Early Endoscopic Intervention Versus Early Conservative Management in Patients With Acute Gallstone Pancreatitis and Biliopancreatic Obstruction

A Randomized Clinical Trial

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Objective: To test the hypothesis that early endoscopic intervention, performed on patients with acute gallstone pancreatitis and biliopancreatic obstruction, reduces systemic and local inflammation.

Summary Background Data: The role of early endoscopic intervention, in the treatment of acute gallstone pancreatitis, remains controversial. Previous randomized trials have not focused on the subgroup of patients with clinical evidence of biliopancreatic obstruction.

Methods: This single-center randomized clinical trial was performed between May 2000 and September 2005. Of 238 patients, admitted within 48 hours after the onset of acute gallstone pancreatitis, 103 with a distal bile duct measuring ≥8 mm combined with a total serum bilirubin ≥1.20 mg/dL, were randomized to receive either endoscopic retrograde cholangiopancreatography followed by endoscopic papillotomy for bile duct stones (EEI, n = 51) or early conservative management (ECM, n = 52). Patients with clinical evidence of coexisting acute cholangitis were excluded. Outcome measures included changes in organ failure score and computed tomography (CT) severity index during the first week after admission, incidence of local complications, and overall morbidity and mortality.

Results: The incidence of bile duct stones at EEI was 72% and 40% of patients in the ECM group had persisting bile duct stones at elective biliary surgery. No significant differences were found between the EEI and ECM groups regarding changes in mean organ failure score (P = 0.87), mean CT severity index (P = 0.88), incidence of local complications (6% vs. 6%, P = 0.99), overall morbidity (21% vs. 18%, P = 0.80), and mortality (6% vs. 2%, P = 1).

Conclusions: The present study failed to provide evidence that early endoscopic intervention reduces systemic and local inflammation in patients with acute gallstone pancreatitis and biliopancreatic obstruction. If acute cholangitis can be safely excluded, early endoscopic intervention is not mandatory and should not be considered a standard indication.

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Biliopancreatic obstruction during gallstone migration is generally accepted to be the triggering event for acute gallstone pancreatitis.[1,2] In many cases, biliopancreatic obstruction is transient because the offending stone passes rapidly into the duodenum; in the remainder, persisting obstruction occurs due to the continued presence of main bile duct stones or to ampullary edema following stone passage.

Persisting biliopancreatic obstruction, leading to progressive pancreatic inflammation, is a commonly held explanation for the pathogenesis of severe gallstone pancreatitis.[3,4] In support of this concept, several clinical and experimental studies have claimed that duration of biliopancreatic obstruction correlates with the severity of pancreatic injury.[5,6] Accordingly, the rationale for early endoscopic intervention (EEI) in acute gallstone pancreatitis is based on the hypothesis that early relief of biliopancreatic obstruction may halt the progression of severe attacks as well as prevent deterioration of mild attacks.[6] Prospective randomized trials comparing EEI with early conservative management (ECM), however, have yielded contradictory results.[7–9] Data interpretation has been hampered by the inclusion of heterogeneous populations,[7,8] by differences in the specific time at which patients were enrolled into the studies,[7–9] or by exclusion of patients with biliopancreatic obstruction who might have obtained benefit from the procedure.[9]

Patients admitted within 48 hours after the onset of acute gallstone pancreatitis can be placed into 1 of 3 categories through physical examination, laboratory studies, and radiologic methods. 1) A small subgroup of patients can be determined to have coexisting acute cholangitis, itself an indication for EEI. 2) Next are patients without clinical and radiologic parameters of biliopancreatic obstruction; in this subgroup, a previous randomized trial showed no benefit with the use of EEI.[9] 3) A third subgroup of patients exhibit laboratory and radiologic parameters of biliopancreatic obstruction without evidence of acute cholangitis. Because these patients are theoretically at risk for progressive pancreatic injury, the present randomized trial has focused on this subgroup. Our aim, therefore, was to assess if EEI performed within 72 hours of the onset of the attack in patients with biliopancreatic obstruction could reduce organ failure scores,

limit the extent of retroperitoneal lesions, and reduce overall morbidity and mortality.

