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Endoscopic Management of Bleeding Gastric Varices—an Updated Overview

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Abstract Gastric varices (GVs) are known to bleed massively and often difficult to manage with conventional techniques. This article aims to overview the endoscopic methods for the management of acute gastric variceal bleeding, especially the advantages and limits of GV obliteration with tissue adhesives, by comparison with band ligation and other direct endoscopic techniques of approach. The results of indirect radiological and surgical techniques of GV treatment are shortly discussed. A special attention is payed to the emerging role of endoscopic ultrasound in the therapy of bleeding GV, in the confirmation of its eradication and in follow-up strategies.

Keywords Gastric varices · Upper gastrointestinal bleeding · Tissue adhesives · Band ligation

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Introduction

Variceal haemorrhage is responsible for up to 10 % of upper gastrointestinal bleedings [1]. Among patients with cirrhosis, mortality due to bleeding from varices reaches 10–30 % [2, 3]. Gastric varices (GVs) may be seen in 18–70 % of the patients with portal hypertension (PHT), and they are the probable source of bleeding in 10–36 % of patients with acute variceal bleeding [1–3]. Gastric varices developed in the absence of oesophageal varices (EVs) are seen in 5–12 % of patients with PHT [1–3]. Gastric varices bleed less frequently than EV, but the haemorrhage is massive and difficult to arrest, with a mortality rate of 10–30 % [4, 5]. The chance of rebleeding is high (35 to 90 %) after spontaneous remission [4, 5].

The prognosis of GV is poorer, as they are associated with more severe blood loss, a higher rebleeding rate and, consequently, a higher mortality rate [6]. The best treatment for acute bleeding from GV is still under evaluation. One of the alternatives of endoscopic treatment is the injection of sclerosing agents or, more recently, tissue adhesives such as *N*-butyl-2-cyanoacrylate (GVO), which appears to have a higher success rate than other sclerosing substances. The other therapeutic options would be gastric variceal band ligation (GVL), which is considered as the optimal endoscopic treatment in case of EV haemorrhage, but the efficacy of band ligation in bleeding gastric varices is still uncertain. On the other hand, both methods involve complications and/or technical difficulties, which have to be considered carefully when making a therapeutic decision. There are few studies comparing band ligation with tissue adhesives, and the results seem to be in favour of GVO [7, 8].

The classification of gastric varices is based on the criteria elaborated by Sarin et al. [5]: gastroesophageal varices (GOVs) are associated with oesophageal varices along the lesser curve (type 1, GOV1) or along the fundus (type 2, GOV2). Isolated gastric varices (IGVs) are divided into two

types: those found isolated in the fundus (IGV1), which usually arise from spleno- or gastro-renal shunts where the feeding vessel arises from the splenic hilum and drains into the left renal vein through gastric cardia/fundus veins. GOV2 and IGV1 are sometimes called together as *fundic varices*. The second type of isolated gastric varices has ectopic sites in the stomach or in the first part of the duodenum (IGV2). They drain in a similar fashion with IGV1 into the left renal vein. It has been observed that fundal varices (GOV2 and IGV1), though less common than GOV1 varices, are noted to account for 80 % of patients with bleeding GV.

Hashizume et al. [9] proposed an alternate classification of GV based on endoscopic findings, taking into account their shape (tortuous, nodular and tumorous), location (anterior, posterior, lesser or greater curvature of the cardia and fundic area) and color (white or red) and further emphasized on the presence of glossy, thin-walled focal redness on the varix called as red color spot as a marker of impending bleeding risk.

Risk Factors for Bleeding

The chance of variceal bleeding is influenced by the pressure changes rather than haemostatic forces. The pressures in the GV are lower than those in the EV because of their larger size and more frequent presence of the shunts like spleno-renal [10]. Despite this, their rupture is more devastating because the wall stress increases dramatically even with small rise in the portal pressures due to their larger radius. When there is increase in transmural pressure, the variceal size increases and wall thickness decreases, which leads to rupture [10].

