



Usefulness of antegrade foam sclerotherapy for portal hypertensive variceal bleeding

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PURPOSE

This study investigates the usefulness of antegrade variceal embolization using sclerosant foam to evaluate technical success and clinical outcomes in cases of hypertensive variceal bleeding.

METHODS

A total of 16 patients underwent percutaneous antegrade variceal embolization using foam sclerotherapy from August 2019 to January 2022. Among the patients, 12 cases were of gastroesophageal varices, two were rectal varices, and one case each was duodenal and jejunal varices, respectively. Sodium tetradecyl sulfate (STS) foam was used as a detergent for variceal bleeding sclerotherapy at various anatomical locations. The detergent was used in a foam form to promote clinical outcomes and enable the effective embolization of the entire blood vessel wall, including the ventral side, against gravity. Furthermore, STS foam could be used to help sufficiently deliver the drug to distal segments. A balloon catheter was also used to block the antegrade flow and prevent the dilution of the sclerosant. Technical success was defined as the completion of sclerotherapy for variceal bleeding as planned before the procedure to achieve the disappearance of variceal bleeding. Clinical success was defined as the complete obliteration of varices without recurrent bleeding during the follow-up period after the procedure.

RESULTS

Technical success was 81.3%, and clinical success was 84.6%. Additionally, 15/16 of the procedures were emergencies, and there were no complications related to the procedure.

CONCLUSION

Antegrade foam sclerotherapy using 3% STS for variceal bleeding is clinically safe and effective. Moreover, antegrade foam sclerotherapy can be a useful treatment option for patients with active variceal bleeding in emergency cases.

KEYWORDS

Portal hypertension, variceal bleeding, percutaneous endovascular variceal embolization, foam sclerotherapy

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Endoscopic management is the recommended first-line treatment for variceal bleeding. However, in a significant number of patients with variceal bleeding, the endoscopic approach may fail due to the patient's unstable vital signs and difficulties in securing the visual field.¹⁻⁴ In these cases, an alternative interventional treatment option, such as transjugular intrahepatic portosystemic shunt (TIPS) and balloon-occluded retrograde transvenous obliteration (BRTO), should be considered. However, although the therapeutic results of TIPS are good, it cannot be performed in patients with hepatocellular carcinoma, and it carries the risk of complications such as encephalopathy.⁵⁻⁹ Conversely, BRTO is known to show a very safe and high success rate while compensating for the shortcomings of TIPS.¹⁰ Nevertheless, there

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are some limitations to BRTO, e.g., it can only be performed when there is an accessible shunt through the systemic venous system, and without such a shunt, the procedure is not possible.

The drawbacks of BRTO can be partially overcome using an alternative method such as direct variceal embolization with an antegrade approach. Percutaneous antegrade varix obliteration (PAVO) can, theoretically, permanently obliterate the varices and all feeding veins. It is performed by approaching from the afferent vessels so as not to increase the risk of variceal development.^{10,11} In addition, PAVO has the advantage of being able to quickly and easily access the bleeding focus in patients with active bleeding.¹¹

Most variceal embolization procedures using the antegrade approach have been performed using liquids such as an n-butyl cyanoacrylate (NBCA) mixture or several detergents.^{4,12-14} For effective bleeding control, the embolic material must be well-delivered to the varix where bleeding is suspected. In the case of the NBCA mixture, there is a high possibility of embolization of only the proximal segment of the selected blood vessel. Therefore, it is often difficult to deliver the NBCA mixture to the varix. This results in insufficient varix embolization, leading to the failure of bleeding control or re-bleeding. Sclerotherapy using a sclerosant is effective for drug delivery along the bloodstream to the distal segment; however, the concentration of the drug is lowered as the blood flow and the drug are mixed, thus decreasing the effect of sclerotherapy. Additionally, due to gravity, there is less contact with the wall of the blood vessel on the ventral side among the blood vessel walls through which the drug passes. Therefore, the effect of liquid

sclerotherapy may decrease. Furthermore, drug distribution to the branching vessels other than the main flow can decrease in the case of multiple branching vessels to the varices. These factors may eventually decrease the therapeutic effect of varix embolization through the antegrade approach, which can potentially cause rebleeding.

