

Feasibility and safety of EUS-guided selective portal vein embolization with a coil and cyanoacrylate in a live porcine model

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ABSTRACT

Background and Objectives: Preoperative portal vein (PV) embolization using the percutaneous transhepatic approach has been performed in patients with hepatobiliary malignancy before extensive liver resection. The aim of this study is to evaluate the technical feasibility and initial safety of EUS-guided selective PV embolization using a coil and cyanoacrylate in a live porcine model. **Methods:** EUS-guided selective intrahepatic PV embolization with a coil and cyanoacrylate was performed in 9 pigs. The selected PV was punctured with 19G fine-needle aspiration (FNA) needle, and the coil was inserted under EUS-guidance. The cyanoacrylate was then immediately injected through the same FNA needle. The blood flow change in the embolized PV was evaluated using color Doppler EUS. A necropsy was performed following the 1-week observation period. **Results:** The success rates for the coil and cyanoacrylate delivery were 88.9% (8/9) and 87.5% (7/8), respectively. In 1 case, the coil migrated into the hepatic parenchyma. In another case, the cyanoacrylate injection failed due to early clogging in the FNA needle. There was a complete blockage of blood flow confirmed by color Doppler EUS in the embolized PV after coil and cyanoacrylate treatment. There was coil migration into the hepatic parenchyma in 1 case. There was no animal distress observed during the 1-week observation period before necropsy. The necropsy showed no evidence of damage to the intra-abdominal organs, and the selected PV was totally occluded with embolus. **Conclusion:** The study findings indicate EUS-guided selective PV embolization is both technically feasible and initially safe in an animal model.

Key words: Embolization, EUS, feasibility, portal vein, safety

INTRODUCTION

Preoperative percutaneous transhepatic portal vein (PV) embolization was first introduced in 1986 in hepatocellular carcinoma patients before hepatic resection.^[1] Preoperative

PV embolization using the percutaneous transhepatic approach is now performed in patients with hepatocellular

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carcinoma, intrahepatic cholangiocarcinoma, and hilar cholangiocarcinoma receiving extensive liver resection including right hepatectomy or extended right hepatectomy.^[1,2] The embolization of the portal venous branch of the hepatic segments to be resected can redirect portal blood flow to nonembolized hepatic segments. The treatment induces atrophy of the embolized lobe to be resected and causes compensatory hypertrophy of nonembolized remnant hepatic segments. As a result, this preoperative management increases remnant future liver volume and prevents postoperative hepatic failure.^[3] Preoperative PV embolization is safe and effective before major liver resection.^[4]

Linear echoendoscopy has been used to image the portal venous system and EUS-guided vascular intervention has expanded to include PV intervention.^[5-7] EUS-guided PV intervention has several advantages over the conventional percutaneous approach. EUS provides detailed images of the portal venous system and both color Doppler, and pulsed-wave Doppler can give real-time blood flow characteristics and delineate vascular structures.^[5,8,9] Furthermore, the use of color Doppler EUS reduces the risk of nephrotoxicity from contrast and exposure to radiation.

Our group previously reported two studies^[8,10] on EUS-guided vascular interventions. We reported the usefulness of the combination of color Doppler and contrast-enhanced harmonic EUS for the evaluation of visceral vascular diseases, including dissection or stenosis of the celiac artery and superior mesenteric artery in humans.^[8] In our recent animal study, we performed EUS-guided transhepatic main PV stenting, which is used to treat malignant PV obstruction by interventional radiologists through the percutaneous transhepatic access route in clinical practice.^[10,11]

Preoperative PV embolization is currently performed by vascular interventional radiologists through the percutaneous transhepatic approach. The aim of this study is to evaluate the technical feasibility and initial safety of EUS-guided selective PV embolization using a coil and cyanoacrylate in a live porcine model.

