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EDITORIAL

New methods for the management of esophageal varices

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Abstract

Bleeding from esophageal varices (EVs) is a catastrophic complication of chronic liver disease. Many years ago, surgical procedures such as esophageal transection or distal splenorenal shunting were the only treatments for EVs. In the 1970s, interventional radiology procedures such as transportal obliteration, left gastric artery embolization, and partial splenic artery embolization were introduced, improving the survival of patients with bleeding EVs. In the 1980s, endoscopic treatment, endoscopic injection sclerotherapy (EIS), and endoscopic variceal ligation (EVL), further contributed to improved survival. We combined IVR with endoscopic treatment or EIS with EVL. Most patients with EVs treated endoscopically required follow-up treatment for recurrent varices. Proper management of recurrent EVs can significantly improve patients' quality of life. Recently, we have performed EVL at 2-mo (bi-monthly) intervals for the management of EVs. Longer intervals between treatment sessions resulted in a higher rate of total eradication and lower rates of recurrence and additional treatment.

Key words: Esophageal varices; Surgery; Interventional radiology; Embolization; Endoscopic treatment; Bi-monthly

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INTRODUCTION

Bleeding from esophageal varices (EVs) or gastric varices (GVs) is a catastrophic complication of chronic liver disease. There are various treatments for EVs. Many years ago, operation was the only treatment option available. In the 1970s, techniques for interventional radiology were developed, improving the survival of patients with bleeding EVs. In the 1980s, endoscopic treatment further contributed to improved survival. In this paper, we review the evolution of treatments for EVs.

DIAGNOSIS OF ESOPHAGEAL VARICES

The Esophagogastric Varices Grading System of the Japan Society for Portal Hypertension[1] evaluates EVs on the basis of color [white (Cw) or blue (Cb)], form [small and straight (F1), nodular (F2), or large or coiled (F3)], and red color signs (RC0-3).

Pathomorphology of esophageal varices

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 transverse the *lamina propria* toward this critical area. EVs consist of multiple dilated veins. Veins that rupture are usually located in the *lamina propria*[2]. The mucosal layer covering an EV is somewhat thinner than that covering a GV. The lamina muscularis mucosa of the esophagus is loose, and venous pressure in the submucosa is transmitted through communicating branches to veins in the *lamina propria*. In contrast, the lamina muscularis mucosa of the gastric mucosa is tough and tightly integrated with the *lamina propria*[3].

Red color signs are elevated red areas that are important for predicting the risk of variceal bleeding. Histologically, red color signs are associated with a thinning epithelial layer.

Incidence and risk factors for bleeding from esophageal varices

The incidence of variceal bleeding in patients with previously untreated EVs ranges from 16% to 75.6%[4,5]. In an earlier study examining the natural course of GVs, our group treated bleeding from GVs in 4 of 52 patients over a mean follow-up of 41 mo. Hemorrhage was successfully controlled in all 4 of these patients. Cumulative bleeding rates at 1, 3, and 5 years were 3.8%, 9.4%, and 9.4%, respectively[6]. The overall incidence of bleeding is thus higher for EVs than for GVs.

In another study, our group examined 70 cirrhotic patients with first episodes of bleeding from EVs or GVs; no patient had received prior treatment[7]. Red color signs were more common in EVs than in GVs. Mucosal

erosions and ulcers at bleeding varices were more common in GVs than in EVs. Gastric erosions and ulcers were also more common in GVs than in EVs. Red color signs were frequently encountered in EVs, but were not found in fundal varices. All cardiac varices showing red color signs communicated with EVs, which also showed red color signs. The lack of red color signs in fundal varices might have been caused by the thick overlying mucosa. Gastric ulcers that develop on GVs invade the protective layer of the gastric mucosa. Invasion of the mucosal barrier overlying GVs increases the risk of massive bleeding, especially when fundal varices are involved. Such invasions might be an important precondition for variceal hemorrhage.

Endoscopic risk factors for bleeding from EVs include the presence of raised red markings, cherry-red spots, blue coloration, and large size[8]. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices[9] reported that red color signs on EVs are predictive of bleeding.

TREATMETN OF ESOPHAGEAL VARICES

Treatment modalities for EVs include surgery, interventional radiology, and endoscopic treatment.

