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Original Article

Endovascular intervention for delayed post-pancreaticoduodenectomy hemorrhage: clinical features and outcomes of transcatheter arterial embolization and covered stent placement

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Abstract: Delayed post-pancreaticoduodenectomy hemorrhage (PPH) is a rare but life threatening complication with high mortality. In this retrospective study, we aimed to evaluate the safety, efficacy and utility of interventional treatment of delayed PPH. From January 2008 to December 2013, 357 patients underwent pancreaticoduodenectomy (PD). 21 patients (5.9%) suffered from the delayed PPH. 18 patients underwent diagnostic angiography and endovascular treatment, either transcatheter arterial embolization (TAE, n = 10) or covered stent placement (CSP, n = 8), and 3 patients underwent laparotomy. The mean time of hemorrhage was 21.4 days. In 10 patients received TAE treatments, 3 got liver damage and 2 presented liver abscesses with 1 died of severe infection and multi-organ failure. Re-bleeding was occurred in 4 of 10 TAE patients. 8 patients received CSP got thoroughly bleeding control and without any ischemic or re-bleeding complications. 2 of 3 laporotomy patients presented hemorrhage recurrence. In all 6 re-bleeding patients, 2 were saved by CSP, while the other 4 died (TAE in 3 and conservative treatment in 1). Early intervention plays an important role of saving patients from delayed PPH. The CSP is considered a fist-line treatment for delayed PPH and an appropriate solution for hemorrhage recurrence. TAE only could be performed in whom placing a covered stent is technically difficult.

Keywords: Pancreaticoduodenectomy, delayed post-pancreaticoduodenectomy hemorrhage, endovascular intervention, covered stent, TAE

Introduction

Post-pancreaticoduodenectomy hemorrhage (PPH) is a less common but potentially life threatening complication with reported incidences between 6-10% and mortality rates of 20-50% in most series [1-5]. The International Study Group of Pancreatic Surgery (ISGPS) proposed a classification systemic diagnosis and to evaluate the severity of the PPH in 2007 [6]. According to this criteria, early PPH (less than, or equal to, 24 h after the end of the operation) is mostly due to technical failure, incomplete homeostasis, or insufficient management of coagulation disorders, and delayed PPH (greater than 24 h after the end of the operation) mostly caused by pseudoaneurysm rupture with inflammatory erosion of the arterial wall or erosive bleeding of skeletonized vessels [6-8].

Although endovascular interventions (EI) managed by percutaneous angiographic, is considered an increasing role in the successful management of PPH, there is no consensus regarding. EI can be performed in the form of transarterial embolization (TAE) or CSP [9]. In this study, we aimed to evaluate the safety, efficacy and utility of interventional treatment of delayed PPH.

Patients and methods

From January 2008 to December 2013, 357 patients underwent pancreaticoduodenectomy (PD) for periampullary tumors (tumors confined

to the head of the pancreas, ampulla, distal common bile duct, or papilla) at the Department of Biliary-Pancreatic Surgery, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University. In this study, we retrospectively evaluated the data of 21 patients who were diagnosed as delayed PPH from the 357 patients. Eighteen of these 21 patients were managed by EI procedure using either TAE (n = 10) or covered stent placement (CSP, n = 8), the others by laporotomy.

The following data were collected: population (age, sex, and indications for PD), hemorrhage characteristics and clinical representation included time of onset, clinical manifestations, bleeding sites, sentinel bleeding (SB), pancreatic fistula (PF), management (diagnostic procedure, units of blood transfused, need for resuscitation, treatment), length of stay in intensive care unit (ICU) and outcomes.

Complications' definition

The term of SB was first presented in 1991 [10]. It was defined as minor bleeding from the abdominal or nasogastric tube drainage or by the presence of melena or hematemesis. It always happens before the onset of massive delayed PPH and requires no emergency interventions.

Amylase level was measured in the fluid from the drain ducts. It was defined as PF that the amylase levels of drain were three or more times higher than the normal level of serum and the volume of drain more than 10 milliliter per 24 hours.

