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EUS-guided cyanoacrylate injection into the perforating vein versus direct endoscopic injection in the treatment of gastric varices

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ABSTRACT

Background and study aims Endoscopic injection of gastric varices (GVs) using cyanoacrylate (CYA) is associated with significant adverse events (AEs). We aimed to compare the efficacy and safety of endoscopic ultrasound (EUS)-guided CYA injection into the perforating vein versus direct endoscopic injection (DEI) of CYA in treatment of high-risk GVs.

Patients and methods This was a randomized controlled trial that included 52 patients with high-risk GVs. Group A underwent EUS-guided injection into the perforator vein and Group B underwent DEI of 1 mL CYA. Endoscopic examination and Doppler EUS were repeated after 3 months to confirm eradication. Obliteration by Doppler EUS was considered by absence of Doppler flow within the varix. Repeated injection was performed in the absence of obliteration. Doppler EUS examination was repeated at 3 and 6 months after each injection.

Results Forty-three patients including 27 males and 16 females with mean age 57 years completed the study. Variceal obliteration was achieved during the index session after 3 months in eight of 21 (38.1 %) in group B compared to 17 of 22 (77.2 %) in group A (P = 0.014). There was a significant difference in the amount of CYA needed to achieve obliteration in group B compared to group A (2 vs. 1 mL, P = 0.027). There was no statistically significant difference in the overall AE rate between group A and group B (4.5 % vs. 14.3 %, P = 0.345).

Conclusions EUS-guided CYA injection into the perforating veins achieved less amount of CYA, fewer number of sessions to obliteration, and similar overall AE rates in the treatment of high-risk GVs compared to DEI.

Introduction

Gastric varices (GVs) are dilated submucosal veins that develop in the setting of portal hypertension due to any etiology with or without cirrhosis [1]. Compared to esophageal varices, GVs are less common in cirrhotic patients. However, they have a higher propensity to bleed severely and are often associated with poor patient outcomes [2]. Based on their stomach location, GVs are classified according to Sarin's classification as gastroesophageal varices (GOV) and isolated gastric varices (IGV) [3].

Standard endoscopic management of GVs is endoscopic intravariceal cyanoacrylate (CYA) injection for treatment of acute bleeding, as well as for secondary prophylaxis [4]. Endoscopic variceal obliteration by direct endoscopic injection (DEI) using tissue adhesives like glue, CYA or histoacryl has provided a positive direction to management of GVs. CYA is a polymer, which

upon encountering blood, polymerizes instantly leading to obliteration of varices. It is called "obliteration" and not "eradication" since the varices may be still visible post-treatment [5].

Nevertheless, CYA treatment is associated with significant adverse events (AEs) like bleeding from post-injection ulcer, needle sticking in the varix, adherence of the glue to the endoscope, and embolization into the pulmonary or systemic vessels [6]. Furthermore, estimation of varix size and presence of feeding vessels, which are important risk factors for GVs rebleeding, are not adequately assessed [7]. Another potential drawback of DEI is that confirmation of variceal obliteration by standard endoscopy is subjective and relies on determining "hardening" of the varix post-injection [8]. This is particularly important as the risk of potentially fatal embolization increases with the amount of CYA injected [9].

In past years, the role of endoscopic ultrasound (EUS) has expanded rapidly into the therapeutic area. EUS offers unique access to abdominal vasculature that has only been accessible to surgeons and/or interventional radiologists. This evolution had the most clinical impact on the treatment of GVs, where EUS can deliver therapy in the form of glue injection, endovascular coil placement or a combination of both [10]. EUS enables an assessment using Doppler to confirm vessel obliteration after treatment leading to more precise manner of determining obliteration [11].

Furthermore, targeting the perforating feeder vessel rather than the varix lumen itself may theoretically minimize the amount of CYA needed to achieve obliteration of GVs and thereby reduce the risk of embolization [12]. Romero-Castro et al. assessed the efficacy of EUS-guided CYA injection at the entrance of the perforating veins to obtain variceal obliteration in uncontrolled series of five consecutive GV patients. This produces the maximal blood flow blockage of the inflow vein with lower amounts of CYA used. Thus, this technique may improve results because of precise targeting and confirmation of varix obliteration by using Doppler [13].

The aim of present study was to compare the efficacy and safety of EUS-guided CYA injection into the perforating veins versus DEI of CYA in treatment of high-risk GVs.

Patients and methods

This was a single-center randomized controlled trial performed at the endoscopy unit of Mansoura Specialized Medical Hospital, Mansoura University, Egypt, between February 2019 and February 2022. The Study population included 52 patients with high-risk GVs classified according to the Sarin and Kumar classification [3] into GOV2 or IGV1. The inclusion criteria were as follows: age > 18 years, primary prophylaxis for high risk GVs varices (> 20 mm) on initial standard diagnostic upper endoscopy, and patients unable or unwilling to undergo alternative therapies for GVs such as transjugular intrahepatic portosystemic shunts (TIPS) or surgery. Patients were excluded if unable to give informed consent for the procedure, concurrent hepatorenal syndrome and/or multiorgan failure, previous endoscopic treatment for GVs, hepatocellular carcinoma or portal and splenic vein thrombosis, esophageal stricture, pregnant, platelets count less than 50,000/mL and International Normalized Rate (INR) > 2.

