Review Article

The management of an episode of variceal bleeding

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Introduction

Variceal bleeding is the most serious consequence of portal hypertension and may be anticipated at sometime during the lifetime in 30% of patients with an underlying cirrhosis.¹ The admission mortality for an episode of variceal bleeding is critically dependent upon the severity of the underlying liver disease but may be as high as 50% for the first haemorrhage.¹ In the absence of specific therapy to prevent it, recurrence of bleeding will occur in 20–60% of patients during the period of admission, the considerable variation, in part, reflecting different definitions of this event.^{2–4} The severity of the liver disease is the most important factor predicting rebleeding.^{2,3} The specific therapy for an episode of variceal bleeding is quite distinct from that required for other causes of gastrointestinal bleeding and as such this places considerable emphasis upon the need for early endoscopic diagnosis following initial resuscitation. At the time of diagnostic endoscopy (carried out within 4 hours of admission) fewer than 50% of patients will be actively bleeding, the remainder having stopped spontaneously.^{2,5} This distinction is important in that the measures directed towards the control of active bleeding may not be the same as those used to prevent early recurrence (in those who have stopped spontaneously – see below).

Resuscitation

Standard resuscitative measures for volume depletion are applicable in patients with variceal haemorrhage and will not be covered in detail. However, there are a number of considerations, specific to patients with cirrhosis, which deserve mention. The normal response to hypovolaemia includes both venous and arteriolar constriction, mediated initially by the low pressure baro-receptor reflex, thereby maintaining venous return and redistribution of blood flow to vital organs. In the presence of

cirrhosis, particularly severe disease, the baro-receptor reflex may be diminished by an attenuated response of the alpha-receptors to noradrenaline.⁶ Furthermore, the ability to mobilize the so-called 'unstressed volume' of blood from the hepatic sinusoids to maintain venous return may also be restricted in the cirrhotic liver.⁷ Both these factors may lead to a greater fall in arterial pressure than would be anticipated from the observed blood loss and emphasizes the need for prompt resuscitation.

The degree to which volume restitution is undertaken has been influenced by the observation that hyper-expansion of the circulation may precipitate variceal bleeding.^{8,9} Two recent studies have assessed the effect of volume depletion and repletion on portal and systemic haemodynamics in rat models of portal hypertension.^{10,11} Venesection (20% of blood volume) produced a significant reduction in portal pressure; however, this then rose above baseline values when the exact volume of blood was replaced.¹⁰ The degree of 'overshoot' in portal pressure appeared to correlate with the extent of the collateral circulation and was secondary to a rise in portal collateral resistance.¹¹ Whether a similar elevation of portal pressure occurs in man and to what extent this might represent a clinical problem in the form of protracted or recurrent variceal bleeding is unknown. The need to protect renal function does not permit inadequate volume restitution although overfilling should be avoided by titration against central venous pressure. Caution should be taken when interpreting the central venous pressure measurements in patients with tense ascites: compression of the right atrium may lead to an overestimate of the value.¹² The measurement of the pulmonary capillary wedged pressure using a pulmonary flotation catheter will provide a more accurate assessment in such cases.

Therapy of active variceal bleeding

The measures used to manage an episode of variceal bleeding may be conveniently categorized

into those that have an effect only for the period they are applied, those which may prevent early (hours to days) rebleeding and those which may reduce the risk of long-term (weeks to months) recurrent haemorrhage (Table I).

This distinction has important clinical implications in that therapy of only short-term benefit should be followed by a more definitive procedure to prevent the high incidence of rebleeding.

Table I The management of variceal bleeding

1) Measures effective only during application
Vasoconstrictor agents
Drugs increasing lower oesophageal sphincter pressure
Balloon tamponade
2) Measures with additional effect on early rebleeding
Injection sclerotherapy
Banding ligation
(Oesophageal transection without devascularization)
3) Measures with additional long-term effect on rebleeding
Portal systemic shunt surgery
Ablative surgery