Surgical procedure

All patients received the classic Whipple resection after resectable assessment. Pancreaticojejunostomy was performed by an end-to-side duct-to-mucosa anastomosis, hepaticojejunostomy was manual anastomosed end-to-side. The gastroduodenal artery (GDA) was ligated with nonabsorbable stitches. A multi-punched silicone drain was placed close to the pancreatic and biliary anastomoses. Somatostatin was routinely administrated in 5 days postoperatively.

Endovascular intervention procedure

EI was performed using either TAE or CSP when PPH was identified, according to the site of bleeding, the vascular anatomy and the devices available. We firstly salvaged patients with intravenous fluids and administration of blood products, till hemodynamic been provisionally stable. The measurement of electrocardiogram and blood pressure were monitored during the whole procedure. All the procedures were carried out in the angiography suite (INNOVA-4100 IQ, GE, USA), and performed under local anesthesia (2% lidocaine).

A 5-French sheath was used to form a femoral access. A 5-French pigtail catheter (Cordis, the Netherlands) was inserted into the abdominal aorta via the access and placed at the level of the 12th thoracic vertebrate. Then the aortography was performed. The celiac trunk, hepatic artery, splenic artery, and superior mesenteric artery were selectively catheterized. Both arterial and portal venous phases were assessed to confirm the bleeding site and the patency of portal vein before EI in all patients. The anatomic variations presentation, the bleeding site, and the diameter and length of the arteries were detected.

TAE was performed using soft platinum microcoils (Hilal microcoils or Tornado microcoils, Cook, USA) of various lengths and diameters. When without pseudoaneurysm, both proximal and distal part to the bleeding site should be embolized. The TAE continuously performed until no contrast agent extravasation. The procedure of cover stent placement was a little complex. A covered stent (Fluency, Bard, USA) with appropriate diameter and length was deployed into the distal part of the bleeding site through an 8 Fr sheath within a 0.035 inch, 300-cm-long guide-wire. Then the stent was properly released to the proximal site of the bleeding site, which was post dilated by inflated balloon (6/20-mm Powerflex 3, Cordis, the Netherlands) to a pressure of 8 atmospheres. If one failed, a second or even a third covered stent was placed in a coaxial overlapping manner to exclude the site of the bleeding or pseudoaneurysm completely. Angiography was repeated to confirm no sign of contrast medium extravasation, and patency of the artery if covered stent elected.

Follow up

All patients accepted EI were sent to the ICU closely monitored. Broad-spectrum antibiotic and blood transfusion were used as needed.

Table 1. Patient characteristics of PPH (early and delayed PPH)

	Number of patients (%)
Age (year)	
Mean	62.7
Range	36-84
Gender	
Men	24 (82.8)
Women	5 (17.2)
Diagnosis	
Pancreatic head cancer	14 (48.3)
Papilla cancer	8 (27.6)
Common bile duct cancer	3 (10.3)
Ampullary cance	2 (6.9)
Other benign disease	2 (6.9)
ASA	
I	3 (10.3)
II	22 (75.9)
III	4 (13.8)
Bleeding time	
Early PPH	8 (27.6)
Delay PPH	21 (72.4)

Blood routine and biochemistry test were performed every day. An abdominal CT scan was implemented 3-5 days after EI and whenever any complication was suspected. If any signs suggested recurrence of bleeding, EI procedure was performed again if possible. The patients were followed with laboratory blood tests and abdominal enhanced CT scan 2 months after discharge.

Results

29 patients of 357 presented PPH both early and delayed PPH with a rate of 8.1%. The mean age of patients was 62.7 years with the range between 36 and 87 years. The detailed demographic data and the main characteristics are shown in **Table 1**. Eight patients presented early PPH with a rate of 2.2%, and 21 patients suffered from the delayed PPH with a rate of 5.9%.

The clinical data of 21 delayed PPH are shown in **Table 2**. The mean time of hemorrhage was 21.4 days (from 2 to 87). Bleeding from the abdominal drain duct was the most common presentation (n = 11, 52.4%). Fifteen patients (71.4%) were identified PF with drain biochemical tests, one was grade A, the others were grade B. The microbiological culture of abdominal drain fluid confirmed 16 positive with various pathogens. SB was presented in 9 of the 21 patients (47.6%) with average 14.3 days (from 2 to 27 days) after PD. Six cases (66.7%) of SB were observed in abdominal drain, 2 in nasogastric tube and 1 in feces. Of these 9 patients, 7 (77.8%) presented both PF and positive results of pathogen culture. Pseudomonas aeruginosa (PA), which was the most common pathogen of nosocomial infection in our department, was found in abdominal drain in 5 SB patients.

