Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2356-18
Intern Med 58: 2291-2297, 2019
http://internmed.jp

【 ORIGINAL ARTICLE 】

Selective Balloon-occluded Retrograde Transvenous Obliteration for Gastric Varices

Atsushi Jogo[1], Norifumi Nishida[2], Akira Yamamoto[1], Ken Kageyama[1], Mariko Nakano[1], Etsuji Sohgawa[1], Shinichi Hamamoto[1], Masao Hamuro[1] and Yukio Miki[1]

Abstract:

Objective Balloon-occluded retrograde transvenous obliteration (B-RTO) for gastric varices (GV) is associated with drawbacks including a postoperative increase in portal pressure and the risk of subsequent worsening of esophageal varices (EV). Selective B-RTO that embolizes only the varices may have the potential to minimize such risks. The aim of this study is to retrospectively compare the postoperative course of patients after selective B-RTO (Group S) and conventional B-RTO (Group B).

Methods One hundred four patients treated from January 2007 to April 2012 were classified into Groups S (n=5) and B (n=99). In the univariate analysis, the volume of 5% ethanolamine oleate iopamiodol (EOI) administered at baseline and the GV blood flow on endoscopic ultrasound after B-RTO were considered as covariates. The rates of GV recurrence and EV aggravation was also compared between Groups B and S.

Results In Group S, the volume of 5% EOI was significantly lower (Group S vs. Group B: 14.6±5.5 vs. 28.5±16.4 mL; p=0.0012) and the rate of EV aggravation was lower in comparison to Group B (p=0.045). However, in Group S, the rate of complete eradication of GV blood flow was significantly lower (Group S vs. Group B: 0% vs. 89.9%; p<0.001) and the rate of re-treatment for GV was higher in comparison to Group B (Group S vs. Group B: 60% vs. 1.0%; p<0.001).

Conclusion Selective B-RTO for GV could minimize the risk of a worsening of EV or reduce the amount of sclerosants; however, the rate of recurrence was high in comparison to conventional B-RTO.

Key words: balloon-occluded retrograde transvenous obliteration (B-RTO), selective B-RTO, gastric varices, portal hypertension

(Intern Med 58: 2291-2297, 2019)
(DOI: 10.2169/internalmedicine.2356-18)

Introduction

Gastric varices (GV) occur in 5-33% of patients with portal hypertension (1-3). Although the bleeding rate in patients with GV (5-25%) is lower than that in patients with esophageal varices (EV) (1, 4), the prognosis-once bleeding occurs-is worse, with a reported mortality rate of 45% (1). Endoscopy is performed as palliative therapy for GV, and transjugular intrahepatic portosystemic shunt (TIPS) can be applied as a therapy in Europe and the United States (5).

In contrast, balloon-occluded retrograde transvenous obliteration (B-RTO) has become an established therapy for GV in Asia (6, 7); however, this method has drawbacks, including a postoperative increase in portal vein pressure and the resultant risk of the aggravation of EV and the formation of ascites.

Selective B-RTO, in which only the varices are embolized has been reported to overcome this risk (Fig. 1) (8), and is able to minimize the elevation in portal pressure in comparison to conventional B-RTO. This selective method therefore has the potential to reduce the postoperative aggravation of EV. In the present study, compare the postoperative courses of patients who underwent selective and conventional B-RTO.

[1]Department of Diagnostic and Interventional Radiology, Osaka City University Graduate School of Medicine, Japan and [2]Department of Radiology, Osaka Saiseikai Nakatsu Hospital, Japan
Received: November 8, 2018; Accepted: February 24, 2019; Advance Publication by J-STAGE: May 22, 2019
Correspondence to Dr. Atsushi Jogo, atsushijz@gmail.com

