Haemorrhage following Pancreaticoduodenectomy: Risk Factors and the Importance of Sentinel Bleed


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Key Words
Pancreaticoduodenectomy • PD complications • Haemorrhage • Angioembolization • Sentinel bleed

Abstract
Aim: To document the prevalence and to evaluate the management strategies of haemorrhagic complications following pancreaticoduodenectomy (PD). Methods: All patients who underwent PD from 1/2000 to 10/2005 and experienced at least one episode of haemorrhage during the 30 first days postoperatively were recorded. Etiology of haemorrhage, treatment strategy and mortality rate were recorded and analyzed. Results: A total of 362 patients underwent PD during this period and 32 (8.8%) had haemorrhage postoperatively of whom 15 died (47% mortality rate). Primary intraluminal haemorrhage was recorded in 13 patients, primary intra-abdominal haemorrhage in 5 patients and secondary haemorrhage in 14 patients. Successful management of haemorrhage with angioembolization occurred in 2 patients in the study group. Statistical analysis revealed sepsis and sentinel bleed as risk factors for post-PD haemorrhage and pancreatic leak and sentinel bleed as risk factors for secondary haemorrhage (p < 0.05). Conclusions: Haemorrhage after PD is a life-threatening complication. Sepsis, pancreatic leak, and sentinel bleed are statistical significant factors predicting post-PD haemorrhage. Sentinel bleed is not statistically significant associated with postoperative mortality, but with the onset of secondary haemorrhage. The effectiveness of therapeutic angioembolization was not demonstrated in our study.

Introduction
Mortality rate after pancreatoduodenectomy (PD) has decreased during the last decade to 0–5%, while the morbidity rate remains high and is currently between 30% and 40% [1–6]. The most common complications after PD are pancreatic leak and pancreatic fistula, gastric stasis, bile leak, intra-abdominal abscess and haemorrhage [1–6].

Haemorrhage occurs in more than 10% of patients following PD [7, 8]. This complication is often fatal and commonly requires prolonged hospital stay and multimodality treatment which might include conservative therapy, angioembolization or surgery.

Haemorrhage occurring in the first week following PD is described as early and if it occurs later is defined as delayed haemorrhage [9–12]. Primary postoperative bleeding after PD due to poor haemostasis of anastomotic suture lines, stress ulcer or bleeding from the pancreatic remnant, the pancreaticogastric (P–G) or pancrea-
Pancreaticoduodenectomy, is categorised as gastrointestinal (intraluminal) haemorrhage [13]. Primary haemorrhage following mainly technical errors in the operative field, is defined as intra-abdominal [13]. Secondary postoperative bleeding following PD, which is usually delayed, may be either intraluminal or more often intra-abdominal [13]. This may be due to rupture of a pseudoaneurysm after pancreatic leak [13–15] or sepsis in the intestinal (intraluminal) haemorrhage [13]. Primary gastrojejunostomy (P–J) anastomosis, is categorised as gastro-intestinal (intraluminal) haemorrhage [13].

The aim of this study is to document the prevalence and to evaluate the management strategies of haemorrhagic complications following PD.

**Patients and Methods**

All patients who underwent PD from 1/2000 to 10/2005 were identified from a prospective database. They were evaluated in the postoperative period and the study group consisted of patients who experienced at least one episode of postoperative haemorrhage during the first 30 postoperative days. Parameters such as pancreatic leak and fistula, bile leak, presence of sentinel bleed, sepsis, intra-abdominal abscess, etiology of haemorrhage, treatment strategy and mortality rate were recorded and analyzed.

The diagnostic procedures for the management of these patients were routine blood tests, blood and drain fluid cultures, abdominal ultrasound and/or computed tomography with or without aspiration or drainage of intraperitoneal collections, upper gastrointestinal endoscopy (diagnostic or therapeutic) and angiography (diagnostic or with angioembolization).

Haemorrhage was defined as drop of mean arterial pressure of 40 mm Hg or more and during the resuscitation, the administration of more than two blood units was necessary. It was demonstrated by the presence of blood in the nasogastric tube, drain or with haemodynamic instability requiring blood products. Blood was also demonstrated on abdominal ultrasound or computed tomography, or at laparotomy. Pancreatic leak was defined as a secretion of amylase-rich drainage fluid (five times greater than serum amylase) on postoperative day 5.