1. Measures effective only during the period applied

Vasoconstrictor therapy

(a) Vasopressin

Despite almost 40 years of continuous use only four controlled trials of vasopressin, as compared to placebo or ‘conventional’ therapy, have been reported.^{13–16} In the first three of these studies a significant benefit was observed for vasopressin with haemostasis being obtained in 44–71% of cases.^{13–15} However, in the most recent trial vasopressin failed to show significant benefit over a placebo infusion (59% vs 45% CI–9– + 39% respectively).¹⁶ Similar low success rates (9–58%) for vasopressin have been observed in a number of studies in which this has been compared to other pharmacological agents.^{17–19} Attempts to improve the efficacy of vasopressin by direct administration into the superior mesenteric artery failed to show benefit when compared to a continuous intravenous infusion.^{14,15}

Two major limitations of vasopressin therapy can be recognized from the available studies: firstly, the frequency of complications associated with its generalized arterial vasoconstrictor effect which have required cessation of therapy in 20% of cases and death in 3% (the majority from myocardial infarction or left ventricular failure); secondly, even in those patients who tolerate the drug,

control of bleeding has been achieved in only 50–65% of cases.²⁰

(b) Vasopressin combined with a vasodilator

The concept of combining vasopressin and a vasodilator was conceived with the aim of reducing the cardiovascular complications associated with the former and to thereby enable a greater proportion of patients to be exposed to the potential benefits of the therapy. Both venous and arterial vasodilators have been investigated and shown to reverse the systemic haemodynamic effects of vasopressin whilst the fall in portal pressure was maintained or enhanced.^{21–23} These changes depend upon the vasodilatation of selective areas of the systemic circulation without reversing the vasopressin effect on the splanchnic arteries. The predominant venodilators, such as nitroglycerin, may also act by reducing pre-load and thereby protecting the left ventricle in the presence of vasopressin induced coronary vasoconstriction.

Three controlled trials have been reported comparing the combination of vasopressin and nitroglycerin with vasopressin alone for the control of active variceal bleeding.^{24–26} The route by which the nitroglycerin was administered differed in each study and included the intravenous,²⁴ sublingual²⁵ and transdermal approach.²⁶ Each of these three trials provided evidence of benefit for the combined regime with respect to either enhanced control of bleeding²⁶ or reduced complications²⁵ or both.²⁴ The observed benefits did not result in an improvement in admission mortality. This may in part be explained by the failure of the combined regime to improve the control of the most severe episodes of bleeding.²⁴ Furthermore, Grade C patients with the most severe liver disease (Chill’s Grade C) account for the majority of deaths and in the presence of severe liver disease it may be the fact of bleeding rather than the extent that is the major determinant of outcome.

Despite the failure of the combined regime to influence mortality as compared to vasopressin alone, the enhanced control of bleeding (with evidence of reduced transfusion requirements)^{24,26} and fewer complications may be anticipated to diminish the resources required to manage active variceal bleeding.

(c) Triglycyl-lysine vasopressin (glypressin)

Glypressin, the triglycyl-lysine analogue of vasopressin, was introduced as a successor to vasopressin for the management of variceal haemorrhage.²⁷ The ability to administer the drug as a peripheral intravenous bolous at 6-hourly intervals offered a major advantage as compared to the continuous central venous infusion required with vasopressin. Early uncontrolled studies suggested a high success

rate in controlling bleeding and with few side effects.²⁸ A controlled study comparing glypressin with vasopressin confirmed enhanced control of bleeding with the former (70 vs 9%, $P < 0.02$) although the number of patients included in the study was extremely small (20) and the efficacy of vasopressin considerably less than would be predicted.¹⁷ The same authors then went on to carry out a placebo based controlled trial and in an inconclusive report showed benefit for glypressin (60 vs 37%), this difference failing to reach significance ($P < 0.05$).¹⁹ Evidence in support of the efficacy of glypressin comes from the largest reported placebo based controlled trial,²⁹ although the routine use of balloon tamponade and injection sclerotherapy in the patients included precludes a confident assessment of benefit.

A recent study has reported the effects of combining glypressin with a venodilator (nitroglycerin) and confirmed a beneficial effect upon the systemic haemodynamic changes observed with the former;³⁰ the addition of nitroglycerin had no effect upon the portal pressure reduction produced by glypressin. The efficacy of glypressin and nitroglycerin for the control of variceal bleeding has been assessed in a single controlled trial in which this combination was shown to be comparable to balloon tamponade (78% and 79% respectively 12 hours after institution of therapy).³¹ The addition of nitroglycerin to glypressin therapy was well tolerated and no serious cardiovascular complications were observed.

