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REVIEW

Update on the management of gastric varices

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Abstract

Gastro-oesophageal varices are the major clinical manifestations of cirrhosis and portal hypertension. Although less frequent than oesophageal varices (EV), bleeding from gastric varices (GV) is generally more severe and associated with higher mortality and a greater risk to rebleed. According to Sarin's classification, GVs are categorized into four types based on their location within the stomach and relationship with EV. Currently, treatment options for the management of GV include beta-blockers, endoscopic band ligation, endoscopic cyanoacrylate injection, EUS-guided coil/cyanoacrylate injection, transjugular intrahepatic portosystemic shunts and balloon-occluded retrograde transvenous obliteration. The best treatment strategy of GV remains controversial because of the heterogeneity of GV, lack of high-quality data and suboptimal trial design of the studies available. The proper treatment algorithm may require adequate endoscopic and imaging evaluation by a multidisciplinary team with multiple treatment options available. This review describes the hemodynamic features of GV, pharmacological, endoscopic and interventional radiological treatment options for GV.

KEYWORDS
balloon-occluded retrograde transvenous obliteration, gastric varices, portal hypertension, transjugular intrahepatic portosystemic shunt

1 | INTRODUCTION

In the course of cirrhosis, portal hypertension causes a vast variety of spontaneous portosystemic collaterals of which gastro-oesophageal varices are the most significant.[1] With disease progression and exacerbation of portal pressure, the collaterals enlarge and eventually rupture causing variceal bleeding. Despite improved clinical management, variceal bleeding is still a major

Abbreviations: BRTO, balloon-occluded retrograde transvenous obliteration; CT, computed tomography; EBL, endoscopic band ligation; EUS, endoscopic ultrasound; EV, oesophageal varices; GOV1, gastro-oesophageal varices type 1; GOV2, gastro-oesophageal varices type 2; GV, gastric varices; HE, hepatic encephalopathy.; IGV1, isolated gastric varices type 1; IGV2, isolated gastric varices type 2; IPV, left inferior phrenic vein; MRI, magnetic resonance imaging; NSBB, non-selective beta blocker; pTIPS, pre-emptive transjugular intrahepatic portosystemic shunt; RCT, randomized controlled trial.

complication of portal hypertension and a leading cause of mortality in cirrhotic patients.

Gastric varices (GV) are found in about 20% of patients with cirrhosis.[1] According to the Sarin classification, GV can be categorized into four types based on their location within the stomach and relationship with oesophageal varices (EV).[2] Gastro-oesophageal varices type 1 (GOV1) are a continuation of EV into the lesser curvature of the stomach. Gastro-oesophageal varices type 2 (GOV2) represents a continuation of EV into the fundus of the stomach. Isolated gastric varices type 1 (IGV1) are those located in the fundus of the stomach and isolated gastric varices type 2 (IGV2) refers to GV located anywhere in the stomach (Figure 1). In 1992, Sarin et al reported that GOV1 represents 75%, GOV2 21%, IGV1 less than 2% and IGV2 4% of all GV.[2]

As a general consideration, GV tend to bleed less frequently than EV; however, rupture of GV is associated with more severe haemorrhage, higher mortality and a greater risk of rebleed after spontaneous haemostasis.[1,3,4] This review will focus mainly on GOV2/IGV1 called thereafter GV, as GOV1 shares a similar vascular anatomy with EV and should be managed equally to EV.

2 | HAEMODYNAMIC FEATURES OF GV

Understanding the vascular anatomy of the draining routes of GV is vital to guide therapy. GV generally drains into the systemic veins via the oesophageal and paraoesophageal varices (gastro-oesophageal venous system), the left inferior phrenic vein (IPV) (gastrophrenic venous system), or both (Figure 2).[5] The left IPV could terminate inferiorly into the left renal vein (gastrorenal shunt), transversely into the left hepatic vein or inferior vena cava (gastrocaval shunt) or ascendingly into pericardiophrenic vein. Accordingly, GOV1 drains via the gastro-oesophageal venous system, IGV1 drains via the gastrophrenic venous system and GOV2 drains via both routes.

