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Review

Treatment of acute variceal bleeding

C.K. Triantos,[1,2] A.K. Burroughs[2]

SUMMARY

Acute variceal bleeding is a life-threatening complication in patients with portal hypertension. Although overall survival may be improving, mortality is still closely related to failure to control hemorrhage or early re-bleeding. Factors that influence this failure include severity of liver disease and active bleeding during endoscopy. In addition increased portal pressure has been proposed as a prognostic factor of early re-bleeding. There is also a strong association between variceal hemorrhage and bacterial infection. Recent meta-analyses confirmed that antibiotic prophylaxis significantly increases the short-term survival rate. Effective resuscitation, protection of the airway, particularly with severe bleeding and disturbed conscious level, especially during endoscopy are initial priorities. The following treatment strategies have been compared: a)Vasoactive drugs (±tamponade) vs Vasoactive drugs (±tamponade)+ sclerotherapy, b)vasoactive drugs vs sclerotherapy, c)vasoactive drugs+ endoscopy vs endoscopy, d)sclerotherapy vs ligation and e)Recombinant factor VII +endoscopy vs placebo+endoscopy. According to Baveno IV Consensus endoscopic treatments are best used in association with pharmacological therapy, which preferably should be started before endoscopy. Lastly in order to identify the group with poor outcome, new diagnostic/treatment algorithms are needed using known predictive factors. In this group more effective vasoactive regimens, early TIPS, and the use of self-expanding covered oesophageal stent could be considered.

Key words: variceal bleeding, management, endoscopy

[1]Department of Gastroenterology, University Hospital, Patras, Greece, [2]The Royal Free Sheila Sherlock Liver Centre and Dept. of Surgery, Royal Free Hospital, London, UK

Author for correspondence:

CK.Triantos, Girokomiou 20-31,M6, 26331 Patra, Tel: 00306972894651, Fax: 00302610625382, e-mail: chtriantos@hotmail.com

INTRODUCTION

Portal hypertension is a major complication of chronic liver disease, leading to the development of portosystemic collaterals of which the most clinically significant are those that form gastroesophageal varices. Variceal haemorrhage is the most serious complication of portal hypertension and is associated with a high mortality rate which ranges from 30% to 50% (1), although recently it is well established that there has been a significant reduction in mortality from bleeding over the past 40 years.[2,3] Although overall survival may be improving, mortality is still closely related to failure to control haemorrhage or early rebleeding, and occurs in high rates in the first days to 6 weeks after admission.[4,5]

Several factors have been validated for the prediction of the outcome of an acute variceal bleeding. Active bleeding at endoscopy, severity of liver disease, encephalopathy, platelet count, history of alcoholism, Child-Pugh grade, shock at admission and the use of antibiotics have been associated with control of bleeding.[5-12] Regarding mortality, prognostic factors include: presentation with haematemesis, failure to control bleeding within 5 days, raised bilirubin, encephalopathy, shorter interval to admission to hospital, plasma urea, bleeding starting in hospital, prothrombin time<40%, recent use of steroid drugs within 7 days of bleeding, age>60 years, hepatic venous pressure gradient (HVPG), concomitant hepatocellular cancer and transfusion need.[13-17]

Several new therapeutic approaches have been introduced for the prevention and treatment of variceal bleeding. The therapeutic armamentarium for portal hypertensive bleeding is now considerably expanded by the use of various drugs, including antibiotics and vasoactive agents, the endoscopic sclerotherapy or ligation of oesophageal varices and the transjugular intrahepatic portosystemic shunts (TIPS). Recently the use of a self expanding covered oesophageal stent, has shown promise as a substitute for balloon tamponade.[18] The most important therapeutic

manoeuvre in terms of increasing survival seems to be the use of prophylactic antibiotics.[19] The relative risk of mortality is reduced to 0.39 (95% CI 0.32 to 0.48), which is a greater reduction than that seen with specific vasoactive drugs. Prophylactic antibiotics also reduce the incidence of early rebleeding, supporting the hypothesis of infection as a trigger for bleeding.[9,11]

