Association of Preoperative Biliary Stenting With Increased Postoperative Infectious Complications in Proximal Cholangiocarcinoma

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Background: The indications for preoperative biliary stenting in patients with obstructive jaundice are controversial. We evaluated the effect of preoperative biliary stenting on bacterobilia and infectious complications following surgical treatment of proximal cholangiocarcinoma.

Design: A retrospective review was performed of all patients undergoing surgical treatment of proximal cholangiocarcinoma.

Setting: A metropolitan cancer surgery service.

Patients and Methods: Seventy-one patients underwent palliative biliary bypass or curative resection of proximal cholangiocarcinoma from March 1, 1991, to April 1, 1997, and were entered into a prospective database. Forty-one patients underwent preoperative biliary intubation and stent placement. We analyzed patient, nutritional, laboratory, and operating room factors. Statistical evaluation was performed using Student t test and χ² analysis.

Main Outcome Measure: Data were recorded for a history of cholangitis, operative time, amount of blood loss, incidence of intraoperative bacterobilia, proportion of patients with postoperative infectious and noninfectious complications, and length of hospital stay.

Results: All patients (n = 14) with a history of preoperative cholangitis had been subjected to previous endoscopic retrograde cholangiopancreatography and/or percutaneous transhepatic biliary drainage. Groups were equivalent for risk for comorbidity, proportion undergoing curative vs palliative procedures, time spent in the operating room, and amount of blood loss. Patients with stents had a significantly lower bilirubin level (P = .005). Patients with stents had a significantly increased risk for bacterobilia (P = .001) and infectious complications (P = .03). Bacterobilia was present in 11 (100%) of 11 patients undergoing endoscopic stenting and in 15 (65%) of 23 patients undergoing percutaneous stenting. There was no increased risk for noninfectious complications, length of hospital stay, or mortality in patients with stents. In 10 (59%) of 17 patients with postoperative infectious complications and positive findings of intraoperative bile culture, the organism was synonymous.

Conclusions: Preoperative biliary stenting in proximal cholangiocarcinoma increases the incidence of contaminated bile and postoperative infectious complications. Endoscopic stents frequently do not relieve jaundice in high biliary obstruction and are rarely indicated, especially in light of their high contamination rate.

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Here are approximately 4500 new cases of cholangiocarcinoma per year in the United States. Proximal cholangiocarcinomas constitute 30% to 60% of these tumors. The prognosis is poor in these patients, with untreated patients having a median survival of 3 months. In almost all series, rates of resection are low at patient presentation; yet surgery remains the mainstay of treatment. Surgical options for proximal cholangiocarcinoma include curative resection or a palliative biliary-enteric bypass. Despite recent technical advances and improved perioperative care, treatment of patients with proximal cholangiocarcinoma is still challenging. In recent series, whereas mortality rates have decreased significantly over the last several years, morbidity rates remain high. A number of studies have indicated that surgery for severe obstructive jaundice is associated with increased risk for complications. Due to this high risk, investigators have studied the role of biliary drainage for preoperative preparation. These studies often have included heterogeneous groups with respect to cause of bile duct obstruction. Patients with benign and malignant causes of proximal and distal bile duct obstruction have been grouped...
PATIENTS AND METHODS

From March 1, 1991, to April 1, 1997, 90 patients with proximal cholangiocarcinoma underwent evaluation by the Hepatobiliary Surgical Division at Memorial Sloan-Kettering Cancer Center, New York, NY, and were entered in a prospective database. Proximal cholangiocarcinoma was defined as tumors originating in the common, right, or left hepatic duct. Of these 90 patients, 10 underwent nonoperative palliation, 9 underwent exploration and biopsy alone, and 71 underwent a curative resection or palliative biliary bypass. Of these 71 patients who form the basis for our study, 42 had a stent in the preoperative period, whereas 29 did not. All patients were admitted to the hospital and underwent preoperative history, physical examination, and laboratory analyses, including determination of serum bilirubin concentration.

Preoperative biliary stents were defined as endoscopic, percutaneous transhepatic, nasobiliary, or T-tube stents that crossed the tumor and/or the ampulla of Vater. Of the 42 patients with stents, 23 underwent percutaneous transhepatic intubation; 13, endoscopic intubation; and 3, T-tube placement. One patient had a nasobiliary drain; another, percutaneous transhepatic and endoscopic stents; and another, endoscopic and nasobiliary stents.

Careful analysis of factors associated with perioperative morbidity was undertaken. Patient factors analyzed were age, preoperative episode of cholangitis, and comorbidity. Comorbidity was defined as the presence of diabetes mellitus, coronary artery disease, or hypertension.

