

REVIEW ARTICLE

Causes, Management and Treatment of Delayed Arterial Hemorrhage after Pancreato-Duodenectomy. A Review Study

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ABSTRACT

In recent years, even if the associated with pancreaticoduodenectomy mortality has been reduced still remains high. Delayed arterial hemorrhage after pancreatoduodenectomy is defined as bleeding 5 or more days postoperatively. Pancreatic fistula and pseudoaneurysm are the most common complications following pancreaticoduodenectomy and are present in most cases of delayed arterial hemorrhage. Most patients presented to ER with episodes of melena and hematemesis. Upper abdominal control by computer tomography, selective angiography of the celiac trunk and the evaluation of superior mesenteric artery set the diagnosis of pseudoaneurysm of the gastroduodenal of arterial stump. Delayed hemorrhage has more complex pathophysiology and requires a multiple management approaches. In this paper, we review the related to postoperative hemorrhage articles after major pancreatic surgery. Initial management, both diagnostic and therapeutic, should be done by angiographic control and trans-catheter embolization. In case of hemodynamic instability or in cases when angiographic embolism is unsuccessful reoperation is the proper treatment.

INTRODUCTION

Nowadays have already determined significant reductions in mortality rates in patients who have already diagnosed with delayed arterial hemorrhage after pancreatoduodenectomy, even if the morbidity rate is still quite high. Early diagnosis and management of pancreatic leak should be crucial in prevention of delayed massive arterial hemorrhage. The morbidity of patients is associated with three main complications such as delayed gastric emptying, the occurrence of pancreatic fistula and bleeding complications [1, 2].

While the state of delayed gastric emptying as complication of the pancreatic resection resolves completely with conservative therapy, the presence of pancreatic fistula and postoperative bleeding often require immediate interventions.

The visceral arterial bleeding represents a rare life-threatening complication occur delay after surgery. Early identification of high-risk patients could helpful to adopt intraoperative and postoperative strategies tailored individually [3, 4]. The main causes of delayed hemorrhage have been associated

with arterial anatomy. The vessels walls could be damaged during lymphadenectomy [5, 6] and the formation of local abscess could destroy the vascular structures. Complications after pancreatic resection that require operative re-intervention are associated with increased mortality, ranging between 13% and 60%. Apart from the surgeon's experience in selecting patients and personal technical skills in performing a pancreaticoduodenectomy, timely anticipation and determined management of postoperative complications are essential of improving the outcome of surgical operation [5, 6].

The necrosis of the vessel wall seems to be caused as a result of mechanical irritation or infection along drainage. Regardless of the possible reasons, the progressive destruction of the vessel wall promotes the formation of pseudoaneurysms especially of superior mesenteric artery (SMA) [5, 6].

Early detection of delayed hemorrhage after pancreatic resection remain difficult because the absence of specific symptoms. Repeated episodes of gastrointestinal bleeding or reduction of serum levels of hemoglobin should be treated quickly in order to prevent the hemorrhagic shock [6].

METHODS

In this study performed a systematic review until March 2015 in the PubMed / MEDLINE and Embase data bases according to delayed bleeding after pancreatic resection. The electronic search was done by Medline and Embase databases using different keywords such as pancreatectomy, duodenopancreatectomy,

Received May 09th, 2015-**Accepted** June 26th, 2015
Key words Pancreatoduodenectomy; Complications; Postoperative Hemorrhage
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pancreaticoduodenectomy, pancreatic resection, postoperative bleeding, postoperative bleeding delayed bleeding, pancreatic bleeding of pancreas resection, complications of pancreatic resection, morbidity or mortality in combination with pancreatectomy, pancreaticoduodenectomy, distal pancreatectomy or left pancreatectomy, arterial hemorrhage, pseudoaneurysm, arterial embolism, covered stent.

Regarding the inclusion and exclusion criteria, selected only original research studies evaluated the effects, symptoms and treatment approach of delayed PPH. As late PPH bleeding was defined based on the classification ISGPS and includes cases of postoperative bleeding occurring at intervals greater than 24 hours after resection in pancreatic interventions.

Selection of papers for inclusion demonstrated by specific criteria such importance, randomized controlled trials, non-randomized case series, experimental data, case reports. Also included studies with few patients, experimental studies and case reports and excluded studies that evaluated the results after other pancreatic procedures as necrosectomy and pancreatic transplantation. Only publications that met the inclusion criteria and address the clinical aspects of this analysis examined further. The selected articles were mainly published in English.

