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Postoperative narcotic use is associated with development of clinically relevant pancreatic fistulas after distal pancreatectomy

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ABSTRACT

Background. Various strategies to decrease postoperative pancreatic fistula after a distal pancreatectomy have proved unsuccessful. Because narcotics can cause spasm of the sphincter of Oddi and thereby increase pressure within the pancreatic duct stump, we hypothesized that increased narcotic use would be associated with increased occurrence of clinically relevant postoperative pancreatic fistula after distal pancreatectomy.

Methods. Retrospective analysis of consecutive distal pancreatectomies (2011–2016) was performed. Postoperative narcotic use was calculated in morphine equivalents. Postoperative pancreatic fistula was graded according to the International Study Group on Pancreatic Surgery. Perioperative variables were evaluated using multivariate logistic regression with clinically relevant postoperative pancreatic fistula as the dependent outcome.

Results. In the study, 310 distal pancreatectomies were analyzed (61% robotic, 20% open, 19% laparoscopic). Average age was 62 (53% female), and median total dose of morphine equivalents was 424 mg (interquartile range 242–768). Clinically relevant postoperative pancreatic fistula occurred in 21.6%. Clinically relevant postoperative pancreatic fistula and not clinically relevant postoperative pancreatic fistula cohorts were similar in most demographics and operative variables, but clinically relevant postoperative pancreatic fistula patients had fewer stapled transections (80 vs 90%, $P = .025$), less pancreatic cancers (11 vs 35%, $P < .001$), and greater median total morphine equivalents (577 vs 403 mg, $P < .009$). On univariate analysis, clinically relevant postoperative pancreatic fistula was associated with body mass index, nonstapled transection, suture ligation of the PD, a nonpancreatic cancer pathology, prophylactic octreotide, and total morphine equivalents >424 (cohort median). On multivariate analysis, only pancreatic cancer pathology was protective against a clinically relevant postoperative pancreatic fistula (odds ratio 0.24, confidence interval, 0.10–0.50, $P = .001$), while increasing total morphine equivalents were predictive of a clinically relevant postoperative pancreatic fistula (odds ratio 1.13, confidence interval, 1.01–1.27, $P = .035$) with a 13% increased risk for every approximate ≈100 mg increase in total morphine equivalents.

Conclusion. In this retrospective analysis, postoperative narcotic use was associated with the development of clinically relevant postoperative pancreatic fistula after distal pancreatectomy. Limiting narcotic use may be one of the few available mitigating strategies against the development of a clinically relevant postoperative pancreatic fistula after distal pancreatectomy.

Postoperative pancreatic fistula (POPF), or drainage of pancreatic secretions from the transected edge of the pancreas after distal pancreatectomy (DP), can occur in up to 60% to 70% of cases.[1] Clinically relevant POPF (CR-POPF), i.e. POPFs that require alterations in clinical management, comprise up to 20% to 30% of fistulae after DP.[2-8] These complications are a substantial source of prolonged hospital stays (both index hospitalization and readmissions) and are associated with a doubling of hospital costs according to one

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retrospective study.[7] Given this important problem in pancreatic resections, various strategies have been evaluated to mitigate the risk of CR-POPF after DP. These have included modifying the site of pancreatic transection, evaluating various techniques of stump closure (suturing of pancreatic duct, stapled transection, modified pancreaticojejunostomy), and the use of different adjuncts, such as stapler reinforcements, mesh coverage, fibrin sealants, and autologous tissue patches.[1-5,8-13] Overall, these measures have been met with variable success, but despite these attempts, CR-POPF remains a major source of postoperative morbidity after DP.

The sphincter of Oddi (SO) is a muscular complex within the second portion of duodenum that controls flow of biliary and pancreatic secretions. A retrospective analysis of DP patients noted decreased risk of CR-POPF in those undergoing preoperative, endoscopic sphincterotomy and/or stenting of the pancreatic duct (PD), suggesting that an intact SO could increase risk of POPF due to increased back pressure in the pancreatic duct.[14] Narcotic pain medications, while providing adequate analgesia after pancreatic surgery, also cause dysfunction of the SO. Morphine, a commonly used narcotic, causes contraction of the SO leading to increases in basal pressure, as well as increased frequency and amplitude of contractions, even at subanalgesic dosing.[15] SO dysfunction, both idiopathic and secondary to SO muscular hypertrophy in the setting of chronic opioid use, can lead to dilation and increased pressure within the PD.[16,17] This increase in PD pressures may predispose to development of a CR-POPF after DP by stressing the freshly transected edges of the pancreatic remnant and the occluded PD margin.

