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Negative predictive value of drain amylase concentration for development of pancreatic fistula after pancreaticoduodenectomy

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ABSTRACT

Background: Post-operative pancreatic fistula (POPF) is the major source of morbidity following pancreaticoduodenectomy. A predictive indicator would be highly advantageous. One potential marker is drain amylase concentration (DAC). However, its predictive value has not been fully established.
Methods: 405 patients undergoing pancreaticoduodenectomy at our centre over a 10 year period were reviewed to determine the value of DAC as a predictive indicator for the development of POPF.
Results: POPF developed in 58 patients (14%). These patients suffered greater morbidity. Overall 30-day mortality was 1.5%. Male gender (OR: 5.1; $p = 0.0082$) and age > 70 (OR 2; $p = 0.0372$) were independent risk factors for POPF, whilst Type 2 diabetes (OR: 0.2321; $p = 0.0090$) and pancreatic ductal-adenocarcinoma (OR: 0.3721; $p = 0.0039$) decreased POPF risk. The DACs post-operatively were significantly higher in those developing POPF, but with significant overlap. ROC curves revealed optimal threshold values for differentiating POPF and non-POPF patients. A DAC°<°1400 U/ml on day 1 and <768 U/ml on day 2, although having a poor positive predictive value (32–44%), had a very strong negative predictive value (97–99%).
Conclusion: Our data suggest that post-operative DAC below the determined optimal threshold values on day 1 and 2 following pancreaticoduodenectomy carries high negative predictive value for POPF development and identifies patients in whom early drain removal, and enhanced recovery may be considered, with simultaneous assessment of operative and clinical factors.

Introduction

Pancreatic cancer is the fifth most common cause of cancer-related mortality in the UK [1,2]. Unfortunately, only 10–20% of patients present with potentially curative disease [3]. Pancreaticoduodenectomy (or Whipple's resection) is the only treatment modality with the potential of achieving long-term survival for periampullary and pancreatic head malignancies [4–6]. The overall 5-year survival following resection of pancreatic cancer is reported to range between 11 and 25% [7–10]. Over the last two decades there have been significant improvements in perioperative mortality, largely due to advancements in postoperative management, the centralization of care to high-volume centers and accumulation of surgical expertise [11–14]. Several major centers now report an in-hospital mortality of less than 1% [4,15]. However, morbidity following pancreaticoduodenectomy still ranges between 30 and 50% largely due to the development of post-operative pancreatic fistula (POPF) and its related complications [16–19].

The development of a POPF frequently results in a prolonged hospital stay and a requirement for further radiological or surgical intervention, and is a common underlying cause of post-operative mortality [17–20]. Being able to predict early which patients will go on to develop a POPF would be advantageous to clinicians caring for patients post-pancreaticoduodenectomy. Those patients identified at high risk could be monitored more closely, enabling early detection and management of POPF-related complications, reducing the associated morbidity. Conversely, patients identified

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at low risk of developing a POPF could follow an enhanced recovery pathway with earlier hospital discharge [21,22].

The incidence of POPF following pancreaticoduodenectomy is reported to range from 3 to 30% [23,24]. This variation likely reflects different definitions used for diagnosing POPF [24,25]. Although drain amylase concentration (DAC) and abdominal drain volumes feature in most definitions, the threshold values for diagnosing a POPF differ significantly between studies [23,26]. More recently the International Study Group of Pancreatic Fistulas (ISGPF) have defined criteria to allow diagnosis and grading of POPF to be standardized internationally [27]. Several studies have attempted to assess the possibility of predicting the development of a POPF based on DAC in the early post-operative period [28–32]. However, limited conclusions have been drawn due to the relatively small numbers of patients enrolled, differences in the definition of POPF and the restricted focus of many of these studies.

Here we report a comprehensive analysis of a large cohort of patients over a 10 year period, examining the predictive value of postoperative DAC for development of POPF and associated complications following pancreaticoduodenectomy. We find that DAC holds more value as a negative, rather than a positive, predictor of POPF development, and may be more important for identifying those patients who are suitable for enhanced recovery.

Methods

Patient recruitment

Cambridge University Hospitals NHS Trust is tertiary referral center for hepatopancreatobiliary diseases serving a population of 2.4 million. Patients undergoing pancreatic resections are enrolled on to a prospectively maintained Pancreatic Cancer Database. All patients undergoing pancreaticoduodenectomy over the 10 year period between April 2002 and July 2012 were included in this study. Patient demographic and clinical data were obtained from the database, electronic clinical laboratory records and retrospective medical case note review where required. Data in the Database was cross-checked with a histopathology database, medical cases notes and HISS (Hospital Information Service) laboratory database for accuracy.