The initial sites of hemorrhage were seen in **Table 3**: stump of gastroduodenal artery (GDA, n = 10, **Figures 1**-**3**), common hepatic artery (CHA, n = 6), CHA and stump of GDA (n = 1), proper hepatic artery (PHA, n = 1), branch of superior mesenteric artery (SMA, n = 1), inferior pancreaticoduodenal artery (IPDA, n = 1), splenic artery (SA, n = 1). Of the 10 patients treated with TAE, re-bleeding occurred in 4, liver damage in 3, and liver abscess in 2. Two of the 3 patients received laporotomy presented hemorrhage recurrence. No re-hemorrhage was occurred in all 8 patients with the CSP treatments (**Figures 1**-**3**).

The managements and outcomes of re-bleeding patients were described in **Table 4**. It was negatively founded both by CT and angiography in patient NO. 2 (**Figure 1**), but hemorrhage was existed certified by clinical manifestations. The stent was tentatively placed into the CHA to cover the stump of GDA, which was the most likely site of re-bleeding. Then, the presentation of bleeding stopped and the hemodynamic stability was retrieved. In patient No. 8, the intestinal mucosa was developed with contrast agent extravasation from the stump of GDA when angiography was carried out. This sign directly demonstrated the existence of the fistula between stump of GDA and the anastomotic stoma. The bleeding was stopped by placement of stent in the CHA to cover the fistula. Because of the severe infection and unstable hemodynamic situation, conservative treatment was administrated to patient No. 14, who died of uncontrolled re-bleeding finally. The other 3 re-bleeding patients accepted TAE as the final intervention and all died of uncontrolled bleeding and/or multi-organ failure.

Table 2. Clinical manifestations about patients with delayed PPH

Patient NO.	Age (yr)/Sex	Surgery indication	SB at POD (day)	Presentation of SB	PF	Culture of drain	Bleeding at POD (day)	Presentation of bleeding
1	36/M	Gastrointestinal Stromal Tumor	21	Abdominal drain	Yes	KPN and EC	25	Abdominal drain
2*	54/M	Carcinoma of the papilla	22	Abdominal drain	Yes	PA and KPN	27	Abdominal drain
3	62/M	Carcinoma Of Pancreatic head	24	Abdominal drain	Yes	PA and EF	27	Hematemesis and melena
4	72/F	Carcinoma Of Pancreatic head	-	No	No	EC	41	Melena
5	67/M	Carcinoma Of Pancreatic head	-	No	No	PA	20	Abdominal drain
6*	77/M	Carcinoma Of Pancreatic head	13	Abdominal drain	Yes	EF	19	Abdominal drain
7	46/M	Carcinoma Of Pancreatic head	27	No	No	PA and EC	38	Abdominal drain and hematemesis
8*	57/M	Distal bile cholangiocarcinoma	-	Nasogastric tube	Yes	PA	87	Hematemesis and melena
9	73/M	Ampullary carcinoma	-	No	No	No	28	Hematemesis
10*	77/M	Carcinoma Of Pancreatic head	4	Abdominal drain	Yes	No	18	Abdominal drain and nasogastric tube
11	71/M	Distal bile cholangiocarcinoma	-	No	Yes	PA	9	Abdominal drain
12	58/M	Carcinoma Of Pancreatic head	7	No	No	EF	10	Abdominal drain, Hematemesis and melena
13	53/M	Carcinoma of the papilla	9	Melena	Yes	PA and KPN	10	Melena
14*	75/M	Carcinoma of the papilla	14	Nasogastric tube	Yes	EC and CA	16	Nasogastric tube
15	80/F	Carcinoma Of Pancreatic head	-	No	No	No	21	Hematemesis
16	54/M	Carcinoma Of Pancreatic head	-	No	Yes	KPN	22	Abdominal drain and nasogastric tube
17*	69/M	Carcinoma of the papilla	2	Abdominal drain	No	No	3	Nasogastric tube
18	70/M	Carcinoma of the papilla	-	No	Yes	PA	6	Abdominal drain
19	45/M	Carcinoma of the papilla	-	No	Yes	No	2	Abdominal drain and nasogastric tube
20	69/F	Carcinoma of the papilla	-	No	Yes	EC	14	Nasogastric tube and hematemesis
21	68/F	Carcinoma Of Pancreatic head	-	No	Yes	No	7	Nasogastric tube

