EDITORIAL

Therapies for bleeding gastric varices: is the fog starting to clear?

The prevalence of gastric varices is 4% in patients with cirrhosis who have never bled,[1] although it has also been reported that 25% of patients with cirrhosis have gastric varices at screening endoscopy.[2] The risk of bleeding from gastric varices is also approximately half that of bleeding from esophageal varices.[1,3] Conversely, mortality from gastric variceal bleeding is higher than esophageal variceal bleeding, with the worst outcomes for isolated type 1 varices.[1,3] The optimal therapy for bleeding gastric varices remains controversial because there are few randomized, controlled studies.

Current guidelines recommend endoscopic therapy as first-line treatment for bleeding gastric varices, with the option of transjugular intrahepatic portosystemic stent-shunt (TIPSS) where endoscopic therapy is not available.[4,5] When interpreting results from studies, it is important to identify the number of patients with active bleeding at endoscopy. Active bleeding is associated with worse outcomes[6] and is particularly challenging with gastric varices, where bleeding can be torrential. Currently, the endoscopic therapeutic options for gastric variceal bleeding include band ligation, tissue adhesives, and thrombin. The greatest evidence exists for tissues adhesives, which are recommended as first-line endoscopic therapies in both the American Association for the Study of Liver Diseases guidelines and by the Baveno IV consensus.[4,5]

Cyanoacrylate (*N*-butyl-2-cyanoacrylate, ''glue'') undergoes rapid polymerization on contact with living tissues. Therefore, meticulous adherence to technique is crucial, not only to ensure successful safe therapy, but also to prevent irreversible damage to endoscopes caused by polymerization. Initial hemostasis rates of 88% to 100% have been achieved in recent uncontrolled studies.[7-9] Two randomized, controlled trials have compared cyanoacrylate with variceal band ligation,[10,11] with mixed results for initial hemostasis, although the outcome was in favor of cyanoacrylate for rebleeding rates (22% versus 44% and 31% versus 54%).[10,11] There were no differences in mortality rates. An interesting development is the use of EUS to guide the injection of cyanoacrylate. A recent article reported on the use of EUS to guide injection of feeding perforator veins with excellent results.[12] However, great care is required with the technique to prevent damage to expensive equipment, and this risk may alone prevent the widespread use of EUS-guided cyanoacrylate injection. Complications of tissue adhesives include embolization, with case reports of cerebral stroke, portal vein embolization, splenic infarction, coronary emboli, and a series demonstrating nonfatal pulmonary emboli in 4.6% of cases.[13-16] When embolic phenomena occur, fatalities have been reported.[7,17,18] Thrombin is a promising agent, and this journal recently published a small UK-based study that used bovine thrombin for gastric varices.[19] The initial hemostasis rate was 92%, and remarkably there were no patients who rebled from gastric varices. Other uncontrolled studies also had promising results.[20-26] Clearly, comparison with other therapies in controlled studies is required before thrombin is universally accepted, although the published studies so far have included more than 200 patients.[19-26] The ease of injection and lack of embolic phenomena are potential benefits.

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Interventional radiologists have come to the rescue of many endoscopists when managing bleeding varices. TIPSS has revolutionalized the management of esophageal varices, and the evidence so far suggests that TIPSS is effective in the prevention of rebleeding from gastric varices.[27] It has been demonstrated that patients with large gastric varices have lower portal pressure than those with esophageal varices,[27-29] possibly as a result of the development of gastrorenal portosystemic shunts.[30] Sanyal et al[31] studied the effect of TIPSS on gastric (isolated type 1) and esophageal varices. Despite a significant reduction in the size of esophageal varices and decrease in the portal pressure gradient (PPG) to less than 12 mm Hg, half of the patients with gastric varices had persistent isolated varices, mainly as a result of splenorenal shunts. These differences may reflect the fact

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that gastric varices are true veins with a large volume, which contributes to increased wall tension.[32] The latter may explain why gastric varices bleed despite lower portal pressures. The efficacy of TIPSS for bleeding gastric varices is likely to be related to a decrease in the PPG rather than a decrease in the size of varices at endoscopy. Indeed, it may be necessary to aim for a lower a PPG after TIPSS insertion for gastric variceal bleeding. This is supported by a study in which most patients who rebled from gastric varices after TIPSS insertion had a PPG greater than 7 mm Hg.[27]

In the past decade, uncontrolled studies have investigated the use of TIPSS in the management of variceal bleeding either from gastric varices alone[33] or gastric compared with esophageal varices.[27,34] In a study of 28 patients with cirrhosis with bleeding fundal varices, the 96% success rate at initial hemostasis and the 29% rebleeding rate were similar to those with esophageal variceal bleeding.[34] Barange et al[33] studied 32 cirrhotic patients with bleeding gastric varices and observed a high rate of hemostasis of 90% with a 1-year cumulative rebleeding rate of 31%. In another small study of predominantly fundal variceal bleeding, there was no significant difference in the rate of hemostasis between gastric and esophageal variceal bleeding.[35] In a large retrospective series, TIPSS was used in 40 cirrhotic patients with predominantly fundal variceal bleeding and in 232 patients with esophageal variceal bleeding.[27] The rates of variceal rebleeding were similar (20% vs 15%). The complications of TIPSS, such as encephalopathy and shunt dysfunction, were also similar. A noteworthy finding was a lower mortality rate in patients who bled from gastric varices (5-year mortality of 49.5% vs 74.9%, $P < .05$). Furthermore, the difference in mortality was confined to those patients who bled from gastric varices at a PPG greater than 12 mm Hg. The reason for this difference was not clear, but one possibility is that the PPG may be a direct predictor of mortality. The patients in this study who bled from gastric varices had a significantly lower PPG. Studies indicate a favorable outcome in patients who bleed at lower portal pressures, particularly if measured shortly after a variceal bleed.[36]