METHODS

Preparation of animals

Nine male minipigs (*Sus scrofa domestica*) (12 months old; 30 kg) were used for the experiments. Food

was withheld for 48 h before the procedure. The pigs received only clear sugar-sweetened water for gastric preparation. All procedures were performed under general anesthesia provided by a qualified veterinarian. The pre-anesthesia medication included intramuscular injection of atropine sulfate (0.05 mg/kg), tiletamine hydrochloric acid (HCl) plus zolazepam (7.5 mg/kg; Zoletil®; Virbac animal health, Fort Worth, Texas, United States), and xylazine HCl (1–2 mg/kg; Rompun®; Bayer HealthCare, Lerverkusen, Germany). The animals were intubated with a 6.5 mm endotracheal tube (Well Lead Medical Co., Guangdong, China). General anesthesia was maintained with 1.5% isoflurane (Forane®; JW Pharmaceutical, Korea). The animal blood pressure, heart rate, respiration rate, and arterial oxygen saturation were monitored continuously during anesthesia. This animal study was approved by the Research Animal Care Committee of Asan Medical Center.

Endoscopic procedure

This study used an anterior oblique-viewing linear array echoendoscope (GF-UCT240; Olympus Medical Systems, Japan) with an EUS processor (EU-ME1; Olympus Medical Systems, Japan). The echoendoscope was advanced into the stomach before the intrahepatic PV branch was identified by EUS and color Doppler at a frequency of 7.5 MHz. The PV was distinguished from the hepatic vein by its thickened hyperechoic wall on EUS view. The blood flow in the intrahepatic PV was confirmed by color Doppler EUS. The embolization coil used in this study was a pushable helical coil (Nester®; MWCE-35-14-12-NESTER; diameter inch 0.035 inch, extended embolus length 14 cm, coiled embolus diameter 12 mm; Cook Medical, United States). The adhesive liquid embolic agent used in this study was cyanoacrylate (Histoacryl®; N-butyl-2-cyanoacrylate; BRAUN Aesculap, Germany). Before beginning the procedure, the helical coil was preloaded into the distal end of a 19G fine-needle aspiration (FNA) needle (Expect™ 19 ga Flex Needle; Boston Scientific Co., Natick, MA, United States). The selected intrahepatic PV was punctured with the FNA needle under EUS guidance, and then, the embolization coil was inserted into the selected intrahepatic PV using a stylet pushing device. We then immediately injected 0.5 cc cyanoacrylate through the same FNA needle, which was followed by 0.8 cc ethiodized oil (Lipiodol®; Guerbet, United States) and 1 cc saline to prevent early clogging and leakage of cyanoacrylate in the FNA

needle. After completing the coil and cyanoacrylate delivery, we monitored the change of blood flow in the embolized intrahepatic PV branch using color Doppler EUS. The echoendoscope was removed after confirming there was complete blood flow block.

Monitoring and necropsy

The animals were monitored for procedural, immediate, and delayed complications. During the endoscopic procedure the blood pressure, heart rate, respiration rate, and arterial oxygen saturation were monitored (procedural complication). After the endoscopic procedure, the animal was monitored closely for 2 h to identify sudden or fatal complications (immediate complication). The animals were then observed for 1 week to assess delayed complications. The animals were euthanized after the 1-week observation period using intravenous potassium chloride under general anesthesia. The injection was performed by a qualified veterinarian, and the animals were necropsied to evaluate the damage to the embolized intrahepatic PV and other intra-abdominal organs.

RESULTS

Feasibility

The branch of the intrahepatic PV was identified by EUS and color Doppler [Figure 1]. The EUS-guided puncture of the intrahepatic PV branch was successfully performed without difficulty using a 19G FNA needle in all nine animals [Figure 2]. The embolization coil was placed successfully into the selected intrahepatic PV in 8 of 9 animals (8/9, 88.9%) [Figure 3]. In 1 case, the embolization coil migrated into the hepatic parenchyma and was not located in the selected intrahepatic PV. The cyanoacrylate injection was successful in 7 animals (7/8, 87.5%) [Figure 4]. In 1 case, the cyanoacrylate injection failed due to early clogging of cyanoacrylate in FNA needle. The feasibility results of EUS-guided selective PV embolization on 9 animals are summarized in Table 1.