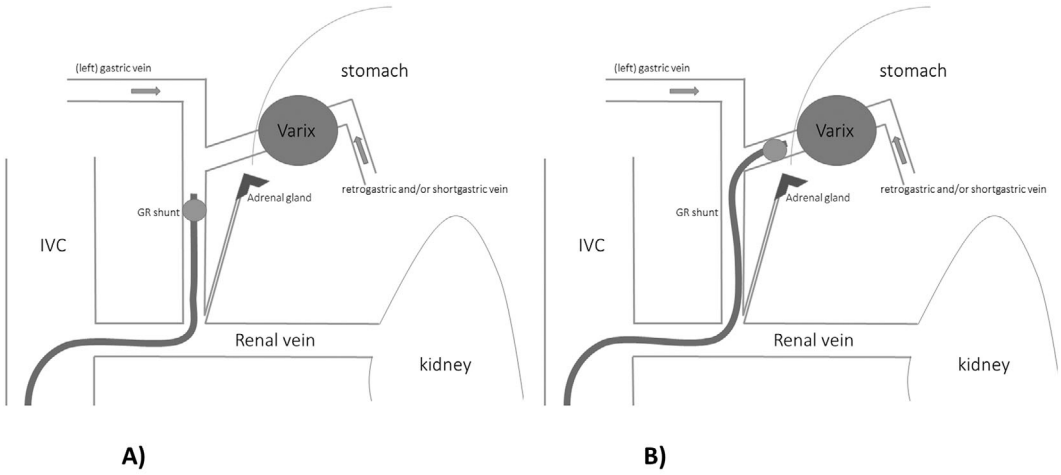

Figure 1. **A schematic illustration of conventional and selective B-RTO. A) Conventional B-RTO is performed from main drainage vessels such as the GR shunt. The varix and afferent vein (e.g., the left gastric and/or retrogastric and/or short gastric vein including the GR shunt) are embolized. B) Selective B-RTO is performed from the efferent vein through the varix. So embolization is mostly restricted to the varix and the GR shunt is preserved. B-RTO: balloon-occluded retrograde transvenous obliteration, GR: gastrorenal**

Materials and Methods

Patients

This retrospective study was approved by the institutional review board of our institution, and the requirement for informed consent was waived in accordance with the requirements of a retrospective study. We performed B-RTO for GV in 204 consecutive patients between January 2007 and April 2012. This study examined the 104 patients who underwent endoscopy after B-RTO. Endoscopic evaluation was performed in accordance with the general rules of the Japan Gastroenterological Endoscopy Society for recording endoscopic findings of esophagogastric varices (9). Briefly, the form of varices was classified as follows: F1, straight, small-caliber varices; F2, moderately enlarged, beady varices; and F3, markedly enlarged, nodular, or tumor-shaped varices.

The indication for B-RTO treatment was a major portosystemic shunt that [based on preoperative contrast-enhanced computed tomography (CECT)] could anatomically be reached transvenously using a catheter, such as a gastrorenal (GR) shunt. The treatment criteria for GV were as follows: 1) GV larger than F2 (moderately enlarged, beady varices, and/or red spot); and/or 2) GV with diameter of >5 mm on color Doppler endoscopic ultrasonography (10, 11). The criterion for performing selective B-RTO was the existence of more than two afferent veins on preoperative CECT, with one flowing into the gastric varices that could be anatomically reached transvenously using a catheter, with the other flowing into an efferent vein without varices based on digital-subtraction angiography (DSA) (Fig. 2). The sclerosing agent consisted of 5% ethanolamine oleate iopamidol (EOI) mixed with 10% ethanolamine oleate (Oldamin; Takeda Pharmaceutical, Osaka, Japan) and the same volume of nonionic contrast medium (iopamidol 300 mg I/mL, Iopamiron 300; Bayer Schering Pharma, Osaka, Japan). That was slowly injected until the feeding veins were visualized under fluoroscopic guidance in all cases, if the varices were adequately visualized with balloon-occluded retrograde transvenous venography (B-RTV). After the infusion of the sclerosing agent, plain CT or cone-beam CT was performed to confirm the intravariceal stagnation of the sclerosants in all cases. If the stagnation was insufficient, sclerosing agents were added. The balloon was kept inflated overnight. The next morning, a small amount of contrast medium was injected from the balloon catheter. If a contrast medium filling defect due to thrombus was confirmed under fluoroscopy, the catheter was removed. If a large amount of sclerosing agent had to be used or the stagnation of intravariceal sclerosants was insufficient, the procedure was completed the next day. Image assessment of varices by postoperative CECT was performed by two radiology diagnosticians (10 and 25 years of experience).

Endoscopic color Doppler ultrasonography (EUS)

EUS was performed as reported using a 120° convex scanning echo-endoscope (FG 34UX; Pentax, Tokyo, Japan) and display unit (EUB 655; Hitachi Medical, Tokyo, Japan) (12). A frequency of 7.5 MHz was used to obtain the optimal axial resolution and penetration depth. EUS was performed without a balloon attached to the tip of the echo-endoscope. EUS provides a color display of the blood flow and evaluates the flow by a fast Fourier transform analysis. GV hemodynamics were assessed by the pulsed Doppler method.