POD: Postoperative day; PF: pancreatic fistula; SB: Sentinel bleeding; KPN: Klebsiella pneumonia; EC: Escherichia Coli; PA: Pseudomonas aeruginosa; EF: Enterococcus faecium; CA: Candida albicans; *: patients with hemorrhage recurrence.

Table 3. Data of clinical intervention in patients with delayed PPH

Patient NO.	Bleeding site	Transfusion (RCS and FFP unit)	Management	NO. of Coils	Follow-up (time after management)
1	Branch of SMA	8 + 6	TAE	1	Survived to the present
2*	PHA	6 + 6	TAE	3	3 days, re-bleeding
3	Stump of GDA	13 + 10	CSP	-	Survived to discharge; 13 months, die of tumor metastasis
4	Stump of GDA	10 + 8	CSP	-	Survived to discharge; 18 months, die of tumor metastasis
5	Stump of GDA	14 + 12	TAE	2	Liver damage, survived to discharge; 6 months, die of cerebral infarction
6*	CHA	4 + 6	TAE	4	Liver damage; 2 days, re-bleeding
7	CHA & Stump of GDA	8 + 10	CSP	-	Survived to discharge; 10 months, die of tumor metastasis
8*	Stump of GDA	8 + 14	TAE	3	14 days, re-bleeding
9#	CHA	6 + 4	TAE	2	5 days, liver abscess; 24 days, die of severe infection & multiorgan failure
10*	Stump of GDA	18 + 10	Laporotomy (suture & re-build)	-	47 days, re-bleeding
11	stump of IPDA	8 + 12	TAE	2	Survived to discharge; 15 months, die of tumor metastasis
12	Stump of GDA	12 + 14	CSP	-	Survived to discharge; 21 months, die of tumor metastasis
13	Stump of GDA	4 + 8	TAE	1	Liver damage, survived to the present
14*	CHA	8 + 6	TAE	4	7days, liver abscess; 16 days, re-bleeding
15	Stump of GDA	15 + 14	CSP	-	Survived to discharge; 7 months, die of tumor metastasis
16	Stump of GDA	15 + 10	CSP	-	Survived to discharge; 3 months, die of tumor metastasis
17*	CHA	14 + 12	Laporotomy (suture & re-build)	-	21 hours, re-bleeding
18	Splenic artery	6 + 10	TAE	2	Survived to discharge; 29 months, die of acute pulmonary embolism
19	Stump of GDA	12 + 14	Laporotomy (suture)	-	Survived to the present
20	CHA	12 + 8	CSP	-	Survived to the present
21	CHA	7 + 4	CSP	-	Survived to discharge; 9 months, die of tumor metastasis

CHA: common hepatic artery; GDA: gastroduodenal artery; IPDA: inferior pancreaticoduodenal artery; SMA:superior mesenteric artery; PD: pancreaticoduodenectomy; PHA: proper hepatic artery; TAE: transcatheter arterial embolization; CPS: covered stent placement; RCS: red blood cell suspension; FFP: fresh frozen plasma; *: patients with hemorrhage recurrence; #: patients with a dead outcome.

