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Endovascular treatment of delayed hemorrhage developing after the pancreaticoduodenectomy procedure

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Summary
Aim and background Delayed hemorrhage after pancreaticoduodenectomy (PD) is still one of the most common causes of mortality. However, the case series regarding interventional treatment of delayed hemorrhage after PD are limited. In this retrospective study, we aimed to evaluate functional outcomes of interventional treatment of late hemorrhages developing after PD.

Material and methods We retrospectively evaluated 16 patients who received endovascular treatment for delayed arterial hemorrhage after PD procedure. Postsurgical nonhemorrhagic complications, time of hemorrhage, site of hemorrhage, endovascular treatment technique, postprocedural complications, and mortality rates were obtained.

Results Mean duration of delayed hemorrhage after PD was 18 days. Computed tomography angiography images for the hemorrhage period were available for 15 patients. We observed extravasation alone in seven patients and pseudoaneurysm alone in five. Pushable coil was used in 15 patients and covered stent in 1. Two patients died due to hepatic failure, and one patient died because of multiple organ dysfunction syndrome (MODS).

Conclusions Delayed hemorrhage after PD is difficult to identify, but accurate and early diagnosis is of vital importance. To date, most appropriate management of this complication remains unclear. Although endovascular treatment techniques may vary for every patient, it is a reliable and effective method for halting hemorrhage. Therefore, interventional procedures must be primarily considered rather than surgical interventions.

Keywords Pancreaticoduodenectomy · Delayed hemorrhage · Interventional procedures

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Endovaskuläre Behandlung von verzögerten Nachblutungen nach Pancreato-Duodenektomie

Zusammenfassung
Ziel und Hintergrund Verzögerte Nachblutungen nach Pankreato-Duodenektomie (PD) sind noch immer die häufigste postoperative Todesursache. Trotzdem gibt es nur eine begrenzte Zahl von Fallserien bezüglich einer interventionellen Therapie von verzögerten Nachblutungen nach PD. In der vorliegenden retrospektiven Studie war es unser Ziel, funktionelle Ergebnisse der interventionellen Behandlung von verzögerten Nachblutungen nach PD zu evaluieren.

Methoden Wir evaluierten retrospektiv 16 Patienten, bei denen eine endovaskuläre Therapie einer verzögerten Nachblutung nach PD durchgeführt worden war. Postoperative nicht-blutungsbedingte Komplikationen,

Zeitpunkt der Blutung, Lokalisation der Blutung, Technik der endovaskulären Therapie, Komplikationen nach der Prozedur und Mortalität wurden erhoben.

Ergebnisse Die mittlere Dauer bis zum Auftreten der verzögerten Nachblutung nach PD betrug 18 Tage. CT-Angiographie-Bilder der Blutungsperiode waren bei 15 Patienten verfügbar. Bei sieben Patienten beobachteten wir ein Extravasat und bei fünf Patienten ein Pseudoaneurysma. Bei 15 Patienten wurden Coils zur Blutstillung verwendet. Bei einem Patienten wurde ein gedeckter Stent plaziert. Zwei Patienten starben als Folge von Leberversagen, ein Patient wegen MODS.

Schlussfolgerungen Verzögerte Nachblutungen nach PD sind schwierig zu erkennen. Eine frühe und korrekte Diagnose ist aber von vitaler Bedeutung. Bis heute ist unklar, welches das am besten geeignete Management dieser Komplikation ist. Obwohl die endovaskuläre Technik bei jedem Patienten anders sein kann, ist die Methode zur Blutungsstillung verlässlich und wirksam. Interventionelle Maßnahmen sollten daher als Therapie erster Wahl – vor chirurgischen Interventionen – in Erwägung gezogen werden.

Schlüsselwörter Pankreato-Duodenektomie · Verzögerte Nachblutung · Interventionelle Blutstillungs-Prozeduren

Introduction

Pancreaticoduodenectomy (PD) is a complex surgery performed to remove tumors in the periampullary region of the pancreas. After developing surgical techniques, the acceptable mortality rate is reported to have fallen to 0–5% [1–3]. Operative morbidity, however, is still high (20–60%) [4, 5]. Intraperitoneal abscess, wound site infection, delayed gastric emptying, bile leakage, pancreatic fistula, and early and late hemorrhage are the main attendant complications. Early postoperative hemorrhage appears in the first 24–48 h. It frequently results from inadequate technique, insufficient hemostasis, anastomotic bleeding, or coagulation disorder [2, 6, 7]. Delayed hemorrhage developing after PD appears in 4% of cases and involves high mortality rates of 11–38% [8, 9].