Definiton, Causes, Sources and Complications of Delayed Bleeding

The usual therapy of visceral arterial bleeding comprises emergency surgery. The procedure can be a simple ligation of bleeding vessel until sophisticated vascular reconstructions. The advent of modern imaging techniques and the latest technological developments in interventional radiology offer new options for surgical treatment of patients with bleeding after pancreatic resection [7, 8].

In a study 1524 patients (studying period 1992 to 2006) were operated for pancreatic diseases and included in a prospective database. The prevalence of PPH was nearly 5.7% identical with the percentage of patients suffering from other malignancies [9]. On the other side the PPH severity and the type of interventional therapy (resection Whipple, pancreaticoduodenectomy and conservative management) appeared to have no effect on PPH gravity [10].

Endoscopy was successful in 3 of 15 patients (20%) who showed intraluminal PPH within the first or second postoperative day and seventeen patients were "false" extrinsic PPH due to mainly intraluminal bleeding at the site of anastomosis [9, 10]. Bleeding can occur either early or late after the onset of PD. Several researchers have reported that the incidence of early bleeding is often caused due to a technical fault during the hemostasis procedure and may caused by unsafe intra data or use anastomotic suture. In contrast the delayed postoperative hemorrhage varies over a period from 24 hours to 2 weeks [9, 10, 11, 12].

The bleeding process may be occurred as hemostasis disorder; a published study revealed that bleeding can only be detected in 30% of surgical bleeding cases [9]. However, it is worth noting that the coagulopathy does not seem to be associated with biliary interventions. Preoperative biliary drainage did not influence the incidence of postoperative complications and can be performed safely in jaundiced patients it should not be used routinely [13, 14].

Most cases of delayed bleeding from the upper gastrointestinal tract include peptic ulcer, cases of intraventricular shunt or vascular injury, such as erosion, pseudoaneurysm of the great arteries or pancreatic fistulas [14, 15]. In several studies 75% of delayed bleeding was observed in patients with complications such as fistula, pancreatic or biliary fistula and intra-abdominal bleeding collections, with estimated rate of abdominal complications range from 40% to 100% [14, 15]. The study of Saleh *et al.* revealed no evidence or adverse effect of preoperative endoscopic biliary stent placement on the outcome of surgery in patients with pancreatic cancer [14].

Vascular lesions are responsible for late bleeding in combination with the presence of surgical wounds (including vascular lesions during lymphadenectomy or too tight ligation of the arteries) and necrosis in the position of the anastomosis. These conditions such as wound or corrosion of the vessel wall may cause local sepsis and proteolytic activity of the pancreatic juice [14, 15].

Incidences of bleeding after pancreatectomy in several studies ranging from 1% to 12%, mainly due to that most studies do not distinguish the classification between immediate and delayed bleeding [16, 17, 18]. The International Study Group of Pancreatic Surgery (ISGPS) recently proposed the evaluation of postoperative bleeding according to position of bleeding, the detection of bleeding and the severity [19, 20] even if the evaluation of ISGPS on the assessment of postoperative bleeding not distinguishes bleeding in early and late [20, 21, 22].

Although ISGPS proposes an evaluation of early bleeding within 24 hours, other investigators have used as threshold the occurrence 5-7 days after surgery making the determination controversial [23, 24].

The mortality rate after pancreaticoduodenectomy has significantly decreased in recent years. The type of pancreas ablation may affect the postoperative mortality. The mortality rate was determined in 2000 at about 9% after PD and less than 3.5% after DP [25, 26, 27]. Therefore we can say that the type of pancreatic surgery and extent of resection is a predictor for the displayed mortality [28, 29].

The main complications after pancreatic resection is delayed gastric emptying, the occurrence of pancreatic fistula (PF) and bleeding late or early. The PF is shown at 10% to 15% of patients after PD and 10% to 30% of patients after DP [28, 29]. The different techniques of pancreatic anastomosis and suture pancreatic sections after surgery show no significant advantages in preventing

PF in the same way with perioperative use of somatostatin and its analogues. The treatment of complications with conservative or invasive treatment of vascular embolism in patients with PF achieves a success rate about 80% [27, 28, 29, 30]. The prophylactic administration of erythromycin can significantly reduce the incidence of complications, and is usually administered for a period of one to three weeks. Hemorrhage (in gastrointestinal tract or in the abdominal area) occurs in a proportion of 4% to 16% of patients with PD and 2% to 3% of DP patients [27, 28, 29].

