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ORIGINAL PAPER

A Modified Percutaneous Transhepatic Variceal Embolization with 2-Octyl Cyanoacrylate Versus Endoscopic Ligation in Esophageal Variceal Bleeding Management: Randomized Controlled Trial

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Abstract *Background* Conventional percutaneous transhepatic varices embolization (PTVE) has rarely been used in recent years due to high rates of variceal recurrence and rebleeding. Herein we report a modified PTVE with 2-octyl cyanoacrylate (2-OCA) in which the whole lower esophageal and peri or para-esophageal varices, the submucosal varices, and the advertitial plexus of the cardia and fundus were sufficiently obliterated. We compared this PTVE with endoscopic band ligation (EVL) in the treatment of esophageal variceal bleeding. *Methods* In this prospective randomized controlled trial, cirrhotic patients with acute or recent esophageal variceal bleeding were assigned randomly to PTVE (52 patients) or EVL (50 patients) groups. Upper gastrointestinal (UGI) rebleeding, esophageal variceal rebleeding, and survival were followed-up. Computerized tomography (CT) scanning and portal venography were used to observe 2-OCA distribution. *Results* During the follow-up period (median 24 and 25 months in the PTVE and EVL groups, respectively) UGI rebleeding developed in eight patients in the PTVE group and 21 patients in EVL group ($P = 0.004$). Recurrent bleeding from esophageal varices occurred in three patients in the PTVE group and twelve in the EVL group ($P = 0.012$, relative risk 0.24, 95% confidence interval 0.05–0.74). Multivariate Cox analysis indicated that the treatment was the only factor predictive of rebleeding. A Kaplan–Meier curve showed there was no significant difference between survival in the two groups ($P = 0.054$). *Conclusions* With the whole lower esophageal and peri or para-esophageal varices, the submucosal varices, and the adventitial plexus of the cardia and fundus sufficiently obliterated by 2-OCA, this modified PTVE was more effective than EVL in the management of esophageal varices recurrence and rebleeding. Survival in these two groups was not significantly different, however.

Keywords Esophageal varices · Rebleeding · Percutaneous transhepatic variceal embolization · 2-Octyl cyanoacrylate · Randomized controlled trial · Endoscopy variceal ligation

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Abbreviations

2-OCA	2-Octyl cyanoacrylate
EIS	Endoscopic injection sclerotherapy
EVL	Endoscopic variceal ligation
PHG	Portal hypertensive gastropathy
PTVE	Percutaneous transhepatic variceal embolization
UGI	Upper gastrointestinal

Introduction

Endoscopic variceal ligation (EVL) and endoscopic injection sclerotherapy (EIS) are commonly used interventions

in the management of variceal esophageal bleeding [1–4]. Previous meta-analysis showed that, compared with EIS, EVL has the advantages of lower rates of rebleeding, mortality, and complications, and eradicates varices more quickly. Therefore, in recent years, EVL is considered the endoscopic treatment of choice for patients with esophageal variceal bleeding [5–8]. However, the EVL dose not cause sufficient injury to the muscularis propria to eradicate perforating venous channels [9–11]; the peri or paraesophageal varices, perforating veins which are the major determinants of recurrence [9, 12–14], were usually missed by ligation [14, 15], thus both early and multiple recurrences of esophageal varices still occurred frequently after EVL [16–18].

Percutaneous transhepatic variceal embolization (PTVE) of gastroesophageal varices was first described by Lunderquist et al. in 1974 [19]. At first it appeared to be a highly promising procedure for management of variceal hemorrhage in cirrhotic patients [20, 21]; reports confirmed its efficacy in controlling bleeding in 70–90% of patients [22–25]. However, variceal recurrence and rebleeding occurred in 37–65% of patients within a few months after PTVE [20, 22]. Its use has declined substantially since the 1990s. Use of gelatin sponge and human thrombin [21, 22], absolute ethanol [26], sodium morrhuate, and stainless steel coils in PTVE [26] are accompanied with high recurrence of varices after embolization, this resulted in regrowth of the residual varices with development of a collateral supply [27].

In conventional PTVE, isobutyl 2-cyanoacrylate is used as embolic material; when mainly introduced into the afferent gastric vein a high rebleeding rate and redevelopment of collaterals were reported [23, 25]. In the current study we used a modified PTVE with 2-octyl cyanoacrylate (2-OCA) for eradication of esophageal varices. 2-OCA is a permanent embolic material. We injected 2-OCA into the whole lower esophageal and para-esophageal varices and into the submucosal varices and the adventitial plexus of the cardia and fundus; in this way, not only the esophageal varices but also the feeders were obliterated sufficiently to prevent variceal recurrence and improve long-term efficacy. A prospective randomized controlled trial was carried out to compare 2-OCA PTVE with EVL to assess variceal eradication, rebleeding, associated complications, and survival.