Mortality and morbidity are reported to be higher in patients undergoing hemorrhage-related relaparotomy [10]. Endovascular treatment, today regarded as an alternative treatment option to surgery, has become the first step in delayed hemorrhage and has led to a significant decrease in relaparotomy rates. Success rates for endovascular treatment of delayed hemorrhage developing after PD vary between 50 and 100% in different series [11–13]. However, the case series regarding interventional treatment of delayed hemorrhage after PD are limited. In this study, we aimed to evaluate the safety, efficacy and the utility of interventional treatment of late hemorrhages after PD.

Materials and methods

Between January 1995 and January 2013, 342 patients underwent PD at the Department of Surgery in Ege University. In this study, we retrospectively evaluated the database of 16 patients who received endovascular treatment for delayed arterial hemorrhage after PD procedure. Data regarding age, gender, pathological diagnosis, surgical technique performed, postsurgical non-hemorrhagic complications, time of hemorrhage, radiological imaging findings, site of hemorrhage, endovascular treatment technique applied, postprocedural complications, recurring hemorrhage and the need for repeat procedure, and late-term morbidity and mortality were obtained for all patients from the archive files.

Definitions of complications

Postpancreatectomy hemorrhage was defined as postoperative bleeding from the surgical site accompanied by a drop in hemoglobin concentration of >3 g/dl, with peripheral circulatory impairment requiring treatment involving the need for blood transfusion (>3 U of packed red blood cells), or invasive treatment (reoperation or interventional angiography). According to the International Study Group of Pancreatic Surgery, postoperative hemorrhage is categorized with respect to the time of onset (early, ≤24 h after end of index operation; or late, >24 h), location (intraluminal, intraenteric; or extraluminal, extra-enteric), and severity (mild or severe). In this study, patients with late (>24 h) and severe hemorrhage were included.

Amylase level was measured in the fluid from the drain placed close to the pancreaticoduodenostomy anastomosis. Values two or more times higher than the normal levels of amylase were defined as pancreatic fistula or pancreaticoduodenostomy leakage. Bile appearing from the drain placed near the hepaticoduodenostomy was defined as bile leakage, and serum alanine transaminase enzyme level >1,000 IU was defined as hepatic necrosis. Finally, infected fluid or purulent fluid collection in the abdominal cavity was defined as intra-abdominal abscess.

Endovascular treatment protocol

The procedure was performed with femoral artery intervention in all cases. After abdominal aortography with a 5F pigtail catheter (Boston Scientific Corp., USA), selective angiograms of the celiac truncus and superior mesenteric artery (SMA) were taken with a 5F Cobra C2 catheter or Simmons-1 catheter (Boston Scientific Corp.). Thereafter, 2.7F microcatheter (Progreat Terumo Medical Corporation, USA) was placed into the diagnostic catheter. Arterial vascular pathology embolization procedures were performed with a 0.018-inch pushable coil (Tornado® Embolization Micro-coils™-Platinum, COOK

Medical Inc., USA), N-butyl cyanoacrylate (NBCA), or covered stent (JOSTENT Graft-Master, Abbott vascular Inc., USA). The procedure was concluded after postprocedural celiac truncus and SMA selective angiographies.

Results

In this study, the bleeding rate after PD procedure was 4.6%. Of the 16 cases studied, 12 (75%) were male and 4 (25%) were female. The patients were aged between 39 and 79 years, with a mean age of 58 years. Classic PD procedure was performed with a diagnosis of pancreas tumor in 12 cases, distal choledocus tumor in 3, and ampulla vateri tumor in 1. Of these patients, pancreatic fistula alone was determined in five, pancreatic fistula and intra-abdominal abscess in five, bile leakage alone in four, bile leakage and intra-abdominal abscess in one, and intra-abdominal abscess alone in one. Mean duration of post-PD hemorrhage was 18 (4–45) days. Extraluminal hemorrhage was observed in 10 patients and intraluminal hemorrhage in 6. Abdominal computed tomography angiography (CTA) images for the hemorrhage period were available for 15 of the 16 patients. Of those 15 patients, pseudoaneurysm was observed in CTA images in 5 patients (47%), pseudoaneurysm + active extravasation in 2 (13%), intraperitoneal hematoma in 3 (20%), and fluid collection/abscess alone in 5 (33%). Pseudoaneurysm + active extravasation was observed in 6 of the 16 patients in celiac and mesenteric angiograms, extravasation alone in 7, and pseudoaneurysm alone in 5. Hemorrhagic focus in angiograms was seen in the gastroduodenal artery (GDA) stump in eight patients, in the hepatic artery in four, in the gastroduodenal and hepatic arteries in two, in the left gastric artery in one, and in the splenic artery in one. Pushable coil (selective embolization of pseudoaneurysm in nine patients and artery embolization in six) was used as the embolizing agent in 15 patients and covered stent in 1. Embolization was established with pushable coil together with NBCA in two cases. Three days after the first embolization, rebleeding occurred in one patient (patient 12). Repeat procedure was performed, and the hemorrhage was successfully controlled with parent artery embolization. No procedure-related complication developed in any other case. No rebleeding in the late period occurred in the other cases. Mortality occurred in 3 (18.7%) of the 16 patients: 2 dying of liver failure and 1 of multiple organ failure (Table 1 and Fig. 1).

