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Research Article

Recent Trend of Variceal Bleeding in Patients with Portal Hypertension and its Treatments Including Ectopic Varices

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- Ectopic varices; Endoscopic band ligation; Endoscopic injection sclerotherapy; Gastrointestinal varices; N-butyl-2-cyanoacrylate; Portal hypertension; Variceal bleeding

Abstract

Aims: We investigated recent trend of variceal bleeding in patients with portal hypertension and its treatments including ectopic varices.

Methods: One hundred forty-four patients with variceal bleeding events and portal hypertension were evaluated retrospectively from December 2012 to June 2016.

Results: Sites of 144 variceal bleeding were as follows; esophageal varices in 67, cardiac varices in 24, fundal varices in 10, and ectopic varices in 43 (29.9%). Ectopic varices were rectal varices in 27, duodenal varices in 4, anastomotic varices after choledochojejunostomy in 2, jejunal varices in 1, gastric body varices in 7 and stomal varices in 2. Endoscopic band ligation (EBL) was successfully performed for 56 esophageal varices and endoscopic injection sclerotherapy (EIS) using 5% ethanolamine oleate (EO) for 6 esophageal varices, and EBL plus EIS for 5 esophageal varices, respectively. EBL was performed successfully for 9 cardiac varices and EIS using EO for 8 cardiac varices, and EBL plus EIS for 7 cardiac varices, respectively. EIS using cyanoacrylate (CA) was successfully performed for 9 fundal varices and EIS using EO for 1 fundal variceal patient. EIS using EO was performed successfully for 21 rectal varices and EBL for 2 rectal varices, and EBL plus EIS for 4 rectal varices, respectively. EIS using CA was successfully performed for 3 duodenal varices and EIS plus balloon-occluded retrograde transvenous obliteration for 1 duodenal variceal patient. EIS using CA was successfully performed for 2 anastomotic varices after choledochojejunostomy, however, jejunal variceal patient who underwent percutaneous transhepatic obliteration (PTO) died 2 days after the treatment due to poor condition. EBL was successfully performed for 6 gastric body varices, and EIS using CA was successfully performed for 1 gastric body varices. Percutaneous injection sclerotherapy using EO was successfully performed for 2 stomal varices. No significant complications were observed.

Conclusions: Recently, the frequency of ectopic varices has been increasing. Endoscopic treatments and interventional radiology have been performed successfully and safety for variceal bleeding including ectopic varices.

INTRODUCTION

Esophageal varices are the most common complication of cirrhosis. Endoscopic treatments were developed in the 1980s. EIS and EBL are effective treatments for variceal bleeding. These endoscopic therapies are important tools for the prevention of esophageal varices. Gastric variceal hemorrhage is associated with higher morbidity and mortality rates than in patients with esophageal variceal bleeding. Gastric varices (GV) classified as gastroesophageal varices type 2 (GOV2) or isolated gastric varices 1 (IGV1) with Sarin classification [1] are more severe and often difficult to treat as compared to the other types of varices. Bleeding GV of these types can be treated successfully by injection of CA. N-butyl-2-cyanoacrylate (CA: Histoacryl®, B.Braun Dexon GmbH Spangenberg, Germany) is a tissue glue monomer that polymerizes and solidifies instantly upon contact with blood. Soehendra et al., were the first to report the usefulness of CA in the treatment of bleeding GV [2].

On the other hand, ectopic varices are portosystemic collaterals along the digestive tract outside the gastroesophageal region and are unusual and their frequency has been increasing on a current survey in Japan [3]. Ectopic varices with portal hypertension are considered to be the cause of hemorrhage presenting as lower gastrointestinal bleeding. The risk of bleeding is quadrupled compared to the esophagogastric area, with a mortality of up to 40% [4]. Recently, interventional radiology and endoscopic procedures have been performed successfully as a treatment option for ectopic varices [5-8].