PATIENTS AND METHODS

This single-center randomized clinical trial was performed at the Cosme Argerich Hospital, Buenos Aires, Argentina, a tertiary care, university-affiliated public hospital, specializing in acute surgical conditions. All procedures, including obtaining written informed consent from the patient or a responsible relative, were conducted in accordance with the recommendations of the Ethics Committee of the Cosme Argerich Hospital. The study protocol was approved on April 19, 2000.

Patients

From May 1, 2000, to September 3, 2005, all patients who presented to the emergency ward within 48 hours after the onset of acute gallstone pancreatitis, were evaluated for study eligibility. The diagnosis of acute gallstone pancreatitis was based on the presence of the following 5 criteria: 1) acute upper abdominal pain; 2) serum amylase 3 times or more the upper limit of normal for our laboratory; 3) biliary lithiasis on admission ultrasound (US); 4) evidence of pancreatic inflammation on admission computed tomography (CT) scan; and 5) absence of other causes of acute pancreatitis.

Inclusion Criteria

Patients with a distal main bile duct diameter measuring ≥8 mm on admission US, combined with a total serum bilirubin ≥1.20 mg/dL, were considered eligible for enrollment (Fig. 1). Our technique for US scanning of the distal bile duct in patients with acute gallstone pancreatitis has been previously reported.[10–12]

Exclusion Criteria

Patients were excluded from entry if they met any of the following criteria: 1) serious comorbid conditions that precluded endoscopic retrograde cholangiopancreatography (ERCP); 2) age <18 years; 3) pregnancy; or 4) acute cholangitis. The diagnosis of acute cholangitis was based on the combination of right upper quadrant pain, hyperbilirubinemia, and axillary temperature ≥38.4°C (Charcot's triad). Patients were also excluded if endoscopy could not be performed within 72 hours after onset of the attack.

Methods

Patient General Management

Initial treatment comprised supportive measures, including intravenous fluids, analgesia, oxygen administration, and nasogastric intubation if necessary. To prevent acute cholangitis, intravenous ciprofloxacin was administered at a dosage of 400 mg every 12 hours, along with metronidazole 500 mg every 8 hours. In the absence of evidence of pancreatic necrosis, antibiotics were discontinued 7 days after admission.

Prediction of the Severity of the Attack

Severity of the attack was predicted on admission according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score.[13] Patients were classified as having a predicted severe attack if 6 or more points of the APACHE II score were met.[14]

Randomization

Patients were randomized using sealed envelopes. The envelopes were randomized in blocks of 50 and opened by a surgeon not otherwise engaged in the study. Randomization was done once CT examination and laboratory studies were performed and the severity of the attack was predicted. Patients were randomized to receive either EEI within 72 hours after admission or ECM.

Intervention

ERCP and endoscopic sphincterotomy (ES) were done by a single experienced endoscopist in the standard manner,[15] using local pharyngeal anesthesia and mild sedation. ES was performed if one or more main bile duct stones were found. In case of incomplete stone removal, a biliary stent was inserted and endoscopy was repeated 24 hours later. In the absence of main bile duct stones, ES was also indicated for insufficient biliary drainage due to ampullary edema. Insufficient biliary drainage was defined as incomplete drainage of the contrast material 30 minutes after injection. Complications of ERCP and ES were defined according to Cotton et al.[16]

Outcome Measures

The primary endpoint of the study was to determine if EEI could reduce organ failure scores during the first week after admission and limit the extension of pancreatic and peripancreatic lesions. Secondary endpoints were to deter-

