Complications of pancreatic surgery

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Abstract

Many diseases, including pancreatitis benign tumors and cancer, may require pancreas surgery. Pancreatic resection can lead to a prolonged survival in pancreatic cancer and even a potential chance for cure. However, the pancreatic surgery can result in complications, and high postoperative morbidity rates are still presence. This article reviews the pancreatic abstracts of American Pancreas Club 2011, which involves the more common complications, their prevention and treatment.

Keywords: Pancreatic cancer, adenocarcinoma, pancreatectomy, endoscopic, Robotic surgery, Appleby operation.

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Prophylaxis Against Infections

To assess the effectiveness of first generation cephalosporins as perioperative prophylaxis in pancreatic surgery from January to November 2010, 43 consecutive patients underwent surgery for periampullary diseases. They were prospectively enrolled in this study. Surgical procedures were: 33 pancreaticoduodenectomies, 3 total pancreatectomies, 5 biliary and gastric bypasses, 2 ampullectomies plus bilio-enteric anastomosis. Bile sampling for culture was intraoperatively collected in 40 (93 %) patients. Twenty-six out of 40 (65 %) patients preoperatively underwent ERCP (group A) and 24 of them received a stent (20 plastic) because of jaundice; 14 (35 %) were not submitted to any endoscopic manoeuvres (group B). All patients received perioperative cefazolin (2g). All patients of group A had positive bile culture while only 29 percent of patients of group B had infected bile; in group A there were 68 isolated germs (65 bacteria and 3 fungi) and 6 (bacteria) in group B (overall: 33 Gram+ and 38 Gram-). Cefazolin was effective against 18 percent of isolated bacteria, but potentially able to sterilize bile in only 2 patients (6 %). Mortality was nihil and morbidity was 56 percent: 11 pancreatic fistulas (33 %), 2 biliary fistulas (5 %), 1 duodenal-jejunal fistulas (3 %), 4 intrabdominal abscesses (9 %), 1 hemoperitoneum (2 %), 13 wound infections (30 %), 5 of which as unique complication. Even if the incidence of complications was similar in both groups, all patients with wound infection as unique complication belong to group A. Forty-six percent (13/28) of bacteria isolated from drainages of patients with abdominal infection were already present in the intraoperative bile culture. It was concluded that even if data are from a small series, cefazolin seems to be effective against very few bacteria present in the bile of operated patients; the same bacteria are then found in about half of patients with postoperative abdominal infection. A different antibiotic prophylaxis seems therefore advisable in patients undergoing pancreatic surgery with previous endoscopic manoeuvres [1].

Cytokines in Drain Fluids

Cytokines play a role in biological pathway through the inflammatory, angiogenetic as well as tissue repair and growth influencing in vitro anastomotic healing, cancer progression and metastasis, but the “in vivo” role remains still unknown. The aim was to test Transforming growth factor beta (TGF-beta), Insulin-like growth factor-1 (IGF1), Epidermal growth factor (EGF) and Interleukine-6 (IL6) levels in drainage liquids from patients undergone to pancreatic surgery for exploring a new translational research way. Liquids from the right and left drainage of 30 patients who underwent to pancreatic resection were collected in postoperative day 1st (POD 1), centrifuged at 15000 rpm for 20 minutes and the total proteins, TGF-beta, IGF1, EGF, IL6 concentration levels and correlated with amylase concentration U/L, patient with or without complications, CA 19.9 with a cut-off less or more than 100 U/L and pancreatic adenocarcinoma (PDAC) versus other conditions. Amylase values correlated to the cytokines.
concentrations was not statistically significant. Comparing the groups with or without complications only the amylase concentration was significant. A significant association was established for IL6 using a CA 19.9 cut-off less or more than 100 u/L as well as in the analysis PDAC versus other conditions. In addition amylase was significant in PDAC versus other conditions. It was concluded that cytokine levels in liquid of drainages after pancreatic surgery still have limitations. Despite that and the small number of patients the study, however, reaches some interesting points confirming amylase level as a good marker of surgical complication, founding IL-6 levels statistically significant in PDAC vs. other conditions and finally opening a new method to extract biological information from biological fluids [2].