Risk factors for gastric variceal bleeding include variceal size (large, medium and small defined as >10, 5–10 and <5 mm, respectively), advanced Child's grade of cirrhosis, decompensated cirrhosis, presence of hepatocellular carcinoma, location of gastric varices and presence of red spots [5, 11]. Another factor implicated in the development of fundic varices and their possible bleeding is the treatment of EV by either endoscopic variceal ligation or endoscopic sclerotherapy [12].

Treatment of Acute Bleeding

Initial Management—General Principles

Variceal haemorrhage should be suspected when a patient with known cirrhosis or evidence of portal hypertension presents with upper gastrointestinal haemorrhage. As bleeding is determined by high portal pressure, it is evident that minimizing portal pressure is one of the objectives in managing these patients, but maintaining the volemic equilibrium and a stable haemodynamic status has at least the same importance without overaggressive volume resuscitation. Volume restitution should be commenced immediately with blood transfusion as necessary, targeting a haemoglobin level of 7–8 g/dL [3, 13]. In Child's grade A or B cirrhotic patients with oesophageal or gastric variceal bleeding, transfusing below a threshold of 7 g/dL reduces rebleeding, the need for rescue therapy and mortality [13].

The administration of frozen plasma in aiming the normalization of international normalized ratio (INR) is no longer recommended.

Prophylactic antibiotics should be administered early to patients with suspected or confirmed variceal bleeding as this has been shown to reduce mortality and risk of infection and complications [14, 15]. Oral quinolones or the third class cephalosporin is often recommended [3].

Vasoactive drugs should be started as soon as possible if variceal bleeding is suspected [1, 3]. The study of pharmacologic treatment (including terlipressin, somatostatin or octreotide) compared to sclerotherapy for variceal bleeding showed that vasoactive drugs are beneficial as first-line treatment [16]. To date, no studies have investigated the use of vasoactive drugs specifically for gastric variceal bleeding.

Early endoscopy should be performed to confirm the diagnosis and to apply the adequate endoscopic therapy. If bleeding cannot be managed despite the proper use of pharmacologic and endoscopic therapies, the temporary use of an intragastric balloon such as the Sengstaken-Blackmore tube to tamponade fundal varices may be helpful. This is often used as a bridge to a more definitive therapy including the placement of a transjugular intrahepatic portosystemic shunt (TIPS) [1, 17].

Endoscopic Therapies

Endoscopic treatment for gastric variceal bleeding includes endoscopic band ligation, sclerotherapy and endoscopic obliteration by injection of tissue adhesives or thrombin.

Gastric Variceal Band Ligation

Variceal band ligation has already taken the first place in the treatment and prevention of oesophageal variceal bleeding and rebleeding. This technique can also be performed in bleeding GV, since banding in both retroflexed and non-retroflexed positions can be performed. Band ligation in gastric pathology is indicated in actively bleeding varices. Most of the studies reported four bands as being sufficient to be applied in one session [7].

Regarding the efficacy of band ligation in GV, in a prospective randomised trial by Tan et al. [8], the arresting of active bleeding GV in cirrhotic patients was comparable to cyanoacrylate injection, but the rebleeding rate was higher in

the banding group with no difference in complications [8]. The rate of haemostasis using band ligation in acute haemorrhages has been reported to be 83–100 % [18, 19].

Band ligation is not included in the National Institute for Health and Care Excellence (NICE) guidelines for the management of gastric variceal bleeding. However, Baveno V and American Association for the Study of Liver Diseases (AASLD) guidelines suggest this type of treatment for the endoscopic management of bleeding GOV1, as these are generally considered extensions of oesophageal varices [1, 3].

AASLD guidelines also accept the EVL as an option for bleeding from gastric fundal varices if cyanoacrylate is not available [1]. Still, band ligation did not prove to be efficient for non-GOV1 gastric variceal bleeding.

For the band ligation, the most frequent complication is rebleeding from ulcers caused by ligation. In a study conducted in our department of endoscopy, this type of complication occurred in 14.28 % of patients, similar to the data reported in the literature.