Discussion

Despite the advancement of surgical techniques, delayed hemorrhage after PD procedure is a serious problem in the postoperative period and carries a high mortality. The mortality rate ranges from 11 to 54%, even in experienced centers [7, 14]. Studies have suggested that late-period hemorrhages develop in association with erosion and ulcer of blood vessels due to pancreatic fistula, bile leakage, and intra-abdominal abscess. Lymph node dissection and advanced skeletization of blood vessels, particularly in malignant cases, make the vessels vulnerable to erosion and ulceration [15]. Vascular erosions developing after PD particularly affect the branches of the celiac artery and SMA. The fact that the GDA is close to hepaticoduodenostomy and pancreaticoduodenostomy and is left in stump form during the operation is thought to increase the rate of exposure to complications. Therefore, GDA is the most commonly affected artery in late-period hemorrhages after PD [7, 14, 16]. Similarly, in our study, the most common foci of hemorrhage were the GDA and the hepatic artery.

Surgical or endovascular intervention is required in cases in which hemorrhage persists despite sufficient blood and fluid replacement. It is difficult to determine the hemorrhage site surgically in the acute period due to fragility in tissues and adhesions [14, 16]. Delayed hemorrhage and pancreaticoenteric anastomotic leak are the most important indications of reoperation after PD procedure. Before advanced interventional radiological techniques, traditional approach to massive hemorrhage after PD was direct surgical intervention. However, surgical intervention for delayed hemorrhages after PD is difficult and reoperation may be the cause of further mortality and morbidity [1, 17, 18]. Therefore, surgery is restricted for patients in whom interventional procedures fail or are not technically feasible [18].

Endovascular treatment has recently become the first option in hemorrhages developing in the late period after PD, due to its high success and low morbidity and mortality rates. Depending on the location and size of the focus of hemorrhage, endovascular interventions can be performed in the form of transarterial embolization or closed stent [16, 19, 20]. Various embolizing agents (coil, NBCA, etc.) are used in transarterial embolization. Transarterial embolization can be performed in the form of selective coil embolization of the pseudoaneurysm or by occluding it together with the vessel from which it originates. Rebleeding after embolization performed by protecting the vessel from which the pseudoaneurysm originates may develop due to incomplete embolization, coil migration, and persisting pseudoaneurysm inflammation. NBCA injection together with coil is reported to be useful for reducing rebleeding [16]. Coil embolization of the pseudoaneurysm must be performed when possible in embolization. When this is not possible, treatment with occlusion of the parent artery and the vessel from which the pseudoaneurysm originates must not be neglected. In cases in which treatment is planned with embolization of the parent artery of the hepatic artery, the presence of normal portal blood flow must be identified [21, 22]. Complications associated with total occlusion of the hepatic artery are abscess formation in the liver, liver insufficiency, and liver necrosis [12, 23]. Parent artery occlusion was performed in six of our cases. Selective embolization was established with coil + NBCA in two cases and with coil embolization in four. Tempo-

Table 1 Summary of clinical data in patients with endovascular treatment of delayed hemorrhage developing after the pancreaticoduodenectomy procedure