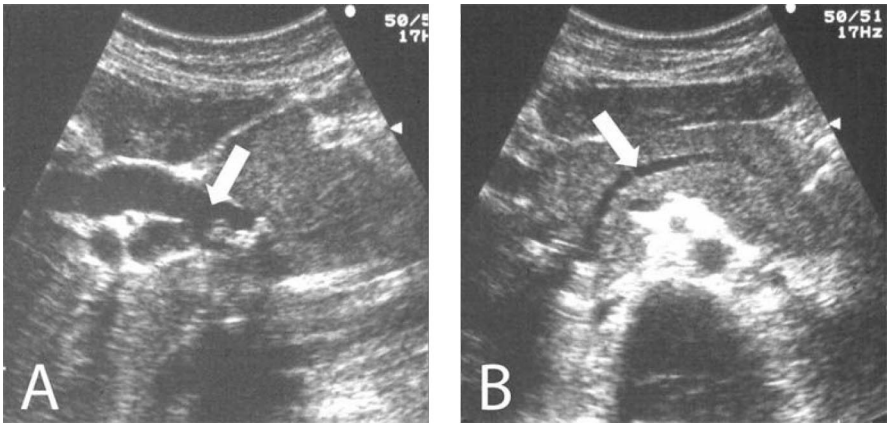

FIGURE 1. Ultrasonography of the pancreas in acute gallstone pancreatitis, showing (A) distal bile duct dilatation (arrow) and (B) pancreatic duct dilatation (arrow).

mine the effect of EEI on the incidence of local complications, overall morbidity, and mortality.

Organ Failure Scores

Organ failure scores were assessed using the Sequential Organ Failure Assessment (SOFA) score.[17] This score has been validated for patients with acute pancreatitis[18] and is composed of scores from 6 organ/systems graded from 0 to 4 according to the degree of dysfunction/failure. Because in acute gallstone pancreatitis, early hyperbilirubinemia is due to biliary obstruction rather than to hepatic dysfunction, the hepatic index was not included for assessment. The SOFA score value was calculated for all patients on admission, and for days 1, 2, 3, and 7. A score of 2 or more in any organ/system defined organ failure.[19] In patients admitted without organ failure, any subsequent organ failure categorized the patient as having "new organ failure." Any organ failure present at day 7 categorized the patient as having "persisting organ failure."

CT Severity Scores

The extent of pancreatic and peripancreatic lesions was assessed using contrast enhanced, thin-section spiral CT scanning, performed on admission and repeated 7 to 10 days after. CT findings were graded using the CT severity index described by Balthazar et al,[20] which is based on combined assessment of peripancreatic inflammation and degree of pancreatic necrosis.

Local complications, including acute pseudocyst, infected necrosis, and pancreatic abscess, were defined according to the Atlanta Classification.[21] Gallbladder empyema and gallbladder perforation, assessed by percutaneous cholecystostomy or surgery, were also documented. Mortality was defined as death within 3 months of admission.

Elective Biliary Surgery

Elective surgery was undertaken during the same hospital admission, once there was evidence that acute pancreatitis had subsided. Laparoscopic cholecystectomy and intraoperative cholangiography were performed throughout. In patients with documented main bile duct stones, laparoscopic ductal stone clearance was performed.

Statistical Analysis

A sample size calculation indicated that 51 patients per group would enable a difference to be demonstrated between the 2 groups of a change in mean organ failure score of 0.5 with $\alpha = 0.05$ and $\beta = 0.20$.[22] Continuous variables were compared using the 2-sample t test if data were normally distributed; if not, the Wilcoxon rank sum test was used. Categorical data were analyzed using the χ^2 and Fisher exact test probability test as appropriate. When comparisons were made within the same study group, the Wilcoxon signed-rank test for paired data was applied. All statistical tests were 2-tailed, and the threshold of significance was set at $P < 0.05$. All data were analyzed according to the intention-to-treat principle.

