Original Article

Post pancreaticoduodenectomy hemorrhage: A retrospective analysis of incidence, risk factors and outcome

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Abstract

Background: The operative mortality after pancreaticoduodenectomy (PD) has declined but morbidity still remains considerable. Post pancreaticoduodenectomy hemorrhage (PPH) occurs in 3–13% of patients following PD. We studied the incidence and outcomes of patients with PPH after PD to determine the associated risk factors and effect on hospital stay.

Methods: We retrospectively analyzed from a prospectively collected data of patients developing PPH following PD between January 2007 and May 2018. ISGPS definition and grading system were used. By using univariate and multivariate analyses, independent predictors of PPH were identified.

Results: Of the 340 patients undergoing PD, PPH occurred in 39 patients (11.5%), of whom 5 (12.8%) had Grade A, 22 (56.4%) had Grade B and 12 (30.8%) had Grade C PPH. Six (15.4%) of the 39 patients with PPH died against an overall mortality in the study population of 16 out of 340 patients (4.7%), reflecting higher mortality ($P = 0.019$) in patients with PPH . The independent risk factors for PPH were a high pre-operative bilirubin (mean 4.7 vs. 7.4 mg/dl, $P = 0.01$) and INR (mean 1.2 vs. 1.72, $P = 0.024$), whereas it was closely followed by but, but not significantly associated with pre-operative biliary stent placement ($P = 0.09$). Pancreatico-jejunostomy (PJ) leak was seen in 20.7% in non-hemorrhage group vs. 41% in hemorrhage group ($P = 0.008$) and was an independent risk factor for PPH.

Conclusion: PPH occurred in 11.5% of patients and resulted in a mortality four times greater than those without a PPH. It occurred more frequently in patents with a high pre-operative serum bilirubin, INR, biliary stenting or those with a PJ leak.

Keywords: Pancreaticoduodenectomy, Post pancreaticoduodenectomy hemorrhage, pancreatico-jejunostomy, leak

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Submitted: 03-Apr-2020 **Revised:** 24-May-2020 **Accepted:** 04-Jul-2020 **Published:** 18-Aug-2020

INTRODUCTION

Pancreaticoduodenectomy (PD) is a "formidable" operation.[1] A series published in the late 1960s reported postoperative morbidity rates of 60% and mortality rates approaching 25%.[2] Since then significant advances in perioperative care and surgical techniques have resulted in a reduction in mortality and morbidity.[3] Pancreatic fistula, delayed gastric emptying, and post pancreatectomy hemorrhage (PPH) are the three most common and significant complications following PD. PPH occurs in 3-13% of patients following pancreatic surgery.[4-6] PPH has

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_145_20

How to cite this article: Das S, Ray S, Mangla V, Mehrotra S, Lalwani S, Mehta NN, *et al*. Post pancreaticoduodenectomy hemorrhage: A retrospective analysis of incidence, risk factors, and outcome. Saudi J Gastroenterol 2020;26:337-43.

been reported to be associated with a significant increase in morbidity and mortality. Little was known about the risk factors for this complication a decade ago.[7] Despite the huge available data in the literature about PPH, the standard approach is not yet clear. This study was done to elucidate the incidence, risk factors, and outcomes in patients who develop PPH.

METHODS

All patients who underwent PD in our unit from January 2007 to May 2018 were included in this study. The study was approved by the institutional review board. An electronic prospective database is maintained incorporating pre-operative, intra-operative, and post-operative investigations, events, treatment, and clinical course for all pancreatic resections performed at our institution. Data were collected and analyzed from this database. The pre-operative parameters, viz. serum hemoglobin, platelet count, international normalized ratio (INR), total bilirubin, aspartate aminotransferase (AST), serum albumin and pre-operative biliary stenting, were analyzed to determine the risk factors associated with PPH. PPH was defined as per ISGPS definition [Table 1] considering three parameters: (1) time of onset, (2) location, and (3) severity.[8] Early PPH was defined as bleeding occurring within 24 h and late PPH if the bleeding started after 24 h postoperatively. The location of bleeding was categorized as intraluminal or extraluminal. Severe hemorrhage required more than three units of packed cells within 24 h, a decrease in hemoglobin of more than 3 g/dL, or a need for relaparotomy or interventional angiography to stop the bleeding.[8] Patients who underwent a median or distal pancreatectomy were not included in the analysis as the focus of the study was to ascertain the incidence and outcome of vascular injury during PD. The various indications for the procedure included periampullary carcinoma, NET of head of pancreas, cystic neoplasms of pancreatic head and trauma.

