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# Angiography is Indicated for Every Sentinel Bleed after Pancreaticoduodenectomy

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**Background:** Delayed massive bleeding is one of the leading causes of mortality after pancreaticoduodenectomy (PD) and is often preceded by sentinel bleed. Immediate and accurate diagnosis of sentinel bleed is essential to save patients from a delayed massive hemorrhage. Angiography is probably the procedure of choice for patients with sentinel bleed after PD, as it will localize the bleeding point and provide interventional embolization. The purpose of this study is to test the efficiency of angiography as the initial management for patients with sentinel bleed after pancreaticoduodenectomy.

**Methods:** The study group consisted of 283 patients who underwent PD from July 2002 to June 2007. Angiography and arterial embolization were performed for every sentinel bleed and detected pseudoaneurysm. Patients ($n$ = 311) from a previous study (July 1996–June 2002) were used as a historical control group.

**Results:** Sentinel bleed was detected in 20 patients in study group. Of these, angiography-detected pseudoaneurysm was evident in seven (35%); all were successfully embolized. Delayed massive hemorrhage occurred in three of 13 patients with sentinel bleed but negative angiography. All three were operated on; one died of uncontrolled bleeding. The number of hemodynamically unstable patients before transfusion, units of transfused packed cells, and bleeding related mortalities were significantly less in study group than the control group.

**Conclusions:** Institution of angiography for every detected sentinel bleed after PD enabled us to embolize seven pseudoaneurysms before massive hemorrhage. Most importantly, bleeding-related mortality was significantly less than in the absence of angiography.

**Key Words:** Sentinel bleed—Pancreaticoduodenectomy—Delayed massive hemorrhage.

The mortality rate after pancreaticoduodenectomy (PD) has decreased markedly over recent decades and currently comprises only up to 5% in centers specialized for pancreatic operations.[1–5] However, morbidity remains high, at 30–40%.[1–6] The most common complications after PD are delayed gastric emptying, pancreatic leakage, and intra-abdominal abscess formation.[6–8] Hemorrhage after PD is a less common but dramatic complication. In particular, delayed hemorrhage occurring 5 or more days following surgery is associated with a high mortality rate, since hemorrhaging often results from arterial erosion after a pancreatic leak.[9–14] Surgical exploration and identification of the bleeding vessel can be difficult and hazardous because of adhesions and surrounding postsurgical tissue friability.[12] In contrast, successful arterial embolization for bleeding from pseudoaneurysms have been reported and is claimed to be technically easier for both the patient and surgeon.[12] The

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latter study concluded that emergency surgery for pseudoaneurysms should rarely be necessary and could be replaced almost exclusively by radiological intervention. However, the reality is that bleeding can be so profuse as to compromise the safety of transcatheter arterial embolization due to hemodynamic instability and vasoconstriction. Therefore, transcatheter arterial embolization will be most useful for patients at the stage of sentinel bleed,[12] before massive bleeding and hemodynamic instability occur. Detection of sentinel bleed and the timely use of angiography could be valuable in treating this serious and sometimes fatal complication.[14] However, most papers, as well as a recent report from an international study group of pancreatic surgery (ISGPS),[15] suggested mild postpancreatectomy hemorrhage should be initially conservatively managed with observation, ultrasonography, computed tomography, or endoscope with transfusion, and angiography should only be used after failure of other diagnostic tools or aggravation of bleeding. A cost–benefit analysis of visceral angiography as the initial diagnostic and hemostatic tool in patients with sentinel bleed after PD has never been addressed. However, in reality, it is almost impossible to institute a prospective randomized study because of limited number of patients. Instead, in 2002, we instituted a prospective study to perform visceral angiography for every sentinel bleed detected after PD and embolization of any detected bleeding pseudoaneurysms. The present paper reports results for 20 patients and compares their outcomes to a conventionally treated historical control group.[16]

## PATIENTS AND METHODS

The study group consisted of 283 consecutive PD patients recruited at National Taiwan University Hospital from July 2002 to June 2007. The historical control group consisted of 311 consecutive patients who received a PD at National Taiwan University Hospital from July 1996 to June 2002. In both groups following PD and hemostasis, the pancreatic remnant was anastomosed to the jejunum (duct to mucosa) or stomach (invagination) and a short nelaton stent was inserted into the pancreatic duct without any external drainage. After completion of this reconstruction, two rubber drains were placed nearby the biliary and pancreatic anastomoses.

