

Treatment of Acute Hemorrhage from Esophageal Varices in Cirrhotic Patients.

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Abstract

Cirrhosis describes the end stages of chronic inflammation and progressive scarring of the liver and may lead to hepatocellular dysfunction and portal venous hypertension. Liver cirrhosis in itself is a major cause of mortality worldwide, accounting from more than 1 million deaths in 2010. Esophageal varices are common in cirrhosis such that Christensen et al. documented their occurrence in 90% of patients with cirrhosis within 10 years of follow up, 40% experiencing variceal bleeding. Acute hemorrhage from esophageal varices will classically appear as hematemesis and/or melena in patients with a history of cirrhosis. It is most often diagnosed by performance of an EGD which will reveal actively bleeding varices. Because of the high rate of morbidity and mortality associated with esophageal variceal bleeding, one must have a high index of suspicion in any patient with chronic liver disease or cirrhosis. As such, empiric management for variceal hemorrhage should be initiated any time this diagnosis is considered.

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Full Text

Introduction

Cirrhosis describes the end stages of chronic inflammation and progressive scarring of the liver and may lead to hepatocellular dysfunction and portal venous hypertension. Liver cirrhosis in itself is a major cause of mortality worldwide, accounting from more than 1 million deaths in 2010. Worldwide, the highest mortality rate of cirrhosis is observed in Egypt at 72.7 deaths per 100,000. In contrast, the mortality rate in the U.S. is 11.3 per 100,000 and in Albania is 5.4 per 100,000 in 2010 (6).

Esophageal varices are common in cirrhosis such that Christensen et al. documented their occurrence in 90% of patients with cirrhosis within 10 years of follow up, 40% experiencing variceal bleeding (7). More generally, 26-48% of patients with varices experience variceal hemorrhage (8, 9). Similarly, in a study of 139 newly diagnosed cirrhotic patients in Albania, 34 (24%) developed esophageal variceal hemorrhage within a median time of 34 months from the time of diagnosis (2). In general, acute variceal hemorrhage accounts for approximately one-third of all deaths in patients with cirrhosis. Typically, hemorrhage occurs at an annual rate of 5-15% in patients with cirrhosis and existing esophageal varices (4). Unlike other upper GI bleeds which typically have a 90% rate of spontaneous

hemostasis, only 50% of patients with variceal hemorrhage stop bleeding spontaneously. Patients with a Child-Pugh class C cirrhosis and large actively spurting varices are even less likely to achieve spontaneous hemostasis (4, 5).

Esophageal varices are enlarged veins in the esophagus that develop due to increased pressure in the portal venous system. Portal hypertension is defined as a hydrostatic pressure of greater than 5 mmHg in the portal system. It can occur for a variety of reason with cirrhosis being the most common. In cirrhotic patients, the outflow of the portal system is decreased due to the resistance of distorted hepatic sinusoids while inflow is increased due to splanchnic arteriolar vasodilation. Varices develop in order to decompress this portal system and return blood to systemic circulation and are seen as the pressure difference between the hepatic and portal vein (HVPG) increases above 12 mmHg. This pressure is measured through hepatic venous catheterization. Here, the difference between the wedged hepatic venous pressure, which approximates the portal pressure, and the free hepatic venous pressure is calculated. Therapies reducing the HVPG to below 12 mmHg significantly reduce the risk of variceal bleeding and mortality in cirrhosis. Patients with HVPG >20mmHg at the time of an acute hemorrhage are at increased risk for rebleeding and death. (1)

There are several factors that predict the risk of hemorrhage of esophageal varices. These factors include location, size, appearance, pressure and clinical features. First, a more distal location within the esophagus increases bleeding risk due to a more superficial position of the varix within the submucosa. Next, risk of bleeding increases greatly with size of the varix as small increases in the radius produce proportionally large increases in the wall tension. The size of varices can be approximated with direct visual estimation during endoscopic evaluation. Esophageal varices can be graded by diameter with 5mm as a cut-off between small or large varices. Third, the appearance on endoscopy of stigmata such as red wale marks, cherry red spots, or diffuse erythema confers an increased risk of rupture. (2)

