deflated in order to avoid any mucosal folds which can be misdiagnosed as varices. GVs are generally described according to the Sarin classification and the presence or absence of red color signs (Figure 2). EVs are usually distinguished according to their location in the lower, middle, or upper esophagus. They are graded as small (<5 mm) or large (>5 mm), with the latter encompassing medium-sized varices when 3 grades are used (small, medium, and large) (98). In addition, the presence of high-risk stigmata of bleeding, that is, red color signs (red wale sign and cherry red spots) must be noted.

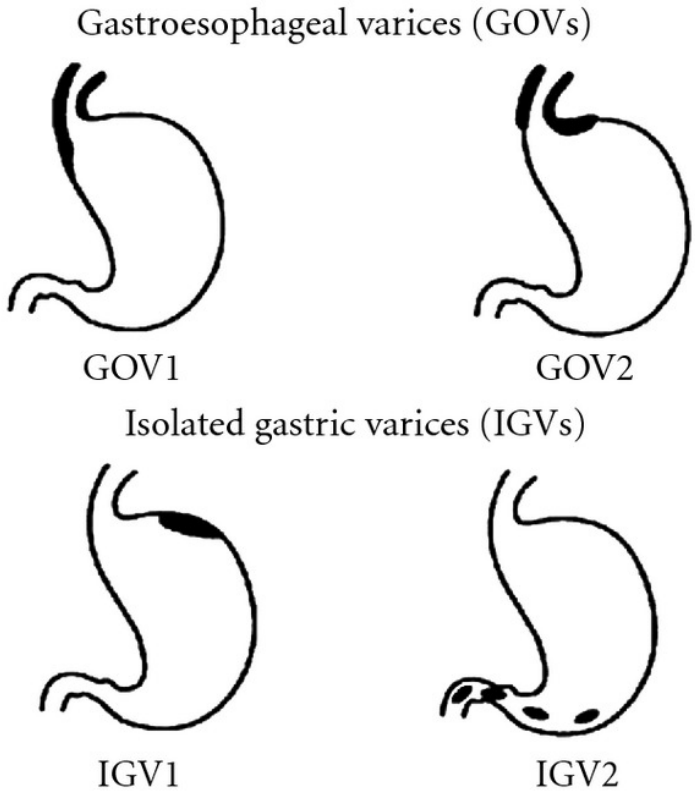

Figure 2 Sarin Classification of gastric varices (adapted from Sarin *et al*. (99))

1.2.5.2. Endoscopic Ultrasound (EUS)

Vascular changes within the esophagus, stomach, or rectum can be accurately confirmed with EUS (100) but, currently, this technique has limited value in clinical practice. EUS appears to perform as well as EGD for detection of clinically significant EVs (101). The diagnosis of GV is probably the most important clinical application of EUS in patients with portal hypertension (PH) (102). However, it could be used to determine predictors for recurrence of varices after endoscopic obliteration, by assessing for the presence and size of para-esophageal veins (103).

EUS has no role in grading the size of esophageal varices, but it may be of some help in guiding endoscopic therapy in some cases (103-105). Future applications may include EUS-guided direct measurement of portal venous pressure and TIPS placement but, to date, safety information is scarce (103).

1.2.5.3. Capsule Endoscopy (CE)

Recent guidelines recommend screening patients with liver cirrhosis with EGD to detect varices (41, 106). However, the need for sedation and invasive nature of EGD may limit acceptability and adherence of patients to screening programs (107). Two different types of CE are available for the evaluation of patients with portal hypertension: esophageal CE and small bowel CE. The main pros of these diagnostic tools are that they are relatively less invasive, potentially increasing patient acceptability and adherence to surveillance programs.

When comparing esophageal CE with EGD, its performance in recognizing the presence and the size of EVs is reliable, but results have varied greatly across studies, and better designed trials are recommended (107). Esophageal CE has some limitations, related to cost, absence of a reliable variceal size grading system, and need for specialized apparatus. Currently, it can only be recommended in patients who are unable to have an EGD and who require endoscopic visualization. In other studies for portal hypertensive gastropathy (PHG), esophageal CE demonstrated

sensitivity (74% to 100%) and specificity (from 17% to 83%) when compared to EGD (108).

Several studies have been published concerning the use of small bowel CE for detection of portal hypertensive enteropathy (PHE), the prevalence of which is higher than what was previously reported (108). CE was able to detect potential sources of bleeding in 89.5% of patients and active bleeding sites in 15.8%. Based on these results, small bowel CE could have diagnostic utility in patients with PH and chronic anemia to identify obscure sources of bleeding (108, 109).

1.2.6. Initial Management of the Acute Bleeding Episode

The first approach in managing patients with an acute bleeding episode is evaluating the severity of the bleeding and achieving a condition of hemodynamic stability through the administration of adequate fluids and blood transfusion to prevent early re-bleeding, deterioration of liver function, and other bleeding-related complications, such as acute kidney injury and HE, and to prevent infection.

Compared to patients with non-variceal bleeding, too much transfusion or administration of fluids in patients with variceal bleeding aggravates the condition and favors rebleeding due to the increase in portal pressure rather than arterial pressure (110).

1.2.7. Blood Volume Restitution

Patients with variceal bleeding are conservatively transfused to a hematocrit of only 27% to avoid exacerbation of bleeding by increasing portal pressure (111). Following current guidelines for critically ill non-cirrhotic patients, the suggested targeted mean arterial pressure should be 65 mmHg, but avoid overexpansion, which may increase portal pressure, impair clot formation, and increase the risk of further bleeding. In fact, a certain degree of hypovolemia and hypotension accelerates activation of endogenous vasoactive systems, leading to splanchnic vasoconstriction, thus reducing portal blood pressure (110). Colloids and crystalloids are considered to be first-line treatment. The use of fresh frozen plasma as a volume expander is not recommended (112). A recent study showed that a restrictive packed red blood cell transfusion therapy improves survival in Child–Pugh class A and B patients. The results also showed that patients with cirrhosis and AVB should be transfused when hemoglobin drops below 7 g/dL, targeting a hemoglobin level of 7–9 g/dL (110). However, if the hemorrhage progress to massive bleeding, the recommended initial transfusion protocol includes four packed red blood cells, 1 L of frozen plasma, one pool of platelets, and 2 g of fibrinogen. Other exceptions are cardiovascular comorbidities (acute coronary syndrome, stroke, symptomatic peripheral vasculopathy, etc.) or conditions inhibiting adequate physiological response to acute anemia. Volume restitution

should be administered cautiously to maintain adequate tissue oxygenation and perfusion (112) because acute hypo-perfusion may decrease hepatic perfusion which, in the setting of underlying chronic liver disease, may lead to ischemic hepatitis and aggravate liver injury (113).

1.2.8. Antibiotic Prophylaxis

Bacterial infections, including spontaneous bacterial peritonitis, are common in cirrhotic patients with variceal hemorrhage and often trigger the episode of bleeding. These bacterial infections are present in 35% to 66% of liver cirrhosis patients with variceal bleeding (114) who must be considered to be infected. Previous studies have shown that prophylactic antibiotics can increase survival rates and probably play a major role in the control of AVB (115). A meta-analysis of 12 randomized controlled trials (RCTs) showed a clear survival benefit with the early use of prophylactic antibiotics during an acute variceal bleeding episode (RR = 0.79, 95% CI 0.63-0.98) (116). These trials also showed that antibiotics reduce the risk of bacterial infections and early re-bleeding. The current guidelines recommend the routine administration of antibiotics, immediately after proper sampling for culture, in all cases of acute variceal hemorrhage regardless of Child-Pugh class and regardless of whether there is an infection or suspected focus of infection. Antibiotics such as quinolones may be administered intravenously when oral administration is impossible. Systemic administration of antibiotics is usually

performed for 3 to 7 days but further studies are recommended to determine the adequate period.

An important consideration in the choice of antibiotics should be local patterns of antibiotic resistance (130,131). The possibility of quinolone resistance is a particular concern in patients who have been receiving prophylactic norfloxacin for the prevention of spontaneous bacterial peritonitis. The American Association for the Study of Liver Diseases (118) recommends the following:

1- Short-term (usually seven days) antibiotic prophylaxis should be initiated in any patient with cirrhosis and GI hemorrhage. The guidelines suggest norfloxacin (400 mg twice daily) or intravenous ciprofloxacin (in patients in whom oral administration is not possible) as the recommended antibiotics. Alternatives include trimethoprim-sulfamethoxazole (one tablet twice daily) or ciprofloxacin (500 mg orally every 12 hours).

2- In patients with advanced liver cirrhosis, intravenous ceftriaxone (1 g/day) may be preferable, particularly in regions with a high prevalence of quinolone-resistant organisms.

1.2.9. Pharmacological Treatment

Vasoactive drugs, selectively constricting the mesenteric arterioles and decreasing portal blood flow, are used as initial treatment of AVB before endoscopy. Many

studies have demonstrated that the early use of vasoactive drugs reduces the rate of active bleeding, making endoscopy easier to perform both for diagnosis and therapy (119). These include vasopressin, somatostatin, and their analogs (terlipressin and octreotide, respectively). Improved hemostasis and reduced seven-day mortality, transfusion requirement, and duration of hospitalization have been confirmed in many studies (120).

The duration of treatment with vasoactive agents is not well defined. It has usually been recommended that it be maintained for 5 days to prevent early rebleeding episodes (60). However, a recent study showed similar efficacy when using terlipressin for 24 h or 72 h (121). Vasoactive agents should be used in combination with endoscopic therapy. In this setting of combined endoscopic and pharmacological treatment, a larger trial reported similar efficacy when using terlipressin, somatostatin, or octreotide (122).

Available evidence does not support a role for proton pump inhibitors (PPIs) for long-term prophylaxis of portal hypertension-related bleeding. However, the use of short-course PPI post-endoscopic variceal ligation may reduce post band-ligation ulcer size (123).

The use of an intravenous prokinetic agent (e.g., erythromycin) should be considered during the pre-endoscopy patient management phase. Barkun *et al*.

reported that an intravenous infusion of different prokinetic agents administered up to 2 h before endoscopy in patients with acute upper GI bleeding UGIB improved endoscopic visualization and significantly decreased the need for repeat endoscopy (124).

1.2.9.1. Timing of Endoscopic Hemostasis

Endoscopic treatment should be performed as soon as the patient with acute variceal bleeding gains hemodynamic stability. In a previous study that included 210 patients with acute variceal bleeding, performing endoscopic treatment at 4, 8, and 12 hours after arrival at the hospital did not significantly affect mortality rates (125). However, in another study, mortality rates significantly increased when endoscopic therapy was performed after more than 15 hours after hospital admission (126). It is recommended that endoscopic treatment should be performed within 12 hours of admission in patients with variceal bleeding (127). However, performance of emergency endoscopic treatment should depend on the patient's condition, conditions at the hospital, and the skills of the doctor. Vital signs and the volume of the hemorrhage as well as the presence of active bleeding (or not) should be considered. In patients who are vomiting bright red blood, those with increasing amount of hematochezia, or those who are hemodynamically unstable, endoscopic hemostasis should be achieved without any delay. However, it may be useful in selected environments to delay endoscopic treatment until a more skilled doctor can

perform the procedure in patients with stable vital signs, and if the patient is not considered to have signs of active bleeding (such as vomiting red blood), has not fasted long enough, or has shown no hematemesis or hematochezia within the last 12 hours (128).

1.2.9.2. Endoscopic Management of Acute Variceal Bleeding

Endoscopy is a cornerstone in the management of AVB because it confirms the diagnosis and allows for specific therapy to be applied during the same endoscopic session. An important consideration before doing endoscopy is choosing the nature of sedation for the procedure, as patients need to be adequately sedated in order to achieve a successful procedure. Intravenous sedation with propofol is a better tolerated option than benzodiazepines plus an opiate (such as meperidine or fentanyl) (129). However, in some countries, including Belgium, this type of sedation requires the presence of an anesthesiologist. Some studies recommend general anesthesia (GA) with intubation but this is very often difficult to implement in emergency settings.

There are two endoscopic methods available for AVB; endoscopic sclerotherapy and endoscopic band ligation as shown in Figures 3

1.2.9.2.1. Endoscopic Sclerotherapy (ES)

Endoscopic sclerotherapy was first described by Crafford and Frenckner in 1938 and involves the use of a rigid endoscope with the patient under general anesthesia (130). Currently, ES is performed by fiberoptic endoscopy using flexible catheters with a short needle tip (23 or 25 gauge). It is performed with the injection of a sclerosing agent, ethanolamine oleate [5%], sodium morrhuate [5%], or polidocanol [1%–2%] into the variceal lumen (intravariceal) or adjacent to it (paravariceal) with rapid thrombus formation and relatively good outcomes (131).

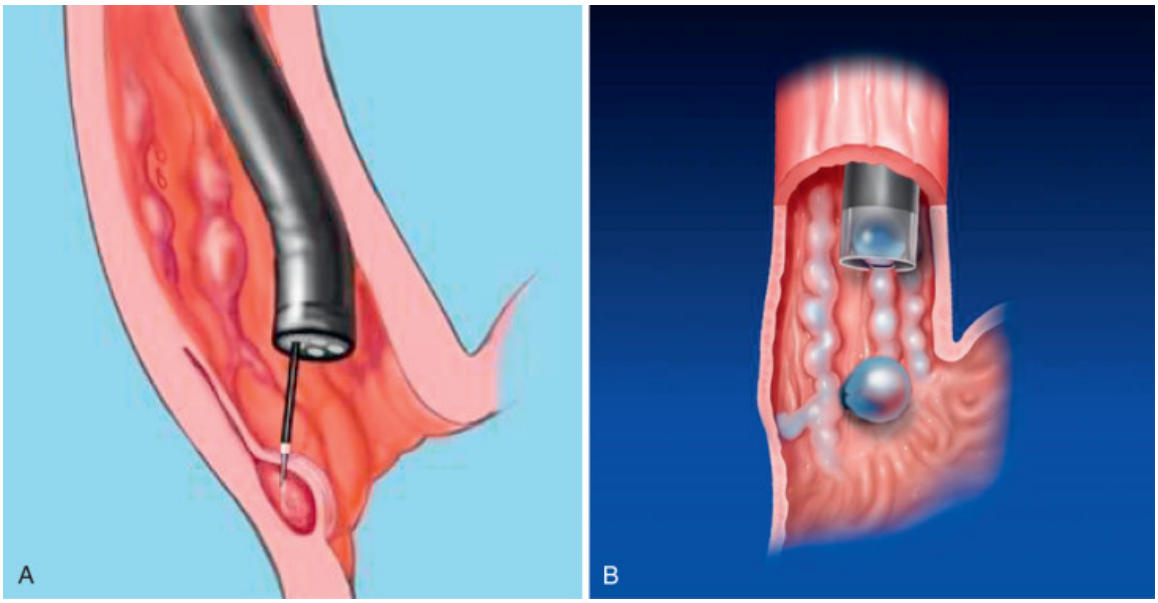

Figure 3 Two endoscopic methods used for the management of varices: A, sclerotherapy and B, band ligation (132).

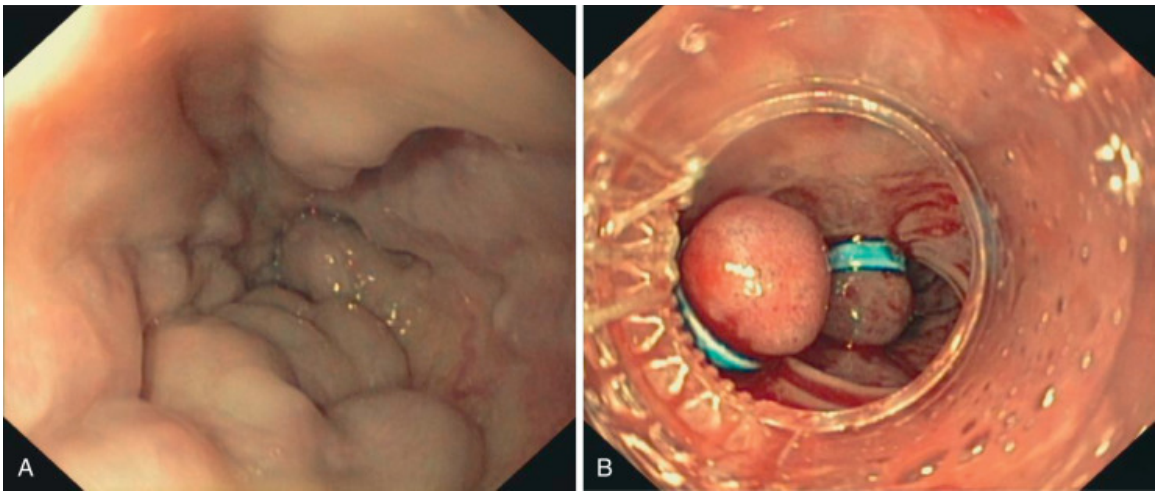

Figure 4 A, Endoscopic view of large varices. B, Endoscopic view of successfully placed bands in the distal esophagus (132).

Although ES is an easy and affordable technique (only an injection catheter and the sclerosant are needed) that can dramatically improve the outcomes of patients, it is associated with many local and systemic complications. These may include esophageal ulcers, strictures, substernal chest pain, fever, dysphagia, development of pleural effusions, increased risk of bacteremia (this can induce spontaneous bacterial peritonitis or distal abscesses), perforation, mediastinitis, pericarditis, chylothorax, and esophageal motility disorders (133-135).

1.2.9.2.2. Endoscopic Variceal Ligation (EVL)

Endoscopic variceal ligation was first described in 1988, and the procedure was developed as an alternative to ES for treatment of AVB (136). EVL requires placement of several elastic bands on the varices (range between 4 and 10) and

causes thrombosis. Ligation of the varix and the surrounding mucosa eventually leads to necrosis of the mucosa. The bands will fall off within a week and leave a shallow ulcer that heals, forming scars. Scheduled repeated sessions need to be performed at 3-4 week intervals after the index treatment of an episode of AVB to completely obliterate the varices and decrease the risk of rebleeding.

Starting the procedure with a 6-7 band device allows for enough bands to be applied in a single session. After the index diagnostic endoscopy is performed in a patient with AVB and the bleeding varix is identified, the endoscope is withdrawn, and the ligation device is loaded. After the bleeding point is identified, the tip of the scope is pushed toward it and continuous suction applied so the mucosa of the varix will fill the cap and causes a “red out” sign. Then the band can be fired, and a click is felt. The bands are applied in a spiral pattern starting at the gastro-esophageal junction and progressing up the esophagus until all major varices of the lower third of the esophagus are banded. Complications of variceal ligation include transient dysphagia and chest pain. These are common but respond well to oral analgesia and oral antacids. Esophageal ulcers are frequent, but seldom bleed. Other complications, such as massive bleeding from variceal rupture, esophageal strictures, and esophageal perforation are extremely rare (137).

Combining EVL and ES confers no advantage (138). Other techniques such as argon plasma coagulation APC, microwave cautery, and clipping also play no role, may be dangerous and must be avoided (139, 140).

1.2.9.3. Endoscopic Management of Bleeding Gastric Varices

Gastric varices (GV) are present in up to 20% of patients with portal hypertension, 65% of these patients experience a bleeding episode within 2 years (141). Intravascular injection of a thrombus-forming material is well established as the preferred endoscopic modality for treating GV bleeding. Although different alternatives exist, tissue adhesives, such as N-butyl-2-cyanoacrylate, remain the best documented endoscopic therapies. Cyanoacrylate requires certain technical skills and, in the context of a severe bleed and/or an uneasy patient, may complicate the procedure. However, proper technique and dosing of the glue injection are still controversial (142). Other techniques, such as thrombin variceal obliteration, have demonstrated promising small scale results but should be evaluated in larger trials before routine application (143).

