Endoscopic Ultrasound (EUS) for Esophageal and Gastric Varices: How Can it Improve the Outcomes and Reduce Complications of Glue Injection

Vikram Bhatia*

*Department of Medical Hepatology, Institute of Liver and Biliary Sciences (ILBS), New Delhi, India

A large part of portal venous system and the paragastric and para-esophageal collateral circulation is within the reach of endoscopic ultrasound (EUS). The EUS is more sensitive than gastroscopy for the detection of gastric varices (GV), and can accurately distinguish GV from thickened gastric folds. Gastric varices are depicted by serpiginous, anechoic, Doppler-positive mural channels, with larger collateral channels visible outside the gastric wall. The EUS has also been used to monitor the completeness of GV obturation after glue injection. There are limited data that this strategy may be clinically beneficial to prevent GV re-bleed. The EUS has been used to deliver glue injections under real-time monitoring into the vascular channels, with or without steel coils as scaffolding for the glue. The potential advantages of this technique include a straight scope position, lack of hindrance from pooled blood in gastric fundus, smaller glue volume requirements, and precise intra-vascular placement of glue with avoidance of intramural injections, and reduced embolic complications. (J Clin Exp Hepatol 2012;2:70–74)

APPLIED ANATOMY OF GASTROESOPHAGEAL PORTO-SYSTEMIC SHUNT PATHWAYS

Gastric varices (GV) have three major inflow tracts: (1) left gastric or coronary vein, (2) short gastric veins, and (3) posterior gastric veins. Most GV are formed by the left gastric or posterior gastric vein.[1,2]

The left gastric or coronary vein decompresses the portal vein directly via hepatofugal blood flow. Gastric varices of the left gastric vein are frequently located at the cardia and sometime extend cephalad to coalesce with the (para)esophageal varices.[3] Hashizume et al showed that the anterior branch of the left gastric vein forms the gastroesophageal varices by directly communicating with the submucosal veins, while the posterior branch extends along the outside of the esophageal wall across the esophagogastric junction to drain into the para-esophageal collateral channels.[4]

The other major inflow route is via the short gastric veins, which decompress the splenic vein at the splenic hilum (Figure 1). Gastric varices of the posterior gastric and short gastric veins are frequently located at the fundus and drain into a major porto-systemic shunt. Iwase et al showed that the feeding vein for the junctional type of GV was mainly the left gastric vein, whereas the fundal type of GV was fed by short gastric veins.[5] Varices of the gastroepiploic vein are rare but often occur after the treatment of other GV with surgery or coil embolization.

The efferent tract of the GV can be upwards into the azygos system, or into one of the major porto-systemic shunt. The majority of varices located at the gastric fundus drain into the inferior phrenic vein, which later joins with the left renal vein to form the gastrorenal shunt (80–85% of cases) or with the inferior vena cava just below

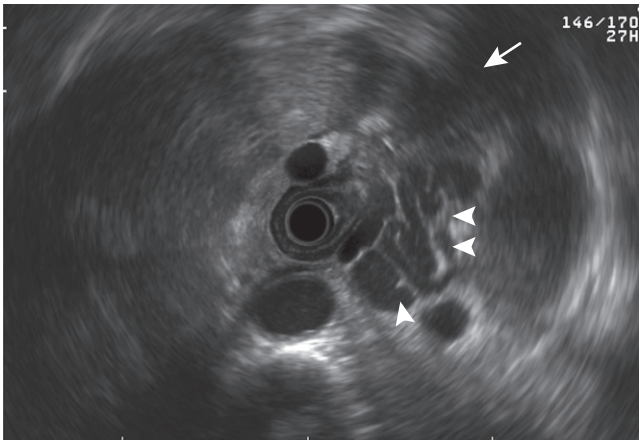

Figure 1 Serpiginous anechoic elongated vascular channels along the upper splenic pole at the gastroesophageal junction and gastric fundus (arrow), suggestive of short gastric vein collaterals (arrowheads).

Keywords: Coil embolization, cyanoacrylate glue, endoscopic ultrasound (EUS), gastric varices, gastroesophageal porto-systemic shunt pathways, *N*-butyl-cyanoacrylate, 2-octyl-cyanoacrylate
Received: 14.11.2011; *Accepted:* 23.12.2011
Address for correspondence: Vikram Bhatia, Associate Professor, Medical Hepatology, ILBS, New Delhi, India
E-mail: vikrambhatiadr@gmail.com; vikrambhatiadr@hotmail.com
Abbreviations: EUS: endoscopic ultrasound; GV: gastric varices; NPV: negative-predictive value; PPV: positive-predictive value
doi: 10.1016/S0973-6883(12)60083-8

the diaphragm to form the gastrocaval shunt (10–15%).[6] Varices at the gastric cardia usually drain through the (para)esophageal veins, but may or may not demonstrate azygos venous drainage.

