Chapter

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Pharmacological Control of Portal Hypertension

MA KABEER

INTRODUCTION

That gastrointestinal bleeding could occur as a consequence of derangement of portal hypertension was certainly appreciated by physicians in the 17th century. The concept that esophageal varices develop as a result of obstruction to portal blood flow was well established by the late 19th century. The term portal hypertension was coined by Gilbert and Carnot in 1902. Whipple made his dour comment in 1945 at a time of considerable surgical innovation. The complication of portal hypertension – gastrointestinal hemorrhages, ascitis and portosystemic encephalopathy – continue to pose difficult challenges to practicing physicians managing end-stage livers diseases. Liver transplantation is a highly successful cure for end stage liver disease but donor livers are in short supply. There remains the need for managing portal hypertension cases who are unfit for surgery and who are awaiting transplant. Etiology and pathophysiology of portal hypertension:

Hepatic blood flow is normally about 1500 ml/min representing 15 to 20% of cardiac ouput – one-third of this flow and 30 to 60% oxygen is provided by hepatic artery. Approximately two-thirds of hepatic blood flow is provided by portal venous blood. The high pressure well oxygenated arterial blood mixes completely with low pressure low oxygen containing nutrient-rich portal venous blood within the hepatic sinusoids. After perfusing the sinusoids, blood flows sequentially into hepatic venules, hepatic vein and IVC. A fraction of plasma entering the space of disse is drained by lymphatics.

Diagnosis

Gastrointestinal hemorrhage in liver disease is the initial presentation of portal hypertension. Anemia, splenomegaly, dilated abdominal veins, venous hum and caput medusae are useful clinical clues. Endoscopy and imaging studies are useful. Imaging studies are useful for elective diagnosis and for more precise definition of portal venous anatomical features before surgical intervention. Measurement of portal hypertension is rarely indicated in clinical diagnosis which often rests on the identification of varices or other collaterals and a compatible cause. Measurements are often used in hemodynamic and therapeutic research studies and have a role after shunt intervention for assessment of reduction of pressure.

Principles and Goals of Management

Acute bleeding from varices or nonvariceal site in portal hypertension often poses a life-threatening emergency. Prompt and appropriate hemodynamic resuscitation should be followed by measures to arrest the bleed and prevent recurrence of bleeding. The main goals of therapy are: (l) Prevention of initial bleed; (2) Control of acute bleeding; and (3) Prevention of recurrent bleeding. The major therapies rely on one of two fundamental approaches – lowering of portal pressure or local obliteration of varices.

PROPHYLAXIS OF INITIAL VARICEAL BLEEDING

Nonselective beta-blockers and long-acting nitrates have extensively been used in attempts to prevent a first variceal hemorrhage. They decrease cardiac output by receptor blockade and unopposed alpha adrenergic activity causes splanchnic vasoconstriction reducing variceal blood flow. With beta-blocker therpy, a 25% decrease in resting pulse rate from baseline is often used as a surrogate marker of efficiency; however, the validity

of this indicator has been questioned. Many trials have demonstrated that beta-blockers are most effective when liver functions are preserved. These also have protective effect in ascitis and advanced liver disease. Many studies showed that alcoholic liver diseases patients are especially likely to benefit with prophylactic therapy. A cost-effective analysis supports the use of propranolol as the most cost-effectve primary prophylaxis in cirrhosis. lt is uncertain whether propranolol or nadolol is more effective. On the basis of available data, it is appropriate clinical practice to perform screening endoscopy in cirrhosis to look for moderate-to-large varices and to treat these with prophylactic betablockers therapy. Long-acting nitrates such as isosorbitrate monotrate are effective in preventing a first variceal bleed and may prove useful in patients not tolerating beta-blockers. These agents produce venodilation by forming NO. They are believe to lower portal pressure by a combination of reducing splanchnic blood flow via venous pooling and by reducing transhepatic sinusoidal resistance. Combination therapy with beta-blockers was associated with marked reduction of first variceal bleeding compared to beta-blockers alone. Management of acute variceal hemorrhage:

Pharmacotherapy is theoretically ideal approach because it is noninvasive, is immediately available and does not require special technical expertise. The major agents used are intravenous vasopressin and its analogs with or without nitroglycerine and somatostatin and its analog octreotide.

Vasopressin and terlipressin: Vasopressin is a potent but non-selective vasoconstrictor that has been used for many years. lt lowers pressure by causing splanchnic arterial vasoconstriction. lt is typically given as a bolus injection followed by continuous infusion. lt controls acute bleeding in about 50% cases. In addition, vaso-spastic effects are seen in 25% patients and rising of myocardial infarction. To reduce the risk and to further lower the portal pressure, nitroglycerine has been used in combination with vasopressin. Nitrates are believed to reduce collaterals and possibly prehepatic resistance by increasing local concentration of NO and causing smooth muscle relaxation. Many trials showed the benefit of the combination. Vasopressin analog triglycyl lysine vasopressin-terlipressin, glypressin which undergoes slow cleavage of the glycyl residue to allow a slow release of lysine vasopressin. It is associated with fewer side effects.