Materials and methods

Patients

The subjects were cirrhotic patients with acute upper gastrointestinal (UGI) bleeding or with esophageal varices admitted to Shandong Provincial Hospital and the General Hospital of Jinan Military Command between June 2002 and December 2005. The inclusion criteria were:

1 cirrhotic patients with acute or recent (within 3 months) esophageal variceal hemorrhage; and
2 the degree of gastroesophageal varices was F2 or F3 in these patients, as revealed by gastroendoscopy.

At the time of enrollment, the severity of liver disease was classified according to the Child–Pugh classification [28]. The size of esophageal varices was classified according to Beppu's criteria [29].

Patients were excluded if they presented with one or more of the following:

1 association with hepatocellular carcinoma or other malignancy;
2 history of gastric variceal bleeding;
3 history of prior shunt operation or transjugular intrahepatic portosystemic stent shunt (TIPS);
4 severe jaundice with serum bilirubin more than 100 mg L^{-1};
5 encephalopathy greater than stage II;
6 history of endoscopic treatment for esophageal varices, for example EIS or EVL;
7 presence of hepatorenal failure with serum creatinine greater than 2 mg dL^{-1};
8 complete obstruction of the portal vein due to thrombosis; or
9 inability or refusal to give informed consent.

Color Doppler ultrasound examination was performed on all patients to evaluate the degree of cirrhosis, ascites, and the portal vein and its branches. For patients in the PTVE group, computerized tomography (CT) portal venography was performed for detection of variceal afferent veins.

The study was approved by the hospital clinical research committee. Informed consent was obtained from each patient before entry into the trial. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Randomization and masking

The enrolled patients were randomized into two groups, the PTVE group and the EVL group, by using opaque, sealed envelopes numbered according to a table of random numbers which was generated using Excel 2003 (Microsoft, Redmond, WA, USA). The randomization was performed by a researcher who was not involved in this study; this was a central randomization for all the patients from the two hospitals.

PTVE procedure

Before the PTVE procedure, B ultra-sound or CT was performed to determine a favorable puncture site. If ascites presented, patients were given diuretics and albumin transfusion, or paracentesis.

Portal vein puncture and catheterization instruments were purchased from Cook (Bloomington, USA); the kit includes a 22 G Chiba needle. 2-OCA is a mixture containing tantalum powder, purchased from Guangzhou Baiyun Medical Glue Company (Guanzhou, China).

PTVE was performed under local anesthesia in all patients, and all procedures were performed under fluoroscopy guidance. The portal vein was first punctured with a 22 G Chiba needle (Cook, USA) and a 5-F sheath was introduced into the portal vein. A 5-F Cobra catheter was then inserted into splenic vein and splenoportography was carried out to assess the varices and the afferent veins. The left gastric vein was then selected for venography to evaluate the size of varices, blood flow velocity, the amount of contrast medium needed to fill the varices, and the duration of contrast medium presence in the varices and in the drainage veins. Based on these data, the injection speed and volume of 2-OCA were determined. Before the 2-OCA was injected, the tip of the catheter was introduced as far as possible into the left gastric vein; the OCA was then injected continuously until all the varices in lower esophagus and the gastric fundus and the cardia varices were filled with 2-OCA and opacified. In most patients the variceal veins were complex and tortuous with low blood velocity, and the presence of the contrast material in the varices lasted more than 5 s. This was long enough for the 2-OCA to be retained and to solidify in the varices, so in these cases the 2-OCA was injected directly and it was not likely that the 2-OCA migrated into the systemic circulation. In patients with very slow blood flow in varices, the 2-OCA can be diluted 1:1 with lipiodol to prolong the polymerization time and to facilitate extensive eradication of the varices and the feeding veins. However, in patients with large gastroesophageal varices, afferent and drainage veins, or when the blood flow in the varices was so rapid that the contrast material disappeared within 3 s, a "sandwich" cyanoacrylate embolization method was used. Briefly, 8–16 mL absolute ethanol was injected into the coronary vein first, then stainless-steel coils (Cook, USA) were advanced through the catheter into the coronary vein to reduce the blood flow. The catheter (3 F microcatheter was used if necessary) was then passed through the coils and 2-OCA was injected. Guided by fluoroscopy, we injected the 2-OCA slowly and continuously until the varices and the surrounding supply veins were totally filled with 2-OCA. When the 2-OCA was seen to flow retrograde into coronary vein, the catheter was withdrawn immediately. Splenoportography with a new catheter was performed to assess the eradication. The above procedure was repeated to immobilize other afferent veins of varices, for example the posterior gastric vein and the short gastric vein, whenever they existed. During withdrawal of the sheath, the needle tract was closed with gelatin sponge or stainless-steel coils. The average volume of 2-OCA injected per patient was 8.7 mL (6–20 mL). Low-molecular-weight heparin was administered subcutaneously 24 h after the procedure for prevention of portal thrombosis.

