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INTERVENTIONAL

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Foam sclerotherapy using polidocanol for balloon-occluded retrograde transvenous obliteration (BRTO)

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Abstract *Purpose* To evaluate the clinical safety and effectiveness of foam sclerotherapy using polidocanol for the treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration (BRTO). *Materials and methods* From November 2005 to June 2009, foam sclerotherapy using polidocanol for the treatment of gastric fundal varices by BRTO was performed in 16 patients (male/female 11:5; age range 46–84years, median 67years). Foam was made of 3% polidocanol (Aethoxysklerol; Kreussler Pharma, Wiesbaden, Germany), room air, and contrast media, with a ratio of 1:2:1, respectively. The amount of polidocanol (2–24mL; median 7mL) depended on the volume of varices. *Results* Technical success was achieved in 15 of 16 patients (93.8%). Technical failure occurred in one patient. All patients were without pain during sclerotherapy. One patient experienced pulmonary edema after the procedure but completely recovered with medical treatment. There was no procedure-related mortality. Patients were followed by endoscopy, computed tomography, or both. Four patients were lost to follow-up. Clinical success was achieved in 10 of 11 patients (91%). Rebleeding occurred in one case during follow-up. *Conclusions* Foam sclerotherapy using polidocanol is clinically safe and effective for the treatment of gastric fundal varices during BRTO.

Keywords Balloon-occluded retrograde transvenous obliteration · Foam sclerotherapy · Polidocanol · Aethoxysklerol

Introduction

Although clinical outcomes after the treatment of variceal bleeding have improved over recent decades, fundal variceal bleeding remains a serious complication in patients with liver cirrhosis or portal hypertension. Various forms of treatment for gastric varices, including endoscopic injection sclerotherapy (EIS), percutaneous transhepatic obliteration (PTO), transjugular intrahepatic portosystemic shunt placement (TIPS), splenic artery embolization (SAE), and surgical treatment, have been described [1–7]. Among these interventional procedures, PTO, TIPS, and SAE, do not always provide a favorable clinical outcome. Moreover, the invasiveness of these procedures is a major problem. Since Kanagawa et al. [8] introduced balloon-occluded retrograde transvenous oblit-

eration (BRTO), the procedure has become the method of choice for the control of gastric fundal varices with a gastrorenal or gastrophrenic shunt because it is minimally invasive and highly effective [8–17]. Traditionally, ethanolamine oleate (EO) was used as a sclerosant for BRTO, and its efficacy as a sclerosant has been confirmed. Unfortunately, hemolysis is a well-known complication associated with EO that results in free hemoglobin release [18], causing renal tubular disturbance and acute renal failure [19, 20]. Although control of variceal bleeding is the most important issue, and the occurrence of acute renal failure is very low, minimizing the latter would be beneficial. Generally, haptoglobin has been used to prevent renal insufficiency [19, 20], but it is not always available. Moreover, the reported occurrence of hemolysis after BRTO is 45% to 100% despite the use of haptoglobin [21–23], and the risk of acute renal failure still exists [24].

Polidocanol (Aethoxysklerol; Kreussler Pharma, Wiesbaden, Germany) is a widely used sclerosant for EIS and varicose vein sclerotherapy in the lower extremities [25–28] that avoids the risk of intravascular hemorrhage. In this study, we applied a different sclerosant, polidocanol in the form of foam, to reduce the amount of sclerosant used to maximize the sclerotic effect by increasing the contacting surface area with the wall of varices, and to avoid the risk of intravascular hemorrhage. Our objective was to evaluate the clinical safety and efficacy of foam sclerotherapy using polidocanol for the treatment of gastric fundal varices by BRTO.

