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Periprocedural management of acute variceal bleeding

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ABSTRACT

Acute variceal hemorrhage is a life-threatening complication of cirrhosis and certain non-cirrhotic conditions. The incidence of esophagogastric varices ranges from 20%-80% among cirrhotic patients, establishing it as a well-known health concern. Management of variceal bleeding has advanced over the past 30 years but an overall mortality rate of 10%-20% remains. Patient death is often due to complications of hemodynamic instability, coagulopathy, infection, malnutrition, or subsequent rebleeding. Herein, we highlight the periprocedural management of variceal hemorrhage and its complications.

1. Introduction

Esophageal or gastric varices (EGVs) are present in 40%-50% of patients at the time of initial diagnosis of cirrhosis. The annual rate of development of varices is 8% among patients with cirrhotic without varices at baseline [1]. The prevalence of EGV is higher among patients with decompensated liver disease (Child Turcotte Pugh [CTP] A cirrhosis: 20%-40% vs CTP C cirrhosis: 80%) and may be seen in selected disease states such as primary biliary cirrhosis in the absence of cirrhosis [2–4]. Acute variceal bleeding (AVB) is a common presentation in patients with decompensated liver disease. Though early recognition and improved therapy for AVB have decreased mortality within 6 weeks from 30%-60% to 10%-20% over the last 3 decades, it remains an important cause of premature mortality [5–8]. This review highlights periprocedural management of AVB and salient features from recent society guidelines across the United States, Europe, and Asia [9–12].

Early recognition and appropriate intervention are essential to the management of patients with AVB. One in 3 patients with EGV will develop AVB. Among those who bleed, nearly half of the bleeding episodes will stop spontaneously without intervention; rates of spontaneous cessation are lower with increasing degree of hepatic decompensation. Approximately, 40% of liver-related deaths are directly attributed to bleeding and shock, and the remainder is attributed to renal failure, hepatic encephalopathy (HE), and sepsis. Hence, anticipation and mitigation of such complications remain important.

2. Predictive models

2.1. Presence of varices

The role of noninvasive serum markers and prediction of presence of varices continue to evolve. Among all patients presenting with upper gastrointestinal bleeding, noninvasive serum markers, such as the platelet count (cutoff 122,000/mm^3), aspartate transaminase (AST) platelet ratio index (AST to platelet ratio cutoff 1.5) and Lok index (cutoff 0.9), were able to predict the presence of varices before endoscopy (area under the receiver operator curve = 0.8) and moderately predict varices as the source of bleeding (area under the receiver operator curve: 0.73-0.77). However, these markers could not distinguish between variceal source vs nonvariceal causes of bleeding in patients with cirrhosis [13].

2.2. Bleeding, rebleeding, and death

Multiple studies have identified independent factors that predict risk of bleeding, rebleeding and death in AVB. However, results are often discordant and often take into account findings on endoscopy as predictors of early mortality after AVB. Predictors of bleeding include presence of decompensated cirrhosis (CTP B or C), size of varices, and presence of high-risk stigmata upon endoscopy (red wale marks) [14,15]. Predictors of rebleeding or treatment failure include model for end-stage liver disease (MELD) score, CTP score, hepatic venous pressure gradient (HVPG) $\geq$20 mm Hg, development of infections, endoscopic appearance (active bleeding and clot on varix), and shock [16,17]. For management of gastric

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varices with balloon-assisted retrograde transvenous obliteration, CTP score predicts a higher risk of perioperative rebleeding and shorter survival [18]. Predictors of mortality include the above factors as well as hepatocellular carcinoma, worsening renal function, use of steroids, and advanced age.

2.3. MELD score

The MELD score has one of the highest performance characteristics as compared to other common predictors, such as the CTP score, to identify premature mortality [19,20]. It was identified as the best model of discrimination and overall performance. A MELD score ≥ 19 predicted $\geq 20\%$ mortality and a MELD score < 11 predicted $< 5\%$ mortality within 6 weeks of an AVB [21,22]. In another study, patients with MELD scores ≥ 18, who require 4 or more units of packed red blood cells within the first 24 hours of AVB (hazard ratio $= 11.3$, $P < 0.001$) or have active bleeding at endoscopy (hazard ratio $= 9.9$, $P < 0.001$) were at increased risk of death within 6 weeks [17]. Every 1-point increase in the MELD score conferred an 8% and 11% increased risk of death at 5 days and 6 weeks, respectively [17].