Detergent agents have been used as sclerosing agents in a liquid or foam form. The effectiveness of foam sclerotherapy for varix bleeding control was first reported in BRTO.¹⁵ According to this report, compared with liquid sclerosants, a foam has several advantages, including reducing the amount of sclerosant needed, maximizing the sclerotic effect by increasing the contact surface area with the wall of the varices, and providing even distribution of the sclerosing agent, thus decreasing the balloon inflation and procedure times.¹² Accordingly, to compensate for the shortcomings of liquid sclerosants, sodium tetradecyl sulfate (STS) was used as a detergent in a foam form to perform varix sclerotherapy for various variceal bleeding sites. Finally, this study aims to evaluate the clinical safety and effectiveness of the antegrade approach using foam sclerotherapy for variceal bleeding.

Methods

Patients

Sixteen patients who were treated with PAVO for gastroesophageal varices or non-gastroesophageal varices between August 2019 and January 2022 at Ewha Womans University Mokdong Hospital were retrospectively evaluated. This patient group comprised 16 men with a median age of 58 years (range, 38–66 years). Of these patients, 12 had gastroesophageal varices, 2 had rectal varices, 1 had duodenal varices, and 1 had jejunal varices. Additionally, 9 patients had a history of endoscopic treatment, such as endoscopic variceal ligation (EVL) or endoscopic injection sclerotherapy (EIS), 1 patient had received both endoscopic treatment and BRTO, and 1 patient had undergone liver transplantation a year before the procedure. Prior to the procedure, all patients underwent enhanced computed tomography (CT) or endoscopy to evaluate the severity of the varices and the effectiveness of the procedure (Figure 1a). All 16 patients underwent enhanced CT, and 13 patients underwent both endoscopy and enhanced CT. The clinical characteristics of the patients are listed in Table 1.

Main points

- The usefulness of antegrade variceal embolization using sclerosant foam to evaluate technical success and clinical outcomes in cases of hypertensive variceal bleeding was studied.
- Technical success was 81.3%, clinical success was 84.6%, 15/16 procedures were emergencies, and there were no complications related to the procedure.
- Antegrade foam sclerotherapy using 3% sodium tetradecyl sulfate for variceal bleeding is clinically safe and effective.
- Antegrade foam sclerotherapy can be a useful treatment option for patients with active variceal bleeding in emergency cases.

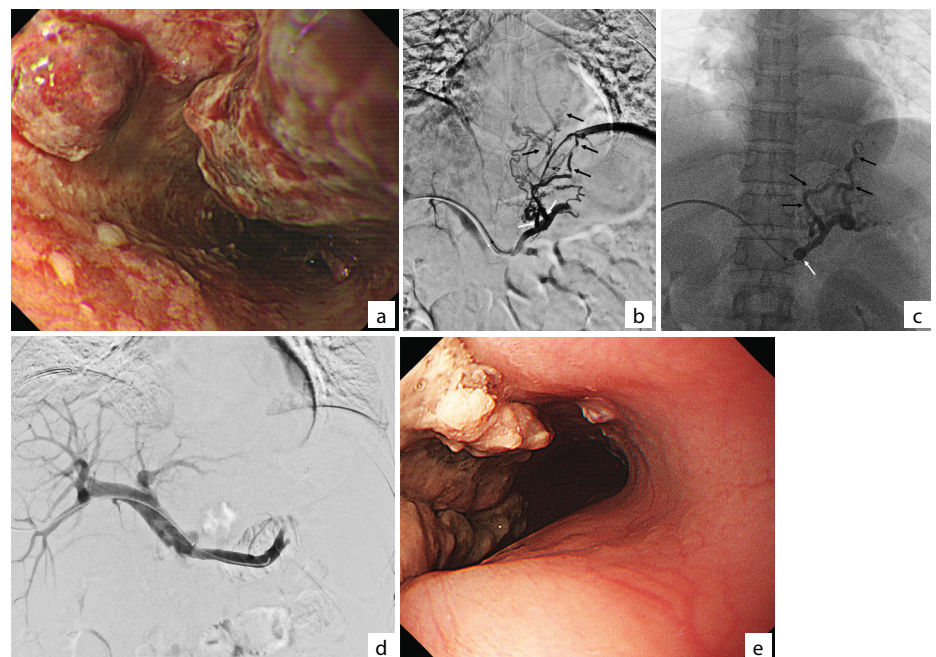


Figure 1. A 52-year-old man with gastroesophageal varices. (a) Endoscopy shows marked engorged gastroesophageal varices, grade GII (red color sign). (b) Antegrade venography through a transportal approach shows multiple gastric and esophageal varices (black arrow). Two branching vessels (white arrow) are denoted as feeding vessels to the varices. (c) Multiple varices (black arrow) are filled with foam sclerosant (3% sodium tetradecyl sulfate) under inflation by the balloon catheter (4Fr Fogarty catheter) (white arrow) at the coronary vein ostium. (d) Follow-up splenoportography after completing sclerotherapy shows the complete obliteration of previously noted gastric and esophageal varices. (e) Follow-up endoscopy nine days after percutaneous antegrade varix obliteration showing the complete thrombotic occlusion of a previously engorged varix with no red color.