Wound Infections
Pancreatoduodenectomy (PD) is a complex surgical procedure with a historically high morbidity rate. In recent years, increasing attention has been given to implementing perioperative quality measures to reduce surgery related complications. The goal of one study was to determine if the implementation of a perioperative surgical care bundle (SCB) was successful in reducing infectious and other complications in patients undergoing PD, as compared to a routine preoperative preparation group (RPP). The SCB included preoperative smoking cessation, absence of remote infection, pre-admission antiseptic skin preparation, timely perioperative antibiotic administration, hair clipper and chlorhexidine-alcohol skin preparation, intraoperative wound edge protection, glycemic and temperature control, deep venous thrombosis prophylaxis, beta-blocker administration, and pre- and postoperative briefing; whereas the RPP included povidone-iodine skin preparation, and a less formalized use of a variable number of the above measures. In one retrospective cohort study utilizing a HPB surgery database it was analyzed clinical data from 233 consecutive PDs from 2005 to 2008 on patients who underwent RPP, and compared them with 233 consecutive PDs from 2008 to 2010 following the implementation of the SCB. The RPP group and the SCB group had similar demographic characteristics. The overall rate of postoperative morbidity was similar between groups (42 % vs. 38 %). However, wound infections were significantly lower in the SCB group (15 % vs. 8 %). The rates of other common complications, as well as postoperative hospital length of stay, readmissions, and 30 day postoperative mortality were similar between groups. It was concluded that implementation of a SCB significantly reduced wound infections in patients undergoing PD. These findings are congruent with the recently published data [3] supporting the use of a SCB with chlorhexidine-alcohol as the topical skin preparation agent of choice [4].

Surgical Site Infections (SSI) are recognized as a preventable cause of morbidity following surgery. The aim of one study was to evaluate the incidence and factors that contribute to SSI in a specific patient population undergoing pancreatoduodenectomy. All pancreaticoduodenectomies from 2001 to 2010 were identified from the National Surgical Quality Improvement Program (NSQIP) dataset which prospectively identifies all surgical site infections. With IRB approval, the databases and patient charts were abstracted for pertinent data related to infection. In the 9 year study period, 204 patients underwent a pancreatoduodenectomy. The incidence of SSI in this study population was 16 percent (33/204 patients). This included superficial incisional infections (n=8, 4 %) and organ space infections (n=25, 12 %). Thirty day mortality was 2 percent (4/204 patients) and did not correlate with the presence of SSI. On univariate analysis age ≥ 65, gender, BMI, diabetes, preoperative albumin, ASA classification, weight loss, smoking, and length of operation were not associated with an increase in SSI. Whipple performed for ampullary neoplasms was associated with a significant increase in SSI when compared to resection of primary pancreatic tumors (39 % vs. 13 %). Patients who developed SSI had a longer length of hospitalization than patients without SSI (17 ± 8 vs. 11 ± 8 days). Patients with SSI were more likely also to have postoperative pneumonia, sepsis or UTI than those without SSI (36 % vs. 9 %). Patients given perioperative antibiotics within the guideline of 5-60 minutes prior to incision had an SSI rate of 19 percent while those treated outside the guideline had a rate of 11 percent. A trend towards improvement in SSI rates over time was observed (18 % from 2001-2005, 15 % from 2006-2010). Surgical site infections remain a common cause of morbidity following pancreatoduodenectomy. Despite adherence to a quality improvement program related to antibiotics administration and control of modifiable risk factors, SSI rates have not decreased significantly. Unlike studies in other operations, risk factors such as obesity, diabetes, hypoalbuminemia, smoking and antibiotics administration do not appear significantly to predict SSI after pancreatoduodenectomy. New approaches to prevent infection after pancreatic surgery are needed [5].

Organ Space Infection
Pancreatic surgery mortality has improved, but morbidity remains high. Organ space infection (OSI) is a major complication which is likely a surrogate for clinically significant pancreatic fistula. Participation in the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) has been shown to improve many outcomes. The aim of this analysis is to determine whether OSI has improved after pancreatic surgery. The ASC-NSQIP database was analyzed from 2006-2009 for pancreatoduodenectomy, distal pancreatectomy, pancreatic-enteric anastomosis (PEA), total pancreatectomy, and pancreatic enucleation. Over the 4-year period, 10943 pancreatic operations were performed in ACSNSQIP hospitals, and the number of operations increased each year from 1581 in 2006 to 3665 in 2009. Pancreatoduodenectomy (57%) and distal pancreatectomy (30 %) were the most common operations, followed by PEA (6 %), total pancreatectomy (5%), and enucleation (2%). OSI rates were higher for
pancreatoduodenectomy (11%) and lower for PEA (7%) when compared to all other operations. No changes in OSI rates were observed over the 4-year period for all pancreatic surgery or for any of the individual operations. It was concluded that while ACS-NSQIP is capturing a large proportion of the pancreatic surgery being performed in the United States, OSI rates are not decreasing in participating hospitals. Since pancreatic fistula is likely a large contributor to OSI after pancreatic surgery, pancreatic surgeons should devise new strategies, such as drain management, to improve this ongoing problem [6].