Eligible patients were randomized in two groups using computer-generated random number sequences using excel software in concealed envelopes with block randomization design. Group A underwent EUS-guided injection of 1 ml CYA into the perforator vein and Group B underwent DEI of 1 mL CYA into the varix. Informed written consent was obtained from each participant in the study after assuring confidentiality. The study protocol and consent form were approved by the Institutional Review Board of Mansoura faculty of medicine, Mansoura University. The study was conducted in accordance with the Declaration of Helsinki and registered at ClinicalTrials.gov under the code NCT04222127.

Endoscopic procedure

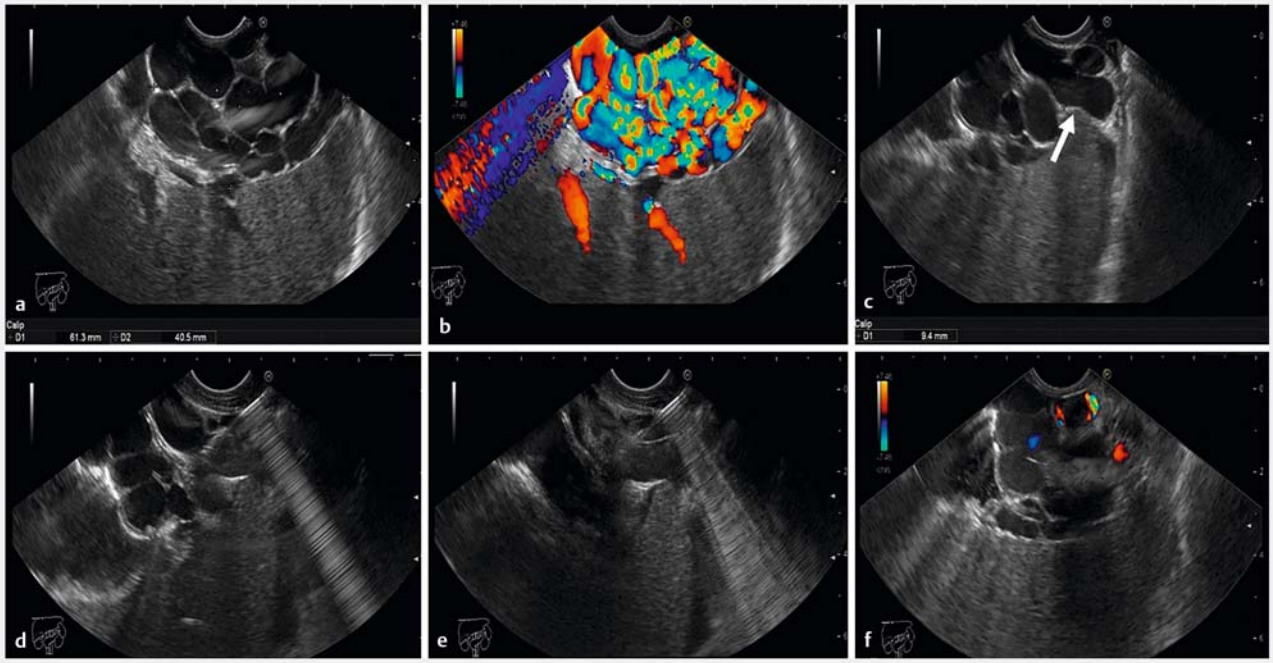
Before endoscopy, all patients were subjected to clinical assessment including history taking and physical examination, routine laboratory investigations including complete blood count, liver function profile and serum creatinine, and assessment of the severity of underlying disease by Child-Turcotte-Pugh (CTP) score and Model for End-Stage Liver Disease (MELD) score. All procedures were performed under deep sedation or general anesthesia in the left lateral position. Standard diagnostic upper endoscopy was performed with Pentax EG2990i (PENTAX medical, Tokyo, Japan) to classify the varices according to the classification of Sarin and Kumar. EUS examination was done in all patients with a Pentax linear Echoendoscope EG3870UTK (PENTAX medical, Tokyo, Japan) attached to a Hitachi Avius ultrasound system (Hitachi Medical Systems, Tokyo, Japan). All EUS examinations were done by single endosonographer. The echoendoscope was positioned in the distal esophagus at the level of the cardia to visualize the gastric fundus and to display the vascular anatomy including the size of the varix, color Doppler flow inside the varix and identification of the perforator feeding vein (one or more vein crossing the gastric wall to feed the GV from the peri-gastric veins).

EUS-guided injection

Using trans-esophageal approach, EUS-guided targeting of the largest perforator feeding vein, when more than one is identifiable, with 19G EUS-FNA needle (Expect Flexible; Boston Scientific, Marlborough, Massachusetts, United States). The needle's tip position inside the vessel was confirmed by injection of 1 mL saline followed by injection of (1:1) mixture of 2-amyl-cyanoacrylate (Amcrylate) & lipidol under real-time EUS guidance then flushing by saline before the needle was withdrawn. Evolving clot inside the perforator feeding vessel was visualized under real-time EUS and immediate effect on color Doppler flow inside varix was assessed (▶ **Fig. 1**).