Table 1. Clinical characteristics of the 16 patients

Pt. no.	Age (years)	Sex	Etiology of LC	Concomitant malignancy	Location of the varix	Past history of varix treatment	Endoscopic varix grade ^a	Pre-procedural imaging
1	65	M	Alcohol	No	Gastroesophageal varix	EVL	GII, LmF2Cb, RC (+)	CT, endoscopy
2	47	M	Alcohol	No	Gastroesophageal varix	EVL	GII, LmF2Cb, RC (+)	CT, endoscopy
3	54	M	Alcohol	No	Gastroesophageal varix	EVL	GII, LsF2Cb, RC (+)	CT, endoscopy
4	58	M	HBV	HCC	Gastroesophageal varix	EVL	GIII, LsF3Cb, RC (+)	CT, endoscopy
5	54	M	Alcohol	No	Gastroesophageal varix	No	GII, LmF2Cb, RC (-)	CT, endoscopy
6	65	M	Alcohol	No	Gastroesophageal varix	EVL	GII, LmF2Cb, RC (-)	CT, endoscopy
7	41	M	Alcohol	No	Rectal varix	No	GII, RC (-)	CT, endoscopy
8	62	M	Alcohol	No	Duodenal varix	No	GI, LiF1Cb, RC (-)	CT, endoscopy
9	38	M	Alcohol	No	Gastroesophageal varix	EVL, EIS, BRTO	GI, LiF1Cb, RC (-)	CT, endoscopy
10	66	M	Non-B and non-C	HCC	Gastroesophageal varix	No	N/A	CT
11	57	M	Alcohol	No	Gastroesophageal varix	EIS	GIII, LsF3Cb, RC (+)	CT, endoscopy
12	59	M	Non-B and non-C	No	Jejunal varix	No	N/A	CT
13	60	M	Alcohol	No	Gastroesophageal varix	EVL	GIII, LsF3Cb, RC (+)	CT, endoscopy
14	58	M	Alcohol	No	Rectal varix	LT	N/A	CT
15	58	M	Alcohol	No	Gastroesophageal varix	EVL	GIII, LsF3Cb, RC (+)	CT, endoscopy
16	52	M	HBV	No	Gastroesophageal varix	No	GII, RC (+)	CT, endoscopy

^aEsophageal and gastric varices were graded by the system presented in Tajiri et al.¹⁶ M, male; Pt. no., patient number; HBV, hepatitis B virus; LC, liver cirrhosis; HCC, hepatocellular carcinoma; EVL, endoscopic variceal ligation; EIS, endoscopic injection sclerotherapy; BRTO, balloon-occluded retrograde transvenous obliteration; LT, liver transplantation; CT, computed tomography; N/A, not applicable.

This retrospective study was approved by the Institutional Review Board of the Ewha Womans University Mokdong Hospital (EUMC 2022-05-044 2022-06-02) with a waiver for informed patient consent.

Procedures

The approach to variceal bleeding was initiated employing either the percutaneous transhepatic or trans-splenic approach under ultrasonographic and fluoroscopic guidance using local anesthesia. The decision to access the liver or the spleen was based on the operators' judgment at the time of the procedure. If liver function was maintained with no or a small amount of ascites, the transhepatic approach was considered first. Otherwise, the trans-splenic approach was used. Using a 22-gauge Chiba needle (Neff Percutaneous Access Set, Cook Medical, Bloomington, IN, USA), a percutaneous puncture of the intrahepatic portal or splenic veins was performed. Then, a pre-flushed vascular sheath (6-Fr Balkin sheath; Cook Medical, Bloomington, IN, USA) was inserted through the portal or splenic veins. Portography or splenoportography via the inserted sheath was performed to evaluate the feeding vein, draining vein, and varix collaterals. Subsequently, a 5-Fr catheter (KMP; Cook Medical, Bloomington, IN, USA) was inserted to select the main antegrade feeding vessel and perform antegrade venography to eval-