Statistical analysis

Statistical analysis was performed using statistical software SPSS version 17.0 (SPSS, Inc, Chicago, IL). Chi square test or Fisher's exact test was used to compare categorical variables. Student's *t* test was used for normally distributed continuous variables, and the Mann–Whitney *U* test for ordinal or asymmetrically distributed continuous variables. Univariate and multivariate analysis were done to identify the risk factors associated with PPH. Receiver operation characteristic (ROC) curve was drawn to calculate sensitivity and specificity of a cut off value in continuous data. *P* value of <0.05 was considered statistically significant.

RESULTS

From January 2007 to May 2018, 340 patients underwent PD at Sir Ganga Ram Hospital in the Department of Surgical Gastroenterology and Liver Transplantation. Mean age of patients was 54.5 ± 13 years, 241 were males and 99 females. Basic demographic profile did not show any significant correlation with PPH [Table 2].

Surgery

This is a single centre study and all the resection and reconstruction techniques were followed using a uniform protocol by all surgeons of the unit. Surgical procedures performed included both pylorus preserving pancreatico-duodenectomy and classical Whipple procedure. The pancreatico-enteric anastomosis was by means of a pancreaticojejunostomy in all cases. Most patients had an isolated loop PJ and external pancreatic stenting. Lesser sac drains were placed routinely. All operated patients were given prophylactic dose of heparin starting on post-operative day 1, except in cases where there was coagulopathy or increased blood loss during surgery.

Incidence

In the study period, 340 patients underwent PD for malignant (n = 251) or benign causes (n = 89). Malignant causes were mostly located in the head of the pancreas (n = 129) accounting for 51.4% of malignant cases. A total of 39 (11.5%) out of 340 patients developed PPH. Early hemorrhage occurred in 8 (20.5%) patients and late hemorrhage in 31 (79.5%) patients. Intra-luminal bleeding was noted in 17 (43.6%) patients and extra-luminal in 22 (56.4%) patients. Five (12.8%) patients had ISGPS grade A, 22 (56.4%) had grade B and 12 (30.8%) had grade C PPH.

Pre-operative parameters

Of all pre-operative parameters, the independent risk factors for PPH on univariate and subsequent

Table 1 : ISGPS grades of PPH

Grade of PPH	Clinical condition	Time of onset, location, and severity
A	Well, Drop in Hb <3 g/dL, Transfusion ≤3 PRBC	Early, Intra-/Extra-luminal, Mild
B	Often well/intermediate, Rarely life threatening, Severity may be similar to Grade A or C	Early, Intra-/Extra-luminal, Severe OR Late, Intra-/Extra-luminal, Mild
C	Impaired, Life threatening, Drop in Hb >3 g/dL, Transfusion >3 PRBC	Late, Intra-/Extra-luminal, Severe

Table 2: Basic demography of patients with and without post pancreatectomy hemorrhage (PPH)

	PPH	No PPH	*P*
No. of patients	39	301	
Mean age (years)	54 (16-69)	54 (16-82)	0.96
Sex (M: F)	30:9 (3.3:1)	211:90 (2.3:1)	0.38
Body mass index (kg/m^2)	22.6	21.7	0.08
Location of lesion			
a) Ampulla	6	79	0.53
b) (Head of pancreas)	22	152	
c) Lower common bile duct	6	38	
d) Duodenum	5	32	
Priority			
Emergency	2 (5.1%)	8 (2.7%)	0.32
Elective	37 (94.9%)	293 (97.3%)	

multivariate analysis were a high pre-operative bilirubin (mean 4.7 vs. 7.4, $P = 0.010$) and INR (mean 1.20 vs. 1.72, $P = 0.024$), whereas it was closely followed 1.72, P = 0.024), whereas it was closely followed, but not, but not significantly associated with pre-operative biliary stent placement ($P = 0.08$) [Table 3]. Amongst post-operative factors, pancreatico-jejunostomy (PJ) leak was the only factor that was significantly associated with PPH, that was seen in 20.7% in non-hemorrhage group vs. 41% in the hemorrhage group ($P = 0.006$).

