Gastric and ectopic varices – newer endoscopic options

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SUMMARY

Bleeding from esophageal and gastric varices is the most life-threatening complication of liver cirrhosis and portal hypertension. While for esophageal varices the endoscopic treatment is well established and common practice is followed worldwide, this is not the case for gastric varices. Gastric varices bleed less frequently but more severely than esophageal ones and are classified in certain subtypes according to their location and their size or configuration. In this review, the treatment options for bleeding esophageal and gastric varices will be presented. Emphasis will be given on the treatment of gastric varices with cyanoacrylate. In addition, a short description of ectopic varices will be made.

Key Words: treatment of gastric varices, ectopic varices, cyanoacrylate, glue, variceal bleeding.

INTRODUCTION

Development of gastroesophageal varices is one of the most common and severe complications of portal hypertension. The prevalence of varices is about 50% among all cirrhotics.1 Cirrhotics develop varices at a rate of 10% per year. Once varices are present, the risk of them becoming large and the risk of bleeding is about 10% per year. Variceal hemorrhage will complicate the clinical course of chronic liver disease in about 30% of patients2 and accounts for 80 to 90 percent of bleeding in those patients.3

The mortality of each episode of variceal bleeding is about 20 to 30 percent and as many as 70 percent of survivors have recurrent bleeding after their first variceal hemorrhage.4 Gastric varices (GV) are less common than esophageal ones, with a prevalence of about 20 percent in patients with portal hypertension.5,6 About 20% of all variceal bleeds are due to gastric varices.7 About 15-25% of gastric varices bleed during their lifetime. Although GV bleed less frequently and with lower pressure than esophageal varices, bleeding from GV is more severe and associated with higher mortality. GV are often associated with large draining splenorenal shunts that complicate the condition and contribute to hepatic encephalopathy. Once gastric fundal varices bleed the mortality rate ranges from 25% to 55%. Patients with GV also have a higher risk of rebleeding and a decreased rate of survival. Ectopic or extra-gastric varices account for 5-10% of cases of variceal bleeding.8

The endoscopic treatment of esophageal varices has been addressed successfully with the use of rubber band ligation and injection sclerotherapy. Band ligation is the treatment of choice and has fewer complications than sclerotherapy,9,10 but has also been related with higher rate of recurrence of the esophageal varices11 and some authors have proposed adjuvant variceal sclerotherapy after band ligation to prevent recurrence of esophageal varices.12,13 For gastric varices, the optimum endoscopic treatment remains to be defined. Band ligation and sclerotherapy with various agents has been tried with various results, but a high risk of rebleeding was found in most studies.14,15 The treatment of gastric varices with cyanoacrylate gives very good results, with high hemostasis rate and reduced early and late rebleeding rate compared to other endoscopic treatment modalities16,17. Despite being the endoscopic treatment of choice in Germany, Italy, India, Canada and other countries for gastric varices, cyanoacrylate has not gained universal acceptance, especially in the United States for unclear reasons, in spite of the small risk of serious complications and risk of scope damage, if used without adequate care.
In this review we will present our experience about treatment of gastric and ectopic varices and emphasis will be given to the endoscopic technique and the fine details of the procedure. Where glue is concerned, any endoscopist who performs injection sclerotherapy and hemostasis injection of bleeding ulcers should be able to use this compound for gastric and ectopic varices.

**Classification of gastric varices**

Gastric varices are generally divided into cardiac and fundic varices. Cardiac gastric varices are supplied by the cardiac branch of the left gastric vein, which enters the stomach wall at a point 2 to 3 cm from the gastroesophageal junction, sending out many branches that are distributed in the cardia. Most veins of the cardia become parallel veins from the gastroesophageal junction as the flow becomes hepatofugal, but dilated winding cardiac veins run in the submucosa and directly join esophageal varices. Fundic varices are quite different from cardiac varices in angioarchitecture. Their supplying route is mostly the short gastric vein, but in some it is the posterior or left gastric vein. The vascular anatomy of fundic varices is something like a shunt running through the stomach wall.

As mentioned, when portal hypertension occurs, an adaptive increase in flow through the portosystemic communications occurs to return blood to the heart. The vessels involved, especially the intrinsic veins around the gastroesophageal junction, become dilated and tortuous, forming varicose veins. Gastroesophageal varices occur in four patterns: (a) varices in the fundus of the stomach; (b) esophageal and palisade zone varices; (c) varices in the perforating zones; (d) paraesophageal varices, which involve the extrinsic veins. In contrast to normal individuals, the valves in the perforating zone become incompetent, permitting reverse flow into the intrinsic plexus from the extrinsic veins.

In common clinical practice though, varices are classified simply by their location into esophageal and gastric varices. Esophageal varices are graded according to size. A common system of classification is as follows: F1 – small straight varices; F2 – enlarged, tortuous, but occupying less than one third of the lumen; F3 - large, coil shaped and occupying more than one third of the lumen.

Gastric varices (GV) are also classified primarily by their location, as follows, according to the Baveno Consensus Conference III, where Sarin’s classification was accepted (Fig 1):

A. Gastroesophageal varices – gastric varices in continuity with esophageal varices

GEV1 – along the lesser curvature (usually 2 to 5 cm in length).

GEV2 – along the greater curvature extending towards the gastric fundus.

B. Isolated gastric varices

IGV1 – isolated cluster of gastric varices in the gastric fundus.

IGV2 – isolated gastric varices in other parts of the stomach.

GEV1 form when a branch of the left gastric vein penetrates the gastric wall (cardiac vein) and joins the deep submucosal veins into the gastric zone directly connected to submucosal veins in the palisade zone. GEV1 are usually associated with large esophageal varices, while GEV2 are associated with large esophageal varices only in 50%. IGV1 are associated with segmental portal hypertension (such as that due to splenic vein thrombosis) or the presence of spontaneous collaterals from the splenic vein to the renal vein to supply these varices. IGV1 drain into the inferior phrenic vein by gastrorenal shunts, gastrophrenic shunts or gastropericardiatic shunts, a part of which projects into the intragastric space. About 50% of cases of ectopic varices, including IGV2 are associated with portal vein thrombosis. The mechanisms responsible for this phenomenon are unknown.

