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EDITORIAL

New methods for the management of gastric varices

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Abstract

Bleeding from gastric varices has been successfully treated by endoscopic modalities. Once the bleeding from the gastric varices is stabilized, endoscopic treatment and/or interventional radiology should be performed to eradicate varices completely. Partial splenic artery embolization is a supplemental treatment to prolong the obliteration of the veins feeding and/or draining the varices. The overall incidence of bleeding from gastric varices is lower than that from esophageal varices. No studies to date have definitively characterized the causal factors behind bleeding from gastric varices. The initial episodes of bleeding from esophageal varices or gastric varices without prior treatment may be at least partly triggered by a violation of the mucosal barrier overlying varices. This is especially likely in the case of varices of the fundus. In view of the high rate of hemostasis achieved among bleeding gastric varices, treatment should be administered in selective cases. Among untreated cases, steps to prevent gastric mucosal injury confer very important protection against gastric variceal bleeding.

Key words: Gastric varices; Esophageal varices; Bleeding

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INTRODUCTION

Bleeding from esophageal varices (EVs) or gastric varices (GVs) is a catastrophic complication of chronic liver disease. Bleeding from GVs is generally thought to be more severe than bleeding from EVs[1], but it occurs less frequently[2-4]. Though many recent developments have improved the outcome of treatments for GVs, no consensus has been reached on the optimum treatment. In this paper we review the pathomorphology, hemodynamics, risk factors for bleeding, and treatments for GVs. In the esophagogastric varices grading system of the Japan Society for Portal Hypertension[5], the varices are evaluated based on color (white [Cw], and blue [Cb]), form (small and straight [F1], nodular [F2], and large or coiled [F3]), and the red color sign (RC0-3). GVs are divided into cardiac varices (Lg-c), fundal varices (Lg-f), and varices involved both the cardia and fundus (Lg-cf). In this review, GVs are divided into two categories and described accordingly: Lg-c (cardiac varices: CVs) and Lg-cf or Lg-f (fundal varices: FVs).

PATHOMORPHOLOGY OF GVs

Arakawa *et al*[6] reported that CVs are supplied by the left gastric vein (cardiac branch), a vessel which enters the stomach wall in the cardia at a point 2 to 3 cm from the esophagogastric junction and diverges into a profusion of branches running throughout the cardia. Some of these veins become markedly dilated, acquiring the features of varices. Most veins in the cardia diverge into parallel veins from the esophagogastric junction as the flow becomes hepatofugal. However, Others will dilate, wind through the submucosa, and directly join EVs. Histologically, nearly the entire cross-section of the wall is the varix itself. The varices are covered by thinning layers of serosa and mucosa through which they can ultimately be seen.

The angio-architecture of a FV is quite different from that of a CV. Most FVs are supplied by the short gastric vein, though in some cases the blood is fed from the posterior or left gastric vein. Thus, the vascular anatomy of a FV is something like a splenorenal shunt running through the stomach wall. Bleeding from an EV most commonly occurs in the "critical area" 3 cm proximal to the esophagocardiac junction. Fine longitudinal veins in the lamina propria originate at the esophagocardiac junction and run in the lamina propria toward this critical area. EVs consist of multiple dilated veins. Those that rupture are usually located in the lamina propria[7].

In the stomach, unlike its counterpart the esophagus a large winding vein runs through the submucosa without causing varicose veins to pile up. The ruptures in CVs occur in the submucosa, where they disrupt the muscularis mucosae and lamina propria mucosae. The mucosal layer covering a FV is somewhat thicker than that covering an EV. The difference between a CV and a FV lies in the

caliber of the varicose vein and the degree of vascular anastomosis. Most FVs are supplied *via* the short gastric vein, though some are fed by the posterior or left gastric vein. Anastomosis of FVs is generally uncommon. The varices within the wall penetrate the muscle layer and wind through the submucosal layer, where they displace and attenuate the muscularis mucosae and propria mucosae. The varicose veins protrude into the gastric lumen.