Nutritional factors analyzed included percentage of weight loss and serum albumin concentrations. In addition, biochemical studies included serum urea nitrogen, serum creatinine, and total bilirubin levels.

All but 3 of the operations were performed by 2 surgeons (Y.F. and L.H.B.). Of the 42 patients with preoperative stents, 18 (43%) had curative surgery and 24 (57%) had a palliative biliary bypass. In the 29 patients without stents, 12 (41%) had curative operation and 17 (59%) had a palliative bypass. Of those patients undergoing curative resection, 22 (73%) underwent liver resection. Of those patients undergoing palliative biliary bypass, 38 (93%) underwent bypass to the right sectoral hepatic duct or segment III duct or hepaticojejunostomy. Operating room factors analyzed were the time under anesthesia, operating room blood loss, and results of routine intraoperative bile cultures. Blood transfusion data included the percentage of patients who received a transfusion during their hospital stay and the median number of units transfused. Other factors compared included length of stay, which was tabulated as total hospital stay and time from the date of operation until discharge home. Reoperation and mortality rates were also determined for both groups.

Complications were retrospectively recorded by evaluation of the prospective database, hospital records, and chart review. These were grouped as infectious and noninfectious in nature. Infectious complications recorded were wound infection, intra-abdominal abscess, pneumonia, cholangitis, Clostridium difficile colitis, and Candida esophagitis. Wound infections were defined as a superficial or deep infection that required antibiotics and/or wound drainage. Intra-abdominal abscesses were defined as an intra-abdominal collection associated with fever and/or leukocytosis that required drainage, culture of which yielded positive findings. Pneumonia was defined as an infiltrate on chest radiogram requiring antibiotic treatment. Cholangitis was defined as positive findings of a bile culture associated with fever. Noninfectious complications included hemorrhage, anastomotic leak, liver necrosis, fascial dehiscence, biloma, biliary fistula, renal failure, cardiac arrhythmia, prolonged ileus, severe ascites, and pancreatitis.

Statistical analyses were performed using χ² for categorical variables and Student t test for continuous variables. Significance was defined as P<.05. Unless otherwise indicated, data are given as mean ± SEM.

RESULTS

DEMOGRAPHICS

Seventy-one patients underwent operative treatment during the 6 years studied. Demographic data are listed in Table 1. There was no significant difference in age, sex distribution, history of cholangitis, or comorbidity between groups. A history of cholangitis was present in 24% of patients (n = 10) who had a previous stent, compared with 14% (n = 4) in those without a previous stent (P = .30).

NUTRITIONAL AND BIOCHEMICAL MEASUREMENTS

Nutritional and biochemical measurements are listed in Table 2. The average weight loss was 6% ± 1% in the no stent group vs 8% ± 1% in the stent group (P = .17). There were no significant differences in preoperative albumin, serum urea nitrogen, and creatinine levels. As expected, in the no stent group, the mean preoperative bilirubin level (222.3 ± 46.2 µmol/L [13.0 ± 2.7 mg/dL]) was significantly higher than in the stent group (95.8 ± 13.4 µmol/L [5.6 ± 0.9 mg/dL]) (P = .005).

OPERATIVE FACTORS

In an effort to evaluate the potential additional operative difficulty with the inflammation that commonly
accompanies stent placement, operating room and blood transfusion factors were analyzed (Table 3). There were no significant differences in the time under anesthesia (no stent group, 253 ± 20 minutes; stent group, 273 ± 16 minutes; P = .42), operating room blood loss (no stent group, 1083 ± 194 mL; stent group, 855 ± 191 mL; P = .42) or type of operation. In addition, the percentage of patients who received a blood transfusion during their hospital stay (48% vs 38%; P = .43) and the median number of units of blood transfused (2 vs 3 U; P = .12) was similar between groups (no stent vs stent, respectively).

## COMPLICATIONS

Complications were recorded as total number of complications and percentage of patients with a complication and were divided into infectious and noninfectious categories (Table 4 and Table 5). The number of noninfectious complications was similar in the stent group (n = 17) and the no stent group (n = 12; P = .85). However, there were significantly more infectious complications in the stent group (n = 28) compared with the no stent group (n = 11; P = .03). Some patients had more than 1 complication, and if expressed as percentage with a complication, patients with stents had a 52% chance (22 of 42 patients) of having an infection compared with a 28% chance (8 of 29 patients) in patients without stents (P = .05). The percentage of patients with a noninfectious complication was similar between groups (stent vs no stent group, 38% [11/29] vs 33% [14/42]; P = .80). There was no significant increase in any 1 complication
BACTEROBILIA