In this study, we investigated recent trend of variceal bleeding events in patients with portal hypertension and its treatments including ectopic varices.

METHODS

Patients

One hundred forty-four variceal bleeding events and portal hypertension were analyzed retrospectively, longitudinally, and

observationally at Sapporo Kosei Hospital, Japan, from December 2012 to June 2016. All 144 were emergency cases or elective cases (104 men and 40 women; age range, 30-81 years; mean, 62.5 years). The pathology underlying portal hypertension was liver cirrhosis (LC) in 127 patients, splenic vein occlusion (left-sided portal hypertension) in 7, extrahepatic portal obstruction in 6 (including 2 patients after choledochojejunostomy), and idiopathic portal hypertension in the remaining four. LC was confirmed by a combination of clinical, biochemical, and ultrasound criteria.

The study was performed according to the Declaration of Helsinki, and was approved by the Ethics Committee at Sapporo Kosei Hospital. Written informed consent was obtained from all patients prior to the procedure.

Methods

In emergency cases, endoscopic examination was performed after stabilizing the general condition of the patients. When bleeding was spurting or oozing, a red or white plug, or tiny erosion, was observed at the gastrointestinal varices during emergency endoscopic examination (Figure 1), and endoscopic treatments for hemostasis was performed immediately. EIS not only blocks esophageal varices but also scleroses the passageways. In Japan, EIS is performed frequently using EO as the sclerosing agent.

EO is injected via a catheter through the working channel of the endoscope to target esophageal varices. This harsh chemical agent acts by denaturing biologic tissue, bringing about complete endothelial destruction and fibrosis following injection into a vein [9]. Ten percent EO is mixed with an equal volume of iopamidol as the contrast medium, resulting in a 5 %

EO-iopamidol mixture. EO is hemolytic, and the resultant free hemoglobin may cause renal failure if large amounts are used [10]. Injection of less EO is advisable to minimize the renal risk. In our institute, EIS for esophageal varices, cardiac varices, stomal varices was performed weekly using EO, which was injected gradually into the esophageal varices under fluoroscopic guidance.

EBL is widely used as an effective and standard treatment for esophageal varices by obliteration of the submucosal varices using a rubber band [11].

EBL is especially effective for actively bleeding esophageal varices, by attaching the rubber band at the bleeding point, and it is the first-choice treatment because of its ease and safety.

For endoscopic obliterative therapy for fundal gastric varices, duodenal varices and anastomotic varices after choledochojejunostomy, we used CA diluted to a final concentration of 70% or 83% (except one case of the duodenal varices) in 5% Lipiodol®, (Guerbet Asia Pacific, Tsuen Wan, Hong Kong). Lipiodol® prevents the tissue adhesive from polymerizing too quickly and also allows for radiographic monitoring. Obliterative therapy was performed repeatedly with a 23-gauge needle until gastrointestinal varices disappeared. Fluoroscopic observation with an infusion of CA (avoiding flow into the systemic circulation) was performed to determine the extent of the varices.

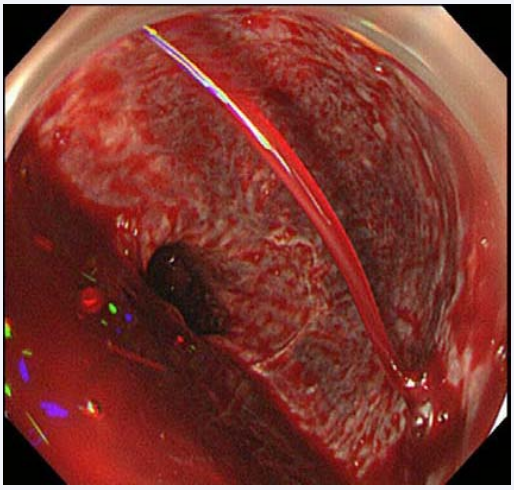

Figure 1 Spurting bleeding from esophageal varices.

