Managment of acute esophageal variceal bleeding

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Abstract

Bleeding from esophageal varices is a severe complication of portal hypertension due to liver cirrhosis. he objectives in managing this condition involve hemorrhage control, minimizing re-bleeding risk, averting complications, and reducing mortality, necessitating a multidisciplinary approach. In acute episodes, interventions encompass vasoactive drugs, antibiotics, and endoscopic techniques. Patient classification, using hepatic venous pressure gradient (HVPG) and scoring systems, aids in risk stratification and timely intervention. Pharmacologically, vasoactive drugs play a pivotal role, and emerging strategies like TEG-guided transfusion and early TIPS contribute to evolving standards. Overall, recent decades have witnessed substantial advancements in esophageal variceal bleeding treatment, enhancing outcomes and refining therapeutic approaches.

Introduction

Bleeding from esophageal varices is one of the most severe complications of portal hypertension caused by liver cirrhosis, associated with a mortality rate of 10-20% within 6 weeks of the incident [1].

The goals of treating bleeding from esophageal varices include controlling the bleeding, reducing the risk of re-bleeding, preventing complications, and decreasing mortality. Achieving these goals requires a multidisciplinary approach involving anesthesiologists, endoscopists, and hematologists, among others. In the acute bleeding from esophageal varices, various interventions are employed, including vasoactive drugs, antibiotics, and endoscopic techniques [2].

After successfully controlling the bleeding, patients should undergo long-term observation to prevent recurrence of bleeding and eliminate esophageal varices. This is a crucial step, as approximately 60% of patients experience re-bleeding within 2 years of the initial incident, with a mortality rate of 30% [3].

Patient Classification

Portal hypertension is defined as a hepatic venous pressure gradient (HVPG) > 5 mmHg, indicating the difference between wedged and free pressures. Wedged pressure is measured by introducing a catheter into the hepatic vein and wedging it in a small vessel or inflating a balloon to occlude a larger branch of the hepatic vein, closely correlating with portal pressure. Free pressure, on the other hand, is the difference between portal pressure and pressure in the inferior vena cava. Clinically significant portal hypertension is considered when HVPG is > 10 mmHg. The risk of bleeding significantly increases when HVPG is >12 mmHg, and a value > 20 mmHg indicates a lack of bleeding control and increased mortality [4].

The development of esophageal varices is likely associated with the degree of liver dysfunction. The incidence of esophageal varices in patients classified as Child-Pugh class B/C is 71.9%, while in class A, it is 42.7%. Moreover, the risk of larger varices is observed more frequently in patients in Child-Pugh class B/C than in class A [5].

The assessment of liver function also involves the Model for End-Stage Liver Disease (MELD) scoring system, which is more accurate than the Child-Pugh scale. A MELD score >19 is associated with a 20% mortality rate within 6 weeks. Both scoring systems are used to identify high-risk patients and initiate appropriate treatment early [4].

Treatment Methods

Resuscitation and Emergency Treatment

Patients with active bleeding from esophageal varices require intensive, multidisciplinary monitoring. The priority is the assessment and protection of the airways, followed by evaluating the respiratory and circulatory systems. In the case of airway obstruction, endotracheal intubation should be performed. In cases of significant blood loss to ensure hemodynamic stability, circulating blood volume should be replenished using red blood cell concentrates. It is also essential to monitor vital signs. Hematocrit and hemoglobin levels should be measured every 6 hours for the first two days and then every 12 hours for the next three days [6].

In a landmark study from 2013, the optimal blood transfusion strategy was investigated. Two methods were compared: liberal and restrictive, with several benefits demonstrated for the latter. According to the restrictive strategy, blood transfusion should be initiated when the hemoglobin level falls below 7 g/dl, and target values are set between 7-9 g/dl, compared to the liberal strategy, which aims for target levels within 9-11 g/dl [7]. The reason for the superiority of the restrictive method over the liberal one is that aggressive resuscitation can worsen portal hypertension. Another meta-analysis, incorporating a total of 5 randomized controlled trials, confirmed the benefits of the restrictive method, with fewer complications in terms of deaths and recurrent bleeding [8]. The preferred method for administering blood products is transfusion guided by thromboelastography (TEG). A randomized study conducted in 2020 demonstrated reduced transfusion of blood products to correct coagulopathy without worsening hemostasis compared to conventional transfusion [9].

One of the treatment methods aimed at quickly controlling bleeding from esophageal varices is the insertion of a Sengstaken-Blakemore tube. This tube was developed by Robert W. Sengstaken and Arthur H. Blakemore in 1950 and has since been used as a temporary method to stop bleeding. It is a type of balloon tamponade placed in the esophagus for a

maximum of 24 hours. The tube is indicated for unstable patients with uncontrolled bleeding, often as a rescue method when other treatment methods are not yielding results. The tube may also be used in situations where endoscopy or specialist physicians are not readily available as a life-saving interim measure to stop bleeding. It is important to note that the Sengstaken-Blakemore tube is not a definitive treatment, and further therapeutic measures are necessary to prevent further bleeding and improve the patient's condition. With proper preparation, technique, and monitoring, the use of the Sengstaken-Blakemore tube can yield positive results and improve the patient's prognosis. However, the risk of complications must be considered, and collaboration between specialists is essential to ensure the highest quality of medical care [10].