Sepsis in the postoperative period was defined as either bacteremia (a body temperature of at least 38.5°C combined with a leukocyte count $\geq 15 \times 10^9$/L) or the presence of intra-abdominal abscesses. According to the International Study Group on Pancreatic Fistula, postoperative pancreatic fistula (POPF) was defined as output via an operatively placed drain (or a subsequently placed percutaneous drain) of any measurable volume of drain fluid on or after postoperative day three, with an amylase content greater than three times the upper normal serum value,[17] with POPFs classified as grades A, B, or C.[16] Bile leakage was defined as the presence of bilirubin-rich drainage fluid in volumes three times greater than normal. Since it is not uncommon to find blood in the nasogastric tube or abdominal drains immediately after abdominal operations, we defined sentinel bleed as the appearance or paradoxical increase in the amount of blood from the abdominal drains or gastrointestinal tract combined with a decrease of hemoglobin of more than 2 g/dl 3 days after PD. Sentinel bleeds were further graded by the ISGPS definition in which three different grades of PPH (grade A, B, and C) are defined according to the time of onset, site of bleeding, severity, and clinical impact.[15] Delayed massive hemorrhage (DMH) was defined as a postoperative bleeding occurring three days after PD that required a transfusion with at least four packed cells within 24 h, or the need for relaparotomy or transcatheter embolization to terminate bleeding. Hemodynamic instability was defined as a mean arterial pressure lower than 70 mmHg (normal range 70–110 mmHg) before resuscitation with intravenous fluids or the administration of blood products. Operative mortality was defined as death occurring during the hospital stay or as a consequence of a postoperative complication.

During the study period, angiography was used as the initial tool for management of sentinel bleed. During angiography, both the celiac trunk including the hepatic and splenic arteries as well as the superior mesenteric artery were visualized. Embolization was performed by coil or/and tissue glue occlusion for every detected pseudoaneurysm. After embolization, patients were closely observed for rebleeding or embolization-related ischemia. Rebleeding after embolization was treated by re-embolization. Surgical intervention was used only for patients with early ($\leq$3 days) massive hemorrhage, patients with delayed massive hemorrhage (>3 days) and unstable hemodynamics, or patients with pseudoaneurysm or delayed massive hemorrhage which could not be successfully embolized. Generally, surgical interventions for delayed massive hemorrhage included exploration, suture ligation of the bleeding vessel, and removal of the intra-abdominal hematoma, with conversion of pancreatic anastomosis into controlled pancreatico-

**TABLE 1.** *Comparison of preoperative and intraoperative parameters between the study and historical control groups*

| | Study group (n = 283) | Historical control group (n = 311) | *P* value |
|---|---|---|---|
| Patient characteristics | | | |
| Mean age (range) | 61.2 (24–88) | 59.2 (16–83) | 0.15 |
| Gender (male/female) | 170/113 | 187/124 | 0.99 |
| Pathology of index operation | | | 0.28 |
| Pancreatic head/periampullary cancer | 230 | 241 | |
| Chronic pancreatitis | 29 | 31 | |
| Benign tumor | 24 | 39 | |
| No. of patients with jaundice | 177 | 174 | 0.11 |
| No. of patients with preoperative drainage | 121 | 137 | 0.75 |
| No. of patients with soft pancreas parenchyma | 189 | 198 | 0.43 |
| No. of patients with dilated pancreatic duct | 69 | 82 | 0.58 |
| No. of patients with pylorus preservation | 129 | 131 | 0.4 |
| Pancreatic anastomosis (PJ*/PG†) | 207/76 | 213/98 | 0.18 |
| No. of patients with vascular resection | 21 | 15 | 0.19 |
| No. of patients with lymph node dissection | 58 | 71 | 0.49 |

*PJ, pancreaticojejunostomy; †PG, pancreaticogastrostomy

cutaneous fistula in patients with POPF. In contrast, during the historical control period, endoscope, ultrasound, or CT was used as initial diagnostic tool for sentinel bleed, and patients were conservatively treated by gastric drainage, antibiotics, blood products, and supportive drugs such as somatostatin for patients with postoperative pancreatic fistula. Patients with delayed massive hemorrhage were treated either by arterial embolization or operation.