Outcomes

The mean hospital stay in PPH group (14.3 days) was significantly higher than in the non-PPH group (11.3 days), $P = 0.024$. Similarly, overall mortality in the study population was 4.7% (16 out of 340), whereas mortality in PPH group was 15.4% (6 out of 39), reflecting higher mortality ($P = 0.019$) [Table 4].

Sentinel bleed

Sentinel or herald bleeding refers to isolated bleeding, usually from an abdominal drain or the gastrointestinal (GI) tract with an asymptomatic interval of at least 12 h until development of severe hemorrhage and shock. It implies the presence of a structural vascular defect and requires immediate evaluation.[9] Sentinel bleeding can be associated with local sepsis and anastomotic dehiscence and warns of impending major PPH.[10]

In our study, there were three patients who had sentinel bleed in post-operative period and were managed conservatively initially. All of them had a massive rebleed after 2-3 days requiring urgent surgical intervention and eventually died.

Intervention

In 21 (53.8%) cases of PPH which resolved with conservative management , the exact source of bleeding could not be localized, either with upper gastrointestinal endoscopy or imaging. Two of them had recurrent bleeding after initial control, which was also managed conservatively. And 18 patients (46.2%) required intervention, namely endoscopic management, angioembolization, or surgical re-exploration. Out of 17 patients with intraluminal bleed, 6 required endoscopic intervention and 3 of them could be managed successfully. Patients with extraluminal bleed not responding to conservative treatment were subjected to angioembolization. Patients with hemodynamic instability with falling hemoglobin and those who were refractory to other modalities of treatment eventually required surgical re-exploration, with bleed from pancreatic cut surface being the most common source [Table 5]. All grade A patients could be managed successfully with conservative management, whereas all patients with grade C PPH required some sort of intervention (angioembolization - 3, re-exploration - 9). Patients with grade B PPH, however, needed individualization of treatment depending on location of bleed. Out of 11 patients of grade B PPH with intraluminal bleed, 7 patients were managed conservatively and 4 required endoscopic control of the bleeder. Similarly, out of 11 patients with extra-luminal bleed in grade B PPH, 6 patients responded to conservative management, 2 patients needed angioembolization of the bleeding vessel [Figure 1], and 3 eventually required re-exploration.

Receiver operation characteristic curve

Across the whole study population, 91.8% sensitivity was obtained with a cut-off value of pre-operative serum total bilirubin of 9.05 mg/dl, which yielded 23.6%

Table 3: Comparison of pre- and intra-operative variables between two groups patients with and without post pancreatectomy hemorrhage (PPH)

Pre-operative Parameters	PPH (*n*=39)	Non-PPH (*n*=301)	*P* (univariate)	*P* (multivariate)
Hemoglobin (g/dl)	11.3	11.4	0.34	No
Platelet count (10^5/ml)	2.49	2.08	0.2	No
Total bilirubin (mg/dl)	7.4 ±7.1	4.7 ±5.3	0.01	0.01
Aspartate aminotransferase (IU/L)	188 ±508	91 ±120	0.45	No
Serum albumin (mg/dl)	2.87 ±0.74	3.01 ±0.74	0.27	No
International normalized ratio	1.72 ±0.36	1.20 ±0.28	0.02	0.049
Pre-op stenting	17 43.6%	89 29.6%	0.09	No
Blood loss (ml)	345 ±98	313 ±75	0.45	No
Transfusion (Aspartate aminotransferase) during surgery	2.6 ±0.7	1.8 ±0.3	0.32	No

