

Folsch UR, Nitsche R, et al for the German Study Group on Acute Biliary Pancreatitis. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. N Engl J Med 1997; 336:237-242. Two RCTs suggest strong evidence that early ERCP reduces the complication rate in patients with severe biliary pancreatitis (Neoptolemos et al. Lancet 1988;2:979-983) as well as the incidence of biliary sepsis (Fan et al. NEJM 1993;328:228-232) despite having no effect on mortality outcome. These studies, however, focused on patients with obstructive jaundice and bilirubin up to 37; do the benefits of early ERCP extend to patients with non-obstructive biliary pancreatitis? In order to address this question, the investigators randomized 238 patients with evidence of biliary pancreatitis (by US or CT or 2/3 of alk phos>125, ALT>75, and bili >2.3) to receive early ERCP (within 72 hours) vs. conservative management. Of note, 101 were excluded for exclusion criteria including temperature >39C, bilirubin >5, and onset of symptoms >72 hours. In the conservative management, 20% required ERCP within 3 weeks of randomization. The overall mortality and mortality due to pancreatitis at 3 months showed no statistically significant difference between the two groups. Respiratory complications were more significant in the treatment group whereas jaundice and cholecystitis were more prevalent in the conservative management group. These data suggest that early ERCP in patient without obstructive jaundice is not beneficial.

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EARLY ERCP AND PAPILOTOMY COMPARED WITH CONSERVATIVE TREATMENT FOR ACUTE BILIARY PANCREATITIS

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ABSTRACT

Background The role of early endoscopic retrograde cholangiopancreatography (ERCP) and papillotomy in the treatment of patients who have acute biliary pancreatitis without obstructive jaundice is uncertain.

Methods We conducted a prospective, multicenter study in which 126 patients were randomly assigned to early ERCP (within 72 hours after the onset of symptoms) and endoscopic papillotomy for the removal of stones in the common bile duct, when appropriate, and 112 patients were assigned to conservative treatment. In the conservative-treatment group, ERCP was performed within three weeks if signs of biliary obstruction or sepsis developed. Overall mortality, mortality due to pancreatitis, and complications were compared in the two groups.

Results Early ERCP was successful in 121 of the 126 patients in the invasive-treatment group. Endoscopic papillotomy was performed to remove bile-duct stones in 58 patients; stones were successfully extracted in 57. ERCP was performed in 22 of the 112 patients in the conservative-treatment group; papillotomy for stone removal was successful in 13 patients. Fourteen patients in the invasive-treatment group and 7 in the conservative-treatment group died within three months ($P=0.10$); 10 patients in the invasive-treatment group and 4 in the conservative-treatment group died from acute biliary pancreatitis ($P=0.16$). The overall rate of complications was similar in the two groups, but patients in the invasive-treatment group had more severe complications. Respiratory failure was more frequent in the invasive-treatment group, and jaundice was more frequent in the conservative-treatment group.

Conclusions In patients with acute biliary pancreatitis but without obstructive jaundice, early ERCP and papillotomy were not beneficial. (N Engl J Med 1997;336:237-42.)

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ALCOHOL abuse and gallstones account for approximately 80 percent of cases of acute pancreatitis.^{1,2} The pathogenesis of acute biliary pancreatitis is not fully understood and may be multifactorial.³⁻⁸ It is uncertain whether gallstones merely initiate or also maintain biliary pancreatitis. Most gallstones that initiate an episode of acute pancreatitis pass spontaneously through the ampulla of Vater into the duodenum and can subsequently be recovered in the feces within a few days.⁹

There has been much interest in early surgical and endoscopic removal of gallstones retained in the common bile duct. Kelly and Wagner randomly assigned 165 patients with acute biliary pancreatitis to early surgery (within 48 hours after admission) or delayed surgery (more than 48 hours after admission).¹⁰ Early surgery was associated with a much higher mortality rate (47.8 percent, vs. 11.8 percent with delayed surgery) in patients with severe pancreatitis. In a nonrandomized, prospective study, Stone et al. found no difference in mortality between 36 patients who underwent early surgery and 29 who underwent delayed surgery.¹¹ In 1980, Safrany et al. recommended endoscopic retrograde cholangiopancreatography (ERCP) combined with endoscopic papillotomy for the treatment of acute biliary pancreatitis.¹² In a randomized trial at one center, reported by Neoptolemos et al., 121 patients with acute biliary pancreatitis were assigned to either ERCP (and papillotomy if bile-duct stones were found) or conventional treatment within 72 hours