(d) Somatostatin

Somatostatin has been shown to reduce portal inflow (mediated by splanchnic artery vasoconstriction) and hence portal pressure without inducing adverse systemic haemodynamic effects.³² The first two controlled trials compared somatostatin to vasopressin as a single agent;^{18,33} both reported fewer side effects with somatostatin although in only one study was there enhanced control of bleeding.³³ Two placebo based controlled trials have recently been reported with markedly contrasting results.^{34,35} In the largest of all the reported studies (120 bleeding episodes) haemostasis was obtained more frequently with somatostatin than placebo (64 and 41% respectively; $P < 0.05$).³⁴ The second placebo based study incorporated a similar trial design and included 84 patients, all of whom had evidence of recent major haemorrhage.³⁵ However, the control of bleeding at 30 hours after randomization was less in the somatostatin group than those receiving placebo (65 and 83% respectively; $P = 0.06$). A most unexpected feature of these results is the extremely high spontaneous cessation of bleeding in the placebo group which could not have been predicted from a review of

established literature. Until further trials have been reported it is difficult to justify the costs incurred by using somatostatin.

Drugs affecting the lower oesophageal sphincter pressure

Drugs which increase lower oesophageal sphincter pressure such as metoclopramide, domperidone and pentagastrin have been shown to reduce azygos blood flow³⁶ and to lower varix pressure.³⁷ There is preliminary evidence to suggest that these drugs might provide temporary control of variceal bleeding and thereby facilitate measures such as injection sclerotherapy.³⁷

Balloon tamponade

Direct compression of the bleeding point by the use of balloon tamponade has been in use for almost 40 years.³⁸ Available reports suggest control of variceal bleeding may be anticipated in 80–90% of cases with an approximate 3% mortality directly associated with the tube.²⁰ However, such results are the product of centres experienced in the use of the technique. A recent report suggests that the efficacy of balloon tamponade may be considerably less and the complication rate higher when appropriate expertise is lacking.³⁹ The optimum design of the tube has been the subject of considerable debate. The use of a 4 lumen tube (incorporating an oesophageal aspirate port) has been shown to reduce the risks of aspiration pneumonia as compared to the earlier 3 lumen Sengstaken-Blakemore Tube.⁴⁰ A second important consideration is the need to use the oesophageal as well as the gastric balloon. Inflation of the oesophageal balloon has been shown to have minor benefits with respect to haemostasis but with an increased risk of aspiration pneumonia.^{41,42} There is evidence to suggest that the single gastric balloon tube (Linton-Nachlas) provides better control of gastric variceal bleeding.⁴¹ However, any observed benefit is most likely to reflect the volume of the gastric balloon (the Linton-Nachlas Balloon can be inflated to 600 ml); any tube in which inflation of the gastric balloon can attain approximately 200 ml should provide similar control. The critical factor for control of both oesophageal and gastric variceal bleeding is the close apposition of the gastric balloon to the gastro-oesophageal junction.³⁹

Balloon tamponade inevitably leads to mucosal damage particularly at the gastro-oesophageal junction and this becomes more marked with prolonged application. These lesions may become a subsequent cause of bleeding when the tube is removed. A period not exceeding 12 hours will minimize the risks of serious damage.

2. Measures with additional effect upon early rebleeding

Injection sclerotherapy

Support for the use of injection sclerotherapy for an episode of variceal bleeding first came from two large uncontrolled studies in which control of bleeding for the period of admission was in excess of 90%.^{43,44} The majority of the patients included had either stopped bleeding spontaneously or had initially been managed by balloon tamponade and as such no conclusions may be drawn with respect to sclerotherapy as single treatment for active haemorrhage. A number of controlled trials have now been reported comparing sclerotherapy as a single therapy with balloon tamponade and/or vasoconstrictor therapy for the period of admission and provide strong evidence to support the efficacy of the former.⁴⁵⁻⁴⁹ However, much of the benefit associated with sclerotherapy may derive from the prevention of early rebleeding, an attribute which is not inherent to vasoconstrictor therapy or balloon tamponade. A recent study has specifically investigated the efficacy of sclerotherapy for active variceal bleeding in comparison to a regime of vasopressin and nitroglycerin.⁵⁰ Control of bleeding was assessed over 12 hours, after which both groups were treated by long-term sclerotherapy (thus removing the bias that may occur if this was restricted to the sclerotherapy group alone). Haemostasis at 12 hours was obtained in a significantly higher proportion of patients treated by sclerotherapy (88 and 65% respectively, $P < 0.05$) with lower transfusion requirements. Overall frequency of rebleeding and admission mortality were not different, almost certainly reflecting the use of long-term sclerotherapy in both groups.