Materials and methods

Patients

Between November 2005 and June 2009 at our hospital, 16 BRTO procedures were performed on 16 patients (11 men and 5 women; age range 46–80 years; median age 67 years) who had gastric varices with acute bleeding or were at risk of rupture. The risk of rupture was determined endoscopically. A schematic diagram of the clinical course of the patients with gastric fundal varices in our hospital is presented in Fig. 1. Indications for BRTO were as follows: insufficient or failed EIS for gastric fundal varices with acute bleeding, gastric fundal varices as the source of bleeding on endoscopy or at a regular follow-up computed tomography (CT), and the presence of a gastrorenal or gastrophrenic shunt on contrast-enhanced CT. All patients

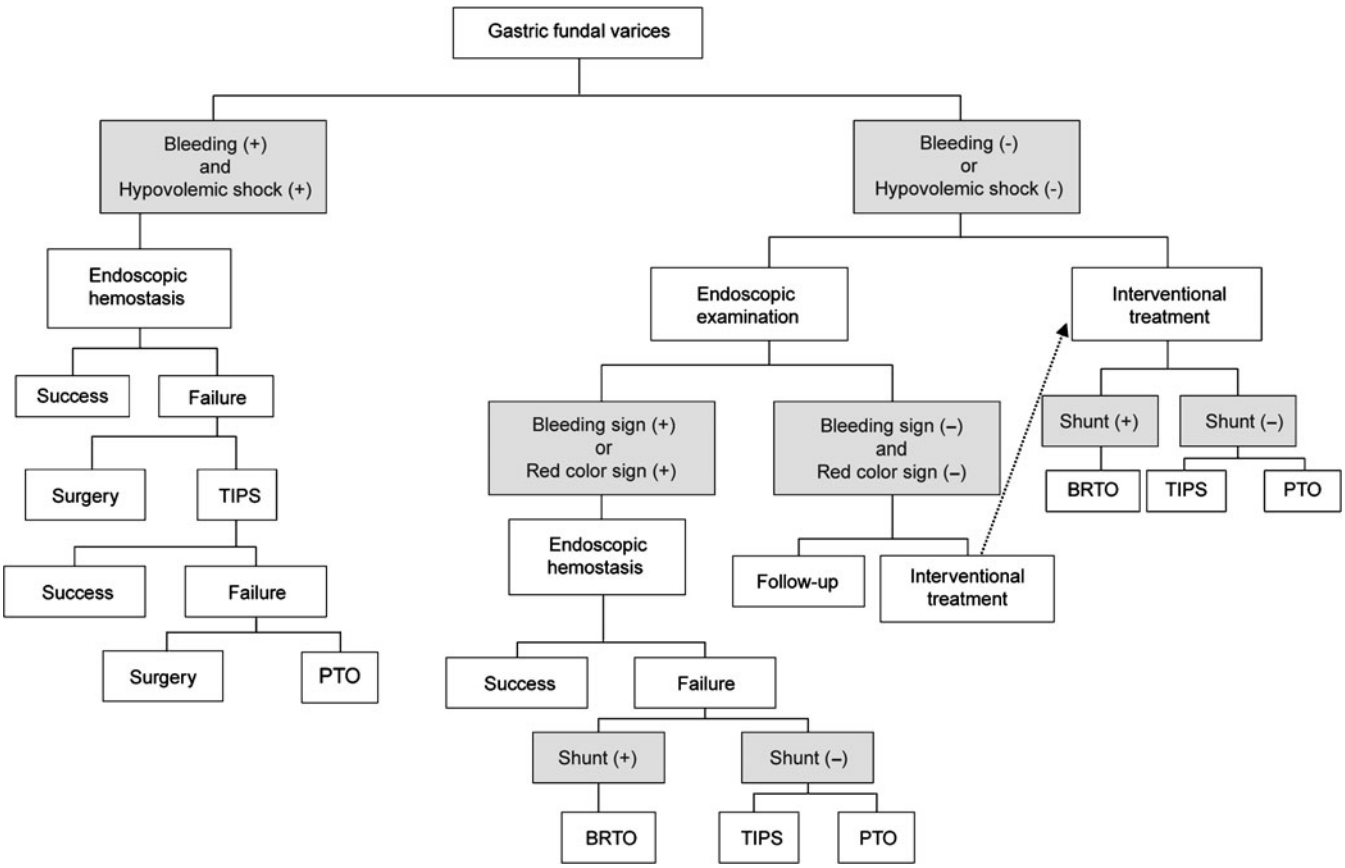

Fig. 1 Schematic diagram showing the clinical courses of patients with gastric fundal varices in our hospital. *BRTO* balloon-occluded retrograde transvenous obliteration, *TIPS* transjugular intrahepatic portosystemic shunt, *PTO* percutaneous transhepatic obliteration

underwent contrast-enhanced CT before BRTO to determine the presence of a gastrorenal or gastrophrenic shunt, and thereafter to evaluate the effectiveness of BRTO for the treatment of gastric fundal varices. Of the 16 patients, 14 had a history of EIS for gastric variceal bleeding, and the other 2 had no history of gastric variceal bleeding. The clinical characteristics of the patients are presented in Table 1.

