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Balloon-Occluded Retrograde Transvenous Obliteration versus Endoscopic Injection Sclerotherapy for Isolated Gastric Varices : A Comparative Study

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Summary: Isolated gastric varices (IGV) have a lower risk of bleeding than esophageal varices, however IGV bleeding is associated with a higher mortality than bleeding of esophageal varices. In recent years, two widely used treatments for IGV have been balloon-occluded retrograde transvenous obliteration (B-RTO) and endoscopic injection sclerotherapy (EIS) using cyanoacrylate or ethanolamine oleate (EO). This study compared these two treatment methods for IGV.

The subjects were 112 patients who were treated at our hospital for IGV bleeding between October 1990 and December 2003. Forty-nine (49) patients were treated with B-RTO and 63 patients with EIS. These two patient groups were compared as regards content of treatment, post-treatment incidence of variceal bleeding, incidence of IGV rebleeding, survival rate, cause of death, and complications. Multivariate analysis was performed on post-treatment variceal bleeding and survival.

Although EO was used in higher amounts in the B-RTO group than in the EIS group, the B-RTO group had a significantly lower number of treatment sessions and a significantly shorter treatment period ($p<0.05$). The EIS group had significantly more patients with IGV rebleeding after treatment than the B-RTO group. Treatment method was the only independent prognostic factor of IGV bleeding after treatment ($p=0.024$). The two groups did not differ significantly in the percentage of patients with aggravated esophageal varices after treatment. Bleeding from ectopic varices was not observed in any patient. There was no significant difference in survival by treatment method. The presence of hepatocellular carcinoma was the only independent prognostic factor for survival ($p=0.003$).

It is concluded that B-RTO was more effective than EIS in the eradication of IGV and prevention of IGV recurrence and rebleeding.

Key words balloon-occluded retrograde transvenous obliteration, isolated gastric varices, endoscopic injection sclerothrapy, cyanoacrylate

INTRODUCTION

Gastric varices are less common than esophageal varices in patients with portal hypertension. However, approximately 20-55% of portal hypertensive patients have been reported to have gastric varices. [1,2] Endoscopic and hemodynamic findings indicate that isolated gastric varices (IGV) lack continuity with esophageal varices. The risk of bleeding is lower for IGV than for esophageal varices, however, the mor-

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Abbreviations: B-RTO, bollon-occluded retrograde transvenous obliteration. EIS, endoscopic injection sclerotherapy. IGV, isolated gastric varices.

tality rate is higher for gastric variceal bleeding because blood flow volume and blood loss are greater. [1,3-7] Treatment options for IGV include open surgery, transjugular intrahepatic portosystemic shunt (TIPS), percutaneous transhepatic obliteration (PTO), endoscopic injection sclerotherapy (EIS), endoscopic variceal ligation (EVL), and pharmacotherapy. In Japan, balloon-occluded retrograde transvenous obliteration (B-RTO) and endoscopic treatment have been widely used. In a large percentage of patients with acute bleeding, hemostasis has been reported using endoscopic treatment with injection of n-butyl-2-cyanoacrylate (CA, Histoacryl®). [8-11] However, the incidence of rebleeding was high when the treatment concluded with hemostasis alone (34-89%). [5,12,13] Thus, recommendations on treatment policy have not been established that address the following: whether a treatment should be given to prevent rebleeding after temporary hemostasis in emergency cases, and what treatment should be given to elective cases with a history of variceal bleeding. IGVs are frequently associated with spleno-renal shunts (SRSs). [14] Kanagawa et al. [15] used this anatomical characteristic to develop and clinically implement B-RTO, which has quickly become used widely in Japan. [16,17] However, only a small number of reports have compared the effectiveness of EIS and B-RTO. This study retrospectively compared B-RTO and EIS for treatment of IGV in cases of acute bleeding and elective cases.

PATIENTS AND METHODS

Patients

One hundred forty-two (142) patients were treated for IGV at our hospital or an emergency and critical care medical center between October 1990 and December 2003. The emergency cases were defined as patients treated 24 hours or less after acute IGV bleeding and the elective cases were defined as patients with a previous history of variceal bleeding. Patients were divided into two treatment groups, B-RTO and EIS.