Efficacy

The baseline blood flow was evaluated using color Doppler EUS before conducting the intrahepatic PV puncture [Figure 5]. There was partial blockage of blood flow in the selected intrahepatic PV noted after inserting the embolization coil [Figure 6]. There was a complete blockage of blood flow in the embolized intrahepatic PV after both coil insertion and cyanoacrylate injection, and the result was confirmed by color Doppler EUS [Figure 7]. The necropsy was

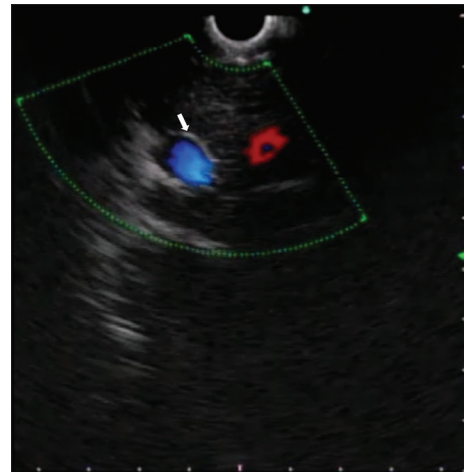


Figure 1. Identification of the intrahepatic PV branch (arrow). PV: Portal vein

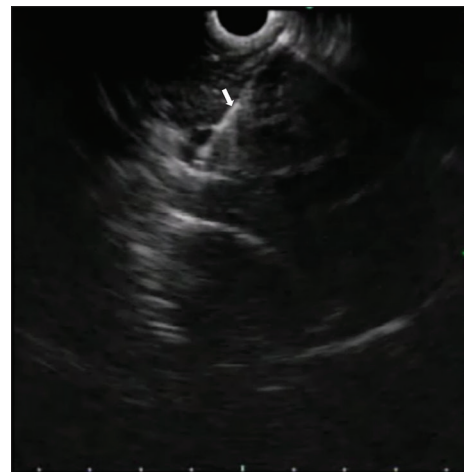


Figure 2. Puncture of intrahepatic PV branch by FNA needle (arrow). PV: Portal vein, FNA: Fine-needle aspiration

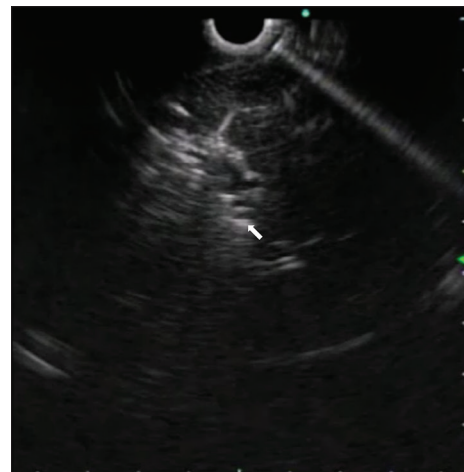


Figure 3. Embolization coil (arrow) placement into the selected PV. PV: Portal vein

performed 1 week postoperatively. The embolized intrahepatic PV was totally occluded with an embolus

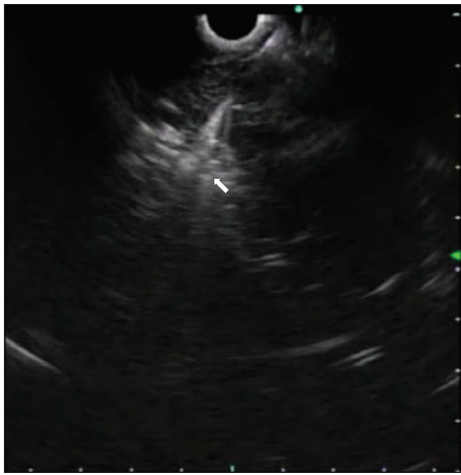


Figure 4: Cyanoacrylate (arrow) injection into the selected PV. PV: Portal vein

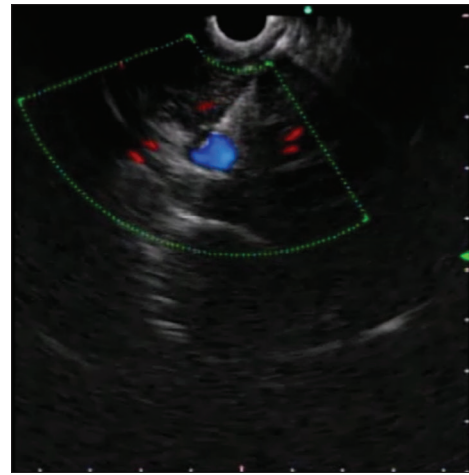


Figure 5: Baseline blood flow in the selected PV on color Doppler EUS. PV: Portal vein