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after admission to the hospital.¹³ Patients with mild pancreatitis had similar outcomes regardless of the treatment. Among the patients with severe pancreatitis, the complication rate, but not the mortality rate, was significantly lower for those who underwent early ERCP. In a study at a center in Hong Kong, reported by Fan et al., 195 patients with acute pancreatitis with various causes were randomly assigned to either ERCP and papillotomy or conservative treatment within 24 hours after admission.¹⁴ The rates of mortality and local and systemic complications were similar in the two groups; the incidence of biliary sepsis was significantly lower with early ERCP and papillotomy. The studies by Neoptolemos et al. and Fan et al. included patients with obstructive jaundice and bilirubin concentrations up to 37 mg per deciliter (630 μ mol per liter).^{13,14}

There is good evidence that early endoscopic intervention is the procedure of choice in patients with stone impaction and cholangitis.¹⁵ We performed a prospective, randomized, multicenter trial to compare early ERCP (within 72 hours after the onset of symptoms) with conservative treatment in patients with biliary pancreatitis but without signs of obstructive jaundice.

METHODS

Study Design

Before study entry, patients had to meet all the inclusion criteria listed in Table 1. Patients who met the criteria for inclusion were randomly assigned to receive early treatment with ERCP (invasive-treatment group) or noninvasive treatment (conservative-treatment group). Hematologic and biochemical tests were performed, according to the protocol, at admission, on days 2, 3, 5, 7, 14, and 21, and at discharge. The pancreatitis was assumed to have a biliary origin if gallstones were seen on ultrasonographic

or computed tomographic scans or if two of the following three laboratory abnormalities were present^{17,18}: an elevated alkaline phosphatase level (>125 U per liter), an elevated alanine aminotransferase level (>75 U per liter), or an elevated bilirubin level (>2.3 mg per deciliter [39 μ mol per liter]).

After three months, all patients were reexamined; studies included red- and white-cell counts; measurements of pancreatic and liver enzymes, renal function, electrolytes, and serum lipids; and ultrasonography.

The severity of the pancreatitis was classified before treatment according to the modified Glasgow criteria.¹⁹ Patients were classified as having severe disease if three or more of the following criteria were met: an age over 55 years, a white-cell count higher than 15,000 per cubic millimeter, a blood glucose level higher than 200 mg per deciliter (11 mmol per liter), a serum urea nitrogen level higher than 45 mg per deciliter (16 mmol per liter), an albumin level lower than 32 g per liter, a calcium level lower than 8 mg per deciliter (2.0 mmol per liter), a lactate dehydrogenase level higher than 600 IU per liter, and a partial pressure of arterial oxygen lower than 60 mm Hg. Patients were classified as having mild disease if fewer than three of the criteria were met and were classified as having disease of undefined severity if two of the criteria were met but not all the values were available.

If stones were detected in the common bile duct at ERCP, papillotomy was performed to extract them. In the conservative-treatment group, ERCP was performed within three weeks after randomization if the patient had a temperature higher than 39°C, an increase in the serum bilirubin level of more than 3 mg per deciliter (50 μ mol per liter) within five days, or persistent biliary cramps. Data from these patients were included in the analysis of the data in the conservative-treatment group.²⁰ After three weeks, ERCP could be performed in any patient, if indicated.

The participating centers agreed on the following principles of conservative treatment: replacement of fluid, electrolyte, and colloid losses according to the levels of urinary excretion and according to the observed values for the hematocrit, serum albumin concentration, central venous pressure, and pulmonary-artery wedge pressure; intravenous alimentation with glucose and lipids if indicated in a patient with a prolonged course of disease; insulin therapy if blood glucose levels exceeded 200 mg per deciliter (11 mmol per liter); assisted ventilation if the partial pressure of oxygen could not be maintained at a level higher than 60 mm Hg with an oxygen mask; nasogastric suction only in the case of gastric paresis and ileus; and antibiotic therapy only if the temperature rose above 39°C.

The study protocol was approved on June 20, 1989, by the ethics committee of the Georg August University in Göttingen, Germany, and the approval was accepted by the other centers. All patients gave written informed consent before randomization.

The outcome measure was mortality due to pancreatitis within three months after enrollment. The incidence of local and systemic complications was compared between groups.