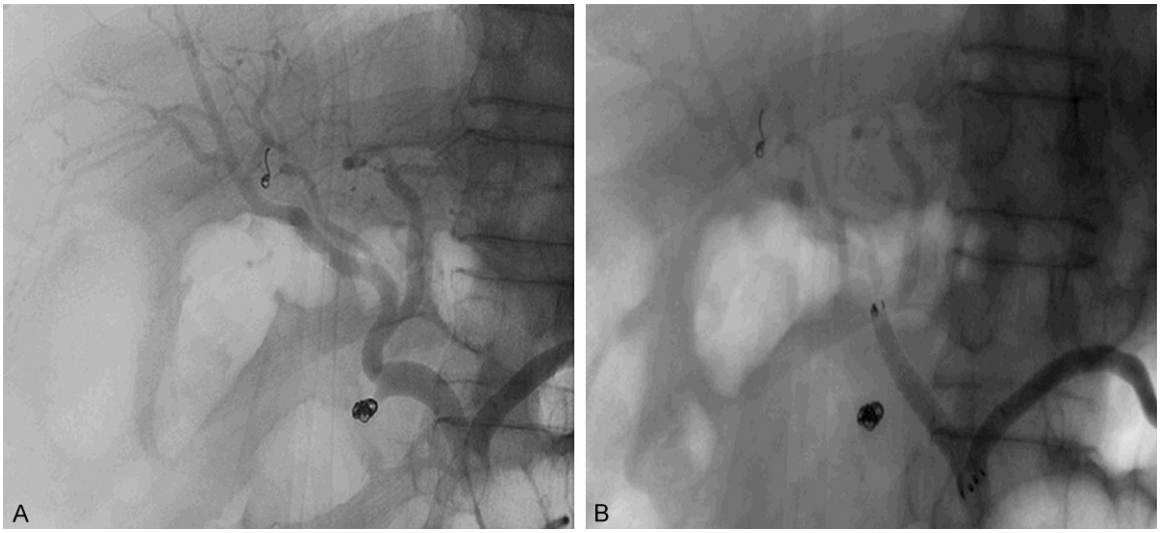

Figure 1. Patient No. 2. A 54-year-old male with adenocarcinoma of the papilla underwent pancreaticoduodenectomy. Selective angiography was performed and TAE was processed in the stump of GDA. But the hemorrhage reoccurred in 3 days. A. The coil was still at the right site, and no diffusion of contrast agent was come to light. B. Covered stent was placed in the main trunk of CHA, and perfusion of the stump of GDA disappeared immediately.

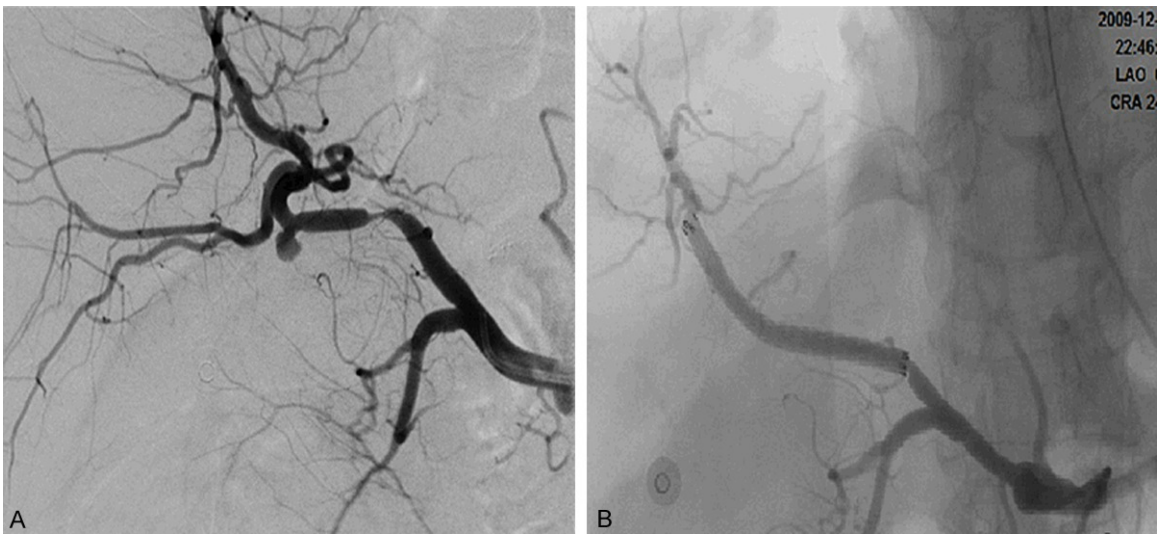

Figure 2. Patient No. 12. A 58-year-old male with Carcinoma of Pancreatic head underwent pancreaticoduodenectomy. A. Contrast extravasation was observed at the stump of GDA without a pseudoaneurysm formation. B. Angiography after CSP procedure.