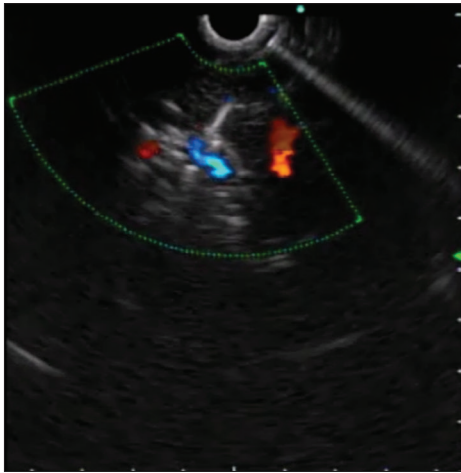


Figure 6: Partial blockage of blood flow after coil placement

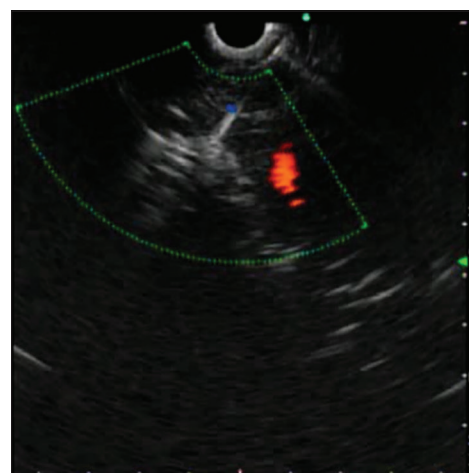


Figure 7: Complete blockage of blood flow in the embolized PV. PV: Portal vein

Table 1. Feasibility of EUS-guided portal vein embolization (n=9)

Case	Portal vein identification	Portal vein puncture	Coil placement	Cyanoacrylate injection
1	Success	Success	Success	Success
2	Success	Success	Success	Success
3	Success	Success	Failure*	-
4	Success	Success	Success	Failure [†]
5	Success	Success	Success	Success
6	Success	Success	Success	Success
7	Success	Success	Success	Success
8	Success	Success	Success	Success
9	Success	Success	Success	Success
Success, n (%)	9/9 (100)	9/9 (100)	8/9 (88.9)	7/8 (87.5)

*Embolization coil migrated into the hepatic parenchyma, not in the selected intrahepatic PV, [†]Cyanoacrylate injection failed due to aspiration needle deflection and early clogging of cyanoacrylate. PV: Portal vein

consisting of the helical coil, adhesive cyanoacrylate, and thrombus [Figure 8].

Safety

The vital signs were stable during the endoscopic procedure in all 9 animals. There were no signs or symptoms of peritonitis and bleeding in the animals during the 1-week observation period. The necropsy was performed 1 week later, and there was no gross evidence of damage to the embolized intrahepatic PV, hepatic parenchyma, and intra-abdominal organs. The safety data for EUS-guided selective PV embolization on 9 animals are summarized in Table 2.

DISCUSSION

Preoperative PV embolization has been widely used in clinical practice. It is an important procedure due to the beneficial effect of preventing postoperative hepatic failure in patients with hepatobiliary malignancy. Preoperative PV embolization is conventionally

Table 2. Safety of EUS-guided portal vein embolization

Case	Procedural adverse event*	Immediate adverse event†	Delayed adverse event‡	Survival for 1 week	Necropsy after 1 week
1	-	-	-	Yes	-
2	-	-	-	Yes	-
3	Migration of coil	-	-	Yes	Coil in the hepatic parenchyma
4	-	-	-	Yes	-
5	-	-	-	Yes	-
6	-	-	-	Yes	-
7	-	-	-	Yes	-
8	-	-	-	Yes	-
9	-	-	-	Yes	-

*Procedural complication was defined as an adverse event that occurred during endoscopic, Procedure, †Immediate complication was defined as an adverse event that occurred 2 h after the endoscopic procedure, ‡Delayed complication was defined as adverse event that occurred 1 week after the endoscopic procedure

