Negligible Effect of Selective Preoperative Biliary Drainage on Perioperative Resuscitation, Morbidity, and Mortality in Patients Undergoing Pancreaticoduodenectomy

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Objective: To examine the effect of selective preoperative biliary drainage (BD) on perioperative resuscitation, morbidity, and mortality in patients undergoing pancreaticoduodenectomy. Biliary drainage prior to pancreaticoduodenectomy remains controversial. Proponents argue that it facilitates referral to high-volume tertiary centers, while detractors maintain that it increases surgical morbidity and mortality.

Design: Retrospective analysis of single-institution tumor registry database.

Setting: University medical center.


Main Outcome Measures: Clinicopathologic data were reviewed and analyzed among patients who did and did not receive BD for their association with perioperative outcomes. \( \chi^2 \) Analysis, independent-samples t tests, and Mann-Whitney U tests were used as appropriate.

Results: Fifty-six patients (62%) underwent BD, and 34 (38%) did not. Intraoperative bile cultures were positive for 1 or more species of microorganisms in 88% of stented patients (35 of 40). There were no significant differences in fluid requirements, transfusion requirements, or surgery duration between patients who did and did not undergo BD. Estimated blood loss was increased in patients who received BD (625 mL vs 525 mL in patients who did not undergo BD; \( P = .03 \)), while reoperation was significantly more common in nonstented patients (4% vs 15% in patients who did not undergo BD; \( P = .02 \)). Intensive care unit stay, overall length of stay, pancreatic leak/abscess/fistula, infectious complications, postoperative percutaneous drainage, hospital readmission, and 30- and 90-day mortality were not significantly different between the 2 groups.

Conclusions: Although preoperative biliary stents may complicate the intraoperative management and lessen the postoperative complications of patients undergoing pancreaticoduodenectomy, only estimated blood loss and reoperation were significantly different in this cohort. Further study may reveal patient subgroups who may specifically benefit or suffer from preoperative biliary stenting. Currently, selective preoperative BD appears appropriate in the multidisciplinary management of patients with periampullary lesions.

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Given the increased use of endoscopic ultrasonography and decreased use of endoscopic retrograde cholangiography in the diagnostic evaluation of periampullary lesions, our center has favored a more selective approach to preoperative biliary stenting. Consequently, we sought to determine the effect of selective preoperative BD on postoperative morbidity and mortality following pancreaticoduodenectomy. Furthermore, given the possibility of increased periportal inflammation from stent placement leading to a potentially more challenging periportal dissection, we also sought to determine the effect of stent placement on intraoperative factors, such as estimated blood loss (EBL), surgery duration, and crystalloid and colloid resuscitation.

### RESULTS

#### CLINICOPATHOLOGIC AND TREATMENT CHARACTERISTICS

Between October 2003 and May 2008, 90 patients underwent surgical resection with curative intent for periampullary lesions at a single institution. Table 1 depicts the clinicopathologic characteristics of the entire cohort of patients. The median age was 66 years (range, 22-89 years), 53% were male, and 60% were considered American Society of Anesthesiologists class 3. Eighty-seven percent of patients had a malignant diagnosis, of whom the majority were diagnosed with adenocarcinoma of the exocrine pancreas. Six percent of patients were ultimately determined to have chronic pancreatitis, despite the radiographic appearance of a focal mass within the pancreatic head. An additional 7% had benign tumors, predominantly noninvasive intraductal papillary mucinous neoplasms.

Preoperative gemcitabine hydrochloride–based chemotherapy was administered to 2 patients (2%) for 3 and 7 months, respectively. Right colectomy was performed in 1 patient for focal involvement of the hepatic flexure, and 11% of patients (n=10) underwent venous resection of the portal vein–superior mesenteric vein confluence. Vascular reconstruction was accomplished by primary repair in 9 of these 10 cases. The majority of patients underwent classic pancreaticoduodenectomy including a partial gastrectomy.

#### PREOPERATIVE BD AND BILIARY SUPERINFECTION

As depicted in Table 1, 62% of patients underwent preoperative BD. Forty-four patients (79%) underwent BD prior to referral for surgical consultation. Among our multidisciplinary treatment team, principal indications for BD included right upper quadrant pain, pruritus, acute renal insufficiency, and anticipation of a several-week delay in preparation for curative resection because of medical comorbidities. Approximately 40% of patients received stents for an asymptomatic elevated serum bilirubin level. The majority of these interventions were performed on presentation to an outside facility without the benefit of multidisciplinary evaluation.