According to a study analyzing clinical data from 66 patients with bleeding from esophageal varices, the Sengstaken-Blakemore tube provided initial hemostasis in 75.8% of patients, but its use was associated with numerous complications. Rebleeding occurred in 22% of patients, and 6% experienced esophageal rupture, while the 30-day mortality rate was 42.4% [11]. Other complications that may occur include airway obstruction and aspiration pneumonia [12].

An alternative to the Sengstaken-Blakemore tube is the use of self-expanding metal stents, which are placed endoscopically without radiological control. These stents can be removed or left in the esophagus for up to 2 weeks. According to a randomized controlled trial, esophageal stents were compared with balloon tamponade in patients with liver cirrhosis and uncontrolled bleeding from esophageal varices. The study demonstrated that survival up to the 15th day and bleeding control were better with the use of stents. Additionally, serious adverse events were less frequent in the stent group compared to balloon tamponade. However, no significant differences were observed in 6-week survival rates [13].

Hemospray is a hemostatic powder approved for endoscopic control of upper gastrointestinal bleeding unrelated to varices. One of the advantages of using Hemospray is that it does not require specialized knowledge in endoscopic therapy due to the ease of powder application to the esophagus. In a prospective, single-arm study from 2015, the effectiveness of the hemostatic powder was investigated in 30 patients with acute bleeding from esophageal varices to determine whether this method could be used as a bridging therapy in the treatment of esophageal variceal bleeding towards more advanced treatment methods. Immediate hemostasis was achieved in all patients after applying the powder. In one patient, six hours after the application, bloody vomiting occurred, necessitating endoscopy and banding of the bleeding varices. No deaths were reported during the 15-day

observation period [14]. In another randomized study involving 86 patients with acute bleeding from esophageal varices, participants were divided into two groups: an intervention group and a control group. The intervention group was treated with immediate endoscopy (within 2 hours) using the hemostatic powder, followed by early elective endoscopy (within 12-24 hours). The control group was treated only with early elective endoscopy. In the intervention group, 4 patients required rescue endoscopy due to bleeding, compared to 13 patients in the control group. The remaining patients achieved better hemostasis in the intervention group than in the control group. Additionally, 6-week survival significantly improved in the intervention group. However, despite the benefits demonstrated in studies, Hemospray is not approved by the Food and Drug Administration (FDA) for the treatment of acute bleeding from esophageal varices, primarily due to theoretical concerns about systemic embolization [15].

Antibiotic Prophylaxis

Individuals suffering from advanced liver cirrhosis and experiencing gastrointestinal bleeding are at significant risk of bacterial infections. Randomized controlled trials have shown that antibiotic prophylaxis can reduce the risk of infections, recurrence of bleeding, and mortality in these patients [16,17]. However, the benefits of antibiotic therapy are not clear-cut for patients with less advanced liver cirrhosis. In a retrospective study, patients in Class A of the Child-Pugh scale did not show a difference in mortality between those using antibiotic therapy and those not using it. Further research is needed for antibiotic prophylaxis in this subgroup [18]. The choice of the appropriate antibiotic should be based on an individual assessment of the patient's risk and local patterns of antimicrobial sensitivity. Intravenous ceftriaxone at a dose of 1g/24h, administered for a maximum of 7 days, should be the first-line treatment for patients with advanced liver cirrhosis in hospital settings. This is particularly relevant in environments where the incidence of bacterial infections resistant to quinolones is high, and for patients who previously received prophylaxis with quinolones. For other patients, oral norfloxacin at a dose of 400 mg twice daily should be used [1]. However, it is worth noting that a randomized controlled trial demonstrated that intravenous ceftriaxone is more effective than oral norfloxacin in preventing infections in patients with liver cirrhosis [19].

Endoscopy

After initial hemodynamic stabilization of the patient, within the first 12 hours of admission, upper gastrointestinal endoscopy should be performed to determine the cause of bleeding and initiate appropriate endoscopic treatment [20]. Delaying endoscopy by more than 15 hours from admission is associated with an increased risk of death [21]. In the case of confirmed bleeding from esophageal varices in the endoscopic examination, based on signs of recent bleeding or the presence of a fibrin plug, endoscopic variceal ligation (EVL) combined with vasoconstrictor drugs should be performed. The combination of these two treatment methods has greater benefits than using each one individually. This treatment is currently the gold standard in the management of acute bleeding from esophageal varices. To facilitate the procedure, in the absence of contraindications (prolonged QT interval), erythromycin at a dose of 250 mg can be administered 30-120 minutes before endoscopy. If endoscopic variceal ligation is not possible for technical reasons, sclerotherapy should be considered [20]. Sclerotherapy involves injecting 5% ethanolamine oleate intravenously during endoscopy to stop bleeding. An alternative treatment method is endoscopic injection of N-butyl-2-cyanoacrylate into the bleeding varix, which also stops bleeding. Both methods have similar efficacy according to a 2019 study involving 113 patients [22].