The vast majority of bleeding cases (89%) are related to pseudoaneurysms and bleeding from fistulas (11%). Most of cases (78%) displayed the blood outflow from the pancreatic anastomosis. According to the literature, the main source of visceral arterial hemorrhage caused by the formation of pseudoaneurysms (90%) [31, 32] due to pancreatic interventions. Consequently, the presence of postoperative pancreatic fistula is the most important predisposing factor for the formation of pseudoaneurysm and delayed visceral arterial bleeding.

Patients with presence of pancreatic fistulas should be evaluated carefully in order to detect the presence of pseudoaneurysms. Although there are small extrinsic hemorrhages in the abdominal area several times remain clinically undetected while bleeding in the gastrointestinal tract is generally clinically apparent easily [33, 34]. Surgical access to the source of bleeding is usually reduced by the presence of pagreato-intestinal anastomoses, postoperative adhesions and inflammatory reactions. As a result, a targeted approach is often not possible and pancreatectomy becomes inevitable in order to achieve successful hemostasis. The radiological assessment provides opportunities for less invasive treatment in order to control serious visceral arterial bleeding ranging from 80% to 100% [25, 33, 34].

According to the major complication of delayed hemorrhage we may refer the clot appearance, which can cause liver failure due to induction of hepatic ischemia or liver abscess [26, 27]. In case of bleeding area is very close to the hepatic artery can be significantly affected by hepatic blood flow [26, 27]. Remedy the bleeding Yoshiro *et al.* used covered stent suggesting that selective TAE distal to PHA or in the SPA is usually successful. TAE proximal to PHA must be restricted to cases where collateral hepatic blood flow exists [28]. In study of Shafer *et al.* the treatment bleeding by stent was selected in patient who had bleeding of right subphrenic artery. Besides displaying transient lysis, the outcome was successful [31]. The stent usage gives significant advantages in maintenance of normal blood flow [29, 35].

On the other hand Brodsky and Turnbull evaluated delayed bleeding in 1,991 patients and were preceded by the study of Shankar and Russell, who reported the existence of a possible less bleeding warning massive bleeding [35].

The sentinel bleeding precedes delay HPD in significant rates from 25% to 100% of the studied cases. Several studies revealed high mortality rate in patients who experienced sentinel bleeding paired that was associated with the type of pancreatic surgery [10, 26, 36, 37]. In patients with incident pancreatic bleeding after surgery should perform spiral CT angiography with concomitant especially in cases of coexistence of sentinel bleeding [25].

TREATMENT

Nowadays the proper treatment of bleeding after pancreatic surgery is the embolization of the bleeding vessel, especially at the bleeding point. The study of Shafer *et al.* has shown that intravascular procedures can be performed almost in all cases, not only as the first line treatment for mild forms of bleeding but also as a second treatment option in cases with massive hemorrhage in order to avoid repetition of surgery and high levels of morbidity and mortality [12]. According to Kusnierz *et al.* serous touch technique appeared to be easy, safe, associated with fewer incidences of pancreatic fistulas, and less time consuming in comparison with classical pancreatojejunostomy [37].

Blanc *et al.* indicated a rate of bleeding at 14.7% while two other randomized studies comparing pancreaticogastrostomy procedures and pancreatojejunostomy determined delayed PD 4% and 16%, respectively [25]. In the study of Rajarathinam *et al.* the PD cases were limited by the use of bipolar diathermy and mortality rate was zero. Although the study sample was limited, however indicating a lower mortality rate in patients treated by conservative treatment comparing with other studies [26, 36, 37, 38].

According to literature the majority of cases of delayed hemorrhage after pancreatic resection has poor prognosis and may be able to treat by endovascular procedures instead of surgery. Most of patients received endovascular treatment without exhibit survival threatening. The incidence of bleeding after PD was 11.5% and 10.3% in cases associated with late PD [36, 37]. Furthermore Damle *et al.* suggest that multiple biliary procedures with common complications increase the difficulty making the correct diagnosis and therefore all possible etiologies of a complication must be evaluated [38]. Even in rare cases of bleeding embolization should be more cautious and selective only in the vessel bleeding in order to minimize ischemia of the organ [38].

The complete embolization of primary hepatic artery should be avoided to prevent possible failure and hepatic necrosis of liver tissue [11, 38]. Additionally if the use of stent is not suggested due to anatomical variations, the bleeding control procedure requires complete embolization despite the risks of hepatic ischemia [11, 19, 34].