Given the evidence that narcotics can induce SO dysfunction with a consequent increase in PD pressure, we hypothesized that postoperative narcotic use would be associated with development of CR-POPF after DP.

Methods

Patient cohort

After approval from the institutional review board of the University of Pittsburgh, a retrospective review of a prospectively maintained database of all consecutive DPs performed at the University of Pittsburgh Medical Center between July 2011 and October 2016 was performed. The cohort included patients undergoing DP via open, laparoscopic, and robotic approaches. The method of pancreatic transection and remnant closure was determined by surgeon preference. Closed suction peritoneal drains were utilized in nearly all patients, but our policy of drain management evolved throughout this study period, commensurate with emerging data supporting early drain removal. Thus, although surgeons may have varied in the exact timing and criteria for drain removal, all surgeons typically used an early drain removal policy (postoperative [POD] 3–5) during this study period based on amylase levels in the drain fluid obtained on PODs 1 and 3. Prophylactic octreotide, defined as use beginning within 24 hours of the operation, was used at surgeon discretion.

Data collection and definitions

Patient demographic variables collected included age, sex, body mass index (BMI), American Society of Anesthesiologist (ASA) class, Charlson Comorbidity Index scores, and type of pathology. Operative data included operative approach, concomitant splenectomy and/or resection of other organs, location of pancreatic transection and length of resected specimen, method of transection (stapler with specific stapler load utilized, hand-sewn, or energy device), suture ligation of main pancreatic duct, estimated blood loss (EBL), need for intraoperative blood transfusion, and operative time. While pancreatic duct diameter and gland texture are known risk factors for development of POPF after a pancreatoduodenctomy, these characteristics have not proven to be risk factors for POFP after DP, and as such, were not dictated regularly for DPs by the operating surgeons at our institution.[18-20] The primary outcome of interest was development of CR-POPF (grades B and C), which was defined and characterized according to the International Study Group on Pancreatic Surgery criteria.[21,22] Briefly, CR-POPF is defined as amylase-rich drainage from the pancreatic remnant (>3 times the upper serum limit of normal on or after POD 3) meeting one of the following criteria: 1) persistence >3 weeks, 2) necessitating change in medical management (need for antibiotics, somatostatin analogues, blood transfusions, and/or enteral/parenteral nutrition, 3) requirement for percutaneous or endoscopic interventions, 4) requirement for reoperation, or 5) organ failure of death. Grade C POPFs are designated specifically as a POPF leading to organ failure or death. Biochemical leaks (formerly categorized as grade A), which are asymptomatic, self-limiting leaks that do not alter medical management, were not captured. All outcomes were followed to 90 days.

The postoperative use of opioid narcotic pain medication was collected and abstracted via the electronic medication administration database and pharmacy medication records. All narcotics (intravenous, enteral, intramuscular, and transdermal formulations) administered within the postoperative hospitalization were recorded and converted to total milligram (mg) of oral morphine equivalents (MEQ). Due to our strategy of early drain removal at our institution, total MEQ administered were characterized for the early postoperative period (days 0–5), and for the complete duration of the operative hospitalization. The use of a patient-controlled analgesia system was documented, as was the use of a structured enhanced recovery after surgery (ERAS) pathway. Given the potential for acquired opioid tolerance, preoperative narcotic use was also documented and included in the intent to treat analysis.

Statistical analysis

The STATA (College Station, TX) statistical software program was used to perform statistical analysis. Descriptive statistics were utilized to describe the cohort with categorical data analyzed as frequencies and percentages, normally distributed continuous data as means and standard deviations, and non-normally distributed as medians with the interquartile range (IQR). Normally distributed data was compared with 2-tailed unpaired *t* tests, while Kruskal-Wallis and Wilcoxon rank-sum tests were used for non-parametric data. The association between narcotics and CR-POPF was tested by examining the total MEQ received during the index hospitalization and for POD 0 to 5, median MEQ, MEQ at the IQR, and increasing doses of morphine. Independent risk factors for development of CR-POPF after DP were determined using logistic regression analysis, in which Akaike information criteria were utilized to build multivariate models by systemically eliminating potential variables with a P value > .3.

Results

Cohort characteristics

The 310 consecutive patients undergoing DP were included in the study (Table 1). For the overall cohort, median age was 62 years (range 21–93), with a slight female predominance (53%). Most patients had an ASA score ≥3 (77.4%) and the median BMI was 29. Forty-nine patients (15.8%) were treated with narcotic pain medications prior to operation. Only about one-third of the cohort (29.7%) had pancreatic ductal adenocarcinoma (PDA), while the majority of procedures were performed for cystic, benign, neuroendocrine

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