2.4. Hepatic venous pressure gradient

Elevated HVPG is an independent predictor of mortality with a 3% increase in mortality per 1 mm Hg increase in HVPG [23]. A single HVPG measurement greater than 20 mm Hg is associated with poor survival (1-year mortality, 64% vs 20%, $P < 0.01$) and early rebleeding from varices [24,25]. Recurrent variceal bleeding is lower among patients who achieve a reduction in HVPG to less than 12 mm Hg or a 20% reduction in baseline HVPG values [26]. However, it is unclear whether the addition of HVPG to MELD or CTP scores significantly improves the predictive capabilities of a prognostic model [25].

3. Periprocedural management

3.1. Volume resuscitation

Patients who develop AVB usually have other clinical signs of decompensated cirrhosis and, in a small subset, evidence of acute on chronic liver failure. The clinical presentation of AVB includes hematemesis, melena, or a combination thereof. The differential diagnosis for acute gastrointestinal hemorrhage is broad, and so a thorough history and physical examination may help differentiate the likelihood of a nonvariceal upper gastrointestinal or colonic bleeding from variceal hemorrhage. Regardless, each of these conditions can result in rapid deterioration in clinical status. Thus, establishing access with 2 large bore peripheral intravenous catheters along with blood type and cross-match is recommended. Additional laboratory work should include complete blood count, metabolic profile, liver enzymes, and coagulation markers.

If the patient displays evidence of decreased organ perfusion, such as altered mentation, decreased urine output or persistent hypotension, then volume expansion with crystalloids should be attempted. Response may be estimated through the placement of a central venous catheter and measurement of central venous pressure. However, recent data suggest pulse pressure variation and variation in inferior vena cava diameter are more reliable [27]. Targeting a systolic blood pressure of > 90 mm Hg or a mean arterial pressure of ≥ 55 mm Hg with resolution of tachycardia may be sufficient but one must take into account other comorbidities and also avoid volume overexpansion as the latter may aggravate variceal bleeding.

3.2. Oxygenation and ventilation

A strategy focused on “airway, breathing, circulation” should be employed to support aerobic metabolism and maintain oxygen transport to tissues. The delivery of oxygen can be achieved through conventional, noninvasive methods. However, endotracheal intubation should be performed in patients with changes in mental status and those with large volume hematemesis at risk of aspiration in anticipation of endoscopy.

3.3. Medications

Some patients may bleed from varices despite being on nonselective β-blockers (NSBB) at presentation. Though bleeding is likely to stop if hypotension develops, prophylactic NSBB treatment is not a negative prognostic indicator for the short-term survival of patients with cirrhosis admitted with AVB [28]. Similarly, patients with cirrhosis are frequently on anticoagulation for specific indications (eg, portal vein thrombosis) or nonliver related reasons. Risk factors for increased mortality and premature mortality are not related to being on anticoagulation agents, but rather reflective of the degree of multiorgan failure and other comorbidities [29].

3.4. Blood transfusion

Excessive blood transfusion and overexpansion of the splanchnic vasculature potentially counteract the reflexive vasoconstriction that occurs in the setting of hypovolemia. This inhibition subsequently leads to increased splanchnic blood flow and pressure, which may impair clot formation and promote further hemorrhage. A restrictive transfusion strategy (transfusion threshold of 7 g/dL) was associated with decreased overall mortality in patients with cirrhosis and AVB [30]. This was particularly notable in patients classified as CTP A and B cirrhosis. There was a decrease in incidence of pulmonary edema, transfusion-related lung injury, recurrent bleeding, and need for rescue measures, such as balloon tamponade or transjugular intrahepatic portosystemic shunt, among patients on a restrictive strategy. Furthermore, the rates of acute kidney injury and bacterial infection did not differ between the control and restrictive strategy groups. Thus, patients with AVB should be transfused if the hemoglobin level falls below 7 g/dL and aim for a level between 7 and 9 g/dL. A more aggressive transfusion strategy can be applied to patients demonstrating organ ischemia or hemodynamic instability.

3.5. Antibiotics

The presence of infection is associated with a higher rate of mortality among patients with AVB [31]. Approximately, 20% of patients with AVB have an active infection at the time of bleeding [32]. In patients without infection at the time of initial variceal hemorrhage, a further 50% may develop a nosocomial infection [32]. Bacterial infection may be a precipitant or consequence of variceal hemorrhage and has been linked to an elevation in HVPG. The exact frequency of the types of infection is debatable, but spontaneous bacterial peritonitis (SBP), urinary tract infection, and aspiration pneumonia are frequently encountered. The most common etiologies of SBP and urinary tract infections are gram-negative bacteria, such as *Escherichia coli*, Klebsiella, and Enterococcus species.

Antibiotics should be initiated before endoscopy and continued for 5-7 days. Prophylactic antibiotics may reduce in-hospital infections from 45% to 14% [33]. A meta-analysis of 12 trials that compared antibiotic prophylaxis with placebo or no intervention favored prophylactic antibiotic use with regard to all-cause