All the abovementioned collateral circulation is within the reach of standard endoscopic ultrasound (EUS) imaging. An EUS with color and pulsed Doppler facilities allows a detailed structural and hemodynamic evaluation of the upper abdominal collateral circulation in portal hypertension, with a potential for directed therapeutics.

The potential application of EUS for improving outcomes in GV treatment includes as follows:

1. Improved detection rates of GV.
2. More accurate delivery of glue into the GV.
3. Confirmation of complete GV obturation after glue treatment, with reduction of re-bleeding rates.

ENDOSCOPIC ULTRASOUND DEPICTION OF GASTRIC VARICES

Gastric varices are depicted by EUS as serpiginous, anechoic channels in the gastric submucosal and mucosal layers, below the esophagogastric junction (Figure 2). They are connected by perforating vascular channels to the larger perigastric and paragastric vascular channels (Figures 3 and 4). It is possible to recognize the inflow and outflow tracts of GV by noting the inflow and outflow perforator channels in the upper gastric wall. Perigastric channels are those that are directly opposed to the gastric wall, while the paragastric channels are those that are separated from the gastric wall by a clear hyperechoic interface. Lee et al found that paragastric collaterals were seen in 81% and perigastric collaterals in 65% of patients with cirrhosis. The number of perforating veins correlated positively with the Child–Pugh score and the size of both esophageal varices and GV.[7]

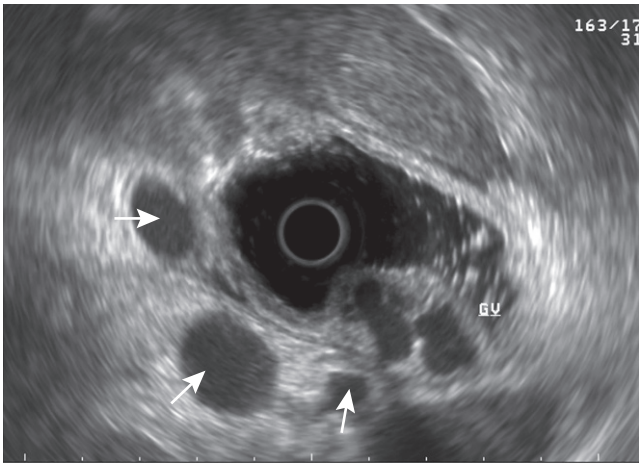

Figure 2 Variable sized anechoic channels in the gastric submucosa, suggestive of gastric varices. Much larger paragastric collaterals are also seen (arrows).
GV: gastric varices.

Several studies have shown that EUS is superior to conventional endoscopy for the diagnosis of GV.[7–9] Endoscopic ultrasound is also more sensitive than gastroscopy to distinguish GV from enlarged gastric folds.[10,11] Boustière et al reported a more than 6-fold increase in the rate of GV detection by using EUS compared with gastroscopy.[8] Using EUS as the gold standard, the sensitivity, specificity, positive-predictive value (PPV), and negative-predictive value (NPV) of endoscopy for the diagnosis of GV were 44%, 94%, 78%, and 79%, respectively.[12] Moreover, EUS can more accurately detect the variceal size, and by measuring the radius of the external and internal walls of the varices, one can also determine the variceal wall thickness.[13]

CONFIRMATION OF COMPLETE GLUE OBTURATION OF VARICES

Most series from India, Japan, Europe, and the United States report good initial hemostasis rates of over 90%. However, the re-bleeding rates from GV may be 15–30%

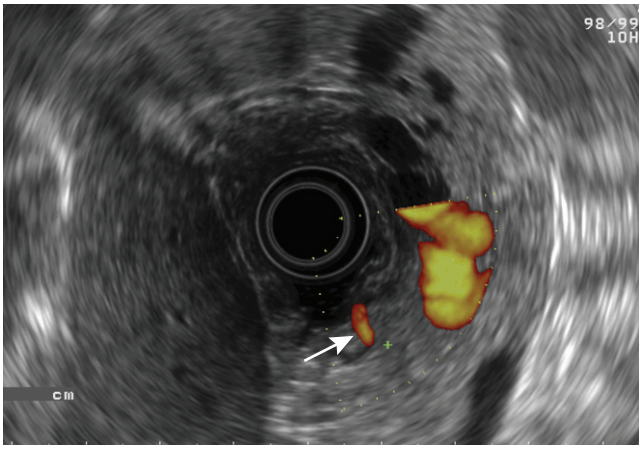

Figure 3 A small perforating vascular channel is seen entering the gastric wall (arrow).

