REVIEW ARTICLE

Management Of Variceal Haemorrhage

M.I. Merican, FRCP
Hospital Besar, Kuala Lumpur

Summary

Variceal bleeding is the most important complication of portal hypertension. Mortality due to the first variceal bleeding is very high (50%) and of those surviving a variceal bleeding episode, up to 80% may rebleed. Proper management of the acute variceal bleeding episode, the prevention of rebleeding and primary prophylaxis for variceal haemorrhage are therefore mandatory in order to improve the morbidity and mortality of cirrhotic patients with variceal bleeding. Injection sclerotherapy would be the treatment of choice for acute variceal bleeding. Drug treatment in the form of either a combined vasopressin-nitroglycerin regimen or somatostatin may be used as an alternative. Patients not responding to these treatments should be referred for surgery. For the prevention of variceal rebleeding, non-selective beta-blockers should be tried first, reserving long-term injection sclerotherapy for patients with contraindications or intolerance to beta-blockers or in whom beta-blocker therapy has failed. Surgical rescue in the form of either shunt surgery or lever transplantation should be considered if either treatment fails. A new technique, transjugular intrahepatic portosystemic stent-shunt (TIPSS) may replace shunt surgery in the future.

Beta-blockers is the treatment of choice for primary prophylaxis of variceal haemorrhage and has a role in preventing acute and chronic bleeding from congestive gastropathy. However, the above sequential approach from the least invasive to the more invasive therapeutic options may not be appropriate for all cirrhotic patients with variceal bleeding.

Key words: Variceal haemorrhage, portal hypertension, management, prophylaxis

Introduction

Variceal bleeding is the most important complication of portal hypertension. At least 90% of all patients with cirrhosis will eventually develop oesophageal varices with time[1]. 30% of cirrhotics with varices will bleed from varices at some time during their lifetime[2] and more than 70% will do so within 2 years of the diagnosis of varices[3]. Up to 50% of patients will die from the first variceal haemorrhage[2]. Of those who survive a variceal bleeding episode, approximately 50% to 80% will rebleed. Many trials of therapy for variceal haemorrhage have been performed over the last 10 years in an attempt to improve the prognosis of affected patients by providing better treatment options, not only for acute variceal bleeding but also for the prevention of rebleeding and primary prophylaxis for variceal haemorrhage. In addition, risk factors for variceal haemorrhage have been evaluated[4]. Portal hypertensive gastropathy or congestive gastropathy has been studied as another source of bleeding in cirrhotics[5].

The purpose of this article is to review the progress made over the last decade in the acute and long-term management of variceal bleeding. Three distinct clinical situations will be discussed: the acute bleeding episode, the prevention of variceal rebleeding and the prevention of the first variceal bleeding episode (prophylaxis).

A. Treatment of Acute Variceal Haemorrhage

Resuscitation of the bleeding patients is obviously the first priority. Upper gastrointestinal endoscopy should be performed as soon as the patient is stable and preferably within 12 hours. At endoscopy bleeding can be attributed to varices if the following are detected: venous spurt or ooze, an adherent clot or the presence of a white nipple sign which is thought to represent a platelet-fibrin plug[6], or no other lesion except varices. Other non-variceal causes of bleeding in cirrhotic patients must be excluded. These include gastric erosions and congestive gastropathy.

Several options may be considered for the treatment of the acute variceal bleeding episode (Table I), which should not be considered as mutually exclusive.

Table I
Treatment of acute variceal haemorrhage

1. **Pharmacological treatment**
   - (i) Vasoconstrictor therapy:
     1. *Vasopressin*
     2. *Vasopressin and vasodilator*
     3. *Glypressin*
     4. *Somatostatin*
   - (ii) Drugs affecting the lower oesophageal sphincter
     1. *Metoclopramide*
     2. *Domperidone*
2. **Balloon tamponade**
3. **Injection sclerotherapy**
4. **Endoscopic variceal ligation**
5. **Staple transection of the oesophagus**
6. **Portasystemic shunt surgery**
7. **Transjugular intrahepatic portosystemic stent-shunt (TIPSS)**

1. Pharmacological treatment

(i) Vasopressin

Vasopressin causes constriction of the splanchnic arteriolar bed which increases the resistance to inflow of blood to the gut thereby lowering the portal pressure.

