



ORIGINAL ARTICLE

Early Aggressive Management of Postoperative Pancreatic Fistulas following Pancreaticoduodenectomy (PD): A Five-Year Single Institution Experience

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Abstract

Background: Pancreatico-duodenectomy for pancreatic tumours remains the standard of care. Morbidity rates are still high, often as a result of post-operative pancreatic fistulae (POPF), leading to prolonged hospital stays and increased costs.

At our institute we treat all pancreatic fistulas defined by ISGPF criteria with parenteral nutrition and an octreotide infusion for a minimum of 7 days. Our experience suggests that early and aggressive management of POPF could prevent Grade C fistulas.

Methods: We retrospectively analysed the data that underwent PD between 2013-2017. We reviewed for all patients who experienced Grade B POPF. Data included details of total parenteral nutrition received, dose of octreotide infusion administered, serial drain amylase levels, effluent volume and anthropometry. Outcome measures were weight changes associated with treatment, the number of lines used per patient, the length of treatment, treatment associated complications and 90-day mortality rates.

Results: 53 patients had a Grade B POPF and all were treated with the 'leak protocol'. The Grade B pancreatic fistulas rate was 13%. Median ages of the patients were 69. Median hospital stay was 30.5 days. Parenteral nutrition was administered for an average of 20 days. The mean BMI on discharge was 26.5 with an average weight difference of -4.9%. There was one 90-day operative mortality. 2 patients had Grade C fistulas requiring re-operation.

Conclusions: Our institutional practice has good results with a Grade C POPF incidence of 0.4% that is much lower than what is in literature. We think this management of pancreatic leaks have promising results.

Keywords

Octreotide, Pancreatic cancer, Pancreaticoduodenectomy, Parenteral nutrition, Post-operative pancreatic fistula

Introduction

Pancreaticoduodenectomy (PD) may have been described as 'the Cadillac of abdominal surgery' in 1979 [1] but in the modern surgical era it has become the standard of care for most patients with resectable pancreaticobiliary tumours. Over the past two decades mortality rates as low as 1-3% have been reported from most high volume centres, but having said that morbidity rates still remain high (30% - 50%), often as a result of post-operative pancreatic fistulae (POPF), leading to prolonged hospital stays and increased costs. As a result several techniques and modifications have been developed for managing the pancreatic remnant [2-4]. Some techniques included suture ligation of the pancreatic duct without enteric drainage [5], pancreatic ductal occlusion with polymers [6] and various modifications of the pancreaticojejunal anastomosis (e.g., end-to-end vs. end-to-side, invagination vs. duct-to-mucosa, iso-

lated Roux-en-Y limb) [7,8]. Pancreatic drainage to the stomach has also been evaluated by many groups [9], with the only prospective randomized trial finding similar pancreatic fistula rates (11-12%) when comparing pancreaticogastrostomy and pancreaticojejunostomy (PJ) [2].

The diagnosis and prevention of POPF have been extensively discussed in the literature, but the management of POPF lacks standardization [10-12]. At our institution we treat all clinically relevant pancreatic fistulas defined by ISGPF criteria [13] with parenteral nutrition and an octreotide infusion. Our experience suggests that early and aggressive management of POPF could prevent Grade C fistulas.

Materials and Methods

We retrospectively analysed the data of 407 patients who underwent open PD from January 2013 to December 2017. Case notes, patient electronic records, and dietician records were reviewed for all patients who experienced Grade B or C POPF. Data included details of total parenteral nutrition (TPN) received, dose of octreotide treatment, serial drain amylase levels, effluent volume and anthropometry (as a measurement of nutritional status) which was monitored on a regular basis and recorded by the dietitians. Outcome measures were weight changes associated with treatment, the number of lines used per patient, the length of treatment, treatment associated complications and 90-day mortality rates.

Technique

All operations were performed with curative intent (patients with locally advanced disease and distant metastases were excluded and referred for neo-adjuvant or palliative chemotherapy). The surgical procedure consisted of a pylorus preserving pancreaticoduodenectomy with a standard lymphadenectomy as per the ISGPS recommendation [14]. If there was suspicion of tumour in-growth in the proximal duodenum, a classical Whipple procedure was performed. If minimal tumour ingrowth of the portal or superior mesenteric vein was

found, a segmental or wedge resection of the vein was performed as part of the procedure. Reconstruction consisted of a retrocolic jejunal loop with a duct to mucosa end-to-side pancreaticojejunostomy, hepaticojejunostomy and ante-colic gastro- or duodenojejunosomy. The usage of pancreatic stents was dependent on surgeons' preference. A Roux limb was used for the biliary and pancreatic anastomoses in a classical Whipple. Two abdominal drains were routinely placed close to the PJ and a nasojejunal tube passed beyond the gastrojejunostomy for enteral feeding. All patients received low molecular weight heparin for thrombosis prophylaxis in the postoperative period. Drains were routinely but not necessarily removed on the third post-operative day, if the drain amylase was normal.