Of 142 patients, 54 underwent B-RTO and 88 underwent EIS with CA and EO injections. Patients were excluded if they had massive hepatocellular carcinoma (HCC), HCC that rapidly enlarged, HCC with tumor embolism of the portal vein, hepatic failure, or decreased renal function (Ccr<40mL/min). HCC was limited to a single nodule 2 cm or less (stage 1 according to the Japanese criteria) and had been controlled by non-surgical treatment such as percutaneous radiofrequency ablation or percutaneous ethanol injection. The final number of subjects was 112 (49 with B-RTO and 63 with EIS). There was no difference between the B-RTO group and EIS group in patient character-

TABLE 1.
Clinical characteristics of the patients studied

	B-RTO (n=49)	EIS (n=63)
Age (years)	62.0±8.5	64.7±11.7
Gender (men/women)	31 / 18	33 / 30
Treatment occasion		
emergency/elective*	23 / 26	57 / 6
Etiology of cirrhosis		
HBV/HCV/alcohol/others	2/33/6/8	2/43/5/13
HCC	8	11
Child-Pugh score		
overall	7.7±1.9	8.4±1.8
emergency/elective	8.0±1.9 / 7.5±1.9	8.4±1.8 / 8.3±2.3
GV Location(f/cf)	13 / 36	16 / 47
GV Form(2/3)*	10 / 39	28 / 35
History of EIS for EV	3	8

*p<0.05. HBV, hepatitis B virus. HCV, hepatitis C virus.
B-RTO, balloon-occluded retrogarade transvenous obliteration.
EIS, endoscopic injection sclerotherapy. HCC, hepatocellular carcinoma.
GV, gastric varices. f, fundal varices. cf: cardiofornical,
EV, esophageal varices.

istics including age, sex, etiology of cirrhosis, presence of HCC, Child-Pugh score, location of varix, and the number of patients with a history of EIS for esophageal varices (Table 1). During the treatment period, B-RTO was performed in 23 emergency cases and 26 elective cases, and EIS was performed in 57 emergency cases and 6 elective cases. Thus, there were more emergency cases treated with EIS than with B-RTO. The EIS group had significantly more cases with moderately enlarged varices (Form 2) compared with the B-RTO group (Table 1). In all patients, treatment was performed after obtaining informed consent.

Endoscopic and radiologic evaluation of IGV

The form of IGV (F) was classified according to the General Rules for Study of Portal Hypertension [18] of Japan: F_1: straight, small-caliber varices, F_2: moderately enlarged, beady varices, and F_3: markedly enlarged, nodular or tumor-shaped varices. The diagnosis of liver cirrhosis was made comprehensively by liver biopsy or biochemical tests, clinical findings, and abdominal ultrasound findings. The severity of liver dysfunction was graded according to the Child-Pugh classification. [19] In all subjects, the hemodynamics of IGV was examined by contrast-enhanced abdominal CT to evaluate the absence or presence of SRS.

Choice of treatment

In emergency cases, temporary hemostasis was performed using CA injection if active bleeding was observed or if many clots were present in the stomach even in periods between bleeding. When endoscopic hemostasis was achieved, treatment was continued to prevent IGV recurrence and rebleeding. B-RTO was performed if SRS was present. EIS was continued using 5% EO and CA injections, if SRS was absent or if SRS was occluded with CA injected during emergency EIS. B-RTO, and not EIS, was immediately performed if no clots were present in the stomach in the period between bleeding and if SRS was present. In elective cases, B-RTO was performed if SRS was present, and EIS was performed if SRS was absent.

Endoscopic injection sclerotherapy (EIS)

Emergency endoscopy (GIFQ230, Q240, or Q260, Olympus, Tokyo, Japan) was performed, and hemostasis was achieved by endoscopic CA injection for acute bleeding of IGV. EIS included 5%EO (ethanolamine oleate) injection as well as CA (cyanoacrylate) injection. In brief, 70% CA (CA diluted with Lipiodol) was injected using a 23-G disposable needle injector (Top, Tokyo, Japan) until endoscopic hemostasis was achieved. In the intravariceal injection procedure, negative pressure was applied after puncturing and backflow of blood into the transparent puncture tube was confirmed. A 50% glucose solution was used for rinsing before and after CA injection. If temporary hemostasis was achieved using CA in acute bleeding cases, elective EIS was begun using 5% EO within 24 hours. In elective cases, EIS was performed under fluoroscopy guidance. If there was poor contrast enhancement of IGV even after injection of 5% solution of ethanolamine oleate with iopamidol (EOI), the amount of blood flow was assumed large. Thus, CA injection was performed in combination with EO injection using the same procedure as previously described. In this study, the EIS techniques were the same as in those described in our previous reports on the treatment of esophageal varices. [20,21] Depending on the size of the varix, 1.0 ml to 20.0 mL of 5% EOI was injected into the varix without exceeding 0.4 mL/kg of the sclerosing agent per treatment session. CA was injected if EIS-related acute bleeding of IGV occurred during the treatment period, or if no backflow of blood was observed even after the sclerosing agent was injected. EIS was determined to be completed when IGV was completely eradicated, and intraluminal injection could not be performed. In general, EIS was repeated every week. All patients took oral famotidine 20 mg twice daily or oral lansoprazole 30 mg once daily during the treatment period until IGV was eradicated. If 20 mL or more of the sclerosing agent was injected during the treatment, haptoglobin 2000 U was intravenously injected to prevent renal dysfunction due to hemolysis induced by EO. [22]