Somatostatin and octreotide: They have a variety of physiological actions including release of several vasodilatory hormones such as glucagon and direct

Table 1: Principles of pharmacologic therapy for portal hypertension

Hemodynamic disturbance	*Pharmacological principle*	*Example*
Increased blood volume	Diuretics	Spironolactone, frusemide
↑ Cardiac output splanchnic arteriolar vasodilation	Sympatholytics vasoconstriction	Beta blockers vasopressin, somato-statin, octreotide beta blockers
Increased hepatic and collateral resistance	Vasodilators	Nitrates, clonidine, prazosin, serotonin receptor antagonist
↑ Variceal blood flow	↑ Esophageal sphincter tone by prokinetics	Metoclopramide, domperidone

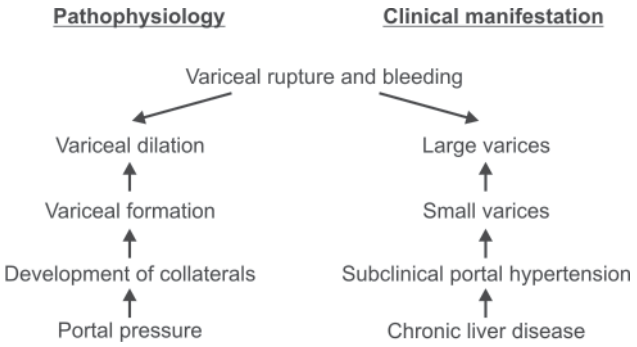

Fig. 1: Natural history of esophageal varices according to pathophysiological evolution of portal hypertension

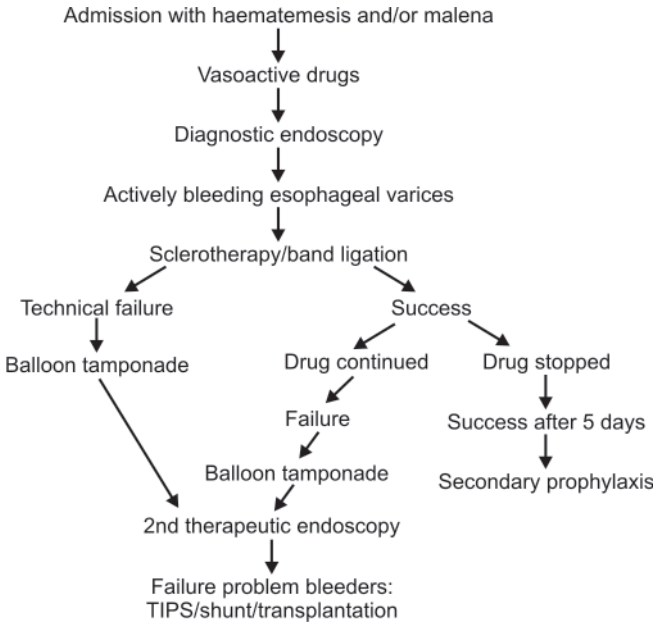

Fig. 2: Common practice for the management of esophageal varices actively bleeding at diagnosis

Table 2: Vasoactive mediators in portal hypertension

Vasodilators	*Vasoconstrictors*
Glucagons	Norepinephrine
Prostacyclin	Serotonin
Substance P	Endothelins
Adenosine	Angiotensin 2
Atrial natriuretic factor	Vasopressin
Bile acid, histamine, vasoactive intestine polypeptide, Gamma amino butyric acid, encephalins Endotoxin, tumor necrotic factor	
NO	

effect on vascular smooth muscle. The net pharmacological effect is to produce splanchnic vasoconstriction selectively. They consistently lower azygos blood flow indicating reduced blood flow through varices. lt is administered as initial bolus dose (somatostatin 250 microgram, octreotide 50 microgram) followed by continuous infusion. Compared to vasopressin, it has a higher success rate with few complications. lt is used as adjuvant to endoscopic therapy to assist in controlling bleeding and for recurrence. Vasopressin plus nitroglycerine, terlipressin and somatostatin or octreotide all appear to be useful in the treatment of acute variceal bleeding. A beneficial side-effect profile favours the use of somatostatins or analog. These agents are not easily available and are expensive. Current opinion favors endoscopic therapy as first line for acute variceal bleed with pharmacotherapy in patients who are unstable for endoscopy and whose bleeding is not controlled by endoscopy; and as a valuable adjuvant to prevent early rebleeding. Prevention of recurrent hemorrhage: Beta-blockers, long-acting nitrates and a combination therapy are used for prevention of subsequent bleeding-secondary prophylaxis. Beta-blockers additionally benefit by reducing the risk of bleeding from portal hypertension gastropathy. Many trials showed the benefit of beta-blockers in significantly reducing the risk of bleeding and significant improvement in survival rates. Combination therapy with nitrates is more effective than monotherapy. lt has more adverse effects. Endoscopic sclerotherapy (EST) was associated with a lower rate of bleeding, but no survival advantage. The rate of complications were higher with EST. Combination therapy EST and isosorbitrate mononitrate showed a trend towards lesser episodes of rebleeding with improved survival.

Table 3: Causes of portal hypertension

- Primary increased flow: arterial portal venous fistula in liver, spleen, splanchnic hemangiomas
- Primary increased resistance: Prehepatic thrombosis/ cavernous transformation of PV
  - Splenic vein thrombosis
- Intrahepatic alcoholic hepatitis
  - NCPH
  - Chronic hepatitis
  - Methotrexate
  - Hypervitaminosis
- Posthepatic IVC web
  - Constrictive pericarditis
  - Tricuspid regurgitation
  - Right heart failure

Prognosis

This depends on the underlying disease. The outlook is much better in patients in whom liver function is well preserved. The prognosis is surprisingly good in children and with careful management of recurrent bleeding, survival to adult life is expected. The number of bleeds seem to reduce as time passes. Women may bleed during pregnancy, but that is unusual. Their babies are normal. The major determinants of poor prognosis of variceal hemorrhage are the magnitude of blood loss, degree of liver failure and occurrence of complications including infections, multiorgan failure and early rebleeding.

SUGGESTED READING

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