A meta-analysis of 4 controlled trials comparing vasopressin versus placebo or conventional therapy has shown only a 52% success rate and a rebleeding rate of up to 45%[7]. Complications, especially cardiovascular, were frequent and there was no effect on survival. It is usually administered as a continuous infusion, starting at a dose of 0.4 U/min and increasing, if necessary, to 0.6-0.8 U/min and continued until bleeding has been controlled for 12-24 hours and then gradually decreasing it before stopping it completely. A lower starting dose of vasopressin (0.2 U) has been found to be as effective[8,9]. By itself, vasopressin is no longer advocated for the treatment of acute variceal bleeding.

(ii) Vasopressin and vasodilator

A combined vasopressin-vasodilator regime is currently popular in the USA. The combined regimen enhances the decrease in portal pressure and the vasodilator offsets the cardiovascular complications

usually seen with vasopressin[10]. A venodilator is preferred because of its predominant effect on the pre-load which decreases venous return and therefore reduces the workload of the left ventricle in the presence of vasopressin-induced coronary vasocontriction. Three controlled trials[11-13] have been reported comparing vasopressin and nitroglycerin used intravenously[13], sublingually[12] or transdermally[11] to vasopressin alone for the control of variceal bleeding. Each of them showed a reduction in transfusion requirements[11]. There was, however, no effect on survival. These trials strongly favour the use of the combined regime instead of vasopressin alone, as it may be more effective[11,13] and complications are definitely reduced.

(iii) Triglycyl-lysine vasopressin (Glypressin)

Glypressin, a synthetic analogue of vasopressin, is slowly broken down to release vasopressin after intravenous injection. Its haemodynamic effect is similar to vasopressin. Two placebo-controlled trials have shown that it is effective in controlling variceal haemorrhage with few complications[14,15]. It is more stable, has a longer half-life and can be given as intravenous boluses at 6 h intervals compared to the continuous central venous infusion regime with vasopressin. In a single controlled trial[16], glypressin and nitroglycerin were found to be comparable to balloon tamponade for the control of acute variceal bleeding. The addition of nitroglycerin was well-tolerated with no serious cardiovascular complications. It is, however, very costly and its superiority over vasopressin is still not proven.

(iv) Somatostatin

Somatostatin, a 14 amino-acid peptide, was considered for the treatment of variceal haemorrhage because it can decrease portal pressure without the adverse effects of vasopressin on the systemic circulation[17]. It causes a selective splanchnic vasocontriction thereby decreasing portal and collateral blood flow and portal pressure[17,18] probably by inhibiting the release of splanchnic vasodilatory peptides such as glucagon and/or via a direct vasoactive action[19]. Results of randomised controlled-trials showed that it is at least as effective as vasopressin but with few side effects[20-23]. Two placebo-based controlled trials[24-25] reported contrasting results. The largest placebo-controlled trial conducted at the Royal Free Hospital[24] showed that it is safer and more effective than placebo in controlling variceal haemorrhage over a 5 day period (64% compared to 41% with placebo; $p<0.05$). The other placebo-based study[25] showed it to be ineffective in controlling bleeding from oesophageal varices compared to placebo (65% and 83% respectively; $p=0.06$). The difference is difficult to explain. Trials comparing somatostatin with sclerotherapy[26] and balloon tamponade[27] showed that it is equally effective. Thus it may be the optimal drug to treat variceal haemorrhage. However, further evidence of benefit is required before recommending its universal use. Its place would be as a useful adjunct in the early management of variceal bleeding before definitive treatment with sclerotherapy and also to reduce the chances of rebleeding following a single injection. The dosage remains empirical but an intravenous bolus of 250 μg followed by 250 μg/hr infusion for 5 days if found to be effective, is the usual recommended dose.