Before the procedure, written informed consent was obtained from all patients or their responsible family members. Institutional review board approval was also obtained for this study.

Techniques

BRTO was performed in the following manner: a preflushed vascular sheath (7-Fr to 8-Fr Balkin sheath or 9-Fr Flexor Check-Flo sheath; Cook Medical, Bloomington, IN, USA) was inserted in the left renal or left adrenal vein through the right femoral or right internal jugular vein. An occlusion balloon catheter (9.5 mm to 20 mm; Boston Scientific, Natick, MA, USA) was inserted into the gastrorenal shunt through the vascular sheath. The size of the balloon catheter depended on the diameter of the gastrorenal shunt as measured on the preprocedural CT. Retrograde venography was performed with the balloon inflated for the confirmation of the feeding vein, draining vein, and gastric varix collaterals. The gastric varices and collateral veins were graded according to the system by Hirota et al. [13]. If collateral gastric variceal drainage veins were identified, they were embolized with microcoils (Tornado; Cook Medical) or gelatin sponge particles (Cutanplast; Mascia Brunelli, Milan, Italy) through a selectively catheterized microcatheter system to prevent leakage of the sclerosant into the systemic circulation. Repeat retrograde venography under occlusion balloon inflation was performed until the gastric fundal varices were fully visualized to determine the variceal volume, then the occlusion balloon was deflated while preparing the foam sclerosant.

The foam sclerosant was prepared by using the following double syringe system (DSS) method [29]: two 10-mL Luer-Lok syringes, containing 3% polidocanol, room air, and contrast media (Xenetix; Guerbet, Villepinte, France) in a 1:2:1 ratio, respectively, were connected through a three-way stopcock, and their contents were mixed until a homogeneous foam was obtained. Polidocanol was used as a sclerosant, room air for foam formation, and contrast media for radiopacity to enable fluoroscopic intervention. The amount of polidocanol used depended on the variceal volume determined by retrograde venography under occlusion balloon inflation. The foam sclerosant was injected into the gastric varices using a coaxially inserted microcatheter (2.0-Fr to 2.4-Fr) through the occlusion balloon catheter [14]. The injected sclerosant remained in the gastric varices for 1 h to 18 h (median 1 h) with the balloon inflated, and this decision was based on the shunt size and variceal volume. In some cases (patients 1, 2, 3, and 11), balloon inflation time was longer compared with their shunt size and variceal volume because these were our early experience cases. The balloon catheter was removed after checking for stable thrombus by fluoroscopy.

Table 1 Clinical characteristics of 16 patients and results of BRTO procedures

Pt. no.	Age (years)	Sex	Underlying liver disease	Concomitant malignancy	Previous gastric variceal bleeding	Initial esophageal varix[a]	Initial gastric fundal varix[a]	Initial Child–Pugh classification
1	73	F	Alcoholic LC	No	Yes	F0	F3, RB(−)	A
2	52	M	Alcoholic LC	No	Yes	F2, RC(−)	F3, RB(−)	B
3	68	M	Alcoholic LC	No	Yes	F1, RC(−)	F2, RB(+)	A
4	53	F	B-LC	No	No	F0	F3, RB(−)	A
5	84	F	Diffuse liver disease	No	Yes	F0	F2, RB(+)	A
6	73	M	Alcoholic LC	Prostate cancer	Yes	F2, RC(−)	F3, RB(+)	B
7	56	M	B-LC	HCC	Yes	F1, RC(−)	F3, RB(+)	C
8	61	M	C-LC	HCC	Yes	F1, RC(−)	F3, RB(+)	B
9	67	M	B-LC	HCC	Yes	F0	F3, RB(−)	A
10	67	M	Alcoholic LC	HCC	Yes	F1, RC(−)	F3, RB(−)	B
11	46	M	Alcoholic LC	No	Yes	No	No	B
12	69	M	C-LC	HCC	Yes	F1, RC(−)	F3, RB(+)	B
13	66	F	C-LC	HCC	Yes	F0	F2, RB(+)	B
14	56	M	B-LC	HCC	Yes	F1, RC(−)	F3, RB(−)	B
15	72	M	Alcoholic LC	HCC	Yes	F0	F3, RB(−)	A
16	50	F	Diffuse liver disease	No	No	No	No	A

