Seminar

Portal hypertension and variceal haemorrhage

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Portal hypertension commonly complicates cirrhosis, and variceal haemorrhage is its worst and most life-threatening complication. The introduction of new pharmacological agents, endoscopic variceal band ligation, and transjugular intrahepatic portosystemic stent-shunt (TIPSS) has increased the therapeutic options available for this disorder. However, despite these advances, mortality remains high.

Pathophysiology of portal hypertension

Increased resistance to portal blood flow is the initiating factor in the development of portal hypertension. In western countries, the most common cause is cirrhosis, in which the main resistance to flow occurs in the hepatic sinusoids. Alternatively, resistance to flow in the portal or splenic veins leads to prehepatic portal hypertension and in the hepatic veins leads to posthepatic portal hypertension.

Collateral vessels open and partially decompress the portal system. Collateral vessels arise most commonly in the retroperitoneal area, but are most visible and troublesome when they occur at the gastro-oesophageal junction. Collateral vessels also arise at the perianal, periumbilical, splenorenal, ovarian, and choledochal regions; in the peritoneum; and at areas of surgical anastamoses or ileostomy or colostomy sites. However, despite formation of these collaterals, portal hypertension is maintained by increased splanchnic arterial flow, leading to increased portal blood flow (figure 1).

Stellate cells (analogous to tissue pericytes) are found in the perisinusoidal space. After liver injury, these cells are transformed into contractile myofibroblasts that are central to the start of fibrogenesis.[1] They also regulate sinusoidal resistance and flow in response to vasoactive substances, especially endothelin and nitric oxide.[2] Therefore, at least part of the resistance to portal venous flow is dynamic.

This resistance to portal flow is the "backward" component of portal hypertension. The "forward" component is the increased splanchnic inflow, secondary to peripheral vasodilatation. This low systemic vascular resistance and the associated raised cardiac output lead to the characteristic hyperdynamic circulation of cirrhosis. Studies have suggested that the main site of low systemic vascular resistance is the splanchnic circulation.[3]

Much work has gone into defining the part played by nitric oxide in the circulatory abnormalities of cirrhosis. Vasodilatation is proposed to result from increased concentrations of nitric oxide, secondary to raised concentrations of endotoxins and cytokines in cirrhosis, although evidence suggests that increases in both the constitutive and inducible isoforms of nitric-oxide synthase are involved. Yet this mechanism remains unproven and studies have reported variable circulatory effects after administration of nitric-oxide-synthetase inhibitors to patients with cirrhosis.[4]

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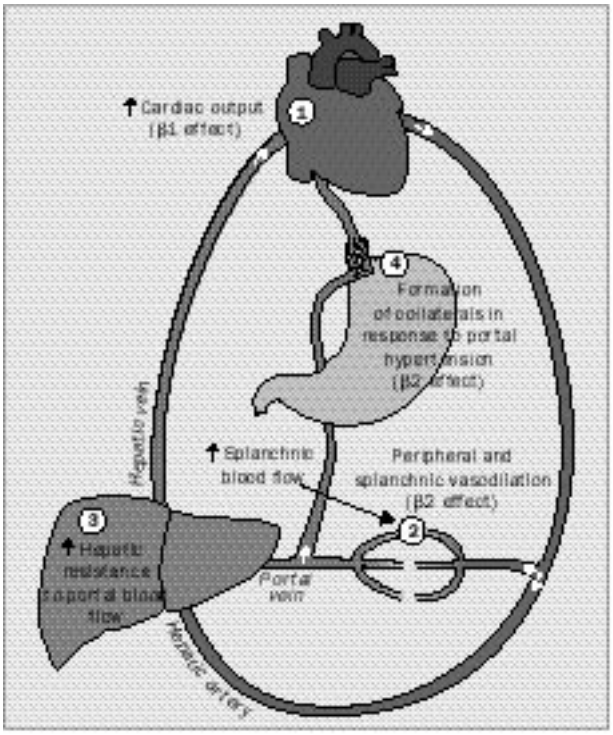

Figure 1: **Haemodynamic changes in portal hypertension and possible targets for therapeutic intervention**

1) reduction of cardiac output by β-1 blockade; 2) reduction of splanchnic blood flow by β-2 blockade or vasoconstrictors such as α-adrenergic agonists or vasopressin analogues; 3) reduction of intrahepatic resistance by vasodilators; 4) reduction of variceal or collateral flow by β-2 blockade, balloon tamponade, or endoscopic therapy.

