Chapter 11
Use of Vasoactive Drugs for Acute Variceal Bleeding

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Introduction

Acute esophageal variceal bleeding is a severe complication of portal hypertension and a major cause of death in patients with hepatic cirrhosis [1]. In the last decades survival has been improved due to the implementation of effective treatments and optimization of general medical care but despite this standard of care, mortality is still closely related to failure to control hemorrhage or early rebleeding, and remains about 15–20 % in most recent series [2, 3]. The first approach to the bleeding patient is aimed at correcting hypovolemic shock and at preventing complications associated with gastrointestinal bleeding such as bacterial infections, hepatic decompensation, and renal failure, which require prompt management because they are associated with increased risk of rebleeding and death. The initial resuscitation should follow the classic Airway-Breathing-Circulation scheme, where it is important to avoid over-transfusion [4] by using a restricted blood transfusion policy (aimed at a hemoglobin level of about 7 g/dl) [5], infusion of plasma expanders and crystalloid solutions to keep systolic blood pressure around 100 mmHg [6]. In this scheme it is paramount to provide as soon as possible specific therapy aimed at controlling the bleeding, as continued bleeding increases dramatically the risk of deterioration of liver function and of multiorgan failure, leading to a situation where the patient survival no longer depends on controlling the bleeding itself [7].

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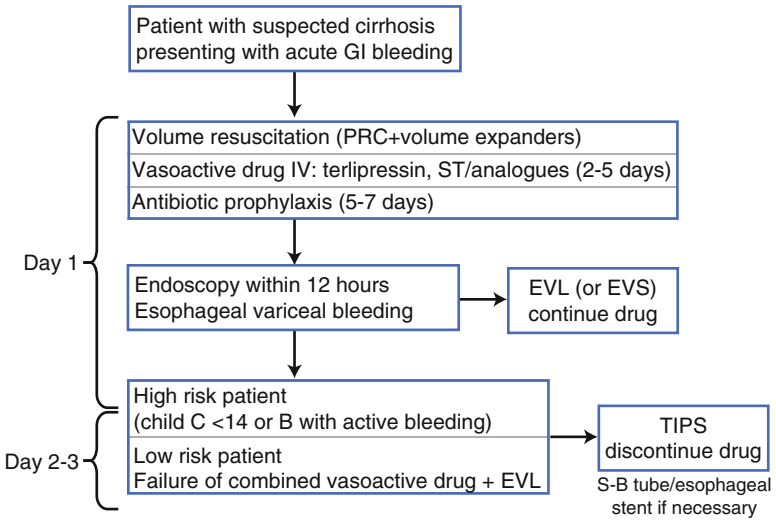

Fig. 11.1 Recommended treatment for acute bleeding from esophageal varices. Please note that volume resuscitation, vasoactive drugs, and antibiotic prophylaxis shall be initiated as soon as possible, in the emergency room. *ST* somatostatin, *EVL* endoscopic variceal ligation, *EVS* endoscopic variceal sclerotherapy, *TIPS* trans-jugular intrahepatic porto-systemic shunt, *S–B* Sengstaken–Blakemore

Current recommended standard of care for patients with acute variceal bleeding is a combined treatment with vasoactive drugs, prophylactic antibiotics, and endoscopic procedures [8] (Fig. 11.1).

This chapter reviews the rationale for the use of drug therapy, its pharmacological and hemodynamic properties, and its clinical use, focusing on agents associated with an improved control of bleeding, decreased transfusion requirements, shorter hospital stay and decreased mortality, as well as its role in combination with endoscopic treatments and TIPS.

The Mechanism of Variceal Bleeding: Rationale for the Use of Vasoactive Drugs in Variceal Hemorrhage

Variceal bleeding is the last step of a chain that is initiated by the increase in portal pressure gradient, clinically evaluated as the hepatic vein pressure gradient (HVPG; normal values 1–5 mmHg). When the HVPG increases above 10 mmHg, the complications of portal hypertension may start to develop [9]; specifically, this is the minimum pressure gradient required for the formation of porto-systemic collaterals and esophageal varices, and for starting sodium retention [10, 11].