Biliary drainage was accomplished endoscopically in 51 of 56 patients (91%), and 5 patients required percutaneous procedures. Among these 5 patients, 1 presented with painless jaundice and a serum bilirubin level greater than

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### METHODS

From October 2003 through May 2008, 90 patients underwent surgical resection for periampullary lesions at a single-institution tertiary referral center. These patients were prospectively entered and tracked in a computerized cancer center database. Following approval for this study by the institutional review board, clinical, pathologic, and treatment data were reviewed and analyzed with respect to the presence or absence of preoperative biliary stents.

Complications were ascertained by retrospective review of the medical record using standardized definitions. Pancreatic leak or fistula was determined in accordance with consensus criteria established by the International Study Group for Pancreatic Fistula. Mortality rates were recorded at both 30 and 90 days because deaths within this period can largely be attributed to the sequela of postoperative complications.

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**Table 1. Clinicopathologic Characteristics of 90 Patients Undergoing Pancreaticoduodenectomy for Periampullary Tumors**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
<td>66 (22-89)</td>
</tr>
<tr>
<td>Sex</td>
<td>M 48 (53), F 42 (47)</td>
</tr>
<tr>
<td>ASA class</td>
<td>2 30 (33), 3 54 (60), 4 6 (7)</td>
</tr>
<tr>
<td>Pathologic diagnosis</td>
<td>Pancreatic carcinoma 57 (63), Ampullary carcinoma 7 (8), Pancreatidts 5 (6), Duodenal carcinoma 3 (3), Cholangiocarcinoma 3 (3), Other 15 (17)</td>
</tr>
<tr>
<td>Preoperative biliary drainage</td>
<td>ERCP 51 (57), PTC 5 (6), Preoperative chemotherapy 2 (2), Vascular resection and reconstruction Primary repair 9 (9), Intercosption graft 1 (1)</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, American Society of Anesthesiologists; ERCP, endoscopic retrograde cholangiopancreatogram; PTC, percutaneous transhepatic cholangiogram.

Other includes neuroendocrine tumors (n=4), gastrointestinal stromal tumors (n=3), benign tumors (n=7), and metastatic tumors (n=1).
20 mg/dL (to convert to micromoles per liter, multiply by 17.104) and the remaining 4 patients had abdominal pain associated with biliary obstruction. In all 5 patients, endoscopic drainage was attempted, with an inability to cannulate the common bile duct. The median number of BD procedures performed per stented patient was 1 (range, 1-4), regardless of whether an endoscopic or percutaneous approach was used. The median duration of stent placement was 39 days (range, 3-218 days).

Among stented patients, serum total bilirubin level dropped from a mean (SD) of 13.8 (8.3) mg/dL to a mean (SD) of 3.0 (4.2) mg/dL (P < .001) following BD. Eighty-eight percent of stented patients (35 of 40) had biliary fluid sampled at the time of operation were demonstrated to have positive cultures for 1 or more species of microorganisms. The most prevalent organisms were enterococcus in 38%, gram-positive cocci in 22%, and gram-negative rods in 22%. Polymicrobial infection and fungi were documented in an additional 12% and 4% of cultures, respectively. Morbidity (40% culture positive vs 34% culture negative; P = .58) and mortality rates (3% culture positive vs 0% culture negative; P = .88) were not statistically different among those with culture-positive compared with culture-negative biliary fluid.

Stented patients were administered broad-spectrum antibiotics for 48 hours postoperatively while awaiting the results of operative cultures. Subsequently, patients with documented bactobilia completed a 7-day course of therapy with antibiotics tailored to the intraoperative culture results. Patients who did not receive stents were administered 1 dose of long-acting broad-spectrum antibiotic at the time of anesthetic induction and did not receive additional postoperative antibiotics unless clinically indicated.

PERIOPERATIVE MORBIDITY AND MORTALITY

The overall complication rate for the entire cohort was 41%. The 30- and 90-day mortality rates were 4% and 8%, respectively (Table 2). Table 2 also depicts the rates of other key morbidities, such as a 9% leak/abscess/fistula rate (as defined by International Study Group for Pancreatic Fistula criteria), an 8% reoperation rate within 90 days of initial operation, and a 9% 30-day hospitalization readmission rate. Use of interventional radiology for percutaneous abdominal drainage was only 4%, likely reflecting a combination of routine use of postoperative closed-suction drains, observation of a proportion of intra-abdominal fluid collections without clear evidence of abscess formation, and reoperation in 2 patients with nonresolving deep space surgical infections. Nineteen percent of patients developed any infectious complication, and 7% of patients developed a postoperative wound infection.