Age (years)/sex	Bleeding site	Hemorrhage time (day)	CT findings	DSA findings	Procedure	Repeat procedure	Mortality
78/male Patient 1	Hepatic artery	10	Pseudoaneurysm + fluid collection + active hemorrhage	Pseudoaneurysm + active hemorrhage	Selective embolization with pushable coil + NBCA	–	–
72/female Patient 2	Hepatic artery, gastroduodenal artery	25	Fluid collection/ abscess	Pseudoaneurysm + active hemorrhage	Selective embolization with pushable coil	–	–
43/male Patient 3	Gastroduodenal artery	45	Pseudoaneurysm + hematoma	Pseudoaneurysm + active hemorrhage	Selective embolization with pushable coil	–	–
63/female Patient 4	Gastroduodenal artery	7	Fluid collection/ abscess	Active hemorrhage	Selective embolization with pushable coil	–	–
58/male Patient 5	Gastroduodenal artery	20		Active hemorrhage	Covered stent	–	–
68/female Patient 6	Gastroduodenal artery	10	Pseudoaneurysm	Pseudoaneurysm	Selective embolization with pushable coil	–	–
48/female Patient 7	Splenic artery	40	Hemorrhage + fluid collection/ abscess	Pseudoaneurysm + active hemorrhage (Fig. 1a, b)	Parent artery embolization with pushable coil (Fig. 1c)	–	–
79/male Patient 8	Left gastric artery	10	Fluid collection/ abscess	Active hemorrhage	Selective embolization with pushable coil	–	
53/male Patient 9	Hepatic artery	7	Fluid collection/ abscess	Active hemorrhage	Parent artery embolization with pushable coil	–	Hepatic failure
39/male Patient 10	Hepatic artery	40	Hemorrhage + fluid collection	Active hemorrhage	Parent artery embolization with pushable coil + NBCA	–	Multipl organ failure
59/male Patient 11	Gastroduodenal artery	4	Pseudoaneurysm fluid collection abscess	Pseudoaneurysm + active hemorrhage	Parent artery embolization with pushable coil	–	–
51/male Patient 12	Hepatic artery, gastroduodenal artery	7	Pseudoaneurysm + fluid collection + active hemorrhage	Pseudoaneurysm + active hemorrhage	Selective embolization with pushable coil	Parent artery embolization	–
57/male Patient 13	Hepatic artery	8	Fluid collection/ abscess	Active hemorrhage	Parent artery embolization with pushable coil	–	–
56/male Patient 14	Gastroduodenal artery	23	Hemorrhage + fluid collection	Active hemorrhage	Selective embolization with pushable coil	–	–
41/male Patient 15	Gastroduodenal artery	23	Pseudoaneurysm + fluid collection/ abscess	Pseudoaneurysm + active hemorrhage	Parent artery embolization with pushable coil	–	
63/male Patient 16	Gastroduodenal artery	14	Pseudoaneurysm + fluid collection/ abscess	Pseudoaneurysm + active hemorrhage	Selective embolization with pushable coil	–	Hepatic failure

CT computed tomography, *DSA* digital subtraction angiography, *NBCA* N-butyl cyanoacrylate

rary elevated transaminase level was observed after the procedure.

Another treatment modality for active arterial hemorrhage is the temporary balloon occlusion technique performed to gain time in patients to be taken for surgery [24]. This technique was not performed on any patient in this series. Establishing hemostasis and continuity of distal blood flow using the covered stent has become increasingly favored in recent years. The focus of hemorrhage in our fifth patient was the GDA. The reason for a covered stent was liver insufficiency together with suitable vascular access in the patient. For anatomical