Statistical Analysis

Assuming mortality rates of 8 percent in the conservative-treatment group and 2 percent in the invasive-treatment group (as reported in previous clinical studies^{13,14}), we estimated that 190 patients would be required per group when a two-sided test was applied to the data ($\alpha = 0.05$, $\beta = 0.2$).^{21,22} The trial was stopped according to the protocol after the second planned interim unblinded analysis by an independent board of reviewers from the departments of medical statistics and internal medicine of the University of Göttingen. The participating investigators in the trial were not involved in this decision. At that time, 10 of 126 patients in the invasive-treatment group (7.9 percent) and 4 of 112 in the conservative-treatment group (3.6 percent) had died of pancreatitis. Therefore, it was highly unlikely that superiority of the invasive treatment would be shown, which was the primary goal of the study. Even if there were no additional deaths in the invasive-treatment group, the mortality rate if the size of that

TABLE 1. CRITERIA FOR THE INCLUSION OF PATIENTS IN A TRIAL OF EARLY ERCP AND PAPILOTOMY AS COMPARED WITH CONSERVATIVE TREATMENT.

Pain in the upper abdomen
Serum amylase or lipase levels higher than three times the upper limit of normal
Signs of acute pancreatitis on ultrasonographic or computed tomographic scans (an enlarged and attenuated gland, abnormalities of the pancreatic duct, peripancreatic fluid collection, and thickening of the peripancreatic fascia) ¹⁶
Bilirubin level lower than 5 mg per deciliter (90 μ mol per liter)
Ability to perform ERCP within 72 hours after the onset of pain
Age over 18 years
Provision of written informed consent
No pregnancy
No coagulation abnormalities
No alcoholism or metabolic cause of pancreatitis
Patient not already included in this study
Patient not simultaneously included in any other study
Biliary origin of pancreatitis (see the Methods section)

group reached 190 would be 5.3 percent, which is higher than the rate in the conservative-treatment group.

Differences in mortality and complication rates were analyzed by logistic regression.²³ The treatment assignment, prognosis (based on whether the disease was classified as severe, mild, or of undefined severity), sex, and age were included in the model. In addition, we included three binary variables for center effects, because the P values for the patients treated at three centers reached the 10 percent level in a forward-selection procedure with the main outcome variable (odds ratio for death in the invasive-treatment group vs. the conservative-treatment group, in one center, 22.6; 95 percent confidence interval, 1.0 to 583.6; P=0.05; odds ratio at the second center, 18.9; 95 percent confidence interval, 0.9 to 472.3; P=0.06; odds ratio at the third center, 6.6; 95 percent confidence interval, 1.1 to 75.8; P=0.02). The results are presented as adjusted odds ratios and 95 percent confidence intervals. The null hypothesis of no treatment effect was tested by the two-sided asymptotic test of Wald.²² P values are two-tailed, and values of less than 0.05 were considered to indicate statistical significance. All analyses were performed according to the intention-to-treat principle.²⁰

RESULTS

From November 1989 to February 1994, 339 consecutive patients at 22 centers were suspected of having biliary pancreatitis. A total of 101 patients could not be randomly assigned to a treatment group because of symptoms requiring early ERCP (a temperature higher than 39°C or a bilirubin level higher than 5 mg per deciliter [90 μmol per liter], persistent biliary cramps, an onset of symptoms more than 72 hours before ERCP could be performed, refusal to participate, or an age under 18 years).

The remaining 238 patients were randomly assigned by means of a stratified block procedure to either early ERCP (126 patients) or conventional management (112). Thirty-two patients (19 in the invasive-treatment group and 13 in the conservative-treatment group) were found after randomization not to have met all the inclusion criteria: in 12 patients ERCP could not be performed within 72 hours after the commencement of symptoms, 12 had serum bilirubin concentrations higher than 5 mg per deciliter, 6 had nonbiliary causes of pancreatitis, 1 was younger than 18 years, and 1 had coagulation abnormalities. These patients remained in the study and their data were analyzed on an intention-to-treat basis.²⁰

Of the 238 randomized patients, 142 were women and 96 were men (Table 2). The percentage of women was higher in the conservative-treatment group than in the invasive-treatment group. The two groups were similar with regard to age, height, weight, severity of disease, and medical history (pancreatic, gallstone, or peptic ulcer disease and earlier gastric or gallbladder surgery). A mean of 10.8 patients (range, 6 to 29) were enrolled at each center. Three centers enrolled 20 or more patients.

Results of ERCP and Papillotomy

In the invasive-treatment group, early ERCP was successful in 121 of the 126 patients (96 percent). In

58 patients (46 percent), bile-duct stones were detected, and endoscopic papillotomy was performed. Stones were successfully extracted in 57 of these patients. In the conventional-treatment group, elective ERCP was performed during the three-week observation period in 22 patients (20 percent) because of increasing jaundice (in 8 patients), a temperature higher than 39°C (in 8), or biliary cramps (in 6). The common bile duct could be visualized in 19 of the 22 patients (86 percent); bile-duct stones were detected in 13 (59 percent). The stones were removed by means of papillotomy in all 13. The main reason for the failure of ERCP in both groups was edema or hemorrhagic inflammation of the duodenum and papillary or juxtapaillary diverticula.