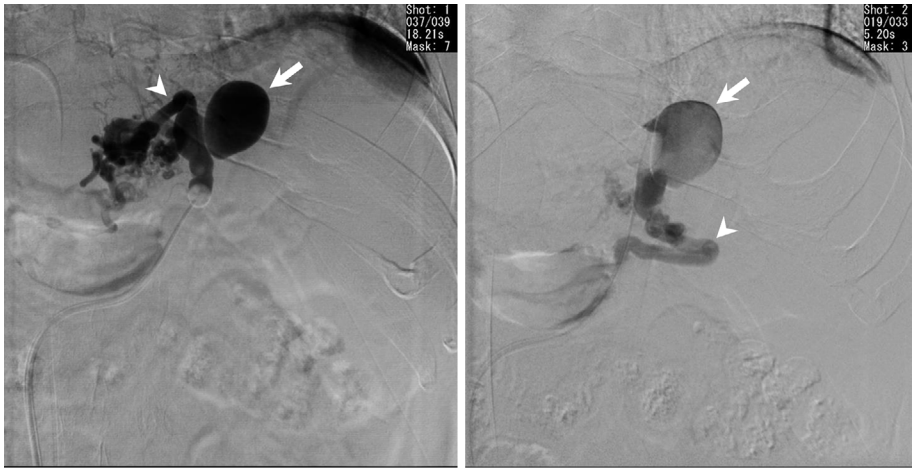

Figure 2. **B-RTV. A) B-RTV from a GR shunt shows the varix (white arrow) and the left gastric vein (white arrowhead). B) Selective B-RTV shows only the varix (white arrow) and retrogastric vein (white arrowhead) as an afferent vein. B-RTV: balloon-occluded retrograde transvenous venography, GR: gastrorenal**

Table 1. **Patient Demographics.**

	Group S (n=5)	Group B (n=99)	p †
Male : Female	4 : 1	65 : 34	0.61 ††
Age (years)	63.4±6.2	65.9±10.1	0.49 †
Underlying disease (virus : alcohol : other)	4 : 1 : 0	56 : 27 : 16	
Child-Pugh classification	A 3 B 2 C 0	A 70 B 37 C 2	
Serum Cre level (mg/dL)	0.81±0.26	0.66±0.04	0.21†

Values are expressed as the number or the mean±standard deviation.
Cre: creatinine
†Analyzed using the unpaired *t* test.
††Analyzed using Fisher's exact test.

Definition of EV aggravation

EV aggravation was defined, based on comparison to the endoscopy findings before B-RTO, as: worsening morphology; appearance of a red spot; development of new varices; or variceal rupture. We determined the number of days from the time of initial endoscopy until the confirmation of EV aggravation by endoscopy.

Evaluations and statistical analysis

All results are expressed as the mean ± standard deviation, median, or percentage. The analysis of non-continuous variables was performed using Fisher's exact test, while the analysis of continuous variables was performed using unpaired *t* tests in a univariate manner with the GraphPad Prism software program (version 6.07, GraphPad Software, San Diego, USA). In all analyses, p values of <0.05 were considered statistically significant. In the univariate analysis, the baseline status of the volume of 5% EOI, complete eradication of GV blood flow, and remnant blood flow on EUS were considered as covariates. The appearance of ascites or the worsening and deterioration of the serum creatinine level within 6 months after B-RTO were also considered. The rates of GV recurrence and EV aggravation after B-RTO were compared between Groups B and S using the Kaplan-Meier method and log-rank test, and a subgroup analysis was also performed to analyze the association between the volume of 5% EOI and the existence of remnant blood flow in GV after B-RTO.

Results

B-RTO was successfully performed for patients in both groups. The selective B-RTO (Group S) and conventional B-RTO (Group B) groups included 5 patients and 99 patients, respectively. The patient characteristics are shown in Table 1. The mean overall follow-up was 15.8 months in Group B and 22.8 months in Group S. The mean volume of 5% EOI used in Group S (14.6 ± 5.5 mL) was significantly lower than that in Group B (28.5±16.4 mL; p=0.0012) (Table 2). The appearance or worsening of ascites after B-RTO was found in 13.2% of the patients in Group B and 0% of the patients in Group S (p<0.01). The serum creatinine levels before and after the procedure did not differ to a statisti-

Table 2. Comparison between Groups S and B.