The vasodilated circulation of cirrhosis is probably due to a disturbed balance between vasodilatory (eg, nitric oxide, glucagon, atrial natriuretic peptide, substance P, vasoactive intestinal peptide, bile acids) and vasoconstrictive substances (eg, endothelin, the renin-angiotensin-aldosterone and sympathetic nervous systems, antidiuretic hormone). The contributions of the parenchymal liver disease itself and the intrahepatic, portosystemic, and intrapulmonary shunts to alterations in this balance remain unclear.

Risk of bleeding

Portal pressure in individuals is dynamic, with circadian change. The highest pressures occur during the night, and increase postprandially and in response to coughing, sneezing, and exercise.[5] Such variations may combine with local factors in vessel walls to contribute to a pressure surge that can lead to a variceal bleed. However, the exact mechanisms that bring about variceal bleeding are unclear.

The risk of a variceal haemorrhage increases with the severity of liver disease, variceal size, and the presence of red markings on the varices.[6] Bleeding has been identified as unlikely with differences in pressure of less than 12 mm Hg between the portal vein and inferior vena cava.[7] The risk of bleeding is also low if a reduction in pressure of 20% or more is achieved.[8]

Acute variceal haemorrhage

About a third of patients with varices will bleed. Mortality from a first bleed is around 50% and most survivors will have a rebleed, with an associated inpatient mortality of 30%.[9] Most bleeding related to portal hypertension occurs from oesophageal varices, but bleeding can also arise from gastric or ectopic varices, or from portal hypertensive gastropathy or enteropathy. A suggested algorithm for the management of suspected variceal haemorrhage is shown in figure 2.

Initial resuscitation

Early and adequate initial resuscitation is vital. Endotracheal intubation with or without ventilation is commonly required to provide airway protection and avoid aspiration, especially in patients with a major bleed or substantial encephalopathy. Restoration of the circulating blood volume with colloid followed by crossmatched whole blood should be guided in most cases by regular monitoring of central venous pressure and urine volume.

Although prompt fluid replacement is essential to protect renal perfusion, overfilling may increase portal pressure, leading to variceal rebleeding. Right-atrial pressure should be kept between 0 and 5 mm Hg. Right-heart catheterisation is an option in patients with ascites or pre-existing cardiopulmonary disease, or haemodynamic instability. Coagulopathy in these patients should be treated with fresh-frozen plasma and platelet infusions, although evidence that this treatment is beneficial is scarce.

Although a 90% success in stopping variceal bleeding with balloon tamponade and endoscopic and pharmacological treatment has been reported, up to 70% of episodes of variceal haemorrhage stop spontaneously.[10]

Endoscopic management

Endoscopy allows accurate identification of the source of bleeding and direct therapeutic intervention. For many years, endoscopic sclerotherapy with sodium tetradecyl sulphate, polidocanol, or ethanolamine has been the therapy of choice to control bleeding from oesophageal varices and for their eradication. However, five randomised studies and a meta-analysis have shown that band ligation reduces complications, speed of variceal eradication, rebleeding rates, and bleeding-related mortality compared with sclerotherapy.[11] Band ligation did have complications related to the overtube, required for repeated banding, but the development of devices with multiple bands has removed the need for the overtube.

Therefore, band ligation should now be the endoscopic treatment of choice for oesophageal varices. However, with active bleeding, injection sclerotherapy may achieve initial haemostasis more easily before band ligation at subsequent endoscopies is undertaken.[12]

Pharmacological management

Although drugs have been used in the management of variceal bleeding for nearly half a century, new interest has arisen after reports and meta-analyses that show similar efficacy to sclerotherapy with somatostatin or its synthetic analogue octreotide acetate in the control of acute variceal haemorrhage.[13] One report showed a reduction in early rebleeding among patients treated with band ligation plus a 5-day infusion of octreotide acetate compared with banding alone.[14] The dose and the length of therapy vary widely in studies and further trials are required to identify the optimum treatment regimen.

Terlipressin, a synthetic analogue of vasopressin with a longer biological half-life, allows bolus administration every