Balloon-occluded retrograde transvenous obliteration (B-RTO)

In acute bleeding cases, B-RTO was performed within 1 week for IGV eradication, if SRS was observed on contrast-enhanced abdominal CT after endoscopic hemostasis using local CA injection. B-RTO was performed if SRS was observed in acute bleeding cases in the period between bleeding and in elective cases. The B-RTO procedure is described below. The patient was placed in a supine position and local anesthesia was administered in the right inguinal area. The Seldinger puncture technique was used, and a 6.5 Fr balloon catheter (Create Medic, Tokyo, Japan) was inserted from the internal iliac vein to the left renal vein. The catheter was placed retrograde through the left renal vein into the draining vein of IGV located at the midpoint

of the spleno-renal shunt. The balloon was inflated in this area, and blood flow was blocked. At this point, retrograde contrast-enhanced varicealography of IGV was performed to assess the level of visualization of IGV and the collateral circulation. A 5% EOI solution was injected slowly through a catheter until IGV and a portion of the feeding vein were visualized. The treatment was deemed complete when partial inflow of the sclerosing agent was observed in the feeding vein.

As in EIS, B-RTO was performed so that the dose of 5% EOI would not exceed 0.4 mL/kg per treatment session. In addition, if a total of 20 mL or more of sclerosing agent were administered, haptoglobin 2000 U was intravenously injected. [22] The catheter was left as is, and retrograde varicealography was performed again 24 hours later. The catheter was removed after IGV embolization was confirmed. Abdominal CT was performed after treatment to confirm thrombosis of SRS and IGV. The first upper gastrointestinal endoscopy after treatment was performed at one week post-treatment.

Follow-up

During the follow-up period, endoscopy was performed every 3 months. Patients were instructed to present promptly to our hospital if any symptoms or signs of complications or rebleeding were observed. Patients were determined to have rebleeding if upper gastrointestinal bleeding was observed in a periodic endoscopic examination, or if bleeding was observed in emergency endoscopy after patients developed hematemesis or melena. EIS using CA was repeated, if needed, to treat rebleeding from recurrent IGV.

Data Analysis

All results were expressed as mean ± standard deviation or frequency (%). For comparison of patient characteristics between the B-RTO and EIS groups, the Mann-Whitney *U* test was used for quantitative measurements, and the chi-square test with Yates correction was used for qualitative data. Fisher's exact test was also used. The Kaplan-Meier method was used for the analysis of the cumulative bleeding and survival rates, and the log-rank test was used for comparison between the B-RTO and EIS groups. Multivariate analysis using the Cox proportional hazards model was performed for the prognostic factors related to variceal bleeding and survival after treatment. Values were estimated relative risk with corresponding 95% CIs . All data analyses were performed using computer software (SPSS Inc., Chicago). Significance was established at $p<0.05$.

RESULTS

Treatment results in both groups

Table 2 shows treatment results of B-RTO and EIS. A significantly larger amount of 5% EO was used in the B-RTO group (29.1±12.1 mL) compared with the EIS group (14.5±13.5 mL) ($p<0.05$). The number of treatment sessions was significantly lower in the B-RTO group (1.4±0.6) compared with the EIS group

TABLE 2.
Treatment results in both groups

	B-RTO (n=49)	EIS (n=63)
Total volume of CA(mL) used	1.0±0.5	1.2±1.0
Total volume of EO (mL) used	29.1±12.1	14.5±13.5**
Number of treatment session	1.4±0.6*	2.3±1.8
Days needed for treatment	4.5±5.4**	12.9±17.1
Recurrence of IGV (%)	0 (0.0) *	12 (19.0)
Aggravation of EV	16	15
Treatment required in EV aggravations	10	15
Variceal bleeding		0
esophageal varices	1	1
cardiac varices	0	3
IGV rebleeding (%)	0 (0.0)**	6 (9.5)
overall (%)	1 (2.4)**	10 (15.9)

CA, cyanoacrylate. EO, ethanolamine oleate. IGV, isolated gastric varices.
EV, esophageal varices. *, $P < 0.01$. **, $P < 0.05$.