BRTO balloon-occluded retrograde transvenous obliteration, *B* hepatitis B virus, *C* hepatitis C virus, *HCC* hepatocelluar carcinoma, *LC* liver cirrhosis, *RC* red color sign, *RB* recent bleeding

[a] Esophageal and gastric varices were graded by the system of Idezuki [57]

During the procedure, each patient's blood pressure, pulse, electrocardiogram, and arterial oxygen saturation were monitored.

Patient follow-up

We reviewed the medical records of the 16 patients retrospectively and maintained telephone contact with the patients who did not have a clinical visit for at least 6 months. A follow-up evaluation included the recurrence and bleeding of gastric varices, and survival, and was measured in days from the BRTO procedure until the date of death or the most recent clinical visit. Upper intestinal endoscopy or contrast-enhanced CT was performed during the hospital admission or within 1 month from the BRTO procedure to evaluate obliteration of the gastric varices. Subsequently, endoscopic or contrast-enhanced CT was performed at the discretion of the clinician.

Technical success was defined as the control of active gastric varices and stable or increasing hemoglobin levels after the BRTO procedure during the hospital admission. Complete obliteration of the gastric varies was defined as complete eradication of targeted gastric varices on follow-up CT or endoscopy after 1 month of initial treatment or thereafter. Rebleeding from the gastric varices was defined as the presence of hematemesis or melena with endoscopic visualization of the bleeding source originating from the gastric varices. Rebleeding was considered significant only if a drop occurred in the hemoglobin level compared with previous values and blood transfusion was required. Complications were defined as any untoward event that required active treatment or prolonged hospitalization.

Results

BRTO was performed once in the 16 patients using a gastrorenal shunt. The median follow-up duration was 273 days (range 3–1,403 days). The amount of polidocanol used ranged from 2 mL to 24 mL (median 7 mL). The transfemoral approach was used in 10 patients, and the transjugular approach in 6 patients. Embolization of the collateral vessels with microcoils or gelatin sponge particles (Cutanplast) was required in eight patients. All patients were comfortable during the procedure and without pain. No urine color change was observed following the procedure.

Technical success was achieved in 15 of 16 patients (93.8%). Technical failure occurred in one patient (patient 14). After completion of BRTO, hemostasis was observed, but massive variceal rebleeding occurred 2 days after BRTO in this patient. Control of variceal bleeding failed despite repeated endoscopy, and death occurred due to hypovolemic shock. Complete obliteration of gastric fundal varices with no recurrent bleeding was achieved in 10 of 11 patients (91%). Patient 7 experienced clinical failure. Massive variceal bleeding occurred in this patient at 2 months after the initial procedure, and emergent EIS

Table 2 Overall results of BRTO procedures

Pt. no.	Gastric varix grade[a]	Amount of polidocanol (mL)[b]	Balloon inflation time (min)	Follow-up esophageal varix[c]	Follow-up Child–Pugh classification	Follow-up duration (day)	Technical success	Clinical result	Complication
1	1	24	1,080	No	A	1,403	Success	Success	Pulmonary edema
2	2	4	360	F1, RC(−)	B	985	Success	Success	No
3	3	8	270	F1, RC(−)	A	1,166	Success	Success	No
4	2	4	60	F0	A	691	Success	Success	No
5	1	2	60	F0	A	4	Success	–[e]	No
6	2	6	60	No	A	327	Success	Success	No
7	2	8	60	F1, RS(+)	C	67	Success	Failure[f]	No
8	3	8	60	No	A	413	Success	Success	No
9	1	5	60	F0	A	420	Success	Success	No
10	3	4	60	No	A	324	Success	Success	No
11	2	3	1,080	No	B	3	Success	–[e]	No
12	2	12	90	No	B	23	Success	–[e]	No
13	1	10	90	No	C	222	Success	Success	No
14	3	8	60	Unchecked[d]	B	13	Failure	–[f]	No
15	2	10	90	No	A	131	Success	Success	No
16	1	2	60	No	A	30	Success	–[e]	No