When repeat upper and lower endoscopies are negative in gastrointestinal bleeding, the small intestine should be investigated. Most bleeding jejunal and ileal varices, generally detected previous intra-abdominal surgery, are serious because of the difficulty of early diagnosis. Location of the bleeding site often is difficult in the intestinal varices. In jejunal variceal case, we suspected rupture of intestinal varices via computed tomography, and PTO was performed for this case.

RESULTS

Sites of consecutive 144 variceal bleeding events were as follows; esophageal varices in 67, cardiac varices in 24, fundal varices in 10, and ectopic varices in 43 (29.9%). Ectopic varices were rectal varices in 27, duodenal varices in 4, anastomotic varices after choledochojejunostomy in 2, jejunal varices in 1, gastric body varices in 7 and stomal varices in 2. GV; according to the Sarin classification [1], IGV1 were present in 9 patients, GOV2 in 1, and ectopic varices seen outside the fundus (IGV2) in seven. On the other hand, cardiac variceal bleeding with esophageal varices was seen in 24. Duodenal varices (DV); location of DV was the second portion of duodenum in 3 cases and duodenal bulb in 1. Anastomotic varices after choledochojejunostomy; endoscopy revealed large, coil-shaped varices in the afferent jejunal loop in 2 cases. One hundred forty-three of 144 patients had stigmata of recent bleeding at endoscopy. Patients underwent endoscopic procedures and interventional radiology, and hemostatic rate was 143 of 144 cases (99.3%) (Table 1).

Esophageal varices (n=67)

EBL was successfully performed for 56 esophageal varices and EIS using EO for 6 esophageal varices, and EBL plus EIS for 5 esophageal varices, respectively. Hemostatic rate was 67 of 67 cases (100%). The incidence of serious complications was 0/67 (0%).

Cardiac varices (n=24)

EBL was performed successfully for 9 cardiac varices and EIS using EO for 8 cardiac varices, and EBL plus EIS for 7 cardiac varices, respectively. Hemostatic rate was 24 of 24 cases (100%). The incidence of serious complications was 0/24 (0%).

Table 1: Sites of variceal bleeding events (n=144).	
Site	**Cases (N)**
Esophagogastric varices (n=101)	
Esophageal varices	67
Cardiac varices	24
Fundal varices	10
Ectopic varices (n=43)	
Rectal varices	27
Gastric body varices	7
Duodenal varices	4
Anastomotic varices	2
Small intestinal varices	1
Stoma varices	2

Fundal varices (n=10)

For endoscopic obliterative therapy for GV, we used CA diluted to a final concentration of 70% in all cases. EIS using CA was successfully performed for 9 fundal varices and EIS using EO for 1 fundal variceal patient (Figure 2). Hemostatic rate was 10 of 10 cases (100%). The incidence of serious complications was 0/10 (0%).

Rectal varices (n=27)

EIS using EO was performed successfully for 21 rectal varices and EBL for 2 rectal varices, and EBL plus EIS for 4 rectal varices, respectively. Hemostatic rate was 27 of 27 cases (100%). The incidence of serious complications was 0/27 (0%).

Duodenal varices (n=4)

EIS using CA was successfully performed for 3 duodenal varices and EIS plus balloon-occluded retrograde transvenous obliteration (B-RTO) for 1 duodenal variceal patient. Hemostatic rate was 4 of 4 cases (100%). The incidence of serious complications was 0/4 (0%).

Anastomotic varices after choledochojejunostomy (n=2)

For endoscopic obliterative therapy of anastomotic varices, we used CA diluted to a final concentration of 83% in 5% Lipiodol. EIS using CA was successfully performed for 2 anastomotic varices after choledochojejunostomy (Figure 3), and the glue mixture filled the varices and did not leak into the liver. Hemostatic rate was 2 of 2 cases (100%). The incidence of serious complications was 0/2 (0%).

