



## Management and outcomes of haemorrhage following Pancreaticoduodenectomy – Our experience

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### Abstract:

**Objective:** Mortality following pancreatoduodenectomy (PD) has fallen below 5%, yet morbidity remains between 30 and 50%. Major haemorrhage following PD makes a significant contribution to this ongoing morbidity and mortality. The aim of this study was to assess the clinical course and outcome of postpancreatectomy haemorrhage (PPH) after major pancreatic surgery.

**Patients and methods:** Between 2019 and 2021, 60 patients who underwent PD for various pancreatic disease were analyzed from prospective database. The risk factors, severity, time of post pancreatomy haemorrhage, site intra luminal or extra luminal, coincident pancreatic fistula, vascular pathologies (pseudoaneurysm) were analyzed. Grading were standardized based on International study group of pancreatic surgery (ISGPS) guidelines. Success rate of Angiography in diagnosis, endoscopy, relaparotomy rates, Blood transfusion rates, length of hospital stay and overall outcomes were analyzed.

**Results:** Our study identifies clinically relevant risk factors for PPH and mortality, Surgical hemostasis is successful if performed in ideal time period. The pathogenesis of PPH is multifactorial in PD. prevalence of PPH was 21% distributed more among patients suffering from malignancy than chronic pancreatitis especially for Distal bile duct malignancy. Grade C PPH have went for relaparotomy with good outcomes. Late, intra luminal bleed were high in our series. PPH patients affects outcome of disease significantly.

**Keywords:** pseudoaneurysm, Angioembolization. stump bleed, Haemorrhage, Pancreaticogastrostomy

### Introduction :

With the development of specialist centres, mortality following pancreatoduodenectomy has fallen below 5%. Despite progress, procedures such as PD are still associated with a morbidity rate of 30-40% [1-6]. The common complications after PD are delayed gastric emptying (DGE), pancreatic leakage, intraabdominal abscess and haemorrhage [3]. Severe haemorrhage occurs in less than 10% of patients [8,9] and accounts for 11-38% of overall mortality [6-8]. The PPH is very worrisome, as the diagnosis and management differs based on patients parameters. The

International Study Group of Pancreatic Surgery (ISGPS) developed an objective, definition for PPH based on three parameters: onset, location, and severity. The onset is either early (<24 hours after the end of the index operation) or late (>24 hours), the location is either intraluminal or extra luminal and the severity of bleed may be either mild or severe. Based on these three different grades of PPH, i.e. grades A, B, and C have been defined [Table 1] [10]. Mild haemorrhage is usually managed conservatively. Severe haemorrhage needs interventions like endoscopy, angioembolization or

surgical interventions to control the bleed. Early haemorrhage following surgery is often due to technical failure (non secured vessel) [11]. Haemorrhage in the late postoperative phase may be from an ulcer, eroded vessel, stump bleed, pseudoaneurysm or dehiscence of an anastomotic suture line [12,13]. Other factors predisposing to PPH are pancreatic leak, bile leak, intraabdominal abscess and intraoperative vascular injury [8,14]. Severe bleed after PD may present initially as an intermittent minor haemorrhage, "sentinel bleed" [14]. Diagnostic workup to identify the site and close observation and management strategy should be started immediately after sentinel bleed. Most post PD haemorrhage were diagnosed and treated only after the occurrence of severe bleeding. The cause, diagnosis and best treatment options for post PD haemorrhage are still not clear [11,14]. Although encouraging results have been reported after embolization [15], since detection rate of pseudoaneurysm by angiography is low and a concomitant septic complication would require surgical management most patients are still managed surgically.

The Aim of the study is to examine the onset, severity, Grading of hemorrhage, as well as hemorrhage-associated outcomes, disease outcome affected by PPH, including overall mortality, occurring after pancreaticoduodenectomy during the index hospital visit. Small sample sizes with high event rates in our centre. The pathogenesis of PPH is multifactorial, clinically relevant risk factors for PPH and mortality were studied.

#### **Patients and methods in clinical studies:**

A total of 60 patients who underwent pancreaticoduodenectomy between January 2019 and September 2021 were included in a prospective database and were analysed with regards to postoperative haemorrhage.