For esophageal variceal bleeding to develop, the varices shall increase in size and the HVPG shall increase further, to at least 12 mmHg, although mean HVPG values at the moment of bleeding are as high as 19 mmHg [12–14]. Brisk, repeated increases in portal pressure and blood flow prompted by meals [15, 16], physical exercise [17], increased intra-abdominal pressure [18, 19], and alcohol intake [20] are thought to be major determinants of this progressive dilatation of the varices [21]. In addition, as the varices dilate their walls become thinner, which is likely to be clinically evidenced by the appearance of red signs over the varices (red whales, red spots, and diffuse redness) [22]. It is widely accepted nowadays that the mechanism of variceal bleeding is the rupture of the varices when the tension exerted by its thin walls exceeds the elastic limit of the vessel ("variceal explosion" theory) [21]. Wall tension is the physical force generated by the variceal wall against the progressive expansion determined by increased intravariceal pressure, and is defined by the equation:

$$Tension = \left(Variceal\ pressure - Esophageal\ luminal\ pressure\right) \times Variceal\ radius\ /\ wall\ thickness$$

This equation indicates that increased variceal pressure plays a key role in determining bleeding. Furthermore, it points out that with equal variceal pressure, a large varix will have greater wall tension and risk of bleeding than one of smaller diameter, and that the same will happen for one with red color signs vs. one without. This is supported by a series of clinical studies measuring variceal pressure, diameter, and wall thickness in portal hypertensive cirrhotic patients [14, 23–25].

The role of increased portal pressure in variceal bleeding is not limited to be the initiating event that finally leads to variceal rupture. In addition, the amount of blood loss during bleeding is also determined by the magnitude of the portal/variceal pressure elevation, as factorized in the equation:

$$Blood\ loss = Intravariceal\ pressure \times Area\ of\ variceal\ rent$$

This is further modulated by two additional factors: decreasing blood viscosity (as caused by a drop in hematocrit) will increase blood loss, and the ability of the hemostatic mechanisms to achieve a plug at the bleeding site (which is mainly dependent of an adequate platelet number and function).

A pathophysiological approach to the treatment of variceal bleeding should therefore aim at decreasing variceal tension, and secondarily, at enhancing/maintaining primary hemostasis.

Decreasing variceal wall tension requires decreasing variceal pressure, which is a function of portal pressure, and variceal radius. This is only possible acutely by decreasing variceal blood flow, which is a function of portal-collateral blood flow. Thus, an ideal agent should be able to significantly reduce portal pressure and blood flow, which is essentially what is achieved by using agents causing splanchnic vasoconstriction. When effective, these agents will predictably result in decreased blood loss (and thus in smaller fall in hematocrit) and earlier and more

effective hemostasis at the bleeding point. An additional advantage of an effective splanchnic vasoconstrictor is that it will prevent "rebound" increases in portal/variceal pressure associated with blood volume restitution [26].

Available Agents: Vasoactive Drugs

Modern pharmacological agents for controlling variceal bleeding include somatostatin and its analogues and Terlipressin (Table 11.1). Other agents, such as vasopressin with or without nitroglycerin, are no longer used due to their side effects and will not be reviewed in detail [27].

Terlipressin (triglycyl lysine vasopressin) is a synthetic analogue of vasopressin that has a longer biological activity as compared to the original compound with fewer cardiac, bowel, and peripheral ischemic side effects and that rapidly reduces portal pressure through its splanchnic vasoconstriction activity [28–31]. Its administration leads to a decrease in cardiac output, an increase in the arterial blood pressure and the systemic vascular resistance, and to vasoconstriction of the splanchnic vascular circulation that altogether induce a decrease in portal pressure of about 20 % after a single injection [30]. It is usually administered by intermittent intravenous injections as its effects are still significant 4 h after administration (although continuous intravenous infusion is also possible) [31–33]. The currently recommended dose is of 2 mg every 4 h for the first 24–48 h (for adults over 40 kg of body weight); afterwards, the drug can be maintained for up to 5 days at a dose of 1 mg every 4 h to prevent early rebleeding and minimize side effects [34–36].

Table 11.1 Summary of the available pharmacological agents used in the treatment of acute bleeding from esophageal varices

Terlipressin
• Long-acting vasopressin analogue with higher affinity for vascular receptors
• Causes intense splanchnic vasoconstriction and increases arterial pressure
• Given IV as injections of 2 mp/4 h[a] for 24–48 h, then 1 mg/4 h for 2–5 days
• Well proven in placebo-controlled RCTs and meta-analysis
Somatostatin
• Very short biological half-life
• Causes moderate vasoconstriction due to glucagon inhibition and facilitation of adrenergic vasoconstriction
• Given as IV infusion of 250–500 μg/h, after an optional bolus of 250 μg, for up to 5 days
Somatostatin analogues (Octreotide, Vapreotide)
• Longer half-life
• Effects on portal pressure jeopardized by rapid desensitization
• Given as IV infusion of 50 μg/h, after an optional bolus of 50 μg, for up to 5 days
• Effective in RCTs when evaluated as an adjunct to endoscopic sclerotherapy

RCTs randomized controlled trials

[a]1 mg/4 h for subjects of <40 kg b.w.