Table 4: Comparison of post-operative outcomes between tpatients with and without post pancreatectomy hemorrhage (PPH)

Post-operative factors	PPH (*n*=39)	Non-PPH (*n*=301)	*P* (univariate)	*P* (multivariate)
PJ leak	16 (41%)	62 (20.6%)	0.008	0.006
Length of hospital stay (days)	14.3 ±9.5	11.3 ±7.3	0.02	-
Mortality	6 (15.4%)	10 (3.3%)	0.02	-

sensitivity and 91.8% specificity of occurrence of PPH. Area under curve (AUC) for the whole study population was 0.627 (95% CI: 0.533–0.722, $P < 0.001$), with a positive predictive value (PPV) of 43.6% and negative predictive value (NPV) of 81.7% [Figure 2a]. The high specificity and NPV suggest that total bilirubin below the cut-off value definitely poses a lower risk of PPH, whereas high bilirubin values above the cut-off cannot accurately predict occurrence of PPH. Similarly, cut-off value of pre-operative INR for predicting PPH was 1.26 (sensitivity-16.5%, specificity-90.9%, PPV-46.2%, NPV-69.8%), with AUC being 0.611 (95% CI: 0.514-0.708, $P = 0.04$) [Figure 2b].

DISCUSSION

PPH is still a challenging and significant complication after pancreatic resections. Till date, there is a lack of uniform definition of PPH. PPH in this study was defined and graded using a standardized (ISGPS) definition. We found that the overall incidence of PPH was 11.5% in our series using the ISGPS criteria, which correlates well with the present literature. Previous studies showed the incidence of PPH to range from 5.7 to 20.2%.[11-19]

PPH is classified into early and late onset because of the difference in pathogenesis and optimum management. Since early PPH is thought to be caused by intra-operative technical factors in terms of inadequate hemostasis in the operative field, bleeding from the suture line of the gastroenteric or entero-enteric anastomosis, or bleeding from the transection surface of the pancreatic anastomosis,[12,17,20,21] surgeons should be familiar with regional anatomy and take adequate precautions to avoid early PPH. Early PPH, especially if higher grade, should be treated with urgent re-laparotomy and ligation of active bleeding site (careful ligation of gastroduodenal artery (GDA), careful tacking of jejunal branches of superior mesenteric artery (SMA), and also of the inferior pancreatico-duodenal artery). In our study, eight (20.5%) patients had early PPH, of which three were Grade C and required surgical exploration to control bleeding.

Most frequently, delayed PPH occurred from the gastrointestinal tract or the visceral arteries. It is well known that pancreatic fistula and intra-abdominal abscess are independent risk factors for late PPH. Unlike early PPH, managing patients with late PPH and co-existing pancreatic fistula is more troublesome. Before 2000, there were many controversies over the optimal treatment of late PPH.[22-24] In a study by Tien *et al*., 61 (15.2%) patients who underwent PD had anastomotic leak and 10 (16.4%) of them had massive hemorrhage, thus suggesting that leaks and intra-abdominal sepsis increased the risk of hemorrhage.[25]

Yekebas *et al*., in their series of 1524 pancreatic surgeries, found hemorrhage in 87 (5.7%) patients; 33 underwent primary laparotomy and 27 underwent laparotomy after failed embolization.[11] Endoscopy was successful in 3 out of 15 patients (20%), who had intraluminal PPH within the first or second postoperative day. The mortality rate in PPH group was 16% ($n = 14$). The risk factors associated with increased mortality in PPH group in their study included pancreatic fistula, vascular pathologies, i.e., erosions and

Table 5: Types of intervention

Type of intervention	No. of patients	Details of intervention
Endoscopic therapy	3	GJ site - 2, JJ site - 1
Angioembolization	5	Jejunal branch of SMA-3, GDA-1, Arteria pancreatica magna - 1
Re-exploration	10	Pancreatic cut surface-6, Jejunal branch of roux loop-1, Pseudoaneurysm of branch of HAP-1, Diffuse oozing (packing) - 2

