REVIEW

Treatment of acute esophageal variceal bleeding in cirrhotic patients

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Esophageal variceal bleeding is the most dangerous complication in cirrhotic patients and is accompanied by high mortality. Treatment strategy involves early diagnosis, maintaining vital body functions and specific therapy aimed at the provision of local hemostasis and reduction of portal pressure. To this end, it is currently recommended to combine vasoactive drug (mainly, terlipressin or somatostatin) therapy with endoscopic methods of hemostasis (sclerotherapy or ligation). The use of Sengstaken-Blakemore tube is appropriate only in cases of refractory bleeding if the above methods cannot be used. An alternative to balloon tamponade may be the installation of self-expandable metal stents. Although transjugular intrahepatic portosystemic shunting is an extremely useful technique for the treatment of acute bleeding from esophageal varices, currently it is viewed as second-line therapy. Urgent surgical intervention is rarely performed and can be considered only in case of failure of conservative and/or endoscopic therapy and being unable to use a transjugular intrahepatic portosystemic shunt for technical or organizational reasons or due to anatomic problems. Among surgical operations described in the literature are various kinds of portocaval anastomoses and azygoportal disconnection procedure. To improve the results of treatment of cirrhotic patients with acute esophageal variceal bleeding it seems important to stratify them by risk groups, which will allow one to tailor therapeutic approaches to the expected results. For example, to initiate early use of more aggressive methods in patients with predictors of poor outcomes, and to protect individuals with a good prognosis from unnecessary invasive procedures. It is hoped that further research will refine this hypothesis.

Keywords: liver cirrhosis; portal hypertension; esophageal varices bleeding; treatment

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Introduction

Esophageal variceal bleeding is the most dangerous complication in cirrhotic patients and is accompanied by high mortality. Diagnostic and therapeutic developments have led to a significant improvement in the prognosis of this complication over the past two decades. However, early mortality after an episode of acute variceal bleeding reaches 20%. Management strategy involves early diagnosis, maintaining vital body functions and therapy aimed at the provision of local hemostasis and reduction of portal pressure [1]. This paper reviews the current knowledge, most recent advancements and research prospects in the treatment of acute esophageal variceal bleeding in cirrhotic patients.

Vasoactive drug therapy

In accordance with current clinical guidelines, specific activities of the first line for esophageal variceal bleeding should combine vasoactive drug therapy with endoscopic methods of hemostasis [2].

The effect of drugs used for the treatment of portal hypertension, is, mainly, the reduction of splanchnic hyperemia and decrease in severity of hyperdynamic circulatory status, which helps reduce the pressure in both the portal vein and varices [3]. Since under the development of bleeding there is a real threat to the patient's life, the drugs should be administered as early as possible, ideally before hospital, and for at least 5 days [4]. A meta-analysis by M. Wells *et al.* [5] showed that timely application of vasoactive drugs ensures effective hemostasis, reduces the need for blood transfusions, the duration of hospitalization and 7-day mortality.

Terlipressin (N-triglycer-8-lysine-vasopressin), a synthetic analogue of vasopressin, the hormone of the posterior pituitary, with a longer biological activity and a better safety profile, acts on specific V_1 receptors of the smooth muscles of the arteries, in particular, the arterioles of the abdominal cavity, and causes their contraction. S. Møller *et al.* [6], having studied the influence of terlipressin on hemodynamics in cirrhotic patients with portal hypertension, found that an intravenous bolus of 2 mg of the drug leads to a rapid reduction of portal pressure and hepatic blood flow (by 17% and 29% respectively), increased blood pressure and systemic vascular resistance (by 26% and 61% respectively), as well as a decrease in cardiac output, heart rate and artery distensibility (by 18%, 11% and 32% respectively).

The effect of terlipressin remains up to 4 hours, which allows one to administer it in periodic intravenous injections, but if necessary, a continuous infusion is also possible [7]. For adults with body weight over 40 kg with esophageal variceal bleeding, terlipressin is injected every 4 hours by 2 mg in the first 1-2 days and by 1 mg for 2-5 following days [8]. In these periods, its efficiency is 75-80% and 67%, respectively [9].

The most frequent side effects associated with the use of terlipressin are moderate abdominal pain, arterial hypertension, and hyponatremia; these are usually reverted after canceling the drug. Severe cardiovascular and ischemic disorders occur in approximately 15% of patients. In this regard, terlipressin is not recommended for patients with a history of ischemic heart or cerebral disease, limb or gut vascular disease, cardiomyopathy, bronchial asthma, chronic obstructive pulmonary disease, or having cardiac rhythm disturbance; caution should be used for elderly and/or hypertensive subjects [10].

Somatostatin is a cyclic 14-amino acid peptide, which is secreted by the nerve, endocrine and enteroendocrine cells in the hypothalamus and the digestive system (stomach, intestines, and Delta cells of the pancreas). Synthetic analogues of the drug (octreotide, octride, vapreotide, etc.) are also used to treat esophageal variceal bleeding in cirrhotic patients.