Sclerotherapy

The therapy of bleeding GV with pure alcohol has a reported haemostatic rate of 66 % [20]. Gastric variceal sclerotherapy appears to be more effective in GOV1 than in GOV2 or IGV1. The complications associated with the procedure include fever, retrosternal and abdominal pain, dysphagia, ulceration and perforation. The recurrent bleeding rates are up to 53 % [20]. Similar to the management of bleeding EV, sclerotherapy has been largely replaced by band ligation when appropriate, due to the latter's lower complication and rebleeding rates.

Occlusion of Varices by Tissue Glues

Tissue adhesives include Histoacryl (*N*-butyl-cyanoacrylate) and bucrylate (isobutyl-2-cyanoacrylate), both of it proved to be efficient for GV obliteration. Cyanoacrylate is a monomer that develops rapid polymerization in contact with ionic substances including blood or tissue fluids. A standard endoscope with forward viewing is used, and the accessory channel and needle catheter are first flushed with Lipiodol. The intravariceal injections are usually performed on actively bleeding varices and/or those with stigmata of the bleeding. Each injection contains dilutions of cyanoacrylate and Lipiodol, a total dose of 1.0 mL cyanoacrylate given at a time being necessary for an effective therapy. Following the injection, the needle together with the scope is withdrawn, followed by a flush of saline or sterile water, the needle being cut without any risk of damage. After each procedure, the endoscopist checks for the effectiveness of the injections by gently touching the varices newly treated with cyanoacrylate with a blunt catheter. A hard fill is considered as a sign of an effectively obliterated vessel. Injections can be repeated until obliteration of the varices is achieved. Paik et al. [21] retrospectively analysed 121 patients with active or recent gastric variceal bleeding who were treated with *N*-butyl-2-cyanoacrylate. Bleeding control was achieved in 91 % of patients with a 4-week rebleeding rate of 13 %. Al-Ali et al. [22•] reported a haemostasis rate of 95 % in a Canadian population, and the same success rate in arresting variceal haemorrhage was reported by Cheng et al. [23]. There are studies that reported an immediate haemostasis rate of 100 % with Histoacryl injection in bleeding GV [24]. Current evidence of the use of tissue adhesives for gastric variceal bleeding suggests haemostasis control in >90 %.

A number of complications have been reported in association with cyanoacrylate injection. Common complications associated with GVO are pyrexia (11 %) and abdominal pain/discomfort. Severe complications after GVO are mostly associated with systemic thromboembolic phenomena such as cerebral, pulmonary (5 %, non-fatal), coronary, portal vein embolization and splenic infarction. Few cases of adrenal abscess were reported [24–27]. Another frequent complication in patients with bleeding GV is infection. It has been documented that 35–60 % of cirrhotic patients with variceal haemorrhage will develop bacterial infection [15]. In the study conducted in our unit, both GVO and GVL groups had an important prevalence of infection (21 and 16.6 %, respectively), with no significant difference between them. The similar rate of infection in both groups does not seem to be related to the procedure applied for bleeding, but rather to the haemorrhage itself.

There are some studies that observed the results after a combination between ligation and tissue adhesive injection (one to nine ligations plus 1 % polidocanol injected in the surrounding submucosa) [19, 28]. The control rate of acute bleeding in 18 patients studied was 100 %. This combination between ligation and obliteration is unlikely to be accepted for the management of acute bleeding because of the risk of iatrogenic complications, the need for greater technical skill and the increase in procedure time.

Considering that this two methods, GVO and GVL, are the most used and accepted for the treatment of variceal bleeding, we checked the data availability until now in this respect. The obliteration of GV proved to be superior to band ligation for acute bleeding GV, with higher initial haemostasis and lower rebleeding rates [7, 8]. As shown by Lo et al., on 26 patients with active bleeding and 34 with stigmata of recent haemorrhage, initial haemostasis was significantly better in the cyanoacrylate group (87 vs. 45 %) [7]. In most series, the initial haemostasis by cyanoacrylate is at least 90 % [8, 29–32]. The rebleeding rate of GVO is approximately 22–37 % [8, 29, 30] The GVO is more effective in achieving variceal obturation, with a higher initial haemostasis and less need for surgery than sclerotherapy [29]. A randomised controlled trial demonstrated higher cumulative survival rate of GVO compared to band