Direct endoscopic injection

Using a Pentax video upper endoscope, GV was examined in the retroflexed position. A 23G sclerotherapy needle (Cook medical, Bloomington, Indiana, United States) primed with saline was utilized to puncture the varix. About 2 mL of saline was then injected into the varix to ensure correct needle placement.



▶ **Fig. 1** EUS-guided injection technique. **a, b** Large GV confirmed by Doppler EUS, **c** perforator feeding vessel identified by EUS (arrow), **d** targeting feeding vessel by 19 G needle, **e** clot formation at feeding vessel after injection of 1 mL CYA, and **f** no flow inside the GV immediately after injection.

Once confirmed, 1 mL of 2-amyl-cyanoacrylate (Amcrylate) was injected into the GV under endoscopic visualization and flushed with an additional 2 ml saline as the needle was withdrawn (▶ **Fig. 2**).

Follow-up after endoscopy

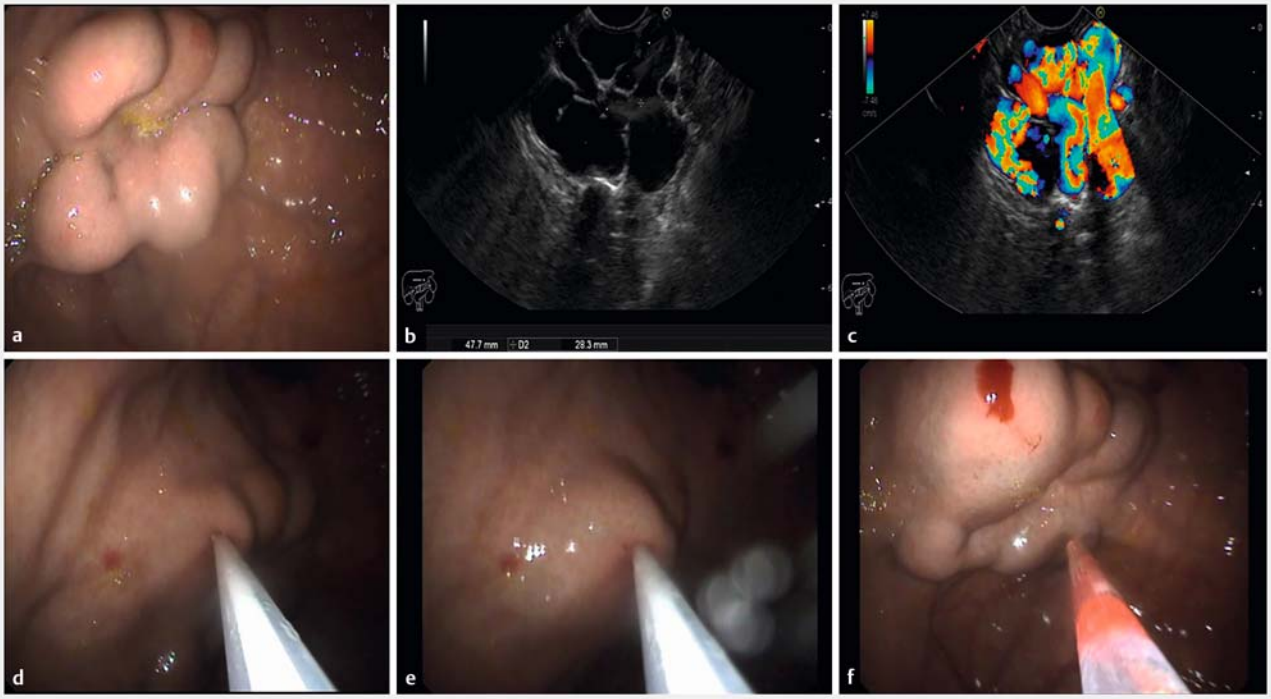
Immediate post-procedure AEs like bleeding at the injection site and needle sticking were reported in both groups. After the procedure, patients were observed for 2 hours in the recovery room before being discharged. Unblinded endoscopic examination and Doppler EUS were repeated in both groups 3 months post-procedure to confirm eradication. GVs were considered obliterated by direct endoscopy when not visible and/or hardened to catheter palpation. Obliteration by Doppler EUS was considered by visualization of clot and absence of color Doppler flow within the gastric wall. Repeated injection with 1mL CYA was performed in the absence of obliteration. Endoscopic and color Doppler EUS examinations were repeated in both groups at 3 and 6 months after each injection, at which patients were questioned about any post-procedure AEs.

Outcome measures

The primary outcome measures of the study were to compare the efficacy and the clinical success defined as complete variceal obliteration and AEs including bleeding, ulcer, needle sticking, and embolism. Secondary outcome measures were amount of CYA used and number of sessions to obliteration.