Jejunal varices (n=1)

PTO has been performed successfully for jejunal variceal bleeding. However, jejunal variceal patient who underwent PTO died 2 days after the treatment due to poor condition.

Gastric body varices (n=7)

EBL was successfully performed for 6 gastric body varices, and EIS using CA was successfully performed for 1 gastric body varices. Hemostatic rate was 7 of 7 cases (100%). The incidence of serious complications was 0/7 (0%).

Stomal varices (n=2)

Percutaneous injection sclerotherapy using EO was successfully performed for 2 stomal varices. Hemostatic rate was 2 of 2 cases (100%). No significant complications were observed.

In summary, endoscopic treatments including the use of CA were effective for esophagogastric variceal bleeding. In addition, Endoscopic treatments and interventional radiology were useful for ectopic variceal bleeding.

DISCUSSION

Portal hypertension results from an increase in the resistance of blood flow in the intrahepatic portal vein and can cause the reopening of embryonic channels [12]. Portal venous pressure is critical in the liver function of cirrhosis and esophageal varices are the most common complication of cirrhosis. Ectopic varices are portosystemic collaterals along the digestive tract outside the gastroesophageal region and are unusual [13,14]. Endoscopic procedures such as EIS and EBL have been carried out for treating esophageal varices [11,15]. B-RTO using EO is an angiographic technique for fundic varices of stomach [16]. Ectopic variceal bleeding is massive and serious condition. A current survey of ectopic varices in Japan has been reported and the most frequent sites of ectopic varices are the rectum in 44.5%, followed by the duodenum in 32.9% [3]. But, the optimal procedure has

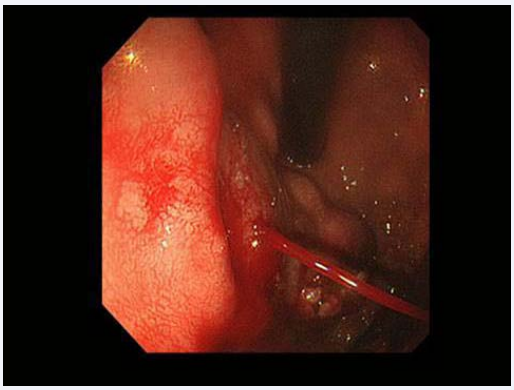

Figure 2 Spurting bleeding from gastric fundal varices (IGV1).

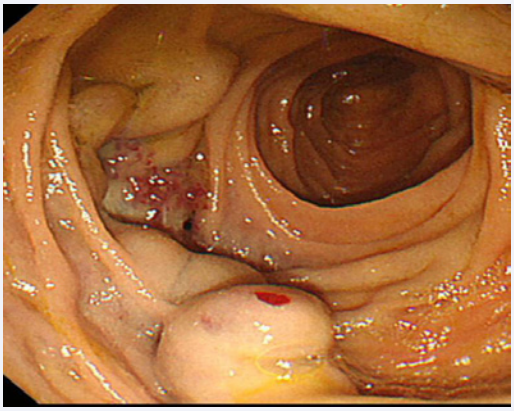

Figure 3 A red plug on anastomotic varices after choledochojejunostomy.

not been defined for hemorrhage from ectopic varices. EIS not only blocks esophago-cardiac varices but also scleroses the passageways to esophageal varices (left gastric vein, short gastric vein, palisade vein, and perforating veins) and is therefore an effective therapy for developed esophago-cardiac varices. It is also safe because of the use of endoscopic varicealography during injection sclerotherapy. To determine the extent of the varices, fluoroscopic observation was performed using a balloon attached to the endoscope to guide and control the infusion of EO. On the other hand, EBL is especially effective for actively bleeding esophageal varices, by attaching the rubber band at the bleeding point, and it is the first-choice treatment because of its ease and safety. Endoscopic treatments such as EIS and EBL were safe and effective for esophageal and cardiac variceal bleeding in our results.