Leak Protocol

We defined POPF as per ISGPF criteria [13]. In those patients with any or clinical concerns, or abnormal laboratory tests, a pancreatic leak protocol was initiated. This consisted of withholding enteral/oral feeds and commencing 50 micrograms an hour of octreotide as an intravenous infusion. Patients were assessed by a Specialist Dietitian and commenced on peripheral TPN via daily intravenous peripheral cannulas until a midline catheter (Leaderflex 22 gauge, Vygon, Aachen, Germany) could be placed. Patients were commenced on off-the-shelf PN formulations (Baxter, Triomel N4-G/L 700E, Lessines, Belgium) providing 2500 ml, 1750 kcal & 10 g Nitrogen. The PN was infused at 139 ml/hr × 18 hrs (daily cannula) or 104 ml/hr × 24 hrs (via a midline cannula). If this PN regimen did not meet the specific nutritional requirements or if it was felt that the protocol was likely to continue more than 2 weeks, a peripherally inserted central line (Turbojet Power-injectable PICC, Cook, Indiana, USA) was inserted by the interventional radiologists. At this point, bespoke PN formulations would be compounded by the hospital pharmacy unit. Drain amylase was serially checked while on treatment and this protocol was stopped if there was minimal effluent or the drain fluid amylase level normalised. Diet was re-commenced slowly after withdrawal of leak treatment.

Table 1: Patient characteristics.

Sex	Patients on protocol (n = 52)
Male, n (%)	35 (67)
Female, n (%)	17 (33)
Age (years), median (range)	69 (31-87)
Day post op protocol started, median (range)	5 (0 - 17)
Duration of protocol (days), median (range)	17 (4 - 64)
Length of stay (days), median (range)	30.5 (13 - 116)
Admission BMI (kg/m ²), median (range)	26.9 (19.2 - 57.5)
Discharge BMI (kg/m ²), median (range)	25.7 (17.8 - 56.1)
Weight change (%) during admission, median (range)	-4.0 (-19.1 - 7.6)

BMI: Body Mass Index.

Results

A total of 407 PD were performed from January 2013 to December 2018 (Table 1). 53 patients were documented as having Grade B POPF and all were treated with the 'leak protocol'. The Grade B pancreatic fistula rate was 13%. Median age of the patients was 69 (Range 31-87). Median hospital stay was 30.5 days (Range 13-117). 90 lines were needed (1.7/patient) and parenteral nutrition was administered for a median of 17 days (Range 5-64). The commonest reason for line removal was suspected infection. The mean BMI on admission was 27.9 (Median 26.9) and on discharge 26.5 (Median 25.7) with an average weight difference of -4.9 % (Median - 4). Three patients had attempted drainage of undrained collections that were diagnosed on a CT scan, only one was successful. In the other 2 patients, drainage was unsafe due to proximity of the collection to stomach and bowel. There was one 90-day post-operative mortality recorded. This patient was high risk with fatty liver disease, obesity and died of postoperative portal vein thrombosis 1 week after discharge. Seven patients underwent re-laparotomy after surgery; 2 had postoperative primary haemorrhage, 2 had bile leaks, and 1 had a gastroenterostomy leak. Two patients had Grade C fistulas requiring re-operation. One patient had a right hemicolectomy along with a PPPD and was re-operated on day 5 for a colonic leak secondary to POPF. The other had a completion pancreaticosplenectomy as a result of the pancreatic stent eroding through the jejunal limb of the pancreaticojejunostomy. The other 5 all underwent laparotomies, washout with adequate drainage.

Discussion

Despite major advances in pancreatic surgery, POPF continues to be a common complication after PD occurring in 9-14% of patients even at high volume centers [1-10]. Classical risk factors associated with POPF have been described in the literature and include the following: patient demographics, pancreatic gland texture, pancreatic duct size, pathology of periampullary lesion, anastomotic technique, and surgeon volume [15-18].