EVL procedure

A multiband ligator (Wilson-Cook Medical, Winston-Salem, NC, USA) and a videoendoscope (XQ230; Olympus Optical, Tokyo, Japan) were used in the EVL procedure. Ligation was started from the region of the gastroesophageal junction with subsequent ligatures applied at a cephalad distance of 3–5 cm, and the therapy was repeated to achieve multiple ligations of individual channels. Up to four or six bands were placed per endoscopic session, and the procedure was repeated every 2–3 weeks until variceal eradication was achieved.

The first author experienced with PTVE and EVL performed both procedures in all patients during this study.

Definition

Acute esophageal variceal bleeding was defined as when bleeding was directly seen from an esophageal varix under endoscopy when the patient was enrolled in the study. If a patient presented with red color signs on the esophageal varices, with a history of variceal bleeding in the 3 months before being included in the study, but without blood in the esophagus or stomach and no other potential site of bleeding identified, it was defined as recent variceal bleeding [30].

Rebleeding was defined as new onset of hematemesis, coffee-ground vomitus, hematochezia, or melena, with an increasing pulse rate over 100 beats min^{-1} and decreasing blood pressure below 90 mmHg after a 24-h period of stable vital signs and hemoglobin after PTVE or EVL treatment. Eradication was defined as non-visualization of patent gastric varices or esophageal varices.

Follow-up

All patients in the PTVE and EVL groups were not administered beta-blocker or other vasoactive drugs after inclusion in this study.

After initial eradication of varices, patients were followed as outpatients every month for 6 months, then every 3 months until the study end. Endoscopy follow-up was performed in the first month after the procedure, then at intervals of every 3 months or for any episode of recurrent bleeding in order to detect the recurrence of any varices for patients from either group. Recurrent varices were treated with further ligation for patients in both groups until clearance of varices was achieved. Patients in the PTVE group were advised to undergo follow-up abdominal ultrasound every 3 months to find if there was thrombosis formation in portal vein. Serum biochemical tests of liver function and renal function (BUN, CR) were performed at 3-month intervals. For patients in the PTVE group, upper abdominal CT scan and portal venography were performed every 6 months in the first year after PTVE, and then performed once a year; this was to follow up the 2-OCA distribution in the gastroesophageal varices. The rebleeding index for each patient was calculated by dividing the months of follow-up evaluation by the number of rebleeding episodes plus 1 [31]. This index reflected the time free of rebleeding during the follow-up period.

End points

The primary end points of this investigation were upper gastrointestinal (UGI) or variceal rebleeding. Secondary end points were survival time, complications, or loss to follow-up.

Sample size

Sample size was calculated on the basis of the previous studies. The incidence of recurrent variceal bleeding after treatment with EIV was around 40% within 2 years of observation [7, 30]. This trial was designed to detect a 25% difference with an α level of 0.05 and statistical power of 80% with the use of a two-sided test. At least 46 patients were required for each group [32].

Statistics

All data were expressed as mean $\pm$ SD. Statistical analysis was based on an intention-to-treat principle. Quantitative variables were compared by use of the Student t test, and qualitative variables were compared by using the Fisher exact test or the chi-squared test (with Yates correction) wherever appropriate. Kaplan–Merier estimation was used to examine the time of first recurrent bleeding and the time to death. The log rank test was used to examine the variation of rebleeding episodes and survival. Cox regression analysis was used to detect possible prognostic variables other than treatment modality on rebleeding rate and survival. All P values were two-tailed. A P value of <0.05 was considered significant. Statistical analyses were performed by use of SPSS 15 software.

Results

Demographics

From June 2002 to December 2005, a total of 116 patients were initially enrolled and randomized into the PTVE and EVL groups, with 58 patients in each group. Six patients in the PTVE group (one had previous endoscopic EIS, one had severe jaundice, two had hepatorenal failure, one had hepatic malignancy, and one had heart failure), and eight patients in the EVL group (two had hepatocellular carcinoma, one had encephalopathy greater than stage II, two had previous endoscopic EIS, one had previous EVL, and two had hepatorenal failure) were excluded because of enrollment error (Fig. 1). Therefore, 52 patients in the PTVE group and 50 patients in the EVL group were included for the final intention-to-treat analysis.

The characteristics of both groups are shown in Table 1. The two groups did not differ in terms of clinical features such as age, gender, etiology of cirrhosis, severity of liver disease, bleeding status, or variceal size. All the 102 patients had intermediate or severe esophageal varices confirmed by gastroendoscopy. The median follow-up period was 24 months in the PTVE group and 25 months in the EVL group.

PTVE

For fifty-two patients PTVE was performed with a procedural success rate of 100%.

Of these 52 patients, for 39 patients PTVE was performed via the left gastric vein since it was the only afferent vein of varices in these patients; in the other 13 patients, the short gastric vein and/or posterior gastric vein were also eradicated. Undiluted 2-OCA injection was performed in 38 patients; 2-OCA diluted with lipiodol in nine patients; OCA was used with ethanol and stainless steel coils in five patients. Immediate portovenography after embolization revealed the disappearance of blood flow in the gastroesophageal varices in 50 patients (96.2%) (Fig. 2). The duration of PTVE was 40–90 min, average 55 min. The injection time of the embolization agent was less than 30 s.