All patients went for classical whipple procedure with Lymphadenectomy with 57 patients pancreaticogastrostomy and 3 pancreaticojejunostomy (2 duct to mucosa and 1 dunking). preoperative and postoperative PPI were routinely administered in all patients.

The parameters that were included for analysis were age, gender, postoperative interval between PD and bleeding, sentinel bleeding, cause and source of

bleeding, risk factors for bleeding, clinical grading of severity according to ISGPS definition, management and outcome.

Totally 13 patients developed PPH, out of which 7 patients had severe haemorrhage. five were women and two men, overall in PPH group men were predominant. late extraluminal bleed seems to be the major cause of severe bleed (P=0.021). severe hemorrhage refers to any haemorrhage that required additional intervention, while moderate haemorrhage refers to haemorrhage with a defined diagnosis, but no further intervention

Clinical grading of severity was assessed according to ISGPS definition as Grade A, B, C based on time of onset, location, and severity of the haemorrhage, and considering the cumulative overall risk and clinical severity of haemorrhage [10]. Pancreatic leak was defined, as drain output of any measurable volume of fluid on or after third postoperative day with amylase content greater than three times the serum amylase activity (ISGPF definition) [21]. Sepsis was defined in the presence of fever ( $>38^{\circ}\text{C}$ ) and leucocytosis (white blood cell count  $>10,000/\text{l}$ ) for more than five days following surgery [8]. An intraabdominal abscess was considered when patient had fever and abdominal pain with complicated fluid collection on abdominal CT. Operative mortality was defined as death occurring during the index hospital stay or as a consequence of a postoperative complication.

#### **Statistical analysis :**

Demographic factors, such as onset/Site; Risk factors, such as clinical severity grading/outcome/hospital stay/management options were compared using Pearson Chi square test, Yates corrected Chi-square test where applicable to identify the factors predicting the outcome.  $P < 0.05$  was taken as statistically significant. Statistical analysis was performed using SPSS 21 version.

#### **Results :**

##### **Onset and site:**

Thirteen patients had PPH in study period following PD. 8 patients had intra Luminal bleed and 5 patients had extraluminal bleed. out of eight, six were Pancreatic stump bleed [46.2%] and 2 from anastomotic site ulcer [15.2%]. Out of five

Extraluminal, three pseudoaneurysm [23%] one common hepatic artery (CHA) and two gastroduodenal artery ligation (GDA) slip [15.4%]. Interesting thing which needed further observation is both ligation patient had aberrant artery (replaced RHA from SMA). The odds of having severe PPH when the bleeding site is GDA bleed/Pseudoaneurysm is 4 times higher compared to the bleeding site being stump or GJ ulcer. This difference is significant with a Fisher's exact **P value of 0.021** and the confidence interval of the odds ratio is 1.205-13.283 which is greater than one (Table 2). Mortality were seen in each one in both extra and intraluminal [Table 3]

### Diagnostic procedure :

Upper gastrointestinal endoscopy was performed in five patients [Table 4]. We usually do endoscopy only after postop day 7. The source of bleed could not be identified in two due to clots. No therapeutic interventions were done even with availability of expert endoscopist and argon plasma device. After resuscitation patients who are stable underwent contrast enhanced computerized tomography (CECT) or Angiography (CTA). Pseudoaneurysms were identified in one patient; common hepatic artery (CHA). That one patient who had extraluminal bleed, CTA did not show any aneurysm initially, later on Repeat imaging after one week patient was found to have CHA pseudoaneurysm. Yield of CTA in diagnosing site of bleed is low, even with 128 slice scan. The presentation of intraluminal bleed usually presents late with Ryles tube aspirate of blood or Tachycardia with hypotension after significant amount of clots in stomach. Endoscopy may be helpful in early bleed. Risk of anastomotic dehiscence should be foreseen.