Median intensive care unit length of stay was 1 day (range, 0-38 days), and median hospital length of stay was 10 days (range, 6-77 days). These figures did not change appreciably over the duration of the study period.

COMPARISON OF PREOPERATIVELY STENTED AND NONSTENTED PATIENTS

Table 3 depicts the clinicopathologic characteristics among patients who did and did not undergo BD. Preoperative serum bilirubin level was almost 2-fold higher in the nonstented group (mean [SD], BD, 3.0 [4.2] mg/dL vs non-BD, 5.9 [8.6] mg/dL; P = .03). A significantly greater number of stented patients had regional lymph node metastasis (73% stented vs 32% nonstented; P = .001) and more advanced overall pathologic staging (stage 2, 78% stented vs 35% nonstented; P = .002). Despite these differences in pathologic stage, there was no significant difference in the status of resection margins. Eighty-two percent of stented patients and 85% of nonstented patients had an R0 resection (P = .34). Rates of R1 resection were also comparable at 12% among stented patients and 18% among nonstented patients. All other key demographic and laboratory values were not clinically or statistically different between the groups (Table 3).

There was a statistically significant increase in EBL in patients who received BD vs patients who did not receive BD (625 mL vs 525 mL; P = .03). No statistically significant difference was noted for intraoperative crystalloid infusion greater than 9 L (12% BD vs 6% non-BD; P = .47), surgery duration greater than 8 hours (21% BD vs 15% non-BD; P = .24), or red blood cell transfusion greater than 2 U (16% BD vs 9% non-BD; P = .28). These end points represent the upper limit of the interquartile range and were chosen for analysis to detect differences in outlier values. Similar results were obtained when values for the central tendency (mean and median) were analyzed (data not shown).

Rates of postoperative morbidities and mortality were similar between the cohorts (Table 4), with the exception of reoperation, which was significantly more common in patients who did not undergo BD (13% vs 4%; P = .02). The indications for reoperation included post-

Table 2. Perioperative Morbidity and Mortality Among the Entire Cohort of 90 Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Length of stay, d, median (range)</td>
<td>10 (6-77)</td>
</tr>
<tr>
<td>Length of ICU stay, d, median (range)</td>
<td>1 (0-38)</td>
</tr>
<tr>
<td>Any complication</td>
<td>37 (41)</td>
</tr>
<tr>
<td>Leak, abscess, fistula</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Any infection</td>
<td>17 (19)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Interventional radiology procedure</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Reoperation</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Readmission within 30 d of hospital discharge</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>4 (4)</td>
</tr>
<tr>
<td>90 d</td>
<td>7 (8)</td>
</tr>
</tbody>
</table>

Abbreviation: ICU, intensive care unit.

a Defined as intra-abdominal fluid collection requiring drainage and/or any measurable amount of drain fluid after postoperative day 3 with an amylase content greater than 3 times the serum amylase level.

b Includes wound infection (6), Clostridium difficile colitis (5), pneumonia (4), urinary tract infection (3), intra-abdominal abscess (2), bacterial peritonitis (2), bactereemia (1), Candida esophagitis (1), and fungal endocarditis (1).

c Includes 4 patients requiring percutaneous drainage of intra-abdominal collections.

d Includes postoperative hemorrhage (2), high-grade small-bowel obstruction (2), uncontrolled enterocutaneous fistula (2), and mesenteric ischemia (1). Excludes 2 patients who required tracheostomy for ventilator dependence.
operative hemorrhage in 2 patients (non-BD), high-grade small-bowel obstruction in 2 patients (BD), uncontrolled enterocutaneous fistula in 2 patients (non-BD), and mesenteric ischemia with infarction in 1 patient (non-BD). There was a trend toward lower mortality at both 30 days and 90 days in the stented group. However, these differences did not reach statistical significance (30 days: 2% BD vs 9% non-BD; \( P = .15 \); 90 days: 4% BD vs 15% non-BD; \( P = .10 \)).