Octreotide, a synthetic somatostatin derivative, has a longer half-life (1-2 hrs vs 1-2 min in normal man) and may well be the drug of choice in acute variceal bleeding as, besides having similar effects to somatostatin[28] and being relatively cheaper, it is easy to administer, has few side effects and can be given subcutaneously in boluses.

A 2-centre randomised controlled trial of sclerotherapy combined with octreotide infusion or placebo for 5 days in the treatment of active variceal bleeding is currently being evaluated at the Royal Free Hospital.

(v) Drugs affecting the lower oesophageal sphincter

Drugs increasing the lower oesophageal sphincter like metoclopramide and domperidone have been shown to decrease the azygous blood flow[29] and lower variceal pressure[30] and might provide temporary control of variceal bleeding prior to injection sclerotherapy. Their value for stopping or preventing variceal bleeding is, however, still uncertain[31].

2. Balloon tamponade

Balloon tamponade achieves temporary control of variceal bleeding by direct compression of the varices at the bleeding site and is used in emergency situations to prevent exsanguination and to stabilise patients prior to more definitive therapy[32].

Though a success rate of 90% has been reported with balloon tamponade[33], there are some drawbacks. The haemostatic effect is temporary, with rebleeding occurring frequently following deflation of the balloon. It is operator-dependent and gives a high complication rate in centres where the expertise is lacking. It should therefore only be used as a temporising measure before sclerotherapy or surgery. At the Royal Free Hospital, about 20% to 25% of admissions for variceal bleeding require balloon tamponade. Mucosal damage at the gastro-oesophageal junction may occur with prolonged application. It should therefore not be applied for more than 12 hours. No study has shown increase in survival in patients treated with balloon tamponade.

3. Injection sclerotherapy

Endoscopic injection sclerotherapy is now considered the treatment of choice for acute variceal bleeding. Five prospective randomised controlled trials comparing sclerotherapy as a single therapy with balloon tamponade and/or vasoconstrictor therapy for the initial control of variceal bleeding, reported a significant advantage for sclerotherapy[34-38]. A study[39] comparing its efficacy for active variceal bleeding to a combined regime of vasopressin and nitroglycerin also showed a significant advantage of sclerotherapy in achieving haemostasis at 12 hours (88% and 65% respectively, $p<0.05$). Gastric varices which cause 15% to 20% of variceal bleeding require a different approach to treatment. Those arising from the fundus have a much poorer prognosis and early recourse to surgery is usually required for control. Intravariceal injection of tissue adhesive may be tried first in centres where the expertise is available. Those occurring below the oesophago-gastric junction (junctional varices) may be treated effectively with conventional sclerosants[40,41].

4. Endoscopic variceal ligation

Endoscopic variceal ligation involves the direct placement of pre-stressed rubber bands on the varix, using a special device at the end of the endoscope. Stiegman, who developed the technique, showed that he was able to control 67% of 21 cases of active variceal bleeders in a single session of ligation and 86% for the duration of admission or until death with few complications[42]. Overall results showed a similar rebleeding and eradication rate to injection sclerotherapy, but with fewer complications[43]. Randomised controlled trials comparing it to endoscopic sclerotherapy are in progress.

5. Staple transection of the oesophagus

Burroughs et al[44] showed that oesophageal staple transection for the emergency control of bleeding varices was superior to a single session of sclerotherapy (88% vs 62% $p<0.01$) and equally effective when compared with a maximum of 3 sessions of sclerotherapy in the control of variceal bleeding. The rate of rebleeding was significantly lower and survival rate was the same. Another study[45] showed similar results. At the Royal Free Hospital, emergency oesophageal staple transection is the usual initial surgical option in patients with whom sclerotherapy has failed. The same group recently published their 7 year experience with staple transection of the oesophagus in patients with bleeding oesophageal varices who were not controlled by emergency sclerotherapy[46]. Of 22 patients who had emergency staple transection because of failure to control bleeding, bleeding was controlled in 20 patients (90%) and 10 patients (45%) were discharged well, including 4 of 10 patients (40%) with Pugh-Grade C liver disease. During a mean follow-up period of 28 months (range: 14-66 months), 4 patients died including 2 with severe bleeding episodes. It would appear from their study that emergency staple transection of the oesophagus is an effective treatment for patients who continue to bleed despite acute sclerotherapy. Other options for treating patients

who continue to bleed despite emergency sclerotherapy include devascularisation, shunt surgery or liver transplantation.