In 15–20% of cases variceal bleeding arises from gastric varices.⁵ Those situated on the lesser curve or within a hiatus hernia may be managed by sclerotherapy with similar efficacy to that attained for oesophageal varices.^{51,52} The results of sclerotherapy for bleeding from fundal varices is poor and there should be an early recourse to surgery.⁵³ In the presence of a bleed-free interval fundal varices may be successfully treated by the intra-varix injection of a tissue adhesive.⁵³

Endoscopic banding ligation of oesophageal varices

The recent introduction of an endoscopic technique enabling the direct placement of pre-stressed rubber bands upon the varices represents an alternative to injection sclerotherapy as a local measure for the management of variceal bleeding. Initial results of this technique appear to justify further evaluation in controlled trials.⁵⁴

3. Measures with additional influence upon late rebleeding

Portal systemic shunt surgery

Support for shunt surgery as an immediate measure (within 8 hours of admission) for variceal haemorrhage comes from a large uncontrolled series in which 180 unselected patients (although only 15% Grade C) received a portal caval anastomosis.⁵⁵ Control of bleeding was attained in 98% of cases but at the expense of a 42% admission mortality. Despite this high admission mortality 30% of the patients were alive at 12 years. From these data it appears that the use of shunt surgery as a first line measure selects out patients who, with prompt control of bleeding and absence of recurrence haemorrhage, have a good prognosis.

In a recently reported controlled trial an 'emergency' portal caval shunt was compared to injection sclerotherapy (immediate and long-term) in patients with Grade C (Cello Modification) liver disease.⁵⁶ During the period of admission 50% of the sclerotherapy group rebled compared to 19% of those treated by shunt surgery ($P < 0.05$). Admission mortality was similar (50 and 56% sclerotherapy and shunt surgery respectively). Contrary to expectations the occurrence of encephalopathy was not different for the two groups.

Despite this evidence in support of immediate shunt surgery, the high admission mortality has consistently deterred more widespread adoption in favour of its use in patients who have failed other therapies. The value of 'rescue' shunt surgery has received support from the results of a controlled trial in which a selective distal spleno-renal shunt was carried out for rebleeding in patients treated initially by sclerotherapy.⁵⁷

A further factor which has an important bearing upon surgical intervention is the prospect of liver transplantation. Although there are no absolute contra-indications to the different shunt operations, any previous upper abdominal surgery increases the risk of transplantation.⁵⁸ The central spleno-renal and meso-caval shunts, which are constructed at a distance from the liver hilum, may have advantages over the portal caval shunt.

Ablative surgery

The adaptation of the surgical stapling gun for transection of the oesophagus has led to a resurgence of interest in ablative therapy for the management of active variceal bleeding. This procedure has been used alone or in conjunction with devascularization. The extent of the devascularization has important implications as to the suitability of a procedure for 'emergency' use.

