

Review Article

Improved Survival with the Patients with Variceal Bleed

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Variceal hemorrhage is a major cause of death in patients with cirrhosis. Over the past two decades new treatment modalities have been introduced in the management of acute variceal bleeding (AVB) and several recent studies have suggested that the outcome of patients with cirrhosis and AVB has improved. Improved supportive measures, combination therapy which include early use of portal pressure reducing drugs with low rates of adverse effects (somatostatin, octerotide or terlipressin) and endoscopic variceal ligation has become the first line treatment in the management of AVB. Short-term antibiotic prophylaxis, early use of lactulose for prevention of hepatic encephalopathy, application of early transjugular intrahepatic portosystemic shunts (TIPS), fully covered self-expandable metallic stent in patients for AVB may be useful in those cases where balloon tamponade is considered. Early and wide availability of liver transplantation has changed the armamentarium of the clinician for patients with AVB. High hepatic venous pressure gradient (HVPG) >20 mmHg in AVB has become a useful predictor of outcomes and more aggressive therapies with early TIPS based on HVPG measurement may be the treatment of choice to reduce mortality further.

1. Introduction

Portal hypertension (PHT) worsens with increasing severity of cirrhosis and is responsible for many of its complications, which lead to clinical decompensation. The prevention and treatment of these complications have therefore been a cornerstone of the management of the patient with cirrhosis. Gastroesophageal varices are present in 50% of patients with cirrhosis, and variceal hemorrhage develops in up to one-third of these patients [1–3]. The initial appearance of varices in patients with compensated cirrhosis indicates a progression of the disease from a low-risk state to an intermediate one. Once bleeding occurs, this indicates decompensation and progression to a high risk of death [4, 5]. The risk of variceal hemorrhage is increased in patients who have large varices and advanced stages of liver disease, as assessed on the basis of the Child-Pugh class [6, 7]. Several studies published between 1942 and 1981 showed poor outcomes after variceal hemorrhage, with mortality rates of 40% at 6 weeks and 70% at 1 year [4, 8–11]. Over the past five decades, a number of randomized trials have shown an improvement in the efficacy of endoscopic, pharmacologic, surgical, and radiologic techniques for arresting hemorrhage [12–14]. Subsequently,

retrospective single-center and multicenter studies have shown a decrease in hospital mortality associated with variceal hemorrhage over the past two decades [14–19].

In a study by Chalasani et al. [14] a total of 231 subjects were included, and their in-hospital, 6-week, and overall mortality rates were 14.2%, 17.5%, and 33.5%, respectively. The mortality rate after variceal bleeding in this study was substantially lower than previously reported. This suggests that advances made in the management of variceal bleeding have improved outcomes after variceal bleeding. Similarly Carbonell et al. [12] reviewed the clinical records of all patients with cirrhosis due to variceal bleeding during the years 1980, 1985, 1990, 1995, and 2000. Whereas balloon tamponade was still the first-line treatment in 1980, patients treated in 2000 received a vasoactive agent, an endoscopic treatment, and an antibiotic prophylaxis in, respectively, 90%, 100%, and 94% of cases. The in-hospital mortality rate steadily decreased over the study period: 42.6%, 29.9%, 25%, 16.2%, and 14.5% in 1980, 1985, 1990, 1995, and 2000, respectively ($P < .05$). Mortality decreased from 9% in 1980 to 0% in 2000 in Child-Turcotte-Pugh class A patients, from 46% to 0% in class B patients, and from 70% to 32% in class C patients. This improved survival

TABLE 1: Antibiotics compared to placebo in acute variceal bleed.