ligation [7]. In another important study in terms of the number of patients enrolled and a large proportion of patients with IGV1, haemostasis was achieved in over 90 % of patients, with both methods [8]. The authors attributed the better efficacy of GVL, as compared to the data reported in other studies, to a greater number of bands used (four to five vs. one to two bands). There was no difference in bleeding-related mortality in both mentioned trials. This study is important, as it is one of the largest controlled studies on patients with gastric variceal haemorrhage [8] and illustrates how a good technique can significantly influence the outcomes of haemostasis, particularly for GVL. On the other hand, the evidence for the use of GVL for acute bleeding is controversial. There were initially a number of case series showing that band ligation was safe and effective for acute bleeding GV [33, 34], but later randomised controlled trials demonstrated that band ligation had lower initial haemostasis and higher rebleeding rates [7, 8]. The rebleeding rate at the 2nd and 3rd years was 63 and 72 %, respectively, for patients undergoing band ligation [7]. As mentioned before, there is only one study showing the same efficacy for the two methods. In our department, a study aiming the comparison between the efficacy of GVO with cyanoacrylate and band ligation showed that the initial haemostasis was achieved in all patients treated with cyanoacrylate and in 88.88 % from the GVL group (p=0.43); rebleeding occurred in 72.22 % of the GVL group and in 31.57 % of the GVO patients (p=0.03). No difference was found in survival rates (p=0.75) [35]. A review of the data in the literature regarding the comparison of endoscopic outcomes and mortality related to the occlusion and ligation of bleeding GV is presented in Table 1.

Considering all these data, tissue adhesives appear to be relatively safe and effective in the management of bleeding gastric varices and are generally the endoscopic treatment of choice for bleeding from IGVs and GOV2. This method is recommended by the Baveno V, NICE and AASLD guidelines [1, 3, 19]. Although there are a few technical issues, appropriate training and use of a unit protocol enable most centers to use it safely and effectively.

New Agents

Thrombin contributes to haemostasis by converting fibrinogen to fibrin clot and also influences platelet aggregation [37]. For endoscopic arrest of bleeding GV, a standard gastroscope is used for with no specific preparation required. There are data that sustain a 100 % rate of haemostasis in bleeding GV when using bovine thrombin with no significant complications and a low rebleeding rate [38]. Other studies reported 92 % rate of haemostasis in acute bleeding, with no rebleeding in short follow-up [39]. No patient had adverse events, and no technical problems were encountered. More recent studies have used human rather than bovine thrombin because of the concerns of spongiform encephalopathy. The largest study to evaluate the efficacy of human thrombin in the management of gastric and ectopic varices bleeding suggests that human thrombin is safe and effective [39]. Thrombin is a promising therapy for bleeding GV, but there are no randomised data to date and no studies with significant follow-up.

Beriplast P consists of two components: fibrinogen with factor VIII and human thrombin. It has been initially used for haemostasis in oozing during intra-abdominal surgery. The procedure requires a double-lumen injector to mix the two contents simultaneously on the surface of bleeding tissue. There are two uncontrolled studies which have been reported to be showing the efficacy of Beriplast P in patients with gastric variceal bleeding [40, 41]. The results were satisfactory, but the number of patients included into the studies was small. Further studies on a significant number of patients are needed to confirm the utility of this method [42].

Role of Endoscopic Ultrasound

It is already known that endoscopic ultrasound (EUS) enables the visualization of oeso-gastric varices and other venous collaterals in patients with portal hypertension. Boustière et al. [43] tried to classify GV endosonographically, considering the size of GVs and gastric wall abnormalities. They concluded that compared to upper endoscopy who evaluates better the EV, EUS is a better tool to classify GV and early signs of portal gastropathy. The role of EUS in estimating the risk of bleeding GV is a field of growing interest. EUS probes can be used to measure the size of varices (diameter) and, furthermore, to estimate variceal wall thickness which is considered a better predictor of bleeding than varices diameter alone.