Portosystemic collateral flow may increase at the expense of reduced portal venous flow in patients with GV. Blood from the superior mesenteric vein may flow away from the portal vein because of the high resistance and, therefore patients with large GV usually have a lower portal pressure than those with EV and unlike EV, patients with GV may bleed at low portal pressure (HVPG below 12 mmHg).[6] Location has been associated with the risk of GV bleeding. The 2-year incidence of variceal bleeding from GV (78% for IGV1 and 55% for GOV2) is significantly higher than GOV1 (11.8%) and IGV2 (9%).[2] Besides, size (>5 mm), presence of red colour signs and poor liver function are independent predictors of GV bleeding.[7,8]

3 | PRIMARY PROPHYLAXIS

There is a paucity of studies regarding the primary prophylaxis of GV bleeding and, therefore evidence is less robust than EV. Only one randomized controlled trial (RCT) by Mishra et al compared the effectiveness of cyanoacrylate injection, non-selective beta blocker (NSBB) and no treatment in patients who had never bled from GV.[8] Eighty-nine patients with GOV2 (eradicated EV) or IGV1 larger than 10 mm were included and allocated to receive endoscopic cyanoacrylate injection or NSBB or no-treatment. Although cyanoacrylate injection had a lower bleeding rate when compared with NSBB or no-treatment, none of the therapies improved survival compared with no-treatment over a median follow-up time of 26 months. Based on this data (small sample, single-centre trial) cyanoacrylate cannot be recommended and further studies are required to evaluate the risk/benefit ratio of cyanoacrylate injection and other treatment options for primary prophylaxis.

Endoscopic ultrasound (EUS)-guided combination of coil and cyanoacrylate injection has also been evaluated in primary prophylaxis of GV in two non-controlled studies. Bhat et al analysed 40 patients with high-risk GV (defined by GV size, red wall mark and poor liver function), and found that only 5% treated GV bled at a

Key points

- Evidence available in the clinical scenario of gastric varices is limited.
- The vascular anatomy of the draining routes of gastric varices is vital to guide therapy.
- BRTO offers a unique opportunity to directly visualize and obliterate gastric varices.