Two patients in the invasive-treatment group had bleeding after the papillotomy. One patient, who needed four units of blood, died from biliary sepsis due to an incarcerated stone that could not be removed. Bleeding in the other patient was controlled by a local injection of epinephrine (at a dilution of 1:10,000) during a second endoscopy; blood transfusion was not needed. There were no other immediate complications, such as perforation of the duodenal wall, in either group.

Mortality and Complications

Twenty-one patients (9 percent) — 14 in the invasive-treatment group and 7 in the conventional-treatment group — died within three months after the onset of pancreatitis (P=0.10) (Table 3). Ten patients in the invasive-treatment group and four in the conservative-treatment group died from the direct consequences of acute biliary pancreatitis (P=0.16) (Table 3). Four patients in the invasive-treatment group and three in the conservative-treatment group died of causes unrelated to pancreatitis. All the patients who died were older than 55 years (range, 56 to 90 years in the invasive-treatment

TABLE 2. CHARACTERISTICS OF THE 238 PATIENTS RANDOMLY ASSIGNED TO INVASIVE OR CONSERVATIVE TREATMENT.

CHARACTERISTIC	INVASIVE TREATMENT (N=126)	CONSERVATIVE TREATMENT (N=112)
Sex — F/M	66/60	76/36
Age — yr		
Median	63	63
Range	24-90	15-93
Weight — kg		
Median	75	75
Range	42-130	38-172
Severity of pancreatitis — no. of patients (%)		
Mild	84 (66.7)	76 (67.9)
Severe	26 (20.6)	20 (17.9)
Undefined	16 (12.7)	16 (14.3)

TABLE 3. RISK OF DEATH AND SELECTED COMPLICATIONS IN THE TWO TREATMENT GROUPS.

DEATH OR COMPLICATION	INVASIVE TREATMENT (N = 126)	CONSERVATIVE TREATMENT (N = 112)	ODDS RATIO (95% CONFIDENCE INTERVAL)*	P VALUE
Death (no. of patients)	14	7	2.62 (0.83–8.32)	0.10
From acute biliary pancreatitis	10	4	4.57 (0.67–62.7)	0.16
From other causes†	4	3		
Complication‡				
Respiratory failure			5.16 (1.63–22.9)	0.03
No. of patients	15	5		
No. who died	8	3		
Renal failure			2.58 (0.44–15.3)	0.10
No. of patients	9	4		
No. who died	6	3		
Cholecystitis			0.49 (0.21–1.12)	0.10
No. of patients	13	20		
No. who died	0	1		
Jaundice			0.08 (0.01–0.64)	0.02
No. of patients	1	12		
No. who died	1	3		

*Odds ratios are for death or complications with invasive treatment as compared with conservative treatment. The ratios have been adjusted for prognosis, sex, age, and the effects of treatment at three of the centers (see the Methods section).

†Other causes of death in the invasive-treatment group were cerebral infarction, cardiac failure (after discharge from the hospital), aspiration due to a misplaced gastric tube, and renal failure due to amyloidosis (two months after discharge). Other causes of death in the conservative-treatment group were cardiac infarction, cardiac failure, and hepatic failure (all after discharge).

‡Some patients had more than one complication.

group and 62 to 93 years in the conservative-treatment group).

The overall rate of complications was similar in the two groups, but patients in the invasive-treatment group had more severe complications (Table 4). Complications occurred in 58 of the patients assigned to early ERCP (46 percent) and in 57 of those assigned to conservative treatment (51 percent). Respiratory failure was more frequent in the invasive-treatment group ($P=0.03$), and jaundice was more frequent in the conservative-treatment group ($P=0.02$) (Table 3). The findings were similar when the 32 patients who did not meet all the inclusion criteria were excluded from the analysis (data not shown).

DISCUSSION

Our multicenter design differed from the design of prior prospective, randomized trials of the effect of ERCP and papillotomy on morbidity and mortality in patients with acute biliary pancreatitis. Patients with obvious biliary obstruction (a serum bilirubin level higher than 5 mg per deciliter) were excluded, since patients who have severe pancreatitis without obvious obstruction pose the greatest therapeutic challenge.