Endoscopic therapy with CA is useful for emergency control of acute gastric variceal bleeding of GOV2 or IGV1 types. CA polymerizes immediately on contact with blood, resulting in rapid hemostasis, and the use of this material is the first-choice for endoscopic treatment worldwide for obliteration of bleeding gastric varices [17]. Recent studies concluded that endoscopic therapy with CA is a highly effective modality for immediate hemostasis of gastric variceal bleeding and is associated with an acceptable rebleeding rate [18,19]. Kumar et al reported that undiluted CA was effective in achieving initial hemostasis in cases of actively bleeding gastric varices, was very safe and was not associated with embolic complications [18]. However, in many institutions, CA is mixed with a contrast medium, radiopaque Lipiodol®, to allow radiologic monitoring during and after injection. Endoscopic therapy with CA was safe and effective for fundal variceal bleeding in our results. Rectal varices are a consequence of portosystemic collaterals from the superior rectal veins to the middle inferior rectal veins. Endoscopy can detect the discrete dilated submucosal varices in the rectum and some investigators have reported that rectal varices occur at a highfrequency [20-22]. Hemorrhage from rectal varices occurs at a low frequency from 0.5% to 3.6% [23,24]. Several medical procedure have been performed for controlling rectal variceal bleeding, however, a standard treatment has not been established. As an endoscopic treatment, Wang et al., used EIS for rectal variceal bleeding [25]. EBL has been performed as an effective procedure for rectal varices [26-28] and Levine et al., used EBL successfully for the rectal varices remaining after EIS [26]. EBL is a safe and effective treatment for rectal varices. However, a retrospective study comparing EIS and EBL concluded that recurrence rate tended to be greater with EBL [29] and stated that 5% EO of the sclerosant should be carefully injected using fluoroscopy, avoiding injection into the systemic circulation. In our results, EIS and EBL were very useful for rectal variceal bleeding.

Hemorrhage from duodenal varices is low frequent, however, it is often serious condition [30]. Hemorrhage from duodenal varices is generally massive and fatal [31,32]. The diagnosis of duodenal varices is done ordinary by endoscopic examination, however, it is often difficult to observe hemorrhaging duodenal varices. In Japan, common site of duodenal varices is the second portion of the duodenum. Recently, interventional radiology and endoscopic treatments have been performed successfully for duodenal varices. Endoscopic therapy using CA is also very useful for massive duodenal variceal bleeding [33,34] because of the high blood velocity and blood flow. Interventional radiologic techniques such as transjugular intrahepatic portosystemic shunts (TIPS), B-RTO are options for hemorrhaging duodenal varices and successful treatments have been reported, including TIPS [32] and B-RTO [35-37]. B-RTO is able to obliterate the afferent and efferent veins and may be considered as a treatment option for duodenal varices. Endoscopic therapy using CA is very useful for duodenal variceal bleeding and B-RTO also was useful as an additional treatment in our results.

Bleeding from jejunal varices may be massive and serious and it is difficult to achieve early diagnosis. Most cases are detected following intra-abdominal surgery. The development of collateral circulation via the post-operative adhesions is a risk factor of small intestinal varices in patients with portal hypertension. Bleeding small intestinal varices are as follows: portal hypertension, hematochezia without hematemesis, and previous abdominal surgery [38]. Several treatments are available for jejunal varices, such as surgery, portal venous stenting [39-41] and percutaneous embolization [42].

Anastomotic varices after choledochojejunostomy are an uncommon cause of variceal bleeding. Anastomotic varices should be considered when evaluating gastrointestinal hemorrhage in patients with previous surgery and mesenteric venous hypertension. Hemorrhaging from varices in the jejunal loop, with extrahepatic portal vein obstruction after choledochojejunostomy, is a rare condition but several articles have been published [41,43]. After choledochojejunostomy, the anastomosed afferent jejunal loop may have a propensity to form varices with hepatopetal flow.