RC red color sign, *RB* recent bleeding

[a] Variceal grade followed that of Hirota et al. [13]

[b] The polidocanol concentration represents the polidocanol concentration alone, not the total volume of the mixture

[c] Esophageal varices were graded by the system of Idezuki [57]

[d] This patient underwent emergent endoscopy for massive upper gastrointestinal bleeding with insufficient evaluation of esophageal varices

[e] These patients refused follow-up examination such as endoscopy or CT after 1 month follow-up. We contacted those four patients by telephone and confirmed no history of hematemesis or melena since BRTO

[f] These patients died

was performed. However, this patient died due to multiorgan failure. Four patients (patients 5, 11, 12, and 16) were lost to follow-up after BRTO. We contacted those four patients by telephone and confirmed no history of hematemesis or melena since BRTO. Pulmonary edema occurred in patient 1, about 10 h after the procedure, and the patient completely recovered with diuretics after 4 days. No procedure-related mortality was observed. No significant deterioration of Child–Pugh classification was observed before or after BRTO. The overall results are summarized in Table 2. See Fig. 2 for results for patient 4.

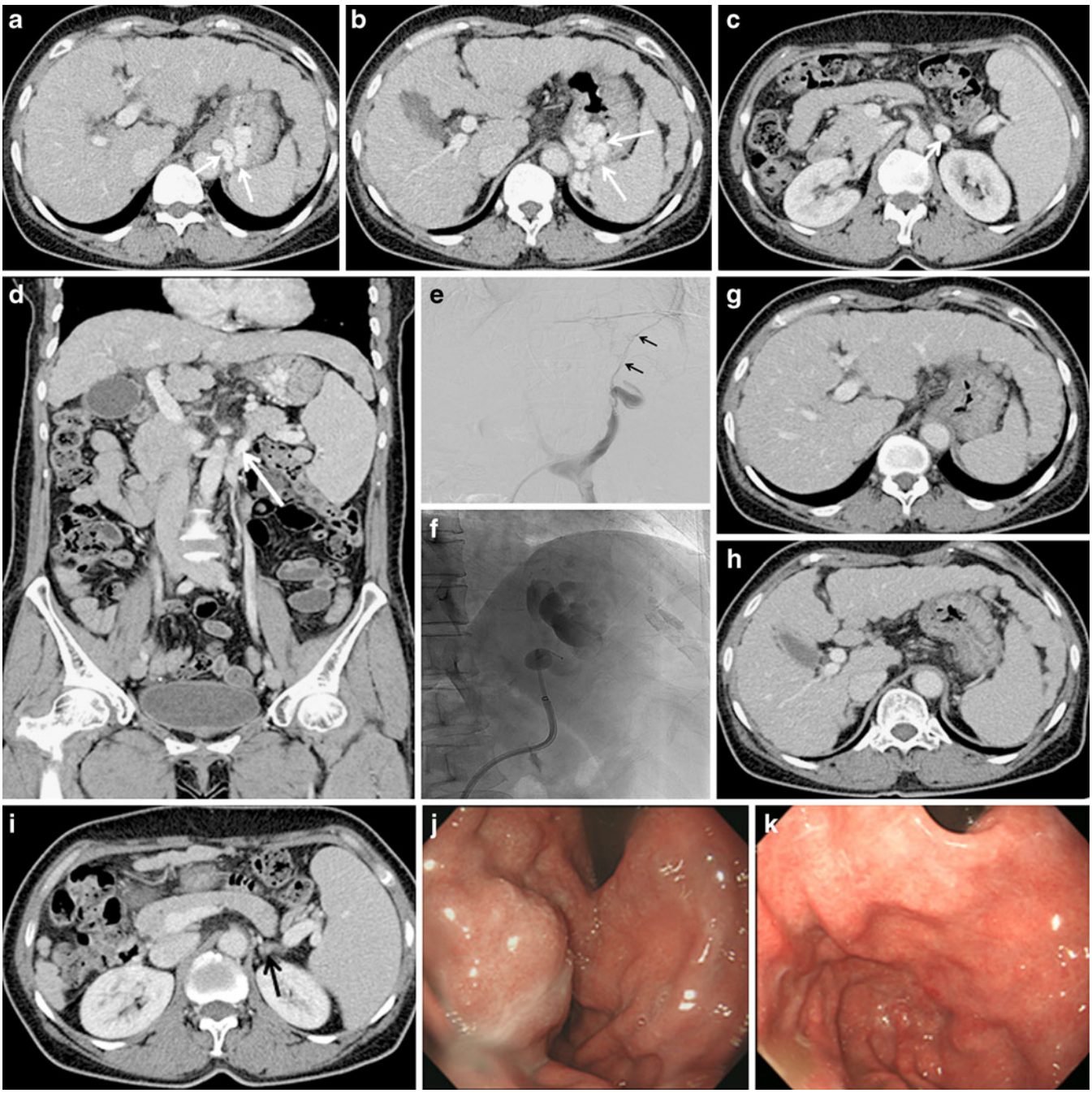

Fig. 2 A 53-year-old woman with gastric fundal varices. **a**, **b** Contrast-enhanced CT obtained before BRTO showed gastric fundal varices (*arrows*). Gastrorenal shunt (*arrow*) was observed in the axial and coronal reformatted image (**c**, **d**). **e**. Retrograde venography was performed by using a gastrorenal shunt. The left inferior phrenic vein (*arrows*) was opacified and was embolized using gelfoam particles. **f** Using a coaxial microcatheter system, fundal varices were selected and filled with the foam sclerosant polidocanol under balloon inflation. **g**, **h** Contrast-enhanced CT obtained 2 years after BRTO showing complete regression of gastric varices. **i** Complete obliteration of the gastrorenal shunt (*arrow*) was also observed. **j** Preprocedural endoscopy shows tortuous and dilated gastric fundal varices. **k** Endoscopy after 2 years of follow-up shows complete regression of previously observed fundal varices

Discussion