1.2.9.4. Salvage Therapy after Failure of Endoscopic Hemostasis

In patients who are severely unstable or when endoscopic hemostasis fails, balloon tamponade, most often with a Sengstaken-Blakemore tube, offers another tool to stop bleeding with a success rate as high as 80% (127, 144, 145). However, this should only be used as a bridge therapy due to high re-bleeding rates.

1.2.10. Balloon Tamponade

The use of balloon tamponade is associated with multiple complications, most commonly aspiration pneumonia, rupture, necrosis or erosion of the esophagus (146). Balloon tamponade is a temporary procedure that may be used in hemodynamically unstable patients undergoing an endoscopic procedure, or in case of failure of endoscopic hemostasis (161). If hemostasis fails within 2 hours, another treatment modality should be considered immediately and, as complications such as migration or aspiration of the tube, or necrosis or perforation of the esophagus could occur, it should not be used for >24 hours. If hemostasis is achieved and the patient is stabilized after balloon tamponade, further treatment such as radiologic intervention or surgical treatment should be considered. Practically, with improvements in pharmacological therapy, balloon tamponade has been abandoned in most referral centers.

1.2.11. Self-Expandable Metal Stents

Self-expandable, covered, esophageal metal stents may be used as a substitute for balloon tamponade for managing refractory bleeding (68). They achieve hemostasis by direct compression of the varices. They can also be deployed in the lower esophagus without any radiological assistance (146). A recent study showed that stents were successfully deployed in 96.7% of patients, and hemostasis was achieved in 93.9% with no stent-related complications at the time of implantation

(147). Another study showed a success rate of 96% in achieving hemostasis within 24 hours, and successful deployment of the stent in 97% of patients (148). One small multicenter randomized trial compared the efficacy and complications of stents and balloon tamponade in 28 patients. It showed that esophageal stent placement was more successful than balloon tamponade in controlling bleeding. It also reported lower transfusion requirements and side effects, however, there was no significant difference in mortality at 6 weeks (149). Potential complications at the time of stent removal remain an unresolved issue

1.2.12. Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Another important modality is rescue TIPS in patients who fail standard therapy, in patients who have persistent severe bleeding, or those with early variceal rebleeding, especially in patients with more advanced liver disease (6).

Multiple RCTs have confirmed an improvement in survival in high-risk patients treated with TIPS, particularly for Child C score patients with a value of 10-13 or those with a Child B score with active bleeding at the time of endoscopy (6, 150).

The current Guidelines recommend TIPS placement in the following circumstances: either *rescue TIPS* in patients with persistent bleeding or early rebleeding despite treatment with vasoconstrictors plus EVL or *early (within 24h-72h) TIPS* to be considered in high-risk patients (Child C with score <14) without

specific contraindications to TIPS (143). However, one outstanding question is the availability of experienced teams that can perform emergency TIPS in such difficult conditions.

1.2.13. Potential Hemostatic Treatment Modality

1.2.13.1. Hemostatic Powders and Adhesives

Hemostatic powders have been initially developed for acute hemostasis in military settings. The powder becomes cohesive and adhesive when it encounters moisture (blood or tissue), forming a stable barrier at the surface of the bleeding site and inducing hemostasis. In addition, the powder enhances clot formation and shortens coagulation time (151).

There are three hemostatic powders currently available for endoscopic usage: hemostatic agent TC-325 (Hemospray™), EndoClot™ polysaccharide hemostatic system (PHS), and Ankaferd Bloodstopper® (ABS).

Hemostatic powder (Hemospray, Cook Medical, Winston-Salem, North Carolina, USA) has been the most widely evaluated in acute non variceal bleeding. It is delivered endoscopically through a dedicated delivery system forming an adherent layer and achieving very rapid hemostasis. After approximately 24 hours, the adherent layer subsequently sloughs off into the lumen from the mucosal wall and is eliminated from the GI tract (152-156).

This technique requires minimal experience in therapeutic endoscopy and could help to solve the problem of delays between admission and definitive endoscopic therapy due to the lack of available expertise.

This powder was initially licensed for endoscopic hemostasis of non-variceal upper GI bleeding including high-risk patients on anticoagulant or antithrombotic therapy, tumor-related bleeding, and lower GI bleeding. In severe peptic ulcer bleeding, it is often considered as a (temporary) salvage therapy (157-160). In case of severe arterial bleeding, it can temporarily stop the bleeding and help to stabilize the patient. However, a second look endoscopy within 24 hours is still recommended

Initially, hemostatic powder was not used in AVB due to the theoretical risk of gas embolization due to pressure gas delivery of the hemostatic agent to the bleeding site. However, this risk is most probably low due to the fact that the technique is a non-contact application with delivery pressure less than 15 mm Hg (i.e. most often lower than intra-variceal pressure)(161). For this reason, and considering that AVB is one of the emergent situations where early management is mandatory, we decided to evaluate powder hemostasis in variceal bleeding settings.

THE AIM OF THE STUDY

2. THE AIM OF THE STUDY

The aim of this research was to evaluate the safety and efficacy of hemostatic powder (Hemospray, Cook Medical, Winston-Salem, North Carolina, USA) added to standard of care (SOC) medical treatment for acute variceal bleeding (AVB) in patients with portal hypertension due to liver cirrhosis. This followed the usual path of clinical research, from a pilot study to a randomized controlled trial.

2.1. Assessing the **feasibility and safety** of the hemostatic powder in acute esophageal variceal bleeding, in the setting of a pilot study.

2.2. **Assessing the efficacy and safety** of the hemostatic powder in acute variceal bleeding in combination with SOC medical and endoscopic treatment in a prospective multicentric uncontrolled study.

2.3. Evaluating the **impact of the hemostatic powder as an add on** therapeutic modality in combination with SOC medical and endoscopic treatment compared to SOC alone. This was tested through a multicenter randomized controlled study.

2.4. The **use of hemospray in other complications of AVB** management or portal hypertension. These were more therapeutic opportunities identified while conducting these studies and reported as case reports.

THE RESEARCH STUDIES

4. THE RESEARCH STUDIES

4.1. Endoscopic Treatment of Acute Variceal Hemorrhage using Hemostatic Powder TC-325: A Prospective Pilot Study.

The first study was designed to assess the feasibility and safety of the hemostatic powder in AVB. The powder was used as an "Off Label" indication under an investigator-initiated protocol. In this study, we conducted a 2-center (Erasme Hospital – ULB, Brussels, Belgium and Theodor Bilharz Research Institute, Giza, Egypt) prospective trial to evaluate the feasibility and safety of this hemostatic powder, administered according to a simple and potentially less operator-dependent protocol in early control of acute esophageal variceal bleeding.

The study was approved by the ethics committees of Erasme University Hospital (B406201214760) and Theodor Bilharz Research Institute (TBRI-IRB01/13), and the study was registered at clinicaltrials.gov under the number NCT01783899.

Materials and Methods

Within 12 hours after admission in patients having a first episode of suspected AVB, the hemostatic powder was administered after standard of care (SOC) medical treatment protocol. Second endoscopy was performed within 24 hours after the initial application of hemostatic powder for definitive bleeding control and possible further endoscopic therapy.

Results

The first study included 14 patients with cirrhosis (13 hepatitis C virus (HCV) patients and 1 alcoholic patient) with a suspected first episode of AVB. Five patients were excluded from the trial (3 patients without acute bleeding and 2 patients with bleeding originating from duodenal varices). Only nine patients had confirmed AVB originating from the esophagus or the GE junction. One application of Hemospray was enough to achieve hemostasis in 8 patients, and one patient required a second Hemospray application because bleeding continued after the first application.

Follow-up endoscopy revealed that the hemostatic powder was eliminated from the upper GIT in all patients without any active bleeding observed. No clinical signs of embolization were observed and no other major adverse events such as bowel obstruction or allergic reaction were observed.

After the confirmation of the safety of the powder as well as the absence of the theoretical risk of embolization, the study group decided to move to the next phase of the research.

Endoscopic treatment of acute variceal hemorrhage by using hemostatic powder TC-325: a prospective pilot study

Mostafa Ibrahim, MD,[1,2] Ahmed El-Mikkawy, MD,[2] Ibrahim Mostafa, MD, PhD,[2] Jacques Devière, MD, PhD[1]

Brussels, Belgium; Cairo, Egypt

Background: Current standard of care of acute variceal bleeding (AVB) combines hemodynamic stabilization, antibiotic prophylaxis, pharmacological agents, and endoscopic treatment. The latter may be challenging in an emergency setting with active bleeding that interferes with visualization.

Objective: To assess the effectiveness of a pre-established delivery protocol of a hemostatic powder to control AVB originating from the esophagus or the gastroesophageal junction.

Design: Prospective, 2-center study.

Setting: Two tertiary-care referral university hospitals.

Patients: Nine patients who received endoscopic hemostatic powder for actively bleeding varices.

Interventions: Endoscopic hemostasis.

Main Outcome Measurement: Primary hemostasis and rebleeding rates.

Results: Nine consecutive patients with confirmed AVB underwent treatment within 12 hours of hospital admission. Bleeding stopped during the endoscopy performed with application of 21 g of hemostatic powder from the cardia up to 15 cm above the gastroesophageal junction. No rebleeding was observed in any of the patients within 24 hours. No mortality was observed at 15-day follow-up.

Limitations: Small sample size.

Conclusion: Hemostatic powder has the potential to temporarily stop AVB. (Clinical trial registration number: NCT01783899.)

Acute variceal bleeding (AVB) is a severe adverse event of portal hypertension in patients with liver cirrhosis. The primary therapy includes the administration of vasoactive drugs, antibiotics, and endoscopic therapy; esophageal banding ligation and/or cyanoacrylate injection when bleeding occurs from gastric varices is preferable.[1]

Although timely endoscopy (within 24 hours of admission) plays a central role in the management of AVB, it

Abbreviations: AVB, acute variceal bleeding; GE, gastroesophageal.

DISCLOSURE: *The authors disclosed no financial relationships relevant to this publication.*

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Current affiliations: Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium (1), Department of Gastroenterology and Hepatology, Theodor Bilharz Research Institute, Cairo, Egypt (2).

Reprint requests: Mostafa Ibrahim, MD, Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels 1070, Belgium.

If you would like to chat with an author of this article, you may contact Dr Ibrahim at mostafa.ibrahim@webgit.net

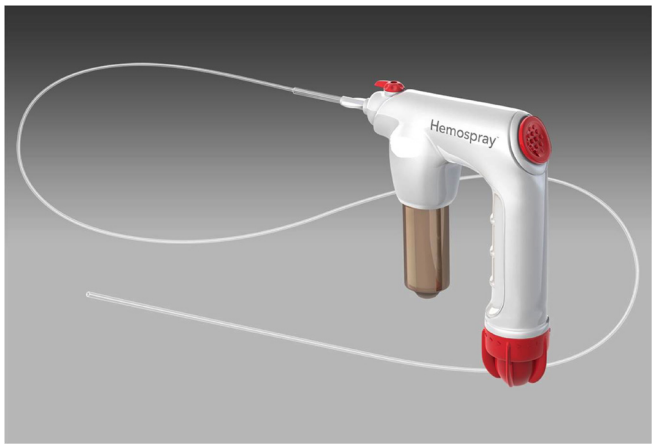

Figure 1. Hemospray Kit

cannot be offered at every center because of the lack of resources and limited access in expert endoscopy services.[2] Moreover, treatment may be technically challenging, and treatment failures are reported in 10% to 15% of the cases. This early phase of AVB management remains important, even when early transjugular intrahepatic portosystemic shunt placement is indicated.[3]

A hemostatic powder (Hemospray; Cook Medical, Winston-Salem, NC) (Fig. 1) was recently introduced for the management of nonvariceal upper GI bleeding and was shown to be effective in preliminary studies for the management of peptic ulcer bleeding[4] and cancer-related bleeding[5] and temporarily control bleeding in severe situations[6]; in addition, the use of Hemospray for salvage hemostasis in variceal bleeding was described in 2 previous case reports.[6,7]

We conducted a 2-center prospective trial to evaluate the use of this hemostatic powder, administered according to a simple and potentially less operator-dependent protocol in early control of acute esophageal variceal bleeding.

PATIENTS AND METHODS

Patients

Fourteen consecutive patients with known liver cirrhosis and suspected acute variceal bleeding originating from the esophagus up to the gastroesophageal (GE) junction consented to be included in the study. The ethics committees of Erasme University Hospital (B406201214760) and Theodor Bilharz Research Institute (TBRI-IRB01/13) approved the protocol, and the study was registered in clinicaltrials.gov under the number NCT01783899.

Take-home message

- Endoscopic treatment of acute variceal bleeding is still challenging in emergency situations.
- Hemostatic powder may have a role in controlling acute variceal bleeding, at least temporarily.

Hemostatic powder

TC-325 is a granular, mineral, nonabsorbable powder used for the management of arterial wounds. It produces hemostasis by increasing the concentration of clotting factors, activating platelets, and forming a mechanical plug on the injured blood vessel.[8] It appears to principally affect hemostasis through its ability to quickly absorb water, creating a physical barrier and a local lattice. It also alters clotting time in ex vivo study.[9]

When the powder comes into contact with moisture in the GI tract, it becomes cohesive and adhesive, forming a stable mechanical barrier that adheres to and covers the bleeding site to achieve hemostasis. As the powder is not absorbed or metabolized by mucosal tissue, there is no risk of systemic toxicity. The covering formed by the powder separates from the intestinal wall and is naturally eliminated from the GI tract.[4] Its delivery system consists of a syringe containing the Hemospray powder (21 g per syringe), a delivery catheter that is inserted into the working channel of the endoscope, and an introducer handle with a built-in CO_2 canister to propel the Hemospray powder out of the catheter.

Endoscopic procedure

All endoscopies were performed within 12 hours after admission in patients having a first episode of suspected variceal bleeding. All patients had confirmed AVB characterized by actively bleeding varices or fibrin plugs and/or red streaks of the mucosa overlying the varices with the presence of fresh blood within the lumen of the esophagus and the stomach.

After identification of a bleeding site located in the esophagus or at the GE junction, the hemostatic powder was administered after a standard protocol, the catheter being located at the level of the cardia and the powder being delivered (21 g per syringe) by a noncontact delivery approach, over the distal 15 cm of the esophagus (ie, always avoiding application within the proximal 5 cm of the esophagus), while slowly pulling back the endoscope (Fig. 2; Video, available online at www.giejournal.org).

Hemospray was then delivered in short spray bursts (for 1–2 seconds) until hemostasis was confirmed. Once bleeding was controlled (first application), the bleeding site was observed for 3 minutes under endoscopy. If bleeding recurred during this 3-minute

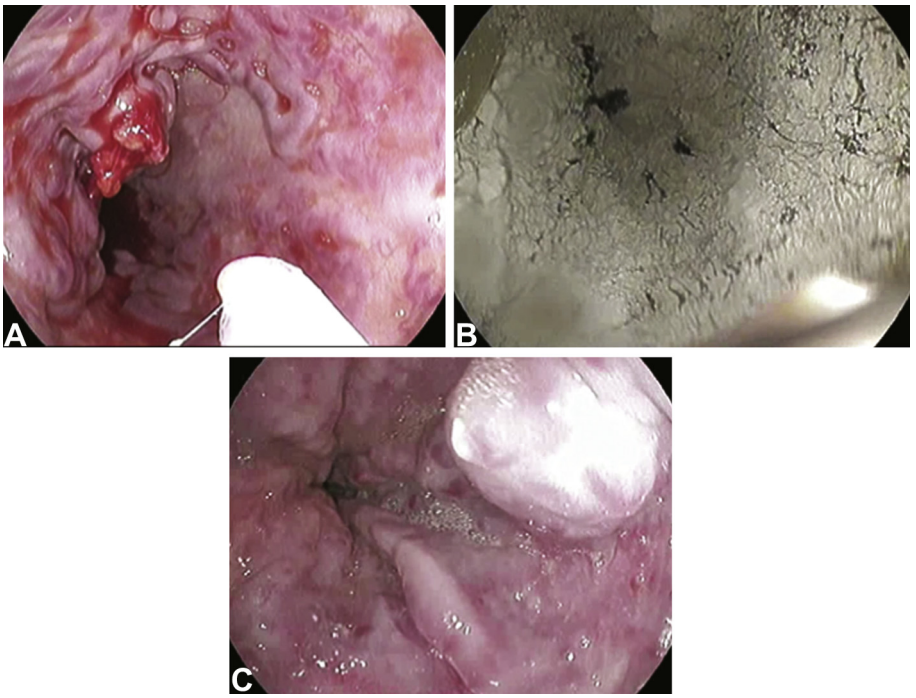

Figure 2. Representative images of treatment of acute variceal bleeding with hemostatic powder and at 24 hours post-procedure endoscopy. **A**, Bleeding esophageal varices before application of hemostatic powder. **B**, Appearance after application. **C**, follow-up at 24 hours.

observation period, Hemospray was reapplied until hemostasis was achieved again (second application). In case of catheter blockage, manual injection of air was done to "flush the plug," or, if that was not possible, the distal tip of the catheter where blockage always occurs was cut before reinsertion.

The bleeding site was again observed for 3 minutes. If bleeding recurred a second time, this would have been considered to be an acute treatment failure, and the patient would have been treated with the institution's standard of care.

Recurrent bleeding occurring within 24 hours after Hemospray application would have been considered a late treatment failure.

All patients were kept under surveillance and monitored for 24 hours, with continuous infusion of somatostatin and the institution's standard of care.

A second endoscopy was performed within 24 hours after the initial application of hemostatic powder for bleeding control and possible further endoscopic therapy (Fig. 2).

RESULTS

Between January 2013 and March 2013, 14 patients with cirrhosis (13 patients after hepatitis C and 1 alcoholic patient) and a suspected first episode of AVB provided consent. Five were excluded (3 patients without acute bleeding and 2 patients with bleeding originating from duodenal varices) and 9 had confirmed AVB originating from the esophagus or the GE junction. Patient characteristics are summarized in Table 1. Endoscopy was performed with patients under sedation without endotracheal intubation. Endoscopic application of the powder allowed hemodynamic stabilization in all of patients, and no clinical sign of ongoing overt bleeding was observed over the next 24 hours.

One application was sufficient to achieve hemostasis in 8 patients, whereas only 1 patient required a second application because bleeding continued after the first application.

At follow-up endoscopy, hemostatic powder was eliminated from the upper GI tract in all patients, and no active bleeding was observed. No clinical signs of embolization were observed and no other major adverse events (eg, bowel obstruction, allergic reaction) were observed. No mortality was reported for all patients over 15 days of follow-up. An elective band ligation was performed in every patient at the time of the second endoscopy, without any interference from previous treatment. The index-bleeding site was identified or suspected in 4 patients.

DISCUSSION

The current series shows that in cases of acute esophageal variceal bleeding, the endoscopic application of a hemostatic powder after a protocol requiring minimal

TABLE 1. Patient characteristics and procedure details

SN	Age, y	Sex	Child-Pugh class	Presentation*	Blood transfusion before Hemospray	Blood transfusion after Hemospray
1	73	M	B	Hematemesis	No	Yes, 1 U‡
2	65	M	B	Hematemesis	No	Yes, 1 U‡
3	67	M	B	Hematemesis	No	Yes, 1 U‡
4	61	M	C	Hematemesis and melena	No	Yes, 2 U‡
5	64	F	C	Hematemesis	Yes, 3 U Whole Blood	Yes, 4 U‡
6	65	M	C	Hematemesis and melena	Yes, 1 U Whole Blood	Yes, 1 U‡
7	61	M	C	Hematemesis	No	Yes, 1 U‡
8	58	F	B	Hematemesis and melena	No	Yes, 1 U‡
9	41	M	C	Hematemesis	No	Yes, 2 U‖

(*Table continued on page 773*)

Hb, Hemoglobin; *M*, male; *F*, female.
*Clinical presentation of the patient at the emergency department.
†Severe, actively bleeding varices or torrential bleeding; mild, fibrin plugs and/or red streaks of the mucosa with the presence of fresh blood within the lumen of the esophagus and the stomach.
‡Unit of whole blood is 450 mL.
§Blood sampling was performed before the onset of overt bleeding.
‖Unit of packed red blood cells is 250 mL.

expertise allows the bleeding to stop, the patient to stabilize, and additional therapy to be performed, if needed, under optimal conditions within the next 24 hours. Early management of AVB with hemostatic powder might therefore avoid failures or delay of acute hemostasis related to technical failures or to the lack of expert endoscopists available to perform advanced procedures.