**Postpancreatectomy Haemorrhage**

Postpancreatectomy hemorrhage (PPH) is seen infrequently after pancreatic surgery but remains a serious complication with high mortality. Recently, the International Study Group of Pancreatic Surgery (ISGPS) has issued a new definition for PPH. To evaluated and validated this new definition we retrospectively analyzed data from a high volume centre. The data sets of 980 patients who underwent pancreatic surgery in one department between 1993 and 2009 were identified from a prospective database with regard to occurrence of PPH. Based on existing data it was graded bleedings according to the ISGPS consensus definition. It was assessed the clinical course, morbidity, mortality and length of stay for PPH grade B and C compared to controls. PPH grade B occurred in 16 patients (1.6 %) after pancreatic surgery, PPH grade C in 38 patients (3.9 %). In patients with PPH it was seen significant elevated mortality compared to controls (25.9 % vs. 2.0 %). Morbidity, too, was elevated in patients with PPH grade B (77 %) and C (95 %) compared to controls (60 %). PPH correlated significantly with incidence of postoperative pancreatic fistula and other complications such as delayed gastric emptying and wound infection. It was concluded that the data show that the new definition correlates very well with morbidity, mortality and length of stay. The definition therefore seems suitable for clinical and scientific application [7].

**Pancreatic Fistula**

One of the more common complications following pancreatectoduodenectomy (PD) is a pancreatic fistula (PF). These can range from trivial to life threatening in nature and previously have been grouped together without regard to severity in published series. In 2005, the International Study Group on Pancreatic Fistula (ISGPF) created a universal definition and grading system stratifying these fistulas from benign to those requiring urgent therapeutic intervention. Patients with grade C fistulas appear clinically unwell, require aggressive intervention, may need reoperation, and have a distinct associated risk of death. Although grade C PFS are reported in the literature, they have been incompletely characterized. It was sought to better define the incidence, management, outcome and variables associated with this severe complication. Two researchers each independently reviewed a PubMed search with the keywords “pancreatectoduodenectomy” and “pancreatic fistula”. Results were limited to humans, adults, and the years 2005-10. Criteria used for inclusion were studies with at least 100 patients, consecutive accrual of unselected patients including all pathologic diagnoses, and use of the ISGPF definition and grading system. After reviewing relevant titles and abstracts with these criteria in mind, a list was compiled of 40 potential articles. Upon further analysis, 14 studies were found to meet the previously stated parameters and contain complete data concerning the incidence and outcome of grade C PFS with most including details of operative management. The review accumulated 2,949 procedures from 18 different institutions in North America, Europe, and Asia with a mean of 34 PD performed annually, 76 percent of which were reconstructed via a pancreatico-jejunostomy. A PF occurred in 510 patients (17 %) including 230 (45 %) with a grade A, 196 (38 %) grade B, and 84 (16 %) grade C (overall incidence 3 %). Ten of the studies included details of operative management. Forty-four percent of patients required remedial surgery for a grade C PF. Of these, 57 percent had drainage alone, 21 percent anastomotic revision and 18 percent completion pancreatectomy. Grade C PFS were directly responsible for 27 deaths for an overall mortality of 32 percent. One study found that ampullary cancer was associated with the highest number of grade C PFS. Two performed multi-variant analyses of patients, surgical and pancreas-related pathology associated with a grade C PF: soft texture approached significance in distinguishing grade A/B from grade C PFS in one and the other did not find any factors that distinguished grade C from grade B PFS. It was concluded [8]: 1) grade C pancreatic fistulas account for approximately one sixth of all pancreatic leaks following PD; 2) these fistulas are associated with the universal need for therapeutic intervention including re-operation in nearly one-half and an associated mortality in one-third; and 3) the published literature incompletely describes patient demographics, pancreas specific pathology, and remnant consistency associated with this devastating complication.