### Clinical grading of severity:

Based on ISGPS definition of clinical grading of severity 9 belonged to Grades B and 4 to grade C. Of the 13 patients with severe bleeding two died, one after reoperation because of uncontrolled infection and respiratory failure. One patient died due to uncontrolled bleed during angioembolization. The mortality rate in PPH group (2/13) is 15%. Overall mortality rate in Whipple was 13% in our series, 3% due to PPH (2/60). Late haemorrhage was associated with high mortality (2/2) in all the two patients belonging to Grade C. One extraluminal and one

intraluminal. P value of  $<0.15$ . Severe bleed, Grade C with proper ICU management and hemostasis, mortality can be avoided. There was no mortality in grade B patients.

### Presentation and Pathology :

Fresh blood in nasogastric tube seen in three patients, drains in four patients. Hematemesis in one patient. Melena in five patients. There was no mortality in drain group, which could favour early identification of PPH as an ideal key to avoid mortality. In high risk cases we favour feeding jejunostomy rather than nasojejunum tube as NG tube gets blocked frequently due to clots. Primary diseases were Periampullary malignancy in eight patients, Ampullary malignancy ductal type in two patients, Head of pancreas in two patients and one patient had inflammatory head mass with chronic pancreatitis [Table 2]. No patient was operated after neoadjuvant therapy. Low molecular weight heparin was used in all patients after 24 hours as DVT prophylaxis, some centres follow pneumatic compression device than anticoagulants in a view of PPH risk, further studies are needed to compare pneumatic device and anticoagulants in PD patients towards outcome of PPH. IV/oral PPI is routinely administered in all PD patients from preoperative day till suture removal.

### Management and Outcome :

Out of 13 patients managed for PPH. 8 intraluminal bleed, two had severe bleed and went for gastrostomy and vessel ligation, other cases managed conservatively. 5 extraluminal bleed, three underwent laparotomy and ligation of ruptured vessel. Surgical hemostasis secured in five out of 13 patients. One severe PPH and seven mild PPH were managed conservatively. One patient was angioembolized and failed [Table 5]. Almost all cases of severe PPH (7/13) were managed surgically with good outcomes. Statistically significant values  $P < 0.002$  with odds ratio of 1.4 – 49.9 (95% CI).

In our series [Table 6], outcome of PPH patients were analysed with various variables. One patient expired in Age  $< 60$  years (1/9) and one patient in Age  $> 60$  years (1/4). One man and lady expired with mortality of 3% ( $p=1.0$ ). No mortality seen in early PPH (0/2). All two mortality 15% were seen in Late PPH ( $p < 1.0$ ). Early PPH patients had extra luminal

bleed only, managed surgically with no mortality suggest early identification is the key to avoid mortality. Patients received more than four packed red blood cell transfusion (PRBC) had high mortality 40% (2/5). No mortality in those who received less than four PRBC. Surgical intervention has good outcome with mortality rate of <16% which is comparable to other series Rajarathinam et al (29%), Yekebes et al (16%) [16]. Only one patient underwent angioembolization, but postprocedural aneurysmal rupture and patient expired of uncontrolled bleeding. Difficult availability of other speciality during sudden haemodynamic instability warrants immediate resuscitation and surgical hemostasis. Moreover, the septic foci warrants lavage and conversion to Nasojejunal tube to feeding jejunostomy, with the amount the clots removed after gastrostomy and peritoneal clots needs to be evaluated, our authors feel endoscopic management will prolong the duration of securing hemostasis. The morbidity in our series in patients with PPH and overall is low, with former group had four with sepsis/POPF (40%). Not all patient with POPF had PPH, POPF patient with PPH had severe PPH (38%) one patient with risk factor as type I portal vein reconstruction had severe PPH. Adjuvant chemotherapy plays a key role in overall survival of the pancreatic malignancy. Outcomes have been affected as the PPH patients may not be fit for adjuvants especially after Severe PPH. Adjuvants were used only in 45.4% (5/11 patients) of the alive patients, considering the fact that PPH is a serious condition where patients general condition deteriorates due to morbidity. When the margins were examined, 16.6% (2/12 malignant specimens) had the margins positive. No impact on mortality. Out of 52 alive patients eight had hospital discharge more than 20 days (mean=12 days) out of which majority (6/11) had morbidity as PPH in our series (p=0.001). It adds financial burden the patient even in government facility.