Discussion

With the development of the surgical techniques, the mortality of PD decreased dramatically over the past decades [6, 11, 12]. However, the overall morbidity is still high at 50%-60% even in experienced centers [13-16]. Severe delayed PPH is a rare but life threatening complication with reported morbidity between 6-10% and associated with a high mortality up to 60% [1-5, 17, 18]. In this study, the morbidity of delayed PPH was 5.9%, which was slightly lower than those reported in the literatures. The end-to-side duct-to-mucosa pancreaticojejunostomy, which has a lower morbidity of PF, is the only anastomotic method we adopted in this series and may play an important role in this satisfying result.

According to the previous literatures [2, 12, 19, 20], the morbidity of SB was ranged from 33%-73% in delayed PPH cases and the subsequent

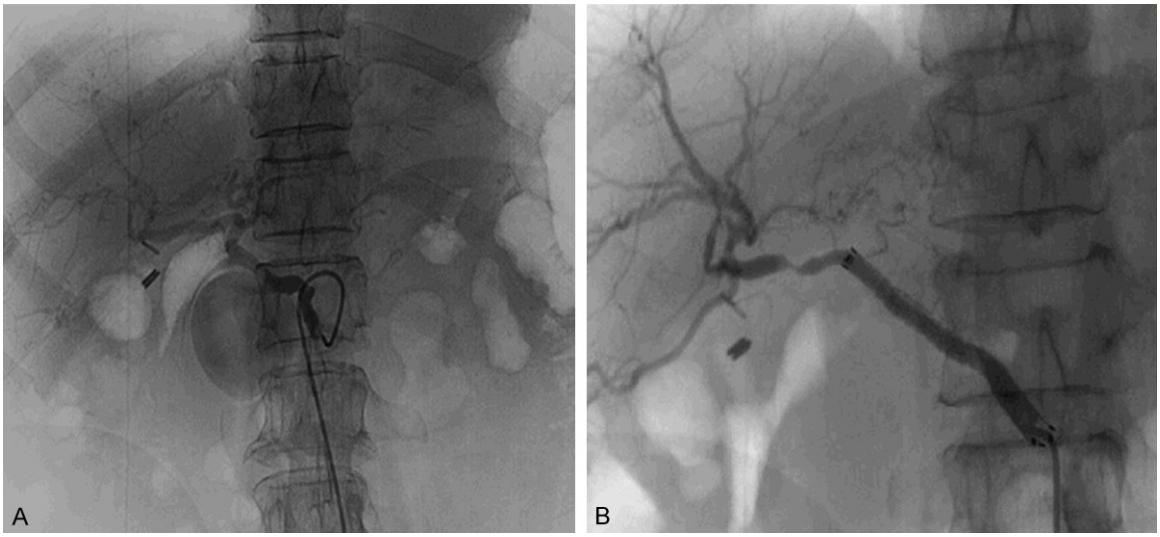

Figure 3. Patient No. 4. A 72-year-old female with Carcinoma of Pancreatic head underwent pancreaticoduodenectomy. Delayed PPH happened 41 days after surgery with a great lot of melena. A. A distinct pseudoaneurysm of the GDA stump was revealed by angiography. B. Angiography after CSP procedure.

Table 4. Management and outcome of re-bleeding patients

Patient NO.	Presentation of re-bleeding	Bleeding site	Management	Follow-up (time after management)
2	Abdominal drain	No active bleeding	CSP	Survived to the present
6#	Abdominal drain	CHA	TAE	died of multi-organ failure
8	Melena	CHA-intestinal fistula	CSP	Survived to discharge; 4 months, died of tumor metastasis
10#	Abdominal drain	Stump of GDA	TAE	died of uncontrolled bleeding and multi-organ failure
14#	Hematemesis	----	Conservative treatment	died of uncontrolled bleeding
17#	Hematemesis	CHA	TAE	died of uncontrolled bleeding and multi-organ failure

CHA: common hepatic artery; GDA: gastroduodenal artery; TAE: transcatheter arterial embolization; CPS: covered stent placement; #: patients with a dead outcome.

hemorrhage had a mortality rate of over 50% [1]. In our study, SB was presented in 50% (9/18) delayed PPH patients. And all re-bleeding (n = 6) and died (n = 4) patients were included in these 9 cases. SB, combined with PF and/or intro-abdominal infection was demonstrated in most of the patients with the miserable results (**Tables 2**, **4**). Thus, SB should be aggressively diagnosed and rigorously monitored for hemorrhagic complications to be avoided, especially when a patient manifested SB, PF, and/or intro-abdominal infection together.