uate the varix (Figure 1b). If the selection was successful, an occlusion balloon catheter (4 or 5.5-F Fogarty catheter, Edwards, USA) was exchanged to occlude the main antegrade flow. Thereafter, a foam sclerosant was directly injected into the feeding veins to the entire varices through the occlusion balloon catheter under fluoroscopic guidance (Figure 1c). If the main feeding vessel was too thin or too tortuous to insert the balloon catheter, the sclerosant was injected through the 5-F catheter directly or by a coaxially inserted microcatheter (1.9-F microcatheter, Progreat Lambda 19, Terumo, Tokyo, Japan). Thereafter, 3% fibroven (STD Pharmaceutical Products Ltd, Hereford, UK) was used as a sclerosant. The foam sclerosant was prepared using the following double syringe system method:¹⁷ two 10 mL Luer-Lok syringes containing 3% STS, room air, and contrast media (Pamiray 300; Dongkook Pharm., Seoul, Korea) in a 1:2:1 ratio, respectively. The syringes were then connected through a three-way stopcock and their contents were mixed until a homogeneous foam was obtained. The approximate amount of 3% STS used depended on the variceal volume determined by antegrade venography. The sclerosant injection was administered until drug filling was observed in both the feeding vein and the target varix on fluoroscopy. Since the volume of the varix was too large, if an excessive amount was needed to fill the entire varix with STS, gelatin sponge

particles (Caligel, 560–710 μm , Hangzhou Alicon Pharm SCI. & TEC. Co. Ltd., Hangzhou City, Zhejiang, China) were mixed and used together. When the operator judged that the sclerosant had been sufficiently injected, the contrast medium was manually injected through the catheter to evaluate whether there were any residual varices. If a residual varix was observed, the process of manually injecting the contrast medium after injecting an additional sclerosant was repeated. After finishing the infusion of the sclerosants, all the catheters used were slowly withdrawn after 30–60 minutes from the onset of infusion. Portography or splenoportography was then again performed to assess the obliteration of the varices, and if any feeding veins remained, the procedure was repeated to completely obliterate the varices (Figure 1d). In cases where the feeding vein was more than 2–3 mm in diameter, proximal segment feeding-vein embolization was performed using metallic materials such as coils. Finally, the puncture tract within the liver or spleen was embolized with an NBCA mixture and microcoils (Cook Medical, Bloomington, IN, USA).

During the procedure, each patient's blood pressure, heart rate, electrocardiogram, and arterial oxygen saturation were monitored. Furthermore, prophylactic antibiotics were administered before the procedure to prevent infection.

Patient follow-up

The medical records of the 16 patients were retrospectively reviewed for follow-up. The evaluation included the recurrence and bleeding of varices and the rate of survival. Moreover, the duration was measured in days from the procedure until the date of death, the most recent clinical visit, or a scheduled surgery, such as liver transplantation. Unless the follow-up examination was not possible due to the patient's death, or if clinical departments considered the exam unnecessary, an endoscopic examination or contrast-enhanced CT was performed after the procedure to evaluate the obliteration of the varices (Figure 1e).

Technical success was defined as the completion of the sclerotherapy for variceal bleeding as planned before the procedure to achieve the disappearance of variceal bleeding. If there was immediate variceal bleeding after the procedure, it was regarded as a technical failure. Clinical success was defined as the complete obliteration of varices without recurrent bleeding during the follow-up period from the procedure date. The recurrence and bleeding of varices were evaluated by endoscopic examination or contrast-enhanced CT after the procedure. Rebleeding from the varices was defined as the presence of hematemesis or melena with endoscopic visualization or confirmed bleeding from the varices in contrast-enhanced CT. Rebleeding was considered significant only if the hemoglobin level dropped compared with previous values and a blood transfusion was required. Complications were defined as any untoward events that required active treatment or prolonged hospitalization. Due to the small number of patients, no statistical analysis was performed.

Results

PAVO was performed in 16 patients using 3% fibrovenin. In all cases, the pre-procedural CT images showed no shunt available for retrograde obliteration of the varices. Of the 16 patients, 15 underwent emergency embolization due to acute bleeding from the varices and 1 (patient 13) had the procedure done for prophylaxis.

Technical success was achieved in 13 of 16 patients (81.3%); 3 of the 16 patients experienced recurrent bleeding during hospital admission (patients 2, 4, and 14 in Table 2) and all 3 had massive variceal rebleeding immediately after the procedure and received blood transfusions due to decreased hemoglobin levels. Patient 2 underwent liver

transplantation 14 days after the procedure and died 38 days after the initial procedure due to multiorgan failure. Patient 4 showed melena 1 day after the procedure and died due to septic shock caused by spontaneous bacterial peritonitis. Patient 14 showed hematochezia immediately after the procedure and died due to hypovolemic shock and hepatorenal syndrome.