TABLE 3.
Pre- and post-treatment Child-Pugh score

	Pre-treatment	post-treatment	p
B-RTO	6.7±1.5	6.1±1.2	N.S.
EIS	7.3±1.4	7.1±1.8	N.S.

B-RTO, balloon-occluded retrograde transvenous obliteration.
EIS, endoscopic injection sclerotherapy.
N.S., not significant

(2.3±1.8) ($p<0.01$). The time until treatment completion was also significantly shorter for the B-RTO group (4.5±5.4 days vs. 12.9±17.1 days, $p<0.05$). Recurrence of IGV was observed in 12 patients in the EIS group (19.9%) but no local recurrence was observed in any patient in the B-RTO group ($p<0.01$). The B-RTO and EIS groups did not differ significantly in the percentage of patients with aggravated esophageal varices after treatment (32.7% vs. 23.8%, NS). In addition, the two groups did not differ significantly in the percentage of patients who required treatment of aggravated esophageal varices (20.4% vs. 23.8%, NS).

The Child-Pugh score is effective to evaluate liver function because it reflects albumin, bilirubin, and prothrombin time as biochemical parameters. Child-Pugh score showed no significant differences between B-RTO (p=0.1906) and EIS (p=0.7405) in the present study (Table 3).

Variceal bleeding during follow-up

Both B-RTO and EIS obliterate a major shunt (SRS) which forms IGV. Thus, the effects on post-treatment systemic hemodynamics were considered, and bleeding from other varices was examined in addition to rebleeding from IGV. Bleeding from other varices included initial bleeding from cardiac varices and esophageal varices. No bleeding was observed from ectopic varices in the duodenum, other parts of the small intestine, colon, or rectum. In the follow-up period, 1 patient had esophageal variceal bleeding in the B-RTO group (2.0%) but no patient had rebleeding from IGV. In the EIS group, a total of 10 patients had variceal bleeding (15.9%): 1 with esophageal variceal bleeding (1.6%), 3 with cardiac variceal bleeding (4.8%), and 6 with IGV rebleeding (9.5%). The EIS group had significantly more patients with variceal bleeding after IGV treatment compared with the B-RTO group ($p<0.05$, Table 2). The EIS group also had significantly more patients with IGV rebleeding (Fisher's exact test, p=0.0342, Table 2). The 1-, 3-, and 5-year cumulative % of patients free of variceal bleeding were 97.7%, 97.7%, and 97.7%, respectively, for the B-RTO group and 89.6%, 76.3%, and 76.3% for the EIS group. Thus, the B-RTO group had significantly lower incidences of bleeding after treatment (p=0.0037, Fig. 1). Multivariate analysis showed that treatment method was the only prognostic factor of variceal bleeding (Table 4A).

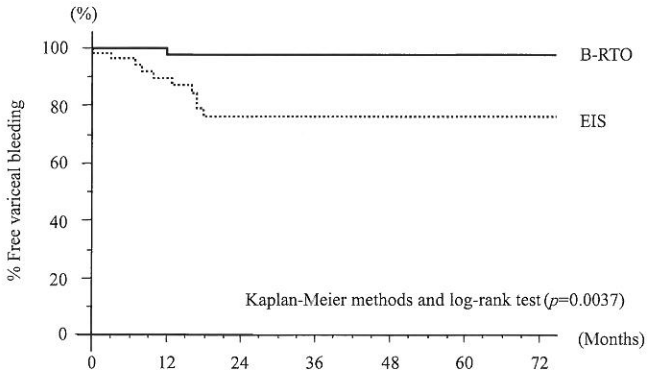

Fig. 1. Cumulative variceal bleeding in B-RTO compared with EIS
The 1-, 3-, and 5-year cumulative % of patients free of variceal bleeding were 97.7%, 97.7%, and 97.7%, respectively, for the B-RTO group and 89.6%, 76.3%, and 76.3% for the EIS group. Thus, the B-RTO group had significantly lower rates of variceal bleeding compared with the EIS group (p=0.0037).
B-RTO, balloon-occluded retrograde transvenous obliteration. EIS, endoscopic injection sclerotherapy.