6. Portasystemic shunt surgery

Orloff et al[47] reported a high success rate (98%) of emergency or urgent shunt surgery (within 8 hours) in patients with active variceal bleeding. However, the high admission mortality (42%) and morbidity (chronic portasystemic encephalopathy and hepatic failure) precludes its use as initial treatment and should now only be considered in patients who have failed other therapies. The prospect for future liver transplantation in centres where such expertise is available also makes it an unreasonable option as it may complicate the operation for the transplant surgeon. In Malaysia, where liver transplantation is not yet available, shunt surgery will still have to be considered. However, although good results have been claimed for shunt surgery as a primary treatment for patients with bleeding varices, its value in controlling acute variceal haemorrhage in patients in whom emergency sclerotherapy has failed, has not been fully evaluated.

7. Transjugular intrahepatic portosystemic stent-shunt (TIPSS)

This innovative interventional radiological technique is derived from the initial experience of Colapinto et al[48] and involves the placement of a Palmaz vascular stent in a tract formed between the hepatic and portal veins[49]. The initial encouraging results in terms of preventing rebleeding have been further supported by the same German group[50,51] with patency rates of at least 90% and few complications[52]. Closing off or stenosis of the shunt is common but can be resolved by balloon dilatation via the hepatic vein. Perarnau et al[53] have made the technique safer by placing TIPSS solely through the transjugular route after localising the portal vein using a sonographic protocol, thus avoiding the risk of intra-peritineal bleeding with the original transhepatic approach. Controlled trials are needed to evaluate its value in the emergency treatment of bleeding varices. It is also not certain whether the incidence of encephalopathy with this procedure is lower compared to shunt surgery, but, from the early experience gathered at the Royal Free Hospital and others, it appears to be so.

B. Prevention of Recurrent Variceal Bleeding

The aim of preventing rebleeding is to improve survival by decreasing the mortality associated with rebleeding. Rebleeding occurs up to 80%. The wide variation (50% to 80%) in the reported incidence of rebleeding is due to the different definitions of rebleeding, the type of treatment used to control the initial bleeding and the severity of the underlying liver disease[54]. The risk of rebleeding is highest just after the acute bleeding and decreases with time. Most trials do not specify whether the early rebleeding episode is part of the initial bleeding or otherwise.

The likelihood of early rebleeding is influenced by the type of treatment used to stop the acute bleeding. It is uncertain whether vasoactive drugs influence rebleeding rates unless they are given over several days. Balloon tamponade, as previously stated, is followed by a high rate of early rebleeding. Only sclerotherapy has been shown to prevent early rebleeding following readmission. Rebleeding rate is also influenced by the severity of the underlying liver disease. There are 3 major therapeutic options in the prevention of variceal rebleeding shunt surgery, sclerotherapy and drug therapy.

1. Shunt surgery

In 4 randomised trials[55-58] comparing portacaval shunt to no therapy in the treatment of patients bleeding from variceal haemorrhage, portacaval shunts did not increase survival despite a significant decrease in rebleeding. This was attributed to operative deaths and an increase in deaths from liver failure following portal venous blood diversion. Warren et al designed a distal splenorenal shunt operation to preserve hepatopetal portal venous blood flow and decrease the incidence of encephalopathy and hepatic failure

while selectively decompressing oesophagastric varices via the splenic vein[59]. Six randomised studies have been carried out in cirrhotic patients comparing distal splenorenal shunt and various non-selective portacaval shunts in patients who have bled from oesophageal varices. There is little difference between the 2 types of operations in terms of rebleeding rates and overall mortality[54]. The anticipated decrease in long-term encephalopathy is not yet proven, suggesting that the place of distal splenorenal shunt in the surgical management of portal hypertension is not paramount. It is also a technically difficult operation and should probably be performed by surgical teams familiar with the technique for optimal results. If the expertise is available, it would be preferable to the non-selective shunt operations as it is easy to deal with at liver transplantation.