The transhepatic approach was used in 11, and the trans-splenic approach in 5 patients. The amount of 3% fibrovenin used ranged from 4–50 mL (median, 15 mL). Additional embolization using gelatin sponge particles (Caligel) was performed in 11 patients, and an occlusion balloon catheter was used in 12 patients. The median follow-up duration was 40 days (range, 1–702 days). The overall results are summarized in Table 2.

Among the 16 patients, 11 underwent follow-up examination (1 underwent endoscopy, 3 underwent CT scans, and 7 underwent both endoscopy and CT). However, 2 patients refused the follow-up examination (patients 4 and 8), and 3 patients died before the follow-up examination (patients 1, 5, and 10).

Clinical success was achieved in 11 of 13 patients (84.6%). Among these 11 patients, 7 with follow-up imaging showed a complete obliteration of varices with no recurrent bleeding during the follow-up period. In addition, 4/11 patients who did not undergo follow-up examinations did not have recurrent bleeding during the follow-up period (Table 2). Recurrent variceal bleeding was noted in 2 patients (patients 6 and 15). Moreover, patient 6 experienced two episodes of recurrent bleeding, the first occurring one year after the initial procedure and the second occurring two years after the procedure. Both episodes were successfully controlled through a sequential treatment approach involving additional PAVO and EVL. Patient 15 also experienced two episodes of recurrent bleeding, the first at 5 months and the second occurring 1 year after the initial procedure; the bleeding was also well controlled using PAVO and EVL, sequentially.

Recurrent bleeding also occurred in patients 3 and 16; however, it was unrelated to the variceal bleeding. Patient 3 developed hematemesis and melena 82 days after the embolization; however, only a gastric ulcer was noted in the endoscopy without evidence of variceal bleeding. Patient 16 developed hypotension and hematochezia 6 days after the procedure; arterial bleeding was confirmed on CT angiography, and hemosta-

sis was achieved by performing trans-arterial embolization of the left gastric artery. There were no complications related to the procedure in any of the patients.

Discussion

Variceal bleeding is a serious complication in patients with portal hypertension and is associated with high mortality. Endoscopic treatments such as EIS or EVL are the first-line treatment options for variceal bleeding.² In case of difficulties performing endoscopic treatment, the alternative treatment is an endovascular procedure such as TIPS or BRTO.^{5,18,19} In patients with portal hypertension, if clinical follow-up is good and endoscopic examinations are performed regularly, bleeding control can be achieved through scheduled procedures involving the above-mentioned treatment options in most cases. However, emergency bleeding situations may occur in patients who do not know their medical history or do not receive regular check-ups. These patients will experience sudden bleeding and are admitted to the hospital in an emergency situation. Most of these patients will exhibit unstable vital signs and active bleeding, making it difficult to achieve proper treatment in a short period, as the visual field cannot be secured endoscopically. There are many risks associated with the TIPS procedure as most of the patients were hemodynamically unstable. Therefore, in these emergencies, it is important to target and treat the bleeding varix quickly using an endovascular method. If the varix has an accessible shunt, BRTO can be prioritized in these cases. Many studies have been published on successful hemostasis with BRTO for ruptured varices.²⁰⁻²² However, if retrograde obliteration is difficult, as in the present study, PAVO may be an alternative and is considered one of the best hemostatic options for bleeding varices in emergencies. Therefore, in this study, 15 of 16 patients received PAVO in an emergency situation.

Different from BRTO, various types of variceal bleeding can be controlled using an antegrade approach. In this study, embolization was performed using an antegrade approach through the portal or splenic vein to access various types of varices, including esophageal, gastric, duodenal, jejunal, and rectal varices.

Detergents have previously been used either in a liquid or foam form in various vascular embolization procedures.^{12,17,23-28} In this study, STS foam was used as a sclerosant.