The management of space-occupying lesions in the pancreatic head remains a challenging clinical problem. Although complete surgical resection typically represents the only potentially curative therapy for tumors in this location, the risks of surgical resection remain substantial.\(^{[10,11]}\) Consequently, efforts to optimize the perioperative management and outcome of these patients could translate into significant patient benefit, particularly as use of this surgical therapy becomes increasingly frequent.

Our study did not suggest an increase in surgical morbidity or mortality in patients who underwent preoperative BD. Specifically, we did not see any increase in infectious complications, including superficial and deep surgical site infections, contrary to the reports of other authors.\(^{[3-6]}\) We did note a high incidence of bacterial growth in intraoperative biliary cultures, although this did not seem to be associated with infectious complications. The lack of increased infectious complications may reflect our more aggressive policy of therapeutic antibiotics in the perioperative period directed against intraoperatively cultured pathogens.

In the current series, the rates of postoperative morbidities and mortality were more favorable in the stented patients than the nonstented patients, although only the rate of reoperation within 30 days of surgery was statistically different (4% stented vs 15% nonstented; \( P = .02 \)). We also noted a trend toward decreased 30- and 90-day mortality in stented patients. Whether this represents a bias in selecting patients for BD or is related to the higher...
The lack of increased postoperative morbidity with BD in this series represents a departure from the previous literature. Although selection bias may potentially explain these findings, our data in Table 3 indicate that, despite the differences in preoperative serum bilirubin level, regional lymph node metastases, and pathologic staging, patients who received BD were otherwise well-matched for standard clinicopathologic features compared with those treated without BD. Furthermore, patients who received BD tended to have more advanced disease, which should bias toward a higher morbidity rate. Additionally, the mean (SD) preoperative serum bilirubin level in the nonstented group of 5.9 (8.6) mg/dL indicates some degree of biliary obstruction, although perhaps not as severe as in the stented group, whose mean (SD) pretest bilirubin level was 13.8 (8.3) mg/dL. It is unclear if these numerical differences in bilirubin level are clinically meaningful in the absence of other established perioperative risk factors, such as synthetic liver dysfunction or cirrhosis. Moreover, despite these differences in serum bilirubin level and staging, it is possible that with refinements in endoscopic techniques and improvements in perioperative management, the current impact of selective preoperative BD on infectious and other morbidities following pancreaticoduodenectomy may not be as significant as previously shown.

Critics of previous studies examining the morbidity of preoperative BD in patients undergoing pancreaticoduodenectomy have maintained that the duration of preoperative drainage in those studies (range, 10-18 days) was insufficient to fully reverse the metabolic and immunological derangements associated with biliary obstruction. The current randomized controlled clinical trial of drainage vs direct operation (DROP) mandates a 4-week waiting period following biliary decompression prior to pancreaticoduodenectomy. Accordingly, our 39-day median duration of stent placement (which is primarily a function of logistical factors, such as referral patterns and the time necessary to perform additional preoperative evaluation) may have improved outcomes among stented patients and contributed to the negligible differences in perioperative morbidity and mortality observed among stented and nonstented patients.

In summary, preoperative placement of biliary stents in patients undergoing pancreaticoduodenectomy significantly increases blood loss, with nonsignificant increases in operative time and perioperative fluid resuscitation. In this cohort, these intraoperative considerations do not translate into increased perioperative morbidity and mortality, with the data overall showing negligible differences to improved outcomes in stented patients. Consequently, preoperative biliary stents may complicate the intraoperative surgical management but lessen the postoperative complications of patients with space-occupying lesions in the head of the pancreas. Ultimately, the question of the true impact of preoperative BD on outcome in patients undergoing pancreaticoduodenectomy remains unanswered without a randomized trial, and the results of the DROP trial are greatly anticipated. Until such time, selective preoperative BD appears appropriate in the current multidisciplinary management of patients with lesions in the head of the pancreas.

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Author Contributions: Drs Coates and Canter had full access to all the data in the study and take responsibility...
Joe Hines, MD, Los Angeles, California: The last 30 to 40 years have seen big improvements in the morbidity and mortality of pancreaticoduodenectomy, especially mortality. We have made improvements in diagnostic imaging and patient selection, but unfortunately, more than 50% of patients with resectable stage I pancreatic adenocarcinoma are never offered resection in the United States. As we learn more about pancreatic disease, early markers are identified, and the medical community understands the importance of offering resection, it is likely we will be performing more of these procedures in the future. Finding ways to improve perioperative morbidity will be important.