As mentioned before, the side effects of Terlipressin are less common and severe than those of vasopressin but still can lead to treatment discontinuation. The most common side effect is abdominal pain, which reverses after drug withdrawal, and increases blood pressure. Serious side effects such as peripheral, intestinal, or myocardial ischemia occur in <3 % of the patients [35]. Because of the possibility to provoke ischemic complications and severe arrhythmias, terlipressin should not be used in patients with a history of ischemic heart or cerebral disease, limb or gut vascular disease [37], and should be used with caution in the elderly and in hypertensive subjects.

During treatment with Terlipressin hyponatremia can be observed [38], especially in patients with a preserved liver function and with better response to treatment, and a few cases of neurological symptoms that reversed after drug interruption have been reported [37].

Somatostatin is a small peptide hormone that regulates the release of numerous secondary peptides. Its actions are mediated by G-protein coupled receptors (somatostatin receptor subtypes 1–5) that regulate ion channels and enzymes mediating the synthesis/degradation of intracellular second messengers including cyclic AMP, cyclic GMP, inositol triphosphate, and diacylglycerol [39]. While it has been shown that the administration of somatostatin in portal hypertensive patients induces splanchnic vasoconstriction and consequently reduces portal pressure [40], the exact mechanisms mediating this effect are incompletely understood. Among those that have been investigated, the inhibition of vasodilatory peptides and in particular of glucagon is the most important [41]. In addition, somatostatin facilitates adrenergic vasoconstriction and blocks the brisk increase in HVPG induced by meals and blood transfusion [42], which is considered a risk factor for rebleeding from portal hypertensive sources. A limitation of somatostatin is its short half-life ranging 1.2–4.8 min in patients with chronic liver disease [39]. Hence, in order to maintain an adequate plasma concentration, somatostatin should be administered by continuous IV infusion. A dose of 250 μg/h preceded by a 250 μg bolus (which can be repeated up to 3 times during the first hour) is effective in lowering the HVPG [27], but HVPG reduction is greater using a higher dose, of 500 μg/h [43], which is further associated with a marked and sustained decrease in collateral (azygos) blood flow. Studies during acute variceal bleeding have shown that the 500 μg/h dose is required to significantly reduce the HVPG in this setting [33], which is in keeping with the observation of a greater effectiveness of this dose when used to control variceal bleeding in high risk patients [44]. Major side effects are rare; minor side effects occur in about 21 % of patients and include vomiting and hyperglycemia that are usually easy to manage [39, 44].

Long-acting analogues of somatostatin have been developed to overcome the drawback represented by its short half-life [39]. These include Octreotide, Vapreotide, Lanreotide, and Seglitide; the latter has not been tested for portal hypertension. *Octreotide and vapreotide* acutely decrease portal pressure probably through a mechanism similar to that of somatostatin [39]. However, despite a longer half-life as compared to somatostatin, the duration of their hemodynamic effects on

portal pressure is not longer, and continuous infusion or repeated injections have much less marked effects on portal pressure [45] probably due to the rapid development of desensitization or tachyphylaxis. In any case, Octreotide is effective in preventing the postprandial splanchnic hyperemia in portal hypertensive patients [46, 47], and this effect is long-lasting [47, 48]. Octreotide and vapreotide are usually given in continuous infusion of 50 μg/h with an optional initial iv or subcutaneous bolus of 50 μg. These doses are empirical since no formal dose response studies have been conducted in portal hypertensive subjects.

Clinical Use of Available Drugs

As discussed previously, vasoactive drugs exert their action by reducing portal pressure mostly by reducing splanchnic blood flow; this results in lowering gastroesophageal varices pressure and wall tension, better control of hemorrhage, and easier performance of endoscopy. Therefore, therapy with vasoactive drugs should be started as soon as possible, before endoscopy [8] in order to facilitate the procedure by reducing the rate of active bleeding and furthermore the rebleeding rate. Terlipressin was even used during ambulance transfer to hospital in a placebo-controlled clinical trial that indeed demonstrated improved control of bleeding and survival [49, 50]. Indeed, treatment with vasoactive drugs alone is able to control bleeding in up to 83 % of patients [51].

