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Risk factors for endoscopic retrograde cholangiopancreatography-related cholangitis: A prospective study

Post-ercp kolanjitte risk faktörleri: Prospektif çalışma

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Background/aims: *Cholangitis is one of the most morbid complications of endoscopic biliary drainage and among the commonest causes of endoscopic retrograde cholangiopancreatography-related death. The aim of this prospective study was to investigate the risk factors for the development of cholangitis after endoscopic retrograde cholangiopancreatography in a tertiary referral center.* ***Methods:*** *The study involved 503 consecutive patients with naive papilla who underwent endoscopic retrograde cholangiopancreatography. We included the cholangitis occurring within 72 hours after endoscopic retrograde cholangiopancreatography for all patients undergoing the procedure. All patients received antibiotic prophylaxis before endoscopic retrograde cholangiopancreatography. Factors including age, gender, presentation, nature of the papilla, therapeutic procedures, and the diagnosis were analyzed to predict post-endoscopic retrograde cholangiopancreatography cholangitis.* ***Results:*** *Median age was 61.2 ± 14.8 years and there were 274 (54.5%) women and 229 (45.5%) men. Seventeen (3.3%) patients (9 F, 8 M) developed cholangitis after endoscopic retrograde cholangiopancreatography. The risk of post-endoscopic retrograde cholangiopancreatography cholangitis development was most probable in patients with hilar cholangiocarcinoma. Post-endoscopic retrograde cholangiopancreatography cholangitis risk was significantly higher in patients with biliary dilatation and biliary stent insertion, and without periampullary diverticula (odds ratio, OR: 4.8, 4.4, 1.2, respectively). Total procedure duration was significantly prolonged and common bile duct diameter was significantly increased in patients who had cholangitis. Five patients (3 F, 2 M; 0.9%) died because of post-endoscopic retrograde cholangiopancreatography complicated sepsis.* ***Conclusions:*** *Increased common bile duct diameter, biliary dilatation, biliary stent insertion, prolonged total procedure time, and hilar cholangiocarcinoma have higher post-endoscopic retrograde cholangiopancreatography cholangitis risk. Moreover, the presence of periampullary diverticula was found to decrease cholangitis risk.*

Key words: Endoscopic retrograde cholangiopancreatography, cholangitis, risk factors

Amaç: *Kolanjit, endoskopik biliyer drenajın en morbid komplikasyonlarından biridir. Aynı zamanda endoskopik retrograt pankreatikografi ile ilişkili ölümün en sık sebepleri arasındadır. Bu prospektif çalışmanın amacı endoskopik retrograt pankreatikografi sonrası kolanjit gelişiminde risk faktörlerini araştırmaktır.* ***Yöntem:*** *Çalışmaya endoskopik retrograt pankreatikografi yapılan naif papillalı 503 hasta alındı. Tüm hastalarda endoskopik retrograt pankreatikografiden sonra 72 saat içinde gelişen kolanjit dahil edildi. Tüm hastalara endoskopik retrograt pankreatikografiden önce antibiyotik proflaksisi verildi. Post-endoskopik retrograt pankreatikografi kolanjitte risk faktörleri olarak yaş, cinsiyet, prezentasyon, papillanın durumu, terapötik prosedürler ve tanılar analiz edildi.* ***Bulgular:*** *Ortalama yaş 61.2 ± 14.8 idi. 274'ü (%54.5) kadın, 229'u (%45.5) erkek idi. Post-endoskopik retrograt pankreatikografi kolanjit 17 hastada (%3.3) (9 kadın and 8 erkek) gelişti. Post-endoskopik retrograt pankreatikografi kolanjit gelişiminde en sık hiler kolanjiokarsinomu risk faktörü olarak saptandı. Post-endoskopik retrograt pankreatikografi kolanjit riski biliyer dilatasyon, biliyer stent uygulaması ve periampuller divertikül olmayanlarda anlamlı olarak daha yüksek bulundu (sırasıyla, OR: 4.8, 4.4, 1.2). Kolanjit gelişenlerde total işlem süresi anlamlı olarak daha uzundu ve koledok çapı da anlamlı olarak artmış idi. Endoskopik retrograt pankreatikografi sonrası sepsis nedeniyle 5 hasta (3 kadın, 2 erkek; 0.9%) öldü.* ***Sonuç:*** *Artmış koledok çapı, biliyer dilatasyon, biliyer stent uygulaması, total işlem süresi ve hiler kolanjiokarsinoma post-endoskopik retrograt pankreatikografi kolanjitte artmış risk faktörleri olarak bulundu. Ayrıca, periampuller divertikül varlığında kolanjit riskinin azaldığı saptandı.*

Anahtar kelimeler: Endoskopik retrograt kolanjiopankreatikografi, kolanjit, risk faktörleri

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) can be associated with unpredictable complications. Infection is one of the most morbid complications of endoscopic biliary drainage and

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among the commonest causes of ERCP-related death. The rate of post-ERCP cholangitis and sepsis ranges from 0.5% to 8.0% (mean 4.3%) (1-4).