The authors have presented data that suggest that perioperative biliary stenting increases intraoperative blood loss, something that other groups have not reported. There have been about a dozen retrospective series looking at the use of biliary stenting and a half a dozen small prospective series. On balance, most of these studies don’t show a difference with regards to perioperative morbidity and mortality. One series of note from Memorial Sloan-Kettering in 1999 reported over 200 patients and found that preoperative biliary drainage was associated with increased infectious complications and perioperative mortality but no difference with regard to blood loss. Another study from Amsterdam [2001] found no difference in morbidity or mortality but that a third of the time the stents failed preoperatively. The M. D. Anderson group found a 2.5-fold increase in relative risk for wound infection following pancreaticoduodenectomy.

It’s always important to have a biostatistician involved in the evaluation of your data, but assuming that there is an increased risk of operative blood loss with biliary stenting, why so? Is a stent simply a surrogate for a more locally advanced lesion requiring more extensive dissection? Was there any difference in the staging between patients with and without a stent? How about the margin status?

Over the past year, we noted an increase in wound infections in our own patients. We engaged the infectious disease and hospital epidemiology group, and through a sophisticated analysis, they were able to identify a particular bacterium that we were not covering with our perioperative antibiotic prophylaxis. Our patients, like yours, had an especially high number of resistant enterococcal wound infections. We switched to piperacillin-tazobactam, and the infection rate has dropped significantly. Can you tell us your current perioperative antibiotic regimen, and do you adjust this based on the bile cultures that you obtain?

Your patients, on average, had an albumin of 3.0. Data from the VA found increased morbidity and mortality for patients undergoing pancreaticoduodenectomy with an albumin less than 3.3, higher than the usual 2.5 cutoff we are familiar with. Do you do anything for your patients who have low albumin to never require intensive care. How about the margin status?

With your data and the reported series, we probably can agree that there may be increased perioperative risk for patients who have preoperative biliary stenting and are scheduled for pancreaticoduodenectomy. On balance, we reserve stenting for patients who have severe, symptomatic jaundice, cholangitis, or patients who will receive neoadjuvant treatment.

Dr Bold: Our catchment area for referrals of patients with pancreatic lesions is very large. As a surrogate for the timeliness of referral, we looked at how long these stents had been in place.
in place preoperatively. The median time was 6 weeks, when patients may see a community gastroenterologist, a gastroenterologist at a referral center, and get through the diagnosis and radiologic studies before a surgeon is actually consulted. We observed that operations on these patients with protracted stenting seemed tougher. The portal dissections seemed more difficult with the subacute cholangitis that came along with the biliary contamination; we hypothesized that we were encountering a different population than had been reported by other tertiary referral centers that often coordinate the endoscopic evaluation.

Why do we see the increased blood loss, and is it a surrogate for advanced disease? Again, our hypothesis was that it was a surrogate for a contamination of the biliary tree, inflammation in the porta hepatis, and a more technically difficult operation. Tumor size was very similar between the 2 groups, as was extent of disease. We didn’t examine our margin status, so I can’t explain the difference in blood loss based on extent of disease. We simply feel that it is due to the complexity of the procedure in patients with prolonged biliary instrumentation and infection.

We have seen more and more infections with resistant enterococcus. During the study, we did change our antibiotic regimen to ertapenem [sodium] for a perioperative dose, routinely discontinued within 24 hours. We use biliary cultures to guide our postoperative antibiotic administration. Patients with enterococcus will get an additional 5 days of specific therapy. Perhaps this strategy has decreased the infectious complications, because we very actively look at the bacteria we isolate in the operating room to guide our postoperative protocol.

Hypoalbuminemia is clearly recognized as a marker for complications, especially after pancreaticoduodenectomy. Unfortunately, we can't often do much to restore nutritional status. The patients often arrive in a malnourished state because of the exocrine insufficiency and receive pancreatic enzyme supplementation from the time that we see them until the time of surgery. We do not use parenteral nutrition.

Regarding the indications for a postoperative admission to the intensive care unit, this can be a very prolonged operation in elderly patients with comorbidity. Most of our patients are ASA 3. We use comorbidities, age (not a hard cutoff, but an age greater than 70 gives us pause), time of day completing the surgical resection, and complexity of the case to decide about ICU care.

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