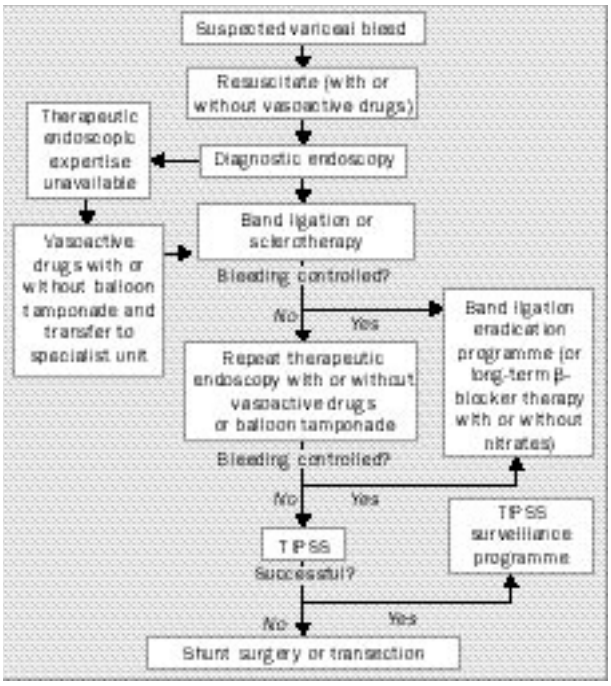

Figure 2: **Suggested algorithm for management of variceal haemorrhage**
Vasoactive drugs: octreotide or somatostatin, or terlipressin.

4 h. It has fewer systemic side-effects than vasopressin, but concomitant administration of nitrates to reduce ischaemic side-effects is still recommended. Terlipressin is as effective as somatostatin, octreotide acetate, or balloon tamponade in controlling variceal haemorrhage and is the only drug shown to lower mortality from variceal bleeding.[15] Benefits are seen with early therapy, with improved bleeding control and survival in cirrhotic patients with gastrointestinal bleeding given terlipressin and nitroglycerine as emergency treatment in the home before transfer to hospital.[16]

Although pharmacological agents are useful alternatives when early endoscopy is unavailable, any beneficial effects are temporary. Therefore, endoscopy should be arranged as soon as possible to confirm the source of bleeding and for endoscopic therapy if required. When substantial bleeding obscures the view of the endoscopist, administration of octreotide, somatostatin, or terlipressin with nitrates may help to achieve haemostasis before repeat endoscopy.

Balloon tamponade

Balloon tamponade with a Minnesota or Sengstaken-Blackmore tube can be lifesaving in the presence of substantial bleeding when carried out by experienced staff. However, placement by inexperienced staff is associated with a death rate of 6–20%, due largely to oesophageal perforation and pulmonary aspiration.

The tube should be passed orally, well into the stomach before inflation of the gastric balloon with about 300 mL air. Firm traction maintains the position of the gastric balloon under tension at the oesophagogastric junction. The oesophageal balloon is only inflated if bleeding continues and should be deflated for 30 min every 4–6 h and not used for more than 12 h. After this time, the risk of complications from the gastric balloon also increases. Because 50% of patients will rebleed when the tube is deflated, immediate definitive endoscopic therapy must be undertaken.[17]

Study	Number of patients receiving TIPSS/sclerotherapy	Follow-up (months)	Rebleeding (%)		Encephalopathy (%)		Survival (%)	
			TIPSS	Endoscopy	TIPSS	Endoscopy	TIPSS	Endoscopy
Cabarera et al	31/32	15	23	52‡	33	13‡	80	84
Sanyal et al	41/39	33	22	21	29	13‡	71	82‡
Cello et al	24/25	19	12	48‡	58	44	79	84 (30 day)
Rossle et al*	61/65	14	15	41‡	36	18‡	90	89 (1 year)
Sauer et al*	42/41	18	9	44 (1 year)‡	29	10‡	77	85 (1 year)
G d'EIAH*	32/33	12	41	61	. .	. .	50	48
Sauer et al†	17/17	7	18	54 (1 year)‡	25	12	89	91 (1 year)
Jolan et al†	31/27	16	10	50§	22	8	81	89 (30 day)
Riggio et al	38/43	19	21	51 (1 year)‡	50	16‖	83	85 (1 year)
Garcia-Villarreal et al	18/19	15	11	47‖	26	22	94	56‖

*Used concomitant propanolol in sclerotherapy group. †Used band ligation as endoscopic therapy. ‡p<0·05. §p<0·001. ‖p<0·01.

Summary of trials comparing TIPSS with endoscopic therapy for prevention of variceal bleeding

TIPSS

TIPSS is a new radiological intervention that creates a portosystemic tract through the liver parenchyma, through which an 8–12 mm expandable metal stent is inserted. In the 8 years since its introduction into clinical practice, TIPSS has become the treatment of choice as rescue therapy for the 10–20% of patients with variceal haemorrhage unresponsive to endoscopic management. Failure of emergency endoscopic therapy has been defined as further variceal bleeding after two endoscopic treatments during a single hospital admission for an acute bleeding episode.[18] Treatment with balloon tamponade should be followed by TIPSS or, less commonly, surgery in this situation.