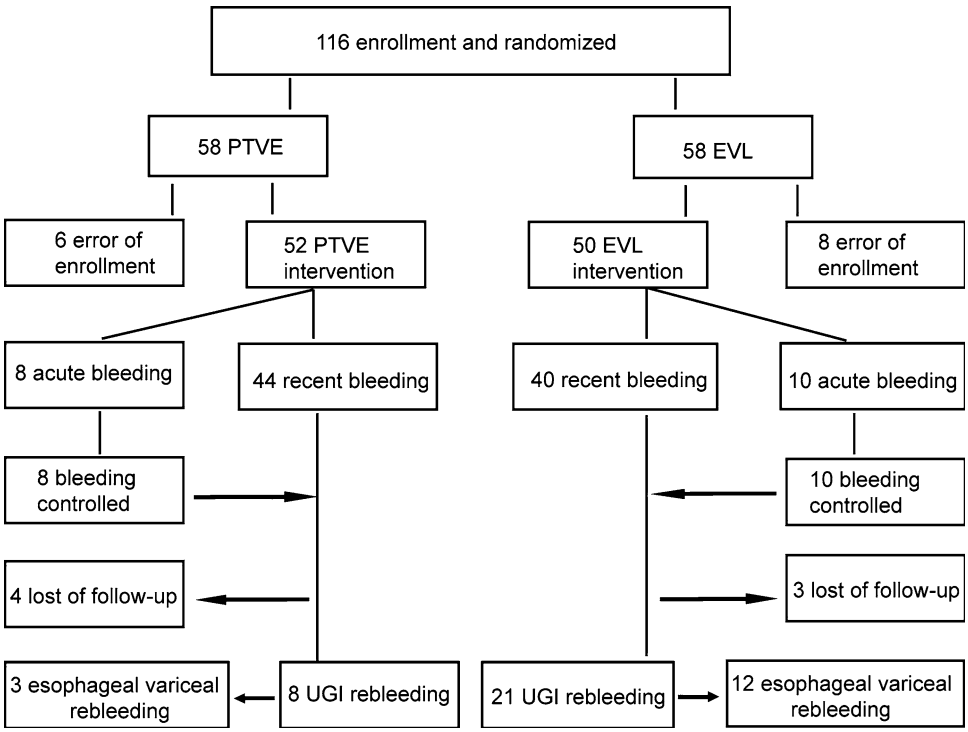

Fig. 1 Flow chart showing the enrollment progress and follow-up after the PTVE and EVL treatment. *PTVE*: percutaneous transhepatic variceal embolization with 2-octyl cyanoacrylate. *EVL*: endoscopic varices ligation

Table 1 Characteristics of the patients

	PTVE $N = 52$	EVL $N = 50$	*P* value
Age (years)	57.3 ± 14.5	54.3 ± 12.9	NS
Male/female	33/19	31/19	NS
Etiology of cirrhosis: viral hepatitis/ alcoholic/other	38/7/7	35/6/9	NS
Child-Pugh class: A/B/C	10/25/17	11/24/15	NS
Acute bleeding	8	10	NS
Recent bleeding	44	40	NS
Varices size: F2/F3	22/30	26/24	NS
Creatinine (mg dL^{-1})	2.23 ± 0.25	1.97 ± 0.63	NS
Albumin (g L^{-1})	30.5 ± 15.3	31.3 ± 16.1	NS
Bilirubin (mg L^{-1})	21.7 ± 19.4	28.4 ± 17.8	NS
Prothrombin time (s)	17.5 ± 4.9	16.4 ± 7.2	NS
Hemoglobin (g L^{-1})	93.6 ± 21.5	85.8 ± 19.6	NS
Ascites	27	25	NS
Encephalopathy	7	9	NS
Platelet (K mm^{-3})	95.37 ± 65.42	103.43 ± 59.72	NS
Prolonged prothrombin time (s)	3.18 ± 2.98	2.87 ± 2.37	NS
Blood transfusion (unit)	5.34 ± 3.26	4.96 ± 3.79	NS
Partial portal vein thrombosis	3	6	NS

Acute variceal bleeding in all eight patients was arrested after the procedure (100%). Eradication of esophageal varices was achieved in 43 of 52 patients (82.7%) within 3 months after the procedure. The time from the treatment to eradication of the varices was 57 ± 18 days.

One month after PTVE, gastrointestinal endoscopy revealed that the varices in the upper and middle esophagus disappeared without 2-OCA, but varices in the lower esophagus filled with 2-OCA and showed esophageal varices and mucosa inflammation, ulceration, and some 2-OCA release from the submucosa varices. About 3 months after PTVE, these signs disappeared, and the 2-OCA was deposited under the esophageal mucosa, without variceal signs (Figs. 3a–c).