Nutritional support is the key element of conservative therapy in patients with POPF, as most of them are in a catabolic state and attempts to accelerate fistula closure usually involve prolonged fasting. However, the decisions between PN and enteral nutrition have not been compared in many randomized trials [19]. Experiments with healthy individuals have demonstrated that intravenous feeding does not stimulate pancreatic secretion, and thus is a reasonable solution when prolonged nutritional support is needed without increasing the exocrine pancreatic function [20]. Previous research has suggested that long-term TPN leads to negative functional and morphological changes, not only within the gastrointestinal mucosa but also atrophy and dys-

function of the exocrine pancreas [21]. Enteral feeding beyond the ligament of Treitz is commonly preferred over the intravenous route due to lower costs and the potential advantage of avoiding infectious and metabolic complications related to the parenteral route. This hypothesis was substantiated in several clinical trials demonstrating that enteral nutrition can be safely used in patients with various disorders, including POPF [22]. In an open-label, randomized, controlled clinical trial, it was demonstrated that enteral nutrition was effective for the treatment of postoperative pancreatic fistula and TPN was associated with higher costs [23]. Our study has no comparison but we have a much lower incidence of Grade C fistulas when compared to other series [24]. Additionally, there is evidence that TPN reduces pancreatic secretion by 50% to 70% compared with enteral nutrition [25,26].

The role of somatostatin analogue in the management and prevention of POPF is also controversial.

A meta-analysis by Connor, et al. demonstrated that somatostatin and its analogues (octreotide) did not reduce the mortality rate after pancreatic surgery but did reduce both the total morbidity and pancreas-specific complications [27]. A Cochrane review by Koti, et al. concluded that somatostatin analogues reduce perioperative complications but do not reduce perioperative mortality but they do shorten hospital stay in patients undergoing pancreatic surgery for malignancy [28]. Another study corroborated the results and estimated that the routine use of octreotide would prevent 16 patients from developing complications per 100 patients treated and would save \$1642 per patient [29]. Randomized, controlled, double blind, multi-institution studies from Europe have evaluated subcutaneous octreotide as prophylaxis against complications in patients undergoing elective pancreatic resection. These trials reported that octreotide (at a dosage of 100 mg three times a day) significantly reduced the overall complication rate [30-33].

On the other hand a prospective, randomized trial from the M.D. Anderson Cancer Centre evaluated 110 patients undergoing only pancreaticoduodenectomy showed no benefit to the use of somatostatin analogues. The rates of clinical pancreatic fistula and perioperative complications were 6% and 25% in the control group and 12% and 30% in the octreotide group [34]. A systemic review by Ling and Irving [35] disagreed with the use of peri-operative somatostatin analogue therapy, as there was no reduction in postoperative complications. Another prospective randomized trial in Northern America concluded that there was no benefit of somatostatin analogue therapy to prevent POPF [36].

One study has shown that postoperative pancreatic fistula, leak, or abscess was significantly lower among patients who received pasireotide than among patients who received placebo (9% vs. 21%) and this was consistent among 220 patients who underwent pancreatic

coduodenectomy [37].

An online survey was conducted by the European-African Hepato-Pancreato-Biliary Association (E-AH-PBA) in which 108 centres performing pancreatic surgery were contacted via email. The survey focused on the use and timing of drainage, nutrition strategies, provision of somatostatin and antibiotic therapies, imaging strategy and indications for reoperation when POPF is diagnosed after pancreatic surgery. 55 centers completed the survey and they disclosed significant disagreements worldwide regarding the management of POPF after both PD and distal pancreatectomy with regards to the route of nutrition and the use of somatostatin analogue therapy [38].

In the prevention of pancreatic fistula, the use of somatostatin analogue therapy and PN is therefore controversial and is used by some surgeons. In the actual treatment of an established postoperative pancreatic fistula, the value of a specific leak protocol has never achieved such a significant result in terms of mortality. This reduction in mortality has, however been achieved in return for an increase in hospital stay in patients who were treated by our leak protocol.

Conclusion

Although our hospital stay is prolonged, our institutional practice has good results with a Grade C POPF incidence of 0.4% that is much lower than what is in literature [24]. Prospective randomized controlled trials are needed in this area, with clearly defined criteria on indications, dose and timing of administration to assess the potential advantage of concomitant use of octreotide and PN. We think this management of pancreatic leaks have promising results.

Conflict of Interest

Rohan Thakkar and other co-authors have no conflict of interest of this study.

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