Bile leak was defined as the presence of bile in the drain fluid with a bilirubin value five times greater than that of serum.

A sentinel bleed was defined as the presence of blood in the drain or gastrointestinal haemorrhage without obvious cause, 24 h prior to an episode of delayed massive haemorrhage [13, 40, 42].

Sepsis was defined as fever (>38.5°C) and leucocytosis (WBC >15 × 10⁹/l) with positive blood and/or urine, and/or central vein catheter culture, or pneumonia on chest X-ray.

Intra-abdominal abscess was defined as a collection in a febrile patient diagnosed by abdominal ultrasound or computed tomography.

Patients with primary intraluminal haemorrhage were treated either conservatively with fluid resuscitation, medication, diagnostic endoscopy, or endoscopically with injection of adrenaline in the bleeding sites or surgically.

Statistical analysis was performed using Spearman’s test and Fisher’s two-tailed test in the ‘Statistical Package for the Social Sciences’ version 12 for Windows (SPSS, Chicago, Ill., USA).

**Results**

Four hundred patients underwent pancreatic resection during the study period, including 362 patients who had PD and 314 of these had a pylorus-preserving procedure. Pancreatic adenocarcinoma was the main indication for surgery (59% of the patients), followed by ampullary carcinoma (21%) and cholangiocarcinoma of distal bile duct (12%). 199 patients were male and 163 were female, ranging in age from 22 to 90 years (median age 66 years).

During the first 30 postoperative days 32 of the 362 patients (8.8%) experienced at least one episode of bleeding. Primary intraluminal bleeding was recorded in 13 patients out of 32 (40.6%), primary intra-abdominal haemorrhage in 5 of 32 patients (15.6%) and secondary haemorrhage in 14 of 32 patients (43.7%).

Fifteen deaths out of 32 patients were recorded (47% mortality rate) mainly due to recurrence of haemorrhage, sepsis and/or multiorgan failure. Three patients (23.1%) with primary intraluminal haemorrhage, 3 patients (60%) with primary intra-abdominal haemorrhage and 9 (64.3%) patients with secondary haemorrhage died.

Pancreatic leak was demonstrated in 11 of 32 patients (34%), of whom 6 died (54.5%). Pancreatic leak occurred in 6 patients with secondary haemorrhage (40%). Intra-abdominal abscess was present in 9 patients (28%), of whom 5 died (55.5%). Intra-abdominal abscess was demonstrated in 2 cases of secondary haemorrhage (14%). Sepsis was diagnosed in 14 cases (42%) and in this group 8 patients died (57%). Sepsis was present in 8 cases of secondary haemorrhage (56%), 6 cases of pancreatic leak and 6 cases of intra-abdominal abscess. Bile leak occurred in 4 patients (12.5%) and was associated with 100% mortality. Of this group of patients, 3 of the 4 were diagnosed with sepsis. A sentinel bleed was demonstrated in 8 of the 14 patients who had secondary haemorrhage (57.1%). The episodes of secondary haemorrhage occurred between the 5th and 20th postoperative days (median 13).

Statistical analysis revealed sepsis and sentinel bleed as risk factors for post-PD haemorrhage and pancreatic leak and sentinel bleed as risk factors for secondary haemorrhage (p < 0.05).

Sentinel bleed was not statistically significantly associated with postoperative mortality (p = 1).
In the subgroup of 13 patients with primary intraluminal bleeding, 9 patients were managed either conservatively (6 patients) or endoscopically (3 patients). In this subgroup of patients 1 died from recurrence of hemorrhage. One patient was treated with successful common hepatic arterial (CHA) embolization. The remaining three patients; two were treated with laparotomy: completion pancreatectomy and splenectomy and oversewing a bleeding point in the pancreatic remnant (one death) and one patient died at home from hemorrhage recurrence. In these patients no collections were found in abdominal computed tomography scan. In 1 patient, with pancreatic leak, successful embolization of splenic artery (SA) was performed. Three patients underwent laparotomy following non-diagnostic angiography. In 2 patients unsuccessful angioembolization of bleeding point in the pancreatic remnant and embolization of LHA were performed respectively, followed by laparotomy and completion pancreatectomy and splenectomy. Two patients demonstrated secondary haemorrhage with large haematomata. In 1 patient, who had an intra-abdominal abscess, laparotomy was performed, and the gastroduodenal artery (GDA) stump was oversewn with completion pancreatectomy and splenectomy. The rest of the patients in this subgroup underwent laparotomy; pancreatic remnant oversewing, completion pancreatectomy and splenectomy, and redo- hepaticojejunostomy, gastrojejunoscopy (G–J) and pancreatojejunostomy (P–J). Subsequent re-laparotomy was necessary in 2 patients.