It was also shown, using portovenography, that the left gastric vein participates as the blood supply in 70% of the isolated gastric varices (IGV1) and in 100% of the esophageal varices. The posterior gastric vein participates as the blood supply of 70% of the isolated gastric varices and in 24% of the esophageal varices. The main blood drainage route in all patients with esophageal varices is the azygos and/or the hemiazygous vein, and all of the cardiac varices drained into esophageal varices. The main drainage

![Figure 1. Classification of gastric varices.](image-url)
Gastric and ectopic varices – newer endoscopic options

The New Italian Endoscopic Club (NIEC) has previously classified gastroesophageal gastric varices as type I GV and isolated gastric varices and ectopic gastric varices as type II GV, but this classification is becoming less popular. Another Japanese classification of gastric varices (GV) is as follows: according to their form they are classified into three types (a) F1- tortuous, (b) F2 – nodular and (c) F3 – tumorous; according to their location they are classified into five areas: anterior (La), posterior (Lp), lesser (Ll) and greater curvature (Lg) of the cardia, and the fundic area (Lf). For example, GV F2Lf means that there are gastric varices of nodular form at the fundic area. This classification is considered more complex and correlates less to the pathophysiology of varices and their prognosis, so it is less popular, but is preferred by some authors because of its analytical descriptive value.23

Diagnosis of gastric varices and risk factors for bleeding

In most cases the gastric as well as the esophageal varices are diagnosed by endoscopy.1 The experienced endoscopist can identify GV easily in the vast majority of cases. If there is doubt and the nature of an enlarged suspicious fundal “fold” cannot be determined, endoscopic ultrasound is the test of choice for confirmation.24 Alternatively, transabdominal ultrasound with Doppler, computed tomography scan with contrast, magnetic resonance angiography, portovenography and interventionial angiography can be used to identify GV, with the latter test being the most sensitive to recognize the presence and the anatomy of gastric and esophageal varices.

Large size of the varices, presence of ascites, advanced chronic liver disease (Child-Pugh class C cirrhosis), high portal pressure (hepatic venous pressure gradient > 12 mm Hg) and red marks indicate high risk of variceal bleeding.5,25 In acute upper gastrointestinal bleeding, the identification of esophageal varices is not difficult, but the appearance of esophageal varices on endoscopy is important, if there is no bleeding present at the time of the procedure. Signs indicating recent variceal bleeding or high risk of bleeding are the red wale marks (longitudinal red streaks on varices), the cherry-red spots (red, discrete, flat spot on varices), the hematocystic spots (red, discrete, raised spots) and at a lesser degree diffuse erythema of the varices. The presence of a venous plug or nipple on a varix indicates the probable site of rupture.

Isolated gastric varices (IGV1) are by themselves a risk factor of variceal bleeding. The risk of bleeding from GV was shown to correlate with variceal size (>10 mm), Child class and the presence of a red spot on the varices, according to the following formula: Prognostic index = 0.53 X Child class + 0.78 X varix size + 0.72 X red spot, where Child class A = 0, B = 1 and C = 2; the varix size is scored as small (<5 mm) = 0, medium (5 to 10 mm) = 1 and large (>10 mm) = 2; and the red spot is scored as absent = 0 and present = 1. The risk of bleeding from IGV1 correlates directly with the above prognostic index. In contrast to esophageal varices, the correlation of GV bleeding with elevated portal venous gradient pressure is less intense.5

In acute upper gastrointestinal bleeding due to GV, identification of the varices and of the bleeding source during emergency endoscopy is sometimes difficult because the fundal pool of blood and clots does not allow proper and detailed examination. It has been shown that the inability to clear a fundal pool of blood at emergent upper endoscopy is associated with significant morbidity and mortality.26 If the fundal pool of blood is not cleared at initial endoscopy, fundal lesions missed at emergent endoscopy can be identified in 41% of patients on follow-up examination, with many being clinically significant. Urgent endoscopy and aggressive evacuation of the stomach in suspected variceal bleeding may necessitate the use of airway protection by endotracheal intubation or an overtube. A large caliber therapeutic endoscope with high saline irrigation for evacuation of clots usually facilitates examination and endoscopic therapy of lesions at the cardia and fundus. A cap at the end of the scope, as used with EMR, may help suction of blood and clot evacuation.

Treatment of gastric varices

The management of gastric varices has not been as well studied as that of esophageal varices. Controversy exists on the evaluation and possible pharmacologic and endoscopic treatment in those who have never bled. In addition there have currently not been any randomized controlled studies on the role of endoscopy and pharmacotherapy in the management of patients that have bled. We prefer to eradicate these varices endoscopically to stop active bleeding and reduce rebleeding rate.

Primary prophylaxis

The general objective of pharmacologic therapy for variceal bleeding is to reduce portal pressure and consequently, intravariceal pressure. So, the rationale for use of pharmacologic therapy is similar for acute bleeding, primary prophylaxis and secondary prophylaxis.3
recommended for patients with large varices. Non-selective beta-blockers, namely propranolol or nadolol are the drugs of choice for primary prophylaxis, because of their ability to reduce splanchic blood flow and portal pressure. Non-selective beta-blockers block b1-adrenergic receptors, with subsequent activation of a-adrenergic receptors and splanchic vasoconstriction. They also block b2-adrenergic receptors eliminating b2-receptor mediated vasodilation. Due to their combined action, non-selective beta-blockers are more effective than selective beta-blockers. These medications should be given at adequate doses, to reduce heart rate at 55 per min or 25 percent from baseline rate. It has been proven, for esophageal varices that if portal pressure is reduced below 12 mm Hg, the risk of variceal bleeding is minimized. Propranolol is given at a dose of 80-320 mg per day in divided doses or as a long-acting preparation and nadolol at a dose of 20-80 mg once daily. A problem is that beta-blockade is not well tolerated in up to 30% of cirrhotics and more so in these with Child C cirrhosis.