HVPG

The measurement of HVPG, in acute variceal bleeding, provides prognostic information on the evolution of the bleeding episode.[417,20-22] Moitinho et al[23] evaluated 65 cirrhotics with acute variceal bleeding: the only independent variable associated with the outcome was HVPG, which was higher in patients with a poor evolution ($p< 0.0004$). An initial HVPG of ≥ 20 mm Hg was associated with a significantly longer intensive care unit stay, longer hospital stay, greater transfusion requirements, and a worse actuarial probability of survival (1-year mortality, 64% vs. 20%; $p < 0.002$). In another recent trial[24] in consecutive cirrhotic patients with acute variceal bleeding from esophageal varices, HVPG was measured within 12-48 hours of acute variceal bleeding. Patients already on vasoactive drugs, Child Pugh (CTP) score of > 12, or concomitant hepatocellular carcinoma were excluded. Patients were treated with either EBL (24 patients) or EBL +I.V.somatostatin 250 mcg/hr (23 patients). HVPG was measured in mean 28±12 hours after variceal bleeding in 47 cirrhotics (M:F=35:12,mean age:44±7 years) with acute variceal bleeding. Fourteen patients (29.7%) rebled. The mean HVPG in patients with and without treatment failure was 22.4 ± 5.4 and 19.1±4.4 mmHg ($p=0.038$) respectively. In univariate analysis CTP ($p=0.05$), HVPG ($p=0.038$), albumin ($p=0.001$) and creatinine ($p=0.038$) were significantly associated with treatment failure, but in multivariate analysis only HVPG and albumin were significantly associated.

Recently Albrades et al[13] evaluated a cohort of 117 cirrhotics concluding that HVPG independently predicted short-term prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. However they showed that similar predictive accuracy can be achieved using only simple clinical variables that have universal applicability ie. that Child grade C patients are the difficult patients for control of bleeding and at greater risk of death. The authors confirm what was already known clinically about these patients with difficult bleeding[25] with the added data, that this is associated with a higher HVPG. This gives the basis for the rationale of using portal pressure lowering agents as soon as possible before admission[26] and/or before endoscopy and allows selection criteria to test new therapies.[27,28]

BACTERIAL INFECTION

Bacterial infections are frequently associated with upper gastrointestinal bleeding in cirrhotic patients.[9,19,29] Goulis et al[9] showed in a prospective study that independent prognostic factors of failure to control bleeding were proven bacterial infection ($p <0 .0001$) or antibiotic use ($p < 0.003$) as well as active bleeding at endoscopy ($p <0 .001$) and Child-Pugh score ($p < 0.02$). In another report (1037 cirrhotics) the 297 with infection had a fourfold increase in the incidence of GI bleeding ($p<0.001$) compared to 346 without infection.[30] In addition others report that presence of bacterial infection in bleeding cirrhotic patients is independently associated with early mortality and failure to control bleeding (31;32). These data from different parts of the world confirm the original study which prospectively set out to assess the association of infection with bleeding.[9]

A recent meta-analysis confirmed that antibiotic prophylaxis prevents infections in cirrhotic patients with gastrointestinal bleeding and significantly increases the short-term survival rate.[19] In a randomized trial[11] cirrhotics with variceal bleeding but without evidence of bacterial infection were randomized to receive prophylactic antibiotics (ofloxacin 200 mg i.v. q12h for 2 days followed by oral ofloxacin 200 mg q12h for 5 days) or receive antibiotics only when infection became evident (on-demand group). Antibiotic prophylaxis decreased infections ($p <0.002$). The actuarial probability of rebleeding was higher in patients without prophylactic antibiotics ($p =0.0029$). Bacterial infection and association with hepatocellular carcinoma were independent factors predictive of rebleeding. There was no difference in survival between the two groups. These data support the original hypothesis[10] supporting the role of bacterial infection in the initiation of variceal bleeding. Jun et al[12] compared prophylactic third generation cephalosporins with on-demand antibiotics for the prevention of gastroesophageal variceal rebleeding. Authors concluded that antibiotic prophylaxis using third generation cephalosporins can prevent bacterial infection and early rebleeding in patients with the first acute gastroesophageal variceal bleeding.