### Discussion :

Post-Whipple pancreatoduodenectomy haemorrhage is a common but important complication with high mortality [15% Aravindan et al\*]. Early clinical diagnosis may be viewed as an initial diagnostic test followed by endoscopy and CTA in stable patients. Intraluminal bleed as usually late need close

observation of parameters to diagnose early and avoid mortality [7]. The capacity of the stomach to accommodate a massive clots, Nasogastric tube may block early. In a patient of normotension and tachycardia it is difficult to avoid a suspicion. Hematocrit, hemoglobin, epigastric tenderness hiccups, malena, drains should be watchful in postop period. The exact pathogenesis is not known in pancreaticogastrostomy with theories of leak, sepsis, gastric acid hypersecretion contributing to PPH. Early haemorrhage is often due to a technical mishap or vasospasm of unknown small vessels in the pancreatic cut surface that tends to get relieved in the postoperative period. We have seen one case with immediate postop intraluminal severe PPH which warranted relaparotomy\*\*. Assessing the high risk PG is difficult, even may not warrant as all cases need high precision in pancreaticoenteric anastomosis. Male have high incidence of PPH, but Severe PPH were seen in female. Relaparotomies rates are high in females.

Early haemorrhage is often due to a technical mishap or vasospasm of unknown small vessels in the pancreatic cut surface that tends to get relieved in the postoperative period. In our series the main site of bleed in haemorrhage was from the pancreaticogastrostomy stump and from the retroportal pancreatic lamina. All the early cases required surgery to secure haemostasis. The odds of having severe PPH when the bleeding site is GDA bleed/Pseudoaneurysm is 4 times higher compared to the bleeding site being stump or GJ ulcer. This difference is significant with a Fischers exact P value of 0.021 and the confidence interval of the odds ratio is 1.205-13.283 which is greater than one, which shows Pancreaticogastrostomy itself is not a risk factor for PPH.

Wente et al. [17], describe eight of 458 patients who underwent PD over a four-year period and had developed major early haemorrhage (<72 hours after surgery) from the pancreatic anastomosis with an aggressive surgical approach with no mortality. Thomas Blanc et al. [18] support routine reoperation for early haemorrhage to avoid delay and to limit the risk of massive transfusion. In their series 11 patients were reoperated for early bleeding; 10 had bleeding from surgical site, and all of them were survived. Our results are also similar with less associated mortality

and suggest that surgery still remains a major tool in the management of this haemorrhage.

In our series the incidence of haemorrhage is 21%, which is high compared to other series like Rajarathinam et al [16] showing 3% and sato et al [15] showing 12%. Our mortality is 15%, less compared to other series showing 29% and 40%. Alertness towards an anticipated post-operative bleed is essential. Patient should be closely monitored for sentinel bleed and clinical signs of malena, Nasogastric/Nasojejunal/jejunal tube bloody aspirate, sanguinous drain, hemoglobin fall, persistent tachycardia. Immediate diagnostic intervention using Upper GI endoscopy, CTA and intervention or immediate laparotomy if hemodynamically unstable. All routine surgical precautions to prevent PPH were concentrated.

\*Present series

\*\*Not in present series

### Conclusion :

First line angiographic assessment for diagnosis of moderate and severe haemorrhage found lower success rates computed tomography angiography can detect bleeding rates of 0.3–1ml only. Our data

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demonstrated increase in mortality resulting from haemorrhage during the second post-operative week compared to the first (day 7 - 20). This suggests that not all late haemorrhages, defined by the ISGPS to occur after 24 hrs post-operatively, are equivalent and perhaps consideration should be given to further subclassifications. Late haemorrhage after 24hrs, without leak, sepsis after PG are high, warrants close observation and delays discharge. Not all patient with POPF had PPH, POPF patient with PPH had severe PPH. PPH incidence is high after Whipple (Pancreaticogastrostomy). Although encouraging results have been reported after embolization, since detection rate of pseudoaneurysm by angiography is low and a concomitant septic complication would require surgical management most patients are still managed surgically. Our study shows no mortality in early bleed with surgical management suggest that surgery remains the major tool for managing early severe PPH (Grade B). Our further studies concentrate on the incidence of PPH with Multivariate analysis regards to duct size, techniques (PJ/PG), material used, anti-coagulation policy, pre op drainage, Interval after pancreatitis/cholangitis, risk factor of native treatment.