RESULTS

The profile of the study is shown in Figure 2. Of 238 consecutive patients admitted within 48 hours after the onset

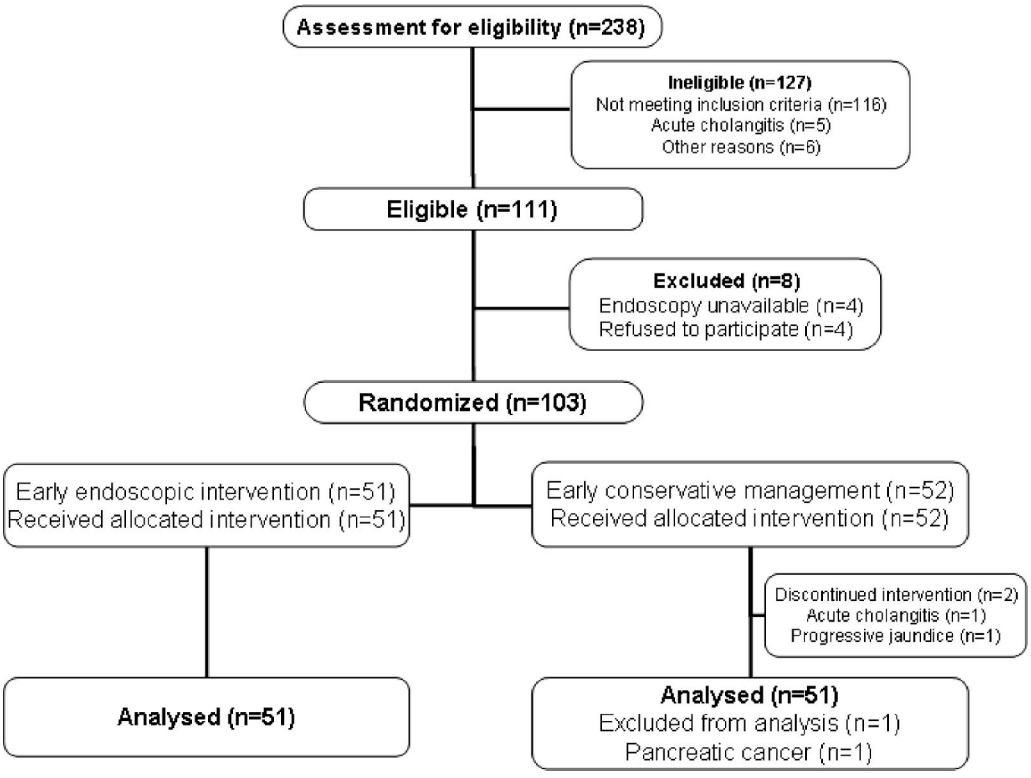

FIGURE 2. Study flow chart.

of acute gallstone pancreatitis, 116 failed to meet the inclusion criteria, 5 had coexisting acute cholangitis, 2 were under 18 years of age, 2 were pregnant, and 2 had serious comorbidities. Of the remaining 111 eligible patients, 4 refused to participate in the study, 4 were not randomized because endoscopy was not available, and 103 were randomized to receive either EEI (n = 51) or ECM (n = 52). In the ECM group, 2 patients were crossed over to endoscopic treatment. One was a 33-year-old man with a predicted mild attack who developed acute cholangitis 24 hours after admission and received EEI with ES. The other was a 79-year-old-woman with a predicted severe attack who developed rapidly progressive jaundice and received ERCP with ES 5 days after admission. Neither of these 2 patients had organ failure at the time of ERCP. One patient in the ECM group was excluded from analysis following randomization due to misdiagnosis (pancreatic head carcinoma). The demographics and baseline characteristics of the study participants are given in Table 1. There were no significant differences between the 2 groups.

Endoscopic Findings and Treatment

ERCP was performed within 48 hours after the onset of the attack in 46 of the 51 patients, and within 48 to 72 hours in the remaining 5 patients. The endoscopic findings are shown in Table 2. Because cannulation failed in 4 of the 51 patients, the adjusted incidence of main bile duct stones was 23 (72%) of 32 patients with predicted mild attacks and 11 (73%) of 15 patients with predicted severe attacks ($P = 0.80$ [odds ratio 0.92, 95% confidence interval 0.23–3.69]). ES was performed on 38 patients, of whom 34 had main bile duct stones and 4 had insufficient biliary drainage; 32 of the 34 patients with main bile duct stones had their stones cleared at the first ERCP. Of the other 2, 1 had his stones removed at a second ERCP and the remaining patient was cleared at elective biliary surgery. Mild postprocedure hemorrhage occurred in 2 of the 38 patients who underwent ES; in each case, repeat endoscopy showed that bleeding had stopped spontaneously. There were no other complications or any mortality related to ERCP or ES.