In most settings of acute cholangitis, it is unclear exactly how bacteria enter an obstructed biliary. Some studies showed that the incidence of bacteremia or appearance of endotoxemia was related directly to the pressure within the biliary system (5-8). Infection is unusual when the obstruction is due to a malignant process in a patient who presents with jaundice (9). However, ERCP can lead to bacterial contamination, proliferation, and cholangitis rapidly (10). An obstructed biliary system promotes bacterial translocation to normally sterile sites (11).

Diagnosis of cholangitis in the critical early phase of the disease is often difficult because clinical features may be obscure. Numerous studies have demonstrated high procedure-related morbidity rates for patients who undergo ERCP (3, 4, 12-15). Because these studies seldom include thorough follow-up data, the factors associated with risk of ERCP-related cholangitis remain obscure. Unlike in acute pancreatitis, well-accepted predicting factors for ERCP-complicated cholangitis are still largely unknown.

The aim of this prospective study was to investigate the risk factors for the development of cholangitis after ERCP in a tertiary referral center.

MATERIALS AND METHODS

Subjects

From December 2004 to June 2006, 503 consecutive patients with naive papilla who underwent ERCP in Türkiye Yüksek İhtisas Hospital were enrolled in this prospective study. Patients with previous endoscopic sphincterotomy (ES) and who were referred to our hospital for ERCP procedure while hospitalized in another center were excluded (to observe and standardize the possible complications). We included the cholangitis occurring within 72 hours after ERCP for all patients undergoing the procedure.

Study Design

All patients signed an informed consent for the endoscopic procedure. A registration form was completed by the endoscopist at the time of ERCP. To identify and to assess complications that occurred within one month of the procedure, a questionnaire was sent to all patients by post and the medical records were reviewed by a physician. Topical pharyngeal anesthesia was administered in all patients with 10% lidocaine spray. For premedication, midazolam (induction dose: 3-4 mg for younger and 2 mg for older patients) and/or meperidine (induction dose: 40-50 mg for younger and 25 mg for older patients) were used. Hyoscine N-butylbromide was used to slow intestinal motility. The dose of all medications was titrated according to patient need as well as duration of the procedure. All procedures were performed by two experienced ERCPists. Standardized techniques with the patients always positioned on the left side were used. ERCP procedures were performed by standard videoduodenoscope with 4.2 mm diameter accessory channels (Olympus; Japan). Blood pressure, heart rate and oxygen saturation were continuously monitored with automated pulse oximetry.

As a routine use, all patients received antibiotic prophylaxis (intravenous ciprofloxacin) before ERCP. Ultrasonography of the liver and biliary tract was performed for every patient on admission. All standard ES procedures were performed over a guide wire (Jagwire 0.035 inch, Boston Scientific; USA) after selective cannulation of the bile duct. A cutting current was used during sphincterotomy and was complemented by coagulation current in the case of immediate bleeding. The papillotome used was a cannulatome with a short nose and a 30-mm cutting wire (Wilson-Cook; USA). The contrast medium used during the endoscopic maneuvers was iopamidol (Iopamiro; Italy), a low osmolality, nonionic substance.

Cholangitis was defined as the development of fever of 38°C within 72 hours after ERCP. The diagnosis of acute cholangitis was made in the presence of abdominal pain, jaundice, fever and deranged liver biochemistry suggestive of biliary obstruction without evidence of other concomitant infections (including cholecystitis and pancreatitis).

Data on patient characteristics, ERCP indications and findings, cannulation techniques, devices used during the procedure, and complications were collected during the procedure, during the recovery period and, if necessary, during hospital admission.

Factors including age, gender, presentation, nature of the papilla, therapeutic procedures, and the diagnosis were analyzed to predict the post-ERCP cholangitis.