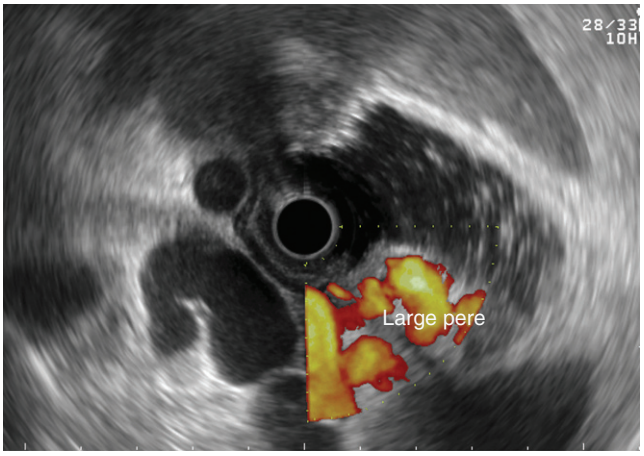

Figure 4 A large perforator channel is seen feeding the gastric fundal varix.

after glue injections.[14] The risk of re-bleeding is mainly related to incomplete obturation of the gastric vascular channels. As a result of the deep-seated location of GV in the submucosal layer of the stomach, residual GV are difficult to detect and eradicate. Mucosal ulceration and scarring after sclerotherapy also make subsequent endoscopic assessment of variceal patency more difficult, and a treatment end point is difficult to define.

Immediately after therapy, the shape and size of the varices may not show any changes under endoscopic observation, but with EUS evaluation the varices are seen to become echogenic, and blood flow can no longer be detected by Doppler. The EUS can thus provide an objective end point for gastric variceal eradication. The paragastric large collateral channels usually persist after glue obturation of the intramural channels. There is evidence that persistence of large para-esophageal collaterals after esophageal variceal eradication is associated with increased rates of variceal recurrence and bleeding. However, there are no data which suggest that the size or number of persisting para-gastric vascular channels is associated with increased recurrence or bleeding from GV.

There are only limited data that more meticulous gastric variceal eradication by EUS monitoring leads to lower re-bleeding rates, compared with the standard practice of evaluating vascular patency by injection catheter palpation. Lee et al performed EUS on day 7 after initial endotherapy with cyanoacrylate glue injection of GV. Any detected residual varices were treated by further glue injections. The EUS study and glue injections were then repeated biweekly until complete obliteration of GV was confirmed. A mechanical radial scanning scope (UM20; Olympus Optical Co) without Doppler facilities was used in this study, while the subsequent glue injections were made with a gastroscope. Fifty-four patients treated with this EUS guidance protocol ('repeated injection' group) were compared with 47 historic patients treated with 'on-demand' injection schedule. Late recurrence of bleeding (>48 h) was significantly reduced in the 'repeated injection' group (18.5% vs 44.7%, $P=0.0053$). Cumulative probability of recurrent bleeding-free interval was higher in the 'repeated injection' group than in the 'on demand' group.[15] However, further evidence is needed before routine EUS-based monitoring strategy for GV obturation can be adopted in clinical practice.

Inaccurate intramural placement of glue injections may also contribute to recurrence of bleeding, by causing deep ulcers. Additionally embolic complications after glue injection, including cerebral embolization with stroke, pulmonary embolization, portal vein embolization, splenic infarction, and coronary emboli, are reported in up to 5% of cases.[14] Glue injections under EUS guidance with accurate intravascular needle placement have the potential to obviate these complications. However, there are no data to support this hypothesis.

REAL-TIME ENDOSCOPIC ULTRASOUND DIRECTED GASTRIC VARICES THERAPEUTICS

There are three published studies that have described real-time EUS-guided delivery of glue, stainless steel coils, or a combination of both into GV. Very high success rates for obturation of GV were achieved, with small injection volumes and limited number of treatment sessions. These studies are briefly reviewed below.

Romero-Castro et al first reported a series of 5 patients in whom *N*-butyl-2-cyanoacrylate glue (1 mL of 1:1 mixture with lipiodol, per injection) was injected into GV through a standard 22G EUS FNA needle (GIP MedizinTechnik, or Cook Endoscopy). The authors targeted the entrance site of the perforating veins in the muscular layer of the gastric wall. After completing the injection, the needle was withdrawn into its outside metallic sheath before removal, to avoid any contact between the glue and the working channel of the echo-endoscope. Gastric varices eradication was successful in all 5 patients. Two patients required a single session, and three patients required two sessions. The mean total cyanoacrylate-lipiodol mixture dose administered was only 1.6 mL (range 1–2 mL). The authors were very careful to identify the inflowing vein accurately, and rule out what would be the outflowing vein. The injection was real-time controlled by using EUS and fluoroscopy. The lipiodolenabled fluoroscopic visualization of the injected vessel.[16]