		Group S (n=5)	Group B (n=99)	p†
Volume of 5% EOI (mL)		14.6±5.5 (4-19)	28.5±16.4 (7-75)	0.0012†
*Complete eradication of GV blood flow		0% (0/5)	89.9% (89/99)	<0.001††
*Remnant blood flow	In varices (%)	20% (1/5)	10% (9/99)	0.46††
	Around varices (%)	100% (5/5)	1.0% (1/99)	<0.001††

Data are provided as the mean±standard deviation (range), or % (number)

EOI: ethanolamine oleate iopamidol, GV: gastric varices

†Analyzed using the unpaired *t*-test;††Analyzed using Fisher's exact test.

*Color Doppler endoscopy

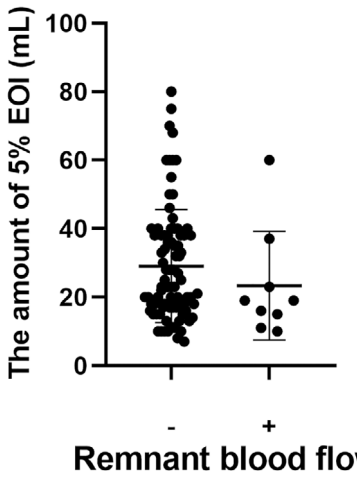

Figure 3. The relationship between the volume of 5% EOI and the remnant blood flow of the GV after B-RTO in Group B. The volume of 5% EOI was 29.1±16.5 mL in the complete eradication group (-) and 23.3±15.9 mL in remnant blood flow group (+) (p=0.22). EOI: ethanolamine oleate iopamidol, GV: gastric varices, B-RTO: balloon-occluded retrograde transvenous obliteration

cally significant extent in Groups B (pre-procedure, 0.81±0.26; post-procedure, 0.82±0.25; p=0.35) or Group S (pre-procedure 0.66±0.04; post-procedure, 0.64±0.04, p=0.50).

GV blood flow on EUS after B-RTO

In the analysis of the EUS findings after B-RTO, the rate of complete eradication of GV blood flow was 0% (0/5) in Group S, with remnant blood flow seen in the varices in 20% of the patients (1/5) and around the varices in 100% of the patients (5/5). In Group B, the rate of complete eradication of GV blood flow was 89.9% (89/99), with remnant blood flow seen in the varices in 10% of the patients (9/99) and around the varices in 1.0% of the patients (1/99) (Table 2). Furthermore, after the procedure, the remnant blood flow in varices disappeared in 6 of the 9 patients and decreased in 2 patients. The rate of complete eradication of GV blood flow in Group S was therefore significantly lower than in Group B (p<0.001). In Group B, the volume of 5% EOI was 29.1±16.5 mL in complete eradication group and 23.3±15.9 mL in remnant blood flow group. No significant association was found between the volume of 5% EOI and the existence of remnant blood flow in GV after B-RTO (p=0.22) (Fig. 3).

Recurrence of GV after B-RTO

In Group B, 1 of the 99 (1.0%) patients experienced variceal rupture after 6 months. Following the performance of endoscopic variceal ligation, a second B-RTO procedure was performed for that patient. In Group S, postoperative CECT confirmed the preservation of the GR shunt in all 5 patients. CT and/or endoscopic examinations following the procedure revealed that blood flow had increased in the residual vessels in 4 of 5 patients (Table 3) (Fig. 4). In one of the patients, GV rupture occurred after 6 months. A second B-RTO procedure was performed for 3 patients. The rate of re-treatment for GV in Group S (3/5) was significantly higher than that in Group B (1/99; p<0.001). A second B-RTO procedure in Group S was performed from a GR shunt under occlusion with a balloon catheter. Thrombosis of varices and GR shunt were confirmed on postoperative CECT in all cases.

Aggravation of EV after B-RTO

The aggravation of EV in the first year occurred in 20% of the patients in Group S and 62.1% of the patients in Group B. A significant difference was found in the aggravation rates of Groups S and B (p=0.045). All 3 of the Group S patients who underwent a second B-RTO procedure showed the aggravation of EV at 2.9, 3.6 and 12.8 months after procedure, respectively (Fig. 5).