Statistical Methods

Results were expressed as mean ± standard deviation. For statistical comparison, the Student's t-test, chi-square test, one-way ANOVA and correlation test and Mann-Whitney U test were used whenever appropriate. Differences were taken as significant when $p<0.05$. The odds ratios (ORs) are presented with their 95% confidence interval (CI). All candidate independent variables were included in the model to identify the most important risk factors for cholangitis complication overall.

RESULTS

Five hundred three patients were included in the study. Median age was 61.2 ± 14.8 years; there were 274 (54.5%) women and 229 (45.5%) men. Seventeen (3.3%) patients (9 F, 8 M) developed cholangitis after ERCP. Demographic data and laboratory findings at presentation are shown in Table 1.

Pre-ERCP diagnosis of patients who had post-ERCP cholangitis were as follows: 6 cases with jaundice of unknown cause, 4 cases with jaundice with biliary mass, 3 cases with postcholecystectomy biliary pain, 3 cases with biliary pain and cholelithiasis, and 1 case with jaundice with pancreatic mass (Table 2).

The risk of post-ERCP cholangitis development was most probable in patients with hilar cholangiocarcinoma ($p<0.05$). The other diagnoses did not increase the risk of development of post-ERCP cholangitis ($p>0.05$) (Table 3).

Patients who underwent biliary dilatation had five times risk for the development of cholangitis in comparison with patients without dilatation ($p<0.05$). Post-ERCP cholangitis risk was significantly higher in patients without periampullary diverticula and with biliary stent insertion ($p<0.05$; OR: 1.2 and 4.4 for patients without periampullary diverticula and with biliary stent insertion, respectively) (Table 4).

Table 1. Demographic and biochemical data of all patients

	Cases without cholangitis n = 486	Cases with cholangitis n = 17	*p* Value
Age	60.6 ± 16.1	61.8 ± 13.5	0.978
Gender (F / M)	265 / 221	9 / 8	0.897
AST (0-40 U/L)	90.4 ± 113.3	65.2 ± 40.9	0.854
ALT (0-40 U/L)	116.7 ± 122.9	75.1 ± 58.9	0.348
ALP (38-155 U/L)	841.8 ± 836.8	725.9 ± 493.4	0.960
GGT (15-60 U/L)	385.8 ± 374.7	347.1 ± 342.9	0.697
Total bilirubin (0.1-2.0 mg/dl)	6.5 ± 9.3	10.4 ± 10.4	0.079
Direct bilirubin (0.1-0.8 mg/dl)	4.3 ± 6.5	7.1 ± 7.7	0.133
Amylase (28-100 U/L)	96.1 ± 225.6	49.1 ± 23.3	**0.030**
Platelet count (150-400x10 ^{9}/L)	299.3 ± 107.2	303.3 ± 185.0	0.525
INR	1.7 ± 14.5	0.99 ± 0.1	0.810

AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. GGT: Gamma glutamyl transpeptidase. ALP: Alkaline phosphatase. PT: Prothrombin time. INR: International normalized ratio.

Table 2. Complaints and diagnoses of patients at presentation

	Cases without cholangitis n = 486	Cases with cholangitis n = 17
Biliary pain and cholelithiasis	210 (43.2%)	3 (17.6%)
Unknown causes with jaundice	83 (17.1%)	6 (35.3%)
Postcholecystectomy biliary pain with jaundice	68 (14.0%)	3 (17.6%)
Biliary mass with jaundice	22 (4.5%)	4 (23.5%)
Pancreatic mass with jaundice	22 (4.5%)	1 (5.9%)
Cholelithiasis and biliary pancreatitis	21 (4.3%)	-
Cholecystectomy with jaundice	13 (2.7%)	-
Gall bladder mass with jaundice	10 (2.1%)	-
Preoperative cyst hydatid communicating with biliary tract	7 (1.4%)	-
Recurrent pancreatitis	5 (1.0%)	-
Postoperative cyst hydatid and bile leakage from drain	5 (1.0%)	-
Liver mass with jaundice	4 (0.8%)	-
Papillary mass with jaundice	4 (0.8%)	-
Stone in the T-tube postcholecystectomy	4 (0.8%)	-
Bilioma after cholecystectomy	3 (0.6%)	-
Intractable pancreatic pain	3 (0.6%)	-
Intractable pancreatic pain and jaundice	1 (0.2%)	-
Postoperative drainage with bile leakage	1 (0.2%)	-