TABLE 1. Demographics and Clinical Characteristics of the Study Participants

Characteristic	EEI (n = 51)	ECM (n = 51)	*P*
Sex (male/female) (n)	16/35	13/38	0.66
Age (yr) (mean ± SD)	49.9 ± 17.4	44 ± 17.7	0.08
Admission delay (hr)	19 ± 11.8	17.3 ± 12.6	0.47
Distal bile duct diameter (mm) (mean ± SD)	10.7 ± 2	10.7 ± 2.4	0.99
Total serum bilirubin (mg/dL) (mean ± SD)	3.16 ± 2.1	4 ± 3.3	0.83
Pancreatic duct diameter ≥2 mm (n)	10	13	0.47
Choledocholithiasis visualized by US (n)	23	19	0.54
Body mass index (kg/m^2) (mean ± SD)	26.3 ± 4	26.2 ± 4.6	0.91
APACHE II score (mean ± SD)	4.6 ± 2	4 ± 3.2	0.37
Predicted mild/severe attacks (n)	34/17	30/21	0.37

EEI indicates early endoscopic intervention; ECM, early conservative management; US, ultrasonography.

TABLE 2. ERCP Findings in the EEI Group According to the Predicted Severity of the Attack

	Mild (n = 34)	Severe (n = 17)	*P*
Main bile duct stones	23	11	1.00
Insufficient biliary drainage	3	1	1.00
Normal	6	3	1.00
Cannulation failure	2	2	0.59

ERCP indicates endoscopic retrograde cholangiopancreatography; EEI; early endoscopic intervention.

Outcome Results

Organ Failure Scores

Changes in the mean SOFA score of all study patients are shown in Figure 3. Regardless of the type of treatment, the response of the mean SOFA score to therapy was not significantly different between the 2 groups in any of the assessments. Mean SOFA scores were 0.71 ± 1.0, 0.90 ± 1.7, 0.71 ± 1.3, 0.48 ± 1.3, and 0.38 ± 0.9 at entry and for days 1, 2, 3, and 7, respectively, in the EEI group. In the ECM group, the respective values were 0.45 ± 0.6, 0.50 ± 1.0, 0.54 ± 0.9, 0.41 ± 0.89, and 0.21 ± 0.7. Mean SOFA score differences at day 7 were −0.32 ± 1.07 in the EEI group and −0.23 ± 0.92 in the ECM group ($P = 0.87$). Similarly, changes in the mean SOFA score did not differ between groups when patients were stratified by severity of the attack (Fig. 4). Mean SOFA scores were 1.5 ± 1.2, 2.17 ± 2.6, 1.76 ± 1.98, 1.35 ± 0.49, and 0.76 ± 1.34 in the EEI group, and 0.85 ± 0.72, 1.23 ± 1.41, 1.04 ± 1.16, 0.95 ± 1.20, and 0.42 ± 0.97 in the ECM group. Mean SOFA score differ-

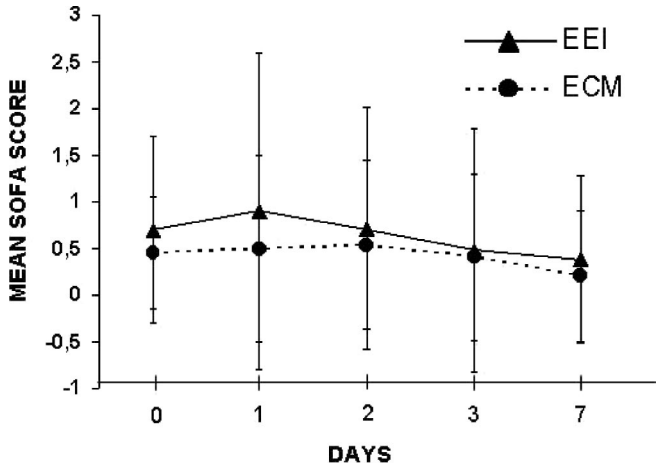

FIGURE 3. Mean organ failure scores (mean OFS) of all study participants. Data are given as mean ± SD. All *P* values are not significant. EEI, early endoscopic intervention; ECM, early conservative management.