2. Long-term sclerotherapy

Although shunt surgery is effective in preventing variceal rebleeding, the relatively high operative mortality and incidence of encephalopathy and liver failure has invoked a renewed interest in sclerotherapy as a means of preventing rebleeding from varices.

Seven trials comparing long-term elective sclerotherapy versus no elective sclerotherapy have been performed[54]. Although the patient population, frequency of sclerotherapy sessions, choice of sclerosants and therapeutic end-points varied, most of the studies show that sclerotherapy reduces the frequency and severity of variceal bleeding. Two studies[60,61] which used sclerotherapy for the initial control of acute bleeding, but did not offer interval sclerotherapy for obliteration of varices to the control group, failed to show a difference in mortality. Meta-analysis shows that sclerotherapy is the only treatment which significantly reduces both variceal rebleeding mortality in contrast to shunt surgery or beta-blockers when they are being compared individually. No technical variation of injection sclerotherapy or choice of sclerosants has been shown to influence efficacy. However, long-term endoscopic variceal ligation (which gives similar results to injection sclerotherapy in controlling acute variceal bleeding) may be a better option as it reduces complications associated with the latter treatment. Results of ongoing trials are awaited.

Rebleeding from varices is infrequent after they have been eradicated with sclerotherapy. Even so, 10% to 23% still rebleed. Varices may reappear within a year[62] and cause bleeding in 30% of affected patients. Endoscopic follow-up is therefore essential in the first year following eradication of varices. Shunt surgery is superior to sclerotherapy in preventing rebleeding with similar mortality rates but a higher incidence of encephalopathy may complicate the prospect of future liver transplantation[54].

3. Beta-blockers

The optimal treatment for preventing variceal rebleeding will be the oral administration of a relatively cheap drug which decreases portal venous pressure with minimal side-effects.

Propranolol has been shown to acutely decrease portal venous pressure in alcoholic cirrhosis[63] and also cause a chronic reduction of portal venous pressure in the long term[64]. Propranolol decreases portal pressure probably by the following mechanisms: reduction of cardiac output, splanchnic vassoconstriction (due to unopposed alpha-adrenergic activity) and decrease in portal collateral flow (thought to be due to a specific beta-2 blockade effect)[65]. However, about 30% of patients do not show any response[66]. Eleven placebo-controlled trials have been undertaken to assess its role in preventing recurrent variceal bleeding[54]. A meta-analysis of these trials show that while 6 of them reported a significant decrease of rebleeding with beta-blockers, all of them showed a reduction in bleeding in the beta-blocker treated group regardless of whether statistical significance was achieved in the individual trial. There is, however, little effect on overall mortality.

Response to beta-blockers appears to be influenced by severity of liver disease in relation to catecholamine concentration and timing of therapy. The incidence of bleeding as a cause of death was slightly higher in the placebo-treated group while the incidence of hepatic failure as a cause of death was higher in those with beta-blockers. The risk of rebleeding and death decrease with time following a variceal bleeding, and the efficacy of drugs in early and late rebleeding may be different[67]. Retrospective analysis suggested that propranolol had little effect on influencing early rebleeding (<6 weeks) but significantly reduced the incidence of first rebleeding after 6 weeks[54].

Propranolol has few side-effects provided it is given only to patients who do not have the usual contra-indications to beta-blockers (eg. bronchial asthma, congestive failure, peripheral vascular disease, etc.).

Trials of long-term sclerotherapy versus beta-blockers showed very similar mortality and rebleeding rates. Addition of beta-blockers does not confer any advantage compared to sclerotherapy alone[54].