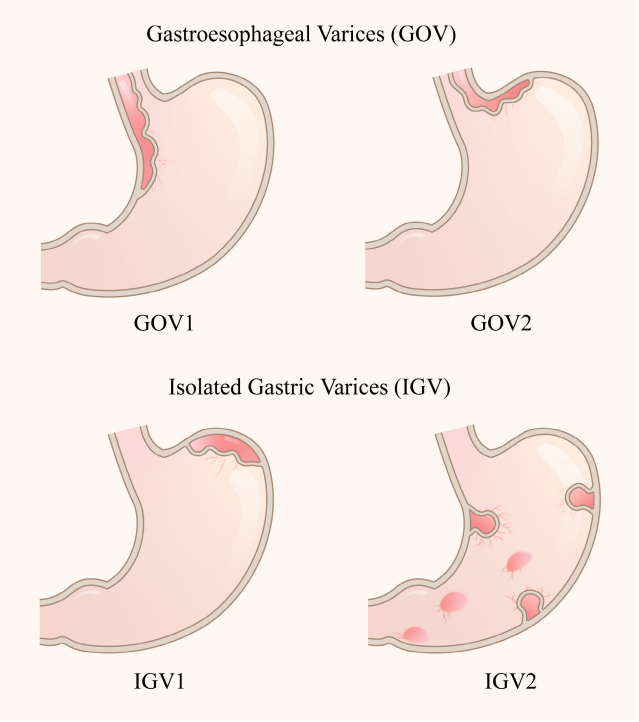

FIGURE 1 Endoscopic classification system for GV

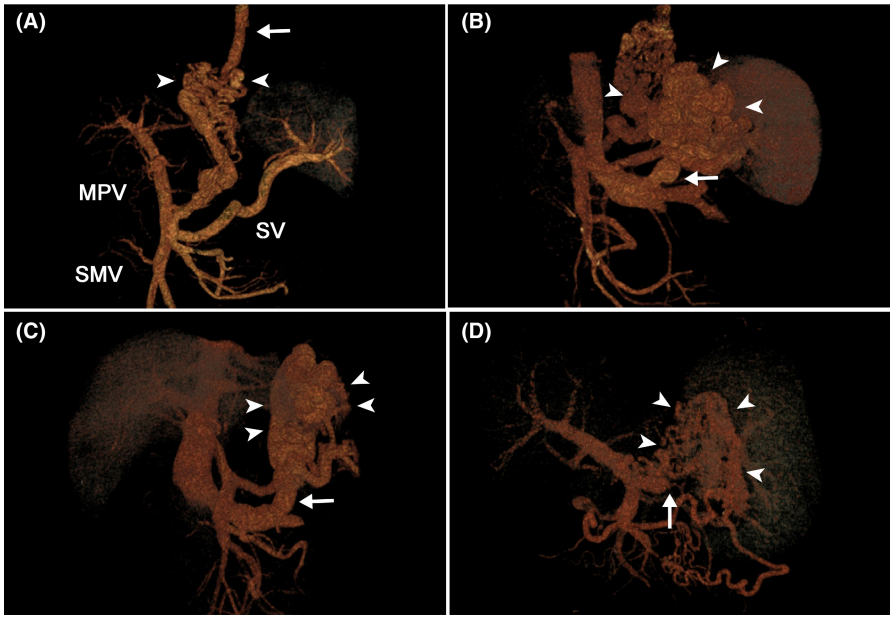

FIGURE 2 Construction of computed tomography scan in patients with four types of gastric varices (GV) according to Sarin classification. (A) Gastro-oesophageal varices type 1 (arrowhead) runs along the lesser curvature and drains into the oesophageal varices (arrow). (B) Gastro-oesophageal varices type 2 (arrowhead) draining through both oesophageal varices and a gastrorenal shunt (arrow). (C) Large isolated gastric varices type 1 (arrowhead) draining through a gastrorenal shunt (arrow) into the left renal vein. (D) 3D reconstruction image shows isolated gastric varices type 2 (arrowhead) caused by splenic vein occlusion (arrows). The GV developed at the collateral pathway between the short gastric vein and the left gastric vein

median follow-up of 449 days.[9] Similarly, an observational study enrolling 80 patients with high-risk GV (GV size >10 mm or red spot) reported low bleeding incidence of 2.5% and adverse events rate of 4.9% during a mean follow-up of 3 years.[10] Despite this encouraging data no control group were evaluated in none of the studies and results should be taken cautiously.

Direct obliteration of GV with balloon-occluded retrograde transvenous obliteration (BRTO) has also been evaluated in primary prophylaxis. A retrospective study compared BRTO, cyanoacrylate and no-treatment in 210 patients with cirrhosis and GV.[11] Both BRTO and cyanoacrylate were superior to no-treatment in preventing GV bleeding, however, there were no differences between them (BRTO 7.3% vs cyanoacrylate 19.4%, P = 0.089). Neither BRTO nor cyanoacrylate was superior to no-treatment when survival was evaluated and, therefore more studies are needed before its wide recommendation.

High-risk GV which may need treatment was considered if GV size ≥5 mm, red spots or Child-Pugh class B or C in Asian Pacific Association for the Study of the Liver consensus recommendation, or redness or severe liver dysfunction in Korean Association for the Study of the Liver clinical practice guidelines. Nevertheless, the definition of high-risk needs unification and validation, as well as different treatment options needs to be compared in well-designed trials. Taking into account, all the evidence available so far, we recommend NSBB as the primary approach, as this is the least invasive treatment and has additional beneficial effects in preventing decompensation of cirrhosis.[1,12-14]

4 | MANAGEMENT OF ACUTE GASTRIC VARICEAL HAEMORRHAGE

4.1 | General management

General management of patients with acute variceal bleeding from GV does not differ from EV. Patients should be managed in (semi) intensive care units. It is critical to protect the cardio-circulatory status and protect the airway of the patient. Volume restitution, administration of prophylactic antibiotics, vasoactive drugs and caution blood transfusion with a restrictive transfusion policy should be initiated as soon as possible.[1,13,15] Vasoactive drugs should be started promptly and maintained after endoscopic therapy for 3–5 days. There is no significant difference on haemostatic effects and safety among terlipressin, somatostatin and octreotide.[16] Patients should undergo abdominal imaging to evaluate the patency of portal venous system, screen liver cancer and analyse porto-collateral circulation in order to guide the following treatment. In authors' opinion, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) are the preferred techniques to use once the patient is hemodynamically stable.