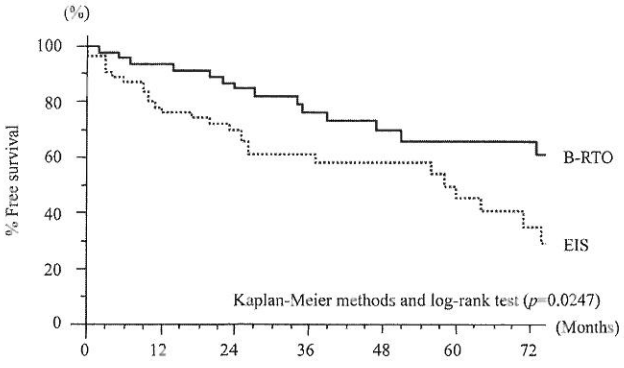

Fig. 2. Cumulative survival rate in B-RTO compared with EIS
The 1-, 3-, and 5-year cumulative survival rates were 91.5%, 76.3%, and 65.8%, respectively, for the B-RTO group and 76.3%, 58.4%, and 45.2% for the EIS group. Thus, the B-RTO group had significantly higher survival rates (p=0.0247).
B-RTO, balloon-occluded retrograde transvenous obliteration. EIS, endoscopic injection sclerotherapy.

TABLE 4.
Multivariate analysis of the prognostic factors for variceal bleeding and survival

A . Variceal bleeding after treatment for isolated gastric varices

Criterion	Variceal bleeding		
	Relative Risk	95%CI	p value
age	95%CI	B-RTO	B-RTO
sex	0.361	0.79-1.640	0.187
HCC	4.098	0.720-23.324	0.112
Child-Pugh class	0.487	0.71-3.332	0.463
Treatment	10.825	1.362-86.064	0.024

B . Survival

Criterion	Survival		
	Relative Risk	95%CI	p value
Age	1.066	1.030-1.102	0.180
Sex	0.793	0.408-1.543	0.495
HCC	3.277	1.511-7.107	0.003
Child-Pugh class	1.015	0.454-2.272	0.971
Treatment	1.712	0.896-3.270	0.104

HCC, hepatocellular carcinoma

TABLE 5.
Causes of death

	B-RTO (n=17)	EIS (n=27)	P
Hepatic failure	10	17	N.S.
Hepatoma	4	6	N.S.
Sepsis	1	1	N.S.
Bacterial peritonitis	0	1	N.S.
Cerebral hemorrhage	0	1	N.S.
Variceal bleeding	0	1*	N.S.
Unknown	2	0	N.S.

*, esophageal variceal bleeding N.S., not significant

TABLE 6.
Complications in both treatment groups

Complication	B-RTO (n=6)	EIS (n=10)	P
Respiratory dysfunction	2	1	N.S
Renal dysfunction	1	1	N.S.
Liver dysfunction	1	1	N.S.
Ascites and/or pleural effusion	2	3	N.S.
Bacteremia	1	4	N.S.
Ulcer on fundal varices	1	5	N.S.
Complication related death	0	0	N.S.

Diagnoses are repetitious N.S., not significant

Survival rate

The mean follow-up period was 42.2±34.7 months (B-RTO group: 50.0±36.1 months and EIS group: 35.6±32.3 months). The 1-, 3-, and 5-year cumulative survival rates were 91.5%, 76.3%, and 65.8%, respectively, for the B-RTO group and 76.3%, 58.4%, and 45.2% for the EIS group. Thus, the B-RTO group had significantly better survival rates (p=0.0247, Fig. 2). Multivariate analysis showed that the presence of HCC was the only independent prognostic factor of survival (Table 4B). In the follow-up period, 17 patients in the B-RTO group (34.7%) and 27 patients in the EIS group (42.9%) died (p=0.2688, N.S.). The major causes of death were hepatoma and hepatic failure. Only 1 patient in the EIS group died due to esophageal variceal bleeding (Table 5).

Complications

Complications of treatment were seen in 6 patients in the B-RTO group (12.2%) and 10 patients in the EIS group (15.8%) (p=0.5902, N.S.). There was no significant difference in complications between the two groups and no patient in either group died due to complications (Table 6). All patients with complications improved with conservative treatment.