Diagnosis of Acute Variceal Bleeding in the Esophagus

Acute hemorrhage from esophageal varices will classically appear as hematemesis and/or melena in patients with a history of cirrhosis. It is most often diagnosed by performance of an EGD which will reveal actively bleeding varices. However, without directly visualizing the esophagus it can be very difficult to rule out other common causes of upper GI bleeding. These causes include gastric ulcers, erosive esophagitis, severe gastritis, a mass

lesion, and Mallory-Weiss syndrome. Because of the high rate of morbidity and mortality associated with esophageal variceal bleeding, one must have a high index of suspicion in any patient with chronic liver disease or cirrhosis. As such, empiric management for variceal hemorrhage should be initiated any time this diagnosis is considered.

Management

Pre-endoscopic management of suspected variceal hemorrhage

The management of suspected variceal hemorrhage begins with pharmacologic therapy and hemodynamic stabilization. Infusion of blood products should be initiated when patients Hgb drops below 7 g/dL as this has been shown to be beneficial when compared to more liberal transfusion thresholds. In a study of 921 patients done by Villaneuva et al studied packed red blood cell transfusions in patients with upper GI bleeding. Patients were randomized to a restrictive strategy (transfusion initiation at a threshold of Hgb<7g/dL with a target range of 7-9 g/dL) versus a liberal strategy (initiation of transfusion at Hgb 9 g/dL with a target range of 9-11 g/dL). In subgroup analysis of 277 cirrhotic patients, a restrictive transfusion strategy demonstrated a mortality benefit among Child's A and B

cirrhotics (HR 0.30 (0.11-0.85), $p=0.02$) but not among Child's C cirrhotics (HR 1.04 (0.45-2.37), $p = 0.91$). (10) As such, when caring for patients with suspected variceal bleeding, pRBC transfusion should only be performed for patients with $Hgb < 7$ g/dL with a target between 7-9 g/dL.

In the setting of an undetermined etiology for GI bleeding, international consensus guidelines recommend pre-endoscopic proton pump inhibitor (PPI) therapy. We recommend administration of a PPI drip, such as omeprazole 80mcg bolus followed by 8mg / hour infusion. After endoscopic confirmation of a variceal bleeding source, PPI can be continued at standard prophylactic doses (e.g. omeprazole 20mg IV daily to twice daily). Reassessment for the need for continued PPI use should be performed after the patient is clinically stabilized (11, 12).

Medical therapies targeting a decrease in HVPG should be implemented according to an increased risk for rebleeding at higher levels. An Octreotide bolus of 50 mcg IV followed by continuous infusion of 50 mcg IV per hour is typically given. Terlipressin is also commonly used when available at an initial dose of 2 mg IV every 4 hours then brought down to 1 mg IV every 4 hours once hemorrhage is controlled. Both agents are vasoactive, working to decrease portal blood flow. While

Octreotide has not been shown to decrease mortality on its own, it does help to achieve hemostasis especially when combined with endoscopic therapy (5,13). Terlipressin is not universally available but has been demonstrated to decrease mortality and is not inferior to Octreotide in hemostasis achievement (14, 15, 16).

Because of the strong association between GI bleeding in cirrhosis and bacterial infections and mortality, antibiotic therapy with IV ceftriaxone or PO norfloxacin (if intolerant or allergic to ceftriaxone), should be implemented upon admission (17, 18).

Endoscopic diagnosis and management

Next, EGD is typically performed in an effort to identify the bleeding varix and to provide an opportunity for endoscopic intervention such as endoscopic variceal ligation (EVL) or sclerotherapy. EVL involves placing a small elastic bands around varices in the distal esophagus. If banding is unsuccessful or infeasible, sclerotherapy is employed by injecting a sclerosant solution into the bleeding varices. This solution can vary widely among endoscopists. It might consist of either 2 mL of 5% sodium morrhuate or ethanolamine per injection and up to 20 mL per session. Hemostasis can be achieved with either band ligation or sclerotherapy in 70 to 100% of patients (19). However, band ligation typically

yields better long term results as sclerotherapy can be associated with stricturing in the long term setting. In the University Hospital Centre "Mother Theresa" in Tirana, Albania sclerotherapy is the mainstay of management of acute variceal bleeding as EVL is not yet available.