Nitrates, mainly isosorbide mononitrate can reduce portal pressure by causing splanchic vasoconstriction and can also reduce hepatic resistance, but are recommended only in combination with beta-blockers, because of their potential to accentuate the peripheral vasodilation in cirrhotics. In fact the combination of beta-blockers and nitrates was shown to reduce portal pressure in more patients than beta-blockers alone. The problem is again, that patients with Child-Pugh stage C cirrhosis cannot tolerate beta-blockers and their combination with nitrates.

In 1999, Sarin et al, showed that in patients with high-risk esophageal varices, endoscopic ligation of the varices is safe and more effective than propranolol for the primary prevention of variceal bleeding. Although there was some criticism about this interventional approach, it has been accepted as an alternative approach for patients with contraindications, intolerance or non-compliance to medical treatment. Neither TIPSS nor sclerotherapy is recommended for primary prophylaxis of esophageal varices.

What about primary prophylaxis in patients with gastric varices who have never bled? This is a controversial area that has never been studied for isolated gastric varices. The factors that influence a decision to start on pharmacotherapy include size of the varices, grade of liver disease and red marks. As most gastric varices that are found in the cardia, are a continuity of esophageal veins, one would think that beta-blockers would act in a similar fashion to traditional esophageal varices.

The role of primary prophylaxis on isolated gastric varices, which tend to have a lower pressure than esophageal varices, is unclear. If the varices are related to cirrhosis and are part of generalized portal hypertension, beta-blockers may be useful and we recommend them in the usual fashion of monitoring. The role of beta-blockade in patients with left sided portal hypertension related to portal vein thrombosis is unclear.

A real dilemma is in considering endoscopic obliteration with cyanoacrylate glue in those patients with large isolated gastric varices who have never bled. This has not been studied. For large grape-like clusters of (isolated) gastric varices with or without red marks our practice is to commence glue obliteration (see below). In patients with portal hypertension due to cirrhosis and endoscopic obliteration we continue surveillance every 6 months with endoscopy as well as prophylaxis with beta-blockers.

Our practice is also in patients with GV who have never bled and are on pharmacotherapy to repeat endoscopy every 1 year. In patients with large isolated GV who have never bled but varices were ablated we perform endoscopic follow-up to assure total obliteration every 2 to 3 months. We may have to repeat injection with glue if the GV are found not obliterated (see below). It is unclear whether beta-blockade should be continued after successful endoscopic obliteration of GV with cyanoacrylate.

Treatment of acute variceal bleeding

Acute variceal bleeding is a medical emergency and prompt medical and endoscopic treatment is required. The mortality rate can be as high as 30-35%. The first step in suspected variceal bleeding is to follow the general measures about upper gastrointestinal bleeding, closely monitor and resuscitate the patient. The patient is best treated in an intensive care unit for close monitoring. Airway protection is of paramount importance. In patients who are combative, comatose or in shock endotracheal intubation should be considered to protect the airway and allow performance of endoscopic procedure. Sufficient fluid replacement, often accompanied by blood and fresh frozen plasma transfusions, is provided to ensure adequate tissue perfusion and oxygenation. For these means it is also useful to administer oxygen.

As soon as the initial measures are taken to maintain adequate oxygenation and blood circulation, pharmacologic therapy is started. One possible option is vasopressin, which reduces splanchic blood flow and portal pressure. The addition of nitroglycerin to vasopressin results in improved therapeutic efficacy and fewer side effects. Vasopressin, due to its side effects, is not used currently if any of the alternative treatment options are available. The newer synthetic analogue of vasopressin, terlipressin, which is used for the treatment of hepatorenal syndrome, has fewer
side effects and longer half-life than vasopressin, so it can be used in bolus form. It appears as effective as somatostatin or endoscopic treatment for suspected variceal bleeding, but it is not widely available at present.\(^{30}\)

Somatostatin, a naturally occurring peptide, and its synthetic analogues octreotide and vapreotide, stop variceal hemorrhage in up to 80 percent of patients and are generally considered to be equivalent to vasopressin, terlipressin and endoscopic therapy for the control of acute variceal bleeding.\(^{31,32}\) Somatostatin and its analogues act by reducing splanchic blood flow and by reducing portal pressure through effects on vasoactive peptides (glucagon, substance P etc.). They are given by continuous intravenous infusion and practically have no side effects, so they are the drugs of choice in acute variceal bleeding. Octreotide is cheaper than somatostatin and is given in general as 50 mcg bolus and then as an infusion of 50 mcg per hour.\(^{33}\) The same dose is used for the other synthetic analogue, vapreotide.\(^{34}\) The treatment should be continued for 5 days and provides an excellent safety interval for the commencement of endoscopic treatment. However, an interesting meta-analysis showed that although somatostatin and its analogues improve the efficacy of endoscopic treatment to achieve initial control of variceal bleeding and 5-day hemostasis, yet they fail to affect mortality.\(^{35}\)

A recent study showed that the administration of recombinant factor VIIa in cirrhotic patients with acute variceal bleeding, which can rapidly correct the prolonged prothrombin time, significantly decreased the proportion of patients with Child-Pugh B or C cirrhosis in whom variceal bleeding failed.\(^{36}\) Dosing with recombinant factor VII appeared safe, but further studies are needed to verify these findings.\(^{37}\)

The role of pharmacologic therapy for the treatment of GV is less clear. Although GEV1 constitute more than 80% of all GV, only 11% of GEV1 ever bleed. For GEV1, all the above guidelines for pharmacologic treatment are standing and endoscopic obliteration of esophageal varices often leads to disappearance of GEV1 too. In contrast, even though IGV1 constitute only 8% of all GV, 80% of IGV1 bleed. IGV1 are often fed by large splenorenal collaterals that partially decompress the portal vein. For this reason, IGV1 are associated with lower portal venous pressure gradient and are less responsive to the reduction of portal pressure by medical treatment. Nevertheless, pharmacologic treatment, with somatostatin or octreotide is of value in acute bleeding from GV.