It is clear that both tissue adhesives and TIPSS can be highly effective in the management of bleeding gastric varices. However, to date, there is only one randomized, controlled trial comparing both therapies.[37] This is in contrast to more than 10 controlled studies comparing endoscopic therapies with TIPSS for esophageal variceal bleeding, with results favoring TIPSS for rebleeding at the expense of increased encephalopathy.[38] Lo et al[37] randomized patients after control of gastric variceal bleeding to TIPSS (n=35) or cyanoacrylate (n=37). Despite greater variceal eradication in the cyanoacrylate arm, the rebleeding rate was significantly higher with endoscopic therapy (38% vs 11%). There was no difference in survival or complication rates. It is important to emphasize that the efficacy of the treatments for secondary prophylaxis was studied and not initial hemostasis of actively bleeding varices. There is another United Kingdom-based retrospective study that provides more information on efficacy of therapies in active bleeding.[39] This study compared cyanoacrylate (n=23) with TIPSS (n=20) in patients with cirrhosis who bled from gastric varices. Active bleeding was noted in 21 patients in total. Both therapies were highly effective in initial hemostasis. The main difference was the reduced rebleeding rate with TIPSS (35% vs 20%). There was no difference in survival. Severe encephalopathy was noted in 2 patients after TIPSS, and 1 patient died after embolization of cyanoacrylate to the chest. However, TIPSS was significantly more expensive. A major limitation of this study is the short follow-up of just 6 months with cyanoacrylate and 12 months with TIPSS, which must be taken into account when interpreting the findings. Therefore, the somewhat limited early evidence suggested that, compared with cyanoacrylate, TIPSS had the advantage of reduced rebleeding, although it can be considerably more expensive.

The study by Procaccini et al[40] in this issue of *Gastrointestinal Endoscopy* comparing TIPSS with cyanoacrylate in the management of gastric variceal bleeding is a welcome addition to the literature. Despite the limitations of a retrospective study, it is the largest such series reported to date and has the longest follow-up. The main aims were to compare rates of rebleeding, survival, and morbidity. Patients with bleeding gastric varices or stigmata of bleeding were treated with TIPSS (n=44) or cyanoacrylate (n=61). Although baseline characteristics were matched, the follow-up for cyanoacrylate was significantly longer (74 vs 48 months). This relates to the use of glue from 1997 to 2004, and the majority of TIPSS procedures performed after 2004, when cyanoacrylate was not available. Despite the potential to bias the results in favor of TIPSS because of advances in the management of bleeding varices over time, the results show similar efficacy for rebleeding (10% and 25% at 1 year for cyanoacrylate and TIPSS, respectively). There was no difference in mortality. There were not enough data to assess the efficacy in actively bleeding patients, which is unfortunate. Likewise, details of PPG reduction after TIPSS insertion were not presented. The significant finding of this study was that of increased morbidity requiring hospitalization after TIPSS, with a striking difference in encephalopathy (11 patients vs 1 patient for cyanoacrylate). It is not clear from the study how many patients were encephalopathic before TIPSS because this is a recognized risk factor for post-TIPSS encephalopathy.[41] This information would also have allowed a clear distinction between de novo encephalopathy and deterioration of preexisting encephalopathy after TIPSS insertion. The use of polytetrafluoroethylene-coated stents in 66% of patients is noteworthy and did not seem to influence the results on subgroup analysis. Seven patients treated with cyanoacrylate were later treated with TIPSS, mainly because of refractory bleeding. One patient died after embolization of cyanoacrylate.

What can we conclude from this study? With careful attention to technique, cyanoacrylate is effective for the treatment of gastric varices and more resource-efficient than TIPSS. It is also associated with a small but clear risk of mortality caused by embolization, despite expert hands. TIPSS has a definite role and should be used when endoscopic therapies fail in the presence of a patent portal vein. Careful patient selection can reduce the risk of post-TIPSS encephalopathy. The experience with endoscopic therapies for gastric variceal bleeding in recent times makes TIPSS more likely to be a second-line therapeutic modality. Perhaps 10 years ago we may have had a lower threshold for the use of TIPSS in bleeding gastric varices. Clearly, more controlled studies are necessary to make valid conclusions. Studies comparing different endoscopic modalities such as thrombin and tissue adhesives would also be welcome. Such studies should also focus on efficacy in acute gastric variceal bleeding.

DISCLOSURE

The author disclosed no financial relationships relevant to this publication.

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Abbreviations: PPG, portal pressure gradient; TIPSS, transjugular intrahepatic portosystemic stent-shunt.

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