Fatty pancreas and increased Body Mass Index (BMI) are risk factors of pancreatic fistula (PF) after pancreatectoduodenectomy (PD), however the influence of fat distribution is still unknown. One study aimed to assess the value of preoperative CT scan to predict incidence and severity of PF after PD, according to fat distribution. From 2006 to 2007, 103 patients (M/F 0.56, mean age 58 years) underwent PD with pancreatectogastrostomy. Visceral fat area (VFA), subcutaneous fat area (SFA), global fat area (GFA), hepatic and splenic density (Dh and Ds) were measured retrospectively on preoperative CT scans at the umbilicus level using a free software. On the pancreatic margin, fibrosis and fatty infiltration were scored by a pathologist blinded to postoperative course and patient characteristics. PD was mainly performed for adenocarcinoma (48 %), IPMN (20 %) and endocrine tumor (11 %). Overall morbidity was 46 percent and PF occurred in 37 percent (grades A, B and C: 47 %, 39 % and 13 % respectively). In univariate analysis, male gender, BMI>25kg/m², abdominal perimeter > 90 cm, VFA > 84
cm², GFA > 240 cm², VFA/GFA > 1 and Dh/Ds<1 (suggesting liver steatosis) were associated with a greater risk of grade B+C PF. In multivariate analysis only Dh/Ds < 1 and VFA > 84 cm², were independent predictors of grade B+C PF. VFA > 84 cm² was associated with fatty infiltration of the pancreas. It was concluded that an increased visceral fat is associated with an increased risk of PF after PD. Thus, preoperative CT scan could help to predict the risk of PF and to tailor preventive measures [9].

**Pancreatic Firmness**

Delayed or decreased enhancement characteristics on computed tomoigraphy (CT) in patients with pancreatic fibrosis have been described. However, studies comparing clinical outcomes following pancreaticoduodenectomy (PD) to preoperative CT enhancement characteristics are lacking. To study the ability of dual-phase CT to assess pancreatic fibrosis and to predict the risk of developing a pancreatic anastomotic failure (PAF) following PD a review of 157 consecutive patients with preoperative dual-phase CT between 2004 and 2009 was performed. Pancreatic CT attenuation upstream from the tumor was measured in the pancreatic and hepatic imaging phases. The ratio of the mean CT attenuation value of the pancreas in the hepatic (late) and pancreatic (early) phase was calculated; L/E ratio and histological grade of pancreatic fibrosis assessed by Masson trichrome immunostaining were then correlated with the development of a clinically-relevant PAF and other clinical parameters. A clinically-relevant PAF was found in 21 patients (13 %) with a morbidity rate of 40 percent. No postoperative death was observed. The PAF group showed maximum enhancement in the pancreatic and washout in the hepatic CT phase, while the control group showed a delayed enhancement pattern. Degree of pancreatic fibrosis and L/E ratio were significantly lower for the PAF group than the control group (21 ± 18 vs. 40 ± 30 and 0.86 ± 0.14 vs. 1.09 ± 0.24); fewer PAF patients showed an atrophic histological pattern (14 % vs. 39 %). The L/E ratio was positively correlated with pancreatic fibrosis. Pancreatic fibrosis and L/E ratio increased with larger duct size, the presence of diabetes, and the surgeon’s assessment of pancreas firmness. In multivariate analyses L/E ratio and BMI were significant predictors for the development of a clinically-relevant PAF; a 0.1 unit increase of L/E ratio decreased the odds of a PAF by 54 percent. It was concluded that pancreatic CT enhancement characteristics quantified by the L/E ratio can accurately assess the histological grade of pancreatic fibrosis and are a powerful tool to predict the risk of developing a clinically-relevant PAF following PD. L/E ratio and pancreatic fibrosis are further associated with pancreatic texture, pancreatic duct size, and the presence of diabetes [10].

**Predictive Clinical Futures**

Recent reports suggested that the drain amylase value in drain on the postoperative day one is the useful predictive factor for postoperative pancreatic fistula (POPF) after pancreatic resection. However, the predictive clinical data for clinically relevant POPF after pancreatic-duodenectomy have not been clearly established. From 2003 to 2010, prospectively collected data from 175 consecutive patients who underwent pancreaticoduodenectomy with two-layered duct to mucosa pancreaticogastrostomy were evaluated. The predictive clinical data (WBC, serum amylase, serum albumin, C-reactive protein, drain amylase, drain fluid volume, etc.) for clinically relevant POPF (ISGPF Grade B and C) were analyzed by logistic regression analysis. Of 175 patients, 31 (18 %) developed pancreatic fistula by ISGPF criteria; grade A in 21 patients (12 %), grade B in 8 (5 %), and grade C in 3 (2 %). By univariate analysis, drain amylase on postoperative day (POD) 2, 3, 4, 5, C-reactive protein POD 3 and 4 were found to be significantly associated with clinically relevant POPF. By multivariate analysis, the independent predictive factor for clinically relevant POPF was C-reactive protein on POD 4. Based on the receiver operating characteristic curve analysis, C-reactive protein >18mg/dL on POD 4 displayed the optimal sensitivity (64 %) and specificity (93 %). It was concluded that C-reactive protein >18mg/dL on POD 4 is the predictive factor for clinically relevant POPF after pancreaticoduodenectomy when diagnose POPF by ISGPF criteria [11].

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