Discussion

With selective B-RTO, only the varices are selected for embolization, without obliteration of the main drainage veins, such as GR shunts. As a result, this approach could theoretically reduce the elevated portal pressure after surgery. The rate of EV aggravation after B-RTO is reported to be 27-56.7% in the first year and 66-67% cumulatively (12-15). In the present study, the worsening of EV occurred less frequently in Group S in comparison to Group B, in which patients received conventional B-RTO. Furthermore, in Group S, the appearance or worsening of ascites was observed significantly less frequently than in Group B. Selective B-RTO can minimize the risk of the aggravation of

Table 3. **The Postoperative Course of Gastric Varices in the Selective B-RTO Group.**

Case	Baseline endoscopic findings	Post B-RTO					
		Remnant blood flow immediately after B-RTO by EUS		Conditions around varices			
				Endoscopic findings		CECT	
		In varices	Around varices	M		M	Residual enhancing area
1	F2RC0	-	+	12.7	No change	9.4	No change
2	F3RC0	-	+	19.7	No change	1.5	Increase
3	F2RC+	-	+	23.8	F2RC0	2.4	Increase
4	F2RC0	-	+	17.3	F2RC0	1.1	Increase
5	F2RC0	+	+	6.5	GV rupture	2.2	Increase

B-RTO: balloon-occluded retrograde transvenous obliteration, EUS: endoscopic color Doppler ultrasonography, CECT: contrast-enhanced computed tomography, M: months, GV: gastric varices

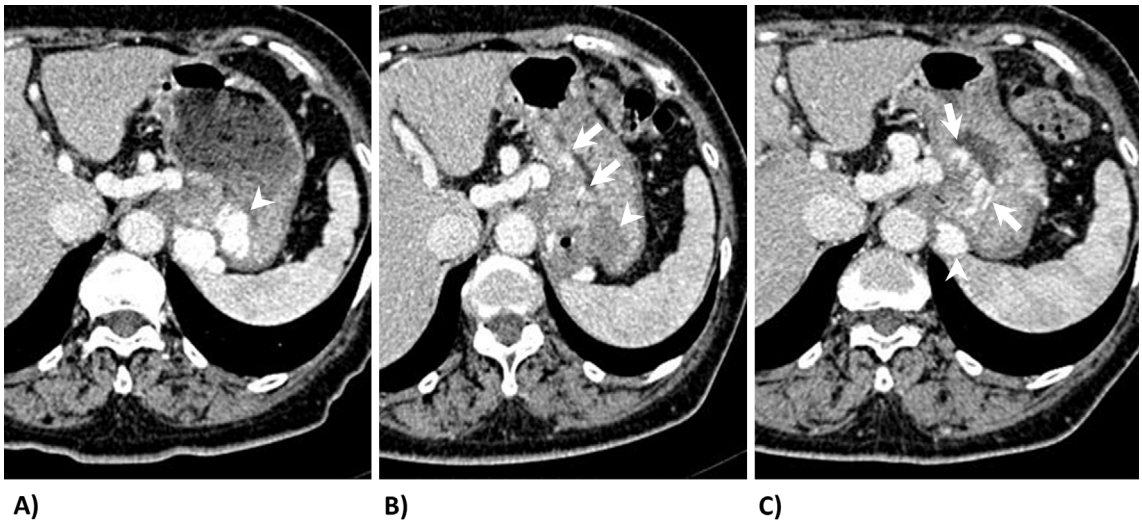

Figure 4. **CECT images from before and after B-RTO. A) Before B-RTO, a gastric varix is evident in the cardia to the fornix (white arrowhead). B) At two weeks after B-RTO, fine blood vessels (white arrows) are seen surrounding the occluded varix (white arrowhead). C) At 23 months after B-RTO, fine blood vessels (white arrows) surround the occluded varix even more prominently. The GR shunt is preserved (white arrowhead). CECT: contrast-enhanced computed tomography, B-RTO: balloon-occluded retrograde transvenous obliteration, GR: gastrorenal**