Six months after PTVE, CT scanning showed that both the submucosal varices and the adventitial plexus of the lower esophagus (Fig. 3d), cardia, and fundus (Fig. 3e) were filled with 2-OCA. Twelve months after PTVE, the amount of 2-OCA in the submucosa was less than before, as observed by endoscopy; the 2-OCA in the peri-esophageal and peri-fundus varices and perforating veins in the fundus remained as before, however. CT potal venography revealed no blood flow in the 2-OCA obliterated varices vessels (Fig 3f).

EVL

The length of the EVL procedure was 15–20 min. Eradication of esophageal varices was achieved in 42 of 50 patients (84%) in the EVL group. The mean number of sessions for variceal eradication was 4.2 ± 1.5. The duration of eradication of the varices was 67 ± 15 days.

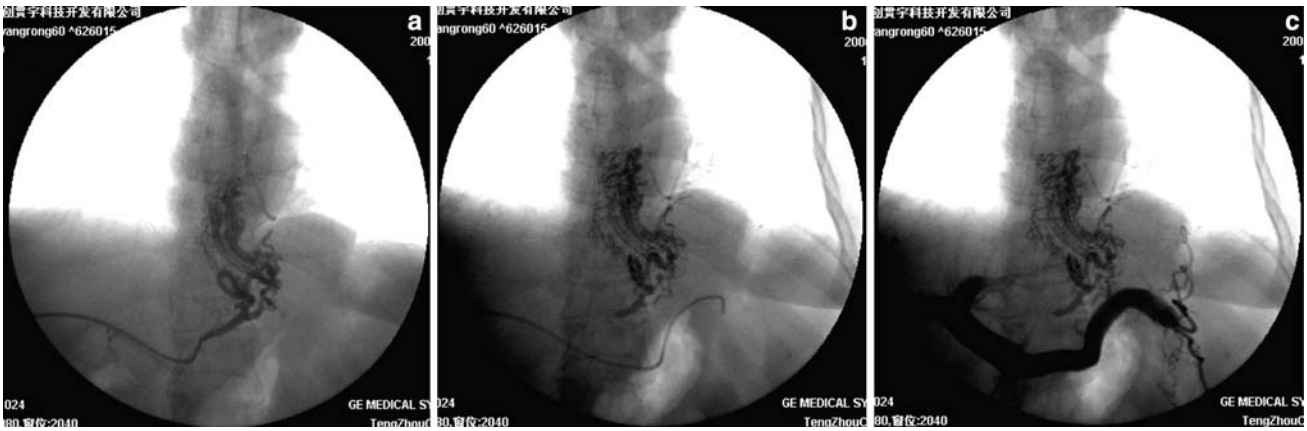

Fig. 2 PTVE in a 61-year-old male patient with esophageal variceal hemorrhage. (**a**) the left gastric vein was selected and the 2-OCA was injected slowly into the low esophageal and paraesophageal varices, and into the vessels in the vicinity of the gastric cardia and fundus via the left gastric vein and its anterior and posterior branches. (**b**) after the esophageal varices and the feeders were completely obstructed, a new catheter was advanced into the splenic vein. (**c**) splenoportography showed that portal-azygos collaterals were completely occluded