Surgery

A number of surgical procedures have been developed to manage EVs. These can be broadly classified as shunting procedures and nonshunting procedures.

Shunting procedures: The goal of shunting is to reduce the incidence of variceal bleeding by lowering the pressure in the portal system with a portal-systemic shunt. A standard portocaval shunt effectively reduces the incidence of variceal bleeding; however, impaired metabolism of hepatic protein after the procedure frequently causes hepatic encephalopathy due to hyperammonemia[10-12]. In 1967, Warren developed the distal splenorenal shunt (DSRS) to preserve portal blood flow through the liver, while lowering variceal pressure[13]. This approach was developed in the hope of preventing bleeding as well as hyperammonemia. Despite these initial expectations, DSRS has been found to effectively prevent rebleeding, but not eliminate the risk of hyperammonemia. To solve this problem, our group designed a DSRS with splenopancreatic disconnection and gastric transection, modifications to prevent the loss of shunt selectivity. Our modified DSRS has been confirmed to reduce the incidence of postoperative hyperammonemia[14].

Non-shunting procedures: As an alternative to shunting, Hassab[15] and Sugiura[16] developed methods for gastroesophageal 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[16] developed a procedure for esophageal transection in patients with EVs and GVs. While both the Hassab and Sugiura procedures solve the problem of hepatic encephalopathy, varices are likely to recur earlier than they do after DSRS[17].

Interventional radiology

In the 1970s, interventional radiology (IVR) techniques were developed for the treatment of EVs. Transportal obliteration, left gastric artery embolization, and partial splenic artery embolization are the principal IVR techniques used to treat EVs. Before performing IVR, portal hemodynamics should be determined. Angiography can determine the hemodynamics of varices during embolization.

Transportal obliteration: Two methods have been used to obliterate the feeding veins of EVs: percutaneous transhepatic obliteration and trans-ileocolic vein obliteration. These methods are performed similarly. A catheter is inserted directly into the portal vein, and the portal circulation is visualized by portography. A balloon catheter is inserted selectively into the inflow site of the feeding veins of the varices. The balloon is inflated, and a test dose of contrast medium is injected to determine the optimal volume of sclerosant. Five percent ethanolamine oleate with iopamidol (EOI), 500 mL/L glucose, or both are injected to obliterate the feeding vein(s). Steel coils are then used to complete obliteration[18]. The procedure is highly effective, although the complete disappearance rate of EVs is not so high after transportal obliteration alone.

Partial splenic artery embolization: Partial splenic artery embolization (PSE) has been performed to treat hypersplenism, EVs, GVs, portal hypertensive gastropathy, pancreatic carcinoma, and portosystemic encephalopathy[18-29].

The femoral artery approach is used for superselective catheterization of the splenic artery. The tip of a catheter 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 gelatin-sponge cubes suspended in a saline solution containing antibiotics[23,30]. Similar to transportal obliteration, complete disappearance of EVs is difficult to achieve by PSE alone. PSE is thus a supplemental treatment for EVs.

Endoscopic treatment

Two endoscopic techniques are used to treat EVs: endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL)[31-37]. Whenever possible, endoscopic treatment was performed at 2-wk intervals by three expert endoscopists, using a television endoscopy system with computer-stored endoscopic images. After premedication with an intramuscular injection of scopolamine butylbromide (20 mg), atropine sulfate (0.25 mg), pentazocine (15 mg), hydroxyzine (25 mg), and diazepam (5 mg) were injected intravenously. A one-channel endoscope was then inserted. A flexible endoscopic sheath (Sumitomo Bakelite, Tokyo, Japan) was used to permit reinsertion of the endoscope and to prevent aspiration.

Endoscopic injection sclerotherapy: EIS can be accomplished by either intravariceal EIS or extravariceal EIS[32-34,38].

(1) Intravariceal EIS. An anal-side balloon was inserted into the stomach, and a 22-gauge needle was inserted into the target EV 2 to 3 cm proximal to the gastroesophageal junction. The sclerosant (50 mL/L EOI) was infused into

the EV, and flow was monitored by X-ray fluoroscopy to confirm filling of the feeder vessel or the pericardiac venous plexus. Suction was maintained at the puncture point while the needle was in the EV. The same procedure was repeated for other variceal columns in the lower esophagus. Additional injections could not be performed, and the injection site was compressed by inflating the anal-side balloon with air.

