Developments in Endoscopic Treatment of Bleeding Gastric Varices

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Bleeding from esophagogastric varices is a serious complication of portal hypertension and chronic liver disease. While hemorrhage from esophageal varices occurs more frequently, gastric variceal bleeding tends to be more serious, often presenting with massive hematemesis, and is associated with a higher mortality.1

Sarin et al.1 categorized gastric varices based on their association with esophageal varices and their location in the stomach. Gastroesophageal varices (GOVs) are esophageal varices that extend to the cardia and lesser curve (GOV1) or along the fundus (GOV2). Isolated gastric varices (IGVs) are those that occur in the fundus only (IGV1) or are found in isolated areas elsewhere in the stomach (IGV2). Gastric varices may also be classified as primary or secondary. Primary gastric varices are those that are found following an initial endoscopic exam, or in an individual who has never undergone endoscopic injection sclerotherapy (EIS) or endoscopic variceal band ligation (EVL). Secondary gastric varices are those that develop after endoscopic treatment (with either EIS or EVL) for esophageal varices.

Gastric varices are found in approximately 20% of patients with portal hypertension, the majority of whom are classified as GOV1.2,3 IGV1 has the highest incidence of bleeding (78%), followed by GOV2 with 55% and IGV2 and GOV1, both at 10%.2 Gastric varices are more common in individuals with non-cirrhotic portal hypertension (NCPH) and extrahepatic portal vein obstruction than in individuals with cirrhosis.2 Endoscopy tends to underestimate the prevalence of dilated gastric varices because, unlike esophageal varices, they lie deeper in the submucosa, making it difficult to differentiate gastric varices from gastric rugae. In a study by Lo et al.,6 the use of endoscopic ultrasound demonstrated that a significant proportion of gastric varices are not apparent by endoscopy alone.4 As for esophageal varices, predictors of bleeding risk exist. In a study by Kim et al.,8 the size of fundal varices, Child's status, and the presence of a red-spot on the fundal varix were identified as risk factors for hemorrhage from fundal varices. The incidence of bleeding from fundal varices was comparable to that of moderate to large esophageal varices. Endoscopic treatment of bleeding gastric varices has not been as successful as for esophageal varices. Some of the proposed treatment modalities include injection sclerotherapy with alcohol or other sclerosants, thrombin injection, cyanoacrylate tissue adhesives, and band ligation.6,8-16

Endoscopic Treatments

Injection Sclerotherapy

Injection sclerotherapy with traditional sclerosants such as ethanolamine oleate and alcohol has been used for treating gastric varices. While it has been successful at achieving hemostasis and eradication of esophageal varices, this technique has had less success in treating gastric varices. This finding is likely due to the high volume of blood flow associated with gastric varices, causing the sclerosant to be washed away prior to achieving hemostasis.5-7 The greater amounts of sclerosant required lead to increased adverse effects (fever and abdominal and chest pain).6

In a long-term follow-up study of patients undergoing intra- and paravariceal sclerotherapy for gastric varices,1 initial hemostasis was achieved in 12 of 18 patients (68%). Of the five patients who continued to bleed and underwent repeat sclerotherapy, bleeding was arrested in only one of five. Gastric variceal obliteration was achieved in 43 of 60 patients (71.6%) who underwent repeated elective sclerotherapy, with higher rates of success in those with GOV1 than in those with GOV2 and IGV1. Re-bleeding occurred in 5.5% of patients with GOV1, 19% of those with GOV2 and 53% of those with IGV1. The overall mortality was 24%, approximately half due to uncontrolled bleeding and half due to liver failure. In other reports, sclerotherapy has been associated with remarkably high rates of re-bleeding.1

More recently, Kojima et al.8 evaluated 30 patients with bleeding gastric varices who underwent injection sclerotherapy with ethanolamine under fluoroscopic guidance plus vasopressin infusion and a transdermal nitroglycerin patch. Initial hemostasis was achieved in 28 of 30 patients (93.3%), with variceal eradication occurring in all 28. Re-bleeding rates ranged from 13% at one year to 19% at five years, and were treated with the same technique.
Gastric Varices

**Thrombin**
Thrombin has been used in a small number of patients with success in controlling acute gastric variceal bleeding, achieving initial hemostasis in 70–94% of patients, with 0–18% incidence of re-bleeding. To date, no randomized controlled trials have been performed in the evaluation of the use of thrombin injection for bleeding gastric varices.