Levy et al first reported EUS-guided coil embolization in a patient with refractory bleeding secondary to ectopic (anastomotic) varices.[17] Romero-Castro et al extended this experience to a case series of 4 patients (2 with active bleeding), and delivered stainless steel coils (MReye; IMWCE, Cook, Limerick, Ireland) into the perforating feeding vein of GV, with the aim of forming a mesh to block the flow of blood. The authors used combined fluoroscopy and EUS guidance to deliver the 0.035-inch diameter, 50–150-mm long coils through a 19G FNA needle (Echotip; Cook Medical). The GV were eradicated in 3 of the 4 patients. No migration or complications were observed in these 3 patients on follow-up at a mean of 5 months.[18]

Binmoeller et al recently reported the feasibility and outcomes of EUS-guided therapy with combined coil and cyanoacrylate glue for the treatment of bleeding GV, in a large series of patients.[19] They treated 30 patients with active or recent bleeding from GV and were treated by using either a prototype forward-view curved linear array (FV-CLA) echoendoscope (GIF-XUCT160J-AL5; Olympus Corp) or a therapeutic curvilinear array echoendoscope (GF-UCT140; Olympus Corp). The gastric fundus was filled with water to improve acoustic coupling. The echoendoscope was positioned in the distal esophagus, and gastric fundus was visualized in an anterograde fashion,

across the diaphragmatic crus. The gastric varix was then punctured in a transesophageal, transcrural approach, with a 19 G FNA needle (Echotip; Cook Medical). Any intervening esophageal varices were avoided by using Doppler. The embolization coil (12–20-mm diameter, MReye Embolization Coil; Cook Medical) was delivered into the varix through the FNA needle by using the stylet as a pusher. This was followed by immediate injection of 1 mL of 2-octyl-cyanoacrylate (Dermabond; Johnson & Johnson) through the same needle over 30 s by using normal saline solution to flush the glue through the catheter. Doppler was used to confirm the absence of flow in the varix after treatment. If persistent flow was identified, an additional 1.0 mL of glue was delivered. If the varix had persistent flow and appeared large enough to accommodate another coil, the varix was re-punctured with a new FNA needle, and the technique was repeated.

The procedure was successful in all patients (100%). Immediate hemostasis was achieved in patients with active bleeding. In 93% of patients, only a single injection was required. The authors hypothesized that the coils improved hemostasis, and reduced the risk of glue embolization by acting as a scaffold to retain the glue. Of 24 patients with follow-up endoscopy, 23 (95.8%) had complete GV obliteration after a single treatment session, with no intra-variceal flow on EUS Doppler imaging.

2-octyl-cyanoacrylate which was used in this study has a longer polymerization time, as compared with *N*-butyl-cyanoacrylate. The former glue therefore has the advantages of eliminating the need to dilute it with lipiodol (which is viscous), making injection through the long FNA needle easier. In addition, there was no premature clogging of the FNA needles or damage to the echoendoscopes related to the glue injections. 2-octyl-cyanoacrylate is not available in India. Lipiodol may be mixed in *N*-butyl cyanoacrylate, but we feel it may make the mixture more viscous and difficult to inject. We usually use lipiodol to flush the injection needle to retard glue sticking to the needle during injection.

What are the advantages of transesophageal EUS-guided treatment of GV? The echoendoscope is in a straight position in the esophagus, eliminating difficulties of instrumental access and manipulation associated with retroflexion in the stomach. The sonographic view is not hindered by gastric contents, such as blood and food, which tend to accumulate in the fundus. There is no disruption of the gastric mucosa overlying the varix, which is usually thinned and at high-risk of bleeding after varix puncture. Lastly, EUS guidance also enables accurate targeting of the varix lumen with avoidance of intervening vessels and intramural injections.

However, despite the abovementioned advantages, clinical experience with EUS-guided glue injection is still preliminary. This should not be a first-line procedure for the treatment of GV, but should be reserved for refractory bleeding from GV, or in special circumstances when endoscopic access to the gastric fundus is hindered by accumulated food or blood.

In the preliminary reports, EUS-guided therapy of GV seems to be a safe procedure. However, larger, multicenter, and preferably controlled studies are needed. In the future, collaboration with the interventional radiologist in the endoscopy suite may be routine for such multidisciplinary procedures. Refinement of the devices and accessories may allow the application of EUS-guided GV therapy emergently, and in the intensive care unit settings.

CONFLICTS OF INTEREST

All authors have none to declare.

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