Although endovascular techniques have improved over the recent decades, there is no consensus about the procedures of delayed PPH except for immediate resuscitation of hemodynamic stability. Many clinicians have demonstrated that TAE is an effective treatment for delayed PPH [9, 21-24]. Meanwhile, in order to avoid ischemia of embolized organs, CSP has been considered as a valid alternative to TAE [2, 25-28]. TAE is a relatively easier interventional procedure using coils to embolize the vessel, but a general angiography was required to assess the perfusion status of the distal organ supplied by the embolized artery. If TAE in CHA is needed, the portal blood flow is required to be confirmed by development of portal venous in angiography. In this study, 3 patients with TAE in CHA got liver damage by elevation of aminotransferases, and the other 2 presented liver abscess with 1 died of severe infection and multi-organ failure (**Table 3**).

Hemorrhage recurrence is another severe complication of TAE. In this study, re-bleeding was occurred in 4 of 10 TAE patients. Of these 4 cases, 2 recovered from re-hemorrhage by CSP

and 2 died of uncontrolled bleeding and multi-organ failure, respectively. Hemorrhage recurrence may be caused by incomplete embolization, migration of the coils, and re-dredged of the bleeding artery. Even if a pseudoaneurysm or bleeding vessel is completely embolized, the shake of organ intro-abdominal activation may induce coil compressed or migration [2, 29]. In this series, the intestinal mucosa development was observed during angiography in patient NO.8, which suggested an artery-intestinal fistula formation. TAE is not suitable for this patient because of the higher possibility of re-bleeding induced by detachment of the coils. For the same reason, TAE is not recommended in patients with a big crevasse, which to be embolized by more than 3 coils by the assessment of angiography (**Table 3**).

CSP was reported in a few series handling delayed PPH [24, 30]. CSP may be not feasible, which is mainly due to the restriction of anatomic reasons. In those with a tortuous celiac or common hepatic artery, celiac artery stenosis or fine common hepatic artery, it may be difficult to push a covered stent into the proper site. The preservation of arterial blood flow is the most obvious advantage of CSP to deal with pseudoaneurysms of the main trunk of CHA or SMA [20, 31], and the redundant portal venous angiography is unnecessary when the CSP is performed. In this study, all patients received CSP (n = 8) got thoroughly bleeding control and without any ischemic complications.

Due to its safety, CPS could be used to handle some uncertain and tricky complications. Patient No. 2 got critical re-bleeding after the TAE treatment at the stump of GDA, but nothing positive was observed in the following emergency angiography. It seemed that bleeding had stopped spontaneously because of hemodynamic instability. Trying to resolve the dilemma, covered stents were empirically placed in the main trunk of CHA to seal the possible bleeding site, and the patient quickly recovered from hypotension and was discharged successfully.

Surgical treatment of massive PPH is related to high mortality and morbidity, which could be up to 90% [11, 30, 32, 33]. In our series, 2 of 3 patients received surgical operations were died from uncontrolled postoperative hemorrhage. Endoscopic procedure is always used in diagnosis and treatment in early PPH patients, and surgical intervention is opted when Endoscopy failed. When delayed PPH presented, EI procedures must be primarily considered rather than surgical interventions unless EI failed.

In summary, prompt and comprehensive assessment and early intervention are as an important role of saving patients from delayed PPH, even after minor bleeding (SB) episodes. SB must be aggressively diagnosed and rigorously monitored for massive hemorrhage to be avoided, especially with PF and/or intro-abdominal infection together. Because the covered stent is better at preserving arterial flow and get lower hemorrhage recurrence than TAE, it is considered a fist-line treatment modality in patients with delayed PPH. TAE could be performed in whom placing a covered stent is technically difficult. When an angiography shows negative but hemorrhage recurrence demonstrated existed after TAE, CSP sealing the possible bleeding lesions may be an appropriate solution and bring forth satisfactory results.

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Disclosure of conflict of interest

None.

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