The lamina muscularis mucosa in the esophageal mucosa is loose, and the venous pressure in the submucosa is transmitted through communicating branches to the veins in the lamina propria. The lamina muscularis mucosa in the gastric mucosa, on the other hand, is tightly integrated with the lamina propria[8].

The red color sign is an elevated red area which has proven to be important in portending variceal bleeding. The histological manifestation is a thinning of the epithelial layer The North Italian Endoscopic Club for the Study and Treatment of Esophageal varices[9] published a report establishing that the red color sign on EVs is predictive of bleeding. It remains unclear whether the endoscopic red color sign in the stomach has the same significance as the red color sign in the esophagus. In the latter case does it denote a thinning of the epithelial layer. The varix in the submucosa of the stomach is covered by the muscularis mucosae and propria mucosae. This generally confers an appearance different from that typical of the thinning epithelial layer of the esophagus[6].

HEMODYNAMICS OF GVs

The portal hemodynamics of GVs should be evaluated in all patients with these varices to determine the most appropriate treatment. CVs are supplied by the left gastric vein (cardiac branch), a vessel which enters the stomach wall in the cardia at a point 2 to 3 cm from the esophagogastric junction and diverges into a profusion of branches running throughout the cardia. The main veins feeding the FVs are the left gastric vein (51%), posterior gastric vein (30%), and short gastric vein (69%). The principal drainage veins for the FVs are the gastro-renal shunt (87%) and gastric-inferior phrenic vein shunt (16%), though about 1% of FVs reported to communicate with neither[10]. FVs are more frequently supplied by the short and posterior gastric veins than CVs. Concomitant collaterals such as EVs, para-esophageal veins, and para-umbilical veins are additionally observed in nearly 60% of FVs.

RISK FACTOR FOR BLEEDING FROM GVs

The incidence of variceal bleeding in patients who have never received treatment for EVs has been reported to range from 16 to 75.6%[11,12]. The incidence of bleeding from GVs stands at 25%[2], while cumulative bleeding rates from FVs at 1, 3, and 5 years have been estimated at 16%, 36%, and 44%, respectively[13]. Thus, the overall incidence of bleeding from GVs is lower than that from EVs[2]. In an earlier study on the natural course of GVs in 52 patients, our group treated bleeding from GVs in 4 patients over a mean follow-up period of 41 mo. Hemorrhage was successfully halted in all 4 of these patients. The cumulative bleeding rates at 1, 3, and 5 years were 3.8%, 9.4%, and 9.4%, respectively. Three of the 4 patients were free of erosive gastritis and gastric ulcer at the time of entry into the study, though ulcers or erosions were found at the bleeding points of the GVs in all 4 when the varices ruptured. There were no significant differences in patient characteristics with ruptured *versus* non-ruptured GVs when the patients entered the study[4].

The endoscopic risk factors for bleeding from EVs include the presence of raised red markings, cherry-red spots, blue color, and large size[14]. The risk factors for bleeding from GVs have yet to be characterized. In another study, our group examined 70 cirrhotic patients with first-time bleeding from EVs or GVs without prior treatment[15]. The red color sign was more common in EVs than in CVs or FVs ($P < 0.0001$). Mucosal erosion over the varices at the site of bleeding was more common in CVs ($P < 0.0005$) and FVs ($P < 0.0001$) than in EVs. An ulcer at the bleeding point was more common in CVs ($P < 0.01$) and FVs ($P < 0.0001$) than in EVs. Gastric ulcer was more common in CVs ($P < 0.05$) and FVs ($P < 0.001$) than in EVs. Erosive gastritis was more common in FVs ($P < 0.02$) than in EVs. The red color sign, a strong risk factor for the ruptures frequently encountered in EVs, was completely absent in the FVs. All of the CVs manifesting the red color sign communicated with EVs which manifested the red color sign themselves. This might have been due to the pronounced thickness of the mucosal layer overlying the FVs. FVs are usually two or three times larger than EVs and drain directly into an extremely dilated left gastric or posterior gastric vein[16]. The volume of blood flow through a FV therefore usually exceeds that through an EV. Gastric ulcers that develop over GVs represent violation of the protective layer of gastric mucosa. Violation of the mucosal barrier overlying GVs place patients at risk of massive bleeding, especially when FVs are involved. Violations of this type could be an important precondition leading to variceal hemorrhage.