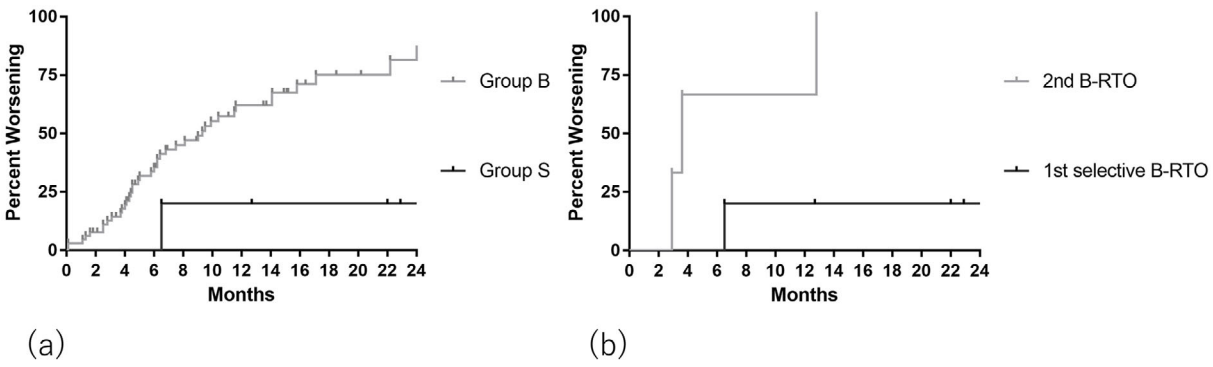

Figure 5. **Graphs showing total rate of esophageal varices aggravation after B-RTO. a) The rates of EV aggravation in the first year were 20% in Group S and 62.1% in B. A significant difference in the aggravation time was found between Groups S and B (p=0.045). b) For Group S, all 3 patients who underwent a second B-RTO procedure showed EV aggravation at 2.9, 3.6 and 12.8 months, respectively (p=0.028). B-RTO: balloon-occluded retrograde transvenous obliteration, EV: esophageal varices**

EV and ascites by reducing the elevation in portal pressure.

Meanwhile, among the patients treated using selective B-RTO, 60% (3/5) experienced retreatment during the follow-up period in comparison to 1.0% (1/99) of the patients who underwent conventional B-RTO. Considering these therapeutic outcomes, conventional B-RTO should be performed for GV. However, if selective B-RTO is performed, careful follow-up is needed to detect the recurrence of GV.

The volume of 5% EOI was not significantly associated with the remnant blood flow in or around the GV after B-RTO in Group B. Furthermore, the remnant blood flow in or around varices tended to disappear or decrease after surgery. This demonstrates that the residual blood flow was increasingly embolized when the drainage vein was completely obliterated. The amount of sclerosants depended on not only on the variceal volume but also the volume of the efferent and afferent veins. The loss of sclerosant from the collateral efferent veins were also affected, in especially in high-grade cases (assessed by Hirota's grade). Meanwhile, remnant blood was found flow in or around the varices in all cases in Group S. However, selective catheterization of the drainage vein near the varices was performed. This result suggests the importance of embolizing all drainage veins of varices.

Similar to our result, the treatment outcomes of conventional B-RTO for GV are very good. In recent reports, the bleeding rates after B-RTO ranged from 2.7 to 3.2% (14, 16). Katoh et al. reported that a small region of the varix remains after conventional B-RTO and that the GR shunt is patent, representing conditions that may induce gradual regrowth of varices (17). We also think that embolization of the drainage vein is important for eradicating varices and that it represents a key difference between conventional and selective B-RTO.

In the present series, postoperative EUS showed remnant blood flow in and/or around the varices of some patients. Consistent with the findings of the present study, in EUS studies conducted by Takagi et al., a postoperative finding of fine blood vessels in the gastric wall after endoscopic injection sclerotherapy (EIS) for GV represented a risk factor for the recurrence of varices (18). EUS can predict early recurrence in B-RTO. In our study, EUS showed remnant blood flow surrounding the varix, which could result in the recurrence of GV. EUS is considered to be useful for clarifying whether varices are completely embolized and for predicting the recurrence of GV.

Selective B-RTO can minimize the amount of EOI required because the main drainage vein can be preserved without obliteration. The volume of the embolized vessel was low in comparison to after conventional B-RTO, and the volume of EOI used in Group S was significantly lower than that in Group B. Generally, patients with cirrhosis tend to show a poor renal function, often due to the use of diuretic or the presence of hepatorenal syndrome (18). The maintenance of the renal function is thus essential for cirrhotic patients. This was confirmed using the model for end-stage liver disease score, which, when added to the renal function, is now considered superior to the Child-Pugh score for predicting the survival of cirrhotic patients (19). EOI shows renal toxicity and limiting the use of 5% EOI to a volume of 40 mL per procedure has been recommended (20). Considering these facts, it is important to pay attention to the amount of sclerosants, although no patient's showed significant renal dysfunction after B-RTO in either group.