| Author | Outcome | Drugs | Placebo (<i>n</i>) <i>P</i> | Antibiotics (<i>n</i>) <i>A</i> | Infections <i>P</i> versus <i>A</i> | efficacy |
|---------------------|----------------------|---|----------------------------------|--------------------------------------|--|---------------------|
| Pauwels et al. [27] | Bacterial infections | ciprofloxacin and a amoxicillin and clavulanic acid | 34 | 30 | 53% versus 13% | <i>A</i> > <i>P</i> |
| Soriano et al. [30] | Bacterial infection | Norflox | 59 | 60 | 10% versus 37% | <i>A</i> > <i>P</i> |
| Hsieh et al. [28] | Bacterial infection | ciprofloxacin | 60 | 60 | 45% versus 10% | <i>A</i> > <i>P</i> |
| Jun et al. [29] | Bacterial infection | Cefotaxime | 62 | 58 | 16% versus 3% | <i>A</i> > <i>P</i> |

TABLE 2: Antibiotics preventing mortality in acute variceal bleed.

| Author | Outcome | Drug | Drug | Relative risk | CI |
|-----------------------|---------------------|--------------------------------------|----------------------------|---------------|-----------|
| Gulberg et al. [34] | Bacterial infection | Ceftriaxone 1 gm (1/40) | Ceftriaxone 2 gm (1/42) | 1.05 | 0.11–9.80 |
| Lata et al. [35] | Mortality | Ampicillin and sulbactam 3 g (12/21) | Norfloxacine 800 mg (7/25) | 2.04 | 0.98–4.23 |
| Fernández et al. [36] | Mortality | Ceftriaxone 1 g (8/54) | Norfloxacine 800 mg (6/57) | 1.41 | 0.52–3.79 |

was associated with a decrease of rebleeding (from 47% in 1980 to 13% in 2000) and bacterial infection rates (from 38% to 14%). On multivariable analysis, endoscopic therapy and antibiotic prophylaxis were independent predictors of survival. Thomopoulos et al. [18] studied 141 patients with acute variceal bleed and found 6-week, 1-year, and overall mortality were 12.1%, 18.4%, 32.6% and 48.2%, respectively. The rate of recurrent bleeding was 10.7% during initial hospitalisation. Being Child-Pugh C ($P = .003$) and shock on admission ($P = .037$) were independent predictors of 6-week mortality, while being Child-Pugh C ($P = .028$), presence of hepatocellular carcinoma or other neoplasia ($P = .04$), and partial thromboplastin time ($P = .021$) during the initial admission were independent predictors for 1-year mortality. Mortality was not affected by the presence of active bleeding and/or white nipple at emergency endoscopy. Also presence of infection was not an adverse factor of clinical outcome in our patients. In all these studies the decrease in mortality was largely due to improvement in general measures, more effective endoscopic therapy in combination with vasoactive medications, prevention of sepsis through the use of antibiotic prophylaxis, and the prevention of rebleeding.

2. Improvement in General Measures

There is evidence that current treatment strategies for acute variceal hemorrhage, including general and specific measures, have resulted in an improved survival [12, 18]. Initial resuscitation by multidisciplinary team involves basic measures including assessing the patient's airway and obtaining peripheral venous access. Blood volume resuscitation should be undertaken promptly but with caution, with the goals of maintaining hemodynamic stability and a hemoglobin of approximately 7–8 g/dL [19, 20]. This recommendation is based on experimental studies that show that restitution of all

lost blood leads to increases in portal pressure to levels higher than baseline [21] and to more rebleeding and mortality [22]. Similarly, vigorous resuscitation with saline solution should generally be avoided because, in addition to possibly precipitating recurrent variceal hemorrhage, this can worsen or precipitate the accumulation of ascites or fluid at other extravascular sites.