Although few trials have been done, TIPSS is easier to carry out than surgical shunt procedures or oesophageal transection, has lower associated morbidity and mortality, and does not compromise subsequent liver transplantation. A study suggested benefits from small-diameter H-graft portacaval shunts compared with TIPSS for refractory variceal bleeding,[19] but TIPSS can be used for patients who are too ill for major surgery.

The main limitations of TIPSS are the development of encephalopathy in about 20% of patients and progressive development of shunt insufficiency.[20] Encephalopathy is generally easy to manage with lactulose and protein restriction, although some patients require a reduction in the size of the shunt. Shunt insufficiency is more difficult to manage and requires regular, long-term Doppler and portographic surveillance and treatment.

Surgery

TIPSS has in many cases replaced surgery for variceal haemorrhage unresponsive to endoscopic treatment. However, technical failure occurs in 5–10% of cases. In these patients, the options are shunt surgery or oesophageal transection with or without devascularisation, but the mortality rate is high, particularly among patients with decompensated liver disease.

Gastric or ectopic varices and portal hypertensive gastropathy

Gastric varices are the source of bleeding in 10–36% of patients with variceal haemorrhage. Higher rates are reported for patients with "sinistral" or left-sided portal hypertension due to portal-vein or splenic-vein thrombosis. Unless the gastric varices are located in a hiatus hernia or on the proximal lesser curve in continuation with oesophageal varices, endoscopic bleeding control is generally unhelpful. For this reason, and because of the difficulty in obtaining adequate endoscopic vision, early TIPSS or shunt surgery have been advocated for gastric variceal bleeding.

The management of gastric variceal haemorrhage with endoscopic injection of thrombin or tissue adhesives needs further study.[21] Ideally, randomised trials should compare endoscopic methods, TIPSS, and surgery. In the meantime, control of any active bleeding with pharmacological agents or endoscopy, if possible, seems valid before proceeding to TIPSS. For similar reasons, the 3% of patients who have troublesome bleeding from ectopic varices are probably best managed by TIPSS.

Bleeding from portal hypertensive gastropathy or enteropathy accounts for 5–8% of bleeding episodes in cirrhosis. Although major bleeding from these sources is uncommon, when it occurs, its diffuse nature precludes the use of endoscopic therapy and the treatment options are pharmacological therapy, TIPSS, or surgery, dependent on the severity of bleeding, the degree of liver impairment, and likely compliance with drug therapy.

Prevention of rebleeding

After an initial variceal bleed, most patients will rebleed, commonly within the first few weeks. To reduce this risk, further treatment, such as endoscopic variceal eradication, pharmacological therapy, or portosystemic shunt creation, is necessary.

Endoscopy

After a variceal haemorrhage, most units enrol patients into an endoscopic sclerotherapy or band ligation programme to eradicate the varices. A meta-analysis of eight trials comparing sclerotherapy with non-active treatment in the prevention of variceal rebleeding showed reductions in rebleeding and mortality in the sclerotherapy group.[13] However, band ligation has advantages over sclerotherapy,[11] and banding should now be the endoscopic treatment of choice for variceal eradication. Generally, band ligation is done every 1–2 weeks until varices are eradicated. Thereafter, periodic endoscopic surveillance is necessary. Unsuccessful long-term endoscopic management has been defined as either recurrent bleeding, despite adequate endoscopic therapy, or oesophageal varices that are difficult to eradicate by endoscopy. For these cases, TIPSS or selective shunt surgery should be undertaken.

Pharmacological agents

The most widely used drugs to prevent rebleeding are β-blockers. The most commonly investigated β-blocker is propranolol, although some studies have assessed nadolol, which can be given once daily and, unlike propranolol, is not metabolised by the liver. 13 randomised trials and three meta-analyses have confirmed the efficacy of β-blockers and have suggested an improvement in survival compared with placebo. Overall, β-blockers seem to lower the risk of rebleeding by about 40% and mortality by 20%.[22,23]

Ideally, reduction in portal pressure in response to drug therapy should be haemodynamically assessed by hepatic venous catheterisation, with measurement of the hepatic venous-pressure gradient. Such assessment is especially important in patients with alcoholic cirrhosis in whom a spontaneous fall of more than 20% is possible with abstinence. Although a reduction of 25% in the resting pulse rate is commonly used to guide the dosage of β-blockers, the splanchnic haemodynamic effects of β-blockers are unpredictable and correlate poorly with systemic effects.

Most studies have shown that β-blockers and sclerotherapy have similar efficacy in the prevention of variceal rebleeding, although complications are more frequent and severe with sclerotherapy. There is no clear evidence of a benefit from combined β-blocker therapy and sclerotherapy compared with either treatment alone.