In conclusion, there is no clear data on the use of vasoactive drugs for gastric varices, but these drugs, especially somatostatin and analogues may be used for the preparation of endoscopy. There is also no data on the duration of treatment in patients with GV. Our practice is to discontinue them after endoscopic treatment with cyanoacrylate.

**Endoscopic treatment**

One should try to optimize the conditions of performing upper endoscopy in patients with suspected variceal bleeding without wasting time (Figure 2). If the patient is combative, unstable or lethargic, endotracheal intubation should be considered. If the patient is stable and well oriented, the procedure can usually be carried out without endotracheal intubation, after explaining the procedure to the patient, obtaining informed consent and administering adequate sedation. As already mentioned, it is usually better to perform the procedure in the intensive care unit, where monitoring and facilities for treatment of procedure-related complications are optimal. The use of a large channel endoscope and repeated lavage of the stomach with tap water during the procedure is required to clear the stomach and optimize the view for therapeutic intervention.\(^{38}\)

In brief, for esophageal varices, there are two options of endoscopic treatment, sclerotherapy and band ligation. The high efficacy of both these methods in the treatment of esophageal varices has been well established.\(^{39}\) Sclerotherapy is an effective method in the treatment of esophageal varices, with excellent results in variceal eradication. The main disadvantage remains the high morbidity of the procedure due to deep ulceration, which may lead to rebleeding, stricture formation or perforation.\(^{40}\) Our the last decade, endoscopic band ligation was found superior to sclerotherapy for the treatment of esophageal varices, especially on the basis of lower rates of rebleeding, mortality, complications, speed of application and the need for fewer endoscopic treatments.\(^{41}\) The main disadvantage of band ligation remains the observed higher rate of variceal recurrence than that seen in sclerotherapy. Some authors have recently tried to combine ligation and sclerotherapy.

**Figure 2.** Endoscopic views of gastric varices (A, B).
(mainly additional sclerotherapy after successful sessions of band ligation) to reduce the recurrence rate of esophageal varices. The results are variable, but usually combination treatment has a lower recurrence rate.\textsuperscript{13,42} It seems that gentle sclerotherapy after successful band ligation to eradicate those varices too small to band may be a beneficial procedure with reduced rebleeding rates, but this has not become standard practice and ligation alone with a careful follow-up is currently recommended as the endoscopic treatment of first choice. In addition, endoscopic ultrasound with colour Doppler has been used to identify the perforating veins and then perform sclerotherapy successfully.\textsuperscript{43}

In contrast to the treatment of esophageal varices, endoscopic treatment of gastric varices (GV) is still a matter of debate.\textsuperscript{44} Endoscopic sclerotherapy of GV with absolute alcohol was found in an interesting study to be partially effective for the treatment of variceal bleeding (success rate 66.7%) and achievement of gastric variceal obliteration.\textsuperscript{4} These results were better for GEV1, intermediate for GEV2 and disappointing for IGV1. Besides common complications (fever, pain, dysphagia), two patients developed deep gastric ulcers following treatment that bled to death. Gastric variceal ligation has been reported successful for the control of acute bleeding and obliteration of GV by some authors,\textsuperscript{15} but the risk of severe rebleeding was present and led to death in one patient. In conclusion, endoscopic sclerotherapy and band ligation affect only part of GV and necrosis caused by sclerotherapy or ligation may induce massive bleeding from still open varices. For this reason, some authors developed very complex techniques for the treatment of GV. Yoshida et al, used a detachable snare to strangle the main gastric varix, sclerotherapy with ethanolamine oleate to inject the smaller GV and then rubber bands to ligate these smaller varices.\textsuperscript{45} Lee et al, used detachable snares for gastric varices larger than 2 cm in diameter and elastic bands for smaller gastric varices and had an overall hemostatic result of 82.9% and variceal eradication rate after repeated treatments of 91.7%.\textsuperscript{46} Such combined techniques can be highly effective, although they are operator-dependent, but can be used whenever no better alternative treatment is available.

In geographic areas where glue is available there is no role for sclerotherapy and/or band ligation. Band ligation can be used only for small gastric varices. If the gastric varices are cardiac, not large and an extension of esophageal varices (GEV1 or GEV2) they can be treated in combination with the esophageal varices with rubber banding. There is growing evidence that treatment with cyanoacrylate (tissue glue N-butyl-2-cyanoacrylate, bucrolate) is the most effective method for the treatment of GV. In a randomized, controlled study of various agents for endoscopic injection sclerotherapy of bleeding canine GV, cyanoacrylate was found to be the best agent overall in terms of immediate efficacy, low volume requirement, time required for initial hemostasis and reduction of gastric variceal size.\textsuperscript{47} A randomized controlled trial showed that cyanoacrylate was more effective and achieved GV obliteration faster than injection sclerotherapy with alcohol.\textsuperscript{6}

Kind et al, treated 174 cirrhotic patients with actively bleeding GV with cyanoacrylate (Bucrolate) and then by weekly sessions until their varices were eradicated.\textsuperscript{48} Concomitant esophageal varices were treated by sclerotherapy with 1% polidocanol. The hemostasis, early rebleeding rate and hospital mortality rate after bucrolate treatment were 97.1%, 15.5% and 19.5% respectively. In about 75% of patients GV were successfully obliterated, while failure to obliterate was frequently related to prehepatic block (portal vein thrombosis, splenic vein thrombosis, or mesenteric vein thrombosis). Hemostasis of rebleeding cases was achieved with bucrolate in all patients.