Various medical treatments, such as interventional radiology and surgery, have been used to control bleeding from anastomotic varices after choledochojejunostomy; however, there is no best treatment strategy for anastomotic varices. Anastomotic varices after choledochojejunostomy drain directly into the intrahepatic portal vein. Therefore, endoscopic treatment is difficult for this condition and endoscopic obliterative therapy with CA is the preferred treatment for this type varices [44,45]. Endoscopic obliterative therapy with a low concentration of CA of has the potential to cause intrahepatic obstruction of the portal vein. Therefore, we carried out endoscopic obliterative therapy in this patient with a high concentration of CA, and this method was very useful for anastomotic variceal bleeding after choledochojejunostomy.

Splenic vein occlusion results in the splenic venous flow draining into collateral veins (the short gastric vein and left gastroepiploic vein) and the increased blood flow in the stomach dilates the submucosal vein, causing gastric veins. Splenic vein occlusion results from compression of the vein by mass lesions, thrombosis and so on. Madson et al. [46], reported that 65% of patients experienced pancreatitis (33% of these patients had a pancreatic pseudocyst) and benign or malignant pancreatic tumors were the cause of splenic vein occlusion in 18% of patients. Several treatment options for gastric variceal bleeding secondary to splenic vein occlusion have been proposed. Splenectomy, which decompresses the short gastric vein by cutting off inflow,

has generally been considered the best treatment of choice in such condition [47,48]. However, it is often difficult to determine whether surgical therapy should be undertaken in patients with advanced disease such as pancreatic carcinoma. EIS using CA, is useful in the treatment of bleeding gastric varices due to splenic vein occlusion [49]. In our study, EBL also is very useful treatment for this condition.

Stomal varices are a rare condition of stomal bleeding. This can occur in patients with surgically created stoma with portal hypertension. The hemorrhage is recurrent and potentially fatal. Massive bleeding from stomal varices occurs rarely but several articles have reported a mortality rate from stomal variceal hemorrhage ranging from 3% to 4% [50-52]. Stomal varices may occur with variceal erosion or trauma of the peristomal skin. Various medical treatments, such as interventional radiology and surgery have been used to control bleeding from stomal varices; however, there is no best treatment strategy for stomal varices. In patients with a poor condition, interventional radiologic techniques, such as TIPS, PTO and B-RTO have been used successfully for stomal variceal bleeding as a non-surgical option. PTO for stomal variceal bleeding also has been performed successfully [53-55]. The potential complications of PTO include bile leakage, bleeding, liver trauma, and portal vein thrombosis. Minami et al., first performed successfully B-RTO for recurrent hemorrhaging stomal varices [56]. B-RTO is also practical for treating stomal varices and also may be used for patients in a serious condition. On the other hand, TIPS is an effective alternative for hemorrhaging stomal varices [57,58]. TIPS is a relatively safe and effective means of decompressing the portal pressure but has certain limitations in patients with severe liver atrophy and complications such as encephalopathy and cerebral embolization. Injection sclerotherapy is effective in controlling acute stomal variceal hemorrhage. Several reports have revealed the usefulness and problems of injection sclerotherapy as a treatment of stomal varices [59-61]. The sclerosant should be injected slowly, taking care to ensure that the agent does not flow into the systemic circulation during treatment and avoiding. Injection sclerotherapy is safe and effective in controlling acute stomal variceal hemorrhage in our results.

Endoscopic treatments and interventional radiology have been performed successfully and safety for variceal bleeding including ectopic varices, and our analysis revealed that the frequency of ectopic variceal bleeding has been increasing recently.

CONCLUSIONS

1. Endoscopic treatments such as EIS and EBL were effective for esophago-gastric variceal bleeding.

2. Ectopic varices in patients with portal hypertension are considered to be the cause of hemorrhage presenting with lower gastrointestinal bleeding, and recently, their frequency has been increasing. Endoscopic treatments and interventional radiology were useful for ectopic variceal bleeding.

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