Statistical analysis

Sample size was calculated by PASS software for Windows (version 11.0.8). The reported rate of obliteration of fundic varices after CYA injection is high (90 %) in control group [14], and we hypothesized this rate to be 99 % in EUS group. Group sample sizes of 21 in Group A and 21 in Group B achieve 99 % power to detect a difference between the group proportions of 0.1000. The proportion in Group A is assumed to be 0.9000 under the null hypothesis and 1.0000 under the alternative hypothesis. The proportion in Group B is 0.9000. The test statistic used is the one-sided Z test with pooled variance. Patient and GVs characteristics, procedure details, and procedural outcomes were summarized as frequencies and proportions for categorical variables and means with standard deviation and medians with interquartile ranges for continuous variables. Continuous variables were tested for normality using Shapiro-Wilk's test with data being normally distributed if $P > 0.050$. Categorical variables were then compared between the two groups using either Fisher's exact test or Chi-square test as indicated and continuous variables were compared using Independent Samples t-test for normally distributed data or Mann-Whitney U-test for non-normally distributed data. Statistical significance was considered if $P \leq 0.050$.



▶ **Fig. 2** Direct endoscopic injection technique. **a** Endoscopic view of large GV, **b, c** confirmed by EUS and color Doppler, **d** varix punctured with 23G needle, **e** about 2 mL of saline was then injected to ensure correct needle placement followed by 1 mL of CYA into the GV under endoscopic visualization, and **f** additional flushing with 2 mL saline as the needle was withdrawn.

Results

Throughout the 3-year study period, 52 patients with high-risk GVs that did not have previous interventions for the management of GVs were included. Eligible patients were randomized in two groups as follows: Group A (27 patients) underwent EUS-guided injection of 1 mL CYA into the perforator vein and Group B (25 patients) underwent DEI of 1 mL CYA into the varix. Of these, nine patients lost to follow-up. Finally, 43 patients including 27 males and 16 females with mean age 57 ± 7.9 years completed the study (▶ **Fig. 3**).

There were no statistically significant differences in the baseline demographic and clinical characteristics between the two groups including age, gender, residency, previous band ligation of esophageal varices, causes of portal hypertension, CTP and MELD scores, and baseline laboratory investigations as shown in ▶ **Table 1**.

Endoscopic findings and procedural details

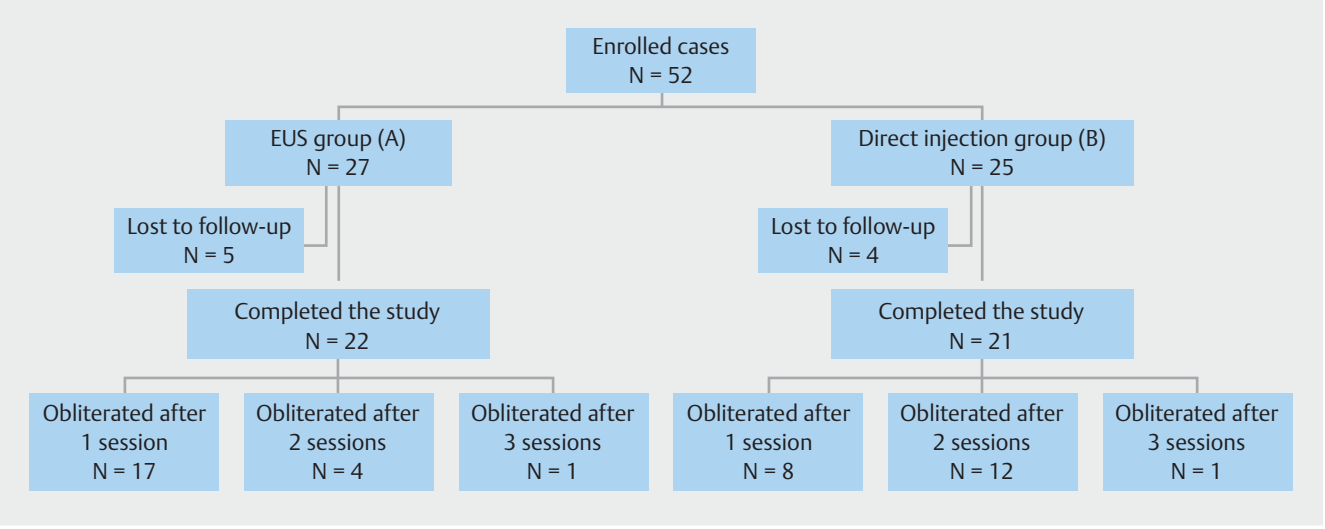
There were no statistically significant differences between the two groups regarding baseline endoscopic findings. In Group A, 21 patients (95.5 %) presented with IGV1, and one (4.5 %) with GOV2, 19 patients (86.4 %) with one perforator, and three (13.6 %) with two perforators. The mean variceal size in Group A was 36.6 ± 10.5 mm. In Group B, 18 patients (85.7 %) presented with IGV1, and three (14.3 %) with GOV2, 19 patients (90.4 %) with one perforator, and two (9.5 %) with two perforators. The mean variceal size in Group B was 32.1 ± 8.0 mm.

