EDITORIAL COMMENT

Developments in the Treatment of Acute Esophageal Variceal Bleeding

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Improved Outcome of Acute Esophageal Variceal Bleeding

Liver cirrhosis has long been considered a chronic, progressive, and irreversible disease with the focus of treatment mainly on its complications. There have been significant advances in the treatment of esophageal variceal bleeding, as reflected by the marked reduction of rebleeding from 47% to 13% and bleeding-related death from 50% to 20%.[1,2] This achievement has been attributed to a better understanding of the pathogenesis of portal hypertension and improved standards of medical care. The introduction of endoscopic variceal ligation, a technique that is at least as effective as sclerotherapy but associated with fewer side effects, as well as the near global use of vasoactive agents, has contributed to this improvement in survival. Moreover, the prophylactic use of antibiotics has resulted in the reduction of infection to 32% and mortality to 9%.[3] In a recently reported trial, antibiotic prophylaxis reduced early variceal rebleeding and rebleeding severity. Although all of these measures have improved outcomes,[4] incidences of failure to control acute bleeding and early rebleeding are still high, at around 20–30%; thus, the continued improvement of outcome in patients with acute variceal bleeding is required.

Emergency Endoscopic Treatment or Vasoactive Agents?

The global use of vasoactive agents for acute variceal bleeding is known to be effective in controlling approximately 70–80% of acute variceal bleeding episodes. A recent meta-analysis by D'Amico et al[5] has suggested reserving endoscopic therapy for use only after failure of pharmacologic treatment. Another randomized trial showed that if hemostasis is achieved by pharmacologic treatment, continuous somatostatin infusion is as effective as sclerotherapy but with fewer side effects,[6] which reinforces the conclusion of D'Amico at al.[5] Indeed, endoscopic treatments are equally effective in controlling acute variceal bleeding in all of the studies that compared sclerotherapy versus vasoactive agents.[5] Endoscopic variceal ligation (EVL) has replaced sclerotherapy as the optimal endoscopic method to treat acute esophageal variceal bleeding, primarily because of its lower complication rate and lower rebleeding rate. Therefore, the hemostatic effects of vasoactive agents versus EVL on acute variceal bleeding should be reassessed before a conclusion such as "endoscopic therapy might be reserved for failure of pharmacological treatment"[5] can be drawn.

Consensus for the Treatment of Acute Esophageal Variceal Bleeding

Evidence for the beneficial effect of early administration of vasoactive agents to patients with suspected acute esophageal variceal bleeding have been gathered from many studies to substantiate the Baveno III consensus that "In suspected variceal bleeding, vasoactive drugs should start as soon as possible, before diagnostic endoscopy. Endoscopic therapy is recommended even when no active bleeding is found at diagnostic endoscopy."[7] Therefore, the consensus of how to treat acute esophageal variceal bleeding changed and a study designed to compare EVL versus vasoactive

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agents in the treatment of acute esophageal variceal bleeding has become impossible. From now on, a delay in giving vasoactive agents to patients with suspected esophageal bleeding before endoscopic diagnosis or treatment is deemed unethical.

Emergency Endoscopic Variceal Ligation or Vasoactive Agents — Which Is Better?

This difficult question is answered by Chen et al[8] in this issue of the *Journal of the Chinese Medical Association*. This unique study was conducted just before the Baveno III consensus was reached in 2001. The study randomized patients with acute esophageal variceal bleeding to receive emergency EVL or somatostatin (250 μg bolus followed by 250 μg/hour for 48 hours). Finding a higher treatment failure rate (3/62 vs 20/63) and more transfusion requirement (4.7 ± 3.2 vs 6.9 ± 7.3 units) in the somatostatin group, regardless of active or nonactive bleeding, the authors suggested that early EVL for patients with acute esophageal variceal bleeding is encouraged if endoscopists experienced in EVL are available. While the study was conducted by a renowned collaborative team and drew some important conclusions from solid results, it does raise several concerns.

Myth or Reality

First, rebleeding was ascertained when a nasogastric tube (NG) showed blood; however, an NG was only inserted to monitor the patients receiving somatostatin, but not in patients undergoing EVL, and this may underestimate the treatment failure rate of the latter group. Second, a time lag in the definitive treatment by either EVL or vasoactives may underestimate the success rate of controlling bleeding because vasoactive agents are known to be more effective when given earlier, if possible at the scene of bleeding, and are less effective if patients already have hypotension or shock.[9] Third, a double dose of somatostatin infusion (500 μg/hour) may be more effective than the standard 250 μg/hour dose in patients with active bleeding at endoscopy.[10] Therefore, it is still uncertain whether the failure rate of double-dose somatostatin is higher than that of EVL. Questions regarding the real efficacy of vasoactive agents versus EVL in controlling acute esophageal variceal bleeding remain unsettled and may be forever a myth. In reality, suspected patients will already have received vasoactive agents, which can be easily administered by a junior resident, before endoscopy. As soon as possible, endoscopy is then performed by a senior resident. If acute esophageal variceal bleeding is found, ligation of the varices would seem proper if endoscopists experienced in EVL are available. But what is the next step? A recent meta-analysis has shown that combination of endoscopic plus pharmacologic treatment is more effective than endoscopic treatment alone in controlling acute variceal bleeding, but has no effect on mortality.[11] Theoretically, it is understandable because control of acute esophageal variceal bleeding by endoscopic treatment and vasoactive agents are mediated via different mechanisms. Actually, the Baveno IV consensus workshop recommends that "Endoscopic treatments are best used in association with pharmacological therapy, which preferably should be started before endoscopy. Vasoactive drug therapy (terlipressin, somatostatin, vapreotide or octreotide) should be maintained in patients with esophageal variceal bleeding for 2–5 days."[12]

Solving the Unsolved

Despite the agreed treatment strategy, failure to control acute bleeding and early rebleeding is still a challenge, especially in patients with high risk of rebleeding, such as active bleeding during endoscopy, severe hepatic decompensation, and association of hepatocellular carcinoma. Hemostasis is markedly impaired since liver plays an important role in the production and clearance of clotting and fibrinolytic factors. The role of coagulopathy and thrombocytopenia in the outcome of acute variceal bleeding, and their therapeutic effect of correction or amelioration have not been well evaluated. A recent multicenter European trial has shown that the administration of recombinant activated Factor VII, in addition to combined endoscopic plus pharmacologic treatment, improves the results of endoscopic plus pharmacologic treatment alone in Child's class B and C patients but not in Child's class A .[13] However, more controlled trials are required to assess its efficacy and cost-benefit.

Going Forward

Since variceal bleeding is a medical emergency associated with significant morbidity and mortality, the design and conduct of good clinical trials for the treatment of this emergency have always been difficult. However, it is our responsibility to continue improving outcomes in patients with acute variceal bleeding.

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