Akakoshi et al, treated 52 patients with bleeding GV with cyanoacrylate.\textsuperscript{49} After initial treatment, patients were followed-up endoscopically and retreatment was administered as necessary. The rate of initial hemostasis was 96.2%, while cumulative non-bleeding rates were 64.7%, 52.7% and 48.2% at 1, 5 and 10 years respectively. When rebleeding occurred, 80.0% was within 1 year after initial injection. The treatment failure-related mortality rate was 4.0% (2 of 52). The cumulative survival rates were 66.9%, 60.4% and 55.5% at 1, 5 and 10 years respectively. The mortality depended on either malignancy or liver function (Child-Pugh classification). The authors concluded that cyanoacrylate was highly effective and should be considered the first choice of treatment for bleeding GV, but still the rate of rebleeding was found rather high.

Huang et al, treated 90 patients with bleeding GV with cyanoacrylate injection for hemostasis within a 6-year period.\textsuperscript{51} Most of the varices were large and were located at the fundus and the posterior wall of the body (94.4%). After injection of cyanoacrylate, patients were followed endoscopically with retreatment as necessary. The rate of hemostasis at one week was 94.4%. From three days to 16 months after the initial injection, rebleeding occurred in 23.3% of the patients. Recurrent bleeding was stopped with reinjections of cyanoacrylate in 16.7% of the patients, resulting in a rate of definitive hemostasis of 93.3%. The rebleeding rate correlated with the form of the varices, with F3 – tumorous having the highest rebleeding rate. The mortality related to treatment failure was 2.2%.
In another interesting study by Iwase et al., it was found that patients with localized-type GV had a better clinical course, in terms of recurrent bleeding, variceal eradication and survival, than those with diffuse-type GV, after endoscopic ablation with cyanoacrylate. These clinical effects were related to the vascular anatomy of the GV as determined by endoscopic ultrasonography and 3-dimensional CT. Type 1 vascular anatomy (one varicosc vessel without noticeable ramifications) was much more common (86%) in localized-type GV, whereas type 2 vascular anatomy (multiple varicosc vessels with complex connecting ramifications) was found almost exclusively (91%) in diffuse-type GV. Overall, endoscopic ablation with cyanoacrylate was found to be an effective and safe procedure for patients with bleeding GV.

Another study by Lee et al. investigated the use of endosonography (EUS) in monitoring cyanoacrylate injection to obliterate GV. Initial gastric variceal bleeding was controlled with cyanoacrylate injection. Then, approximately half of the patients received “on demand” repeat injection of cyanoacrylate only in response to recurrent bleeding, while the other half underwent biweekly EUS followed by repeated injection of cyanoacrylate until all GV were obliterated. Although the rates of early (<48 hour) bleeding recurrences were similar with repeated or on demand injection (7.4% versus 12.8%), late recurrence of bleeding was significantly reduced in the repeated injection group (18.5% versus 44.7%). There was also a numerical trend toward improved survival in the repeated-injection group. This study emphasized that EUS, especially with color Doppler, is a useful method for the evaluation of GV and endoscopic obliteration with cyanoacrylate glue. In addition, EUS is helpful in the imaging of paraesophageal and gastric varices after sclerotherapy or band ligation of esophageal varices. EUS appears to be more accurate and less invasive than percutaneous transhepatic portography in the assessment of peri-esophageal and paraesophageal collateral veins.

Secondary prophylaxis

For the secondary prophylaxis of variceal bleeding from esophageal varices, prevention of recurrent bleeding), endoscopic band ligation appears to be the treatment of choice, alone or combined with beta-blockers, with or without isoboride mononitrate. Nevertheless, two large studies have questioned the efficacy of endoscopic treatment for secondary prophylaxis. The first, published in 1996 found that as compared with sclerotherapy, nadolol plus isoboride mononitrate significantly decreased the risk of rebleeding from esophageal varices. The second, published in 2001, showed that combined therapy with nadolol and isoboride mononitrate was more effective than endoscopic ligation for the prevention of recurrent bleeding and was associated with a lower rate of major complications. The probability for recurrent bleeding was lower for patients with a hemodynamic response to medical therapy, defined as a decrease in the hepatic venous pressure gradient of more than 20 percent from the baseline value or to less than 12 mm Hg. Despite these findings, the overall mortality rate was not significantly different between the two groups. In addition, it should be taken into consideration that patients with Child-Pugh C cirrhosis are often unable to tolerate the medical treatment.

Primary and secondary prophylaxis from gastric variceal bleeding with beta-blockers with or without nitrates is also used if tolerated, but is probably less effective than prophylaxis for esophageal varices. The role of secondary prophylaxis with cyanoacrylate has been discussed above and in our opinion is essential to minimize the rebleeding rates after initial endoscopic treatment with cyanoacrylate.

Technique of injection of cyanoacrylate

According to the literature and in our experience, cyanoacrylate injection in bleeding GV is effective and safe treatment and obviously the best endoscopic approach, wherever cyanoacrylate is available. Herein we will describe in detail the technique we use for cyanoacrylate injection. Every endoscopist who has performed sclerosis therapy or even injected bleeding ulcers should be able to do cyanoacrylate injection, if certain key points are taken into consideration.

1. It is always better to do the procedure after initial re-suscitation of the patient. If the procedure is done soon after acute bleeding the patient should be on somatostatin or octreotide infusion, because it is always easier to perform the injection under controlled circumstances. If the patient is agitated, non-cooperative or unstable, endotracheal intubation should be considered. If the patient is in stable condition, the procedure should be explained along with its risks and the patient should be advised to remain calm to facilitate the manipulations.

2. If it is known that a gastric variceal bleed is to be treated, the cyanoacrylate solution should be prepared. The endoscopist and endoscopic assistant should wear gloves and have eye protection during cyanoacrylate mixture preparation. Commercially available sclerotherapy injection catheters, with a 6 mm 21-gauge needle are used. The injection catheters are flushed with lipiodol. Lipiodol is a contrast agent that prevents cyanoacrylate to become solidified prematurely. The cyanoacrylate is then mixed with Lipiodol in a ratio of 1:1 (0.5 ml of cyanoacrylate, Histoacryl, with 0.5 ml
of Lipiodol) in a 1 ml syringe. Usually, 4 to 5 syringes of 1 cc are prepared with the mixture. Also, some 10 cc syringes are prefilled with water for injection and some others with Lipiodol.