During the follow-up endoscopy, there was a statistically significant greater reduction of Doppler flow inside the varix at 3-month follow-up in EUS-guided injection group than the DEI group (77.3 % vs. 38.1 %, $P = 0.009$), thereby the need for reinjection at 3 months was less in Group A than Group B (22.7 % vs. 61.9 %, $P = 0.009$) (▶ **Table 2**). However, no statistically significant difference as regards follow-up variceal size at 3 to 6 months, Doppler flow and need for reinjection at 6-month follow-up.

Primary outcome measures

Clinical success in the form of complete variceal obliteration by significant decline of Doppler flow and lack of need for reinjection was achieved at 6-month follow-up in both groups (95.5 % in Group A vs. 95.2 % in Group B). However, variceal obliteration was achieved during the index session after 3 months in eight of 21 (38.1 %) in the DEI group compared to 17 of 22 (77.2 %) in the EUS-guided injection group ($P = 0.014$) (▶ **Fig. 4**). There was no statistically significant difference in the overall AE rates between Group A and Group B (4.5 % vs. 14.3 %, $P = 0.345$) (▶ **Table 2**).

Immediate post-procedure bleeding which required re-injection of 1 mL CYA occurred in one of 21 patients (4.8 %) in Group B. Needle sticking occurred in two of 21 patients (9.5 %) in Group B and none were reported in Group A. In the two patients, the needle was withdrawn successfully with no major AEs. Compared to EUS-guided injection, DEI showed exclusively post-injection ulcer (61.9 % and 81 % at 3- and 6-month follow-



▶ **Fig. 3** Flowchart of enrolled cases.

up, respectively). Most ulcers were small except for two cases (9.5 %) in which large ulcers with extrusion of glue cast into the gastric lumen. In Group A, one patient (4.5 %) developed abdominal pain, fever, and elevation of total leucocytic count after 1 day from endoscopic therapy. Abdominal computed tomography (CT) revealed remnants of CYA and lipidol in the splenic vein with non-enhancing splenic parenchyma, suggesting splenic infarction. Intravenous fluids and antibiotics were immediately started with gradual improvement of the abdominal pain, fever and total leucocytic count. On the other hand, there was improvement in the patient's platelets count due to less sequestration effect caused by hypersplenism.

Secondary outcome measures

There was a statistically significant difference in the amount of CYA needed to achieve obliteration in DEI group (median = 2 mL) compared to the EUS-guided injection group (median = 1 mL), $P = 0.027$. There was also statistically significant difference in the number sessions to obliteration between the two groups; being higher in DEI group (median = 2 sessions) compared to the EUS-guided injection group (median = 1 session) (▶ **Table 2**).

Discussion

GVs may be present in up to 20 % of portal hypertensive patients with a bleeding rate up to a 65 % over 2 years [15]. However, the risk of bleeding depends on the size and location of the varices, and it increases with the duration of the disease. The highest risk of bleeding is associated with Type IGV1 followed by GOV2 [16]. Baveno VII consensus stated that: although a single study suggested that CYA injection is more effective than propranolol in preventing first bleeding in patients with large GOV2 or IGV1, further studies are required in these patients using new therapeutic approaches in addition to non-selective beta blockers (NSBBs) [17]. Though the use of CYA injection as a tool for primary prophylaxis for hemorrhage seems to be a good option [18], it is associated with a higher AE rate as many patients may require multiple CYA injections during repeated treatment sessions which increases the risk of adverse events [19].

While EUS may be useful as a diagnostic adjunct, its therapeutic potential has gained greater recognition over the past few years. Under EUS guidance, different haemostatic adhesives and devices can be injected into GVs including CYA (EUS-CYA), coils (EUS-coil), coils with CYA (EUS-coil/CYA), thrombin (EUS-thrombin), and coils with absorbable gelatin sponge (EUS-coil/AGS) [11]. Vascular coils can be applied using 19-gauge FNA needles which serve as a scaffold to retain the glue within the varix and reduce the amount of the CYA required to obliterate the varix, thus reducing the risk of systemic embolization [20, 21]. A metanalysis and systematic review was conducted comparing EUS-guided coil embolization and CYA injection combined, EUS-guided CYA injection alone and EUS-guided coil injection alone. Combined EUS-guided CYA and coiling were found to have better technical and clinical success rate compared coil embolization alone (99 % vs 97 %; $P < 0.001$ and 96 % vs 90 %; $P < 0.001$) and CYA alone (100 % vs 97 %; $P < 0.001$ and 98 % vs 96 %; $P < 0.001$) [22]. These data support consideration of combined EUS-guided coil embolization and CYA injection for the treatment of high-risk GVs. However, the high cost of vascular coils has limited the widespread implementation of this technique.

In our study, there was no statistically significant difference between the two studied groups in baseline demographic and clinical characteristics which matches with previous studies comparing EUS-guided techniques versus conventional endoscopic technique [8, 23]. The most common cause of portal hypertension in our study was chronic HCV-induced cirrhosis, this matches with data about prevalence of chronic HCV in Egyptian population; being the most common cause of portal hypertension [24]. As regards liver function assessment, our results found that most cases have CTP class A (83.7 %) and median MELD score nine which matches with the results published by

▶ **Table 1** Demographic, clinical data, and laboratory investigations of the studied groups.