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**Table : 1**  
**ISGPS**

Grade	Time of onset, location, severity and clinical impact of bleeding	Clinical condition	Diagnostic consequence	Therapeutic endoscopy
Early, intra or extraluminal mild	Late, intra or extraluminal, mild	Well	Observation, blood count, USG and, if necessary CT	No
Early, intra or extraluminal severe	Late intra or extraluminal, severe	Often well/intermediate Very rarely life-threatening Severely impaired life-threatening	Observation, blood count, USG, angiography, CT endoscopy Angiography, CT endoscopy	Transfusion of fluid/blood, ICU, therapeutic embolisation relaparotomy for early PPH Localisation of bleeding, angiography and embolisation,

**Table 2 :Patients characteristics of post pancreaticoduodenectomy haemorrhage (PPH)**

	n	%
PPH	13/60	21
Patient characteristics		
Mean age (range)	56 +/- 3 (42-64)	
Gender (men/women)	8/5	
Pathology of index operation		
Periampullary cancer	10	76
Pancreatic head cancer	2	15
Chronic Pancreatitis	1	8
Time of onset		
Early (<24 hours)	2	15
Late (>24 hours)	11	85
Location		
Extraluminal PPH	5	38
Intraluminal PPH	8	72
Significant Pancreatic leak	1	7
DGE	3	23
No. of patients with sepsis	2	15
severe PPH *	6/13	

\*Severe PPH was defined as a major bleed from the drains and or the gastrointestinal tract requiring transfusion of at least 4U of packed cells within 24 hours, a decrease in haemoglobin level by 3 g/dl or more or need for invasive treatment.



**Table 3 :Bivariate analysis of bleeding site and severe PPH**

Bleeding site	Severe PPH		Total	P value	OR (95% CI)
	severe PPH	PPH			
<b>GDA bleed and Pseudoaneurysm</b>	5	0	5	0.021	4.0 (1.205-13.283)
	100.0%	0.0%	100.0%		
<b>Stump &amp; GJ ulcer</b>	2	6	8	0.021	4.0 (1.205-13.283)
	25.0%	75.0%	100.0%		

**Table 4:Source of bleeding, diagnostic yield, severity of grading( 13/60)**

<b>Source of bleeding -</b>		
• Pseudoaneurysm	3	7.7%
Common hepatic artery(1)		
Gastroduodenal artery (2)		15.3
• Artery from pancreatic parenchyma(stump)	6	46.2
• Anastomosis site ulcer	2	15.4
• GDA ligature (aberrant anatomy)	2	15.4
<b>Diagnostic Procedure</b>		
• Endoscopy (5/13)	3/5	Low yield
• CT abdominal angiography(6/13)	1/6	
One patient underwent angiography twice, during first(sentinal) bleed, angiography failed to localize		
<b>Clinical grading of severity</b>		
• Grade B	9	69.2%
• Grade C	4	30.7

**Table 5: Management and outcome**

	n	%
Observational monitoring	7	-
Surgical management	5	33.3%
Gastrostomy and vessel ligation(2)		
Ligation of the ruptured vessel(3)		
Angioembolization	1	100%
PPH associated mortality		
Overall in PD	8/60	13%
Overall in PD due to PPH	2/60	3
Overall in PPH	2	15.4%
Result of uncontrolled bleeding	1	7%
Result of POPF/sepsis	1	7%

**Table 6 - Analysis of factors predicting outcome :**

	Alive	Death	P value
Age group			
<60 years	8	1	p = 1.00
>60 years	3	1	
Sex			
Men	7	1	p = 1.00
Women	4	5	
Onset			
Early(<24hours)	2	0	p < 1.00
Late(>24hours)	9	2	
Presentation			

Extraluminal	4	1	$p < 1.00$
Intraluminal	7	1	
Grading			
Grade B	9	0	$p < 0.1$
Grade C	2	2	
Blood Transfusion			
four or more Packed cell	3	2	$p < 0.125$
less than four Packed cell	8	0	
Intervention			
Surgery	4	1	$p = 0.192$
Embolization	0	1	
Conservative	7	0	