For the treatment of gastric fundal varices, endoscopic treatment is the first-choice therapy [30]. However, when an endoscopy fails or cannot be performed, interventional treatment is the second choice therapy for gastric fundal varices. Traditionally, several interventional treatments such as TIPS, SAE, and PTO have been performed for the treatment of gastric fundal varices, but the invasiveness of these procedures poses a serious problem.

BRTO is a minimally invasive interventional procedure, requiring only local anesthesia at the puncture site. This method has been widely performed for the treatment of gastric varices using a gastrorenal shunt, and it has achieved excellent treatment results, with an initial success of 87% to 100% [8, 11, 12, 21, 31].

Detergents have been used as sclerosing agents in either liquid or foam forms. Traditionally, liquid sclerosant, especially EO, is used for BRTO [11, 13, 21, 24, 31–34]. Foam sclerosant is applied for the conventional treatment of varicose veins in the lower extremities [35, 36]. Foam sclerotherapy using the detergent polidocanol is well known for its safety and efficacy in varicose vein treatment [37–39]. Breu and Guggenbichler [40] reported that the larger the diameter of the vein, the more viscous the foam should be to obtain better results. Taken together, we chose polidocanol as the sclerosing agent, contrast media for fluoroscopic visualization, and room air for foam formation. In addition, the DSS method, a standardized procedure for foam sclerosing agents, was used for viscous foam formation [29].

Compared with liquid sclerosants, foam sclerosants have several advantages, including reducing the amount of sclerosant needed, maximizing the sclerotic effect by increasing the contact surface area with the wall of varices, providing an even distribution of the sclerosing agent, and decreasing the balloon inflation and procedure times. According to several previous reports, the median EO volume was between 20 mL and 35 mL, and the balloon inflation time ranged from 30 min to overnight [11, 13, 31, 33, 41]. However, in our results, the median polidocanol volume was 7 mL, and the median balloon inflation time was 60 min. Most importantly, the serious complications associated with EO, hemoglobinuria and renal failure, are avoided. Clinical success and complications were comparable to previous BRTO reports [42]. Moreover, since polidocanol was originally developed as a local anesthetic, patients felt more comfortable during the procedure because of its anesthetic effect [43, 44].