If endoscopic therapy in combination with a pharmacologic agent does not produce effect hemostasis, a more definitive therapy is required. TIPS placement by an interventional radiologist involves passing a needle catheter into the hepatic vein via the jugular vein. A needle is then passed into the portal vein and a stent is deployed to decrease portal blood pressures. A balloon tamponade is used to stabilize the patient prior to the procedure. If a balloon tamponade is used for any extended period of time, a self-expandable esophageal covered metal stent should be considered instead due to its greater efficacy and decreased serious adverse events compared to a balloon tamponade (20). Patients with high HVPG (>20 mmHg) and acute variceal bleeding have a better survival with TIPS than with endoscopic therapy (21). This treatment is usually preferred to surgery since the survival rate for the same patient population would be much lower. Relative contraindications to a TIPS procedure include hepatocellular carcinoma, obstruction of all hepatic

veins, portal venous thrombosis, hepatic encephalopathy, moderate pulmonary hypertension and severe coagulopathy or thrombocytopenia. Absolute contraindications include congestive heart failure, severe tricuspid regurgitation, severe pulmonary hypertension, multiple hepatic cysts, uncontrolled systemic infection or sepsis, and unrelieved biliary obstruction (21).

While TIPS is the preferred method for management of acute variceal bleeding which is not able to be managed endoscopically, availability of this modality is limited in Albania. In these cases temporary hemostasis may be achieved through a balloon tamponade with a device such as a Blakemore tube. The Blakemore tube has two balloons that are inflated in esophageal and gastric cardia and cephalad traction is applied in order to tamponade the gastroesophageal varices proximal to the source of bleeding. Balloons should be deflated after 24 hours to prevent pressure necrosis. This is a temporizing modality until more definitive therapy, such as surgery, can be rendered.

While emergency portocaval shunt surgery is effective at producing hemostasis, it has up to a 50 percent mortality rate and a higher complication rate than the TIPS procedure (22-23). We recommend surgical management of variceal bleeding only be performed by an experienced surgeon. Specific

surgical procedures are outside the scope of this manuscript. However, a brief review of surgical procedure types includes open splenectomy and esophagogastric devascularization (OSED) which may result in lower rates of rebleeding but likely higher rates of pleural effusion, splenic vein thrombosis, pulmonary infection, and a longer post-operative hospital stay than the TIPS procedure (24). Another surgical option would be a splenorenal shunt plus pericardial devascularization (PCVD). However, in a study of 83, the rebleed rate was higher than that typical of either TIPS or OSED procedures (25). Surgical management at the University Hospital Centre "Mother Theresa" in Tirana, Albania especially in cases of portal hypertension due to thrombosis of the portal vein, includes spleno-renal shunt and splenectomy. Patients with severe hemorrhage, deep coma, aspiration pneumonia, renal failure, or sepsis are at a particularly high risk of complications from surgery. A decision for surgical management should be individualized based on the clinical scenario and the overall patient prognosis.

Case Example Conclusion

After several unsuccessful attempts at EVL, 5 mL of ethanolamine was injected resulting in improved visualization. EVL was then performed with placement of 6 bands and hemostasis was achieved. Following this

procedure continued blood transfusions were required. A computerized tomography (CT) of the abdomen suggested bleeding gastric varices as the source for ongoing blood loss and radiology performed an embolization of his coronary vein. Given the overall clinical instability, repeat endoscopy was not performed. Additionally, attempts at TIPS revascularization were unsuccessful. A therapeutic paracentesis revealed hemoperitoneum. Unfortunately, due to his clinical status, he was deemed to be a poor candidate for an exploratory laparotomy. After a multi-disciplinary review, the patient's family transitioned his goals of care to palliation and he expired 2 days later.