Intravenous 3rd generation cephalosporines, compared to oral quinolones are a good option for prophylaxis in upper GI bleeding in cirrhosis being active against gram negative bacteria and non enterococcal streptococci. In addition many cirrhotics receive quinolones already as

prophylaxis for spontaneous bacterial peritonitis. Current trials have started antibiotics after endoscopic diagnosis. Possibly the administration should be started at admission before endoscopy with the potential to increase therapeutic benefit.

An additional issue surrounding infection is that it is known that severe sepsis is associated with a subnormal adrenal response, also in cirrhosis, and that steroid therapy improves survival.[33,34] Studies should be performed in patients who bled to assess whether adrenal insufficiency is present with bleeding per se, and/or only in the presence of infection, mild or severe.

GENERAL MEASURES

Effective resuscitation, protection of the airway, particularly with severe bleeding and disturbed conscious level, especially during endoscopy are initial priorities. Sedation may be required during endoscopy and endotracheal intubation is needed if there is concern about the safety of the airway as well as assessment of vital signs, meausurement of central venous ressure is usually necessary and preferred and cardiac function by echocardiography may be needed. Preferably the access to the circulation should be both peripheral and central. The presence of coagulopathy and thrombocytopenia is not a contraindication to central venous access. The infusion of plasma or a colloidal preparation depends on the degree of hypovolemia. Blood should be transfused to achieve a hemoglobin of 8 g/dl. Overtransfusion should be avoided as it may exacerbate increases in portal and variceal pressure. In animal models this provokes continued bleeding due to a portal pressure increase but in humans the balance should be towards establishing an effective circulating volume to maintain renal function. A normal central venous pressure should be maintained taking into account the severity of ascites if present in order to reduce the likelihood of renal failure. Clotting and platelet deficiencies may be ameliorated with fresh frozen plasma (FFP) and platelet transfusions, but there is no formal study assessing whether this helps to treat bleeding and/or improve outcome. Lastly rapid imaging should include a chest X-ray and the use of ultrasound/doppler to establish the patency of portal vein and exclusion of hepatocellular carcinoma.

TREATMENT STRATEGIES

The following treatment strategies have been compared in acute variceal bleeding: a) Vasoactive drugs (± tamponade) vs Vasoactive drugs (± tamponade) + sclerotherapy, b) vasoactive drugs vs sclerotherapy, c) vasoactive drugs + therapeutic endoscopy vs therapeutic endoscopy, d) sclerotherapy vs ligation and e) Recombinant factor VII + therapeutic endoscopy vs placebo + therapeutic endoscopy.

Vasoactive drugs

The vasoactive drugs that are currently used in the management of acute variceal bleeding are terlipressin, somatostatin and octreotide. Data favour the use of terlipressin, as mortality is reduced (35;36), and it may have an added role in maintaining renal function. Starting vasoactive therapy before diagnostic endoscopy is supported by trials and prolonged therapy up to 5 days has been used, as this is the period of greatest risk of early rebleeding.[5,37-39]

Moitinho et al evaluated[40] a total of 174 patients with acute variceal bleeding who were randomized to receive somatostatin for 48 h: (A) one 250 microg bolus +250 microg/h infusion; (B) three 250 microg boluses +250 microg/h infusion; (C) three 250 microg boluses +500 microg/h infusion. The 500 microg/h infusion dose achieved a higher rate of control of bleeding (82 vs. 60%, P<0.05), less transfusions (3.7 +/- 2.7 vs. 2.5 +/- 2.3 UU, P=0.07) and better survival (93 vs. 70%, P<0.05) than schedules A and B. Others have confirmed the above results using somatostatin 500 microg/h.[41,42] Lastly octreotide has been reported to cause a reduction in portal pressure but others have not confirmed these data. In a recent trial octreotide only transiently reduced portal pressure and flow, whereas the effects of terlipressin were sustained, suggesting that terlipressin may have more sustained hemodynamic effects in patients with bleeding varices.[43]