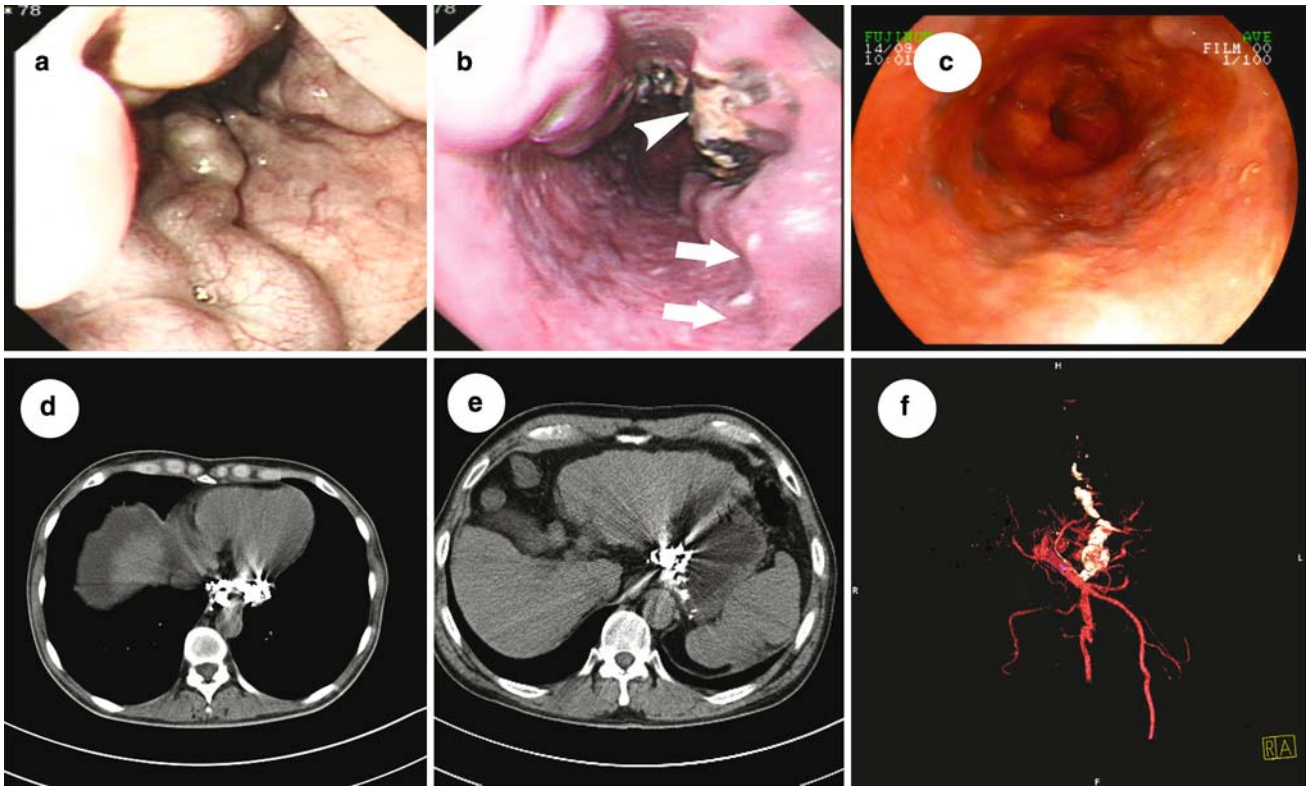

Fig. 3 Endoscopy and CT follow-up of PTVE. (**a**) Endoscopy showed severe esophageal varices before PTVE. (**b**) One month after PTVE, in the lower esophagus, variceal vein and mucosa inflammation and ulcerative lesion (*arrow head*) and cyanoacrylate release from the submucosa variceal vein (*arrow*) were seen. (**c**) Three months after PTVE, endoscopy showed cyanoacrylate deposited under the esophageal mucosa, without variceal signs. (**d**) After six months lower esophageal varices, and peri and para-esophageal varices were filled with 2-OCA. (**e**) After six months, gastric fundal varices and perforating veins in the wall of stomach were filled with 2-octyl cyanoacrylate. (**f**) After twelve months, CT portal venography showed no blood flow in the eradicated varices

Hemostatic results

The hemostatic results are shown in Table 2. There were no significant differences in eradication rate between the two groups. The success rate for arresting acute variceal bleeding was the same in both PTVE (8/8) and EVL (10/10) groups. There were no significant differences in eradication concerning variceal size and Child-Pugh classification (Table 2).

Table 2 Results from PTVE and EVL

	PTVE $N = 52$	EVL $N = 50$	P value
Arrest of acute bleeding	8/8	10/10	NS
Varices eradication	43/52	42/50	NS
Eradication according to Child-Pugh class (%)			
A	9/10 (90)	10/11	NS
B	21/25 (84)	21/24	NS
C	13/17 (76.5)	11/15	NS
Eradication according to variceal size(%)			
F2	19/22 (86.4)	24/26 (92.3)	NS
F3	24/30 (80)	18/24 (75)	NS
UGI rebleeding	8/52	21/50	0.004
Esophageal varices	3/52	12/50	0.012
Gastric varices	2	3	NS
Esophageal/gastric ulcer	2	3	NS
PHG	1	2	NS
Undetermined	0	1	
Rebleeding episodes	18	36	
Rebleeding episodes per patient	0.4 ± 0.2	0.7 ± 0.3	NS
Rebleeding index (mo per episode)	39 ± 10	18 ± 9	<0.001

NS: not significant

UGI tract rebleeding from all sources occurred in eight patients (8/52) in the PTVE group and 21 patients (21/50) in the EVL group ($P = 0.005$; Fig. 4a).

When considering only rebleeding from esophageal varices, three patients (3/52) rebled in the PTVE group, and 12 patients (12/50) rebled in the EVL group ($P = 0.012$, relative risk 0.24, 95% confidence interval 0.05–0.74). The probability of rebleeding from esophageal varices was significantly lower in the PTVE group than in the EVL group (Fig. 4b).

The rebleeding index was also significantly larger in the PTVE group than in the EVL group (39 ± 10 vs.18 ± 9 mo per episode, $P < 0.001$). The incidence of bleeding from gastric varices was not significant between the EVL group (3/50) and the PTVE group (2/52) ($P = 0.68$). The number of bleeding episodes per patient was not significantly different in the two groups. Cox regression analysis revealed that the treatment was the only predictive factor of rebleeding (PTVE vs. EVL; relative risk, 0.52; 95% confidence interval, 0.31–0.75).

Portal hypertensive gastropathy (PHG) was noted in 33 (63.5%) patients of the PTVE group and 26 (52%) patients of the EVL group ($P = 0.31$). The prevalence of gastric varices was four (7.7%) patients in the PTVE group and 25 (50%) in the EVL group ($P < 0.001$). The frequency of patients with ascites was not significantly different between the two groups (twelve cases in the PTVE group and nine cases in the EVL group).