TREATMENT OF GVs

Treatment modalities for GVs include balloon tamponade, endoscopic treatment, embolization, and surgery.

Balloon tamponade

Balloon tamponade with the Sengstaken-Blakemore or the Linton-Nachlas tube is an emergent procedure for active hemorrhaging from GVs. The procedure is effective in the short term, but permanent hemostasis is obtained in fewer than 50% of cases[17,18].

Endoscopic treatment

Two endoscopic treatment modalities are used for the treatment of esophagogastric varices: endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL)[19-26]. EIS can be accomplished by either intravariceal EIS or extravariceal EIS[21-23,26]. In the treatment of EVs, intravariceal EIS obliterates both the interconnecting perforating veins and the veins feeding the EVs. Most veins in the cardia become parallel veins from the

esophagogastric junction at the point at which the flow becomes hepatofugal. Nearby, however, a number of dilated winding cardiac veins run through the submucosa and directly join the EVs. This makes it possible to treat most CVs concomitantly with EVs when correcting the latter by intravariceal EIS.

EIS and EVL are both effective for the treatment of bleeding from EVs and CVs. EIS has been less successful in the treatment of bleeding from FVs, however. When used with 1% polidocanol, 5% ethanolamine oleate iopamidol (EOI), or thrombin for this purpose, EIS has a high rate of operative mortality[27-29]. Fortunately, the rate of initial hemostasis has been significantly improved since the introduction of *N*-butyl-2-cyanoacrylate (Histoacryl) as the sclerosant in EIS[30,31]. We should note, however, that bleeding from the GVs injection site and rebleeding from the rupture point have been reported in patients receiving EIS[2,29].

While EVL is generally safe and effective for the treatment of CVs and FVs[32], it sometimes causes deep or extensive ulcers and increases the risk of ensuing ulcer hemorrhage or secondary bleeding[33]. FVs are usually twice or three times larger than EVs and are directly connected to an extremely dilated left gastric or posterior gastric vein[16]. The volume of blood flow through an FV therefore usually exceeds that through an EV[34]. A mucosal injury remains on the varices after endoscopic treatment. If the blood flow in the varices cannot be stopped completely, bleeding may recur at the site of this mucosal injury. This underlines the importance of ensuring the complete obliteration of the blood flow when treating FVs endoscopically. It may be dangerous to treat FVs by EVL alone.

GVs have also been treated by a combined endoscopic method using a detachable snare and simultaneous EIS and O-ring ligation[35]. This technique is not yet in widespread use, however. Our group published a report on the treatment of ruptured GVs by EIS with Histoacryl followed by O-ring ligation (endoscopic scleroligation: EISL)[24]. EISL was developed as a treatment modality for EVs to prevent bleeding from the injection site during needle removal[21,36]. When treating GVs by EIS with Histoacryl, the immediate freezing of the Histoacryl around the needle hinders the removal of the needle after the injection. In some cases, bleeding from the GV injection site or rebleeding from the rupture point also occurs[2,29]. Our group used the EISL procedure to treat ruptured GVs with punctures near the rupture points by simultaneous ligations of the injection sites and rupture points. EISL effectively stopped the bleeding from the GVs, enabled swift and easy needle removal, and successfully eliminated both bleeding from the injection site and rebleeding from the rupture point. An O-ring was placed at the point of the EISL injection with Histoacryl and left in position for a long time. As of this writing, EISL with Histoacryl is considered the most promising treatment for hemorrhaging GVs.