Endoscopic treatment

In a recent metaanalysis (38) we have evaluated sclerotherapy in randomized trials: a) combined with vasoconstrictors versus these alone, b) versus vasoconstrictors alone, c) versus combination of vasoconstrictors and sclerotherapy, d) versus ligation. The efficacy of acute sclerotherapy was highest versus ligation at 95%, with a small advantage for ligation 2.5% (95% CI, 0.4%-4.6%) (p=0.018), but no survival difference. The efficacy combined with vasoconstrictors versus these alone was 86%, whereas it was 83% versus vasoconstrictors alone. In both these groups sclerotherapy was superior for control of bleeding, respectively 16.3% (95% CI, 8.7% to 23.9% (p=0.0001) and 5.9% (95%CI, 1.5% to 10.3%) (p=0.008), with increased survival in the latter. In the combination group of sclerotherapy with vasoconstrictors, the efficacy of sclerotherapy alone was 69%, with the combination superior in controlling bleeding: 13.2% (95% CI, 8.4% to 18.1%) (p<0.0001)) but with no survival difference. This

comparison of sclerotherapy across trials demonstrates a problem in defining its real efficacy. Our data support the conclusion that sclerotherapy remains the 'gold standard' in acute variceal bleeding.

In recent trial published after the metaanalysis favouring ligation (44) endoscopy was performed within 6h and those with esophageal variceal bleeding were randomized to receive either sclerotherapy (N=89) or ligation (N=90). Failure to control bleeding occurred in 15% vs 4%, respectively (P=0.02). Six-week survival probability without therapeutic failure was better with ligation (P=0.01). However in those with active bleeding or grade C, who are the patients with the most likelihood of having difficulty in controlling bleeding there was no difference between ligation and sclerotherapy.[45]

The early effects of endoscopic injection sclerotherapy and endoscopic band ligation on hepatic venous pressure gradient during acute bleeding have also been investigated.[46] In 50 cirrhotic patients HVPG measurements were performed before and immediately after endoscopic treatment and every 24 hours for a 5-day period. In both groups, a significant increase was observed in mean portal pressure immediately after treatment as compared with pretreatment ($p < 0.0001$). However in the EBL group, HVPG returned to baseline values within 48 hours after treatment, while in the EIS group it remained high during the 120-hour study period ($P < 0.0001$). Thus during acute variceal bleeding EIS, but not EBL was associated with a sustained increase in HVPG. During the 42-day follow-up period, the rebleeding rate over time was lower in the EBL group compared with the EIS group ($p = 0.024$) confirming previous studies of repeated endoscopic therapy. The mechanism of the increased HVPG with endotherapy and why portal pressure returned to baseline values within 48 hours of banding but not EIS is not clear. In addition Vlachogiannakos et al[47] showed that somatostatin but not octreotide effectively prevents the post-endoscopic increase of HVPG.

Recombinant coagulation factor VIIa (rFVIIa)

Recombinant coagulation factor VIIa (rFVIIa) has been shown to correct the prolonged prothrombin time in patients with cirrhosis and UGIB (upper GI bleeding). Bosch et al[48] aimed to determine efficacy and safety of rFVIIa in cirrhotic patients with variceal and nonvariceal UGIB. 245 cirrhotics (Child-Pugh < 13; Child-Pugh A = 20%, B = 52%, C = 28%) with UGIB (variceal = 66%, nonvariceal = 29%, bleeding source unknown = 5%) were randomized equally to receive 8 doses of 100 microg/kg rFVIIa or placebo in addition to pharmacologic and endoscopic treatment. rFVIIa significantly decreased the number of failures ($P = 0.03$) and the 24-hour bleeding control end point ($P = 0.01$) in the subgroup of Child-Pugh B and C variceal bleeders. There were no significant differences between rFVIIa and placebo groups in mortality (5- or 42-day). More recently the same group in a randomized trial (49) aimed to determine the efficacy and safety of rFVIIa in patients with advanced cirrhosis and active (oozing/spurting) variceal bleeding. There were no significant differences between groups (placebo, 600 μg/kg and 300 μg/kg), in terms of bleeding however treatment with 600 μg/kg significantly reduced 42-day mortality, which cannot be explained via a control of bleeding. Adverse events were comparable between groups.