Parameter	Total (n = 43)	Group A (n = 22)	Group B (n = 21)	*P* value
Mean age (years) ± SD	57 ± 7.9	56.2 ± 8.7	57.9 ±7.1	0.505
Sex				0.252
▪ Male	27 (62.8 %)	12 (54.5 %)	15 (71.4 %)	
▪ Female	16 (37.2 %)	10 (45.5 %)	6 (28.6 %)	
Residence				0.795
▪ Rural	32 (74.4 %)	16 (72.7 %)	16 (76.2 %)	
▪ Urban	11 (25.6 %)	6 (27.3 %)	5 (23.8 %)	
Current smoking	12 (27.9 %)	4 (18.2 %)	8 (38.1 %)	0.146
Diabetes mellitus	14 (32.6 %)	7 (31.8 %)	7 (33.3 %)	0.916
Previous EBL	21 (48.8 %)	10 (45.5 %)	11 (52.4 %)	0.650
Cause of portal hypertension				0.339
▪ Chronic HCV	33 (76.7 %)	15 (68.2 %)	18 (85.7 %)	
▪ NASH	8 (18.6 %)	6 (27.3 %)	2 (9.5 %)	
▪ NCPH (Bilharzial)	2 (4.7 %)	1 (4.5 %)	1 (4.8 %)	
Child-Turcotte-Pugh (CTP)				0.240
▪ Class A	36 (83.7 %)	20 (90.9 %)	16 (76.2 %)	
▪ Class B	7 (16.3 %)	2 (9.1 %)	5 (23.8 %)	
MELD	9 (6–18)	9 (6–14)	10 (6–18)	0.073
Hemoglobin level (g/dL)	10.8 (9.7–12.3)	10.2 (9.5–11.7)	11.4 (10.1–12.4)	0.141
WBCs count (10^9/L)	4.1 (3.1–5.6)	4.3 (3.2–6.7)	3.6 (2.8–4.7)	0.158
Platelet count (10^9/L)	100 (87–126)	108 (94.3–126.5)	99 (87–143)	0.535
INR	1.3 (1.1–1.4)	1.2 (1.1–1.3)	1.4 (1.2–1.4)	0.094
Serum albumin (g/dl)	3.6 (3.2–4)	3.8 (3.3–4.1)	3.6 (3.1–4)	0.601
Serum total bilirubin (mg/dL)	0.9 (0.8–1.4)	0.9 (0.8–1.2)	0.9 (0.8–1.5)	0.686
Serum creatinine (mg/dL)	0.8 (0.8–1)	0.8 (0.7–1)	0.8 (0.8–1)	0.709

EBL, endoscopic band ligation; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; NCPH, non-cirrhotic portal hypertension; MELD, model for end-stage liver disease; WBC, white blood cell; INR, international normalized ratio.
Data are N (%) unless otherwise stated, data are median (Q1–Q3). Test of significance is Independent-Samples t-test for age, and Chi-square test for others. Data are median (minimum-maximum) for CTP and MELD scores and test of significance is Mann-Whitney U-test.

Robles-Medranda et al. which stated that median MELD score among 60 cases with GVs was 9.5 and CTP class A was the most common class [25].