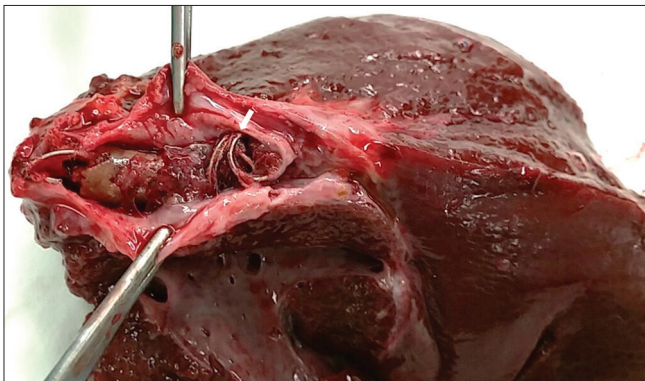


Figure 8. Complete blockage of the selected PV with embolization coil (arrow) on necropsy. PV: Portal vein

performed through the percutaneous approach. The EUS-guided intervention technique was recently developed, and the indications have expanded to include vascular therapy.^[6,7] There have been several attempts to evaluate the feasibility of EUS-guided vascular interventions, including transjugular intrahepatic portosystemic shunt,^[12] portal venous pressure measurement,^[13,14] and main PV stenting.^[10] These indications have been conventionally performed by an interventional radiologist through the percutaneous approach. A human pilot study examining EUS-guided portal pressure gradient measurements was successful in all 28 patients with liver disease and showed no adverse events.^[15]

There was an experimental report of EUS-guided PV embolization in 2005.^[16] One animal was involved, and the selected PV was punctured using a 22G FNA needle via the transduodenal route. The authors measured PV pressure before and after PV embolization. The embolization was conducted with 4 cc of Enteryx[®] (ethylene-vinyl alcohol mixed with dimethyl sulfoxide). In this study, EUS-guided selective

intrahepatic PV embolization was conducted in nine animals. We used permanent embolic agents including a 0.035 inch/14 cm coil and 0.5 cc cyanoacrylate and delivered the agents with a 19G FNA needle. The success rates of coil and cyanoacrylate delivery were 88.9% (8/9) and 87.5% (7/8), respectively. The complete blockage of blood flow to the embolized PV was confirmed by color Doppler EUS. There was one case of coil migration into the hepatic parenchyma. The necropsy findings indicated there was no evidence of damage to the embolized PV and intra-abdominal organs. In addition, the selected PV was totally occluded with embolus.

The study has several strengths compared to the previously reported study.^[16] First, the 19G FNA needle was selected to insert the 0.035 inch diameter helical coil and adhesive cyanoacrylate. Furthermore, to prevent early clogging and leakage of cyanoacrylate we injected Lipiodol[®] (ethiodized oil) after completing the cyanoacrylate injection through the same FNA needle. Therefore, sufficient embolic agents were delivered to the selected PV. The PV embolization was performed more effectively, which would be limited by a 22G FNA needle. Second, two types of permanent embolic agents including a pushed helical coil and adhesive liquid cyanoacrylate were used in this study. These agents are commonly used for therapeutic embolization in clinical practice.^[17-19] The adhesive cyanoacrylate (Histoacryl[®]) has several advantages over nonadhesive ethylene-vinyl alcohol copolymer (Enteryx[®]). The cyanoacrylate works instantly and completely occludes vessels. In addition, it is nontoxic and rarely causes vasospasm or vascular necrosis.^[20] Therefore, our method is a more practically preferred and favorable strategy for EUS-guided selective PV embolization.

This study has several limitations. First, there was no assessment of liver volume change performed in this study. The primary aim of the preliminary study is to evaluate the technical feasibility and initial safety. Furthermore, 3-dimensional volumetric computed tomography or technetium-99 m-galactosyl human serum albumin scintigraphy^[4] used for liver volume measurements in clinical practice is not available for animal models. The compensatory hypertrophy of the nonembolized hepatic segment can reach its maximum in 2–6 weeks after PV embolization in humans, and this was not confirmed in the current experiment. Thus, the final therapeutic effect of this intervention could not be evaluated. Second, the procedure was conducted in healthy animals without portal hypertension, coagulopathy, and biliary obstruction. As a result, the risk of procedure-related complications including bleeding and bile peritonitis can be underestimated. Further studies of portal hypertensive or biliary obstructive animal models are required to determine the long-term safety and efficacy of EUS-guided PV embolization.

CONCLUSION

This experimental study indicates that EUS-guided selective PV embolization with a coil and cyanoacrylate is technically feasible and shows initial safety in a live porcine model. Further animal studies are required to reveal the long-term efficacy and safety.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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