The risk of embolization in this group of patients is most probably low or negligible because of the fact that the technique described uses a noncontact application with a delivery pressure less than 15 mm Hg (Cook Medical, press communication, 2012), ie, most often less than intravariceal pressure. It must be noted, however, that the use of Hemospray in our series was off-label and should be used only in research protocols having institution review board approval.

Early hemostasis might prevent the onset of further adverse effects related to hemodynamic support and/or transfusion in these patients. This simple technique might be considered and should be investigated as a bridge to further therapy, the latter being either early transjugular intrahepatic portosystemic shunt placement in patients who meet the criteria (Child-Pugh class B or C with a score ranging from 7 to 13) or further band ligation for variceal eradication (Child-Pugh class A or C with a score of ≥ 13).[3] Although the current study was obviously not designed for testing this hypothesis, an interesting area of investigation would be identifying those patients who could benefit from nonendoscopic band ligation–associated hemostasis for the management of AVB or from secondary prophylaxis.

Our study has several limitations, namely, a small number of patients and a nonrandomized design. However, to the best of our knowledge, this is the first pilot study assessing the use of hemostatic powder in AVB.

In summary, hemostatic powder appeared to be effective in controlling, at least temporarily, AVB in this series of patients. This of course does not imply that this technique should be currently used as primary therapy for AVB. Further studies, preferably randomized, controlled trials, are required to determine its role and effectiveness in AVB management, either primarily or as a rescue therapy in patients with failed hemostasis or in those with severe bleeding, and its potential impact on patient outcome.

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TABLE 1. Continued

Hb before Hemospray (within 12 h), g/dL	Hb 6 h post-Hemospray, g/dL	Blood pressure before Hemospray (systolic/diastolic)	Blood pressure 6 h post-Hemospray (systolic/diastolic)	Bleeding severity†	No. of Hemospray applications
6.9	7.5	120/80	130/80	Mild	1
8.2	8.6	70/40	110/60	Mild	1
11.2§	8.1	110/70	100/60	Severe	1
11.9§	6.4	70/30	80/50	Severe	1
3.5	6.5	70/30	90/50	Severe	2
6.2	8.1	90/60	110/70	Mild	1
6.6	7.6	90/50	100/60	Mild	1
6.9	7.9	110/60	120/60	Mild	1
7.7	8.9	100/50	120/60	Mild	1

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4.2. Management of Acute Variceal Bleeding using Hemostatic Powder.

The second study was designed to assess the efficacy of the powder as well as to confirm its safety profile.

Background and Aim of the Study:

In this study, we conducted a prospective bicentric single arm study, at Erasme Hospital – ULB, Brussels, Belgium and Theodor Bilharz Research Institute, Giza, Egypt, to confirm the results of the first study and to assess the effectiveness of Hemospray application for emergency control of variceal upper GI bleeding in esophageal varices, gastric varices, and ectopic varices.

Materials and Methods

Patients with AVB after urgent medical hemodynamic stabilization and within twelve hours of admission were included. The first endoscopy was performed to confirm active variceal bleeding and to deliver the hemostatic powder. Patients were followed until the second definitive endoscopy (definitive therapy) was performed after 24 hours.

The study protocol was approved by the ethics committees of Erasme University Hospital, ULB, Brussels, Belgium, (B406201214760) and Theodor Bilharz Research Institute, Giza, Egypt (TBRI-IRB01/13). The study was registered with ClinicalTrials.gov under number NCT01783899.

Results

This study included 38 patients with known liver cirrhosis with AVB. Eight patients were excluded from the trial because the cause of their bleeding was determined not to be variceal. Spurting bleeding and acute bleeding were observed in 43.4% and 56.6%, respectively. Immediate hemostasis after the application of the hemostatic powder was achieved in all patients at the time of application with no clinical signs of embolization or other major adverse event. Clinical hemostasis was achieved in 29/30 (96.7%) patients. Only one patient experienced hematemesis six hours after Hemospray application and was treated by emergency endoscopy and band ligation. Follow-up endoscopy showed that the hemostatic powder was completely removed from the upper GIT in 28/30 (93.4%) patients and endoscopic hemostasis was achieved in all patients. An elective band ligation was performed in patients with esophageal varices and cyanoacrylate injection in patients with gastric varices and duodenal varices.

Based on the findings from this study, the research group concluded that early hemostasis with a simple technique in clinically challenging patients might render definitive treatment more effectively and reduce early hemodynamic instability with potential prevention of mental deterioration and liver ischemia. Therefore, the

study group decided to enter the next research phase and to independently investigate the added effect of the powder compared to SOC alone.

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Management of acute variceal bleeding using hemostatic powder

Mostafa Ibrahim[1,2], Ahmed El-Mikkawy[2], Haitham Abdalla[2], Ibrahim Mostafa[2] and Jacques Devière[1]

Abstract

Background and objectives: This study aimed to test the safety and efficacy of Hemospray® for emergency control of acute variceal bleeding (AVB) due to portal hypertension in cirrhotic patients.

Patients and methods: This single-arm, prospective trial, conducted at two hospitals in Belgium and Egypt, included patients admitted to the emergency room with hematemesis and/or melena and known or suspected liver cirrhosis. All patients received urgent hemodynamic stabilization, octreotide (50 mcg bolus then 25 mcg/hour for 24 hours) and intravenous ceftriaxone (1 g/hour). Endoscopy to confirm AVB and Hemospray® application (if indicated) was performed within six hours of admission. Patients were kept under observation for 24 hours and underwent second endoscopy and definitive therapy (band ligation and/or cyanoacrylate injection in cases of gastric varices) the next day.

Results: Thirty-eight patients were admitted for suspected AVB, and 30 of these had confirmed AVB (70% male; mean age 59.5 years (range, 32.0–73 years)). Child-Pugh class C liver disease was present in 53.4%. Esophageal varices were observed in 83.4% of patients, gastric varices in 10%, and duodenal varices in 6.6%. Spurting bleeding at the time of endoscopy was observed in 43.4%. One patient developed hematemesis six hours after Hemospray® application and underwent emergency endoscopic band ligation. No major adverse events or mortalities were observed during 15-day follow-up.

Conclusion: Hemospray® application was safe and effective at short-term follow-up for emergency treatment of AVB in cirrhotic patients.

Keywords

Variceal bleeding, hemostatic powder, portal hypertension

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Introduction

Portal hypertension is a typical feature of liver cirrhosis. Esophageal varices are present in 30% to 60% of cirrhotic patients and variceal bleeding is a severe complication of portal hypertension.[1] Associated mortality related to acute variceal bleeding (AVB) is reported to be 20% within the first six weeks and rebleeding from varices occurs in 60% of patients within one year after the first acute episode.[2]

Treatment of AVB, which has been clearly shown to positively influence outcomes, includes restricted transfusion (with a threshold hemoglobin level of 7–8 g/dl),[3] vasoactive drugs, antibiotics, and endoscopic therapy.[4,5] The latter consists of variceal band ligation of esophageal varices and obturation of gastric varices with cyanoacrylate injection.[6,7]

Early treatment is universally recommended and is considered to be mandatory within 24 hours of admission. Better outcomes are reported in those patients who receive endoscopic therapy within 12 hours.[5] Although this is still a matter of debate, it seems reasonable that the earlier the bleeding is stopped, the better the expected outcome.[8,9] This is, however, not always possible in daily practice, both because of the

[1]Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
[2]Department of Gastroenterology and Hepatology, Theodor Bilharz Research Institute, Cairo, Egypt

Corresponding author:
Mostafa Ibrahim, Department of Gastroenterology, Erasme Hospital, University Libre de Bruxelles, 808 Route De Lennik B 1070, Brussels, Belgium.
Email: mostafa.ibrahim@webgit.net

lack of treatment capabilities available in every center in an emergency setting, and due to the fact that endoscopic therapy in acute bleeding is technically demanding and not always successful.[10]

Hemospray® (COOK Endoscopy, Winston Salem, NC, USA) is a novel hemostatic powder licensed for endoscopic hemostasis of non-variceal upper gastrointestinal (GI) bleeding that has been shown to be effective in preliminary studies for the management of patients with peptic ulcer bleeding,[11] including those on anticoagulant or antithrombotic therapy.[12] Recently, two case reports[13,14] and a pilot study that included the first nine patients of this series[15] reported that hemostatic powder may be useful in emergency management of variceal bleeding as a bridge toward more definitive therapy. The major advantage of such treatment, particularly in the case of esophageal variceal bleeding, is that its application does not require technical expertise in therapeutic endoscopy since the powder is delivered in a pre-established manner from the cardia to the mid-third of the esophagus during withdrawal of the scope.[15] In order to confirm the published preliminary results and to assess the effectiveness of the powder in spurting esophageal varices, gastric varices and ectopic varices, we conducted a prospective multicenter study that evaluated the safety and effectiveness of Hemospray® application for emergency control of variceal upper GI bleeding.

Patients and methods

Ethics

The ethics committees of Erasme University Hospital, ULB, Brussels, Belgium, (B406201214760) and Theodor Bilharz Research Institute, Giza, Egypt (TBRI-IRB01/13), approved the protocol and the study was registered with Clinical-Trials.gov under number NCT01783899. All patients signed informed consent before inclusion.

Aim of the study

This prospective, bicentric, single-arm study was designed to evaluate the safety and efficacy of Hemospray® for achieving short-term hemostasis in patients presenting with AVB.

The primary outcomes of the study were the following:

a. The efficacy of Hemospray®, that is, endoscopic hemostasis, was defined as the absence of fresh hematemesis less than two hours after the application of the hemostatic powder and the absence of hemoglobin drop more than 3 g/dl in absence of blood transfusion, and clinical hemostasis, defined as the absence of a single episode of clinically significant rebleeding within the following 24 hours after Hemospray® application.

All patients were followed up throughout the period of the acute bleeding episode (five days)[5] while intravenous infusion of octreotide was administered only for 24 hours after powder application because all patients have a second endoscopy and definitive treatment within the next 24 hours. Rebleeding at five days and survival at 15 days were also recorded.

b. Safety was defined as the incidence of procedure- and treatment-related serious adverse events.

The hypothesis of the study was that the combination of Hemospray® with medical treatment in patients with proven ABV would allow for control of variceal bleeding in more than 90% of cases during the 24 hours following its application.

Patients

Eligible patients were older than 18 years of age, and must have had endoscopic confirmation of AVB defined as either active bleeding or fresh blood in the stomach with red signs on the varices, and no other identified cause of bleeding.[16] Exclusion criteria included: (a) non-variceal bleeding at the time of endoscopy, (b) inability to consent, (c) contraindication to undergo endoscopy, (d) already hospitalized for another illness, (e) pregnant or lactating, (f) patients with altered post-surgical anatomy of the stomach, (g) previously placed intrahepatic portosystemic shunt and (h) patients treated by other endoscopic or surgical modalities within 30 days prior to the intended application of Hemospray®.

Study design

Patients admitted to the emergency room with hematemesis and/or melena with known or suspected liver cirrhosis were included. Urgent hemodynamic stabilization was performed and patients received octreotide (50 mcg bolus at admission then 25 mcg/hour for a period of 24 hours only) and intravenous ceftriaxone (1 g/24 hours). Within six hours of admission, endoscopy was performed in every patient to confirm active variceal bleeding and then to apply the Hemospray®.

Following endoscopy, patients were kept under surveillance for 24 hours and another endoscopy with "definitive therapy" was performed the next day. This therapy consisted of band ligation and/or cyanoacrylate injection in cases of gastric varices, as previously described.[17,18]

Description of the device

The device used for powder application (Figure 1) consisted of an application catheter, which was passed through the working channel of a therapeutic gastroscope, a chamber containing approximately 21 g of powder, and a propellant CO_2 canister. Hemostatic powder (TC-325) is a granular, mineral non-absorbable powder that produces hemostasis by increasing the concentration of clotting factors, activating platelets, and forming a mechanical plug on the injured blood vessel.[19] When the powder comes into contact with moisture in the GI tract, it becomes cohesive and adhesive, forming a stable mechanical barrier that adheres to and covers the bleeding site. As the powder is not absorbed or metabolized by mucosal tissue, there is no risk of systemic toxicity. The covering formed by the powder separates from the intestinal wall and is naturally eliminated from the GI tract.[11]

Endoscopic technique

After confirmation of AVB (actively bleeding varices or fibrin plugs and/or red streaks of the mucosa overlying the varices with presence of fresh blood within the lumen), a bleeding site was identified that encompassed the definitive or most probable source (esophageal, gastric, or duodenal varices). The hemostatic powder was then administered diffusely to cover the mucosa over the bleeding varices in order to obtain immediate endoscopic hemostasis.

For esophageal varices, the protocol for application was simplified further, and consisted of positioning the catheter at the level of the cardia in the center of the lumen and applying the powder continuously while pulling the endoscope backward over the 12–15 distal cm of the esophagus. Once bleeding was controlled (first application), the bleeding site was observed for three minutes under endoscopy. If bleeding recurred during this three-minute observation period, Hemospray® was reapplied until hemostasis was achieved (second application). All patients were kept under surveillance and monitored for 24 hours, with continuous infusion of octreotide (25 mcg/hour for a period of 24 hours) and institutional standard of care.

A second endoscopy was performed the next day following initial therapy with hemostatic powder for control and definitive endoscopic therapy.

Data analysis

Analysis was performed using SPSS 20.0.0 (SPSS Inc, Chicago, IL, USA). In the event of missing data values, data were not replaced. Data were expressed as percentages, means ± SD, or medians and ranges, as appropriate.

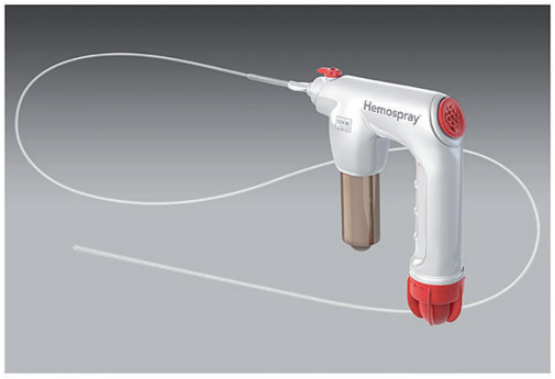

Figure 1. Hemospray® device.

Results

Thirty-eight consecutive patients with known liver cirrhosis and suspected AVB were included in the study. Eight patients were excluded because the cause of their bleeding was determined not to be variceal (Figure 2).

The median age of the 30 patients with AVB was 59.5 years (range, 32.0–73 years) and there were 21 males (70%). The cause of cirrhosis was post-hepatitis C in all patients, and 16 patients (53.4%) had Child-Pugh's classification C disease. Baseline demographics of patients are summarized in Table 1.

Endoscopic procedure and follow-up

Endoscopy was performed under sedation without endotracheal intubation. Bleeding originated from esophageal varices in 83.4%, from gastric varices in 10%, and from duodenal varices in 6.6%. Spurting bleeding, defined as actively bleeding varices at the time of endoscopy, was observed in 13/30 (43.4%) and acute bleeding, defined as presence fibrin plugs and/or red streaks of the mucosa overlying the varices with presence of fresh blood within the lumen, in 17/30 (56.6%).

Primary endoscopic hemostasis, defined as immediate hemostasis after the application of the powder, was achieved in all patients at the time of Hemospray® application using one device in 29 patients and two devices in one patient. All patients were O_2 saturation-monitored for 24 hours with no clinical signs of pulmonary embolism observed. Clinical hemostasis, as defined above, was achieved in 29/30 (96.7%) patients during the next 24 hours after powder application. One patient experienced hematemesis six hours after Hemospray® application and was treated by emergency endoscopy and band ligation for actively bleeding esophageal varices. At follow-up endoscopy,

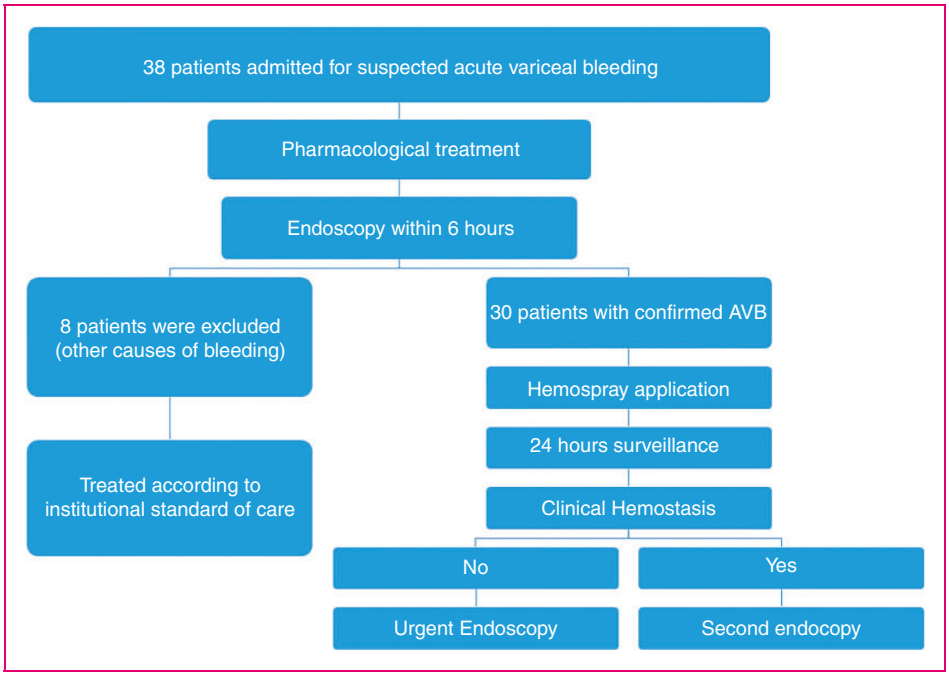

Figure 2. A flowchart describing the study design and procedures. AVB: acute variceal bleeding.

hemostatic powder was completely eliminated from the upper GI tract in 28/30 (93.4%) patients and endoscopic hemostasis was achieved in all patients. Clinical characteristics are summarized in Table 2. No major adverse events (e.g. embolization, bowel obstruction, allergic reaction) were observed. Although all patients were treated with sedation without endotracheal intubation, no patients experienced inhalation pneumonia mainly because we always stop powder spray at least 5 cm below upper esophageal sphincter. No mortalities were reported during 15 days' follow-up.

An elective band ligation was performed in patients with esophageal varices and cyanoacrylate injection in patients with gastric varices at the time of second endoscopy, while both patients with duodenal varices were treated with beta blockers and were followed up for three months without further bleeding.

Table 1. Baseline demographics of patients

Age (year)	59.5 (32.0–73)
Sex (M/F)	21 (70%)/9 (30%)
Child-Pugh's classification (CHILD A/CHILD B/CHILD C)	2 (6.7%)/12 (40%)/16 (53.4%)
Clinical presentation at admission	Hematemesis: 16 (53.4%) Melena: 6 (20%) Hematemesis and melena: 8 (26.6%)

[a]Data are presented as medians for continuous variables and as numbers (percentages) for categorical variables. M: male; F: female.