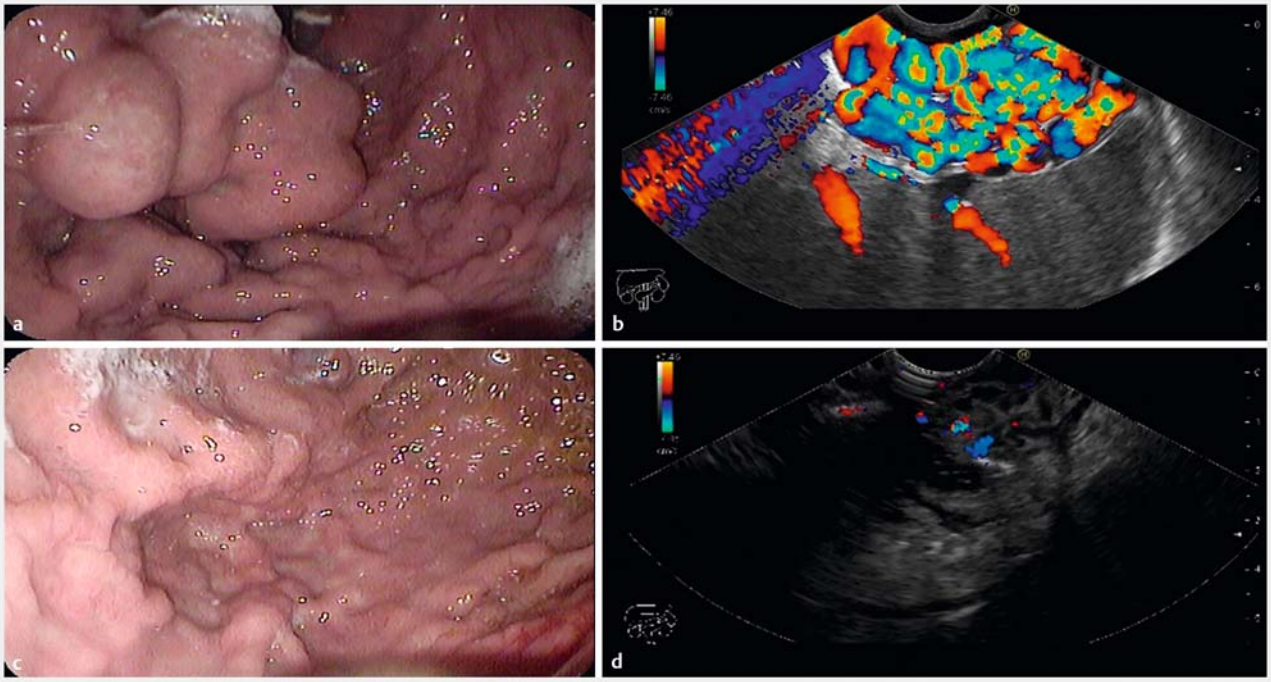
Out of the 43 patients evaluated in our study, 39 (90.7 %) had IGV1 and only four (9.3 %) had GOV2. However, there was no statistically significant difference between the two groups in the type of varix, mean size of varix, and presence of red spots over varix. This matches with results of study done by Romero-Castro et al. who stated no statistically significant difference in the type of varix between the groups [20]. On the other hand, Bick et al. found statistically significant higher frequency of IGV1 in the EUS-guided injection group compared to the DEI group ($P<0.001$), but no difference as regards presence of red spots & size of varix between the two groups [23]. During the follow-up endoscopy in our study, there was a statistically significant greater reduction of Doppler flow inside the varix at 3-month follow-up in the EUS-guided injection group than DEI group (77.3 % vs. 38.1 %, $P=0.009$), thereby the need for re-injection at 3-months was less in Group A than Group B (22.7 % vs. 61.9 %, $P=0.009$). This result disagrees with Lôbo et al. who found no statistically significant difference between EUS-guided coil/CYA injection and DEI in the reduction of Doppler flow inside the varix at 1 and 4 months follow-up, respectively [8]. This may be explained by targeting the perforator vein in our study that produces maximal blood flow blockage of the inflow vein; thus, reducing the Doppler flow inside the varix.

▶ **Table 2** Endoscopic findings and outcome measures between the studied groups.

Parameter	Total (n = 43)	Group A (n = 22)	Group B (n = 21)	*P* value
Mean index size of varix (mm) ± SD	35 ± 10.2	36.6 ± 10.5	32.1 ± 8.0	0.126[1]
Type of varix				0.272[2]
▪ IGV1	39 (90.7 %)	21 (95.5 %)	18 (85.7 %)	
▪ GOV2	4 (9.3 %)	1 (4.5 %)	3 (14.3 %)	
Number of perforators				0.674[2]
▪ 1 perforator	38 (88.3 %)	19 (86.4 %)	19 (90.4 %)	
▪ 2 perforators	5 (11.6 %)	3 (13.6 %)	2 (9.5 %)	
Presence of red spots	29 (67.4 %)	14 (63.6 %)	15 (71.4 %)	0.586[2]
Overall adverse events	4 (9.3 %)	1 (4.5 %)	3 (14.3 %)	0.345[3]
▪ Post-procedure bleeding	1(2.3 %)	0 (0 %)	1(4.8 %)	[2]
▪ Needle sticking	2 (4.7 %)	0 (0 %)	2 (9.5 %)	0.488[3]
▪ Splenic infarction	1 (2.3 %)	1 (4.5 %)	0 (0 %)	0.233[3]
▪ Symptomatic pulmonary embolism	0 (0 %)	0 (0 %)	0 (0 %)	1.000[3]
Ulcer over varix at 3 months	13 (30.2 %)	0 (0 %)	13 (61.9 %)	**< 0.001**[3]
▪ Small	12 (27.9 %)	0 (0 %)	12 (57.1 %)	
▪ Large	1 (2.3 %)	0 (0 %)	1 (4.8 %)	
Ulcer over varix at 6 months	17 (39.5 %)	0 (0 %)	17 (81 %)	**< 0.001**[3]
▪ Small	15 (34.9 %)	0 (0 %)	15 (71.4 %)	
▪ Large	2 (4.7 %)	0 (0 %)	2 (9.5 %)	
Follow up variceal size (mm)				
▪ 3 months	19 (11–42)	18.5 (11–42)	21 (12–42)	0.670[1]
▪ 6 months	15 (7–38)	14.3 (7–25)	15 (8–38)	0.715[1]
Improved Doppler flow				
▪ 3 months	25 (58.1 %)	17 (77.3 %)	8 (38.1 %)	**0.009**[3]
▪ 6 months	41 (95.3 %)	21 (95.5 %)	20 (95.2 %)	1.000[1]
Number of sessions to obturation				0.014[1]
▪ 1 session	25 (58.1 %)	17 (77.3 %)	8 (38.1 %)	
▪ 2 sessions	16 (37.2 %)	4 (18.2 %)	12 (57.1 %)	
▪ 3 sessions	2 (4.7 %)	1 (4.5 %)	1 (4.8 %)	
Median total amount of cyanoacrylate (ml)	1 (1–4)	1 (1–3)	2 (1–4)	0.027
Median number of sessions	1 (1–3)	1 (1–3)	2 (1–3)	0.015

Data are N (%) unless otherwise stated.
[1] Independent sample t-test.
[2] Chi-square test.
[3] Fisher's exact test.