4.2 | Endoscopic techniques

Endoscopic examination and therapy should be performed within 12 hours of admission with the main aim of achieving haemostasis.[1]

Cyanoacrylate injection is the globally accepted intervention to control acute bleeding from GV as most cohort studies have reported satisfactory haemostasis rates (>90%).[13,17,18]

Small-sample RCT comparing cyanoacrylate injection (n = 31) with endoscopic band ligation (EBL) (n = 29) has proven that cyanoacrylate injection is more efficient than EBL in controlling acute bleeding and preventing rebleeding.[19] Cyanoacrylate injection requires specific training to minimize complications such as postinjection ulcer, rebleeding because of glue extrusion, gastric ulcer, sepsis and ectopic embolism (Figure S1A and S1B).[18,20,21] A protocol for correct use of cyanoacrylate injection is provided in the Table S1. As sclerotherapy and EBL have also shown efficacy in controlling acute bleeding, even if cyanoacrylate is the recommended option, election of the technique should be used based on the local expertise and resources available with the final aim of stopping the bleeding.

EUS-guided coil and cyanoacrylate injection have been appointed as a safer strategy able to reduce the risk of procedure-related complications, mainly embolism, however, data are limited although it is questionable the real utility of EUS endoscopy under the circumstance of acute bleeding.[9,22]

Besides cyanoacrylate, thrombin injection for the endoscopic management of acute GV haemorrhage has received increasing attention. Thrombin acts as a haemostatic agent by promoting fibrin clot formation and platelet aggregation. One of the advantages of thrombin injection is that post-procedure ulcer at the puncture site is rare.[23] Gillespie et al. reported an initial haemostasis rate of 93.8% and a 30-day rebleeding rate of 29% for management of acute GV bleeding.[24] A recent RCT comparing cyanoacrylate injection (35 patients) with thrombin injection (33 patients) for the control of acute GV haemorrhage found that both techniques present proximate rates of initial haemostasis (90% vs 90.9%), treatment failure (6.1% vs 5.7%) and mortality at 6 weeks (3.0% vs 2.9%).[25] By contrast, thrombin injection had a significantly lower incidence of complications (12.1% vs 51.4%) and can be considered when available.[25]

4.3 | Transjugular intrahepatic portosystemic shunt

In patients with EV, once the acute bleeding episode is controlled, guidelines recommend the use of early or pre-emptive TIPS (pTIPS) in patients with a high risk of failure and/or rebleeding.[13]

The first study evaluating the role of pTIPS in the setting of variceal bleeding selected the high-risk population based on the haemodynamic criteria (hepatic venous pressure gradient [HVPG] >20 mmHg). As HVPG is not widely available in all centres, Garcia-Pagan and colleagues defined high risk based on clinical criteria, that is Child C < 14 or Child B plus active bleeding on initial endoscopy which have become the most accepted criteria.[26,27] It should be noted that pTIPS was performed within 72 h (ideally <24 h) after bleeding control. A few patients with GOV1 and GOV2 were included in the studies evaluating pTIPS but no specific data in the subpopulation of patients with GV are available. Currently, two RCT evaluating the role of pTIPS in GOV2/IGV1 are being conducted (NCT02364297 & NCT03705078). Although it is reasonable to adopt pTIPS strategy for high-risk patients with acute GV bleeding, more data are needed before formally recommending its use.

4.4 | Salvage treatment

Salvage TIPS is the treatment of choice in patients with failure to control GV bleeding.[28,29] Salvage TIPS is equally effective in the immediate control of GV bleeding compared with EV bleeding.[29] The initial haemostasis of TIPS for acute GV bleeding is between 87% and 100%.[29-31] Combination of TIPS with embolization (Figure S2A and S2B) has been proposed to further reduce the rebleeding risk compared with TIPS alone.[32]

In massive uncontrolled bleeding with hemodynamic instability, balloon tamponade should be used as a temporary 'bridge' until more definitive treatment is performed. Balloon tamponade should be only sustained for a maximum of 24 h. Haemostasis can be achieved in 90% of the patients although about 50% of the patients rebleed when the balloon is deflated.[33,34] However, its efficacy in controlling the bleeding is shadowed by the high-rate serious complications such as oesophageal ulceration and aspiration pneumonia. A study demonstrated that Linton-Nachlas tube was more effective than Sengstaken-Blakemore tube in bleeding GV possibly because of its large volume gastric balloon (600 ml).[33]