3. Prophylactic Antibiotics in Acute Variceal Bleed

Currently, it is recommended that short-term antibiotic prophylaxis, a measure that reduces bacterial infections [23], variceal rebleeding, and death [24], be used in every patient with cirrhosis admitted with gastrointestinal hemorrhage [20, 25, 26]. Different antibiotics have been used in different trials compared with placebo (Table 1, [27–30]). Bacterial infection is commonly associated with variceal hemorrhage and appears to be an independent risk factor for failure to control bleeding [31] and predicts both early rebleeding and death [32, 33]. The routine use of prophylactic broad-spectrum antibiotics has shown a marked improvement in outcome in acute variceal hemorrhage. Routine intravenous ceftriaxone or postendoscopic norfloxacine reduces rebleeding rates compared to on-demand antibiotics (Table 2) [24, 29, 34–36]. A Cochrane meta-analysis of antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding involving 12 trials with 1241 patients evaluated antibiotic prophylaxis compared with placebo or no antibiotic prophylaxis. Antibiotic prophylaxis compared with no intervention or placebo was associated with beneficial effects on mortality (RR 0.79, 95% CI 0.63 to 0.98), mortality from bacterial infections (RR 0.43, 95% CI 0.19 to 0.97), bacterial infections (RR 0.36, 95% CI 0.27 to 0.49). They concluded that prophylactic antibiotic use in patients with cirrhosis

and upper gastrointestinal bleeding significantly reduced bacterial infections, and seems to have reduced all-cause mortality, bacterial infection mortality, rebleeding events, and hospitalisation length. These benefits were observed independently of the type of antibiotic used [37, 38]. The rationale behind the oral administration of norfloxacin, a poorly absorbed quinolone, is the selective eradication (or at least reduction) of Gram-negative bacteria in the gut, the source of bacteria. However, quinolone antibiotics with similar spectrum of activity, such as ciprofloxacin, could also be recommended. When oral administration is not possible, quinolones can be administered intravenously (IV). In a recent study performed in patients with advanced cirrhosis (Child B/C) and GI hemorrhage, IV ceftriaxone (1 g/day) was more effective than oral norfloxacin in preventing bacterial infections mostly those due to Gram-negative organisms [36]. It has now become standard practice to administer prophylactic antibiotics in acute variceal hemorrhage and in cirrhotic patients with gastrointestinal bleeding of any cause. The clear survival benefit associated with prophylactic antibiotics in gastrointestinal hemorrhage associated with cirrhosis is not in doubt. Both American and British guidelines recommend the administration of antibiotics prior to endoscopy in patients with AVB [39, 40].

4. Use of Newer Pharmacologic Treatment in Reducing Mortality

Pharmacological therapy has the advantages of being generally applicable and capable of being initiated as soon as a diagnosis of variceal hemorrhage is suspected, even prior to diagnostic EGD [20, 25, 26]. Newer development of drugs like somatostatin and analogues such as octreotide and vapreotide also causes splanchnic vasoconstriction at pharmacological doses due to an inhibition of the release of vasodilatory peptides mainly glucagon. The advantage of somatostatin and analogues such as octreotide and vapreotide is that they are safe and can be used continuously for 5 days or even longer [20].

However, results of meta-analysis of trials of octreotide are controversial [41, 42]. In a recent metaanalysis twenty studies were identified for all the comparison groups that indicates that terlipressin was associated with a statistically significant reduction in all-cause mortality compared to placebo (relative risk 0.66, 95% confidence interval 0.49 to 0.88). There was no significant difference between the terlipressin group and any of the comparison groups in the number of adverse events that caused death or withdrawal of medication. On the basis of a 34% relative risk reduction in mortality, terlipressin should be considered to be effective in the treatment of acute variceal hemorrhage [43].

Endoscopic therapy with either band ligation or injection sclerotherapy is an integral component of the management of acute variceal bleeding and of the long-term treatment of patients after a variceal bleed. Regarding the best endoscopic therapy, a metaanalysis of 10 randomized controlled trials including 404 patients shows an almost significant benefit of EVL in the initial control of bleeding compared to

sclerotherapy (pooled relative risk of 0.53 with a confidence interval of 0.28–1.01) [44]. Variceal eradication with endoscopic ligation requires fewer endoscopic treatment sessions and causes substantially less esophageal complications than does injection sclerotherapy. Although the incidence of early gastrointestinal rebleeding is reduced by endoscopic ligation in most studies, there is no overall survival benefit relative to injection sclerotherapy.