All therapeutic interventions performed were analyzed regarding success rate in controlling the bleedings. Specific parameters of patients with DMH analyzed included patient characteristics, symptoms and signs between index pancreaticoduodenectomy and DMH, bleeding characteristics, diagnostic workup, therapeutic intervention, and outcome.

Statistical analyses comprised the chi-squared test, two-tailed Fisher exact test, and Mann–Whitney *U* analysis. When applicable, the analyses utilized the Statistical Package for Social Science for Windows, version 10.0 (SPSS, Chicago, IL). The tests were two-sided, and $P < 0.05$ was considered statistically significant.

## RESULTS

In the study group of 283 patients who underwent PD from July 2002 to June 2007, the indications for PD included neoplasms of the pancreatic head or periampullary malignance ($n = 230$), complicated chronic pancreatitis ($n = 29$), and benign tumor ($n = 24$). Pancreaticojejunostomy (PJ) was performed in 207 patients and pancreaticogastrostomy (PG) was performed in 76 patients. The historical control group of 311 patients was comprised of people who underwent PD from July 1996 to June 2002. Indications for PD were neoplasms of the pancreatic head or periampullary malignance ($n = 241$), complicated chronic pancreatitis ($n = 31$), and benign tumor ($n = 39$). PJ was performed in 213 patients and PG was performed in 98 patients. Comparison between study and historical control groups revealed no significant differences in preoperative and intraoperative parameters such as age, gender, pathology, jaundice, preoperative drainage, type of pancreatic anastomosis (pancreaticojejunostomy versus pancreaticogastrostomy), parenchyma texture at neck resection site, and type of resection (Table 1).

Of the 283 patients in study group, POPF occurred in 31 (11%) with sentinel bleeding evident in 20 of the patients (5.8%), seven extraluminal (from abdominal drains) and 15 intraluminal (from gastrointestinal tract, hematemesis, bloody or tarry stool, blood in the nasogastric tube), and all grade B PPH by ISGPS definition. Angiography was the initial diagnostic tool for all 20 patients with sentinel bleed and revealed pseudoaneurysm in seven (35%); all immediately received arterial embolization (Table 2). Of these seven, two (28.5%) again presented with bleeding, and all were successfully treated by a second arterial embolization. No further bleeding occurred. However, two cases of hepatic ischemia (a multiple live micro-abscess and a lateral segment liver abscess) developed after arterial embolization; the lateral segment liver abscess required computed-tomography-guided drainage, but recovery was ultimately complete in both cases. DMH occurred in 3 of 13 patients with sentinel bleeding but negative angiography (Table 2). One patient with bleeding from the splenic artery was initially treated by arterial embolization. This failed, prompting emergency surgery.

**TABLE 2.** *Number, initial diagnostic tool, and management of patients with sentinel bleed and/or DMH*[a]

| | Study group (n = 283) | Historical control Group (n = 311) |
|---|---|---|
| Sentinel bleed | 20 | 13 |
| Initial diagnostic tool for sentinel bleed | | |
| Gastroscope | 0 | 6 |
| Abdominal computed tomography | 0 | 5 |
| Abdominal sonagraphy | 0 | 2 |
| Angiography | 20 | 0 |
| Pseudoaneurysum shown by angiography | 7 (35%) | 0 |
| DMH after negative angiography | 3 (23%) | 0 |
| Initial management of sentinel bleed | | |
| Embolization of detected pseudoaneurysm | 7 | 0 |
| Conservative treatment | 13 | 12 |
| Operation | 0 | 1 |
| Sentinel bleed without subsequent hemorrhage | 10 | 6 |
| Marginal ulcer | 6 | 2 |
| Abdominal drain related trauma | 4 | 4 |
| DMH without preceded sentinel bleed | 0 | 5 |

[a] DMH, delayed massive hemorrhage.