Uncontrolled variceal bleeding

The definition of uncontrolled variceal bleeding includes the continued/early variceal rebleeding (despite 2 sessions of therapeutic endoscopy), continued variceal bleeding despite balloon tamponade and continued/early gastric or ectopic variceal bleeding despite vasoconstrictor therapy.

Balloon tamponade has most often been used to arrest life-threatening hemorrhage or if other measures fail. It has also been used in the absence of a definite diagnosis but bleeding from varices is strongly suspected. The usual tube is a modified four-lumen Sengstaken-Blakemore tube (SBT). The airway should be protected by an endotracheal tube under a short general anesthetic, as the risk of aspiration is very high, particularly in unskilled hands (50). If blood is still coming up the gastric aspiration lumen, then varices are less likely to be the cause of blood loss although gastric fundal varices are not always controlled by tamponade. In fact, whenever this occurs, if the position of the SBT has been checked and adequate traction applied, the diagnosis of variceal bleeding should be questioned.

In a recent report[18] the use of self-expandable metallic stents was evaluated to arrest uncontrollable acute variceal bleeding. The patients had not been successfully managed with prior pharmacologic or endoscopic therapy. The stents were successfully placed in all of the patients and were left in place for 2-14 days. Bleeding from the esophageal varices ceased immediately after implantation of the stent in all cases. No recurrent bleeding, morbidity, or mortality occurred during treatment with the esophageal stent. All of the stents were extracted without any complications after definitive treatment had been started.

TIPS stops bleeding in a significant percentage.[51] In

uncontrolled studies TIPS is effective in stopping variceal haemorrhage,[52-56] but presents high mortality.[57] Monescillo et al[17] evaluated variceal bleeders with HVPG≥ 20 mmHg and there were randomly allocated to receiving TIPS (HR-TIPS group, n = 26) within the first 24 hours after admission or not (HR-non-TIPS group). The HR-non-TIPS group had more treatment failures (p =0.0001). Early TIPS placement reduced treatment failure (p=0.003) and in-hospital and 1-year mortality (p <0.05). Overall TIPS remain a good choice as a rescue therapy although when it is not available staple transection of the oesophagous could be considered.[58]

New diagnostic and treatment algorithms in acute variceal bleeding are needed using known predictive factors of failure to control bleeding and mortality in order to identify the group of bleeders with poor outcome. In this group more effective vasoactive regimens, early TIPS after diagnostic endoscopy, and the use of self-expanding covered oesophageal stent could be considered.[27]

Gastric varices

In actively bleeding from gastric varices the use of sclerotherapy and ligation is not effective.[59] Endoscopic therapy with tissue adhesive (e.g. N-butyl-cyanocrylate) is recommended for acute variceal bleeding.[25] Glues[59] and TIPS[52] are also effective. In a recent trial[60] TIPS proved more effective than glue injection in preventing rebleeding from gastric varices, with similar survival and frequency of complications.

Conclusion

The available data suggest that emergency endoscopic treatment with banding ligation or sclerotherapy, at the time of the initial diagnostic endoscopy, should be the gold standard for the management of the acute variceal bleeding episode. Ligation is the recommended form of endoscopic therapy although sclerotherapy may be more applicable in some acute situations. Endoscopic treatments are best used in association with pharmacological therapy, which preferably should be started before endoscopy. The drugs of choice for this combination are terlipressin and somatostatin (which has less side effects and has been successfully tested over 5 days). The role of emergency TIPS as "salvage therapy" for uncontrolled bleeding from esophageal or gastric varices has been justified, although randomized trials to compare it with emergency surgical shunts or other therapies are still required. Endoscopic therapy with tissue adhesive (e.g N-butyl-cyanocrylate) is recommended for acute gastric variceal bleeding.

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