The addition of isosorbide mononitrate to propranolol has been shown to convert propranolol 'non-responders' to responders. A randomised trial comparing oral propranolol alone with the combination of propranolol and isosorbide mononitrate showed a decrease of more than 20% of the hepatic venous pressure gradient in 50% of the combined group compared to only 10% of the propranolol group[68]. The advantages observed with similar improvements in drug therapy may well make drug therapy the treatment of choice for the prevention of variceal rebleeding.

4. Transjugular intrahepatic portosystemic stent-shunt (TIPSS)

Controlled studies evaluating the efficacy of TIPSS are awaited and, if found to be effective, it may become the treatment of choice for patients who bleed whilst awaiting a liver transplant.

C. Prophylaxis for Variceal Haemorrhage

The aim of preventing the initial variceal bleeding in cirrhotic patients is to improve survival. Although portasystemic shunt surgery proved to be effective in preventing the variceal bleeding, the high incidence of encephalopathy and liver failure leading to an increased mortality made prophylactic surgery a non-starter as prophylactic treatment.

Sclerotherapy was then tried for the prevention of the initial variceal bleeding. To date 18 randomised controlled trials evaluating prophylactic sclerotherapy have been reported and, although the results are conflicting in terms of efficacy, most of them have been disappointing. This is borne out by the more recent and larger trials which showed sclerotherapy to be ineffective in preventing haemorrhage or increasing survival[69].

Beta-blockers provide the most promising option. They are easy to administer and have few side-effects. A comprehensive meta-analysis[70] showed that the incidence of first bleeding is significantly reduced by propranolol compared to no treatment. Patients with cirrhosis and portal hypertension should undergo routine endoscopy and those with large varices should be offered beta-blocker therapy as this will decrease the incidence of bleeding and death from bleeding. Not all patients, however, will respond to propranolol despite adjustment in the dosage of the drug and there is no reliable clinical or haemodynamic variable that can be used to select those patients who will respond. There is, however, a recent report regarding gradient changes in hepatic venous pressure measurements following propranolol which may predict response[71]. A reduction to less than 12 mmHg in hepatic venous pressure gradient was accompanied by the absence of bleeding in both placebo and propranolol groups. However, this requires invasive measurement and will not therefore be of general clinical use.

D. Portal Hypertensive Gastropathy

Portal hypertensive gastropathy is now a recognised entity and may lead to upper gastrointestinal bleeding in cirrhotic patients[5]. Several studies have indicated that it may account for between 10% to 59% of bleeding in patients known to have portal hypertension[72]. The first propranolol trial for the prevention of variceal rebleeding included patients who had bled from the gastric mucosa. The numbers were too small to prove benefit statistically. A single blind randomised study[73] showed that beta-blockers have an additional role in preventing both acute and chronic bleeding from severe congestive gastropathy (red spots on mucosa). Survival was not affected.

Conclusion

Injection sclerotherapy would be the treatment of choice for acute variceal bleeding in centres familiar with this technique and can be carried out at the initial endoscopy. An alternative approach would be to use the combined vasopressin-transdermal nitroglycerin regime or somatostatin for patients with minor variceal bleeding and reserving injection sclerotherapy for patients with more severe acute bleeding. Staple transection of the oesophagus would be the next option for treatment failures before considering emergency shunt surgery. If expertise for TIPSS is available it could replace surgery. A sequential approach is, however, not necessarily appropriate for all patients, as individual variations do occur in the natural history and prognosis of variceal bleeding.

In the prevention of variceal rebleeding, non-selective beta-blockers should be tried first, in patients with no contra-indication to beta-blockers. Long-term sclerotherapy is an alternative and is the best option for those with contraindications or intolerance to beta-blockers and those who rebleed despite taking beta-blocker therapy. Surgical rescue in the form of either shunt surgery or liver transplantation is considered if either treatment fails. The type of operation will depend on the patient's age, the type of liver disease, previous abdominal surgery and the experience of the resident surgical team. TIPSS may also replace surgery in the elective situation in the future. For the prevention of the initial variceal bleeding, beta-blockers are without doubt the treatment of choice. Based on present data, injection sclerotherapy is no longer justified for this purpose.

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