In a recent metaanalysis pharmacotherapy is found to be as effective as emergency sclerotherapy in patients with acute variceal bleed. Seventeen trials including 1817 patients were identified. No significant differences were found comparing sclerotherapy with each vasoactive drug for any outcome. Combining all the trials irrespective of the vasoactive drug, the risk differences (95% confidence intervals) were failure to control bleeding -0.02 (-0.06 to 0.02), five-day failure rate -0.05 (-0.10 to 0.01), rebleeding 0.01 (-0.03 to 0.05), mortality (17 randomised trials, 1817 patients) -0.02 (-0.06 to 0.02), and transfused blood units (8 randomised trials, 849 patients) (weighted mean difference) -0.24 (-0.54 to 0.07). Adverse events 0.08 (0.03 to 0.14) and serious adverse events 0.05 (0.02 to 0.08) were significantly more frequent with sclerotherapy [45].

5. Combination Therapy as Standard of Therapy

Combination of both pharmacologic and endoscopic therapy in the treatment of AVB is strongly supported by numerous trials showing that the efficacy of both emergency EST and EBL is significantly improved when they are associated with pharmacologic treatment [41, 46]. Although both methods are highly effective in controlling AVB, EBL has become the treatment of choice both for controlling variceal hemorrhage and for variceal obliteration in secondary prophylaxis [20, 26]. A meta-analysis has shown that EBL is better than EST for all major outcomes including initial control of bleeding, recurrent bleeding, side effects, time to variceal obliteration, and survival [47]. Thus, combination therapy with a vasoactive drug plus EBL is considered the standard of care for AVB, and it is currently recommended by guidelines [20]. Combination therapy improves the 5-day success rate compared with endoscopic ligation therapy alone [48, 49], but this is not associated with any differences in mortality. Given these reasons, EBL at present is the endoscopic method of choice to treat esophageal varices in most cases. However, EST is an accepted method if EBL cannot be performed.

6. Evaluation of Hepatic Venous Pressure Measurement in Patient with Acute Variceal Bleed

Assessment of portal pressure by the hepatic venous pressure gradient (HVPG) has been a useful predictor of outcomes in both stages. In patients with compensated cirrhosis, an HVPG greater or equal to 10 mmHg is the most important predictor of the development of varices and clinical decompensation [50, 51]. Prospective cohort studies in which

HVPG has been measured within 48 hours of admission for hemorrhage show that levels greater than 20 mmHg are associated with increased rebleeding and mortality [52–54].

A more recent study performed in the era of combined vasoactive drug plus endoscopic therapy confirms this HVPG cutoff and shows that an index including CTP score and blood pressure at admission has similar prognostic value [55]. Furthermore, a drug-induced HVPG reduction of less than 10% predicts 5-day failure. This response may improve by doubling the dose of somatostatin or switching to another agent (such as terlipressin).

In acute complications of cirrhosis, such as variceal bleeding, there have been fewer studies of portal pressure, but, also in this setting, HVPG has been shown to be prognostic for both survival and the course of bleeding. Vinel et al. [56] documented that short-term prognosis in alcoholic cirrhotic patients with variceal bleeding was independently associated with portohepatic gradient measured within 48 h of admission. This was confirmed in a small study of 22 patients, in which the best cutoff for continued bleeding or early rebleeding was HVPG >16 mmHg [53]. Villanueva et al. [57] showed that HVPG > 20 mmHg and a decrease <10 mmHg under vasoactive therapy were independent predictors of further bleeding. An HVPG > 20 mmHg has been shown to correlate with important clinical outcomes such as more difficulty in controlling acute variceal bleeding, more early rebleeding, more blood transfusion need, more days in intensive care and increased hospital mortality [58]. Lastly Avgerinos et al. [59] showed that HVPG > 16 mmHg was independently associated with death and/or early rebleeding evaluating HVPG measurements before and immediately after endoscopic treatment and every 24 h for a 5-day period.