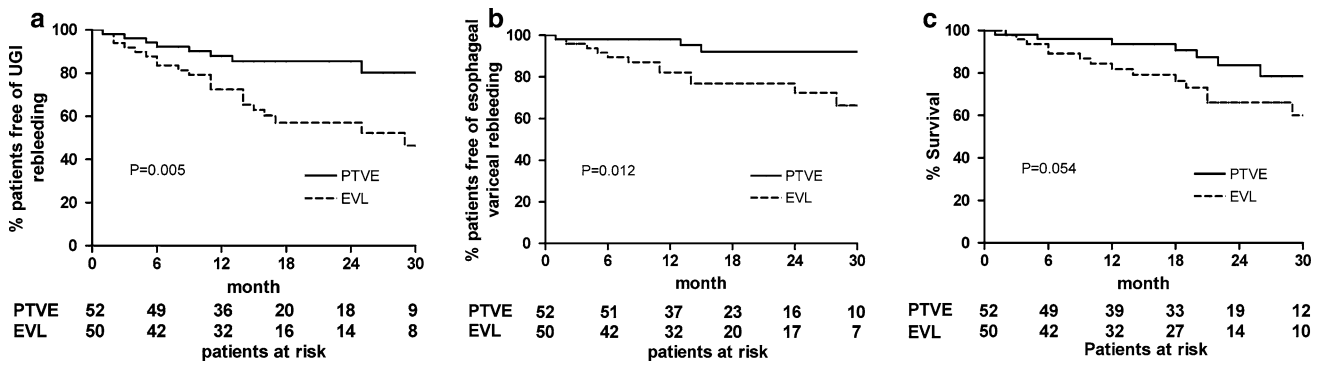

Fig. 4 (**a**) Probability of being free from rebleeding from the upper gastrointestinal tract in the PTVE and EVL groups. (**b**) Probability of being free from esophageal varices rebleeding in the PTVE and EVL groups. (**c**) Probability of survival in the two treatment groups

Table 3 Etiology of mortality in both groups

	PTVE $N = 52$	EVL $N = 50$
Total mortality	7	14
Variceal bleeding	2	9
Hepatic failure	2	3
Peritonitis	1	0
Cerebral vascular accident	1	1
Sepsis	1	1

Survival

There were fourteen deaths in the EVL group and seven deaths in the PTVE group. The etiology of the deaths is shown in Table 3.

The Kaplan–Merier survival curve is shown in Fig. 4c. Survival in these two groups was not significantly different ($P = 0.054$, log-rank test). Two patients in the PTVE group and nine patients in the EVL group died of variceal bleeding. Two patients in the PTVE group and three patients in the EVL group died of hepatic failure. The multivariate Cox regression results indicated that the Child-Pugh score was the only predictive factor of mortality.

Complications

The complications in both groups are shown in Table 4. A higher proportion of patients in the PTVE group experienced complications than in the EVL group ($P < 0.001$). The number of patients complicated with fever and abdominal pain was greater in the PTVE group than in the EVL group ($P = 0.008$ and $P = 0.018$ respectively); they were given conventional treatment and the fever and abdominal pain were usually alleviated within 2–4 weeks. Most of the procedure-related complications were mild in the two groups. There was no complication-related mortality in either group.

Table 4 Complications after PTVE and EVL

	PTVE $N = 52$	EVL $N = 50$	P value
Total complications	49	20	<0.001
Sepsis	2	1	NS
Fever	21	8	0.008
Abdominal pain	14	4	0.018
Ascites	22	19	NS
Ulcer bleeding	3	3	NS
Spontaneous bacterial peritonitis	2	1	NS
Portal vein thrombosis	1	0	NS
Abdominal bleeding	1	0	NS

NS: not significant

Discussion

Endoscopic injection of the tissue adhesive *N*-butyl cyanoacrylate was originally proposed by Soehendra in 1986 as a therapeutic option for bleeding esophagealgastric varices [33]. It has been reported that sclerotherapy using *N*-butyl cyanoacrylate is effective for treatment of gastric fundal varices because *N*-butyl cyanoacrylate will embolize blood vessels immediately and completely after injection, by forming a polymer. As a result of its excellent efficacy, *N*-butyl cyanoacrylate injection is considered to be the optimum initial treatment for gastric fundal variceal bleeding [34–37]. But in the management of esophageal varices, EIS with *N*-butyl cyanoacrylate has not been used widely. One of the reasons is that *N*-butyl cyanoacrylate is more difficult to control than other sclerosants, such as ethanolamine oleate and absolute ethanol. Furthermore, EIS with *N*-butyl cyanoacrylate can be associated with serious multiple organ embolism as a result of dispersion into the systemic circulation [38, 39]. Since the late 1980s, EVL has been used increasingly and is currently a standard treatment for esophageal varices because of its safety and convenience. Pathophysiologically, however, the higher rebleeding and recurrence rate in EVL patients may be because it has effect mainly on the superficial collaterals in the mucosal and submucosal layers, it is difficult to block blood flow in vessels of the esophageal wall and the collateral vessels in the vicinity of gastric cardia and fundus, relapse is frequent, and the procedure usually has to be repeated many times.