The endovascular treatment tends nowadays to become more widespread treatment in patients who develop postoperative bleeding due to significant success, low morbidity and reduced mortality rates. Depending on

the anatomical site of the bleeding area and the size of the affected vessel, the respective operations can be performed in the form of intra-arterial embolization or closed template [19, 39, 40]. Also a combination of CRP levels and the color of surgical drain fluid may be the most accurate indicators for safe drain management following PD [39].

An additional form of treatment in order to control the active bleeding focuses on transient occlusion process [41, 42]. In retrospective analysis patients who have undergone pancreatectomy the soft texture of the pancreas was associated with a significant risk of fistula appearance which confirmed also in other cases [14, 42]. Patients who developed chronic pancreatitis treated conservatively by pancreatic resection, while none of the patients with chronic pancreatitis undergoing surgical resection revealed delayed hemorrhage [14].

Additional data have shown that the soft texture of the pancreatic tissue remaining an important risk factor for late PPH which may be associated with erosions of vascular tissue and pseudoaneurysm. The appearance of the pseudoaneurysm is the main reason for the fatal outcome of the disease and is may associated with chronic pancreatitis [42, 43].

Additionally fistula has been associated with delayed onset PPH with loss of significant amounts of blood. The occurrence of bleeding can activate successive harmful situations of arterial bleeding from pseudoaneurysms or vascular lesions [44]. According Grendar *et al.* there was no difference in the rates of pancreatic leak/fistula, overall complications or mortality between patients undergoing PG and those undergoing PJ after PD [44]. It has been observed that early diagnosis can be essential to prevent a negative evolution [15].

Furthermore in cases where there are concomitant diseases such as celiac disease requires the use of stent in the affected arterial segment to maintain patency of vascular permeability and prevent extensive mesenteric obstruction [21, 45].

Although the endovascular treatment techniques may vary for each patient remain not the most reliable and effective method to halt bleeding. Therefore, invasive procedures should be primarily non-surgical procedures [46]. Alexiou *et al.* suggested initial management should be both diagnostic and therapeutic according to the angiographic control and trans-catheter embolization of the bleeding vessel. In case of hemodynamic instability or when angiographic embolism is unsuccessful reoperation should be the proper treatment [46].

According to literature, there is no prospective, randomized clinical trial compared surgery with endovascular management procedures in cases of delayed bleeding after PD. Therefore, the proper treatment of this complication remains unclear. Limongelli *et al.* reviewed 24 published articles referring to the management of delayed bleeding after PD in a total 163 cases. This meta-analysis showed

no significant difference between invasive procedures and endovascular interventions on successful management of delayed bleeding [47].

Meta-analysis results suggest that the minimal invasive procedures such as pancreaticoduodenectomy related with shorter hospitalization and less blood loss. Additionally procedures such as robotic resection could even have similar results with laparotomy. According these minimal invasive approaches could be proper alternative methods undergoing pancreaticoduodenectomy [48, 49].

Postpancreatectomy bleeding can be treated successfully with low mortality (3%). However treatment approaches of delayed bleeding should be guided according to position of the bleeding [50, 51]. EUS and laparoscopy are useful modalities in the preoperative investigation and staging of patients being considered for PD [52, 53].

The Whipple intervention therefore associated with a unique set of common post-operative complications, such as surgical hemorrhage, postoperative pancreatitis, portomesenteric venous thrombosis, hepatic infarction, delayed gastric emptying and anastomotic conjunction. Therefore the maintenance of postoperative anatomy becoming essential and may be determined by CT scan analysis in order to set the correct treatment approach and minimal invasive procedure [53, 54].

As interventional radiology becomes more sophisticated, it should be used as the first option of diagnosis and treatment in this complex group of patients. During PD, there is a considerable excision of collateral vessels; therefore, it is reasonable to assume that the liver abscesses formed after therapeutic embolization of hepatic artery caused by the interruption of blood circulation in the biliary tree. Khorsandi *et al.* reported a case of biliary ischemia after embolization of pseudoaneurysm after PD, which was treated with percutaneous drainage and corresponded to an intrahepatic biloma [54].

The research data has shown that complications such as mortality or morbidity rates were higher in patients who underwent in second surgical approach [55]. Among the fatal cases the location of bleeding was the hepatic artery and treated with embolization of the uterine artery. Bleeding was successfully controlled, but the operating indicators of liver functions were increased after the procedure and the patient died due to liver failure after 17 days. Both infectious clinical signs and bile content in the drainage fluid considerably increase the risk of massive bleeding after pancreatic leak [55].