Terlipressin is considered the drug of choice in this setting, since it significantly improves control of bleeding as compared to placebo [50]. It is the only drug, up to date, that has been shown to improve survival as compared to placebo in individual trials and meta-analysis, so there is robust evidence for its use [49, 50]. Terlipressin has been compared to somatostatin in two trials, showing similar results of the two drugs in terms of control of bleeding [52, 53]. Its overall efficacy in controlling acute variceal bleeding has been reviewed in a meta-analysis [50], resulting of 75–80 % at 48 h and of 67 % at 5 days across trials. The reduction in all causes mortality risk induced by Terlipressin as compared to placebo was of 34 % (RR 0.66; 95 % CI 0.49–0.88), and was mainly attributed to a significant reduction in the failure to control bleeding (RR 0.63; 95 % CI 0.45–0.89) [50]. An additional advantage of Terlipressin is that its use may prevent the onset of the hepatorenal syndrome, which is sometimes precipitated by bleeding, as Terlipressin is also effective for the hepatorenal syndrome [54].

With regard to *somatostatin and its analogues*, a randomized trial demonstrated that somatostatin added to endoscopic therapy significantly improves the control of acute variceal bleeding when compared to placebo (63 % vs. 46 %), but does not improve survival [2]. Placebo-controlled trials of somatostatin vs. placebo as single agent yielded divergent results [2]. It should be underlined that in a study comparing two doses of somatostatin in patients with acute variceal bleeding (standard dose,

250 μg/h vs. high dose, 500 μg/h) [44] the rate of control bleeding was significantly higher in the subgroup of high-risk patients treated with a high dose, and the survival increased in this subgroup, suggesting that this dose should be preferred in patients at high risk of treatment failure [8, 13, 55]. Both somatostatin and octreotide had equal efficacy on the control of bleeding as endoscopic sclerotherapy, with a lower rate of side effects [2, 56]. Even if *octreotide* has not been evaluated in this setting in double-blind randomized trials vs. placebo (only one has been presented in abstract form, with negative results) [57], a meta-analysis of its effects in combination with endoscopic therapy suggests that it improves the control of bleeding without impacting mortality [58]; however, the strength of this evidence is limited and should be interpreted with caution [59]. *Vapreotide and lanreotide* have been used in trials in combination with endoscopic treatment; while vapreotide was reported to be better than placebo in a randomized controlled trial [60], a large trial involving lanreotide gave negative results and remained unpublished.

Selection of the Drug

According to what was stated previously, Terlipressin is the drug of choice in patients with acute variceal bleeding and without contraindications, due to its ability of improving survival [49, 50]. Nonetheless, as in any other setting in medicine, the selection of the drug depends on the local resources and Terlipressin is not available in all countries. Remarkably, octreotide is the only vasoactive drug for variceal bleeding control available in the United States.

Somatostatin, especially when used at high dose, appears to be as effective as terlipressin although an effect on survival has never been confirmed out of the subgroup analysis of high risk patients receiving high-doses of somatostatin [44]. It represents a reasonable alternative [8], taking into account its excellent safety profile. The somatostatin analogues octreotide and vapreotide can be used, especially where somatostatin and terlipressin are not available. In some countries, the combination of vasopressin infusion (0.2–0.4 U/min) plus transdermal nitroglycerin is still used [8].

Duration of the Treatment

According to current recommendations [8], vasoactive drugs should be used in combination with endoscopic therapy and continued for up to 5 days, since this frame time identifies the period at higher risk of rebleeding. However, there are limited and conflicting data to show the best treatment duration when drug therapy is used together with endoscopic band ligation, as it is currently recommended. In this situation the minimal duration of drug therapy should be until achieving a

24 h bleeding-free period, although in our hospital if there are no adverse effects we continue therapy until day 5.

Conclusions

Vasoactive drugs are the first-line therapy in acute variceal bleeding and should be administered from arrival to hospital or even during ambulance transfer, since treatment with these agents before endoscopy has been shown to ameliorate patient's outcome and allows a safer endoscopic procedure. The choice of the specific drug has to be done according to each center possibilities but when available terlipressin is the best option.

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