GJ-Gastrojejunostomy, JJ-Jejunojejunostomy, SMA-Superior mesenteric artery, GDA-Gastroduodenal artery, HAP-Hepatic artery proper

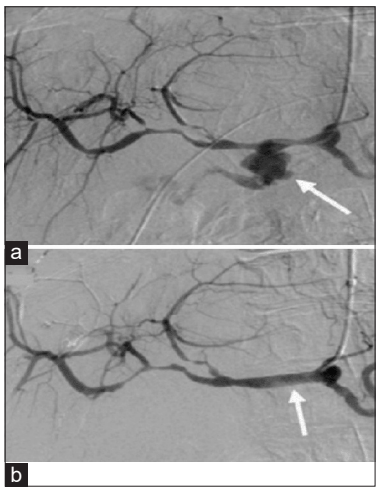

Figure 1: CT angiography showing (a) contrast extravasation (white arrow) from gastroduodenal artery stump, (b) post angioembolization, showing no extravasation of contrast

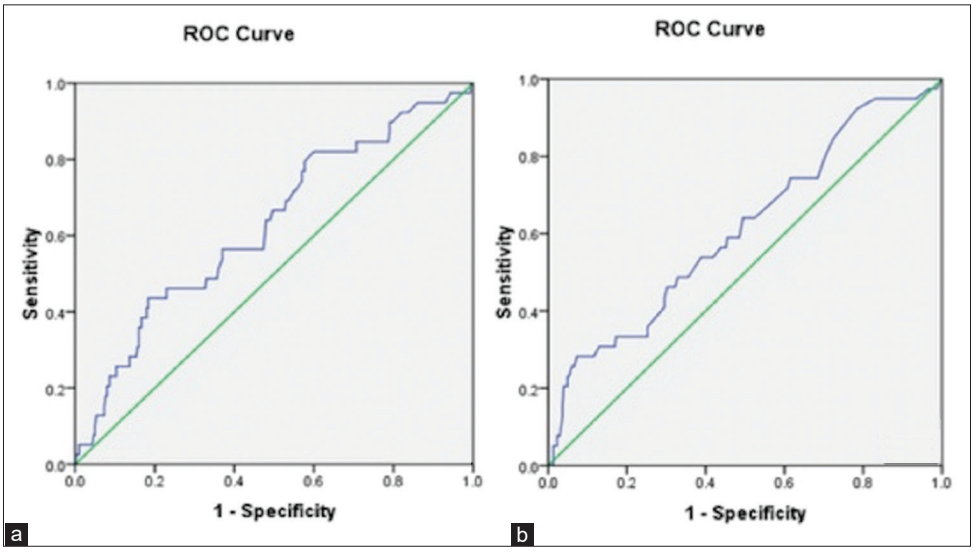

Figure 2: ROC for preoperative serum bilirubin (a) and INR (b)

pseudoaneurysms, delayed PPH occurrence, and soft texture of the pancreatic remnant.

In a study of 438 PD patients by Rajarathinam *et al*., 14 (3.1%) developed severe hemorrhage.[26] Early hemorrhage occurred in 5 and late hemorrhage in 9 patients. Seven had grade C and 7 had grade B PPH. Hemostasis was achieved by surgery in 10, angioembolization in 2, and endoscopy in 1 patient. The overall mortality was 29%. The risk factors with increased mortality in PPH were old age >60 yrs ($P = 0.02$), sentinel bleeding ($P = 0.04$), pancreatic leak ($P = 0.04$), and ISGPS grade C hemorrhage ($P = 0.02$). The independent risk factors for PPH and associated higher mortality in our study were high serum bilirubin and high INR at the time of admission as well as PJ leak and associated intraabdominal sepsis during the post-operative period. Preoperative cholangitis and stenting were closely, but not significantly associated with PPH. The study by Wellner *et al*. reported that although pancreaticogastrostomy (PG) was associated with more bleeding episodes than with PJ, it was independently associated with reduced mortality due to PPH.[27] However, as an institutional policy, we have always reconstructed the pancreas with PJ rather than PG.