The patient died of uncontrolled bleeding. The other two patients were operated on immediately after bleeding evident in mesentery and artery in the pancreatic parenchyma. Recovery of both patients was uneventful and they were discharged 23 and 35 days after their surgeries. No pseudoaneurysm or DMH occurred in another 263 patients without sentinel bleed. Ten patients in study group had sentinel bleed but no subsequent massive hemorrhage (Table 3). Endoscopy revealed a marginal ulcer in six of these ten patients; bleeding stopped after application of a mucosa coating agent. Bleeding stopped after gradual withdrawal of abdominal drains in the remaining four patients with sentinel bleed from abdominal drain but negative angiographic and endoscopic results, consistent with bleeding related to trauma related to abdominal drains (Table 3).

Of the 311 patients in historical control group, POPF occurred in 43 (13.8%). Sentinel bleed was detected in 13 patients (4.2%), 11 extraluminal and 6 intraluminal, and all grade B PPH by ISGPS definition (Table 2). Initial diagnostic tools for sentinel bleed included gastroscope for six patients, abdominal CT for five patients, and abdominal sonography for two patients (Table 2). Of the 13 patients, one received an exploratory laparotomy immediately after detection of sentinel bleed; disruption of pancreaticojejunostomy and bleeding from pancreatic stump was evident. Takedown of pancreaticojejunostomy with jejunal closure and external catheter diversion of pancreatic secretions and suture ligation of bleeder were done. Recovery was uneventful and the patient was discharged 43 days after the second surgery. Twelve of the 13 patients with sentinel bleed were initially conservatively treated; six developed DMH within seven days. All six patients underwent surgery. Four patients died postoperatively and the remaining two recovered uneventfully and were discharged 25 and 81 days later. DMH occurred in five patients who did not display sentinel bleed; treatment included emergency surgery ($n = 3$) or arterial embolization ($n = 2$). Of the three patients treated surgically, one died of multiple organ failure 39 days postoperatively and the other two patients recovered uneventfully and were discharged 44 and 69 days postoperatively. One of the two patients treated via arterial embolization redeveloped bleeding. Bleeding was stopped by a second arterial embolization. However, this patient as well as the other patient treated via arterial embolization died of multiple organ failure 65 and 27 days after development of DMH. Six patients in the study group had sentinel bleed but no subsequent massive hemorrhage (Table 3). Endoscopy revealed a marginal ulcer in two of these six patients; bleeding stopped after application of a mucosa coating agent. Bleeding stopped after gradual withdrawal of abdominal drains in the remaining four patients with sentinel bleed from abdominal drain, consistent with bleeding related to trauma related to abdominal drains (Table 3).

The incidence of pseudoaneurysm and/or DMH after PD was virtually the same in the historical control group (11 of 311 patients, 3.5%) and the study group (10 of 283 patients, 3.5%). Comparison of characteristics, location of bleeding, hemostatic procedure, and outcome in patients with pseudoaneurysm and/or DMH between the two groups revealed no significant differences in age, gender, pathology, incidence of septic complications, incidence of anastomotic leakage, and incidence of

**TABLE 3.** *Comparison of characteristics, location of bleeding, management, and outcome in study and historical group patients with pseudoaneurysm and/or DMH*[†]