The addition of nitrates (generally isosorbide-5-mononitrate) to β-blockers improves the portal hypotensive response. Reduced rebleeding has been reported with this drug combination compared with endosopic sclerotherapy.[24]

Studies are needed to compare pharmacological therapy with band ligation for the prevention of rebleeding, since this is now the endoscopic treatment of choice and is widely used by hepatologists.

TIPSS

Although TIPSS is an accepted treatment for recurrent variceal haemorrhage unresponsive to endoscopic therapy, current debate centres on whether or not TIPSS should be placed after an initial variceal haemorrhage to prevent rebleeding. Ten randomised studies have been published (including six in abstract form) comparing TIPSS with endoscopic treatment, with or without β-blockers, to prevent variceal rebleeding (table). Generally, the studies show reduced rebleeding in the TIPSS group, but higher rates of encephalopathy and no difference in survival. Data on cost and quality of life are awaited before advice can be given about the optimum treatment for this patient population.

Surgery

Early randomised trials comparing portacaval shunt surgery with non-specific treatment in the prevention of variceal rebleeding reported reductions in rates of bleeding but increased rates of encephalopathy in surgical groups. The use of more selective distal-splenorenal or small portacaval H-shunts seems to lower the incidence of encephalopathy. A meta-analysis of trials comparing shunt surgery with sclerotherapy to prevent variceal rebleeding found reduced bleeding rates but higher encephalopathy rates in the surgical group.[13] No difference in mortality was detected.

Orthotopic liver transplantation

Liver transplantation is the definitive treatment for deteriorating liver disease. Any patient with advanced cirrhosis and a variceal haemorrhage should be considered for transplantation. Unlike most surgical shunts, TIPSS does not seem to compromise subsequent transplant surgery and has been successfully used as a bridging therapy in patients with variceal bleeding.[25]

Primary prophylaxis of variceal haemorrhage

Because of the availability of proven primary prophylactic therapies, all patients with cirrhosis should have a screening endoscopy to confirm the presence of varices. If no varices are found, surveillance endoscopy should be done every 1–2 years, dependent on the severity of liver disease. If varices are present and thought to have a high risk of bleeding, the patient should be offered primary prophylactic therapy. Treatment should probably be limited to patients with such varices, because many studies have excluded patients with varices with low bleeding risk. If varices at low risk of bleeding are found, surveillance endoscopies should be more frequent to assess any changes.

Pharmacological agents

Nine controlled studies and three meta-analyses have confirmed the efficacy of β-blockers compared with placebo in the prevention of a first variceal haemorrhage. The risk of bleeding is reduced by about 45% with β-blocker therapy and in most studies there is a trend towards improved survival. Benefits seem to have been consistently found for patients with moderate or large oesophageal varices from all forms of liver disease. Side-effects of β-blockers are reported in about 15% of patients, requiring withdrawal of therapy in less than half of these cases.[26]

Nitrates may be as effective as β-blockers in the primary prophylaxis of variceal bleeding and offer an alternative to patients who are intolerant of β-blockers.[27] A reduced incidence of first variceal haemorrhage among patients given combined nitrates and β-blockers has been reported, compared with those given β-blockers alone.[28] No effect on survival was seen. This drug combination may, therefore, be the optimum therapy in the primary prophylaxis of variceal bleeding, but confirmatory studies are awaited.

Various other drugs have been shown to reduce portal pressure in haemodynamic studies, including diuretics, α-adrenoreceptor antagonists, endothelin antagonists, and vasodilating β-blockers. However, clinical studies of these drugs for primary prophylaxis of variceal bleeding are limited.

Endoscopy

19 trials have compared sclerotherapy with non-active treatment in the primary prophylaxis of variceal bleeding. Although meta-analysis shows reduced bleeding risk and improved survival, there is substantial heterogeneity between the trials and a higher mortality in the sclerotherapy group in the largest study.[29] In addition, complications of sclerotherapy seem to outweigh the benefits, especially among patients with smaller varices at low risk of bleeding.

Two studies have compared sclerotherapy with propranolol to prevent first variceal haemorrhage. One study showed a lower rate of bleeding in the propranolol group but no difference was found in the other study. Propranolol is also superior to combined propranolol and sclerotherapy in this situation.[30]

Trials are needed to compare band ligation with drug therapy for the primary prophylaxis of variceal haemorrhage. However, at present, patients with known high-risk varices should receive non-selective β-blockers (or nitrates if β-blockers are contraindicated or not tolerated) as primary prophylaxis against bleeding.

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