Discussion

This prospective study shows that in cases of AVB, the endoscopic application of a hemostatic powder provides control of bleeding and stabilization of patients for the initial 24 hours, and changes their condition from an acute situation to an elective one that allows additional definitive therapy to be performed under optimal, non-emergency conditions.

Consensus guidelines[5] recommend that patients with ABV undergo endoscopic therapy within 12 hours of admission. The time from initial presentation to endoscopy and severity of underlying liver disease are predictors of rebleeding. [20] In patients presenting with hematemesis, six-week rebleeding and mortality rates are lower in patients undergoing endoscopic therapy within 12 hours of admission than in those for whom it is more delayed.[20]

In daily practice, however, the picture is different and delays in performing endoscopy occur, often because of the lack of available expert endoscopists able to manage upper GI bleeding. A recent United Kingdom survey[21] reported that a very low rate (55%) of endoscopies were performed within 24 hours of admission and that standard endoscopic therapy was underused, particularly in AVB.

Table 2. Hemodynamics profile of all patients before and after therapy

Patients	Blood transfusion before Hemospray®	Blood transfusion after Hemospray®	Hemoglobin before Hemospray® (within 12 hours) (g/dl)	Hemoglobin six hours post-Hemospray® (g/dl)	Blood pressure before Hemospray® (systolic/diastolic)	Blood pressure six hours post-Hemospray® (systolic/diastolic)
1	No	Yes (1 unit)[a]	6.9	7.5	120/80	130/80
2	No	Yes (1 unit)[a]	8.2	8.6	70/40	110/60
3	No	Yes (1 unit)[a]	11.2[c]	8.1	110/70	100/60
4	No	Yes (2 units)[a]	11.9[c]	6.4	70/30	80/50
5	Yes (3 units)	Yes (4 units)[a]	3.5	6.5	70/30	90/50
6	Yes (1 unit)	Yes (1 unit)[a]	6.2	8.1	90/60	110/70
7	No	Yes (1 unit)[a]	6.6	7.6	90/50	100/60
8	No	Yes (1 unit)[a]	6.9	7.9	110/60	120/60
9	No	Yes (2 units)[b]	7.7	8.9	100/50	120/60
10	No	No	9.8	9	110/70	100/60
11	No	No	8.3	7.9	110/70	120/80
12	Yes (1 unit)[a]	Yes (2 unit)	4.7	5.2	90/60	110/70
13	No	Yes (3 units)	7.9	9.6	90/60	130/90
14	No	Yes (1 unit)	5	5.8	110/70	110/70
15	No	Yes (1 unit)[a]	8.9	9.6	90/60	130/90
16	No	Yes (1 unit)[a]	10	8.4	100/60	110/70
17	No	Yes (1 unit)	6.0	7.5	150/100	120/70
18	No	No	11.6	11.5	110/70	110/80
19	No	No	11.0	11.1	110/70	110/70
20[d]	No	Yes	8.0	NA	NA	NA
21	No	Yes (2 units)	9.2	8.2	90/60	110/70
22	No	Yes (2 units)	9.0	10.2	120/80	120/60
23	No	No	10.1	9.1	110/60	110/70
24	No	No	10.7	10.3	110/70	110/70
25	No	No	11.5	8.9	80/50	110/70
26	No	No	11.2	11	130/100	130/80
27	Yes (1 unit)	No	7.1	8.2	110/70	110/70
28	Yes (2 units)	No	5.4	7.5	100/60	120/70
29	No	No	8.1	8.8	80/50	90/60
30	No	No	8.5	8.6	110/70	110/60

[a]Unit of whole blood is 450 ml. [b]Unit of packed red blood cells is 250 ml. [c]Blood sampling was performed before the onset of overt bleeding. [d]Patient number 20: The patient who experienced hematemesis after six hours of Hemospray® application.

Development of a technique that allows physicians to obtain immediate hemostasis, that can be performed by any endoscopist, and does not require expertise in management of upper GI bleeding is therefore of major interest for its potential impact on the treatment and outcome of patients with ABV in daily practice.

This is even more vital in patients admitted with hematemesis in whom the importance of early endoscopy is paramount.[22] Indeed, risk factors for in-hospital mortality in patients with AVB not only include delayed endoscopy but also failure of first endoscopy, hematemesis, and severity of cirrhosis. If the application of hemostatic powder, through its simplicity, could reduce the proportion of delayed endoscopies, it would compare favorably with the best series reported to date[23] in terms of immediate hemostasis and failure to control bleeding. When comparing our results with those obtained by tertiary referral centers,[23] which used a combination of drug therapy and banding, our 100% rate of immediate control of bleeding and 3.3% rate of clinical failure over 24 hours suggests that, despite its simplicity, powder application might equalize the results of immediate hemostasis and offer an option in every center for patients to be treated later, once their condition has stabilized, by the most experienced endoscopist.

Recently, transjugular intrahepatic portosystemic shunt (TIPS) has been recommended in the early management of AVB, especially in patients with Child-Pugh class C cirrhosis or those with Child-Pugh C disease and persistent bleeding after endoscopy.[24] This requires availability of a TIPS procedure within 72 hours of admission and is not available in one of the centers that participated in this study. Moreover, when applied to patient populations where endemic AVB has been observed, such as the Middle East, there are currently no available resources to offer this treatment to every patient in whom it could be potentially indicated. However, even in optimal conditions, TIPS placement is associated with less morbidity in hemodynamically stable patients[25] and a technique that would allow centers to ensure that active bleeding has been controlled in every patient prior to undergoing TIPS is of major interest. In addition, the results we observed in our patients with Child-Pugh class C cirrhosis (92% hemostasis at 24 hours and a therapeutic failure rate similar to class B and A patients) may suggest that generalization of the use of hemostatic powder could provide a window that would allow clinicians more time in which to decide about mid- and long-term management of variceal bleeding and its impact on secondary prophylaxis.

Bleeding from duodenal varices is a rare presentation of portal hypertension that accounts for less than 3% of variceal bleeding and was observed in two cases in the current series. The treatment strategies currently used to control duodenal variceal bleeding are all either technically demanding or associated with procedure-related severe complications. Endoscopic obliteration using cyanoacrylate injection is an effective first-line treatment[26] but carries a major risk of portal or systemic embolization.[27] Endoscopic variceal band ligation is technically difficult in the duodenum and can cause severe ulcerations.[28,29] Hemospray® could play a role in this instance as a bridge to secondary prophylaxis consisting of β-blockers or TIPS according to the severity of underlying liver disease.

Hemospray® is currently not approved for routine management of AVB since a theoretical concern is that its application with a CO_2 cartridge delivers the powder at the end of the catheter with an outflow pressure of 15 mmHg that might be associated with a risk, never observed in the current and previous studies, of venous thromboembolization. This is, however, highly improbable since, by definition, Hemospray® is a noncontact method and, in the case of esophageal or esogastric variceal bleeding, it is delivered with the catheter positioned in the center of the lumen and pulled backward, making the risk of impact with a millimeter-sized bleeding site almost null.

In conclusion, management of AVB using hemostatic powder is feasible and safe. It offers immediate hemostasis using a simple, minimally operator-dependent technique in all cases and clinical and endoscopic hemostasis in >95% of cases until the next day. Further studies comparing strategies involving powder hemostasis are needed to confirm whether this technique might affect the paradigm of AVB management.

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Conflict of interest

None declared.

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Ibrahim Mostafa was responsible for study supervision.

Jacques Devière was responsible for study design, interpretation of data, statistical analysis and study supervision.

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4.3. Early Application of Hemostatic Powder Added to Standard Management for Esophagogastric Variceal Bleeding. A Randomized Trial.

This study was designed to determine whether a new approach to AVB, namely the addition of an early and easy-to-perform treatment with hemostatic powder to classical medical standard of care, as a bridge therapy before definitive treatment can improve outcomes in patients presenting with liver cirrhosis and a first episode of severe AVB. The study was not powered to assess differences in mortality.

Materials and Methods

The study protocol was registered at Clinicaltrials.gov under the number NCT03061604.

Patients with endoscopic confirmation of AVB were included and randomized either to the study group: Hemospray application during an immediate endoscopy within 2 hours with application of Hemospray in all cases, followed by early elective endoscopy within 12–24 hours, or control group: only medical therapy on admission, followed by early elective endoscopy within 12–24 hours.

Results

The present study included 105 patients with cirrhosis with acute hematemesis with a suspected first episode of AVB. A total of 19 patients were excluded at the time

of endoscopy due to non-variceal causes. A total of 86 patients had confirmed AVB and were randomly assigned to either the standard of care group (43 patients) or the powder group (43 patients). In the powder group, 5/43 required urgent endoscopy for uncontrolled spurting bleeding (n=4) after powder application or for early bleeding recurrence in one patient who died before repeating emergency endoscopy. In the control group, 13/43 patients required urgent hemostasis for failure of clinical hemostasis (12% vs. 30%, p=0.034). In the remaining patients, early, elective endoscopic hemostasis was achieved in all 38 patients in the study group, while all of the remaining 30 patients in the control group had fresh gastric blood or spurting bleeding (10%) at elective endoscopy with successful hemostasis in all patients. Even though the study was not powered to assess mortality, six-week survival was significantly improved in the study group (7% vs 30%, p=0.006).

OPEN ACCESS

ORIGINAL ARTICLE

Early application of haemostatic powder added to standard management for oesophagogastric variceal bleeding: a randomised trial

Mostafa Ibrahim,[1,2] Ahmed El-Mikkawy,[2] Mohamed Abdel Hamid,[2] Haitham Abdalla,[2] Arnaud Lemmers,[1] Ibrahim Mostafa,[2] Jacques Devière[1]

[1]Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
[2]Theodor Bilharz Research Institute, Department of Gastroenterology and Hepatology, Cairo, Egypt

Correspondence to
Dr Mostafa Ibrahim, Department of Gastroenterology, Erasme Hospital, University Libre de Bruxelles, Brussels 1070, Belgium; mostafa.ibrahim@webgit.net

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ABSTRACT

Background Acute variceal bleeding (AVB) requires early therapeutic management by experienced endoscopists that often poses logistical challenges for hospitals. We assessed a different management concept with early application of haemostatic powder—which does not require high endoscopic expertise—added to conventional management in a randomised trial.

Methods Cirrhotic patients with AVB received standard medical therapy and were randomised to either immediate endoscopy with haemostatic powder application within 2 hours of admission, followed by early elective endoscopy on the next day, that is, within 12–24 hours of admission for definitive treatment (study group) or to early elective endoscopy only (control group). In both groups, failures to achieve clinical haemostasis until the time of early elective endoscopy underwent rescue endoscopy with attempted conventional haemostasis. Primary outcome was endoscopic haemostasis at the elective endoscopy.

Results Of 86 randomised patients with AVB, 5/43 in the study group required rescue endoscopy for failure of controlling spurting bleeding (n=4) after powder application or for early bleeding recurrence in one patient who died before repeating rescue endoscopy. In the control group, 13/43 patients required rescue endoscopic haemostasis for failure of clinical haemostasis (12%vs30%, p=0.034). In the remaining patients, early elective endoscopic haemostasis was achieved in all 38 patients in the study group, while all remaining 30 patients in the control group had fresh gastric blood or (10%) spurting bleeding at early elective endoscopy with successful haemostasis in all of them. Six-week survival was significantly improved in the study group (7%vs30%, p=0.006).

Conclusion The new concept of immediate powder application improves early clinical and endoscopic haemostasis. This simplified endoscopic approach may have an impact on early and 6-week survival.

Trial registration number NCT03061604 .

Significance of this study

What is already known on this subject?

- Acute variceal bleeding (AVB) is the most life-threatening complication of liver cirrhosis and associated with increased mortality.
- Combined treatment with vasoactive drugs, prophylactic antibiotics, and endoscopic techniques is the recommended standard of care but requires considerable endoscopic expertise.
- TC-325 is a haemostatic powder which, when put in contact blood or tissue in the GI tract, becomes adherent to the bleeding site, achieving very rapid haemostasis.

What are the new findings?

- Early (2 hours) haemostatic powder application on actively bleeding varices improves clinical and endoscopic haemostasis in patients admitted with a first episode of AVB.
- There is a significant improvement in survival at 6 weeks in the powder group compared with the pharmacotherapy–endotherapy group, although this was not the primary endpoint of the study.

How might it impact on clinical practice in the foreseeable future?

- Endoscopic powder application, an easy procedure requiring minimal expertise, shows clinical benefit when performed early after admission of a cirrhotic patient with a first episode of AVB and overt haematemesis.
- This new concept might improve management of these patients, particularly when admitted in centres where advanced endotherapy is not available 24/7.

INTRODUCTION

Liver cirrhosis is the end stage of chronic liver disease, independent of aetiology, and is characterised by accumulation of fibrotic tissue and conversion of the normal liver parenchyma into abnormal regenerative nodules.[1] Complications include portal hypertension with gastro-oesophageal varices, ascites, hepatorenal syndrome, hepatic encephalopathy, bacteraemia and hypersplenism.[2 3] The most life-threatening complication of liver cirrhosis is acute variceal bleeding (AVB), which is associated with increased mortality that, despite recent progress in management, is still around 20% at 6 weeks.[4] Combined treatment with vasoactive drugs, prophylactic antibiotics and endoscopic techniques is the recommended standard of care for patients

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with AVB.[5 6] However, not all patients with AVB have the same risk of unfavourable outcome. The most consistently reported risk indicators of death were Child-Pugh classification, model for end-stage liver disease score and increased hepatic venous pressure gradient.[7] Severe bleeding (fresh blood in the stomach with high-risk stigmata on varices or active bleeding at endoscopy) is also associated with higher mortality[8] and demands early endoscopy (within 12 hours of patient presentation).[9] Nevertheless, data from bleeding registries show that a significant proportion of patients with AVB have a delay of greater than 24 hours before undergoing upper endoscopy, mainly due to the lack of experienced endoscopists.[10]

TC-325 (Hemospray, Cook Medical, Winston-Salem, North Carolina, USA) is a haemostatic powder which, when put in contact with moisture (eg, blood or tissue) in the GI tract, becomes cohesive and adhesive forming a mechanical barrier that adheres to and covers the bleeding site, achieving very rapid haemostasis.[11] After approximately 24 hours, the adherent layer subsequently sloughs off into the lumen from the mucosal wall and is eliminated from the GI tract.[11] Using a delivery system dedicated to endoscopic applications, it has been shown to be effective in peptic ulcer bleeding,[11 12] including high-risk patients[13] on anticoagulant or antithrombotic therapy,[14] those with tumour-related bleeding[15] and patients with lower GI bleeding.[16] In two pilot studies[17 18] and two case reports,[19 20] Hemospray was reported to be useful in emergency management of AVB as an added treatment modality to the medical management that serves as a bridge towards more definitive endotherapy, with no major adverse events or device-related mortalities. As such, this therapy offers an interesting option for transient haemostasis that does not require specific expertise in therapeutic endoscopy.

The present randomised controlled study aimed to determine whether a new approach to AVB, namely the addition of an early and easy to perform treatment with haemostatic powder to classical medical and endoscopic therapy can improve outcomes in patients presenting with liver cirrhosis and a first episode of severe AVB.

METHODS

Patients

Patients were enrolled at two tertiary centres (Erasme University Hospital, ULB, Brussels, Belgium and Theodor Bilharz Research Institute, Giza, Egypt) between November 2014 and November 2016. *Eligible patients* were over 18 years of age with proven AVB and liver cirrhosis who presented to the outpatient emergency room.

Exclusion criteria included patients already hospitalised at the time of bleeding, contraindication to endoscopy, pregnant or lactating women, patients with altered postsurgical anatomy of the stomach, previously placed intrahepatic portosystemic shunt and patients treated by other endoscopic or surgical modalities within 30 days prior to the intended inclusion in the study.

All patients provided written informed consent. The study protocol was registered at Clinicaltrials.gov under the number NCT03061604.

Definitions

Immediate endoscopy for Hemospray application (in the study group only) was defined as endoscopy within 2 hours with attempted universal Hemospray application.

Early elective endoscopy on the next day, that is, with 12–24 hours was defined as endoscopy to achieve haemostasis by specific endoscopic therapy such as banding or cyanoacrylate injection. This was performed in all patients in both groups on the next day, if clinical haemostasis could be achieved in the time until then.

Rescue endoscopy in the study setting was defined as an early emergency endoscopy within 60 min in patients in whom either Hemospray or medical management could not achieve clinical haemostasis. This endoscopy included specific therapeutic measures as described for early elective endoscopy. Rescue endoscopy was done (A) in the study group, either during immediate endoscopy when Hemospray could not achieve haemostasis or after initial Hemospray with haemostasis but recurrent overt bleeding before early elective endoscopy within 12–24 hours and (B) in the control group if medical management was not able to bridge the time until early elective endoscopy.

Clinical haemostasis was defined as a haemodynamically stable patient (ie, the systolic blood pressure >80 mm Hg and heart rate <100 beats per minute) without overt bleeding or haemostasis in whom rescue/emergency endoscopy was considered not to be indicated and who could be endoscoped on the next day, that is, within 12–24 hours. Rebleeding during the first 12–24 hours of admission was manifested by acute haematemesis or a combination of decreased blood pressure (systolic blood pressure under 80 mm Hg), increased heart rate (more than 100 beats per minute), transfusion need (requirement of 4 units of blood or more) and haematocrit drop (more than 10%). Thus, failure of clinical haemostasis was defined in the study group as either failure of Hemospray to achieve haemostasis during immediate endoscopy or recurrent bleeding, thereafter necessitating rescue endoscopy before early elective endoscopy. In the control group, failure was defined as necessity to perform rescue endoscopy before early elective endoscopy.

Endoscopic haemostasis was defined as no active bleeding and no blood in stomach at the time of the early elective endoscopy (defined based on the BAVENO criteria)[6] in both groups.

Study design and clinical approach in both groups

The flow chart of the study design is shown in figure 1.

The study was a randomised controlled trial (RCT) comparing two different approaches:

1. Gastric lavage using a soft 14 French nasogastric tube was done for all patients at admission. This measure is still controversially discussed in the literature[21]; however, in our experience, it helps in the clearance of the blood from the fundus of the stomach and hence facilitates assessment and management of the bleeding source especially in gastric varices. Acute bleeding was confirmed by the presence of fresh blood in the stomach.
2. Drug therapy was administered in both groups: treatment with vasoactive drug (octreotide) was started at admission and continued until patients were free of bleeding for at least 24 hours after the early elective endoscopy in both groups. Octreotide (Sandostatin, Sandoz International GmbH, Germany) was administered at a dosage of 50 µg bolus at admission then 25 µg/hour for 24 hours after the early elective endoscopy.
3. Patients were then randomised to:
   a. Study group: Hemospray application during an immediate endoscopy within 2 hours with application of Hemospray in all cases (except for those with non-variceal bleeding sources who were excluded), followed by early elective endoscopy on the next day, that is, within 12–24 hours.