Endoscopy and angiography, and not surgical approach, are currently the standard procedures for initial management of late PPH. Surgery is considered only if there is a failure of endovascular or endoscopic hemostasis, extraluminal bleeding from the venous system such as the portal vein or its tributaries or if the patient is too hemodynamically unstable because of the ongoing hemorrhage. Yekebas *et al*. showed that endoscopy is one of the lines of management in early PPH and 20% of early PPH in their study was managed endoscopically.[11]

In a review article by Roulin *et al*., 248 (3.35%) patients of the 7400 patients who underwent pancreatic resection included from 15 studies had delayed PPH. Of the 248 patients, location of the site of bleeding was reported in 154 patients.[28] The site of bleeding was eroded or ruptured visceral artery (66%), the pancreatic stump (12%), the enterojejunostomy site (6%), and other sites (6.5%). In 10% (16 out of 154) patients, the exact source could not be found. Of the bleeding from the visceral artery, GDA was the most common site in 50% followed by common hepatic artery in 21%, hepatic artery proper and its branches in 11%, splenic artery in 8%, SMA, and its branches in 8% and other sites in 3% of patients. In our study, all extraluminal grade B patients (10) underwent computed tomography (CT) angiography, and we could successfully embolize the bleeding vessel in 5 patients, the branches of SMA being the most common [Table 5]. In the remaining 5 patients, source of active bleeding could not be identified and they responded well to conservative management later. All except 2 patients with extraluminal severe bleeding cases were managed with urgent re-exploration ($n = 9$) with mortality in 3 patients (33%). The other 2 patients were managed with successful timely angioembolization (GDA stump and branch of SMA).

In some cases of non-severe PPH, the exact source of bleeding remained unknown. In most such cases, the bleeding was not clinically significant. Despite good imaging and endoscopy the bleeding source could not be localized and the bleeding stopped without any specific intervention. Bleeding in these patients could possibly be related to an element of coagulopathy. In some case, there might have

been a minor bleeding from the gastrojejunostomy site not requiring any intervention.

The importance of sentinel bleed in the management of late PPH should not be overlooked. We found that 25% (3 out of 12) patients with PPH Grade C had sentinel bleeds. All of them underwent re-exploration and all died. Data from previous studies suggest that between 30 and 100% of patients with late PPH present with sentinel bleeds.[11,26] The presence of a sentinel bleed after pancreatic surgery should lead to an emergency CT angiography to localize the source of bleeding. Ignoring the initial sentinel bleed can lead to life threatening massive hemorrhage later.

We had a mortality of 15.4% in the PPH group, which is similar to previous observations that describes a mortality rate of 16-20%.[11,26] One out of five patients (20%) with ISGPS grade A PPH died, not related to ongoing hemorrhage, but due to associated acute coronary syndrome. However, patients with ISGPS grades B and C had mortality related to worsening hemorrhage and its consequences, thereby conferring disease specific mortality of 4.5% and 33.3%, respectively. Rajarathinam *et al*., reported old age >60 years to be one of risk factors of increased risk of PPH[26]; but in our study neither the sex nor age was associated with higher risk of PPH.

We have drawn the ROC for preoperative serum bilirubin and INR, and derived the cut off value for PPH as 9.05 mg/dl and 1.26, respectively. As an institutional policy, we usually do biliary stenting in our patients in case of pre-operative cholangitis or if total bilirubin is greater than 15 mg/dl. However, because of the small sample size of our study population, these values lack reproducibility and need further validation.

There are some limitations of the present study. This is a retrospective study with a moderate sample size. As we correlate PJ leak with the occurrence of PPH, we would further like to do a sub-group analysis of PPH with the known risk factors of PJ leak including duct size and gland texture, on a prospective set of patients.

CONCLUSION

PPH is a serious complication after PD. Higher pre-operative bilirubin and INR as well as post-operative PJ leaks were found to be independent predictors for PPH and it was associated with an increased mortality as well as a longer duration of hospital stay.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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