Somatostatin, by blocking G-protein coupled ET_A receptors, prevents stellate cells of the liver from contraction induced by endothelin-1, and contributes to the expansion of sinusoids and the reduction of hepatic vascular resistance. A similar effect of octreotide is associated with a decrease in intracellular Ca^{2+} [11].

The reduction of portal inflow caused by somatostatin is explained by the weakening of splanchnic hyperemia due to somatostatin's antisecretory effect on the secretion of glucagon and other gastrointestinal vasodilating peptides. The positive effect of octreotide on splanchnic blood flow is due to the potentiation of protein kinase of C-dependent vasoconstrictors through subtype 2 somatostatin receptors [12].

In cirrhotic patients with portal hypertension an intravenous bolus of 250 µg of somatostatin contributes to a 28.4% reduction of wedged hepatic venous pressure and a 15-71% reduction of the pressure in the esophageal varices. Continuous infusion of the drug reduces wedged hepatic venous pressure by 17% and hepatic blood flow by 17.4%. High doses of somatostatin (500 µg/h) have a more pronounced effect on these indicators, also reducing azygal blood flow by 45% in the case of bolus injection and by 23% with continuous infusion. Unfortunately, the positive effect of the drugs in this group on the hemodynamics is short, despite the much larger half-life of synthetic analogues of somatostatin, compared with the natural hormone; this is probably due to the desensitization or tachyphylaxis [13].

With bleeding from esophageal varices, 250 µg of somatostatin is initially injected as a bolus, and then in the form of continuous infusions, 250-500 µg/h for 2-5 days. The first dose of octreotide and vapreotide is 50 µg followed by an infusion of 50 µg/h. Severe complications in the course of this therapy are rare. Approximately 21% of patients may have vomiting and hyperglycemia, which, as a rule, can be easily remedied [14].

In general, somatostatin showed sufficient efficacy in the treatment of esophageal variceal bleeding, and in its effects on hemostasis and mortality it was similar to terlipressin, with a better safety profile [15]. At the same time, the efficacy of octreotide as monotherapy of portal hypertension is not currently established [16].

Endoscopic methods of hemostasis

Endoscopic sclerotherapy of esophageal varices has been developing since the mid 1970-ies of the last century. In this method, a sclerosant is injected directly into the varicose veins of the gastroesophageal junction region (5% solution of ethanolamine oleate), and paravasally (1% solution of aethoxysklerol (polidocanol)) [17]. According to L. Laine *et al*. [18], endoscopic sclerotherapy can control esophageal variceal bleeding in at least 62% of patients, it significantly reduces the frequency of early recurrence and has a positive impact on early mortality. It had no advantages over vasoactive drugs [19], but with simultaneous use of both methods, the hemostatic effect was higher than with each of them individually [20].

There are early (within the first 24 hours after injection) and late (a few days or weeks) complications of endoscopic sclerotherapy, which can be local and systemic. Moderate transient impairment of esophageal motility in the presence of varices is often observed. However, persistent dysphagia is usually associated with the formation of cicatricial strictures, the risk of which depends on the number of procedures and the amount of sclerosant injected. A serious late complication are ulcers of the esophageal mucosa, with extensive lesions of which they can cause bleeding and lead to necrosis of the wall, its perforation and mediastinitis. Although bacteremia after endoscopic sclerotherapy is observed in every second patient, it is normally latent, and the majority of infectious complications such as meningitis, paranephritis, brain abscess, endocarditis, and pneumonia, are rare [21]. One disadvantage of the procedure, noted in a number of cases, is the increase of the hepatic venous pressure gradient (HVPG), which may be the cause of early recurrent bleeding [22].

Ligation of esophageal varices, proposed by G. V. Stiegmann in 1986, is currently the endoscopic method of choice for the treatment of variceal bleeding. Unlike the induction of chemical inflammation and thrombosis after the introduction of sclerosing agents, the elastic ring ligature, covering the areas of the mucosal and submucosal layers of the esophagus in the area of varix, causes strangulation and subsequent fibrosis. Since the involved tissue volume is small, ulceration that occurs is always superficial, and pathological changes are insignificant. Compared with endoscopic sclerotherapy, ligation of esophageal varices obliterates them more rapidly and is accompanied by a smaller number of early recurrence of bleeding [23]. In addition, the combined use of endoscopic ligation with terlipressin or octride was more effective than therapy with vasoactive drugs alone [24; 25].

Sengstaken-Blakemore tube and self-expandable metal stents

The use of Sengstaken-Blakemore triple-lumen tube allows achieving primary hemostasis in 40-90% of patients with acute esophageal variceal bleeding. However, the high frequency of early relapses after deflation and the risk of developing life-threatening complications make its use appropriate only in cases of refractory bleeding if the above methods cannot be performed [26].