DISCUSSION

There are reports on endoscopic treatment for IGV, including endoscopic CA injection for acute bleeding cases. [8,11] For elective and prophylactic cases, there are reports on endoscopic CA injection, pharmacotherapy, [23] EIS, EVL, TIPS, [24-26] angiographic sclerotherapy, B-RTO [15,27-29] (which can be said to be a type of catheter sclerotherapy), and balloon-occluded endoscopic injection sclerotherapy [30] (which is a combination of EIS and interventional radiology). In Japan, the most widely used treatments are B-RTO and EIS in which CA or EO is locally injected endoscopically. There is currently a controversy regarding whether B-RTO or EIS should be the first-line treatment.

Although endoscopic CA injection cannot be considered a complete cure, it is considered the only effective treatment for patients with acute IGV bleeding, [7-9,11] which has had a high mortality rate. [1,3-6] Since the clinical implementation of B-RTO, it has been used for the eradication of IGV to prevent recurrence and rebleeding after temporary endoscopic hemostasis. Prior to its implementation, EIS using CA or EO had to be continued for such IGV eradication, but this treatment was considered unreliable. In our study, 12 of 63 patients (19.0%) in the EIS group had IGV recurrence (Table 2). In contrast, the B-RTO group had complete eradication of IGV regardless of whether the patients were emergency cases or elective cases and had no recurrence. In addition, the B-RTO had no IGV rebleeding after treatment, while 6 patients in the EIS group had IGV rebleeding ($p<0.01$, Table 2). These results suggest that EIS is inadequate as a treatment for IGV. Multivariate analysis showed that treatment method was the only prognostic factor of variceal bleeding. When the aforementioned are considered, B-RTO is a better treatment than EIS for acute bleeding cases, and should be performed after temporary hemostasis is achieved with endoscopic CA injection or immediately in cases with temporary hemostasis in the period between bleeding. Contraindications for B-RTO have not been established yet. However we usually do not perform this procedure in patients with small liver (advanced liver pathology), bilirubin 5mg/dL or more, or renal dysfunction.

In this study, complete eradication of IGV was achieved after approximately one treatment session of B-RTO, and no patient had local recurrence of IGV. In contrast, two or more endoscopic treatment sessions were required for EIS. In the EIS group, the recurrence rate of IGV and rebleeding rate were significantly higher compared with the B-RTO group.

There are some reports of a high incidence of aggravated esophageal varices after B-RTO. [31,32] In our study, there was no significant difference between the B-RTO group and EIS group in the incidence of aggravated esophageal varices requiring treatment (Table 2). The cause is thought to be the vascular architecture of IGV. That is, IGV is an aneurysm formed in the midportion of SRS. Arakawa et al. [33] conducted an anatomico-pathological study of IGV and reported that one vessel entered the gastric wall and became tortuous, forming IGV. Both B-RTO and EIS embolize SRS, and blood flow to the esophageal varices would increase. This increased blood flow in both methods was speculated to be the reason why two groups did not differ significantly in the percentage of patients with aggravated esophageal varices. Portal venous pressure is elevated at 24 hours after B-RTO, but returns to prior level pressure in 4 weeks. It might be possible to prevent the aggravation of esophageal varices if EIS can selectively embolize IGV and the feeding vein and if a communication can be preserved between the draining vein of SRS and other veins (including the left renal vein), preserving its function as a portosystemic shunt at some level. However, preservation of such a major shunt is controversial. The reason is that occlusion of a major shunt by B-RTO has been reported not only to eradicate IGV but also to improve encephalopathy, [34,35] liver function, [35,36] and impaired glucose tolerance. [37] When the above information is considered, it would appear more beneficial to use B-RTO to completely occlude the portosystemic shunt that forms IGV.

There are other aspects of B-RTO that make it superior to EIS. Only one treatment session is sufficient for B-RTO. Therefore, patients do not need to be on a post-treatment restricted diet several times as in EIS. When B-RTO is performed, the nutritional status is not adversely affected in patients in whom the underlying disease is liver cirrhosis in the majority of the cases. Since only one treatment is normally needed for B-RTO, patients will spend fewer days in the hospital than those undergoing EIS, resulting in lower medical costs. In addition, since B-RTO does not require needle puncturing of the varix, it will reduce stress on doctors.

In conclusion, when patients have IGV bleeding and a major shunt such as SRS, B-RTO is a significantly superior treatment to prevent IGV recurrence and rebleeding after hemostasis compared with continuation of EIS using CA or EO. Thus, B-RTO is recommended as a first-line treatment for isolated gastric varices after achievement of hemostasis.

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