Contamination of bile has been associated with biliary tract manipulation, and therefore we examined intraoperative bile culture data (Table 6). Bile culture results from intraoperative cultures were available in 61 (86%) of 71 patients. Since a large number of patients underwent preoperative diagnostic endoscopic retrograde cholangiopancreatography (ERCP), we evaluated the incidence of bacterobilia in patients subjected to this procedure. Intraoperative bile cultures yielded positive findings in 7 (37%) of 19 patients who did not undergo preoperative diagnostic ERCP, whereas these cultures were positive in 23 (55%) of 42 patients who did undergo preoperative ERCP (P = .20). There was a significant increase in bile cultures that yielded positive findings in patients in the stent group (69%, n = 27) vs those in the no stent group (14%, n = 3; P = .001). In addition, there was a significantly increased incidence of bacterobilia in patients who had an endoscopic stent compared with those who had a percutaneous transhepatic stent (100% [11/11] vs 65% [15/23], respectively; P = .03). Finally, we found that the time that a stent was in place was associated with a significantly greater incidence of positive findings of intraoperative bile cultures. Those stents that were in place for less than 28 days were associated with a 53% incidence (10 of 19 patients) of bacterobilia, compared with an 89% incidence (16 of 18 patients) of bacterobilia in stents in place for longer than 28 days (P = .02).

BILE CULTURES VS CULTURES FROM INFECTIOUS COMPLICATIONS

There were 31 intraoperative bile cultures that yielded negative and 30 that yielded positive findings (data not available for 10 patients). In those patients with positive findings, postoperative infectious complications were seen in 17 (ie, wound infection [n = 7], intra-abdominal abscess [n = 5], pneumonia [n = 2], cholangitis [n = 2], and Clostridium difficile colitis [n = 1]). At least 1 organism in the intraoperative bile culture was similar to the organism(s) that grew from the postoperative infectious complication culture in 10 (59%) of the 17 patients. The greatest similarity was seen in findings of intraoperative bile and wound cultures, where there was some agreement in 6 of the 7 patients. The types of organisms obtained from intraoperative bile cultures are shown in the following tabulation:

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of Cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus species</td>
<td>21</td>
</tr>
<tr>
<td>Candida species</td>
<td>7</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>7</td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>5</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>5</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>4</td>
</tr>
<tr>
<td>Pseudomonas species</td>
<td>3</td>
</tr>
<tr>
<td>Enterobacter coli</td>
<td>3</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>3</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>1</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>1</td>
</tr>
</tbody>
</table>

In some cultures, more than 1 organism was present.

LENGTH OF HOSPITAL STAY

There was no significant difference in hospital stay (stent group, 17 ± 8 days; no stent group, 16 ± 7 days), postoperative stay (stent group, 14 ± 5 days; no stent group, 14 ± 7 days), reoperation rate (stent group, 10%; no stent group, 12%), or mortality (stent group, 5%; no stent group, 14%).

COMMENT

Our retrospective study compares 2 homogeneous groups of patients with proximal cholangiocarcinoma. The patients were well matched with respect to age, history of cholangitis, comorbidity, and weight loss. The major difference is the presence of a biliary stent with associated improvement in serum bilirubin level in the stent group. We have shown that the presence of a preoperative biliary stent before curative or palliative surgery for hilar cholangiocarcinoma is significantly associated with increased infectious complications. Patients with preoperative stents had 28 infectious complications compared with 11 infectious complications in those patients without stents (P = .03). Routine placement of biliary stents in patients with potentially resectable tumors cannot be endorsed.

The role of preoperative biliary drainage has been examined previously. The difference in most of these studies compared with ours is mainly that the previous trials enrolled patients with lesions at varying locations in the biliary tree and some patients with benign disease.

McPherson et al14 randomized 65 patients with low and high malignant bile duct obstruction to preoperative percutaneous transhepatic biliary drainage followed by laparotomy vs laparotomy alone. Drainage reduced the serum bilirubin level as expected, but there was no difference in overall postoperative mor-

Table 6. Preoperative Intervention and Bacterobilia*

<table>
<thead>
<tr>
<th>Preoperative Intervention (No. of Patients)</th>
<th>Intraoperative Bile Cultures, % With Positive Findings</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ERCP (19)</td>
<td>37</td>
<td>.20</td>
</tr>
<tr>
<td>No stent group (22)</td>
<td>14</td>
<td>.01</td>
</tr>
<tr>
<td>Stent group (39)†</td>
<td>69</td>
<td>.001</td>
</tr>
<tr>
<td>Percutaneous (23)</td>
<td>65</td>
<td>.03</td>
</tr>
<tr>
<td>Endoscopic (11)</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

*Intraoperative bile culture data were available in 61 of 71 patients. ERCP indicates endoscopic retrograde cholangiopancreatography. Groups are described in the “Patients and Methods” section.
†Diagnostic ERCP was performed in the preoperative period.
‡Bile culture data were available in 39 patients. Five patients had a nasobiliary stent, T-tube, or a percutaneous stent and endoprosthesis and were not included.
bidity or mortality. Therefore, it was concluded that there was no proven place for preoperative percutaneous transhepatic biliary drainage in the management of malignant obstructive jaundice. In a randomized trial by Hatfield et al, a similar conclusion was made after studying patients with benign and malignant obstructive jaundice.