We experienced no statistically significant difference in the overall adverse AE rates between Group A and Group B (4.5 % vs. 14.3 %, $P = 0.345$). This comes in agreement with Bick et al. who found no statistically significant difference in AE rates between the EUS-guided injection group (20.3 %) and the DEI group (17.5 %, $P = 0.361$) [23]. In contrast, Romero-Castro et al. found higher incidence of adverse events in DEI group (57.9 %) than EUS guided group (9.1 %) [20]. In our study, immediate post-procedure bleeding which required reinjection of 1 mL of CYA occurred in one of 21 patients (4.8 %) in Group B. On the other hand, Lôbo et al. reported mild post-procedure bleeding in two of 16 patients (12.5 %) in the EUS-guided coil/



▶ **Fig. 4 a, b** Large GV confirmed by Doppler EUS before injection and **c, d** significantly reduced size with no flow inside after 3 months.

CYA injection group compared to one of 16 patients (6.3 %) in the DEI group.

Also in our study, needle sticking occurred in two of 21 patients (9.5 %) in the DEI group and none were reported in the EUS-guided injection group. This could be attributed to the precise intravascular injection by EUS compared to relatively blind targeting by DEI. In a large retrospective study including 628 patients with GVs treated with DEI of glue, needle sticking occurred in nine patients (1.4 %) [19]. Compared to EUS-guided injection, DEI showed exclusively post-injection ulcer in our patients (61.9 % and 81 % at 3- and 6-month follow-up, respectively). Most ulcers were small except for two cases (9.5 %) were large ulcers with extrusion of glue cast into the gastric lumen. In a large retrospective study including 753 patients with GVs treated with DEI of glue, rebleeding associated with large ulcers and glue extrusion into the gastric lumen occurred in 33 patients (4.4 %) [26]. Another study suggested that extrusion of glue cast is almost inevitable [27]. We documented one patient who developed splenic infarction in the EUS-guided injection group, which was managed conservatively. Splenic infarction is an uncommon AE, which may occur secondary to retrograde splenic venous embolization from the portal circulation due to forceful injection of a large volume of lipiodol [28]. Delayed polymerization of histoacryl/lipidol mixture has been suggested as a possible explanation in most cases with distal embolization [29].

Clinical success in the form of complete variceal obliteration by significant decline of Doppler flow was achieved at 6-month follow-up in both groups (95.5 % in EUS-guided injection group vs. 95.2 % in DEI group). However, there was a statistically significant difference in the amount of CYA needed to achieve obliteration in DEI group (median = 2 mL) compared to the EUS-guided injection group (median = 1 mL), $P = 0.027$. This matches with previously reported results by Romero-Castro et al. who used a mean volume of 1.6 mL CYA/lipidol mixture to achieve obliteration [13]. Also, Bick et al. reported a significant difference in the amount of CYA needed to achieve obliteration in the DEI group (median = 3.3 mL) compared to the EUS-guided injection group (median = 2 mL), $P < 0.001$ [23]. We reported also a statistically significant difference in the number sessions to obliteration between the two groups; being higher in the DEI group (median = 2 sessions) compared to the EUS-guided injection group (median = 1 session). However, we noticed that three of five patients who needed more than one session to achieve obliteration in the EUS-guided injection group had two perforator veins, which could explain the presence of Doppler flow inside the GVs after 3 months.

The present study has some limitations. First, the number of patients included in the study was relatively small, with significant loss to follow-up. Second, all procedures were performed by a single endoscopist at a single tertiary center. Finally, the generalizability of these findings may depend on the availability of endoscopists trained to offer these EUS interventional procedures. Therefore, larger multicenter studies should be conducted to clarify the potential real-world clinical impact of EUS-guided CYA injection into the perforating veins in treatment of high-risk gastric varices.

Conclusions

In conclusion, EUS-guided CYA injection into the perforating veins achieved excellent clinical success with less CYA, fewer sessions to achieve obliteration, fewer post-injection ulcers, and similar overall AE rates in the treatment of high-risk GVs compared to DEI. Given the high cost of vascular coils, EUS-guided CYA injection into the perforating veins could be a cost-effective and safe alternative in expert hands.

Competing interests

The authors declare that they have no conflict of interest.

Clinical trial

ClinicalTrials.gov (http://www.clinicaltrials.gov/)
NCT04222127
TRIAL REGISTRATION: prospective randomized controlled study NCT04222127 at ClinicalTrials.gov (http://www.clinicaltrials.gov/)

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