The present study was associated with some limitations, include its retrospective design and the low number of patients treated using selective B-RTO. This latter was partly because of the technical difficulty of B-RTO and the rarity of anatomically suitable cases.

Conclusion

Selective B-RTO for GV could minimize the risk of worsening EV and reduce the amount of sclerosants in comparison to conventional B-RTO; however, it was associated with a higher rate of recurrence.

The authors state that they have no Conflict of Interest (COI).

References

1. Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. Hepatology **16**: 1343-1349, 1992.
2. Sarin SK, Sachdev G, Nanda R, Misra SP, Broor SL. Endoscopic sclerotherapy in the treatment of gastric varices. Br J Surg **75**: 747-750, 1988.
3. Chen YI, Ghali P. Prevention and management of gastroesophageal varices in cirrhosis. Int J Hepatol **2012**: 750150, 2012.
4. Rose JD, Smith PM. The management of variceal bleeding. Baillieres Clin Gastroenterol **5** (3 Pt 1): 511-535, 1991.
5. Saad WE, Darcy MD. Transjugular intrahepatic portosystemic shunt (TIPS) versus balloon-occluded retrograde transvenous obliteration (BRTO) for the management of gastric varices. Semin Intervent Radiol **28**: 339-349, 2011.
6. Hirota S, Matsumoto S, Tomita M, Sako M, Kono M. Retrograde transvenous obliteration of gastric varices. Radiology **211**: 349-356, 1999.
7. Saad WE. The history and evolution of balloon-occluded retrograde transvenous obliteration (BRTO): from the United States to Japan and back. Semin Intervent Radiol **28**: 283-287, 2011.
8. Nishida N, Ninoi T, Kitayama T, et al. Selective balloon-occluded retrograde transvenous obliteration of gastric varix with preservation of major portacaval shunt. AJR Am J Roentgenol **186**: 1155-1157, 2006.
9. Tajiri T, Yoshida H, Obara K, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc **22**: 1-9, 2010.
10. Kim T, Shijo H, Kokawa H, et al. Risk factors for hemorrhage from gastric fundal varices. Hepatology **25**: 307-312, 1997.
11. Girotra M, Raghavapuram S, Abraham RR, Pahwa M, Pahwa AR, Rego RF. Management of gastric variceal bleeding: role of endoscopy and endoscopic ultrasound. World J Hepatol **6**: 130-136, 2014.
12. Elsamman MK, Fujiwara Y, Kameda N, et al. Predictive factors of

worsening of esophageal varices after balloon-occluded retrograde transvenous obliteration in patients with gastric varices. Am J Gastroenterol **104**: 2214-2221, 2009.
13. Jogo A, Nishida N, Yamamoto A, et al. Factors associated with aggravation of esophageal varices after B-RTO for gastric varices. Cardiovasc Intervent Radiol **37**: 1243-1250, 2014.
14. Ninoi T, Nishida N, Kaminou T, et al. Balloon-occluded retrograde transvenous obliteration of gastric varices with gastrorenal shunt: long-term follow-up in 78 patients. AJR Am J Roentgenol **184**: 1340-1346, 2005.
15. Cho SK, Shin SW, Lee IH, et al. Balloon-occluded retrograde transvenous obliteration of gastric varices: outcomes and complications in 49 patients. Am J Roentgenol **189**: W365-W372, 2007.
16. Akahoshi T, Hashizume M, Tomikawa M, et al. Long-term results of balloon-occluded retrograde transvenous obliteration for gastric variceal bleeding and risky gastric varices: a 10-year experience. J Gastroenterol Hepatol **23**: 1702-1709, 2008.
17. Katoh K, Sone M, Hirose A, Inoue Y, Fujino Y, Onodera M. Balloon-occluded retrograde transvenous obliteration for gastric varices: the relationship between the clinical outcome and gastrorenal shunt occlusion. BMC Med Imaging **10**: 2, 2010.
18. Gines P, Schrier RW. Renal failure in cirrhosis. New Engl J Med **361**: 1279-1290, 2009.
19. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology **45**: 797-805, 2007.
20. Sabri SS, Saad WE. Balloon-occluded retrograde transvenous obliteration (BRTO): technique and intraprocedural imaging. Semin Intervent Radiol **28**: 303-313, 2011.