**Band and Snare Ligation**
Endoscopic variceal ligation has been shown to be an effective treatment for gastric varices. Band ligation is as effective as non-selective beta-blockade in the prevention of initial variceal bleeding, as demonstrated in a randomized controlled trial involving 100 patients. Shiha et al. described the use of band ligation in 27 patients with gastric varices. Of those, ligation effectively achieved hemostasis in 16 of 18 patients (88.8%), with recurrence of bleeding in five of 27 (18.5%). Of eight patients with isolated gastric varices, five experienced acute hemorrhage; all were treated successfully with band ligation. The main complication was the presence of ulcerations at the sites of banding, which occurred in all of the patients. Healing had occurred at two weeks of follow-up on repeat endoscopy.

One concern regarding band ligation of esophageal varices is the adverse effect it has on portal hypertensive gastropathy and gastric mucosal hemodynamics. The exacerbation of portal hypertensive gastropathy after variceal ligation is related to increased vascular congestion of the gastric mucosa. The presence of large fundal varices prior to ligation is potentially protective against these changes.

Endoscopic ligation of bleeding gastric varices has also been performed successfully using a detachable snare. Lee et al. used detachable snares and elastic bands in the treatment of 41 patients with large (>2cm in diameter) gastric varices, either with active bleeding or with evidence of recent hemorrhage. Hemostasis was achieved in 82.9% of patients and, of the patients who underwent repeated ligation, variceal eradication occurred in >90%. Only one person had a recurrence of bleeding, and no serious complications were noted in the 16 months of follow-up. While treatment with detachable snares effectively achieved hemostasis and eradication of varices, there was a high rate of recurrence of previously eradicated varices. Furthermore, the technical complexity of this procedure precludes it from being a widely accepted treatment modality.

The use of combination techniques with snare ligation and injection sclerotherapy, previously used for esophageal varices, has also been shown to be safe and effective at achieving hemostasis and obliteration of varices. Yoshida et al. studied 35 patients with gastric varices who underwent combined therapy with endoscopic variceal banding and EIS with ethanolamine oleate. Hemostasis was achieved in all eight emergency-treated patients, and variceal eradication occurred in 97%. Bleeding recurrence occurred in one patient. The recurrence rate of varices was 15% at two years. There were no significant complications.

**Cyanoacrylate Injection**
Cyanoacrylate is a tissue adhesive that works by solidifying in the varix, causing obliteration of the vessel and hemostasis. The glue conglomerate is extruded over weeks to months. Several studies have demonstrated the efficacy of endoscopic injection of N-2-butyl cyanoacrylate for the treatment of gastric varices. Comparison studies have shown cyanoacrylate to be more effective than ethanolamine oleate in achieving initial hemostasis in cardiac variceal bleeding. As the use of N-2-butyl cyanoacrylate is not currently US Food and Drug Administration (FDA)-approved, most of these studies have been performed outside the US. In a prospective trial, Sarin et al. studied 37 patients with IGV who were randomized to receive endoscopic intervention with either alcohol or cyanoacrylate glue. Cyanoacrylate was significantly more effective at achieving variceal obliteration (100 versus 44%) and hemostasis (89 versus 62%). Interestingly, in the follow-up period of 15 months there was no recurrence of gastric varices in either group.

In a US study by Greenwald et al., 44 patients were treated with intravariceal injection of N-2-butyl cyanoacrylate for gastric varices. Initial hemostasis was attained in 95%, and a cost analysis using historical controls suggested marked cost reduction and improved survival in the cyanoacrylate-treated group. A study by Rengstorff and Binmoeller used 2-octyl-cyanoacrylate for intravariceal injection of gastric varices, which is approved in the US for skin closure, as an available alternative to N-2-butyl-cyanoacrylate. They achieved immediate hemostasis in 100% of the 25 individuals in the study, with a recurrence rate of 4% at 11 months.