| | Study group (n = 10) | Historical control group (n = 11) |
|---|---|---|
| Patient characteristics | | |
| Mean age (range) | 62 (53–78) | 62 (39–86) |
| Gender (male/female) | 5/5 | 8/3 |
| Pathology of index operation | | |
| Pancreatic head/periampullary cancer | 6 | 9 |
| Chronic pancreatitis | 1 | 1 |
| Benign tumor | 3 | 1 |
| No. of patients with sepsis in postoperative phase before DMH | 3 (30%) | 7 (64%) |
| No. of patients with anastomotic leakage before DMH[†] | 6 (60%) | 7 (64%) |
| Pancraeticojejunostomy | 5 | 6 |
| Hepaticojejunostomy | 1 | 1 |
| No. of patients with sentinel bleeding before DMH | 10 (100%)* | 6 (55%)* |
| Postoperative interval in days, mean (SD[#]) | 18.9 (7.4) | 22.8 (11.7) |
| No. of hemodynamic unstable patients before transfusion | 1 (10%)* | 7 (64%)* |
| Units PC within 24 h, mean (SD[#]) | 6.9 (5.1)* | 12.5 (4.8)* |
| Bleeding sites | | |
| Gastroduodenal artery | 4 | 5 |
| Hepatic artery | 2 | 6 |
| Splenic artery | 1 | 0 |
| Artery in mesentery | 2 | 0 |
| Artery in pancreatic parenchyma | 1 | 0 |
| Hemostatic method (TAE[‡]/Operation) | 8/3* | 2/9* |
| Rebleeding after arterial embolization | 2/7 (29%) | 1/2 (50%) |
| Bleeding stopped by TAE[‡] | 8/10 (80%)* | 2/11 (18%)* |
| Outcomes (Alive/Death) | 9/1* | 5/6* |
| Length of hospital stay after DMH (survival), mean (SD[#]) | 25.1 (19.7)* | 50.4 (21.9)* |

*$P < 0.05$.
[†]DMH, delayed massive hemorrhage; [#]SD, standard deviation; [‡]TAE, transcatheter arterial embolization.

sentinel bleeding (Table 3). However, significantly fewer study patients were noted in the categories of state (hospitalization or discharged) at time of bleeding, number of hemodynamic unstable patients before transfusion, and units of transfused packed cells used (Table 3). Arterial embolization was used significantly more often as the initial hemostatic procedure in the study group of patients (Table 3, $P = 0.02$). There were significantly fewer bleeding-related deaths in the study group (1 of 10 patients, 10%) than in the historical control group (6 of 11 patients, 55%) (Table 3, $P = 0.04$).

## DISCUSSION

While the importance of early detection of sentinel bleed in the timely prevention or intervention of delayed massive hemorrhage after pancreaticoduodenectomy has been widely recognized, paradoxically sentinel bleed has only been vaguely mentioned as bleeding from the gastrointestinal tract or abdominal drains and as a prelude to a subsequently more significant hemorrhage.[13,18–20] In clinical practice, it is not unusual to detect blood in nasogastric tubes or abdominal drains in the immediate few days after an operation and angiography for all early-onset minor hemorrhage after PD will expose patients to procedure-related risk with unclear benefit because almost all reported delayed massive hemorrhage occurred 1 week after index operation and sentinel bleed occurred 1–5 days before it.[9–14,16,19–23] Therefore, in the present study, we defined sentinel bleed as the appearance or paradoxical increase in the amount of blood from the abdominal drains or gastrointestinal tract combined with a decrease of hemoglobin of more than 2 g/dl and which occurs 3 days after index PD. Using this definition, we detected a slightly higher incidence in the study group of patients (20 sentinel bleeds after 283 PD) than in the historical control of patients (13 sentinel bleeds after 311 PD). The higher incidence of sentinel bleed in the study group may be explained by a prospective study with more attention paid.

In the historical control group, upper gastrointestinal endoscopy, abdominal CT, or abdominal sonography was used as the initial diagnostic procedure when sentinel bleed was detected after PD. However, the precise bleeding focus could not be determined in nine of 13 patients. As a result, 12 of 13 patients with sentinel bleed in the historical control group were initially conservatively treated and mas-