The presence of pancreatic fistula usually treated conservatively with a high success rate [17, 39] but often need reoperation when complicated by hemorrhage [17, 34]. The principal complication of embolism is obstruction of the hepatic artery leading to ischemia of biliary tree and possibly fatal recurrent abscesses of the liver [54, 55, 56]. The use of covered stents appears more suitable for the treatment of the pseudoaneurysm of the abutment of the stomach and

duodenum in patients not encountered occlusion of the hepatic artery [47, 55, 56].

In most cases endovascular treatment is mainly performed in patients who developed intermittent or moderate bleeding without severe abdominal sepsis [56]. If a pancreatic fistula has already addressed preservatives due to clinical symptoms, this appearance will be considered seriously. In most cases, the bleeding permits management before be massive and lead to circulatory failure [16, 34, 42, 43].

The introduction of an adaptive stent into the portal vein or SMV in order to verify bleeding from the portal circulation is not often used, although there are reports indicating this therapeutic approach reveal significant advantages [57]. Risk factor analysis suggests that appropriate patient selection especially for extended resections and pancreatogastrostomy is crucial succeed [58]. Hellman *et al.* who used adapted stents reveal improvement of abdominal symptoms and only limited bleeding complications [59].

Transcutaneous transhepatic vein stent placement therefore seems to be safe and effective therapy for the treatment of stenosis in the portal vein in cases of benign disease or due to relapse after curative pancreatic or biliary tree surgery [59]. On the other hand Kim *et al.* have reported significant major complications such as sepsis, liver abscess and acute venous thrombosis in patients managed with stent placement [60].

The process of pancreatectomy is technically demanding procedure with significant blood loss up to 2L which can lead to unstable diabetes affecting quality of life [41, 42, 61, 62]. On the other hand while the importance of detecting sentinel bleeding in early prevention of delayed massive bleeding after pancreaticoduodenectomy is widely recognized this type of bleeding is reported in the literature as bleeding in the gastrointestinal tract, or as outflow of the surgical drains. Sentinel bleeding determined by paradoxical increase in the amount of blood in the abdominal drains and by the decrease in hemoglobin greater than 2g / dl which occurs 3 days after PD. This type of hemorrhage may detect in patients with pseudoaneurysms could be determined by angiographic analysis and in some cases may lead to delayed massive bleeding [61, 62].

In patients with delayed bleeding spiral three-dimensional computational tomography allows early diagnosis while in case of reoperation recommended pancreatectomy [61, 62]. Apart from a number of patients who reported no deaths after completion, this process is associated with high mortality rates. PG seemed to be superior to PJ in reducing the incidence of PF and intra-abdominal fluid collection after PD [62].

CONCLUSION

In conclusion, the management of delayed bleeding after major pancreatic surgery procedures should be attributed

to bleeding pseudoaneurysm of main visceral arteries until proved guilty. Repeated episodes and minor bleeding may precede fatal bleeding situations and therefore will be instant diagnostic procedure to avoid the occurrence hemorrhagic shock.

Endoscopy may be useful for the diagnostic process and the exclusion of intraluminal bleeding induced ulcer and the stitching regions. Mass endoluminal bleeding can determine the location of bleeding. According to pathogenesis of pseudoaneurysm formation, the scheduled monitoring by CT analysis should be performed perioperatively, especially in cases suspected pancreatic fistula. Interventional radiology must be performed by experienced radiologist who will indicate the proper treatment of major visceral arterial bleeding and should be preferred over emergency surgery whenever is possible.

The surgical operation should be restricted due to major bleeding complications (e.g., intra-abdominal abscesses and bleeding of the pancreas). With advances in interventional radiology procedures have led to a reduction in mortality and morbidity, being effective methods for the treatment of delayed bleeding after PD. Stroke due to delayed bleeding pseudoaneurysm after PD can be selectively performed, especially in embolization of uterine artery.

Therefore both embolization and surgery have an important role in the management of bleeding after PD. The delayed bleeding commonly associated with abdominal complications and should be controlled by either direct embolization or reoperation according to the severity of the bleeding and incidence of sepsis. Early diagnosis with CT can increase the probability of success of endovascular therapy. If the stroke is impossible or fails, the bleeding after PD should be treated with aggressive surgery that should not affect the endocrine function of the pancreas.

Authors' Contributions

AK, AI, ID, NE participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

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