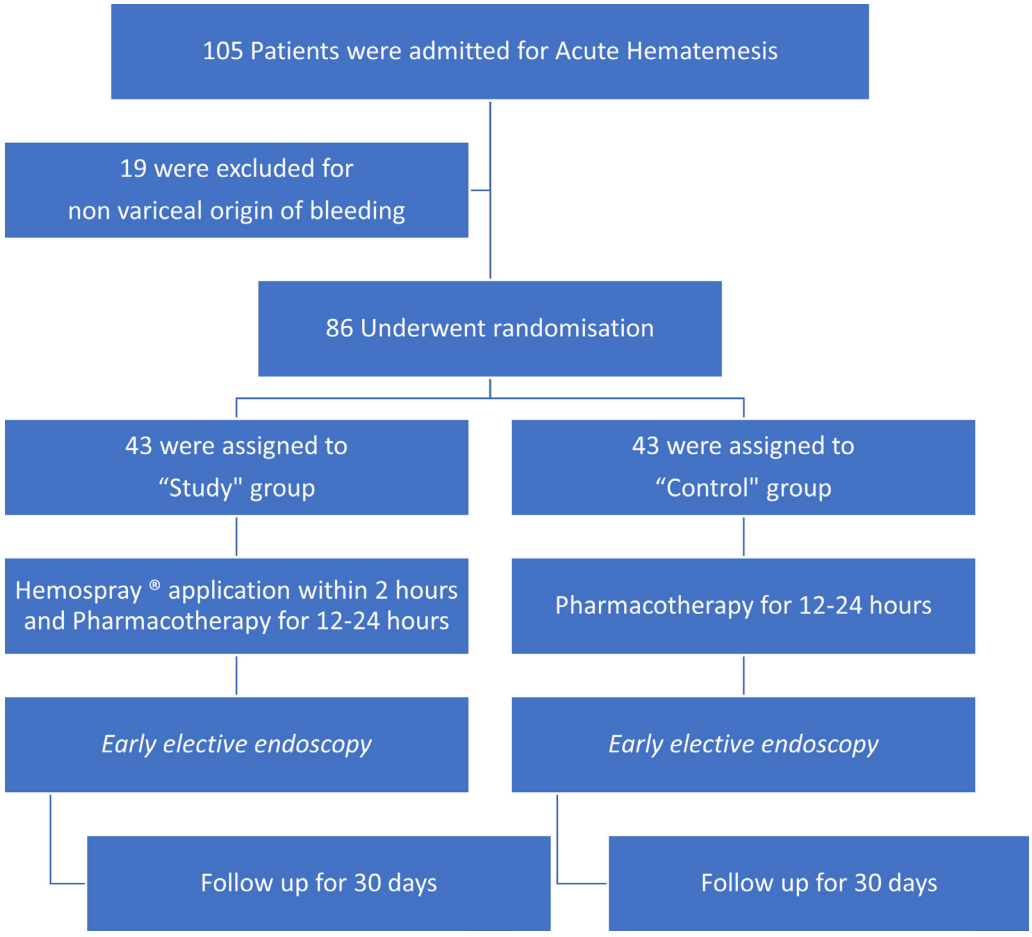

Figure 1 Flow chart of the study.

b. Control group: only drug therapy on admission, followed by early elective endoscopy on the next day, that is, within 12–24 hours.

For obvious ethical reasons, rescue/emergency endoscopy with targeted haemostasis was performed in patients who failed to achieve clinical haemostasis (in both groups) before elective endoscopy or in whom spurter bleeding was not controlled by powder application (these were also censored as failure of clinical haemostasis; see below).

The randomisation sequence was generated with the use of a concealed block size of four. The coded treatment assignments were kept with the study coordinator at coordinating centre in sealed, consecutively numbered, opaque envelopes. Randomised assignments to the study groups were made by contacting the coordinating centre (available 24 hours a day) by telephone or fax. There were no changes that have been made to the trial design after commencement.

General therapy (both groups)

Blood volume replacement was initiated with plasma expanders, aiming to maintain a systolic blood pressure of around 100 mm Hg. A restrictive packed red blood cell transfusion strategy was used following BAVENO criteria.[6] Therapy with octreotide is described above. All patients received cephalosporin (ceftriaxone 1 g intravenously once daily) for 7 days.

The definitive endoscopic therapy (early elective endoscopy, 12–24 hours after admission) consisted of endoscopic band ligation (EBL), in cases of oesophageal varices, and/or N-butyl-2-cyanoacrylate injection (Glue) in cases of gastric varices. EBL was performed with the use of multiband devices (Cook Medical). Glue injection was performed using a mixture of 0.5 mL of cyanoacrylate with 0.5 mL of lipiodol and repeating intravariceal injections of 1.0 mL using a 21 G needle (Cook Medical; MTW, Dusseldorf, Germany) until haemostasis was achieved.

Hemospray application (study group)

The device used for powder application consists of a 10 French application catheter, which passes through the working channel of a therapeutic gastroscope, a chamber containing approximately 21 g of TC-325 powder and a propellant CO_2 canister. A therapeutic scope (3.8 mm working channel, EC-600W, Fujifilm, Tokyo, Japan or Olympus GIF 1T190) was used in all patients. After confirmation of AVB, which was defined based on the BAVENO criteria (actively bleeding varices or fibrin plugs and/or red streaks of the mucosa overlying the varices with presence of fresh blood within the lumen), a bleeding site that encompassed the definitive or most probable source (oesophageal or gastric varices) was identified. The haemostatic powder was then administered diffusely to cover the mucosa over the bleeding varices area to obtain immediate endoscopic haemostasis. In case of spurter bleeding, the bleeding site was observed for 3 min under endoscopy. If bleeding recurred during this 3 min observation period, Hemospray was reapplied once. If after three more minutes bleeding recurred, this was considered as treatment failure and, for obvious ethical reasons, conventional endoscopic therapy (with cyanoacrylate injection) was successfully applied during early endoscopy. Patients were censored as treatment failures and failures of clinical haemostasis, even if none of them

presented with rebleeding during the next 24 hours, and were excluded from the mortality analysis in a subgroup survival analysis.

Follow-up

Follow-up of patients was done at 1, 2 and 5 days, and follow-up visits were scheduled on day 15 and day 30 of first admission, where clinical assessment was done in combination with endoscopic therapies, if indicated.

Study end points

The *primary study endpoint* was a combined endpoint of endoscopic haemostasis at conventional endoscopy performed at 12–24 hours and clinical haemostasis during the 24 hours following admission. *Secondary endpoints* were the need for immediate emergency endoscopy, rebleeding at 5 days and survival at days 5, 15, and 30. Subanalysis were asked for reviewing, namely spurter bleeding rate during early elective endoscopy and 6-week mortality.

Statistical analysis

The sample size was calculated with the reference to the pilot study conducted on the effect of addition of Hemospray on the conventional standard of care (SOC)[19] and literature-based studies[21] that tested SOC in AVB. We assumed in our population receiving pharmacotherapy and endotherapy a 75% rate of haemostasis at 5 days based on results of previous meta-analyses.[21 22] Based on the results of two pilot studies[18 19] that assessed the addition of Hemospray to drug therapy and endoscopic therapy, we hypothesised that the rate of haemostasis would increase to 96% when Hemospray was added to standard therapy at 2 hours after admission. A sample size of 43 patients in each group was assumed to allow for a confidence level (1-α) of 95% and a study power (1-β) of 85% to guarantee such results.

All data analyses were performed on an intention-to-treat basis according to a pre-established analysis plan. Dichotomous variables were compared by means of Fisher's exact test, and continuous variables were compared by means of the non-parametric Mann-Whitney rank-sum test. Survival was estimated by the Kaplan-Meier method, and groups were compared by means of the log-rank test. A p value of less than 0.05 was considered to indicate statistical significance, and all tests were two sided. The statistical software package used for the analysis was SPSS (V.20.0).

RESULTS

Study patients

One hundred and five patients with acute haematemesis who were admitted to one of the participating hospitals (Erasme Hospital, ULB, and Theodor Bilharz Research Institute) were included in the study. A total of 19 patients were excluded at the time of endoscopy due to non-variceal causes of bleeding (figure 1), and the remaining 86 patients (1 patient in Erasme Hospital, ULB, and 85 patients in Theodor Bilharz Research Institute) were randomly assigned to either the pharmacotherapy–endotherapy group (43 patients) or the powder group (43 patients). There were no significant differences in baseline characteristics between the two groups at the time of entry into the study (table 1).

Powder group (study group)

In this group, at the time of Hemospray application, all patients had active bleeding with fresh blood in the stomach and seven of them showed spurting bleeding. Five patients did not achieve

Table 1 Baseline patient characteristics

Characteristics	Study group (n=43)	Control group (n=43)	P values
Age (years), mean (range)	58.5 (31–76)	59.3 (50–77)	0.6749
Male, no. (%)	25 (58)	27 (63)	0.6591
Clinical presentation*			
Haematemesis, no. (%)	43 (100)	43 (100)	NA
Melena, no. (%)	20 (47)	19 (44)	0.8285
Both, no. (%)	20 (47)	19 (44)	0.8285
Child-Pugh classification			
Child A, no. (%)	14 (33)	12 (28)	0.6386
Child B, no. (%)	21 (49)	21 (49)	1.0000
Child C, no. (%)	8 (19)	10 (23)	0.5960
MELD score, mean (range)	15.26 (7–39)	15.18 (7–36)	0.9604
Ascites (at ultrasound), no. (%)	27 (63)	32 (74)	0.1667
Total bilirubin* (mg/dL) mean (range)	1.92 (0.3–10.45)	1.60 (0.26–14.96)	0.6209
Haemoglobin* (g/dL) mean (range)	8.86 (4.5–13.6)	8.46 (4.2–12.1)	0.4287
Platelets* (/mm^3) mean (range)	132 720 (10 000–310 000)	130 302(53 000–146 000)	0.8355
Total leucocytic count* (/mm^3) mean (range)	10 353 (2200–38 200)	9941 (2000–24 800)	0.7451
Albumin* (g/dL) mean (range)	2.68 (1.7–3.8)	2.43 (1.2–3.4)	0.0332
Prothrombin time* (%) mean (range)	19.92 (13.5–60)	18.63 (14.2–27.3)	0.3007
Creatinine* (mg/dL) mean (range)	1.23 (0.5–4.11)	1.22 (0.5–4.71)	0.9428
Systolic blood pressure* (mm Hg) mean (range)	117 (50–170)	112 (70–180)	0.3993
Heart rate* (pulse/min) mean (range)	100 (70–135)	100 (78–120)	0.9165
Positive blood culture*, no. (%)	10 (23)	18 (42)	0.0656
Positive urine culture*	7 (16)	6 (14)	0.7634

*At admission.
MELD, model for end-stage liver disease.

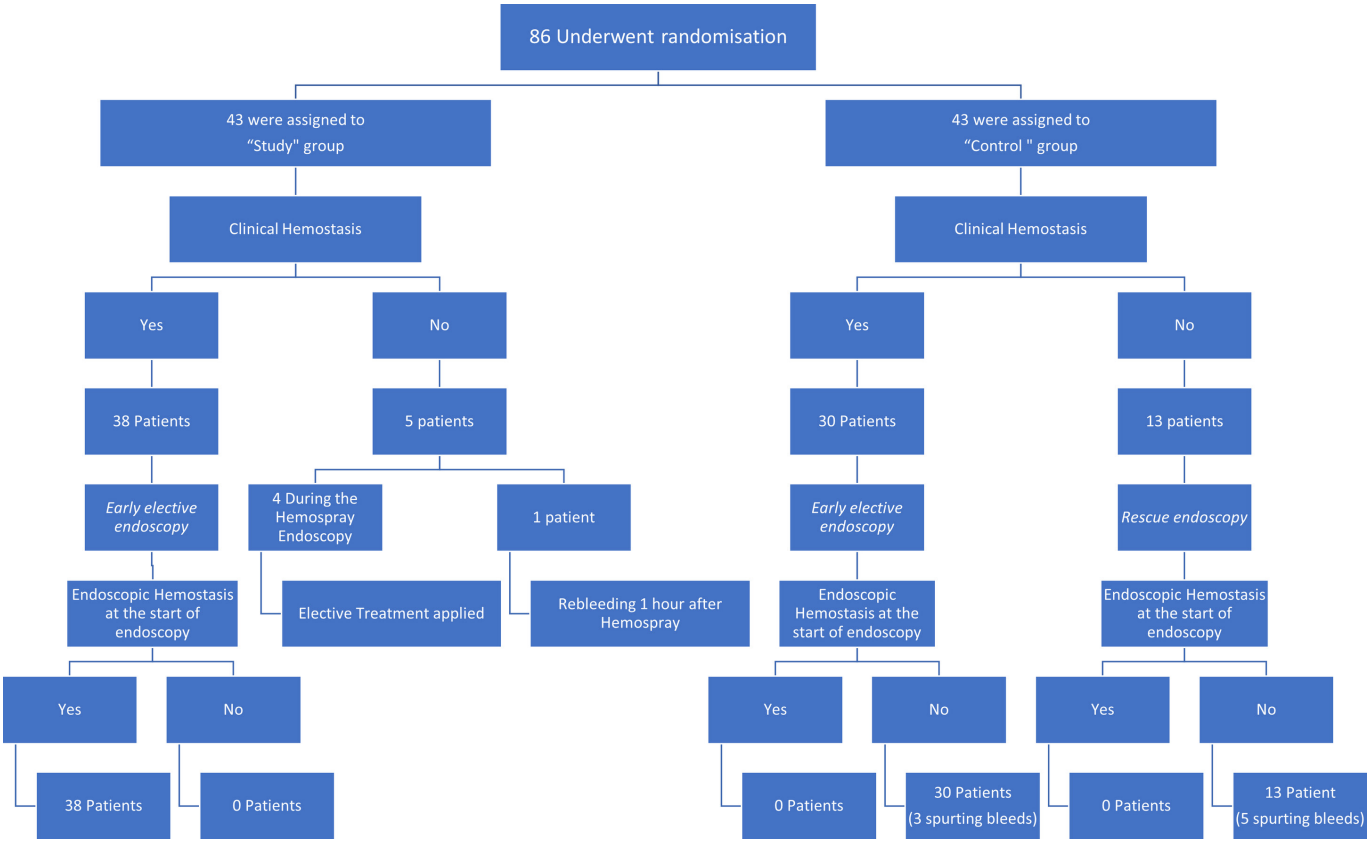

Figure 2 Overview of both groups in the first 5 days.

clinical haemostasis after the Hemospray application. For four of them, definitive endoscopic management was applied directly after failure of Hemospray as mentioned: they were treated by classical endotherapy despite the absence of relapsing overt haematemesis and censored as clinical haemostasis failures and were excluded from the mortality analysis in a subgroup survival analysis.

One patient had a relapsing haematemesis 2 hours after Hemospray with overt hepatic encephalopathy, and death before immediate urgent endoscopy could be performed and before elective endoscopy at 12–24 hours.

The remaining 38 patients achieved clinical haemostasis after Hemospray application and early elective endoscopy (performed at a median of 18 hours (range 12–24 hours after admission) demonstrated endoscopic haemostasis in all of them (no active bleeding and no fresh blood in the stomach) before performing treatment with EBL in 24 patients, glue injection in 5 patients and combined techniques in 9 patients. Flow chart in figure 2 describes the overview of both groups in the first 5 days.

Pharmacotherapy–endotherapy group (control group)

In this group, 13 patients did not achieve clinical haemostasis due to a second attack of overt haematemesis within the first 12 hours before the early elective endoscopy and required an immediate rescue/emergency endoscopy. Five of them had spurting bleedings at the time of rescue endoscopy and fresh blood in the stomach was observed in all patients. Band ligation was applied in eight patients, and combined EBL and glue injection for gastric varices was applied in five patients. All targeted haemostasis was successful.

The remaining 30 patients underwent their early elective endoscopy as planned at a median of 16 hours (range 12–24) after admission. All 30 patients had active bleeding at the time of endoscopy, either fresh blood into the stomach (n=27) or spurting bleeding (n=3). EBL was performed in 22 patients with oesophageal varices; four patients had isolated gastric varices treated by glue injection and four patients had both oesophageal and gastric varices treated by EBL and glue injection with therapeutic success being achieved in all patients. Figure 2 provides an overview of both groups in the first 5 days.

Rebleeding and rescue or emergency endoscopy

This overview on results combines the rebleeding and emergency endoscopy rates within 5 days of admission, that is, before the early elective endoscopy (within 12–24 hours) and thereafter. In the *control group*, treatment failure at 5 days, that is, rebleeding, was observed in 16 patients (13 early, within the first 12 hours as described above, and 3 after the elective endoscopy within the first 5 days), and these were treated by additional EBL and/or glue injection. In the *study group*, five patients had rebleeding within the first 12 hours (four of them during the Hemospray endoscopy, immediately treated as described above and one within the first 12 hours) and none had rebleeding later after elective endoscopy, within the first 5 days (table 2).

Survival

A total of 13 patients in the *control group* died within the first 6 weeks with 1 patient lost to follow-up, while 3 patients died in the *study group*. Survival at 5, 15 and 30 days is shown in figure 3. Causes of death are summarised in table 3. A trend for more positive blood cultures at admission was observed in the control group as compared with the study group at admission (table 1), but a subgroup analysis of mortality at 6 weeks among

Table 2 Summary of efficacy measurements

Variable	Study group (n=43)	Control group (n=43)	P values
Composite endpoint (clinical haemostasis+endoscopic haemostasis*), no. (%)†	38/43 (88) (95% CI 87.52 to 88.48)	27/43 (63) (95% CI 61.94 to 64.06)	0.0057
Clinical haemostasis, no. (%)	38 (88) (95% CI 87.52 to 88.48)	30 (70) (95% CI 69.04 to 70.96)	0.034
Haemostasis after Hemospray application at 2 hours endoscopy, no. (%)	39 (91) (95% CI 90.63 to 91.37)	NA	NA
Endoscopic haemostasis at 12 hours endoscopy*, no. (%)†	38/38 (100)	27/30 (90) (95% CI 89.41 to 90.59)	0.0466
Treatment failure at 5 days, no. (%)‡	5 (12) (95% CI 11.52 to 12.48)	16 (38) (95% CI 36.93 to 39.07)	0.006
Death within 5 days, no. (%)	2/43 (5) (95% CI 4.78 to 5.22)	4/43 (9) (95% CI 8.63 to 9.37)	0.397
Death within 15 days, no. (%)	3/43 (7) (95% CI 6.70 to 7.30)	10/43 (23) (95% CI 22.19 to 23.81)	0.035
Death within 30 days, no. (%)	3/43 (7) (95% CI 6.70 to 7.30)	13/43 (30) (95% CI 29.04 to 30.96)	0.006
6 weeks mortality, no. (%)‡	3/43 (7) (95% CI 6.70 to 7.30)	13/43 (30) (95% CI 29.04 to 30.96)	0.006
6 weeks mortality, no. (%)§	3/39 (8) (95% CI 7.63 to 8.37)	13/43 (30) (95% CI 29.04 to 30.96)	0.0101
6 weeks mortality, no. (%)¶	3/10 (30)	3/18 (16.7)	0.4122
Deaths according to Child-Pugh score			
Child A, no. (%)	0/14 (0)	2/12 (17) (95% CI 14.70 to 19.30)	0.112
Child B, no. (%)	0/21 (0)	2/21 (10) (95% CI 9.16 to 10.84)	0.147
Child C, no. (%)	3/8 (38) (95% CI 32.23 to 43.77)	9/10 (90) (95% CI 88.24 to 91.76)	0.019

*Before EBL±cyanoacrylate injection.
†Patients having no actively bleeding (spurter) during *Early elective endoscopy*.
‡BAVENO VI endpoint (BAVENO VI recommends mortality at 6 weeks to be a reasonable endpoint for RCTs.).
§Subgroup analysis after removing of the four patients that had been censored as treatment failures and failures of clinical haemostasis in the powder group.
¶Subgroup survival analysis comparing death in the subgroup of patients having positive blood culture within both groups.
EBL, endoscopic band ligation; RCT, randomised controlled trial.

these patients showed a similar number of deaths in both groups. A flow chart summarising mortality in line with clinical and endoscopic haemostasis is presented in figures 4 and 5. Interestingly, most of the deaths (12/13) and all delayed rebleeders (6/6) at 6 weeks in the control group were from the subgroup of 30/43 patients who achieved clinical haemostasis with drug and medical therapy before early elective endoscopy.