All the above data are summarized in tables 1 and 2.

**Table 1. Patients’ characteristics studied as risk factors for post-PD haemorrhage**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Associated deaths</th>
<th>p (post-PD in study group)</th>
<th>p (secondary haemorrhage group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic leak</td>
<td>11</td>
<td>6</td>
<td>0.353</td>
</tr>
<tr>
<td>Bile leak</td>
<td>4</td>
<td>4</td>
<td>0.213</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>9</td>
<td>5</td>
<td>0.315</td>
</tr>
<tr>
<td>Sepsis</td>
<td>14</td>
<td>8</td>
<td>0.003</td>
</tr>
<tr>
<td>Sentinel bleed</td>
<td>8</td>
<td>5</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Table 2. Management and outcome of the patients with post-PD haemorrhage**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary intraluminal (n = 13)</td>
</tr>
<tr>
<td>Conservative treatment</td>
<td>9</td>
</tr>
<tr>
<td>Angiography negative</td>
<td>0</td>
</tr>
<tr>
<td>Angiography failed</td>
<td>1</td>
</tr>
<tr>
<td>Angiography successful</td>
<td>1</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>2</td>
</tr>
<tr>
<td>Deaths</td>
<td>3</td>
</tr>
</tbody>
</table>

In the subgroup of 13 patients with secondary haemorrhage, a total of 9 patients underwent laparotomy and 1 patient was treated conservatively. All patients with severe shock were treated by laparotomy immediately. The patients who had diagnostic or failed angiography were treated the next day by laparotomy after they were stabilized; only 2 patients with secondary haemorrhage underwent laparotomy after 6 and 8 days from failed angiography, respectively, because of intermittent bleeding. In these patients no collections were found in abdominal computed tomography scan. In 1 patient, with pancreatic leak, successful embolization of splenic artery (SA) was performed. Three patients underwent laparotomy following non-diagnostic angiography. In 2 patients unsuccessful angioembolization of bleeding point in the pancreatic remnant and embolization of LHA were performed respectively, followed by laparotomy and completion pancreatectomy and splenectomy. Two patients demonstrated secondary haemorrhage with large haematomata. In 1 patient, who had an intra-abdominal abscess, laparotomy was performed, and the gastroduodenal artery (GDA) stump was oversewn with completion pancreatectomy and splenectomy. The rest of the patients in this subgroup underwent laparotomy; pancreatic remnant oversewing, completion pancreatectomy and splenectomy, and redo- hepaticojejunostomy, gastrojejunoscopy (G–J) and pancreatojejunostomy (P–J). Subsequent re-laparotomy was necessary in 2 patients.

**Discussion**

Haemorrhage after PD is one of the major complications of the procedure with mortality rates ranging from 14 to 38% [13, 17–19]. In our study the incidence of postoperative haemorrhage was 8.8% with an associated 47% mortality rate, which is similar to that reported elsewhere [20–23]. Primary intra-abdominal haemorrhage usually occurs early due to a technical mishap [13] and was accompanied by a 60% mortality rate in our study group. Rumstadt et al. [13] reported that in 30% of the subsequent laparotomies technical errors were found. In our series all patients with primary intra-abdominal haemorrhage were treated with laparotomy and technical errors were found in 60% of them, mainly due to bleeding from small vessels in the area of the superior mesenteric vessels.

Primary gastrointestinal haemorrhage patients had a 23% mortality rate in our study and endoscopy can often
determine the source of haemorrhage. This approach, however, has limitations because the endoscopist cannot determine the precise bleeding site in cases of moderate bleeding, since the afferent and the efferent loops of the gastrointestinal tract are filled with large amounts of clotted blood [13, 15].