In the treatment of EVs, intravariceal EIS obliterates both interconnecting perforating veins and feeding veins of EVs. Nearby, however, some dilated winding cardiac veins transverse the submucosa and directly join the EVs. This allows most cardiac varices to be treated concomitantly with EVs when correcting the latter by intravariceal EIS. Intravariceal EIS is useful for obliterating feeding veins of recurrent EVs after operation[34]. However, EIS is associated with high incidences of local and systemic complications[39].

(2) Extravariceal EIS. Extravariceal EIS was performed with 10 mL/L polidocanol to treat remaining varices by paravariceal injection[40]. The end point of primary treatment was the failure to detect any residual varices between the ulcers created by extravariceal EIS during the first hospitalization. Extravariceal EIS achieves local eradication, but does not completely disrupt the interconnecting perforating and feeder vessels[41].

Endoscopic variceal ligation: There are various EVL devices for the treatment of EVs. We use a pneumo-activated EVL device (Sumitomo Bakelite) to treat EVs. EVL is increasingly used because of its safety and simplicity and because no sclerosant is required. EVL achieves local eradication, but does not completely disrupt the interconnecting perforating and feeder vessels[41].

We have devised a new intensive EVL method to more consistently eradicate EVs[31]. In comparison, the average total number of rubber bands used per patient was 9.6 in the standard EVL group and 19.9 in the intensive EVL group. EVs were completely obliterated in all patients in the intensive EVL group, but not in all patients in the standard EVL group[31]. Nevertheless, early recurrences of EVs after EVL have been reported[32].

Combination of endoscopic treatment and interventional radiology

Our group previously reported that endoscopic treatment combined with IVR techniques significantly reduced long-term rates of rebleeding and retreatment in patients with EVs[18,24,26,27].

Combination of endoscopic variceal ligation and partial splenic artery embolization: Cumulative recurrence rates at 1 and 2 years were lower in the EVL + PSE group than in the intensive EVL group ($P = 0.042$), suggesting that EVL + PSE therapy is effective for the management of EVs[24].

Endoscopic treatment versus endoscopic treatment combined with interventional radiology: Cumulative retreatment rates in patients with Child's class C disease were lower after endoscopic treatment + IVR than after endoscopic treatment alone ($P = 0.025$). A combination of endoscopic therapy and IVR is effective therapy for EVs, especially in patients with poor liver function[18].

Combination of endoscopic injection sclerotherapy and endoscopic variceal ligation: Several investigators have examined the efficacy of EVL combined with EIS for the treatment of EVs[42-44]. Saeed *et al*[42] and Laine *et al*[43] compared a single session of treatment with EVL plus low-volume EIS with a single session of EVL alone and concluded that EVL alone is superior to combination therapy. EVL was performed first, followed by intravariceal EIS immediately proximal to the ligature. The main limitation of this method is that only half of the feeding vessels are treated because the sclerosants are injected into the EV proximal to the ligature; distal vessels therefore do not undergo sclerosis.

EVL followed by EIS intrinsically differs from EIS followed by EVL. Moreover, the combination of intravariceal EIS and EVL differs from that of extravariceal EIS and EVL. EVL and extravariceal EIS both eradicate varices locally, with no effect on interconnecting perforating or feeding vessels[41]. Takase *et al*[45] concluded that feeder vessels must be obliterated to prevent recurrence.

Beginning in November 1994, we developed a new technique combining EVL with EIS, called endoscopic scleroligation (ESL). In this technique, intravariceal EIS is performed before ligation. The puncture needle was removed after sclerosant infusion, and EVL was done simultaneously, including the placement of bands at the injection site. The same procedure was repeated for other EVs around the lower esophagus. Additional sclerosants were not injected. Intensive EVL was performed for EVs in the lower to middle esophagus[32].