Surgical technique

All 405 pancreaticoduodenectomies were performed using the standard Whipple-Kausch technique [33]. After resection, the reconstruction was performed using a Roux-en-Y loop. Retrocolic pancreatic and biliary anastomoses were completed on a 70 cm Roux loop. Pancreatico-jejunostomy was typically performed using a two-layer duct-to-mucosa technique, using 5-0 non-absorbable sutures (Prolene, Ethicon) and an internal stent (infant feeding tube, Fr 5, Unomedical) for the pancreatic duct layer and 4-0 Prolene (Ethicon) for parenchyma. Single layer duct-to-mucosa anastomosis was carried out if the pancreatic duct was dilated (>1 cm) or if the pancreas was atrophic. Pancreatic stump invagination and dunking techniques were occasionally used, particularly for a soft pancreas with a non-dilated pancreatic duct. Distal to the pancreatico-jejunostomy, a hepatico-jejunostomy was formed with absorbable sutures (PDS, Ethicon). A gastro-jejunostomy and jejuno-jejunostomy were fashioned to complete the Roux-en-Y reconstruction. Extended lymphadenectomy was not routinely performed at our centre.

At the end of the operation, two or three surgical drains (30F; PFM Medical) were placed. The right drain positioned posteriorly to the hepatico-jejunostomy, and the left drain anterior to the pancreatico-jejunostomy. Some patients had a third drain placed posterior to the pancreatico-jejunostomy via the tunnel resulting from resection of the duodeno-jejunal flexure.

Post-operative management

All patients received standard post-surgical care. They were managed in an intermediate dependency area until suitable for transfer to the hepatobiliary surgical ward. All received somatostatin analogue prophylaxis (100–200 mcg subcutaneously three times a day) for five days (Octreotide, Sun Pharmaceuticals UK Ltd). Standard biochemical and haematological blood tests and drain amylase levels were measured daily.

Clinical outcomes

Postoperative pancreatic fistula (POPF) was defined as the persistent drainage of amylase rich fluid (more than three times the upper limit of normal serum level) for more than 5 days, or a clinical leak requiring radiological and/or surgical intervention (Cambridge definition). The upper limit of normal serum amylase at our centre is 125 U/L. The ISGPF definition, published in 2007, was retrospectively applied to the study cohort for comparison. Using this definition, POPF was deemed to be present if the amylase level on or any time after postoperative day 3 exceeded three times the upper limit of normal serum levels. Grading of POPF was based on the patient's clinical course: grade A POPF requires no specific treatment; grade B POPF requires prolonged drainage or specific medical treatment, and grade C POPF requires aggressive clinical intervention [27].

In this study, the highest DAC from any of the existing drains was recorded for each post-operative day (POD) and considered for

Table 1
Patient characteristics and demographics.

	No POPF	POPF	*p* Value
Number of patients	347	58	–
Age (years)			
Median (range)	64 (20–85)	68 (34–84)	0.0218
Gender			
Female	170 (49%)	17 (29%)	**< 0.0001**
Male	177 (51%)	41 (71%)	
Comorbidities	257 (74%)	46 (79%)	0.6923
Hypertension	132 (38%)	15 (25%)	0.8242
Diabetes m. type 2	73 (21%)	5 (8%)	**0.0085**
COPD	14 (4%)	5 (9%)	0.8345
Ischemic heart disease	45 (13%)	8 (13%)	0.9005
Previous cancer history	31 (9%)	15 (26%)	**0.0136**
Pathology			
Ductal adenocarcinoma	143 (41%)	12 (21%)	**0.0010**
Ampullary cancer	45 (13%)	12 (21%)	0.1888
IPMT/IPMN	37 (11%)	4 (7%)	0.3209
Benign changes	26 (7%)	8 (2%)	0.1081
Pancreatitis	15 (4%)	2 (3%)	0.7459
Cholangiocarcinoma	27 (8%)	8 (2%)	0.1302
GP NET	21 (6%)	4 (7%)	0.8110
Duodenal cancer	8 (2%)	2 (3%)	0.6021
Colon cancer	5 (1%)	1 (2%)	0.8762
Others	20 (6%)	5 (9%)	0.4642
Median DAC values (U/ml)			
POD1	280	6193	<0.0001
POD 2	217	4261	<0.0001
POD 3	93	1650	<0.0001
POD 4	35	646	<0.0001

COPD – chronic obstructive pulmonary disease; DAC – drain amylase concentration; GEP NET – gastroenteropancreatic Neuroendocrine Tumors; IPMT/IPMN – intraductal papillary mucinous tumour/intraductal papillary mucinous neoplasm; POPF – postoperative pancreatic fistula; OTV – optimal threshold value. *p*-values were obtained using t-test for continuous variables and fishers exact chi-squared test for categorical variables. *p*-value°<°0.05 indicates statistical significance.

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