In a study evaluating the effect of preoperative endoscopic biliary drainage, Lai et al randomized 87 patients with high and low malignant biliary obstruction to undergo laparotomy or endoscopic biliary drainage followed by exploration. There was a significant reduction in serum bilirubin concentrations in the stent group but no difference in morbidity or mortality between groups.

The only prospective, randomized study that has shown a benefit with preoperative biliary drainage included patients with low bile duct obstruction and endoscopically placed drains. There were fewer complications in the patients undergoing preoperative drainage. That study has been criticized due to the high incidence of cholangitis in the group without preoperative drains, and the presence of clear signs of infection without drainage before operation is the likely reason for the increased rate of complications in that group.

In our study, patients who had a preoperative stent placed had a 69% incidence of positive results of bile cultures, compared with 14% incidence in patients without a preoperative stent (P = .001). Also, there was a significantly higher incidence of positive findings in bile cultures in patients who had an endoscopic stent (100%), compared with patients with a percutaneous stent (65%; P = .03). The bile infection rate in our study is similar to that in other studies. Investigators have reported that infected bile occurred in 61% to 95% of patients with percutaneous drains, with the figures varying with the position of the catheter tip. In addition, Karsten et al demonstrated that in patients undergoing pancreatic resection, bile cultures in the presence of a biliary endoprosthesis showed bacterial growth in 94%, compared with a 62% incidence in patients with percutaneous drains (P = .01). The cause of the increased infection rate with an endoprosthesis may be due to contamination when the stent is inserted or ascent of microorganisms from the open passage to the duodenum and subsequent reflux of duodenal contents. Nonetheless, it is clear that in our study and others, in the absence of a biliary stent, bile contamination is much less frequent.

In our study, stents that were in place for longer than 28 days were associated with a significantly higher bile infection rate (89%), compared with stents in place for less than 28 days (53%; P = .02). Various factors predispose to infections in the presence of biliary drains. Bacterial β-D-glucuronidase has been shown to lead to biliary sludge formation and colonization of bacteria on drains. Surface defects on drains may contribute to the process of bacterial adhesion and colonization. In addition, the presence of side holes in drains is thought to cause an accumulation of debris and sludge and to create surface irregularities that allow for bacterial attachment. The longer a stent is in place, the greater the likelihood that these mechanisms will be in effect.

Controversy still exists concerning the implications of infected bile in biliary tract surgery. Most investigators have shown that patients undergoing biliary tract operations are at a higher risk for development of postoperative sepsis if bacteria are present in their bile at the time of operation. In an experimental model of cholestasis in dogs, distal bile duct obstruction followed by biliary drainage resulted in infected bile. Subsequent construction of a biliary-digestive tract anastomosis was associated with an increase in the incidence of postoperative infective complications.

We found 17 infectious complications in the 30 patients with positive findings of bile cultures. There was a correlation between organisms cultured from infectious complications and bile in 10 of these 17 patients. Comparisons of bacteria between those found in bile and in cultures from infectious complications have frequently indicated close similarity in the types of organisms isolated. In a prospective evaluation of 644 patients undergoing biliary tract surgery, Wells et al found that organisms cultured from 27 wound infections correlated with organisms isolated from the bile in 17 (63%) of these patients. Others have shown a close correlation in bacteria between positive findings of postoperative blood cultures and bile culture data.

Whereas mortality rates from curative resection of hilar cholangiocarcinoma have decreased significantly in the last several years, morbidity remains a significant problem. Patterns of morbidity have not been well reported in this disease. Our analysis clearly indicates that infectious complications were the greatest source of postoperative morbidity. The use of preoperative biliary stents was associated with increased infectious complications in our series. Judicious use of biliary stents should be the rule in this disease, since prospective trials have not demonstrated their benefit, and since retrospective data document their potential harm. At present, an analysis of bile bacteria may help predict bacteria present in infectious complications after surgery for hilar cholangiocarcinoma. To help guide patient treatment, a knowledge of bile bacterial isolates may direct appropriate early antibiotic therapy before results are available from cultures taken from infectious complications.

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REFERENCES

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