Patients in the conservative-treatment group underwent ERCP if signs of biliary obstruction or acute cholangitis developed. There is convincing ev-

idence that early ERCP and papillotomy are indicated in patients with stone impaction or cholangitis.¹⁵

Patients were enrolled only if endoscopy could be performed within 72 hours after the onset of symptoms, not within 72 or 24 hours after admission, as in earlier studies.^{13,14} Since many patients with abdominal pain remain at home for some time before seeking care, a considerable number of patients with acute biliary pancreatitis could not have met this inclusion criterion.

The rate of successful ERCP and papillotomy was high in both groups, and the rate of immediate complications was low. There were only two hemorrhages after papillotomy (2.8 percent), and no perforations of the duodenal wall were reported. This rate of immediate complications in our study is similar to the rates reported in a retrospective, single-center study²⁴ (hemorrhage, 4.8 percent; perforations, 0.8 percent) and a recent prospective, multicenter investigation²⁵ (hemorrhage, 2.0 percent; perforations, 0.3 percent). Since other complications of endoscopic papillotomy, such as cholangitis, cholecystitis, and pancreatitis, are also related to biliary pancreatitis, it was difficult to evaluate them in our study.

Whereas Fan et al.¹⁴ included in their study patients with various causes of acute pancreatitis, we confined our study to patients with suspected biliary pancreatitis, identifying such patients with a combi-

TABLE 4. COMPLICATIONS IN THE TREATMENT GROUPS.

COMPLICATION*	INVASIVE TREATMENT (N = 126)	CONSERVATIVE TREATMENT (N = 112)
	no. of patients (%)	
Total	58 (46.0)	57 (50.9)
Pancreatic pseudocyst	5 (4.0)	9 (8.0)
Pancreatic necrosis	21 (16.7)	15 (13.4)
Pancreatic abscess	3 (2.4)	1 (0.9)
Peritonitis	2 (1.6)	3 (2.7)
Respiratory insufficiency	15 (11.9)	5 (4.5)
Renal failure	9 (7.1)	4 (3.6)
Sepsis	13 (10.3)	16 (14.3)
Cardiovascular shock	6 (4.8)	4 (3.6)
Disseminated intravascular coagulation	4 (3.2)	2 (1.8)
Thrombosis	1 (0.8)	1 (0.9)
Diabetes	12 (9.5)	12 (10.7)
Jaundice (icterus)	1 (0.8)	12 (10.7)
Cholecystitis	13 (10.3)	20 (17.9)
Cholangitis	17 (13.5)	13 (11.6)

*Respiratory insufficiency or failure was considered to be present if the partial pressure of oxygen could not be maintained above 60 mm Hg with an oxygen mask. Renal failure was defined as oliguria lasting more than 24 hours. Sepsis was considered to be present if the temperature exceeded 39°C. Cardiovascular shock was considered to be present if an inotropic agent was required for more than 24 hours to maintain the systolic blood pressure at a level higher than 100 mm Hg. Thrombosis was confirmed by phlebography or duplex sonography. Diabetes was defined as a blood glucose level exceeding 200 mg per deciliter. Jaundice was defined as a bilirubin level exceeding 5 mg per deciliter. Some patients had more than one complication.

nation of laboratory and imaging methods.^{17,18} This group of patients was selected because there is no rationale for ERCP and sphincterotomy in the treatment of other forms of pancreatitis.

Like Fan et al.¹⁴ but unlike Neoptolemos et al.¹³ and Nowak et al., in their recent prospective trial,²⁶ we found no significant differences in the overall incidence of local and systemic complications between the two treatment groups. This finding was unaffected by classifying the patients according to the severity of disease. The incidence of respiratory failure was significantly higher in the invasive-treatment group than in the conservative-treatment group. We found no explanation for this difference; an increased rate of pulmonary failure has not been reported in other controlled trials of ERCP and papillotomy.^{13,14} The incidence of jaundice was significantly higher in the conservative-treatment group. According to our protocol, ERCP was performed if jaundice developed. None of the patients in the conservative-treatment group died of biliary complications. Ten patients in the invasive-treatment group died from acute biliary

pancreatitis, as compared with four in the conservative-treatment group, a result contradicting the hypothesis that early ERCP lowers the mortality rate. Variables for center effects were included in all statistical analyses to eliminate any potential bias due to the differences in numbers of patients and outcomes among the centers.

In conclusion, our controlled, randomized trial of early ERCP and papillotomy in patients with acute biliary pancreatitis demonstrated that patients without biliary obstruction or biliary sepsis did not benefit from these interventions.

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