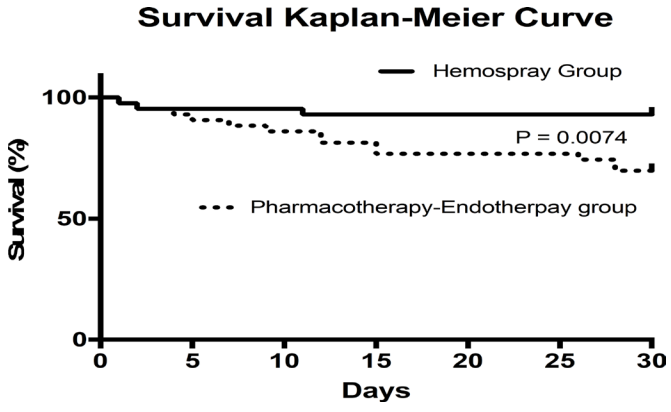

Figure 3 Kaplan-Meier survival curves at 5, 15 and 30 days for patients treated with Hemospray plus pharmacotherapy and endotherapy (Hemospray group) or with pharmacotherapy and endotherapy alone (pharmacotherapy–endotherapy group).

Adverse events

Twenty-three patients experienced 36 adverse events, 16 of them died within the first 6 weeks (table 4). No adverse event was related to the powder application.

DISCUSSION

The current study shows that in patients with cirrhosis admitted for a first episode of AVB with overt haematemesis, a novel approach consisting in a very early application of a haemostatic powder in addition to standard pharmacotherapy and endotherapy significantly reduces clinical rebleeding within 24 hours compared with standard pharmacotherapy plus endotherapy

Table 3 Causes of death

Variable	Study group (n=43)	Control group (n=43)
Liver failure, no.		1
Hepatorenal syndrome, no.		3
Hepatic encephalopathy, no.		3
Bleeding, no.	1	5
Hyperkalaemia, no.	1	
Respiratory failure, no.		1
Spontaneous bacterial peritonitis, no.	1	
Total deaths, no.	3	13

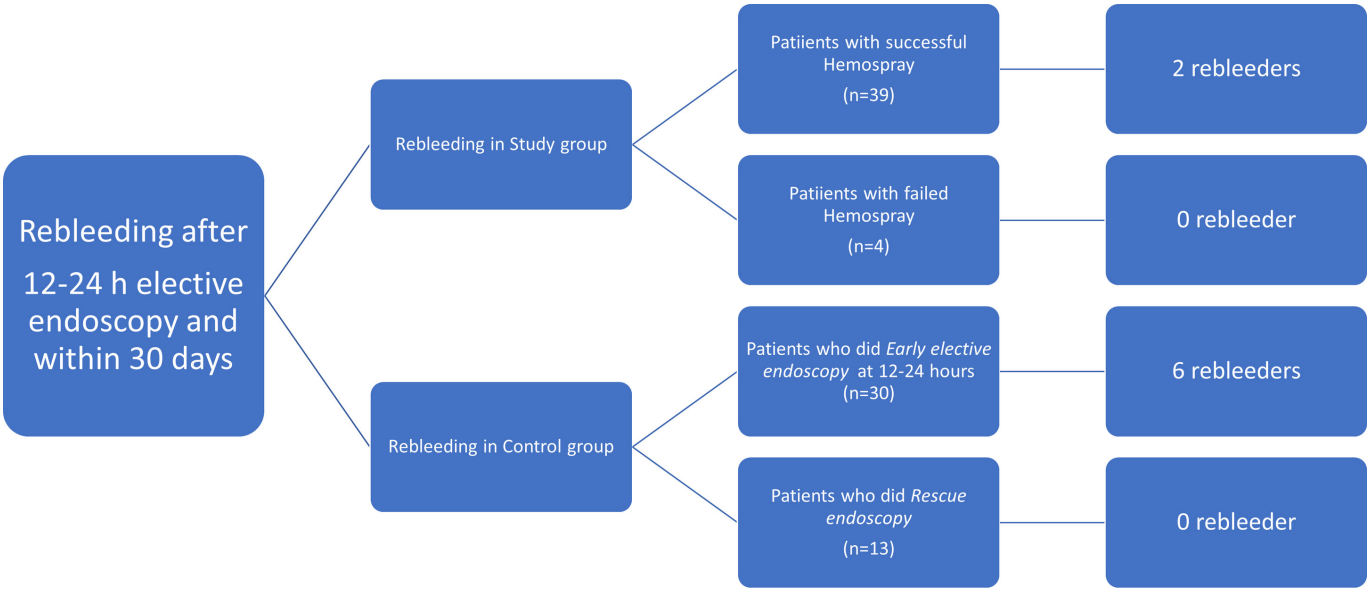

Figure 4 Flow chart summarising rebleeding in line with clinical and endoscopic haemostasis.

alone. This easy-to-perform procedure does not require the usual endoscopic expertise needed for bleeding management. Furthermore, all patients who received haemostatic powder therapy and did not have early clinical rebleeding achieved endoscopic haemostasis prior to elective endotherapy. This study also suggests that this early procedure may have an impact on survival at 6 weeks and 30 days by decreasing early and late rebleeding and its associated complications and by providing a more effective early haemostasis than pharmacotherapy. However, the study was not powered for survival, and therefore these results should be viewed with caution and should be confirmed by further randomised trials. Nevertheless, the concept that (very) early successful haemostasis may have an influence on final outcome with regards to survival is an interesting one and should prompt further research. It must be mentioned, however, that Hemospray application is considered a temporary haemostatic measure and should not obviate the use of later (early) elective endoscopy to apply specific endoscopic measures for bleeding control and variceal eradication. In our study, it appeared that this effect lasted for 12–14 hours until early elective endoscopy was scheduled.

The timing and required expertise of endoscopic haemostasis in AVB has been a topic of discussion that has recently been revitalised with the availability of effective vasoactive pharmacotherapy, also leading to reconsidering the availability of endoscopic expertise. The current recommended therapy for AVB combines vasoactive drugs from admission with endoscopic therapy within 12 hours plus prophylactic antibiotics.[7 23] Only the availability of both an on-call experienced GI endoscopists proficient in endoscopic haemostasis and support staff with technical expertise in the usage of endoscopic devices enable high-quality performance of endoscopy on a 24/7 basis.[21] In a study by Cheung *et al*,[22] the optimal timing of endoscopy in AVB was evaluated. They compared different timeframes for endoscopy (≤4 hours vs >4 hours, ≤8 hours vs >8 hours and ≤12 hours vs >12 hours) and reported no difference in mortality and

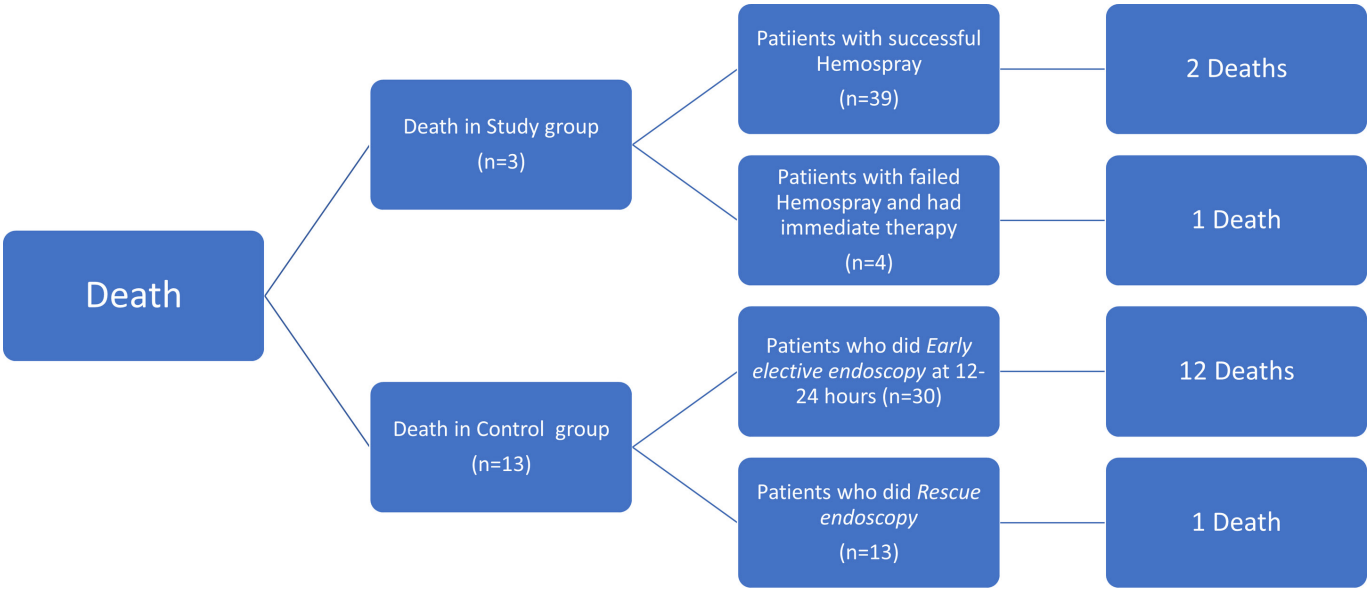

Figure 5 Flow chart summarising mortality in line with clinical and endoscopic haemostasis.

Table 4 Adverse events (AEs)

AE	Study group (n=43)	Days until AE (mean±SD)	Control group (n=43)	Days until AE (mean±SD)	Management
Hepatic encephalopathy	3	0.3±0.6	10	6.9±9.7	Anticoma measures
Hepatorenal syndrome			4	5.5±5.3	Terlipressin and albumin
Leukocytosis			1	2	Antibiotics shift
Spontaneous bacterial peritonitis	4	4.8±1.7	2	1.5±0.7	Antibiotics adjustments
Leukocytosis	1	1			Antibiotics shift
Tense ascites causing abdominal pain	1	1			Tapping of ascites
Rebleeding after elective endoscopy					
Bleeding during follow-up upper endoscopy on day 15	1	15	1	15	Injection sclerotherapy and band ligation
Rectal bleeding			1	2	Medical treatment (octreotide/PPI/blood transfusion)
Rebleeding (haematemesis±melena)			1	5	Actively bleeding PHG → Medical management
Rebleeding (haematemesis±melena)	1	7			Postband ligation ulcer → Hemospray and PPIs
Rebleeding (haematemesis±melena)			2	3±2.8	Medical treatment (octreotide/PPI/blood transfusion)
Rebleeding (haematemesis±melena)			1	15±4.2	Injection sclerotherapy and band ligation

PHG, portal hypertensive gastropathy; PPI, proton-pump inhibitors.

rebleeding rates. However, they also showed that significantly more bands were used to stop active bleeding in the group treated within 4 hours. This observation aligns with the recommendation to have an experienced endoscopists available at the time of band ligation, something which is not always possible before 24 hours.[10] The availability of a simple endoscopic haemostatic technique that could be performed even by physicians with basic expertise in endoscopy might allow us to revisit the current treatment recommendation if it was associated with improved outcomes.

The application of Hemospray only consists of spraying powder into the upper GI tract from the upper part of the stomach up to the mid-third of the oesophagus and requires only limited experience in this indication. This study was designed to test whether this powder application, when performed very early after admission, can improve the outcome for patients with variceal bleeding. Even after considering as failures those patients for whom bleeding was not controlled by powder endoscopy during early endoscopy, and for whom, in our environment, it was considered unethical not to perform classical haemostasis during the same procedure, we observed a significant reduction of clinical rebleeding during the first 24 hours. Besides that, all the patients who had received previous powder application were treated with band ligation and/or glue injection in the absence of endoscopic bleeding and in a hemodynamically stable condition, a feature that was proven to be beneficial in terms of prognosis and mortality.[7] Thus, in an unexperienced setting as described, the concept of early powder application would not have worked in 5/43 cases (four during and one after the early endoscopy with powder application), all or some of whom should be strictly speaking considered as failures in this concept in which no experienced endoscopist is available. For ethical reasons we treated these four cases with immediate powder failed also immediately by targeted endoscopic therapy which was successful in all cases. This must be considered as limitation of this concept with some 10% of failures that would have been benefited from the presence of an experienced endoscopist. Whether a less experienced endoscopists would have been able to manage these cases as well during the night can only be speculated on. For the study outcomes and under worst case assumptions, that is, counting all four immediate failures under mortalities (the fifth failure patient died anyway), mortality rates would still be different (7/43 vs 13/43) but not significant any more with the case numbers chosen for the primary outcome. This, however, is entirely speculative and only shows the limitations of dealing with a secondary outcome, which did not influence case number calculation.

Success in managing AVB is multifactorial; the effectiveness of vasoactive agents in achieving haemostasis and preventing rebleeding has been well documented, while the optimal duration of pharmacological therapy has been reported to be between 8 hours and 6 days.[4 5 7] A recent study found that after successful haemostasis by EBL, adjuvant therapy with vasoactive drugs for 24 hours was as effective as 72 hours.[24] Another recent study found that, in patients initially treated with vasoconstrictors in which initial haemostasis was achieved by EVL at the diagnostic endoscopy, the extension of treatment with either terlipressin or the proton pump inhibitor, pantoprazole, achieved similar 5-day haemostasis, 96% and 98%, respectively.[25] A third recent RCT demonstrated that the addition of somatostatin (vs placebo) infusion for 5 days after successful endoscopic variceal ligation for AVB did not reduce bleeding recurrence at 5 days or mortality.[26]

In our study, drug administration alone did not provide full endoscopic haemostasis: 10% of patients still had spurting bleeding at early elective endoscopy, and all patients in whom clinical haemostasis was achieved (ie, haemostasis from a clinical standpoint not necessitating earlier rescue endoscopy) still had fresh blood in the stomach at early elective endoscopy (performed within 12–24 hours). In contrast, all patients remaining in the powder group, after exclusion of the five patients who underwent immediate urgent endotherapy and the one who had clinical rebleeding and died after powder application, showed maintained endoscopic haemostasis (no spurting bleeding and no fresh blood into the stomach) at the start of elective endotherapy. This raises some interesting questions with regards to full (endoscopic) versus partial (clinical) haemostasis and their influence on outcome. It could be speculated that, even if clinical haemostasis is achieved on

drug therapy, there is ongoing low-level bleeding until early elective endoscopy. Early cessation of bleeding (which occurs much earlier after powder application in our management concept) could be a feature possibly associated with overall better outcomes.

Although the risks of treatment failure and death were higher in patients with Child-Pugh class C disease than in those with class A and B disease, our trial was not powered to conduct appropriate subgroup analyses. Therefore, further evaluation will be needed to determine whether the use of Hemospray equally benefits these subgroups of patients. It is, however, notable that no mortality was observed among child A and B patients in the powder group.

Previous studies evaluating the role of powder application in non-variceal bleeding and in AVB demonstrated its efficacy for transient control of bleeding and haemodynamic stabilisation. It has always been recommended mainly as a rescue therapy. This restriction is obviously challenged by the present study where early haemodynamic stabilisation using an easily applied technique affected the development of additional complications in these frail patients and, therefore, overall patient outcomes, as shown by potentially reduced mortality. Moreover, early haemodynamic instability is a well-known factor affecting the development of complications and mortality in cirrhotic patients with AVB.[9 27] In this line, it is of interest to notice that most of the mortality in the control group (12 out of 13 patients who died within 6 weeks) occurred in patients who did not require (or benefited from) immediate emergency endoscopy with targeted haemostasis for failure of clinical haemostasis within the first 12–24 hours after admission until early elective endoscopy. However, also other reasons for these differences in survival outcome—unusual in studies in endoscopic variceal haemostasis—should be considered and be the topic of further research.

Survival was however not the primary endpoint of this study, and sample calculation was not made with this purpose. In addition, although not significant, there was an inhomogeneity in the number of patients with a documented bacteraemia within 2 hours after admission, which might have affected our results. However, subgroup survival analysis—if possible in this limited patient sample—did not show significantly different mortality rates in patients with positive blood cultures between both groups. The limited sample size—based on the primary outcome—is a limitation of our study with respect to further analyses. Furthermore, the study was almost unicentric, since all but one patients were recruited in one centre due to the much larger case load of acute variceal bleeders as well as patients in Europe usually receive primary endoscopic management in community hospitals where the issue of proper endoscopic expertise for treating severe bleeding in unstable conditions is precisely the problem addressed by the current study.

Thus, it might be worthwhile to repeat this study in a true multicentre setting and also with endoscopists of different experience levels.

There are also other limitations of this study: transjugular intrahepatic portosystemic shunt (TIPS) was not offered to child B and C patients. There is no direct comparison between early EBL and early Hemospray. Although the risks of treatment failure and death were higher in patients with Child-Pugh class C disease, our trial was not powered to conduct appropriate subgroup analyses. Therefore, further evaluation will be needed to determine whether the early use of Hemospray followed by TIPS equally benefits this subgroup of patients.

To date, the commercial use of Hemospray is restricted to non-variceal bleeding mainly because of the theoretical fear of systemic embolisation similar to that complicating cyanoacrylate injection.[28] The current application in AVB is a non-contact technique where the above risk is most probably non-existent due to the fact that the pressure of powder delivery, even at the tip of the catheter is only around 12 mm Hg,[29 30] that is, below the variceal pressure in most cases. In this series, no complications related to the powder itself were observed.

In summary, our study introduces a new concept of early, simple, therapeutic procedure that might be offered in places where expertise in endoscopic therapy is not available 24/7 and that would allow to safely bridge to more definitive therapy with a potential effect on overall outcomes (including mortality), the latter still having to be confirmed.

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Contributors MI was responsible for the study design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, technical support and material support. AE-M, HA, AL and MAH were responsible for acquisition of data and technical support. IM was responsible for the study supervision. JD was responsible for study design, interpretation of data, statistical analysis, study supervision and final revision of the manuscript.

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Competing interests The study is an investigator-initiated study, MI received an educational grant from Cook Medical. The Hemospray kits were provided from Cook Medical within the educational grant. Disclosure forms provided by the authors are available with the full text of this article.

Patient consent Obtained

Ethics approval Institutional review board (IRB) of Erasme hospital ,Université libre de Bruxelles (ULB) and Theodor Bilharz Research Institute IRB. Medical ethical committees of both participating centres

Provenance and peer review Not commissioned; externally peer reviewed.

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4.4. Active Bleeding Caused by Portal Hypertensive Gastropathy

The research group investigated the effect of the hemostatic powder on diffused bleeding secondary to portal hypertensive gastropathy.

Hemospray monotherapy was applied with immediate hemostasis to bleeding portal hypertensive gastropathy with no procedure-related complications.

VIDEOGIE

Todd H. Baron, MD, G. S. Raju, MD, *Editors for VideoGIE*

Active bleeding caused by portal hypertensive gastropathy

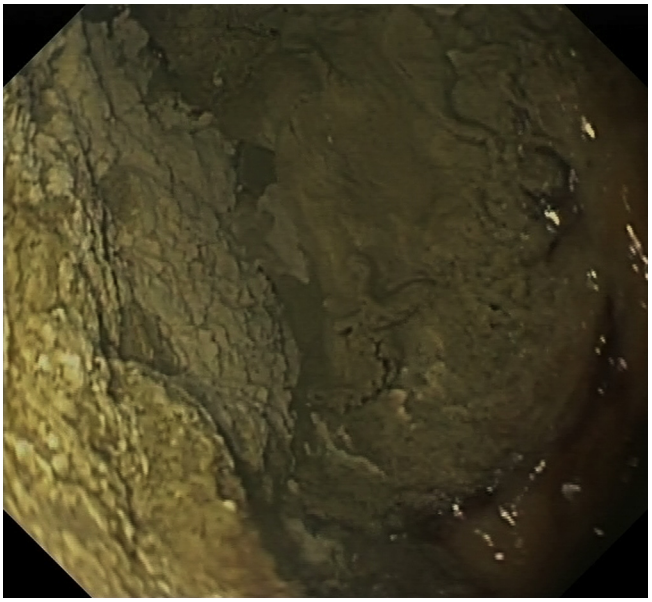

Figure 1. Hemostatic powder diffusely covering the bleeding site.