Interventional radiology (IVR)

The portal hemodynamics of GVs, the main feeding veins from the portal system, and the main drainage veins into the vena cava should be determined in all patients with the GV. Angiography can determine the hemodynamics of the GV simultaneously during treatment by embolization.

Transportal obliteration: Two methods have been used to obliterate the feeding veins of GVs: percutaneous transhepatic obliteration and trans-ileocolic vein obliteration. The catheter is inserted directly into the portal vein, the portal circulation is visualized by portography, a balloon catheter is inserted selectively into the inflow site of the feeding veins for the varices, the balloon is inflated, and a test dose of a contrast medium is injected to determine the optimal volume of sclerosant fluid. Five percent EOI and/or 500 g/L glucose is injected to obliterate the feeding vein, then steel coils are used to complete the obliteration[37]. The procedure is quite effective, though only transportal obliteration is sometimes incomplete, especially in FVs.

Balloon-occluded retrograde transvenous obliteration (BRTO): BRTO is a notable IVR procedure developed specially for the treatment of FVs. The technique is performed by inserting a balloon catheter into the outflow shunt (gastric-renal shunt or gastric-inferior phrenic vein shunt) *via* the femoral or internal jugular vein. Any existing collateral veins are treated with coils, absolute ethanol, or a small amount of 5% EOI. The balloon is inflated and a test dose of contrast medium is injected to determine the optimal volume of the sclerosant solution. Five percent EOI is slowly injected through the catheter until the shunt is filled with the sclerosant fluid. The catheter is removed after 24 h of balloon occlusion[38-40]. A remarkably high rate of FV eradication or reduction in FV size can be expected if the BRTO procedure is technically successful. Indeed, long-term eradication of treated FVs without recurrence is achieved in most patients[38,41]. Kanagawa *et al*[38] confirmed eradication of FVs in 97% of 32 patients treated by this procedure, and no FVs recurred in any of those patients within an average follow-up period of 14 mo. In earlier reports, the eradication rate of FVs exceeded 89% and the recurrence rate was less then 7%. In light of the minimal invasiveness and high safety of the procedure, BRTO is applicable not only for elective cases, but also for emergency cases with FVs.

FV treatment by BRTO has two significant effects, namely, eradication of the FVs themselves and obliteration of the unified portal-systemic shunt. Thus, most of the benefits and adverse effects of BRTO are related to obliteration of the unified portal-systemic shunt. Benefits such as decreased blood ammonia levels and improved porto-systemic encephalopathy are sometimes observed. Possible adverse effects include transient ascites, increases of ascites, pleural effusion, and the appearance of EVs manifesting the red color sign. These adverse effects may be due to elevation of the portal pressure in reaction to the occlusion of the portal-systemic shunt.

Partial splenic artery embolization (PSE): The femoral artery approach is used for super-selective catheterization of the splenic artery. The catheter tip is placed as distally as possible in either the hilus of the spleen or in an intrasplenic artery. Embolization is achieved by injecting 2-mm cubes of gelatin sponge suspended in a saline solution containing antibiotics[42,43]. PSE has been

performed to treat hypersplenism, EVs, GVs, portal hypertensive gastropathy, pancreatic carcinoma, and portosystemic encephalopathy[37,43-53]. Our group evaluated PSE in a long-term study of 26 patients with hepatic cirrhosis alongside 26 patients who did not undergo the PSE procedure[42]. The red blood cell counts of the PSE (+) group increased significantly by 6 mo after the procedure and remained increased for up to 7.5 years. The platelet counts peaked only 2 wk after PSE and gradually fell thereafter. Even so, the platelet counts remained significantly higher than the pre-PSE level for up to 8 years. No significant changes were observed in the aspartate aminotransferase and alanine aminotransferase activities in serum during the follow-up. Cholinesterase activity was increased significantly by 6 mo after PSE and remained increased for more than 7 years. The serum albumin concentration increased significantly from 6 mo after PSE and the level remained significantly increased for 6 years. Survival did not differ between the PSE (+) and PSE (-) groups. PSE, a non-surgical treatment, can benefit patients with cirrhosis by improving the capacity of hepatic protein synthesis and conferring protection against hemorrhage due to thrombocytopenia.