5 | SECONDARY PROPHYLAXIS

5.1 | Endoscopic techniques and NSBB

EBL is well established and widely accepted for the management of EV.[13] However, ligation may be difficult or even impossible because of the large size of GV and thick overlying mucosa and complications such as severe ulcer bleeding are more frequent than in the setting of EV. Endoscopic cyanoacrylate injection is more effective than band ligation for the prevention of rebleeding from GV and it is the recommended endoscopic treatment for bleeding GV.[35]

Endoscopic injection sclerotherapy for GV is less effective than in EV. High blood flow through GV rapidly flushes away the injected sclerosants and therefore, large volume of the sclerosants is required, increasing the probability of causing adverse events. The rebleeding rates with sclerotherapy alone can be as high as 90%, of which around 50% bleeds are caused by injection site ulcerations and is difficult to control.[36] Therefore, sclerotherapy has been almost abandoned for the management of GV.

Mishra et al found that endoscopic cyanoacrylate injection (33 patients) is superior to NSBB (34 patients) in the prevention of rebleeding from GV, with a lower rebleeding rate and mortality rate during a median follow-up of 26 months.[37] In patients with EV, the addition of NSBB to endoscopic band ligation is the best approach for preventing variceal rebleeding.[13] Whether endoscopic

cyanoacrylate injection in combination with NSBB is superior to endoscopic treatment alone has been evaluated in two RCTs.[38,39] In an RCT by Huang and colleagues, 95 patients with cirrhosis and GV were randomized to repeated cyanoacrylate injection with or without propranolol after the haemodynamics were stable for at least 3 days.[38] The overall rebleeding and survival rates were not different between the two groups. In another trial, 121 patients with endoscopy-proven GV bleeding were randomly allocated to cyanoacrylate injection group or cyanoacrylate injection plus carvedilol group.[39] GV rebleeding rates were similar in cyanoacrylate injection group and cyanoacrylate injection plus carvedilol group. However, cyanoacrylate injection plus carvedilol was associated with less recurrent upper gastrointestinal bleeding. Based on the evidence available and because of the beneficial effects of NSBB in portal hypertension, the addition of NSBB to cyanoacrylate could be considered with the aim of decreasing rebleeding rate and/or mortality.

5.2 | EUS-guided therapy

Cyanoacrylate injection-related adverse events such as cerebral or pulmonary embolism, splenic infarction, haemorrhage from postinjection ulcers and damage to the endoscope cannot be neglected, particularly in patients with a large portosystemic shunt.[3,40-42] Several improvements of endoscopic technique, or in combination with interventional approach have been developed.

In 2007, Romero-Castro et al firstly reported EUS-guided cyanoacrylate injection in patients with GV, which successfully eradicated GV in five patients without recurrent bleeding or other adverse events during follow-up.[43] EUS guidance allows for real-time visualization of GV, precise targeting of GV and feeding vessels. The amount of cyanoacrylate needed for complete obliteration of GV could be minimized, which may, in turn, reduce associated complications. EUS is also a reliable tool to confirm the obliteration of GV after treatment. This novel technique has gained wide interest and became increasingly popular.

Bick et al. compared EUS-guided cyanoacrylate injection with direct endoscopic injection in a retrospective cohort of 104 patients with GV.[44] EUS-guided technique used a lower mean volume of cyanoacrylate (2.0 vs 3.3 ml) and injected a greater number of varices (1.6 vs 1.1) with comparable adverse events compared to direct endoscopic injection. Furthermore, GV rebleeding and non-GV-related gastrointestinal bleeding were less frequent in the EUS-guided group. EUS-guided coil application with or without following cyanoacrylate injection has also been proposed and evaluated. Romero-Castro et al. demonstrated that EUS-guided coil application could reduce endoscopy sessions and have fewer adverse events compared with direct injection.[22] Coil placement prior to the cyanoacrylate injection may theoretically accelerate immediate polymerization of the glue and reduce the risk of embolization, which function as a 'scaffold' to keep the cyanoacrylate within the varices and reduce the volume of glue needed for obliteration. Robles-Medranda et al. conducted an RCT comparing EUS-guided coil application plus cyanoacrylate injection (n = 30) and EUS-guided coil application alone (n = 30) in the management of GV.[45] The technical success rate was 100% in both groups, combined therapy has the superiority over coils alone in terms of rebleeding rate and reintervention rate (6.7% vs 40%; p = 0.01, odds ratio 0.27, 95 %CI 0.095–0.797).