An alternative to balloon tamponade may be the installation of self-expandable metal stents specifically designed for the treatment of acute esophageal variceal bleeding. This method has fewer side effects, allows enteral nutrition, and the possibility of long-term stent placement makes it possible to stabilize the patient's condition and plan for bridge therapy, e.g. transjugular intrahepatic portosystemic shunting (TIPS) or repeated endoscopic treatment. If the procedure is performed successfully, the efficiency of primary hemostasis reaches 70-100%. The main drawback is stent migration, which occurs in 20% of patients [27].

TIPS

Numerous studies have shown that TIPS is an extremely useful technique for the treatment of acute esophageal variceal bleeding, allowing to achieve final hemostasis in up to 90-95% of cases. However, current clinical guidelines classify it as an event of the second line and recommend using it only if conservative and/or endoscopic therapy is ineffective. This approach is explained by TIPS-related high mortality, especially in patients with decompensated liver cirrhosis. Yet, it was noticed that in some of them, the initially stable liver function by the time of using TIPS was compromised by refractory bleeding, which caused the unfavorable outcome [28].

Gained experience in the use of TIPS, as well as the development of new technologies, in particular, the introduction of expanded polytetrafluoroethylene-covered stents with significantly prolonged passability and reduced incidence of encephalopathy, was the impetus for a reconsideration of the role of this method in the treatment of esophageal variceal bleeding. An early use of TIPS was suggested for cirrhotic patients at higher risk, in particular with HVPG $\geq$ 20 mm Hg [29], Child-Turcotte-Pugh (CTP) B liver cirrhosis with active bleeding or CTP C liver cirrhosis with less than 14 points. The correctness of choosing the last criterion was confirmed by the results of an international randomized retrospective clinical trial, in which 30 cirrhotic patients with esophageal variceal bleeding received standard first-line therapy, and 45 underwent TIPS. During a follow-up observation for 13-14 months, the recurrence of bleeding occurred in 50% of patients in the first group and

only in 7% in the second; the mortality was, respectively, 33% and 13% [30].

Surgical treatment

Surgical intervention under acute esophageal variceal bleeding is rare, and can only be considered if conservative and/or endoscopic therapy fails, and TIPS cannot be used for technical or organizational reasons or due to anatomic problems. Among surgical treatments are various portocaval anastomoses and operations of azygoportal disconnection.

A unique experience of applying emergency direct portocaval anastomoses for over fifty years was recently presented by the surgical clinic of University of California in San Diego. In two prospective randomized clinical trials involving a total of 365 cirrhotic patients, they compared the efficiency of this operation with endoscopic sclerotherapy and TIPS. Patients were almost identical in terms of the degree of liver dysfunction, a third of them had CTP C liver cirrhosis. In all groups, the time of the start of therapy did not exceed 8-12 hours. In the end, primary hemostasis was achieved in the group of endoscopic sclerotherapy in 20% of cases, TIPS in 22%, portocaval shunting in 97-100%; recurrent encephalopathy occurred in 35%, 61%, and 15% of cases, respectively. Survival was 5 times higher in patients having undergone surgery [31]. It should be noted that other authors have not obtained similar results.

D. Voros *et al*. [32] reported that a modified Sugiura operation performed urgently on 46 cirrhotic patients (4 of CTP A, 16 of CTP B, and 26 of CTP C), helped to stop the esophageal variceal bleeding in all of them. Postoperative mortality amounted to 23.9%, with nine patients of CTP C and two of CTP B. In the long-term observation period of 14 months to 22 years, the recurrence of bleeding occurred in 58.4% of cases, and 5-year survival rate was 62.5%.

In Russia, the operation most commonly performed in urgent situations was proposed in 1959 by M. D. Paziora; it constists in proximal gastrotomy and careful suturing of varicose veins of the gastric cardia and cardioesophageal junction. Supplementing it with the devascularization of the stomach contributed to an increase in two-year survival rate from 77 to 97%, increased hemostatic effect from 51 to 89%, less frequent relapses of vein formation from 25 to 5%, and the reduction of gastropathy in the long-term postoperative period [33].

Conclusion

Progress in understanding the pathogenesis of portal hypertension under liver cirrhosis and the development of new technologies has led to notable advances in controlling esophageal variceal bleeding. Yet, even despite using current standards of treatment, mortality associated with esophageal variceal bleeding remains high. We can assume that stratification of patients by risk groups will enable tailoring therapeutic approaches to the expected results for each of the groups, namely, initiating early use of more aggressive methods in patients with predictors of poor outcomes, and to protect individuals with a good prognosis from unnecessary invasive procedures. Further study of this issue will contribute to improved treatment of this severe complication.

Conflict of Interest

No potential conflicts of interest.

Acknowledgments

Abbreviations

HVPG: hepatic venous pressure gradient; TIPS: transjugular intrahepatic portosystemic shunting; CTP: Child-Turcotte-Pugh scale.

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