Concerns exist regarding the maximum dose of polidocanol. According to the manufacturer's guidelines, the maximum daily dose of polidocanol based on body weight is 2 mg/kg/day [45]. Theoretically, systemic complications such as cardiotoxicity can occur after the systemic diffusion of polidocanol, when it passes into the systemic circulation from the injection site, such as during varicose vein treatment [46]. However, in BRTO, polidocanol has no chance to pass into the systemic circulation from the injection site. Moreover, in BRTO, complete filling of the foam sclerosing agent in the fundal varices is mandatory for the treatment of gastric fundal varices. There are a few reported studies using polidocanol above the maximum daily dose, based on body weight, for the treatment of variceal bleeding and venous malformation [43, 47, 48]. One report demonstrated the use of polidocanol by paravariceal injection at concentrations greater than the recommended daily dose for the treatment of gastric varices [47]. According to this report, the authors used 1% polidocanol for paravariceal injection sclerotherapy in 56 patients, and range of total volume of the 1% polidocanol was 20–54.9 mL. Another report demonstrated intravariceal injection of polidocanol above the maximum daily dose, based on body weight, for the treatment of esophageal varices [48]. In this report, the authors used 1% polidocanol for intravariceal injection up to the 30 mL. Recently, a new reported trial was published about polidocanol sclerotherapy for the treatment of venous malformations in *European Radiology* [43]. These authors used 3% polidocanol in 31 patients, and according to their report, mean dose of polidocanol was 212 mg/session, which also exceeded the recommended maximum dose based on body weight. All three studies reported no complication related to overdose of the polidocanol. In two of the reports, polidocanol had little chance to pass into the systemic circulation and so no complication occurred despite its overdosage. Therefore, we hypothesized that dose limitation of polidocanol was less important in BRTO, and we completed the filling of the foam sclerosant in the fundal varices. In our study, despite 10 of 16 patients undergoing the BRTO procedure using polidocanol at greater than the maximum daily recommended dose (except patient 1), no complication occurred. However, we agree that reducing the polidocanol dose is important for the prevention of systemic complications and that is why we made foam—to reduce the actual amount of polidocanol as well as to maximize the sclerotic effect. And, closer monitoring and meticulous handling for avoidance of balloon rupture should be mandatory to escape unwanted systemic complication.

Until now, very few severe systemic complications have been reported, including cardiac complications, neurologic deficits, pulmonary embolism, and stroke [46, 49–53]. In our study, one patient (patient 1) experienced a complication. Dyspnea occurred 10 h after BRTO in this patient, and the clinical and radiologic manifestation of this condition was pulmonary edema. After 4 days of treatment with diuretics, the pulmonary edema was completely resolved. The polidocanol dose used in this patient was 24 mL, the highest dose used in our study. No previously reported data exist regarding the relationship between the polidocanol dose and the occurrence of pulmonary edema. However, 24 mL was much greater than the median polidocanol volume used in our study; therefore, we thought that the pulmonary edema was related to an overdose of polidocanol. Among the complications, cardiotoxiticty is related to the local anesthetic properties of polidocanol, and this is proportional to the patient's blood levels, not solely the dose

[54]. However, the incidence of this complication is extremely rare [46, 55, 56]. Stroke is related to the underlying patent foramen ovale [51, 52], and the neurologic deficit is transient [53]. Therefore, close monitoring with detailed evaluation is helpful to manage and reduce the complications associated with polidocanol use.

Our results demonstrated that foam sclerotherapy using polidocanol has a high efficacy and an excellent safety profile in BRTO. Moreover, haptoglobin was not necessary to protect against renal failure. This pilot study demonstrated that foam sclerotherapy using polidocanol was clinically safe and effective for the treatment of gastric fundal varices during BRTO.

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