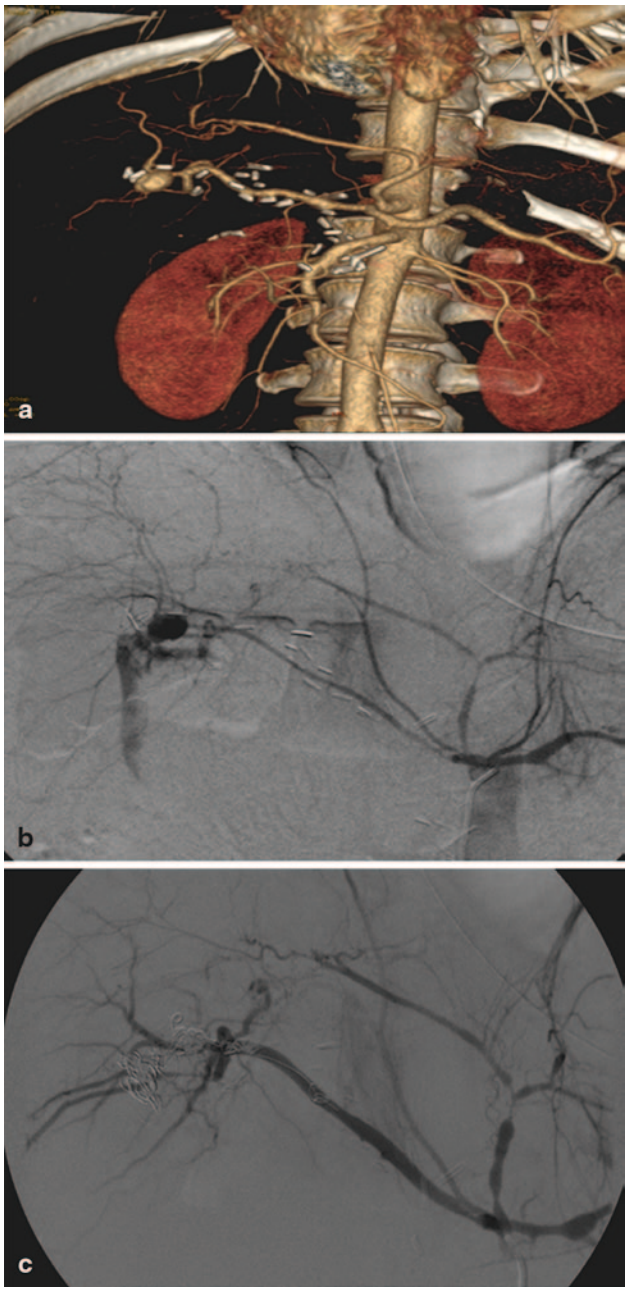

Fig. 1 **a** Coronal volume-rendering technique reformatted MDCT image shows vascular anatomy and the site of pseudoaneurysm. **b** Digital subtraction angiogram obtained because the patient was in hemodynamically unstable condition shows active bleeding from the right hepatic artery. **c** Digital subtraction angiogram shows embolization coils (seventh case)

reasons, it may not always be possible for the covered stent to be placed in the celiac artery and its branches [23]. Additionally, rupture may occur during placement of the covered stent because the vessel in which hemorrhage develops is fragile due to inflammation, and the covered stent itself may turn into a septic focus [25]. The long-term outcomes of covered stent use are unknown. It should therefore only be preferred in selected cases and patients with a suitable arterial structure.

The most frequent complications after embolization are again hemorrhage and ischemia [26]. Postprocedural rebleeding occurred in our 12th patient and was stopped by the application of embolization of the hepatic parent artery.

Reviewing the literature, no prospective randomized clinical trial comparing surgery with endovascular intervention in the management of delayed hemorrhage after PD was found. Therefore, the most appropriate management of this complication remains unclear. Limongelli et al. evaluated 24 published articles about the management of delayed hemorrhage after PD including 163 cases. This meta-analysis did not reveal a significant difference between surgery and endovascular intervention in successfully arresting hemorrhage. However, complication, mortality, and morbidity rates were higher in patients who underwent resurgery [27]. The mortality rate in our cases was 19 %. Among the fatal cases, focus of hemorrhage in our ninth case was the hepatic artery, and embolization of the parent artery was performed. Hemorrhage was successfully controlled; however, liver function tests were elevated after the procedure, and the patient died due to hepatic failure on the 17th day. Our 10th patient was in a state of shock on arrival due to advanced hemorrhage. Coil embolization of the pseudoaneurysm in the hepatic artery was performed. Although hemostasis was established, the patient died due to multiple organ failure on the ninth day. Hemorrhage in the GDA trunk in our 16th patient was successfully controlled with coil embolization, but the patient died due to secondary biliary cirrhosis-related hepatic failure on the 16th day. Hemostasis was successfully achieved in the other 13 cases, and the patients were discharged. One of the factors that increase mortality rates is hemorrhage originating from the SMA. In a series published by Miura et al. [28], four cases with SMA involvement followed a mortal course. Another factor increasing mortality stems from foci of abscess developing in the liver after embolization of the hepatic artery [28]. Hepatic artery embolization was performed in six (38 %) of our cases, and no hepatic abscess developed in any.

With advances in interventional radiology, minimally invasive interventional procedures are reducing mortality and morbidity, and are used as an effective method for treatment of delayed hemorrhage after PD. Coil embolization of pseudoaneurysm due to delayed hemorrhage after PD can be performed selectively. In cases where this is not possible, embolization of the parent artery and the vessel from which the hemorrhage originates should be performed. It should always be borne in mind that recurrent hemorrhage may occur after selective embolization of pseudoaneurysm in some cases.

The fact that data were collected retrospectively and that the percentage of patients reoperated due to post-PD hemorrhage is uncertain represents limitations of the study. No comparison was therefore performed in terms of surgical and interventional procedures.

In conclusion, interventional treatment is a reliable, safe, and effective method for delayed hemorrhage after

PD. According to the present retrospective study, we suggested that it should be primarily considered due to the high rates of mortality and morbidity attendant upon surgical interventions.

Conflict of interest

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

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