Other endoscopic techniques include argon plasma coagulation (APC), tissue glue injection, endoloop (detachable nylon loops as an alternative to EVL), and endoscopic variceal ligation. However, additional studies on larger populations are needed to confirm the effectiveness and safety of alternative treatment techniques [23].

According to guidelines, the optimal time for performing endoscopy is within 12 hours of the incident. However, a recent meta-analysis of five studies suggested that the timing of endoscopy does not have a visible impact on mortality and the risk of re-bleeding. The analysis involved a total of 1307 patients with liver cirrhosis. Two groups of patients were compared: those who underwent urgent endoscopy (<12h) - 857 patients and those with non-urgent endoscopy (>12h) - 457 patients. There was no significant difference in the mortality rate between the groups, and the frequency of re-bleeding was similar. However, the results of this study require careful interpretation due to the heterogeneity of the included studies in the meta-analysis, and endoscopy should be performed in a time adapted to the patient's condition [24].

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

In cases where endoscopic methods are ineffective in acute bleeding from esophageal varices, the transjugular intrahepatic portosystemic shunt (TIPS) procedure is applied. This involves creating an intrahepatic shunt between the portal vein and one of the hepatic veins using a stent, accessed through the internal jugular vein. Studies indicate that the use of rescue TIPS allows for bleeding control in 90-100% of patients, with a re-bleeding rate of 6-16% [25].

Increasing evidence from recent studies suggests that the early application of TIPS (before treatment failure) in patients at high risk of treatment failure is associated with a significant reduction in treatment failure and mortality [26, 27, 28]. These are patients with a hepatic venous pressure gradient (HVPG) > 20 mmHg or belonging to Class C in the Child-Pugh scale, or meeting both criteria [29,30]. Especially in a pivotal randomized controlled trial from 2010, researchers found that patients with liver cirrhosis and active bleeding may benefit from early TIPS within 72 hours of diagnostic endoscopy. In that study of 63 patients, 31 were assigned to the group treated with pharmacotherapy combined with endoscopic band ligation (EBL), and 32 were assigned to the group that underwent early TIPS. The results clearly demonstrated that in patients classified in Child-Pugh Classes B and C with active bleeding, early TIPS was associated with a lower risk of uncontrolled bleeding, reduced re-bleeding, and mortality, without increasing the risk of developing hepatic encephalopathy [27]. According to a meta-analysis from 2020, which included 5 studies evaluating the role of early TIPS in high-risk patients, the efficacy of preventing uncontrolled bleeding was 2% compared to 17% in those treated conventionally [31]. However, additional studies are necessary to clarify which criteria should be preferred for classifying high-risk patients before the application of early TIPS and whether appropriate risk stratification can optimize treatment [1].

Pharmacology

The standard therapy for bleeding from esophageal varices involves the use of vasoactive drugs in combination with endoscopic therapy. These drugs include terlipressin, somatostatin, and octreotide. According to current recommendations, vasoactive drugs are initiated when there is suspicion of bleeding from esophageal varices and are administered for 3 to 5 days. Starting drug administration before endoscopy reduces bleeding, facilitates endoscopic therapy, improves bleeding control, and potential survival. Their mechanism of

action involves narrowing splanchnic vessels, reducing portal pressure due to decreased blood flow in the portal system [1]. A meta-analysis from 2012 demonstrated that the use of vasoactive drugs reduces 7-day all-cause mortality and the need for blood transfusion. These drugs also provide better bleeding control and shorter hospital stays [32]. The effectiveness of these drugs was assessed in the aforementioned meta-analysis and a randomized controlled trial in 2014, with no significant differences in hemostatic effects and safety between them [32, 33]. Guidelines recommend the use of vasoactive drugs for 3-5 days, but a randomized controlled trial from 2015 showed that octreotide use for 2 days is sufficient and equally effective as a 5-day infusion, with the added benefit of being more cost-effective [34]. It's worth noting that in patients treated with terlipressin, especially those with preserved liver function, hyponatremia occurred. Therefore, monitoring sodium levels is recommended during the use of this drug. Since acute bleeding from esophageal varices often leads to encephalopathy, lactulose can be used prophylactically to prevent it [1].

Summary

Significant progress has been made in the treatment of esophageal variceal bleeding in recent decades, contributing to improved survival in this serious complication of portal hypertension. The improvement involves better overall management in emergency situations and a deeper understanding of the fundamental mechanisms of portal hypertension, leading to the rational use of drugs based on this understanding. The development of patient classification systems allows for better identification of high-risk groups and the implementation of more personalized therapies tailored to individual patient needs. Research into new management strategies, such as transfusion based on TEG protocol or early TIPS application, has contributed to advancements in the treatment of esophageal variceal bleeding.

Disclosures

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