Combination modalities with IVR: Our group also reported the long-term results of PSE as supplemental treatment for portal-systemic encephalopathy. We divided 25 patients with portal-systemic encephalopathy due to portal-systemic shunts into two groups, one treated by transportal obliteration and/or BRTO of portal-systemic shunt, followed by PSE (PSE (+) group; $n = 14$), the other treated by transportal obliteration and/or BRTO of the portal-systemic shunt without PSE (PSE (-) group; $n = 11$). The serum ammonia levels and grades of encephalopathy were lower in the PSE (+) group than in the PSE (-) group at 6, 9, 12, and 24 mo after treatment. Obliteration of the portal-systemic shunt raised the portal venous pressure in every case. As all of the patients had cirrhosis, the portal-systemic shunt drainage reduced portal hypertension and the obliteration of the portal-systemic shunt led to portal congestion and increased portal venous pressure. Our study thus confirmed the benefits of obliteration of the portal-systemic shunt by PSE in patients with portal-systemic encephalopathy[43].

PSE is performed incrementally during the monitoring of the portal pressure in order to reduce the portal venous pressure to the level measured before obliteration of the veins feeding and/or draining the GVs[22,42,43,49,54]. PSE is a supplemental modality to prolong the effect of obliteration of the veins feeding and/or draining the GVs.

Combination of endoscopic treatment and IVR

Treatment of GVs solely by endoscopic modalities or by IVR is occasionally incomplete. Our group previously reported that combined treatments with IVRs and endoscopic modalities had significant impacts on long-term rebleeding and retreatment rates in patients with EVs or GVs[37,48,50,51]. In elective cases, complete GV treatment should be administered in order to prevent rebleeding with greater assurance.

Surgery

A number of surgical procedures have been developed to manage esophagogastric varices. These can be classified as shunting and nonshunting procedures. The goal of shunting is to reduce the incidence of variceal bleeding by lowering the pressure in the portal system using a portal-systemic shunt. While the standard portocaval shunt effectively reduces the incidence of variceal bleeding, impairment of the hepatic protein metabolism in patients undergoing the procedure frequently leads to the development of hepatic encephalopathy due to hyperammonemia[55-57]. The distal splenorenal shunt (DSRS) was developed by Warren *et al*[58] in 1967 as a way to preserve portal blood flow through the liver while lowering variceal pressure. The hope, in developing this approach, was to prevent both bleeding and hyperammonemia. While DSRS effectively prevents rebleeding, patients who undergo DSRS still can develop hyperammonemia. Our group responded by designing a DSRS with a splenopancreatic disconnection and gastric transection, modifications to prevent the loss of shunt selectivity. This modified DSRS has been proved to reduce the incidence of postoperative hyperammonemia[59].

As an alternative to shunting, Hassab[60] and Sugiura *et al*[61] developed a method of gastro-esophageal decongestion and splenectomy for the treatment of varices. The Hassab operation devascularizes the distal esophagus and proximal stomach. Splenectomy, selective vagotomy, and pyloroplasty can be performed concomitantly with the procedure. Sugiura *et al*[61] developed a method of esophageal transection for patients with GVs and EVs. Sugiura's method is performed concomitantly with the Hassab operation to divide and reanastomose the distal esophagus in order to disrupt the blood supply to the EVs. While both procedures may solve the problem of hepatic encephalopathy, varices are likely to recur earlier than they are in patients undergoing DSRS[62].

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