While studies comparing EUS-guided technique and direct endoscopic injection suggest benefits with EUS guidance, much of the published reports are limited by retrospective design and small numbers of patients. A recent meta-analysis by Mohan et al. compared EUS-guided treatment with direct endoscopic cyanoacrylate injection using data from 23 studies (851 patients) and 28 studies (3467 patients) respectively.[46] In total, 28% of included patients had GOV1, 48% had GOV2 and 24% had IGV1. There was no difference in pooled treatment efficacy (94% vs. 91%), the pooled rate of recurrence (9% vs. 18%), the pooled rate of early rebleeding (7% vs 5%) or the pooled rate of late rebleeding (12% vs 17%) between EUS-guided treatment and direct endoscopic cyanoacrylate injection. The pooled rate of GV obliteration was significantly higher in the EUS-guided group (84% vs. 63%). Subgroup analysis of EUS-guided therapy revealed that coil placement followed by glue injection had significantly fewer incidences of recurrence when compared with coil placement or glue. However, EUS-guided therapy is complex, expensive and requires specific training, all factors that may limit its broad utility.

Although these data are promising, further large comparative studies are needed to clarify the role of EUS-guided therapy and the optimal embolization technique that has a significant impact on patient's outcomes.

5.3 | TIPS

TIPS is an effective therapy to decompress the portal venous system and prevent rebleeding in patients with cirrhosis and GV. Indeed, TIPS and BRTO are recommended as first-line therapies to prevent rebleeding in the AASLD guidelines.[1] Lo and colleagues compared the effectiveness and complications of TIPS and endoscopic cyanoacrylate injection in an RCT including 72 patients.[47] The TIPS group had a lower rebleeding rate (11% vs. 38%; p = 0.014; odds ratio 3.6, 95% CI 1.2 ± 11.1) and higher variceal obliteration rate than the cyanoacrylate injection group, however, the survival and complication were similar in both groups. GOV1 accounted for 50% of the patients, and rebleeding from GV occurred more frequently for GOV1 than for GOV2 in both groups. In a retrospective cohort analysis of 105 patients with cirrhosis and prior GV bleeding, rebleeding, short-term complication and survival were similar in TIPS and cyanoacrylate injection arm.[48] Nevertheless, there was a significantly higher frequency of long-term complications in the TIPS arm, mainly hepatic encephalopathy (HE). However, covered stents were only used in 29 (65.9%) patients in Procaccini NJ's study and none in the previous trial. Moreover, the coexistence of portosystemic shunt known to be associated with post-TIPS HE was not reported and, therefore these data should be interpreted cautiously.[49-52] Post-TIPS HE has been reported to be as high as 34.1% in patients with GV and coexisted portosystemic shunt.[49-52]

Similar to what has been observed in patients with EV, in the setting of secondary prophylaxis TIPS could reduce the risk of rebleeding from GV without survival benefit, and is associated with increased occurrence of HE and, therefore in our opinion its use should be recommended in an individualized manner.

The ideal post-TIPS pressure target in patients with GV has not been identified and a combination of TIPS plus GV embolization has been suggested with the aim of increasing TIPS efficacy. Our group retrospectively analysed 82 cirrhotic patients with GV treated with TIPS with and without adjunctive embolization.[49] GV embolization using coils was performed in 67.1% of patients. The 1- and 2-year variceal rebleeding rates were significantly lower in the TIPS plus embolization group (3.8% and 13.4% vs. 13.0% and 28.0% respectively). A very recent study found that there was a higher rate of GV eradication (92% vs. 47%, $p = .01$) and a trend towards a lower rate of GV rebleeding (0% vs 23%, P = .056) in TIPS plus transvenous obliteration arm compared with TIPS alone arm.[53]

GV embolization technique is another tricky issue worth discussing. Lakhoo J et al found that GV patency was as high as 61% despite TIPS decompression and variceal embolization using coils or plug.[54] This study suggests that coil or plug deployed in the proximal portion of afferent veins of GV maybe a suboptimal treatment for GV. It may be more reasonable to directly embolize the GV which is responsible for the bleeding. The embolization/obliteration method with durable eradication of varices, such as BRTO, may have a great potential in this scenario. Further studies including a larger number of patients with GV evaluating the addition of embolization to TIPS and the best embolization approach are required before making a firm recommendation.