Intravariceal pressure measurement could be a better surrogate for risk of bleeding, but this is not largely practiced because of the high associated risk. Still, there has been an attempt to predict the risk of bleeding by measuring the EV pressure assisted by EUS which proved to have a reasonable correlation with hepatic venous pressure gradient (HVPG) [44]. Finally, EUS-assisted injection sclerotherapy for both GV and EV [45] is effective, achieving high eradication and low recurrence rates in long-term follow-up. In fact, the risk of rebleeding after EUS-assisted sclerotherapy seems to be lower than the use of endoscopic technique alone. Recently, additional attention has been paid to EUS-assisted therapies to control bleeding in acute variceal setting, using tissue adhesives (Histoacryl) [46], thrombin [47] and EUS-guided injection for gastric [48] and ectopic duodenal varices [49]. Another advantage of EUS could consist in confirmation of adequate occlusion of GV practiced instead of endoscope

Table 1 Outcomes of haemostasis, rebleeding and mortality after endoscopic treatment of GV bleeding (GVO and GVL), as reported in previous articles (adapted after Tantau et al. [35])

Authors	Treatment	Haemostasis (%)	Rebleeding (%)	Mortality (%)
Ramond et al. [18]	GVO	100	37	30
Feretis et al. [36]	GVO	96	4	17
Kind et al. [31]	GVO	97	15	20
Akahoshi et al. [32]	GVO	96	65	44
Sarin et al. [29]	GVO	84	22	19
Hou et al. [30]	GVO	90	29	7
et al. [19]	GVL	100	8	20
Cipolletta et al. [33]	GVL	94.2	10.2	7.7
Shiha and El-Sayed [34]	GVL	88.8	18.5	22.2
Lo et al. [7]	GVO/GVL	87/45	31/54	48/29
Tan et al. [8]	GVO/GVL	93/93	22/44	55/69
Tantau et al. [35]	GVO/GVL	100/88.8	31.5/72.2	10/11.1

GVO gastric variceal occlusion (using cyanoacrylate), *GVL* gastric variceal ligation

probing, increasing overall efficacy of this technique [50••]. There is a study conducted in Taiwan in which the authors used miniature ultrasound probe (MUP) sonography for cyanoacrylate injection in acute bleeding GV and for endoscopic follow-up. The authors demonstrated a significantly greater free-of-rebleeding rate and a trend towards better survival for patients in MUP group compared with conventional endoscopy group [50••]. Using a mini probe may counter the disadvantage of a conventional scope with large diameter. The non-availability of paediatric sizes is still a limitation. Furthermore, future studies are needed to compare radial and linear EUS scopes in the diagnosis and management of varices [51].

Indirect Techniques—Radiologic Therapies

Radiologic therapies for GV include TIPS and balloon-occluded retrograde transvenous obliteration (BRTO).

TIPS has been well studied in the management of EV, but fewer studies aimed its use in bleeding GV. TIPS might be a choice for salvage treatment in uncontrolled bleeding GV with pharmacologic and endoscopic treatment. An American retrospective study compared TIPS with cyanoacrylate injection for bleeding GV. No differences were found in survival or rebleeding, but the group treated with TIPS had an increased morbidity, requiring prolonged hospitalization because of encephalopathy [52].

TIPS can also be used if bleeding from GV is not controlled with *N*-butyl-cyanoacrylate injection; however, the portal vein must be patent and careful patient selection is required to minimize risks of encephalopathy [14, 53].

A randomised trial of cyanoacrylate injection vs. TIPS for gastric variceal bleeding showed similar survival and complication rates in both groups, but TIPS was more effective in preventing rebleeding (11 vs. 38 %) [54]. Cyanoacrylate was also compared to TIPS in another two (non-randomised) studies, again with similar haemostasis rates reported between both groups [52, 55].