Comparing cyanoacrylate with band ligation, Lo et al. prospectively studied a total of 60 cirrhotic patients with a history of gastric variceal bleeding. Patients were randomized to N-2-butyl-cyanoacrylate (n=31) or band ligation (n=29), with active bleeding occurring in 15 and 11 patients, respectively. Initial hemostasis was achieved in 87% of patients in the cyanoacrylate group compared with 45% in the band ligation group, a statistically significant difference (p=0.03). Rates of re-bleeding and treatment-related ulcer bleeding were significantly higher in the band ligation group (54%) versus the cyanoacrylate group (31%). The cyanoacrylate group had fewer blood transfusions and lower mortality (nine versus 14 patients; p=0.05).

More recently, Tan et al. prospectively studied 97 patients with cirrhosis or with gastric variceal hemorrhage, randomized to either endoscopic band ligation (n=48) or cyanoacrylate injection (n=49). Of the 15 patients with active bleeding in each of the groups, adequate hemostasis was achieved in 14 (93%) in both groups. Gastric variceal re-bleeding occurred more frequently in the group receiving band ligation (21/48) than in the cyanoacrylate group (11/49, 44 versus 22%). Gastric variceal eradication rates between the groups were similar (66.7% in the band ligation group and 63.3% in the cyanoacrylate group), but rates of GV recurrence were significantly higher in the ligation group (59.4 versus 22.6%). There was no significant difference in mortality and there was no difference in rates of complications, most of which were infectious in nature.
A variety of reasons exist for the failure of N-2-butyl-cyanoacrylate to have attained FDA approval for use in the US. The major reason is the potential for adverse effects, particularly those related to embolism, infection, and technical difficulties with the administration of the agent. The most common complications of cyanoacrylate injection are those related to embolization of the glue, evidenced by a number of case reports. In a retrospective study, Hwang et al. found radiographic evidence of pulmonary embolism in six of 140 patients who had undergone cyanoacrylate injection for gastric variceal bleeding. These six patients had received a higher mean volume of injection—4.2ml compared with 1.8ml in patients without embolism—which suggests that the volume of cyanoacrylate injected may be a predictor of embolism.

One factor that increases the risk of embolism with cyanoacrylate is the use of lipiodol, which is commonly used to dilute the glue and to prevent immediate polymerization on contact with blood. Undiluted cyanoacrylate has been associated with gluing of the injector needle to the varix potentially causing massive hemorrhage in its removal, although successful removal has been reported. The risk of bacteremia is another concern with the use of cyanoacrylate. In a group of 47 cirrhotic patients with acute or recent gastric variceal bleeding who were treated with N-butyl-2-cyanoacrylate, Chen et al. found positive blood cultures in 32% (15/47) compared with 2% (1/47) in a group of matched controls. The controls consisted of cirrhotics undergoing endoscopy for non-variceal bleeding. Most of the strains of bacteria cultured from blood were identical to those found on the needle injector and accessory channel. It is likely that in passing through the oropharynx the accessory channel and needle become the source of infection. Compared with conventional injected sclerosants, cyanoacrylate may be associated with a greater rate of bacteremia due to the source of infection. Compared with conventional injected sclerosants, cyanoacrylate may be associated with a greater rate of bacteremia due to the source of infection. Compared with conventional injected sclerosants, cyanoacrylate may be associated with a greater rate of bacteremia due to the source of infection.

Studies have shown that the techniques of balloon-occluded retrograde transvenous obliteration (B-RTO) and percutaneous transhepatic obliteration (PTO) are safe and effective in the management of varices when appropriate expertise is available.

**Recommendations**

Currently, the proper therapy of bleeding gastric varices remains in dispute and depends largely on local expertise. Baveno IV, an international consensus group convened to address therapies for portal hypertension, recommends N-butyl-cyanoacrylate, TIPS, or beta-blockers in patients who have bled from IGV type 1 or GOV2. The group recommends the use of cyanoacrylate, band ligation of esophageal varices, or beta-blockers in patients who have bled from gastro-esophageal varices type 1. The Baveno IV consensus recommends TIPS or surgical shunts in cases of active bleeding in which medical and endoscopic treatment has failed. The inability to obtain N-butyl cyanoacrylate in the US severely limits endoscopic options. While the experience is limited, further studies may document 2-octyl-cyanoacrylate to be a worthy alternative for the endoscopic management of bleeding gastric varices.

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