5.4 | BRTO

BRTO was first introduced by Olson et al. in 1984, and then further established in Japan by Kanagawa et al. and has proven to be safe and effective in the setting of bleeding GV.[55,56] Once GV are confirmed on endoscopy, contrast-enhanced CT/MRI is mandatory to study the vascular tree and eventually evaluating and plan the BRTO procedure. Imaging evaluation should be intented to identify feasibility (a portosystemic shunt is needed to perform the procedure) and discard contraindications (severe portal vein thrombosis). Although very popular in Asia, the use of BRTO is less used than TIPS worldwide. As it happens, it comes with a learning curve and is not available everywhere. With the increase in evidence, it is becoming more acceptable and it can be predicted that access to BRTO will improve in the near future.

BRTO procedure is performed via either transjugular or transfemoral approach.[57] Balloon size is determined based on the narrowest point of the outflow of the shunt close to the renal vein. After inflation of the balloon, a retrograde venogram is generally recommended to evaluate the draining veins, GV and feeding veins. However, it should be performed gently to avoid intimal damage to the vessels. The balloon could be pulled back or advanced in the shunt to halt the blood outflow completely.

Several classifications of GV have been proposed, Saad modification of the Kiyosue efferent classification may be the most practical method to guide BRTO procedure.[58] Type-A: GV is drained by the gastrorenal shunt solely. Mixed sclerosant are directly injected into the GV via the inflated balloon (Figure S3A). Type-B: GV is drained by the gastrorenal shunt and other small draining veins including inferior phrenic veins, intercostal veins, adrenal veins et al. Pure sclerosant could be injected into these small collaterals firstly, then satisfactory filling of GV could be achieved (Figure S3B and S3C). Type-C: GV is drained by the gastrorenal shunt and other large draining veins including inferior phrenic veins, a second gastrorenal outflow, pericardiophrenic vein et al. Embolization of these collaterals should be performed to avoid sclerosant spillage into the systemic circulation (Figure S3D and S3E). Utilization of a second balloon to occlude the outflow is also feasible in selected cases. Type D: GV is drained by other veins such as inferior phrenic veins without the presence of a gastrorenal shunt. The feasibility of BRTO depends on whether the efferent veins are accessible or not (Figure S3F).

The concerns about the complication of sclerosing agents and without access to the antidote may also limit the application of BRTO. Ethanolamine oleate and 3% sodium tetradecyl sulphate may cause haemolysis, haemoglobinuria, pulmonary oedema, renal dysfunction, allergy and acute respiratory distress.[59] Complications related to polidocanol are generally minor, especially used in foam form.[60] Recently, foam sclerotherapy has been proposed to reduce the amount of sclerosing agent and improve the efficacy.[57,61] Compared with liquid sclerosant, foam sclerosant could increase the contact surface with the vascular wall to the greatest extent and minimize the dose of the sclerosant.[57] Modified BRTO procedure using permanent vascular plugs or coils to replace the indwelling balloon may decrease the procedure time and hospital resource.[62,63]