Table 2. Overall results of percutaneous antegrade varix embolization

Pt. no.	Approach vessel	Amount of STS (mL) ^a	Additional embolic material (varix)	Embolic material (feeder ostium)	Used catheter	No. of feeding veins	Follow-up duration (procedure to 1 st following imaging) (day)	Follow-up imaging modality	Overall follow-up duration (day)	Technical success	Clinical success
1	Portal vein	15	Gelfoam	Microcoils	5.5-F balloon, 5Fr catheter*	2	N/A	None	4	Success	Success
2	Portal vein	15	None	Vascular plug	Microcatheter	1	17	CT	38	Failure	N/A
3	Portal vein	15	None	Microcoils, NBCA mixture	Microcatheter	1	6	CT, endoscopy	109	Success	Success
4	Splenic vein	20	None	No	4-F balloon	1	N/A	None	17	Failure	N/A
5	Splenic vein	5	Gelfoam	No	4-F balloon	1	N/A	None	1	Success	Success
6	Portal vein	10	None	No	4-F balloon	1	395	Endoscopy	702	Success	Failure
7	Portal vein	5	Gelfoam	No	4-F balloon	1	8	CT, endoscopy	353	Success	Success
8	Portal vein	25	None	No	5.5-F balloon	2	N/A	None	12	Success	Success
9	Splenic vein	15	Gelfoam	No	Microcatheter	3	24	CT, endoscopy	42	Success	Success
10	Portal vein	15	Gelfoam	No	5.5-F balloon	2	N/A	None	2	Success	Success
11	Splenic vein	15	Gelfoam	No	4-F balloon	1	30	CT	49	Success	Success
12	Portal vein	4	Gelfoam	Microcoils	Microcatheter	1	637	CT	645	Success	Success
13	Portal vein	50	Gelfoam	Microcoils	5.5-F balloon	2	28	CT, endoscopy	606	Success	Success
14	Splenic vein	10	Gelfoam	No	5.5-F balloon	1	10	CT, endoscopy	34	Failure	N/A
15	Portal vein	6	Gelfoam	No	4-F balloon	1	8	CT, endoscopy	633	Success	Failure
16	Portal vein	6	Gelfoam	No	4-F balloon	1	6	CT, endoscopy	19	Success	Success

^aRepresents a 3% STS concentration, not the total volume of the mixture. *A 5.5Fr balloon catheter was used in one feeding vein, and a 5Fr catheter was used in another feeding vein. Pt. no., patient number; STS, sodium tetradecyl sulfate; NBCA, N-butyl cyanoacrylate; 4Fr/5.5Fr balloon, 4-French/5.5Fr balloon catheter; CT, computed tomography; N/A, not applicable.

The safety of using STS foam sclerotherapy has been well-documented in previous studies.^{24-27,29} In addition, it is believed that the treatment effect was maximized, as the drug was sufficiently delivered to the varix, as embolization was performed using foam rather than a liquid. Foam sclerosant has low density, and its concentration is maintained along the bloodstream. It can be delivered not only in the main branch vessels but also in small branches and can be well-delivered to distal segments, providing even distribution of the sclerosing agent. Moreover, foam sclerosant is less affected by gravity; it can, therefore, contact the ventral side of the vessel wall, maximizing the sclerotic effect by increasing the contact surface area with the variceal walls. Therefore, a foam sclerosant can provide an increased sclerotic effect with a reduced drug amount compared with a liquid agent. For this reason, the results of the procedure were encouraging. In this study, 81.3% technical and 84.6% clinical success was achieved. There were also no complica-

tions related to the procedure. These results may have been due to embolization using a safe sclerosant, performing the antegrade approach appropriately in an emergency situation, and, finally, using the sclerosant in foam form. Therefore, PAVO is considered a safe and effective procedure for various forms of variceal bleeding in emergency situations.

Although there have been limited studies comparing the recurrent bleeding rate of BRTO and PAVO, one study compared the recurrence of gastric varices and rebleeding rates among BRTO, percutaneous transhepatic obliteration (PTO), and combined BRTO and PTO. In that study, the gastric varix recurrence and rebleeding rate were higher in PTO than in BRTO.³⁰ However, the size of the PTO group was relatively smaller than the BRTO group (13 and 75 patients, respectively), and an ethanolamine oleate solution with iopamidol was used as a sclerosing agent, which may have limited the comparability of that study's results with those of the current

study. Another study that used polidocanol foam in BRTO showed a technical success rate of 93.8% (15/16) and a clinical success rate of 91% (10/11).¹⁵

Although antegrade foam sclerotherapy showed effectiveness, this study has some limitations, including its retrospective design, small sample size, and the absence of long-term follow-up results. A prospective study with a larger sample size is necessary to further evaluate the effectiveness of the approach.

In conclusion, the study results demonstrate that antegrade foam sclerotherapy using 3% STS for variceal bleeding is clinically safe and effective. Additionally, antegrade foam sclerotherapy can be a useful treatment option for patients with active variceal bleeding in emergency cases.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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