Table 3. Diagnoses of patients

	n	Cholangitis (%)	*p* Value
Choledocholithiasis	212	1.4	NS
Passed choledocholithiasis	62	1.6	NS
Pancreas carcinoma	31	6.5	NS
Sphincter of Oddi dysfunction	27	3.7	NS
Hilar cholangiocarcinoma	24	20.8	NS
Oddi tumor	18	-	NS
Distal cholangiocarcinoma	17	5.9	NS
Failure ERCP	14	-	NS
Biliary injury (postsurgical)	12	8.3	NS
Normal cholangiography	12	-	NS
Gallbladder cancer	10	-	NS
Miscellaneous cases*	64	-	NS

*Preoperative cyst hydatid communicating with biliary tract, postoperative cyst hydatid communicating with biliary tract, benign biliary stricture secondary to chronic pancreatitis, malignant biliary stricture etc. NS: nonsignificant

Total procedure duration was significantly prolonged and common bile duct diameter significantly larger in patients with cholangitis (p values 0.028, 0.002, respectively) (Table 5).

Seventy-one of 105 cases with periampullary diverticula had biliary stone. None of the cases with periampullary diverticula had post-ERCP cholangitis. Only 1 of 212 patients with biliary stone developed cholangitis.

The other complications were as follows: pancreatitis (11 cases, 2.2%), bleeding (4 cases, 0.8%), and duodenal perforation (3 cases, 0.6%). Five patients (3 F, 2 M; 0.9%) died because of post-ERCP-complicated sepsis.

DISCUSSION

In this prospective study, we showed that cases with hilar cholangiocarcinoma and larger common bile duct diameter had increased post-ERCP cholangitis risk. Procedure-related risk factors were biliary dilatation, biliary stent insertion and prolonged total procedure time. Presence of periampullary diverticula was found to decrease cholangitis risk.

ERCP has a greater potential for procedure-related complications than other endoscopic procedures in the gastrointestinal tract. Bacteremia is a rare complication of ERCP and biliary stents. Though ERCP can lead to transient bacteremia in up to 27% in therapeutic procedures (1,16,17), the rate of post-ERCP cholangitis and sepsis ranges from 0.5% to 8% in the literature (1-4). That rate was 3.4% in the present study. Bacteria enter the biliary tract via hematogenous or retrograde route. In patients with a normal biliary tract, anatomical barriers impede both these routes. However, patients who have biliary obstruction have impaired bacterial defenses (16). When biliary pressure rises because of obstruction (i.e. stone, stricture, endoprosthesis), bacteria and bacterial products such as endotoxin can leak from the bile into the systemic circulation and cause septicemia and the clinical picture of cholangitis.

Although various studies have demonstrated high procedure-related morbidity rates for patients who undergo ERCP, the exact risk factors for post-ERCP cholangitis are still largely unknown. Because other studies seldom include thorough follow-up data, the factors associated with risk of ERCP-related cholangitis remain hidden (3,4,12-15). To our knowledge, there are only a few studies defining post-ERCP cholangitis. Prior cholecystectomy, low-volume endoscopist, cholestasis, inadequate biliary drainage, bile duct malignancy, precut papillotomy, and stent insertion were found to be risk factors (3,18-20). In our study, we have further widened the factor analysis and

Table 4. ERCP procedures and the risk of cholangitis development

	Cases with cholangitis (%)	*p* Value
Pancreatic sphincterotomy (yes/no)	0 / 3.4	0.571
Precut papillotomy (yes/no)	5.4 / 2.2	0.058
Nasobiliary drainage (yes/no)	4.3 / 3.3	0.703
Nasopancreatic drainage (yes/no)	0 / 3.4	0.851
Biliary stent (yes/no)	8.4 / 2.0	**0.001**
Pancreatic stent (yes/no)	0 / 3.5	0.791
Biliary dilatation (yes/no)	13.3 / 3.1	**0.030**
Dilatation of the ampulla of Vater (yes/no)	0 / 3.4	0.618
Papilla stenosis (yes/no)	0 / 3.5	0.433
Pancreatic duct manipulation (yes/no)	4.3 / 2.9	0.421
Periampullary diverticula (yes/no)	0 / 4.3	**0.031**
Mechanical lithotripsy (yes/no)	0 / 3.5	0.494
Extracorporeal shock wave lithotripsy (yes/no)	0 / 3.4	0.791
Biliary opening anomaly (yes/no)	0 / 3.4	0.618

specifically evaluated risk of cholangitis. Moreover, cases with naive papilla were enrolled in our study to homogenize the analysis.