3. Then the patient is well sedated and the endoscopic procedure starts. After complete endoscopic examination, a clear endoscopic view of the fundus is obtained by sucking remaining clots of blood and by flushing through the biopsy channel with normal saline. Then the injection catheter is inserted with the instrument in a straight view and after the catheter reaches the tip the instrument is retroflexed again, slightly withdrawn to approach the fundal area and rotated appropriately to aim with the injection catheter the fundal varix at its bulge or near the sign of recent bleeding. Then the injection catheter is advanced and its needle is advanced by the assistant. The length of the needle is tested at this point by the endoscopist and should be long enough for intravariceal injection (usually about 5-6mm).

4. Some at this point prefer to prefill the injection catheter with 0.5 cc of the cyanoacrylate solution, a manipulation which aims to replace the lipiodol solution inside the injection catheter with cyanoacrylate mixture (the injection catheter in its full length of lumen contains about 1 cc of fluid). Others avoid this short step.

5. The injection catheter is inserted into the varix, 1 cm of cyanoacrylate-lipiodol mixture is rapidly injected and immediately 2-3 cc of water for injection (and not normal saline) is injected into the varix (simply by replacing the injecting syringe of cyanoacrylate-lipiodol with one of the syringes containing water for injection).

6. The injection catheter is slowly withdrawn from the varix and its lumen is flushed first with water for injection again and then with a small amount of lipiodol, to protect its potency. At no stage is the catheter tip brought close or into the tip of the endoscope and no suction is applied after the injection stage, to avoid obstruction of the accessory channel of the instrument by the cyanoacrylate. If suction is required, this is done gently and away from cyanoacrylate remnants into the gastric lumen and after some time has passed to allow glue to solidify.

7. The procedure is repeated as above, until all fundal varices are treated. If the injection catheter becomes obstructed after glue injection, it is carefully removed and replaced by a new one.

Taking into account these guidelines and performing the procedure in a relaxed, coordinated and controlled fashion is the key of success (Figures 3,4). Cyanoacrylate (“the crazy glue”) is a powerful sticky agent that can obliterate large GV if adequate amount is injected intravariceally. Excessive injections should be avoided though, to reduce the risk of complications. The endoscopic procedure is repeated after 7-14 days and thereafter as appropriate (usually in 1, 3 months and 1 year). During repeat endoscopy, the injected varices are gently touched with a blunt accessory, such as the closed tip of a biopsy forceps. Obliterated varices are very firm and non-elastic, while patent varices have a soft feel expected by venous structures. The injection of the mixture of cyanoacrylate-lipiodol into the varix can be seen in fluoroscopy, because lipiodol is radioopaque and a contrast agent.

Some prefer to use glue alone without lipiodol for the treatment of gastric varices, after flushing the injection catheter with lipiodol. Although this strategy can minimize the risk of migration of glue to other organs, it carries out a much higher risk of plugging the accessory channel of the instrument or the injection catheter, so most experts prefer the mixture of glue with lipiodol.

Newer agents are being investigated for the endoscopic treatment of GV. Both human and bovine thrombin have achieved adequate control of variceal bleeding in initial experimental studies. These results have been confirmed in human studies with limited numbers of patients with either esophageal or gastric varices. This treatment appears to be very safe and effective and the only reported complication was recurrence of bleeding. Human thrombin was evaluated in a more recent study for the treatment of fundal GV, some of which were previously unsuccessfully treated with TIPS. Treatment was found safe and effective for the management of acute gastric variceal bleeding. The main disadvantage of the study was the rather limited number of patients. Although no complications were noted, 3 of 12 patients had recurrence of their bleeding. Treatment was applied in 1 to 4 sessions. Another agent that was evaluated only in experimental studies

Figure 3. Gastric varices after glue injection.
is poly-N-acetyl-glucosamine, a substance isolated from marine microalgae and that seems to have similar properties with thrombin.

Complications from cyanoacrylate injection

Cyanoacrylate injection of gastric varices, although highly effective and with a good safety profile, has been criticized for its potential to cause rare but severe complications. The most common complications of the procedure include transient chest pain and self-limiting fever. Transient difficulty in swallowing, as in upper endoscopic procedure and bleeding from the site of injection can also be considered complications, but the most severe, but fortunately also the most rare complication is systemic embolization. Most cases of embolization by cyanoacrylate have been presented as case reports and the frequency of this complication in the published series of patients was extremely low or zero. Embolization has been reported the lungs, spleen and brain. Brain embolization was seen in patients with a right to left heart compartments communication, because glue enters the systemic circulation directly and then usually follows the route of the internal carotid artery into the brain. Tan et al reported a case of near fatal multiple pulmonary embolisms and splenic infarction with septicemia after 2 sessions of elective obliteration of gastric varices with cyanoacrylate. A case of portal and splenic vein thrombosis after cyanoacrylate injection was also reported, as well as another one with splenic infarction. Slower injection of cyanoacrylate into a previously treated gastric varix is recommended by the authors to avoid this complication. Usually splenic infarction can be treated conservatively, but 7% will require a splenectomy.

Microembolization into the lungs is more common. This incident usually self-limiting and patients are either asymptomatic, or experience minor symptoms, such as transient cough and mild chest pain. Microembolization into the pelvic region has also been reported. Another serious complication of cyanoacrylate injection is fistula and abscess formation. Battaglia et al reported two cases of visceral fistula as a complication of treatment of esophageal and gastric varices with cyanoacrylate. In the first of these two cases, a fistula between the gastric fundus and the left pleural cavity was seen 6 months after two sessions of injection of cyanoacrylate were carried out to control a severe recurrent gastric variceal bleeding. Complete recovery and closure of the fistula was achieved by conservative measures. In the second case an esophageal-mediastinal fistula was developed after glue injection of large esophageal varices in a patient with hepatocellular carcinoma. Conservative and surgical treatment failed and the outcome was fatal. However, in another study three cases of fistula arising from the gastrointestinal tract (esophageal-pleural, gastric-pleural, colonic-cutaneous) were successfully treated after injection of cyanoacrylate into the fistulous tract.