Three controlled trials have compared oeso-

phageal transection to injection sclerotherapy.⁵⁹⁻⁶¹ The first of these trials compared sclerotherapy (immediate and long-term) to stapling transection (with or without splenectomy) in 76 patients; only a minority were actively bleeding at the time of treatment.⁵⁹ Rebleeding during the hospital admission occurred significantly less often in the transected patients (3 and 49%, $P < 0.01$) although the mortality for the same period was similar (24 and 33% respectively). The second trial divided 70 patients with ongoing haemorrhage into good and poor risk groups on the basis of the severity of liver disease; in the former, stapling oesophageal transection (without devascularization) was compared to shunt surgery and, in the latter, to injection sclerotherapy (immediate and long-term).⁶⁰ Oesophageal transection controlled bleeding in 79% of good risk and 71% of poor risk patients: this was less than observed with shunt surgery (100%) and similar to that observed with sclerotherapy (83%). Rebleeding occurred in 26 and 43% of the transected patients which was more than observed after a shunt (13%) but similar to that observed following sclerotherapy (50%). Severe encephalopathy in 15% of the good risk group following shunt surgery was considered a major limitation. There were no differences between the comparative groups with respect to mortality. The most recent and largest trial compared stapling transection (without devascularization) to injection sclerotherapy (single session) in 101 patients (56% Grade C) the majority with active bleeding at the time of treatment.⁶¹ This was controlled in 88% of those transected and 82% of the sclerotherapy treated patients. Rebleeding during the period of admission was significantly less frequent following transection (7 and 42%, $P < 0.01$). Admission mortality was similar (35 and 44%).

These data support the efficacy of stapling transection for the management of an episode of variceal bleeding. Previous concerns that transection without devascularization might be associated with a high rate of rebleeding remain largely unsubstantiated. However, a beneficial effect upon rebleeding represents the only major advantage over sclerotherapy. The possible adverse effects of abdominal surgery for subsequent liver transplantation have been referred to above.

A strategy for the management of an episode of variceal haemorrhage

The diagnostic endoscopy in a patient suspected of bleeding from varices should be timed to follow initial restoration of the circulating volume (usually within 4 hours of admission). Such early endoscopy is likely to improve diagnostic accuracy and also to minimize the delay in starting specific

treatment. The diagnostic endoscopy also provides the opportunity to carry out immediate sclerotherapy in both those who continue to bleed and those in whom this has stopped spontaneously. The efficacy of this approach both for the control of active bleeding and for the prevention of early rebleeding, favours immediate sclerotherapy as the optimum initial management.

In the absence of the appropriate endoscopic expertise the therapeutic options lie between vasoconstrictor therapy and balloon tamponade. It is unlikely that any vasoconstrictor regime will influence severe haemorrhage (sufficient to prevent blood volume restitution) and balloon tamponade may be life-saving in this situation. There are few other indications for this unpleasant and hazardous treatment. The choice of a vasoconstrictor regime has been influenced by recent evidence documenting the poor results with vasopressin as a single agent. There is now considerable evidence to support the addition of nitroglycerin to vasopressin or glypressin therapy. There is no evidence to suggest that somatostatin has any advantage over vasopressin and nitroglycerin and therefore price should caution against its use. Vasoconstrictor therapy and balloon tamponade are temporary measures which should be used for short periods (6-12 hours) to obtain initial haemostasis. Failure to control bleeding over a 6 hour period is an indication to change therapy.⁵⁰ Temporary measures should only be discontinued when more definitive therapy has been instigated.

Injection sclerotherapy is the most widely used treatment to prevent early rebleeding although there is no evidence to suggest that this is superior to stapling oesophageal transection, particularly in Grade A and B patients. The failure to control bleeding by a single session of sclerotherapy usually reflects incomplete treatment or an incorrect diagnosis of the bleeding point. In such circumstances a full endoscopic examination should exclude other bleeding points before repeating sclerotherapy. Failure to control bleeding by two consecutive sessions of sclerotherapy is an indication to change therapy. Stapling oesophageal transection (with or without devascularization) and several types of portal systemic shunt have been used with success as 'rescue' measures; the decision between these options is based upon several factors including the available expertise, the severity of liver disease and the possibility of future liver transplantation.

The endoscopic diagnosis of bleeding arising from fundal varices requires an alternative strategy. Attempts at sclerotherapy during active bleeding are seldom successful and the admission mortality considerably higher than observed in patients bleeding from oesophageal varices. Surgical intervention almost certainly represents the optimum approach; the options are between devas-

cularization or a portal systemic shunt. Splenectomy alone is the operation of choice in patients with splenic vein thrombosis and isolated fundal gastric varices. In patients considered unfit for

surgery measures such as vasoconstrictor therapy or balloon tamponade may provide a bleed-free interval during which tissue adhesive can be injected into the fundal varix.

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