The prophylactic administration of antibiotics before ERCP when there is a potential for cholangitis is controversial. The mean rate of sepsis without antibiotic prophylaxis was estimated to be approximately 6.3%, ranging from 2.2 to 29% based upon data from the placebo arm of controlled trials of antibiotic prophylaxis (1, 21). In the same studies, the mean incidence of post-ERCP sepsis under antibiotic cover was as high as approximately 4.3%. Post-ERCP cholangitis developed in 3.4% of our cases, though all had pre-procedure antibiotic prophylaxis.

The risk of cholangitis varies depending upon the nature and site of the obstruction. The highest cholangitis risk has been observed in patients with malignant hilar strictures, which are difficult or sometimes impossible to drain adequately (22, 23). The incidence of septicemia is significantly higher in cases of malignant obstruction than in benign obstruction due mainly to the problems of drainage associated with tumoral infiltration. Similarly, hilar cholangiocarcinoma was the unique risk factor for post-ERCP cholangitis among the diagnoses. In our study, acute bacterial cholangitis was uncommon in malignant obstruction other than hilar cholangiocarcinoma unless there was a biliary intervention attempt. Instrumentation of the biliary tract with ERCP may result in cholangitis if an attempt to decompress an obstructed biliary system is unsuccessful or only partially successful (19). Bacterial migration as a result of loss of the enteric-biliary barrier after stent placement may be an important cause of ascending bacterial ductal colonization and polymicrobial cultures (8). The frequency of bacteriobilia in patients with cholestasis and biliary stent in place was 8.4% in the present study.

ERCP and stenting in patients with hilar cholangiocarcinoma is a controversial issue because of the increased sepsis risk (up to 30%) resulting from incomplete drainage imposed by tumor extension (24, 25). In patients with cholangitis, complete biliary drainage with multiple catheters is required. Although early cholangitis rates as low as 6% have been reported (without prophylactic antibiotics) (26), strong concerns on the wide applicability of these results have been expressed (11). Five of our 24 cases (20.8%) with hilar cholangiocarcinoma in whom biliary stents were inserted had post–ERCP cholangitis. Different definitions for successful drainage and different methods for management of complications make it difficult to draw general conclusions (26, 27). The answers to use of no or minimum injection of contrast and to stent insertion through one or both left and right hepatic ducts are not clear (23, 28).

Periampullary diverticula may cause bacterial overgrowth and motility disturbance. Because periampullary diverticula were associated with biliary and pancreatic complications, possibly as a result of stasis in the diverticula, relaxed sphincter of Oddi and bolus impaction of food in the diverticulum with secondary inflammation (21, 29), the clinical course in patients with and without diverticula was compared. Periampullary diverticula reportedly cause bacteriobilia and increase the risk of primary bile duct stones; however, whether or not diverticula constitute a risk factor for choledochal complications after ERCP is controversial. It has been suggested that the periampullary diverticula interfere with biliary drainage by external compression of the biliary duct, thereby predisposing to bile stasis and stone formation (1, 17). However, duodenal diverticula, discovered incidentally in patients during ERCP, are usually asymptomatic. In contrast to those hypotheses, diverticula increased neither stone formation nor post-ERCP cholangitis.

Endoscopic biliary drainage in patients with septicemic shock entails a mortality of 4.7-10% (30, 31). In the setting of ERCP, it most commonly occurs in patients with malignant biliary obstruction that results from incomplete drainage of an infected and obstructed biliary system or occluded

Table 5. Relationship between cholangitis and duct diameter and procedure time

	Cases without cholangitis	Cases with cholangitis	*p* Value
Common bile duct diameter (mm)	7.0 ± 4.3	11.8 ± 6.2	**0.002**
Pancreatic duct diameter (mm)	2.1 ± 2.7	1.5 ± 1.0	0.914
Total procedure duration (min)	22.4 ± 11.1	31.4 ± 19.8	**0.028**
Precut duration (min)	4.5 ± 4.1	5.3 ± 3.3	0.260
Cannulation duration (min)	4.8 ± 4.1	4.7 ± 2.3	0.559

biliary stents (32). With only one exception, all of our patients who died of cholangitis had pancreatobiliary malignancy.

In conclusion, cases with hilar cholangiocarcinoma had increased risk of post-ERCP cholangitis. Procedure-related risks including biliary dilatation, biliary stent insertion and prolonged total procedure time also increase cholangitis risk.

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