2-OCA, a similar agent to *N*-butyl cyanoacrylate, was found to induce equivalent vascular occlusion and histological changes similar to those observed with *N*-butyl cyanoacrylate [40]. In this study, we performed PTVE with 2-OCA and introduced the catheter as far as we could into the left gastric vein or other afferent veins, and 2-OCA was injected slowly into the varices under fluoroscopic guidance.

Anatomically, the left and short gastric veins connect with the adventitial plexus of the gastric cardia and fundus, which connect with tortuous vessels within the gastric cardia via perforating vessels. The cardial submucosal vessels often form cardial varices, and communicate with esophageal varices via palisade zones. Therefore, not only the paraesophageal varices via perforating vessels but also the collateral vessels in the vicinity of gastric carsia and fundus play as feeders for esophageal varices. In this study, the 2-OCA could disperse into the whole lower esophageal and para-esophageal varices, the submucosal varices, and

the adventitial plexus of the cardia and fundus. Extensive 2-OCA obliteration of the varices and their feeders has been demonstrated by endoscopy, CT scan, and portal venography. This facilitated a high percentage of esophageal varices eradication and a low recurrence of varices. Furthermore, cardiac and gastric varices that developed concurrently with esophageal varices frequently disappeared after 2-OCA injection, because the gastric vein was obliterated at the same time; this is unlike EVL which can induce and aggravate the gastric varices. We observed a lower recurrence of esophageal varices and a lower rebleeding rate in the PTVE group than in the EVL group.

To achieve sufficient 2-OCA obliteration of esophageal varices and their feeders, some procedural skills need to be addressed. First, before 2-OCA injection, varices angiography should be performed via the left gastric vein to evaluate the size of varices, blood velocity, volume of the varices, and draining vessels. Based on this information, the speed and volume of 2-OCA injection can be determined. Second, the injection of OCA should be slow and continuous. Even one second interruption of the injection can induce the glue to polymerize and deposit in the left gastric vein, which leads to left gastric vein embolization. If this happens, the varices and the vessels in the lower esophagus and gastric fundus, 3–5 cm above and below the cardia, will not be filled with 2-OCA; this will result in the recurrence of the residual varices and rebleeding, because of the development of new collateral supplies. Third, in patients with slow flow in varices and without large draining vessels, the 2-OCA can be diluted 1:1 with lipiodol to delay its polymerization time; in this way the 2-OCA can reach wide range of varices. Fourth, during the 2-OCA injection, the distribution of the agent can be visualized by fluoroscopy. When the varices and the feeding veins are obliterated completely, the 2-OCA will not flow forward but will deposit in the coronary vein; injection of 2-OCA should be terminated immediately at this point, otherwise the 2-OCA will flow retrograde into the portal vein. The catheter should be withdrawn from the coronary vein as quickly as possible to prevent the catheter from being stuck in the vein.

Migration of 2-OCA into the systemic circulation is a potential severe complication. Multiple organ embolism (including pulmonary infarction) have been reported during endoscopic *N*-butyl cyanoacrylate sclerotherapy [39, 41, 42]. In this study, we used the following methods to prevent the 2-OCA from migrating to unwanted sites. First, the 2-OCA injection speed and volume were adjusted according to the varices angiography and the extent of the agent in the varices. The slower the 2-OCA injection and the lower the volume of 2-OCA used in the varices, the longer time it will take to block the varices and thus more extensive obliteration is achieved. If, however, 2-OCA injection is too slow or the amount is too small, the 2-OCA will not block and deposit in the varices, but instead might be washed away into systemic veins. Second, in most cases, varices were tortuous with slow blood flow so 2-OCA had sufficient time to solidify and occlude in the target varices and could not migrate into the systemic circulation. In patients with large varices, fast blood-flow varices, or extraordinarily large draining collaterals, however, migration of the sclerosant is possible. In these cases, 10–20 mL absolute ethanol was first injected to reduce the blood flow. If it was still unsatisfactory, a stainless steel coil was placed through the catheter into the major afferent gastric vein, until a suitable blood flow was achieved. This was apparent if the disappearance time of the contrast material in the varices was more than 3 s; 2-OCA injection was then begun. By using the above approaches, systemic embolization was not encountered in our study.

In conclusion, with the whole lower esophageal and para-esophageal varices, the submucosal varices, and the adventitial plexus of the cardia and fundus sufficiently obliterated with 2-OCA, the modified PTVE, compared with EVL, has lower variceal recurrence and rebleeding. It is a promising modality of embolization not only for esophageal varices but also for their feeders.

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