Portal hypertensive gastropathy (PHG) hemorrhage is a serious adverse event of portal hypertension. It is difficult to treat because of the diffuse nature of bleeding. Management includes medical therapy to decrease the portal pressure, endoscopic thermal therapy requiring multiple sessions, and a transjugular intrahepatic portosystemic shunt in refractory cases.

Hemospray (TC-325) is a novel hemostatic powder licensed for nonvariceal bleeding, and it has shown effectiveness in achieving hemostasis in bleeding peptic ulcers and bleeding secondary to gastric and colonic malignancies as well as preliminary encouraging results in the off-label management of acute variceal bleeding. There were no reported technique-related adverse events except rebleeding. Systemic embolization and mucosal injury have never been observed. In this video (Video 1; available online at www.giejournal.org), we present acute hemorrhage secondary to diffuse PHG bleeding treated off-label with Hemospray. A 41-year-old woman with alcohol-related cirrhosis (CHILD B) presented to the hospital with hematemesis. She was hemodynamically stable, and her hemoglobin level was 8.8 g/dL. Intravenous somatostatin and proton pump inhibitors were started immediately. An urgent gastroscopy was performed within 2 hours of admission that revealed active bleeding from severe PHG localized at the fundus. Hemospray monotherapy was applied, leading to hemostasis. The patient was kept under surveillance for 24 hours with a hemodynamically stable profile and no decrease in hemoglobin level. A follow-up control endoscopy was performed 24 hours later that showed moderate PHG with no active bleeding. Hemospray could play a role in management of acute PHG bleeding, whereas long-term medical therapy must be considered for all endoscopically treated patients.

DISCLOSURE

All authors disclosed no financial relationships relevant to this publication.

Mostafa Ibrahim, MD, Delphine Degré, MD, Jacques Devière, MD, PhD, *Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium*

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4.5. Novel Application of Hemospray to Achieve Hemostasis in Post-variceal Banding Esophageal Ulcers That Are Actively Bleeding

The research group investigated the use of Hemospray in an extremely challenging condition, post band ligation esophageal ulcer.

A case report of two cases of effective hemostasis using the novel hemostatic powder in acute bleeding that originated from post band ligation ulcer.

Novel application of Hemospray to achieve hemostasis in post-variceal banding esophageal ulcers that are actively bleeding

Esophageal variceal band ligation (EVL) has been described as the best treatment option for esophageal variceal bleeding (EVB) [1]. Following EVL, a local ulcer is commonly found that heals within 2 – 3 weeks, allowing the development of fibrosis in the submucosa. If the rubber band detaches prematurely, before variceal thrombosis has occurred, massive bleeding may occur at the site of the detached band [2]. This complication is rare but difficult to manage and is associated with mortality of up to 52 % [3 – 5]. Management is based on endoscopic injection of cyanoacrylate when available, or balloon tamponade as a bridge to a rescue transjugular intrahepatic portosystemic shunt (TIPS) procedure [5].

We report two cases of effective hemostasis using the novel hemostatic powder Hemospray (Cook Medical, Winston-Salem, North Carolina, USA). The nonabsorbable nanopowder is propelled to the area of bleeding by means of a carbon dioxide-containing cartridge with a positive outflow pressure; the noncontact technique allows the diffuse spray of the powder.

The first patient was a 56-year-old man who was admitted for hematemesis 13 days after endoscopy and EVL for EVB. Resuscitation was started and emergency endoscopy confirmed an actively bleeding post-banding esophageal ulcer (PBEU). Four injections of 1 ml of cyanoacrylate into the bleeding ulcer were done, with temporary hemostasis. However during the next 12 hours, the patient experienced exteriorized blood loss and transfusion of 2 units of red blood cells was required. The second patient, a 53-year-old woman with hepatitis C cirrhosis, was transferred to our institution because of hematemesis 7 days after endoscopy and band ligation for acute variceal bleeding in another institution. Endoscopy was performed in both patients confirming the actively bleeding PBEU. In each patient treatment with one kit of the hemostatic powder was applied until hemostasis was confirmed (**Fig. 1**, **Video 1**). Both patients were kept under surveillance for 24 hours. A follow-up endoscopy 24 hours later disclosed fibrinous deposits on the ulcer with no active bleeding.

This technique may offer a convenient treatment method for controlling hemorrhage in this potentially life-threatening situation.

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Competing interests: None

Video 1

Use of hemostatic nanopowder for hemostasis of an actively bleeding post-variceal banding esophageal ulcer.

Mostafa Ibrahim[1,2], Arnaud Lemmers[1], Jacques Devière[1]

[1] Department of Gastroenterology and Hepatopancreatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
[2] Department of Gastroenterology and Hepatology, Theodor Bilharz Research Institute, Cairo, Egypt

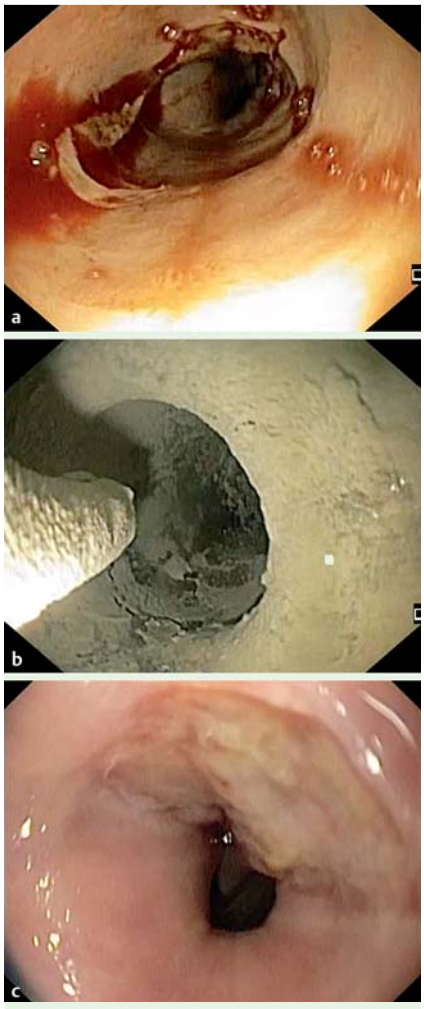

Fig. 1 **a** Actively bleeding ulcer following esophageal variceal band ligation (EVL). **b** Application of hemostatic powder. **c** Appearance at 24-hour follow-up endoscopy.

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Corresponding author
Mostafa Ibrahim, MD
Department of Gastroenterology
Erasme Hospital
Université Libre de Bruxelles
Brussels, Belgium
Fax: +32-2-0106107100
mostafa.ibrahim@webgit.net

4.6. New Developments in Management of Variceal Bleeding

The research group emphasized the novel endoscopic modalities available for variceal bleeding and the gaps in current therapeutic modalities for acute variceal bleeding in a literature review article.

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New Developments in Managing Variceal Bleeding



Mostafa Ibrahim[1,2] Ibrahim Mostafa[2] Jacques Devière[1]

[1]Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; and [2]Department of Gastroenterology and Hepatology, Theodor Bilharz Research Institute, Cairo, Egypt

Liver cirrhosis is the end stage of chronic liver disease, independent of etiology, and is characterized by accumulation of fibrotic tissue and conversion of the normal liver parenchyma into abnormal regenerative nodules. Complications include portal hypertension (PH) with gastroesophageal varices, ascites, hepatorenal syndrome, hepatic encephalopathy, bacteremia, and hypersplenism. The most life-threatening complication of liver cirrhosis is acute variceal bleeding (AVB) which is associated with increased mortality that, despite recent progress in management, is still around 20% at 6 weeks. Combined treatment with vasoactive drugs, prophylactic antibiotics, and endoscopic techniques is the recommended standard of care for patients with acute variceal bleeding. There are many promising new modalities including the combination of coil and glue injection for management of bleeding or nonbleeding gastric varices and hemostatic powder application, that requires minimal expertise, when performed early after admission of a cirrhotic patient with AVB and overt hematemesis acting as a bridge therapy till definitive endoscopic therapy can be performed in hemodynamically stable conditions and without acute bleeding.

Keywords: Portal Hypertension; Variceal Bleeding; Hemostatic Powder.

Portal hypertension is a clinical syndrome defined by pathologic increase of portal venous pressure gradient between the portal vein and inferior vena cava.[1] The hepatic venous pressure gradient (HVPG) accurately reflects the portal pressure gradient in most common causes of cirrhosis. HVPG measurement is the criterion standard method for assessing the presence of clinically significant portal hypertension (CSPH), which is defined as HVPG $\geq$ 10 mm Hg. Ascites and gastroesophageal varices are the most frequent manifestations of CSPH.[2]

The ability to assess liver stiffness, a physical property of liver tissue influenced by the amount of liver fibrosis content, has represented a major advance in this field. Liver stiffness by transient elastography (FibroScan, Echosens, France) can be considered the backbone of the noninvasive diagnosis of liver fibrosis and has proven very accurate for discriminating patients with and without CSPH, with a mean area under the receiver operating curve of 0.93.[3]

Three different risk stages have been proposed for compensated liver cirrhosis, based on 1-year mortality data: low-, intermediate-, and high-risk cirrhosis. Each category of risk is presented with the clinical features, HVPG value, main outcome to be prevented, and main pathophysiologic factor related to that category of risk. The 1-year mortality in these stages is $\leq$1%, 1%–20%, and $\geq$20%, respectively.[2,4]

Patients with a liver stiffness $<$ 20 kPa and a platelet count $>$ 150,000 have a very low risk of having varices requiring treatment and can avoid screening endoscopy.

Varices are present in 50% of patients with cirrhosis, and they form at a rate of 5%–15% per year. Variceal bleeding is the most serious complication; it occurs in one third of patients with varices and causes 70% of all upper gastrointestinal (GI) bleeding episodes in cirrhotic patients. Standardization of supportive care and new therapeutic options reduced bleeding-related mortality from about 50% to 15%–20% in the last 3 decades.[4]

Primary prophylaxis of variceal bleeding consists of one of two approaches: pharmacologic prophylaxis using nonselective beta blockers (NSBBs) or endoscopic prophylaxis using endoscopic variceal ligation (EVL). Both NSBB and EVL are superior to no treatment for the prevention of a first variceal hemorrhage in patients with medium- and large-sized varices and patients with small varices who have red signs.[4]

Propranolol and nadolol at a starting dosage of 20–40 mg/day are used in patients with good tolerability and no contraindication to beta blockers.[5,6]

Abbreviations used in this paper: **AVB, acute variceal bleeding; BRTO, balloon-occluded retrograde transvenous obliteration; CSPH, clinically significant portal hypertension; ES, endoscopic sclerotherapy; EVL, endoscopic variceal ligation; GI, gastrointestinal; HVPG, hepatic venous pressure gradient; NSBB, nonselective beta blocker; SEMS, self-expandable metallic stent.**

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Carvedilol has been recommended at a dosage of 12.5 mg once daily for patients with Child–Turcotte–Pugh class A cirrhosis and 6.25 mg twice daily for patients with Child–Turcotte–Pugh class B or Child–Turcotte–Pugh class C cirrhosis.[4] Furthermore, the recent UK guidelines on the management of variceal haemorrhage[7] advise not exceeding 12.5 mg daily, because higher doses were not more effective in reduction of HVPG and were associated with more adverse effects.

EVL is recommended for patients with medium or large varices who are intolerant of or have contraindications to beta blockers. Its effectiveness versus NSBB for primary prophylaxis has been widely studied. The overall data suggest that EVL is as effective as NSBB with somewhat less hemorrhage but no changes in overall mortality.[8]

EVL should be performed by expert endoscopists to avoid complications including banding-induced ulcerations and bleeding. Also, patients require routine endoscopic surveillance after EVL because of the probability of variceal recurrence. The frequency of endoscopic evaluation depends on multiple factors such as whether the patient has varices or not, size of varices, risk signs, and severity of liver disease. In general, patients require 2–4 sessions for eradication of varices. Combination therapies are not recommended.[7,9]

For patients with large gastric varices, BAVENO VI consensus did not recommend cyanoacrylate injection for primary prophylaxis of gastric variceal bleeding.[10] For the time being, patients with gastric varices should continue to receive NSBB for primary prophylaxis. There are no data supporting the use of transjugular intrahepatic portosystemic shunting (TIPS) or surgery for primary prophylaxis.[2]

Acute variceal bleeding (AVB) mortality differs whether it presents as an isolated complication of cirrhosis (20% 5-year mortality) or whether it presents in association with other complications (over 80% 5-year mortality). Rebleeding contributes to an important part of mortality that ranges between 15% and 25% at 6 weeks.[11]

Management of the Acute Variceal Bleeding Episode

Pharmacologic therapy should be started in all patients with advanced cirrhosis and upper.

GI bleeding known or at risk for having varices.[4,12]

Vasoactive drugs, selectively constricting the mesenteric arterioles and decreasing portal blood flow, are used as initial treatment of AVB before endoscopy. Many studies have shown that the early use of vasoactive drugs reduces the rate of active bleeding, making endoscopy easier to perform for diagnostic and therapeutic purposes.[13] These include vasopressin, somatostatin, and their analogs (terlipressin and octreotide, respectively). Improved hemostasis and reduced 7-day mortality, transfusion requirement, and duration of hospitalization have been confirmed in many studies.[14] The combination of vasoactive drugs with EVL was clearly shown to be superior to EVL alone for improvement of the 5-day success rate.[7,15]

Available evidence does not support a role of proton pump inhibitors for long-term prophylaxis of portal hypertension-related bleeding; however, the use of short-course proton pump inhibitor postendoscopic variceal ligation could reduce postbanding ligation ulcer size.[16]

The use of an intravenous prokinetic agent (e.g., erythromycin) should be considered during the pre-endoscopy patient management phase. Barkun et al[17] reported that an intravenous infusion of different prokinetic agents administered up to 2 hours before endoscopy in patients with acute upper GI bleeding improved endoscopic visualization and significantly decreased the need for repeat endoscopy.

Sedation use before diagnostic endoscopy is routine in North America and Australia but varies considerably among countries in Europe, Asia, and Africa.[18] Midazolam and propofol are both widely used for EVL. The role of general anesthesia with endotracheal intubation is still controversial and cannot be routinely recommended.[19]

Endoscopic sclerotherapy (ES) and EVL are the 2 available endoscopic methods for treating bleeding esophageal varices. ES consists in the injection of a sclerosing agent intravariceally or paravariceally. A variety of sclerosant solutions are used, the most common being ethanolamine oleate (5%), polidocanol (1%–2%), and cyanoacrylate, which proved equally effective for bleeding esophageal varices.[20] Emergency ES for bleeding esophageal varices was shown to be an effective procedure in expert hands[21]; however, it is no longer recommended as the first line of treatment because of high complication rate (systemic bacteremia being the most frequent).[22]

EVL is the standard care for management of AVB.[2] Actively bleeding varices or those with stigmata indicating recent bleeding (such as a fibrin plug or a “red wale” sign) should be primary targets even if they are not located at the gastroesophageal junction. The use of ligating devices may be difficult in patients with severe bleeding because of limited visibility caused by blood accumulating in the tip of the device.[23] It requires experience in therapeutic endoscopy.

After the initial target, additional banding can be performed and is started in the most distal part of the esophagus at the gastroesophageal junction. Bands are applied in a spiral pattern up the esophagus until 28 cm from incisors on all major columns of varices (Supplementary Video 1). For the next procedures, a 1-week ligation interval is often recommended.[24] The decision regarding ligation intervals may be individualized based on physician and patient preferences and local logistics and resources.

EVL combined with a vasoactive drug is considered the standard care for AVB, and it is currently recommended by BAVENO VI.[2] Combining EVL and ES has no advantage.[25] Other techniques such as APC, microwave cautery, and clipping play no role, may be dangerous, and must be avoided.[26,27]

Gastric varices are present in up to 20% of patients with portal hypertension; 65% of these patients bleed within 2 years.[28]

Cyanoacrylate injection is the globally accepted primary intervention for bleeding gastric varices and is highly satisfactory in controlling bleeding.[29] It has proven to be more effective and safer than band ligation and sclerotherapy in this subset of patients and has been considered as standard therapy in Europe, the Middle East, and Asia for more than 25 years.[30]

In our daily practice, we use always a mixture of *N*-butyl-2-cyanoacrylate and lipiodol for bleeding gastric varices using a dedicated 21-gauge needle with the purpose of obliterating the bleeding gastric varices and those at risk to bleed (Supplementary Video 2).[31]

Novel Endoscopic Modalities for Variceal Bleeding

Self-Expandable Metallic Stents (SEMSs)

Dedicated fully covered SEMS (ELLA Danis, Hradec Kralove, Czech Republic) may provide a useful alternative in those cases for which balloon tamponade is considered.[32] In a recent meta-analysis included 13 studies, mainly case series, ranging from 2 to 34 patients (134 patients total) with refractory bleeding from esophageal varices, a SEMS was successfully placed in 95% of patients, achieving hemostasis within 24 hours in 96%.[33] Overall, the pooled estimate rates for failure to control bleeding during follow-up was 0.18.

The major adverse events include rebleeding after 48 hours, ulceration, rebleeding after removal (16%), and stent migration (28%). Hence, retrieval of the stent is recommended within 7 days to avoid development of pressure-induced ulceration of the esophageal wall.[33]

This technique finds a niche of application mainly for patients with esophageal (and not gastric) bleeding varices for whom hemostasis cannot be controlled by pharmacologic or drug therapy. In this high-risk group of patients, SEMS could be considered as a bridge to transjugular intrahepatic portosystemic stent shunting or liver transplantation.

Hemostatic Powder

Recently, hemostatic powders have been added to the endoscopic armamentarium to treat GI bleeding. There are three hemostatic powders currently available for endoscopic usage: hemostatic agent TC-325 (Hemospray; Cook Medical, Bloomington, IN), EndoClot polysaccharide hemostatic system (EndoClot Plus, Santa Clara, CA), and Ankaferd Bloodstopper (Ankaferd Health Products Ltd, Istanbul, Turkey). All three powders, when they have contact with moisture, form a stable mechanical barrier that covers the bleeding site, inducing hemostasis. Only the first one has been investigated in AVB management.

Hemostatic powder (Hemospray) is delivered endoscopically through a dedicated delivery system. It acts as a mechanical barrier when put in contact with moisture (e.g., blood or tissue) in the GI tract: the powder becomes cohesive and adhesive, forming a mechanical barrier that adheres to and covers the bleeding site, achieving very rapid hemostasis.[34] After approximately 24 hours, the adherent layer subsequently sloughs off into the lumen from the mucosal wall and is eliminated from the GI tract.[35]

This technique requires minimal experience in therapeutic endoscopy, a feature that might help solve the problems of delay between admission and definitive endoscopic therapy due to a lack of available expertise. This hemostatic powder is currently licensed for endoscopic hemostasis of nonvariceal upper GI bleeding,[35] including high-risk patients receiving anticoagulant or antithrombotic therapy,[36] those with tumor-related bleeding, and those with lower GI bleeding.[37] In severe peptic ulcer bleeding, it is often considered as a (temporary) salvage therapy.[38]

Hemospray was reported to be useful in emergency management of AVB as an added treatment modality to the medical management before definitive endotherapy, with no major adverse events or device-related mortalities.[39]

There is theoretical risk of gas embolization due to high-pressure gas delivery of the hemostatic agent to the bleeding site; however, the risk of embolization in this group of patients is most probably low because of the fact that the technique is a noncontact application with delivery pressure less than 15 mm Hg, that is, most often inferior to intravariceal pressure.[40] However, use of hemostatic powder in variceal bleeding is off label, and it should be used only within research protocols with institutional review board approvals.