In another study, it was reported that about 30% of patients who undergo endoscopic injection with cyanoacrylate for GV develop transient and usually uneventful bacteremia. The accessory channel of the endoscope was the major source for bacteria. For patients with a poor reserve and severe blood loss, the cost and benefit of the prophylactic use of antibiotics should be considered until evaluated in future trials.

Finally, in one case a 10 mm pedunculated polypoid lesion was noted in the gastric curve of the stomach after previous cyanoacrylate injection of GV. After polypectomy, the lesion proved to be a chronic inflammatory process surrounding refractory foreign body material, probably sequestrated cyanoacrylate within submucosal vessels. In another report, the injection needle was disengaged from its plastic sheath and got stuck into the varix after cyanoacrylate injection, but was removed without complications with a biopsy forceps. This potential complication is seen most commonly in cases where cyanoacrylate is used without lipiodol.

As it was noted, complications with cyanoacrylate are rare. The procedure can be life saving for patients with a dismal prognosis. To increase the safety of the procedure, injections should be given strictly intravariceally and the dilution ratio between cyanoacrylate and lipiodol should be 1:1. Injections should be limited to a few milliliters of the mixture, 1cc at each injected site (usually up to 4-5 ml, but preferably between 2-3 ml). If larger amounts are required to obliterate the varices, this should be done sequentially. The personnel handling cyanoacrylate should use gloves and eye protection.
Radiologic technique / Combined radiologic endoscopic technique

Balloon-occluded retrograde transvenous obliteration (B-RTO), developed by Kanagawa et al, represents a new treatment for gastric fundal varices that achieves variceal obliteration with infrequent recurrence. This angiographic technique was initially carried out via the femoral vein, but can be performed using a transjugular approach. An angiographic catheter with a balloon of either 11 mm or 20 mm in diameter is inserted via the femoral or internal jugular vein into the spontaneous gastrorenal shunt that is found in more than 90% of patients with gastric varices. With the occluded balloon, sclerosant (usually 10 ml of 5% ethanolamine olate) can be injected to obliterate the fundal varices and the balloon is left in place for 24 hours, to permit thrombosis of the varix. The technique is highly effective, but it is interventional and is usually reserved for patients to whom endoscopic approach fails. In addition, the balloon transvenous obliteration of splenorenal shunt has been used as a safety measure to apply either conventional sclerosant or cyanoacrylate endoscopically into the GV with excellent results. This combined radiologic – endoscopic technique has a role in complicated cases of gastric variceal bleeding, but further studies are required for its evaluation.

Transjugular intrahepatic portosystemic shunts (TIPS)

Transjugular intrahepatic portosystemic shunts (TIPS) are another treatment option that should be reserved for recurrent variceal bleeding. TIPS are intrahepatic shunts between the hepatic and portal vein created by angiographic methods. This low-resistance channel between the portal and hepatic venous systems decompresses the portal vein in a way similar to a side-to-side portocaval shunt and avoids the need of general anesthesia and surgery. There is no doubt about the short-term efficacy of TIPS in reducing the high portal pressure. The main problems though with the use of TIPS are the increased incidence of clinically significant encephalopathy, which affects at least 25% of patients and the high rate of shunt occlusion, which is about 31% in one year and 47% in two years. Doppler ultrasonography can be used to assess the patency of TIPS and balloon dilatation or replacement of the occluded stent of TIPS may be required.

Two meta-analyses with a high number of patients showed that TIPS are more effective in preventing esophageal variceal bleeding than endoscopic therapy with either sclerotherapy or band ligation. The final conclusion of those studies was that TIPS could not be recommended as first-line treatment for the prevention of variceal bleeding because of the risk of encephalopathy and failure to improve survival. Furthermore, TIPS occlusion can lead to significant recurrence of variceal bleeding. Another study recommended TIPS as a rescue measure for uncontrolled or recurrent bleeding from GV. Occlusion of the shunt was associated though with recurrence of the bleeding and de novo encephalopathy occurred in 16 percent of patients.

In our experience, most episodes of gastric variceal bleeding can be controlled endoscopically with the use of cyanoacrylate and recurrent episodes can be treated likewise. TIPS though can be used, where available, as an emergency treatment for the immediate short-term control of uncontrolled gastric fundal variceal bleeding or esophageal bleeding and can serve as a bridge to liver transplantation. Their long-term effect is questionable though.

Surgical therapy

The surgical treatment for variceal bleeding currently is reserved only for patients who are not compliant to medical and endoscopic treatment and are not candidates for liver transplantation. Devascularization procedures (transection of esophageal varices and devascularization of the stomach) can be used in patients who have splanchic vein thrombosis and require great expertise. In addition these procedures have a high morbidity and mortality rate. Elective and non-elective portosystemic shunts have been used in the past quite frequently for the portal decompression and treatment of refractory varices, but now with the evolution of advanced endoscopic techniques they are only rarely performed in patients who are not good candidates for liver transplantation. Elective distal splenorenal shunts do not preclude liver transplantation in the future and are associated with a lesser degree of encephalopathy and preserve liver function, but their effectiveness in portal decompression is limited. Portocaval shunts are highly effective for the treatment of recurrent of refractory varices, and also for the treatment refractory ascites, but are associated with high procedural morbidity and mortality, high risk of encephalopathy (up to 40-50%) and accelerated progression of the underlying liver failure.