BRTO is a radiologic technique used for the treatment of GV, in which the veins draining GV are embolised and a sclerosant agent is injected until all varices are obliterated. In a study comparing BRTO with an endoscopic occlusion of GV with cyanoacrylate in high-risk varices (≥5 mm with red spots and Child's grade B or C), the haemostasis and rebleeding rates were 76.9 and 15.4 % for BRTO compared to 100 and 71.4 % for cyanoacrylate, with similar rate of complications [56]. The percentage of rebleeding in the group treated with tissue adhesive is high compared to the other data reported in this domain, but the study included a higher proportion of patients with active bleeding than most of the studies. The complications were similar. These results suggest that BRTO may have a role as bleeding GV. Another small study compared BRTO with TIPS for the urgent treatment of active GV haemorrhage with no differences reported regarding immediate haemostasis, rebleeding or encephalopathy [57]. BRTO can be an alternative to TIPS for the management of acute bleeding GV if gastro-renal shunts are present. Recent guidelines (AASLD, NICE or Baveno V) did not specifically mentioned BRTO as a treatment for GV.

Surgery

The therapy of bleeding GV also involves surgical techniques which consist in total shunts, partial (lower diameter) shunts, selective shunts and devascularization procedures. These procedures are able to control and prevent variceal bleeding but do not improve survival and often precipitate encephalopathy.

The theme of our review aims to study the endoscopic procedures used for the treatment of bleeding GV, not a holistic approach of the haemorrhage with variceal origin.

It is generally considered as rescue therapy, due to the associated risks and the increasing use of simpler endoscopic and radiologic procedures as previously described. Liver transplantation should also be considered for eligible patients.

The Use of Endoscopy in Prevention of Rebleeding

Secondary prophylaxis includes the use of beta-blockers, endoscopic procedures, radiology and surgery techniques. We will focus briefly on the importance of endoscopy in the prevention of rebleeding GV.

Regarding the variceal banding, as previously described, it is generally used as secondary prophylaxis for GOV1 varices. Of the group including tissue adhesives, cyanoacrylate injection is significantly more effective than β-blocker treatment for the prevention of rebleeding from GV [58••] and has a lower rebleeding rate compared to band ligation in this situation [9]. On the other hand, when comparing the GVO with TIPS, the rebleeding rate is higher in the first group [8], even though both therapies have similar survival, and the complications rate is lower in the case of cyanoacrylate injection [8, 52, 55]. The rebleeding rate in a long-term follow-up after GVO with cyanoacrylate is 16–28 %. Current evidences on the use of tissue adhesives report rebleeding rates of 7–38 %, with relatively few complications [33, 34, 36]. Regarding the use of thrombin, it seems to be an effective and safe method to decrease rebleeding without the need for repeated injections to achieve eradication [38, 39]. More studies are needed on larger groups, performed in comparative manner to provide data for the use of thrombin injection in the prevention of rebleeding GV.

The use of TIPS in the prophylaxis of rebleeding is effective, although it is more invasive than endoscopic procedures, has the risk of encephalopathy and is not always available [7, 59, 60].

Radiological techniques like BRTO are used if TIPS is not possible, provided that there are gastro-renal shunts [61].

Conclusions

This short review aims to describe the endoscopic management of bleeding from GV. Endoscopic variceal obliteration with tissue adhesives is the currently accepted strategy for the control of bleeding and eradicating GV. To date, GVO proved to have better results than GVL and sclerotherapy in terms of immediate haemostasis and rebleeding. It is not clear if GVO should be performed only in case of rebleeding or as a routine procedure until the eradication of varices. The use of combined techniques has been studied on small groups of patients, and a conclusion is premature to be drawn. The Baveno V guidelines suggest the use of cyanoacrylate or TIPS for the prevention of rebleeding in patients with IGV1 and GOV2. The AASLD guidelines consider TIPS as a treatment in patients with recurrent bleeding from fundal varices despite pharmacological and endoscopic therapy. Emerging use of EUS is a promising procedure for the diagnosis, classification, accurate strategies of treatment and confirmatory method for eradication of GV.

Compliance with Ethics Guidelines

Conflict of Interest Dana Crisan, Marcel Tantau and Alina Tantau declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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