sive hemorrhaging developed in six. In contrast, in the study group, angiography was used as the initial diagnostic procedure for all 20 patients with sentinel bleed and seven pseudoaneurysms were found and managed before occurrence of massive hemorrhage. Although angiography failed to identify source of sentinel bleed in 13 patients, there was no angiography-related complication in any patient. Theoretically, angio CT scan would be less invasive than traditional angiography and may identify pseudoaneurysm too. However, angiography provides precise identification and offers a therapeutic advantage with embolization. We do not have much experience of angio CT for the identification of source of sentinel bleed. The cost and benefit of angio CT scan as the initial tool for sentinel bleed awaits further study. In the study group, 3 (23%) of the 13 patients with sentinel bleed but negative angiographic results had subsequent DMH. There are two possible explanations for the negative angiographic results. Firstly, not all cases of DMH may be caused by ruptured pseudoaneurysm. Secondly, intermittent bleeding may limit angiographic detection. In the three patients noted presently, operative findings showed main bleeding from splenic arterial root, and the mesenteric and pancreatic parenchyma arteries. Therefore, a negative angiography does not exclude the possibility of subsequent massive hemorrhage, and close observation and timely intervention of these patients is warranted.

After the institution of the prospective study, arterial embolization was more consistently used as the initial hemostatic procedure in the study group than had previously been the norm in the historical control group. This was a prudent step; arterial embolization successfully stopped bleeding in seven patients in study group but in only one patient in the historical control group. We attribute the high success rate of arterial embolization in the former to early intervention, i.e., before hemodynamics destabilized. This supposition is consistent with earlier observations,[23] which prompted the suggestion that arterial embolization be employed for pseudoaneurysm with evidence of sentinel bleeding, but reoperation for delayed active hemorrhage.[23] Presently, recurrent bleeding occurred in two of seven within 5 days of the initial arterial embolization, but bleeding stopped after re-embolization. Therefore, it is important to monitor for resumption of bleeding after arterial embolization and, if needed, re-embolization. Most importantly, the present data supports the idea that the use of angiography for every detected sentinel bleed after PD and arterial embolization of detected pseudoaneurysm is a prudent way to reduce bleeding-related mortality.

However, arterial embolization did lead to hepatic ischemia in two patients with embolization of proper hepatic artery. Fortunately, recovery was uneventful. Theoretically, selective embolization of a bleeding pseudoaneurysm to maintain hepatic arterial flow will minimize the risk of hepatic ischemia. However, it is not always possible to embolize a detected pseudoaneurysm without compromising hepatic arterial blood flow even in the case of a gastroduodenal artery pseuoaneurysm because they are often too short to be effectively selectively embolized and, instead, embolization of the proper hepatic artery is needed to stop bleeding. Embolization of common or proper hepatic artery carries a risk of hepatic ischemia and even fatal hepatic necrosis when combined with portal venous thrombosis. Gastroduodenal and common hepatic artery pseudoaneuryms can be successfully treated by placement of a covered stent in the hepatic artery without compromising blood flow to liver.[24–27] However, covered stent placement is not always feasible, especially for small side branches of the hepatic artery due to tip inflexibility of covered stents.[28] Despite this, a covered stent may prove to be ideal to address bleeding from the main branch of the hepatic artery.

Of course, it is not appropriate to compare the study group with a historical control group, but, as stated before, it is almost impossible to perform a prospective randomized study because of limited number of patients (bleeding occurs in somewhere between 1% and 8% of pancreatic resections).[15] Moreover, comparison of patients' preoperative and intraoperative parameters such as age, gender, pathology, jaundice, preoperative drainage, type of pancreatic anastomosis (pancreaticojejunostomy versus pancraeticogastrostomy), parenchyma texture at neck resection site, and type of resection revealed no significant differences in age, gender, pathology, incidence of septic complications, incidence of anastomotic leakage, and incidence of sentinel bleeding (Tables 1 and 3). The presented data shows the effect of institution of angiography as the initial tool for sentinel bleed — bleeding-related mortality was significantly less in the study group than in the historic control group.

In conclusion, we instituted a prospective study to perform angiography for every sentinel bleed after PD and embolization of any detectable bleeding pseudoaneurysm. Sentinel bleed was detected in 20 of 283 patients. Of these, angiography-detected pseudoaneurysm was evident in seven (35%); all were

successfully embolized. Although angiography failed to identify the source of sentinel bleed in 13 patients, there was no angiography-related complication in any patient. Most importantly, bleeding-related mortality was significantly less than in the absence of angiography.

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