Summary

So in this review, all the treatment options for GV were presented with a short reference to the current standard of treatment for esophageal varices, since these complications of cirrhosis are anatomically and physiologically related. Emphasis was given to the treatment of GV with cyanoacrylate and we presented in detail the endoscopic technique we use to treat this severe complication of cirrhosis. In our experience (unpublished data) cyanoacrylate
is highly effective and safe for the obliteration of bleeding GV, but the question of whether primary prophylaxis of GV with cyanoacrylate should be performed remains to be addressed by future studies.

**Ectopic varices**

Ectopic varices represent porto-systemic collateral veins that develop in patients with portal hypertension. Apart from the common pathways that lead to the development of gastric and esophageal varices, varices can develop in many other sites. Ectopic varices involve other pathways, such as the inferior mesenteric vein (with communications through the superior hemorrhoidal to the inferior hemorrhoidal and iliac veins and the splenic hilar veins (with communication to retroperitoneal veins, which then communicate with veins on the abdominal wall, inferior phrenic veins and renal veins). The highest incidence of ectopic varices has been reported to be between 1 to 5%. Patients with extrahepatic portal hypertension have the highest incidence of bleeding from ectopic varices, and the prevalence of bleeding in this population may be as high as 40%. The highest incidence of ectopic varices has been reported in those patients with previous abdominal surgery and portal hypertension and in patients who have undergone successful endoscopic obliteration of esophageal varices by band ligation or sclerotherapy. Approximately 7-10% of patients with portal hypertension have visceral varices remote from the gastroesophageal junction. Visceral variceal hemorrhage usually occurs at sites where especially large adhesions form. Postmortem and angiographic studies have shown that the majority of patients with gastroesophageal varices have ectopic varices as well. Creation of an ileostomy or colostomy allows for communication between the splanchnic and systemic venous system and this results in development of peristomal varices in many patients with portal hypertension.

**Duodenal varices**

Duodenal varices present usually with hematemesis and melena. Usually, esophageal varices are present as well or have been treated in the past. Endoscopic treatment of esophageal varices can predispose in the development of ectopic duodenal varices. For the treatment of duodenal varices, sclerotherapy or band ligations have been used with variable results. In other cases, transjugular intrahepatic portosystemic shunts (TIPS) were successfully performed. Embolization of the duodenal varix and surgery have also been used. In our opinion, treatment with cyanoacrylate for duodenal varices is one of the best options and can achieve obliteration and disappearance of the duodenal varices (Figure 5). TIPS, where available, seem to be a reasonable approach for those rare cases where endoscopic treatment with cyanoacrylate fails.78

**Jejunal and ileal varices**

These varices are usually seen in patients with previous surgery involving the small bowel (e.g. Billroth II gastrectomy, small bowel resection). They can rarely be the cause of severe recurrent gastrointestinal bleeding of obscure origin. Diagnosis is usually established by enteroscopy, double-balloon enteroscopy, small bowel capsule endoscopy and angiography.79 Therapeutic options are similar to duodenal varices. The absence of esophageal varices does not exclude the presence of small bowel varices, because about one third of patients with ectopic varices do not have esophageal varices.

**Colonic varices**

Colonic varices can rarely be the cause of gastrointestinal bleeding in patients with or without portal hypertension. Diagnosis is made by emergency colonoscopy, red blood cell scan and angiography. The colonic varices, similarly to the other ectopic varices can develop after sclerotherapy for esophageal varices. Diagnosis is made by endoscopy, endosonography and angiography. Usually endoscopy, after moderate preparation of the patient, can identify the colonic varices in case of bleeding. For the treatment of bleeding colonic varices, cyanoacrylate has been reported to be effective in case reports and is the preferred treatment by the authors.

Figure 5. Endoscopic view of a duodenal varix injected with glue.
**Stomal varices**

About 50 percent of patients with portal hypertension and stomas develop stomal varices and stomal varices bleed in one third of cases. Variceal bleeding from stomal varices usually occurs at the mucosal cutaneous junction. Diagnosis is usually established by endoscopy and sometimes confirmed by angiography. The bleeding can be controlled by local applications of silver nitrate and pressure over the stoma. Sclerotherapy has been used with good results, but we believe that cyanoacrylate may be more effective. Surgical approaches include ligation of collaterals and devascularization, but rebleeding within 1 year is common and finally liver transplantation or portocaval shunts are required.

**Anorectal varices**

Anorectal varices should be separated from hemorrhoids. Anorectal varices are portosystemic collaterals that develop in patients with portal hypertension and can occur in the rectum, anal canal and external anal margin. Hemorrhoids are vascular cushions with no direct communication to the portal vein and do not occur in the rectum. The varices form between the superior hemorrhoidal vein of the portal system and the inferior hemorrhoidal of the systemic circulation.

Patients with portal hypertension and rectal bleeding should be investigated to define the source of bleeding. Endoscopy is the main method used, but angiography or injection of contrast into the varix is also used. The incidence of anorectal varices in patients with portal hypertension is between 46 and 78%. In rare instances, anorectal varices can cause significant bleeding. For their treatment, sclerotherapy and rubber band ligation have been used, but cyanoacrylate is usually more effective. Injection of cyanoacrylate at the anal area can be very painful and it should be avoided. Hemorrhoidectomy is disastrous and should not be performed. Angiographic embolization and TIPS are other options that should be used in the rare cases that endoscopic treatment fails.

**Biliary varices**

Biliary varices are very rare, but have been reported in patients with portal vein thrombosis. They represent collaterals between the cystic branch of the portal vein and veins of the abdominal wall or portal vein branches within the liver. Hemobilia has been reported as a result of biliary varices, but usually diagnosis is established incidentally in ultrasound with Doppler, CT scan, ERCP, endoscopic ultrasonography or MRCP. On standard ultrasound without Doppler, biliary varices can be mistaken for mucous retention cysts, heterothropic pancreas or mucosal edema. On ERCP, biliary varices may be mistaken for cholangiocarcinoma. If biliary varices are found, Doppler sonography should also be performed to rule out portal vein thrombosis. The surgeon should be informed about the presence of biliary varices in case of planned cholecystectomy, because intraoperative bleeding can be severe.

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