References

1. D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. *Gastroenterology* 2006; 131:1611.
2. Kraja, B., Mone, I., Akshija, I., Kocollari, A., Prifti, S., Burazeri, G., Predictors of esophageal varices and first variceal bleeding in liver cirrhosis patients. *World J Gastroenterol* 2017; 23(26): 4806-4814
3. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and

- management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; 46:922.
4. Prandi D, Rueff B, Roche-Sicot J, et al. Life-threatening hemorrhage of the digestive tract in cirrhotic patients. An assessment of the postoperative mortality after emergency portacaval shunt. *Am J Surg* 1976; 131:204.
 5. Habib A, Sanyal AJ. Acute variceal hemorrhage. *Gastrointest Endosc Clin N Am* 2007; 17:223.
 6. Mokdad AA, Lopez AD, Shahrz S, Lozano R, Mokdad AH, Stanaway J, Murray CJL, Naghavi M. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Med*. 2014;12:145. doi: 10.1186/s12916-014-0145-y.
 7. Christensen E, Fauerholdt L, Schlichting P, et al. Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effects of prednisone. *Gastroenterology* 1981;81:944-52.
 8. Gores GJ, Wiesner RH, Dickson ER, et al. Prospective evaluation of esophageal varices in primary biliary cirrhosis: Development, natural history and influence on survival. *Gastroenterology* 1989;96:1552-9.
 9. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices: A prospective multicenter study. *N Engl J Med* 1988;319:983-9.
 10. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñoz E, and Guarner C. Transfusion Strategies for Acute Upper Gastrointestinal Bleeding. *N Engl J Med* 2013; 368:1.
 11. Barkun AN, Bardou M, Kuipers EJ, et al. International Consensus Recommendations on the Management of Patients with Nonvariceal Upper Gastrointestinal Bleeding. *Ann Intern Med*. 2010; 152:101-113.
 12. Chan WH, Khin LW, Chung YF, et al. Randomized controlled trial of standard versus high-dose intravenous omeprazole after endoscopic therapy in high-risk patients with acute peptic ulcer bleeding. *Br J Surg*. 2011;92(5):640.
 13. Wells M, Chande N, Adams P, et al. Meta-analysis: vasoactive medications for the management of acute variceal bleeds. *Aliment Pharmacol Ther* 2012; 35:1267.
 14. Gotzsche PC. Somatostatin or octreotide for acute bleeding oesophageal varices. *Cochrane Database Syst Rev* 2000; :CD000193.
 15. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane*

- Database Syst Rev 2003; :CD002147.
16. Abid S, Jafri W, Hamid S, et al. Terlipressin vs. octreotide in bleeding esophageal varices as an adjuvant therapy with endoscopic band ligation: a randomized double-blind placebo-controlled trial. *Am J Gastroenterol* 2009; 104:617.
 17. Soares-Weiser K, Brezis M, Turkaspa R, et al. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. *Cochrane Database Syst Rev* 2002:CD002907.
 18. Banerjee S, Shen B, Baron TH, et al. Antibiotic prophylaxis for GI endoscopy. *Gastrointest Endo.* 2008; 67(6): 791-798.
 19. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. *Ann Intern Med* 1995; 123:280.
 20. Escorsell A, Bosch J. Self-expandable metal stents in the treatment of acute esophageal variceal bleeding. *Gastroenterol Res Pract.* 2011;2011:910986. doi: 10.1155/2011/910986.
 21. K.R. Patidar, M. Sydnor, A.J. Sanya I Transjugular intrahepatic portosystemic shunt *Clin Liver Dis*, 18 (2014), pp. 853-876
 22. Rikkers LF, Jin G. Emergency shunt. Role in the present management of variceal bleeding. *Arch Surg* 1995; 130:472.
 23. Villeneuve JP, Pomier-Layrargues G, Duguay L, et al. Emergency portacaval shunt for variceal hemorrhage. A prospective study. *Ann Surg* 1987; 206:48.
 24. Su AP, Zhang ZD, Tian BL, Zhu JQ Transjugular intrahepatic portosystemic shunt versus open splenectomy and esophagogastric devascularization for portal hypertension with recurrent variceal bleeding *Hepatobiliary Pancreat Dis Int*, 16 (2017), pp. 169-175
 25. Yang L, Yuan LJ, Dong R, Yin JK, Wang Q, Li T, Li JB, Du XL, Lu JG. Two surgical procedures for esophagogastric variceal bleeding in patients with portal hypertension. *World J Gastroenterol* 2013; 19(48): 9418-9424