The most challenging group of patients to deal with are those with secondary haemorrhage who had a 64% mortality rate in our study. The main cause of bleeding in this situation is the rupture of arterial pseudoaneurysms in the operating field. Different pathophysiological mechanisms have been suggested for this entity which mainly causes delayed massive haemorrhage [13, 24–31].

In our series, there were very few patients in whom we could not identify the presence of at least one of the abovementioned statistically significant factors in every episode of post-PD haemorrhage. In the secondary haemorrhage subgroup, 10 of the 14 patients had at least one of the above risk factors.

Delayed massive haemorrhage, especially with the presence of pancreatic or bile leak or sepsis, should raise the suspicion of a ruptured pseudoaneurysm. The recommended intervention of this entity includes computed tomography scan, angiography which offers the option of embolization and three-dimensional angiographic imaging helical CT [15, 31–33]. Transcatheter arterial embolization (TAE) has been efficacious for the treatment of pseudoaneurysms associated with pancreatitis [25, 34] and post-PD [11, 35–39]. Emergency surgery for pseudoaneurysms is often hazardous and remains the solution to haemodynamically unstable patients and after failure of angiographic embolization [31]. One angiography of five performed in patients with secondary bleeding was successful and 20% of patients with secondary haemorrhage were caused by rupture of a pseudoaneurysm. The mortality rate in patients who underwent angiography was 80%, while the mortality rate in patients with secondary haemorrhage treated with laparotomy was 78%. The limited detection rate of angiography is attributed to the intermittent pattern of the bleeding and the amount of blood loss [10, 40].

The importance of sentinel bleed has been recognized by several authors [10, 12, 40]. Rumstadt et al. [13] advocate in early laparotomy if pancreatic leak is diagnosed and a sentinel bleed occurs. In a reported series of five visceral post-PD pseudoaneurysms complicated by haemorrhage, all had sentinel bleeds and were treated with angiembolization [31]. de Castro et al. [41] showed that sentinel bleed was not followed by delayed massive haemorrhage in the absence of postoperative septic complications. Furthermore, it was reported that there was no difference in mortality between patients having a sentinel bleed and those who did not [16]. In our study, 57% of patients with secondary haemorrhage had a sentinel bleed and all of them had sepsis or pancreatic leak; sentinel bleed was not associated with postoperative 30 days mortality.

Turrini et al. [16], in order to prevent the formation of pseudoaneurysm, suggested leaving a 1-cm GDA stump and performing subtotalization of the pancreas by moving to the left side of the P–J to avoid direct contact of pancreatic juice with adjacent vessels in case of pancreatic leak.

Kurosaki et al. [42] suggested spreading an omental flap behind the pancreaticojejunostomy after completing the reconstruction which allows complete isolation of the skeletonized major vessels from the pancreatic anastomosis, in an attempt to prevent postoperative formation and erosion of pseudoaneurysms. Our policy – not evaluated yet by a trial in our Unit – is to spread the round ligament around the common hepatic artery after PD and to mobilize the pancreatic remnant before performing the P–G or P–J anastomosis.

The surgical treatment of secondary delayed massive haemorrhage is controversial with exponents of both completion pancreatectomy and oversewing the pancreas with external drainage of pancreatic fluids [13, 43, 44]. In our study, both completion pancreatectomy and spleenectomy were carried out without recurrence of bleeding, while in the case where the pancreatic remnant was oversewn there was recurrence of bleeding.

Haemorrhage after PD is a life-threatening complication and this was confirmed in our study. Sepsis, pancreatic leak, and sentinel bleed were statistical significant factors for post-PD haemorrhage. If a sentinel bleed is detected in patients with septic complications and/or pancreatic leak, angiography or CT angiography should be performed to identify the possible cause. Subsequent embolization of bleeding vessels or pseudoaneurysms can be carried out, although the effectiveness was not demonstrated in our study.

In haemodynamically unstable patients or when angiembolization fails to stop the bleeding, laparotomy should be carried out, but despite an increasing experience and improved technology, the mortality rate after postoperative haemorrhage remains high.