A meta-analysis of 1,016 patients from 24 studies has demonstrated that BRTO is a safe and effective treatment for GV with a high rate of technical (96.4%) and clinical success (97.3%).[64] GV rebleeding rate is generally considered to be under 10% and as low as 2.7%.[65] Recurrence of GV is rare, possibly because the injected sclerosing agent could destroy venous endothelium completely and lead to permanent eradication. Comparison of BRTO with endoscopic cyanoacrylate injection has also been evaluated.[66-69] In one study evaluating 27 patients with GV bleeding or high-risk GV (size ≥5 mm, red spot and Child B-C cirrhosis) treated with BRTO or cyanoacrylate injection, endoscopic cyanoacrylate injection was associated with a higher rebleeding rate (71.4% vs. 15.4%), although the proportion of active bleeding was also higher in the cyanoacrylate injection group.[66] A retrospective study by Stein et al. assessed the efficacy of cyanoacrylate injection ($n = 90$) and BRTO ($n = 71$) for the prevention of GV rebleeding.[69] A significantly higher 1-year rebleeding rate was observed in the cyanoacrylate injection group (22.0% vs. 3.5%). 28.2% of the patients in the BRTO group and 38.9% of the patients in the cyanoacrylate injection group experienced a new portal hypertensive complication in the year after the procedure. Our recently published study is the first RCT comparing endoscopic cyanoacrylate injection and BRTO in patients with cirrhosis who recovered

TABLE 1 Advantages and disadvantages of TIPS and BRTO

	TIPS	BRTO
Technical	Stent placement by passing the liver and connecting portal and systemic territory	Occlusion of portosystemic shunt using sclerosing agents
Advantages	• Reduce portal hypertension and other PH-related complications (ascites, EV…) • Can be used in patients with portal vein thrombosis	• Increase portal vein flow and may improve liver function • Does not increase HE
Disadvantages	• May induce hepatic failure and aggravate cardiac myopathy • Increase risk of postprocedure HE	• Increase portal hypertension and may aggravate EV and ascites • Cannot be performed in cases of portal vein thrombosis

Abbreviations: BRTO, balloon-occluded retrograde transvenous obliteration; EV, oesophageal varices; HE, hepatic encephalopathy; PH, portal hypertension; TIPS, transjugular intrahepatic portosystemic shunt.

from bleeding from GV.[70] BRTO was superior to cyanoacrylate injection with a lower all-cause rebleeding rate at 1 and 2 years (77% vs. 96.3% and 65.2% vs. 92.6%, respectively, $p = 0.004$) and fewer hospitalizations, inpatient stay and lower medical costs. The survival and frequency of complications including worsening of EV and ascites were similar in both groups.

While TIPS is associated with an increased risk of HE, BRTO is considered a more attractive alternative treatment option. Current studies comparing TIPS and BRTO are also limited by mixed treatment indication (with or without previous bleeding history), heterogeneous distribution of patients among groups and lack of high-quality prospective studies.[71-73] In a recent meta-analysis, there were no significant differences in technical success rate, haemostasis rate and procedure-related complication, but BRTO was associated with lower rates of postoperative rebleeding, postoperative HE and mortality at 1 year.[74] The advantages and disadvantages of these two interventional techniques are summarized in the Table 1.

Aggravation of EV and ascites appears to be a major concern and reflects increased portal hypertension following BRTO.[75,76] Improved follow-up strategy, prophylactic ligation or in combination of NSBB may reduce the occurrence of the EV and the risk of bleeding.

BRTO offers a unique opportunity to directly visualize and obliterate GV, hence it should be considered in patients with GV and portosystemic shunt.

6 | MANAGEMENT OF IGV2

The mechanism of development of IGV2 is poorly understood. IGV2 is frequently caused by dilation of the gastroepiploic veins or pancreatico-duodenal veins when there is obstruction to the splenic or portal blood flow.[3,77] Regional portal hypertension (RPH) resulting from splenic vein stenosis/occlusion could lead to the formation of IGV2 and the portal axis should always be carefully evaluated in these patients to understand the haemodynamics of IGV2 and guide the following treatment. NSBB is the treatment option in patients with asymptomatic RPH. When bleeding occurs, endoscopic therapy including sclerotherapy, EBL and cyanoacrylate injection should be performed to control acute bleeding.

Surgical correction of the primary cause in combination with splenectomy should be considered after controlling the bleeding episode.[78]

7 | CONCLUSION

The evidence available in the clinical scenario of GV is still limited and hampers strong evidence-based recommendations. A careful anatomical evaluation should be performed to guide therapy. Election of the technique uses should be taken based on resources and local expertise. The treatment of GV is quite difficult and complex, and needs proper endoscopic and imaging evaluation by a multidisciplinary team with multiple treatment options available. Large studies are required to assess the recent emerging endoscopic and endovascular approaches with or without NSBB.

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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SUPPORTING INFORMATION

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