7. Transjugular Intrahepatic Portosystemic Shunt in Acute Variceal Hemorrhage

Transjugular intrahepatic portosystemic shunt (TIPS) is a reasonable alternative in the face of failure of combined pharmacologic plus endoscopic therapy. In the Baveno conference, it was considered that a second attempt at endoscopic therapy was one possibility but that one could perform TIPS after failure of the first endoscopic therapy. An elevated hepatic venous pressure gradient (>20 mm Hg) measured within 24 hours after the start of bleeding is the best predictor of treatment failure [26]. The use of TIPS to control variceal bleeding has largely been reserved for patients who require rescue therapy because hemostasis has not been achieved, either during the index bleeding or during the secondary-prophylaxis period. TIPS is extremely effective in controlling bleeding, with a reported rate of immediate hemostasis of 93% and with rebleeding in only 12% of patients. Nevertheless, mortality at 6 weeks among patients treated with rescue TIPS for uncontrolled index bleeding and rebleeding is very high (35%), reflecting the severity of their underlying liver disease as well as additional organ dysfunction that may have occurred owing to hypotension, infection, and aspiration [60].

Recently García-Pagán and colleagues report the results of a randomized, multicenter study that compared early TIPS with optimal medical therapy (endoscopic therapy plus vasoactive drugs) in patients at high risk for rebleeding who were either in Child-Pugh class B with active bleeding at endoscopy or in Child-Pugh class C. This study shows the benefit of early TIPS in patients with Child-Pugh class B or C disease who are at high risk for uncontrolled bleeding with standard therapy. Patients who were randomly assigned to receive TIPS had a significantly better chance of remaining free of bleeding than did those who received the standard care (97% versus 50%), possibly owing to a greater reduction in portal pressure with TIPS than could be achieved with pharmacologic therapy. The rate of survival at 6 weeks was 97% in the TIPS group as compared with 67% in the medical therapy group, as a result of reductions in rebleeding, sepsis and liver failure [61]. Use of the newer stents, which are covered with extended polytetrafluoroethylene (e-PTFE), probably has an important bearing on the outcome of this study [15].

8. Newer Methods

The recent introduction of a fully covered self-expandable metallic stent for AVB may be useful in those cases where balloon tamponade is considered. The stent is placed over a guide wire previously passed to the stomach. The stent has a distal balloon that is inflated with a syringe to ensure proper location in the cardia and lower esophagus so no fluoroscopy is needed. The stent can be left in place for up to 14 days, and it can be retrieved by endoscopy with a hook system. There are limited data with its use. A pilot study of 20 patients who failed standard of care treatment reported 100% success without any significant complications [62].

9. Summary

AVB is a dreaded complication of patients with portal hypertension. Initial management includes appropriate volume replacement, transfusion of blood to keep hemoglobin levels at 7–8 g/L, antibiotic prophylaxis, and endotracheal intubation in selected cases. Standard of care mandates for early administration of vasoactive drug therapy and then EBL or injection ES (if EBL cannot be performed) within the first 12 hours of the index bleed. The use of pharmacologic agents may be prolonged for up to 5 days. Patients who fail endoscopic therapy may require temporary placement of balloon tamponade or stents. All patients surviving an episode of AVB should undergo further prophylaxis to prevent rebleeding. However, despite the application of these gold-standard treatments, 10% to 15% of cirrhotic patients still have treatment failure. Despite the high success of rescue TIPS in controlling bleeding in treatment failures, the mortality of patients in whom the initial approach failed is high due to liver failure. It is possible that in the near future, patients may be treated “à la carte.” Indeed, in high-risk patients, more aggressive therapies with early PTFE TIPS based on HVPG measurement may be the treatment of choice to reduce mortality further.

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