Intravariceal endoscopic injection sclerotherapy followed by endoscopic variceal ligation (ESL) *versus* intensive endoscopic variceal ligation: Both methods were equally effective with respect to complete eradication of EVs. Among patients in whom complete eradication was achieved, cumulative recurrence rates at 1 and 3 years were lower in the ESL group than in the intensive EVL group ($P < 0.01$). ESL was thus superior to intensive EVL in preventing variceal recurrence[32].

Intravariceal endoscopic injection sclerotherapy followed by endoscopic variceal ligation (ESL) *versus* EVL followed by extravariceal EIS: Cumulative recurrence rates at 1 and 3 years in the ESL group were much lower than those in the EVL + extravariceal EIS group ($P < 0.0001$)[33]. Because intravariceal EIS was performed before ligation in ESL, all interconnecting perforating veins and feeder vessels were obliterated. This study supports the conclusion that the incidence of variceal recurrence is lower after ESL than after EVL + extravariceal EIS, although both methods were equally effective initially in terms of completely eradicating EVs.

Endoscopic variceal ligation followed by extravariceal endoscopic injection sclerotherapy *versus* intensive endoscopic variceal ligation: Fewer treatment sessions were needed ($P < 0.005$), and more O-rings were required ($P < 0.0001$) in the EVL group than in the EVL + extravariceal EIS group. Cumulative recurrence rates at 1 and 3 years were higher in the EVL group

than in the EVL + extravariceal EIS group ($P < 0.05$). Endoscopic examination at first recurrence showed that varices were more severe in form ($P < 0.001$), but less frequently associated with red color signs ($P < 0.0001$) and intramucosal venous dilatation ($P < 0.0001$) in the EVL group than in the EVL + extravariceal EIS group. Fewer rehospitalizations were required for additional treatment ($P < 0.0001$), and more patients received only endoscopic treatment for recurrent varices ($P < 0.05$) in the EVL group than in the EVL + extravariceal EIS group. These findings indicate that multiple EVL sessions are an effective treatment strategy for EVs[38].

New methods for the management of EVs: EVL at 2-mo intervals

EVL and extravariceal EIS are not always effective, and early recurrences have been reported[32]. Furthermore, most patients with endoscopically treated EVs require follow-up therapy for recurrent varices. Proper management of recurrent EVs can significantly improve patients' quality of life.

In our previous study, the number of EVL sessions during the first hospitalization was 2.5 ± 0.5[38]. Most EVs were ligated and deprived of blood after the first session. The remaining EVs were ligated in the second and subsequent sessions of EVL. Our findings suggested that the first EVL session had the most important role in blocking blood flow and stimulating shunt formation. After EVL alone, 1.8 subsequent hospitalizations were required for additional treatment of recurrent varices[38]. We judged that multiple blockages (at least three) of blood flow to EVs effectively stimulated shunt formation. We therefore defined three sessions to be one course in subsequent studies. The second treatment session after recanalization of variceal blood flow had a greater impact on the stimulation of shunt formation than did prior treatment sessions. This finding suggested that a prolonged interval between EVL sessions may improve treatment outcomes for EVs. However, we found that the bleeding rate of incompletely eradicated EVs was high and that bleeding from completely eradicated EVs occurred after only 6 mo[32]. We therefore based the following study on the premise that three treatment sessions performed at 2-mo intervals (i.e., the third session begins 4 mo after the first session) would effectively prevent bleeding from EVs.

Endoscopic variceal ligation bi-weekly *versus* bi-monthly: We conventionally performed EVL treatment once every 2 wk (bi-weekly). We compared the short- and long-term results of EVL performed in three sessions with a total of 16 O-rings at two different intervals, i.e., bi-weekly (conventional interval) *versus* bi-monthly. A total of 63 patients with EVs were randomly assigned to receive one of these EVL treatments. Outcomes were assessed by an experienced physician who was blinded to the patients' treatment assignments. The overall rates of variceal recurrence and additional treatment were both higher after EVL bi-weekly than after EVL bi-monthly ($P < 0.001$). We concluded that EVL once every 2 mo (bi-monthly) resulted in better outcomes than EVL once every 2 wk (bi-weekly) in patients with EVs. Treatment sessions separated by a longer interval had a higher rate of total eradication and lower rates of recurrence and additional treatment[36].

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