The timing of endoscopic hemostasis in AVB has been a topic of intense recent discussion. The current recommendations for management of AVB combine vasoactive drugs at admission with endoscopic therapy within 12 hours plus prophylactic antibiotics, although the availability of an on-call, experienced GI endoscopist proficient in endoscopic hemostasis is not always easy in most centers, a limitation that raised the need for a bridging maneuver until more definitive endoscopic therapy could be provided.[40]

We recently performed a randomized controlled trial in which 86 patients with AVB were randomized to receive medical therapy plus classical endotherapy within 12–24 hours of admission or medical treatment plus hemostatic powder application within 2 hours of admission (Supplementary Video 3) followed by classical endotherapy within 12–24 hours. This novel policy consisting of early application of a hemostatic powder in addition to standard pharmacotherapy and endotherapy significantly reduced clinical rebleeding within 24 hours compared with standard pharmacotherapy plus endotherapy alone and had an impact on early and 30-day survival,[41] suggesting a role for this powder as a bridge therapy.

Also, hemostatic powder application had been studied on a small scale for such difficult bleeding situations as postbanding ligation ulcer[42]; however, to date the only validated option in this situation is a high dose of proton pump inhibitors and injection of cyanoacrylate underneath the ulcer.[43]

Transjugular Intrahepatic Portosystemic Shunting

TIPS involves the creation of a low-resistance channel between the hepatic vein and the intrahepatic portion of the portal vein (usually the right branch) using angiographic techniques. The tract is kept patent by deployment of a dedicated expandable metal stent across it, thereby allowing blood to return to the systemic circulation. Positioning of TIPS as a rescue treatment has been challenged in recent studies, which recommend TIPS as the initial treatment of choice in high-risk patients, which improves their prognosis.[44]

TIPS with covered stents is the rescue therapy of choice if combined pharmacologic and endoscopic treatment have failed. Rebleeding during the first 5 days may be managed by a second attempt at endoscopic therapy, and if severe, polytetrafluoroethylene-covered TIPS is likely the best option.[45]

Randomized controlled trials have shown that, compared with standard therapy, early TIPS (placed within 72 hours of admission) is associated with significantly lower treatment failure and mortality rates in carefully selected high-risk patients with Child-Pugh class B liver cirrhosis and active bleeding during endoscopy or patients with Child-Pugh class C liver cirrhosis. Furthermore, any patient who experiences rebleeding should be considered for TIPS placement.[4] Even if clinical evidence exists for selected patients that TIPS is the treatment of choice after initial failure of endotherapy,[46] its availability within the recommended time frame (48–72 hours) remains a matter of concern in many places.

Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)

From the interventional radiologist's perspective, the main tools available for the management of gastric varices are TIPS and BRTO.

BRTO is an interventional radiologic technique that involves occluding blood flow by inflation of a balloon catheter within a draining vessel, followed by instillation of a sclerosant proximal to the site of balloon occlusion.[47]

BRTO requires the presence of a spontaneous shunt into which a balloon catheter is retrogradely introduced. Ethanolamine oleate has been used most commonly in Asia as a sclerosant.[48]

However, reported complications include renal dysfunction, pulmonary edema, cardiogenic edema, and anaphylaxis.

A recent meta-analysis of a total of 1016 patients from 24 studies showed that the technical success rate for BRTO was 96.4%, the clinical success (defined as no recurrence or rebleeding of gastric varices, or complete obliteration of varices on subsequent imaging) rate was 97.3%, and the esophageal variceal recurrence rate was 33.3%.[48]

Endoscopic Ultrasonography (EUS)–Guided Angiotherapy

In the last few years, EUS-guided vascular access and injection emerged as a new option to achieve hemostasis. EUS provides real-time, high-quality images of both the GI wall and major arterial and venous vessels like the confluence, splenic artery, and hepatic artery that can be accessed and obliterated.[49]

This technique may allow a rescue EUS-guided therapy via injection of cyanoacrylate or insertion of coils.

The safety and efficacy of the EUS-guided sclerotherapy were shown in a randomized controlled trial that compared endoscopic sclerotherapy with EUS-guided sclerotherapy in which 50 cirrhotic patients were randomized to undergo either endoscopic sclerotherapy or EUS-guided sclerotherapy. EUS-guided sclerotherapy was at least as effective as endoscopic sclerotherapy, with a lower recurrence rate.[50]

EUS has a higher sensitivity to detect gastric varices because even in situations with active bleeding or clots in the stomach, EUS visualization is not impaired, enabling a safer and faster therapeutic hemostatic procedure. Romero-Castro et al[51] compared cyanoacrylate injection with coil deployment and showed a similar efficacy but fewer adverse events in the coil group (9%) compared with the cyanoacrylate injection group (58%). It must be noticed, however, that 9 of the 11 complications observed in the cyanoacrylate group were asymptomatic glue micro-embolisms observed in the lungs on computerized tomography scan.

As an alternative approach to glue injection, coils usable for intravascular embolization treatments via EUS fine needle aspiration have become commercially available. Hence, combining coil and cyanoacrylate (Supplementary Video 4) is a hybrid approach that may offer the advantages of both techniques. When used in conjunction with cyanoacrylate injection, coils may favor immediate polymerization of the glue and reduce the risk of embolization. The synthetic fibers ("wool coils") covering the coils function as a scaffold to retain cyanoacrylate within the varix and may decrease the amount of glue injection needed to achieve obliteration.[52]

A recent series was published regarding combining cyanoacrylate and coil for the treatment of gastric fundal varices with more than 150 patients. Technical success was 99%; the mean number of inserted coils was 1.4, and the mean amount of cyanoacrylate injected was 2 mL. To our knowledge, there are no data analyzing the cost of using coils for hemostatic EUS-guided procedures.[53]

Limitations of coils include the relative technical difficulty of deploying multiple coils within the varix lumen and the cost when multiple coils are required for varix obliteration.

Conclusions

The management of variceal bleeding combining appropriate medical support, pharmacologic therapy, and endoscopic treatment is well established. TIPS has become a new modality that should be offered, if possible, early after a first episode of bleeding in patients with severe liver diseases. Other new modalities might find their place in the future armamentarium to improve the outcomes of these patients. In the case of failure to control bleeding from esophageal varices, temporary stent placement may offer a bridge to TIPS or liver transplantation.

Gastric varices are usually considered more difficult to manage, and glue injection is associated with potential risks. EUS-guided coil application, used alone, offers a possible alternative with a lower risk and is particularly useful in areas where variceal obliteration with cyanoacrylate is not approved. The combination of coils and glue might offer a lower-risk alternative at a reasonable cost. Finally, in the case of relapsing bleeding due to gastric varices and TIPS contraindication, BRTO could find a niche of application.

The powder application by endoscopy is a simple technique that does not require expertise in endotherapy; it

could be proposed with few logistical hurdles early after clinical presentation, offering a possibility for early hemostasis that could potentially improve outcomes and lead to elective therapy in stable conditions. Its role as a rescue therapy for failure of elective therapy or early relapse of bleeding after EBL should not be neglected.

All of these modalities may influence different parts of variceal management. Some have not yet found their place in the currently accepted recommendations for treatment, but it is highly probable that their roles will soon be better defined in improving overall outcomes for these patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.02.023.

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Reprint requests
Address requests for reprints to: Mostafa Ibrahim, MD, Department of Gastroenterology, Erasme Hospital, University Libre de Bruxelles, 808 Route De Lennik, B 1070, Brussels, Belgium. e-mail: mostafa.ibrahim@webgit.net.

Conflicts of interest
The authors disclose no conflicts.

DISCUSSION, PERSPECTIVES, AND RECOMMENDATIONS

5. DISCUSSION, PERSPECTIVES, AND RECOMMENDATIONS

5.1. DISCUSSION

The present PhD thesis work included a pilot study followed by two confirmatory prospective clinical trials (the first was a single arm trial and the second was a randomized clinical trial). The trials investigated the safety and efficacy of hemostatic powder TC-325 (Hemospray, Cook Medical, Winston-Salem, North Carolina, USA) added to standard of care medical treatment for acute variceal bleeding (AVB) in patients with portal hypertension due to liver cirrhosis who presented to the outpatient emergency room of Erasme Hospital, ULB and Theodor Bilharz Research Institute. These were the first studies to evaluate this treatment in this indication and to assess its impact on outcomes when compared to the current standard of care. We established the safety and efficacy of the hemostatic powder treatment in AVB, showed that it could play a pivotal role in early management of this severe clinical occurrence, and demonstrated the potential impact of the treatment on outcomes, findings which could potentially establish it in the standard of care for such patients.

The initial management of patients with AVB includes hemodynamic resuscitation, prevention or treatment of infection, and pharmacologic drug therapy and should be initiated at the time of admission to reduce portal blood flow and should not be delayed pending confirmation of AVB (162). These treatments have been shown to

decrease mortality and improve hemostasis in patients with acute variceal bleeding (163). The purpose of this therapy is to decrease the period of liver ischemia due to the acute episode.

Bleeding gastroesophageal varices are typically managed with endoscopic therapy (band ligation or histoacryl therapy). If endoscopic therapy fails to achieve hemostasis, treatment options include transjugular intrahepatic portosystemic shunt (TIPS) placement or creation of a surgical shunt (164).

Although endoscopy is the cornerstone of AVB management, the timing of endoscopy is controversial and challenging in many instances (164). In general, the endoscopic procedure should be performed within 12 to 24 hours of admission, after the patient is hemodynamically stabilized, and antibiotic and vasoactive drugs have been received (126). Immediate endoscopy on admission is discouraged because the patient is usually unstable, and enough time has not been allowed for vasoactive drugs to take effect. In addition, a large amount of blood in the stomach increases the risk of aspiration and limits the ability to complete a diagnostic examination (126) and identify the bleeding site.

AASLD guidelines suggested the timing of endoscopy should be within 12 hours for acute variceal bleeding (98). In a retrospective study, Cheung and colleagues reported that among patients who presented with hemodynamically stable variceal

bleeding, there was no significant difference in mortality in patients with endoscopy performed within 4 hours versus 8 hours or 12 hours (165). This study could not answer the full question of timing of endoscopy for AVB and the major issue concerns unstable patients. Another study reported delayed endoscopy (endoscopy time > 15 hours) as a risk factor for increased mortality in acute variceal bleeding (125). Many of the limitations currently outlined in the guidelines state that early endoscopy can be complex with the need to clearly identify the bleeding site in emergency situations.

Endoscopy in AVB may be feasible when endoscopy services are already available in the hospital with continuous coverage. However, many endoscopic services do not provide continuous coverage. In addition, particularly in Western countries, the appropriate measures for primary and secondary prophylaxis for AVB render the incidence of this type of bleeding less frequent and, as a consequence, the ability to train doctors to perform these procedures decreases, making it preferable to perform the treatment as an elective procedure performed by experienced physicians available in a dedicated unit.

Both organizational and human resources are needed, and sometimes difficult to obtain, in order to perform urgent endoscopy before the next working day. Urgent endoscopy during active bleeding requires technical expertise in therapeutic endoscopy by a highly qualified endoscopist and is technically demanding and not

always successful (166). Endoscopy in this situation is probably less effective, even in expert hands, than elective therapy performed under stable conditions and in a routine environment. There is, therefore, an obvious need to have a simple endoscopic intervention that can stop the bleeding, even temporarily, and allow for optimization of the overall management of these patients.

An audit performed 10 years ago in the United Kingdom reported that only 55% of endoscopies were performed within 24 hours of admission and that standard endoscopic therapy was underused, particularly in AVB (167). Indeed, the risk factors for in-hospital mortality in AVB patients not only include delayed endoscopy but also failure of first endoscopy, severity of cirrhosis, and hematemesis.

Therefore, the development of an easy endoscopic technique that allows physicians to achieve successful immediate hemostasis and that can be performed by any senior or junior endoscopist and does not require expertise in therapeutic endoscopy could have a major impact on the treatment and outcomes of patients with ABV in daily practice.

The idea behind our first study was that the application of hemostatic powder, through its simplicity, could solve the problem of early hemostasis and availability of expert endoscopists. Our pilot study in 2013, that included the first nine patients,

showed that hemostatic powder was useful in emergency management of AVB as a bridge towards more definitive therapy (168).

We evaluated the efficacy of the hemostatic powder in a larger population and showed that the endoscopic application of hemostatic powder after a protocol requiring minimal expertise allowed us to stop the bleeding, stabilize the patient, and provide additional therapy under optimal conditions within the next 24 hours. In addition, early application of hemostatic powder for management of AVB could avoid failures/delay of acute hemostasis related to technical failures or to the lack of expert endoscopists available to perform advanced procedures (168). We confirmed the results of our pilot study by conducting single arm trial with a larger number of patients and reported that primary endoscopic hemostasis was achieved in all patients (n=30) at the time of Hemospray application and that clinical hemostasis was achieved in 29/30 (96.7%) patients through the first 24 hours after powder application while only one patient experienced hematemesis six hours after Hemospray application. No clinical signs of embolization were observed, confirming the safety of this procedure in this particular indication, and no other major adverse events such as bowel obstruction or allergic reaction were observed. The results from these trials illustrated that hemostatic powder application can be done safely in a simple procedure that does not require precise identification of the bleeding sites. In addition, the procedure can be done quickly and usually stops the

bleeding, providing a time window to plan more definitive elective endoscopy therapy. Another benefit is that later elective therapies become easier since, in most cases, the bleeding has been stopped hours before.

Early clinical experience for the efficacy of Hemospray in achieving hemostasis was investigated for acute peptic ulcer bleeding by Sung *et al*. (155) and revealed that acute hemostasis was achieved in 95% of 20 patients and that rebleeding occurred in two patients within 72 hours without any cases of mortality or major adverse events reported during 30-day follow-up. Additional investigations (169)(170, 171) including more severe cases illustrated the fact that hemospray, especially when applied in cases of severe bleeding, cannot always be considered to be a definitive therapy but is a bridge of hemodynamic stability that allows physicians to perform additional treatment under more optimal conditions. A similar rationale was behind the design of the next evaluation in AVB, since the cause of bleeding is obviously not treated by the powder in such patients.

We designed a randomized clinical trial that compared the early addition of hemostatic powder application to the standard pharmacotherapy plus endoscopy to the standard pharmacotherapy plus endoscopy alone (158). We showed that early powder application, in addition to standard pharmacotherapy and endoscopy, dramatically reduces clinical rebleeding within 24 hours compared with standard management alone and allows for achievement of endoscopic hemostasis at the time

of second endoscopy (at a mean of 16 hours) in all cases, rendering treatment easier. These were the primary end points. Survival was a secondary endpoint and the results of the survival analysis suggested that early application of hemostatic powder may have an impact on survival rates of patients with AVB at 6 weeks and 30 days by decreasing early and late rebleeding and its associated complications and by providing a more effective early hemostasis than pharmacotherapy. However, these results should be viewed with caution and should be confirmed by further randomized trials because this trial was not powered for survival analysis.

It must be noted, however, that very few randomized controlled trials designed to provide a technical evaluation have been associated with such a clear difference in outcomes. One of the major effects of early hemostasis could be to dramatically reduce the duration of liver ischemia due to persistent bleeding. It is clear from our observations that even if medical and pharmacological therapy can control clinical and endoscopically-visualized bleeding at 12-24 hours, it takes much more time than powder application. This is illustrated by the fact that, at elective endoscopy, all the patients treated with Hemospray had no more blood in the stomach.

The availability of a simple hemostatic endoscopic technique that could be performed by physicians with basic expertise in endoscopy could allow us to revisit the current treatment recommendation if it was associated with improved outcomes. The application of hemostatic power basically consists of spraying powder into the

upper GIT from the upper part of the stomach to the mid-third of the esophagus and requires only limited experience in endoscopy to perform this technique. Using Hemospray in the treatment of upper gastrointestinal hemorrhage in patients on antithrombotic therapy was effective and showed that Hemospray could be a promising treatment in both patients with and without antithrombotic therapy (172).

Hemostatic powder provides a local covering effect with little or no tissue injury (153, 155, 157, 158, 166, 168, 173-175) unlike many of our endoscopic therapies (e.g., thermal devices, sclerosants) which produce significant tissue injury. Our clinical trials did not report any adverse events related to the powder application itself.

Theoretical concerns, including perforation due to the agent's delivery system, vascular injury, local tissue injury, embolization, GI obstruction due to the impaction of sloughed powder, allergic reactions, and inhalation, were not observed but should be assessed in a follow-up clinical trial (176).

The major concern regarding the risk of embolization is most likely to be non-existent since the pressure of powder delivery, even at the tip of the catheter is only around 12 - 15 mm Hg. That is below the variceal pressure in most cases, and the principle of application is non-contact.

A limitation of our research is that TIPS was not offered to CHILD B and C patients.

There is no direct comparison of efficacy between early EVL and early Hemospray. Further evaluation will be needed to determine whether the early use of Hemospray followed by TIPS equally benefits the subgroup of patients with more severe liver disease. More importantly, other studies might compare the sequence of emergency powder-elective banding followed or not by TIPS in this group of patients, considering that TIPS might be less useful for early management of bleeding in such conditions but also that, being performed in more stable conditions, it could be safer at mid- and long-term.

Very early hemostasis could prevent liver ischemia with its deleterious consequences. Performing other endoscopic therapies very early is complex and could be associated with a high risk of complications. Therefore, in our research we designed a study using a simple technique that could be performed very early and doesn't require the identification of the bleeding point. This is why this technique can be performed under conditions that are difficult for other definitive endoscopic treatments due to massive bleeding. The application of the hemostatic powder theoretically induces immediate interruption of bleeding which prevents liver ischemia in a temporary fashion that lasts until the definitive treatment, endoscopic hemostasis in our studies. Therefore, this could hypothetically impact the reduction of the duration of ischemia and dramatically improve the patient's condition, even more than vasoactive medications.

5.2. PERSPECTIVES AND RECOMMENDATIONS FOR FUTURE RESEARCH

We believe that the present research could have a significant impact on future recommendations and guidelines regarding the initial management of cirrhotic patients with AVB due to increased portal hypertension. The research also evaluated the efficacy of a therapeutic technique for treatment of AVB by developing a new simple hemostatic endoscopic technique that could be performed by physicians with basic expertise in endoscopy and allow us to revisit the current treatment recommendations for AVB.

We reported that the risks of treatment failure and death were higher in patients with Child-Pugh class C disease than class A and B disease. Due to small sample size, our trial was not powered to conduct appropriate subgroup analysis according the Child-Pugh classification. Therefore, further evaluation will be needed to determine whether the use of Hemospray equally benefits these subgroups of patients.

Furthermore, given that the current recommendations of early TIPS performance in AVB occurring in patients with advanced disease are difficult to fulfill, our planned future large trial will investigate whether early hemostasis in such patients allows better and easier definitive endoscopic control of AVB, rendering the early

performance of TIPS unnecessary. The ideal would be to be able to apply a powder during the emergency without the need of endoscopy.

In this regard, we are working on a specifically-designed catheter for powder application that facilitates the application even in the emergency room within a few minutes of patient admission. The technique will be tested in a safety and efficacy study to assess whether this technique for early hemostasis can provide hemodynamic stabilization and endoscopic hemostasis.

Our future step is to investigate the efficacy of early endoscopic band ligation versus early TIPS placement after Hemospray application for all patients with AVB.

We also plan to design a multicentric trial in high volume centers of AVB with early and late survival as primary end points.

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