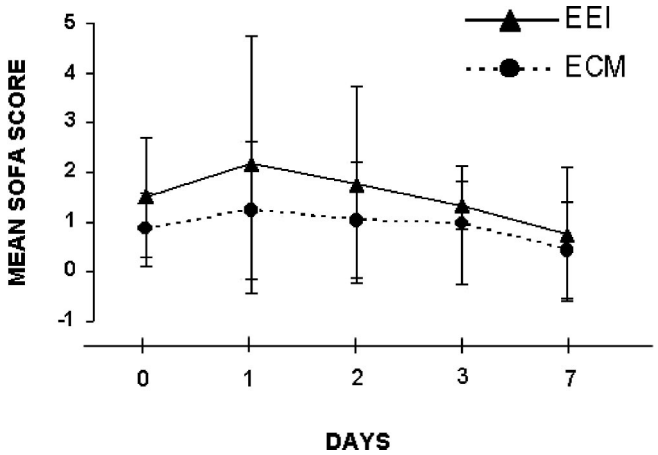

FIGURE 4. Mean organ failure scores (mean OFS) of patients with predicted severe attacks. Data are given as means ± SD. All *P* values are not significant. EEI, early endoscopic intervention. ECM, early conservative management.

ences at day 7 were −0.83 ± 1.2 in the EEI group and −0.42 ± 1.28 in the ECM group ($P = 0.63$).

The incidence of different categories of organ failure, according to the predicted severity of the attack, is shown in Table 3. There was no significant difference between the 2 groups in the incidence of organ failure on admission, nor there was a difference in new or persisting organ failure. All of the 5 patients in the EEI group who developed new organ failure had undergone ES with stone extraction within 48 hours of onset of the attack (at 36, 40, 8, 40, and 36 hours, respectively). Among the 5 patients with persisting organ failure in the EEI group, 4 had undergone ES with stone extraction and the remaining patient had a normal ERCP.

CT Severity Index

Changes in CT severity index scores were not significantly different between the 2 groups (Table 4). Mean CT severity index differences at day 7 were −0.12 ± 0.85 in the EEI group and −0.12 ± 1.3 in the ECM group ($P = 0.88$). When patients were stratified by severity of the attack, mean CT severity index differences were 0.2 ± 1.3 in the EEI group and 0.09 ± 1.9 in the ECM group ($P = 0.87$).

Overall Morbidity and Mortality

The total number of systemic and local complications are detailed in Table 5. There was no significant difference between the 2 groups in the incidence of any specific organ failure or local complication. Similarly, there was no difference in the overall morbidity rate; 11 (21%) of 51 patients in the EEI group developed complications, versus 9 (18%) of 51 patients in the ECM group ($P = 0.80$ [odds ratio 1.28, 95% confidence interval 0.48–3.42]).

Four patients (4%) of the 102 study patients died within 3 months of onset of the attack (3 in the EEI group and 1 in the ECM group [$P = 1$; odds ratio 2.04, 95% confidence interval 0.17–23.24]). Of the 3 deaths in the EEI group, 1 occurred in a 70-year-old woman admitted with multiple organ failure and 80% pancreatic necrosis, in whom ERCP was normal; this patient died of multiple organ failure after repeated operations for infected pancreatic necrosis. Another death occurred in an 80-year-old woman with a predicted severe attack, in whom sphincterotomy and stone extraction had been performed. Death occurred 12 days after admission due to progressive respiratory failure. The third death, occurring in a 76-year-old woman with a predicted severe attack, was due to complications of elective biliary surgery and could not be attributed to pancreatic inflammation. The one death in the ECM group occurred in a 50-year-old man who presented with respiratory failure and extensive peripancreatic necrosis; this patient died 55 days after admission, of massive retroperitoneal hemorrhage.

TABLE 3. Incidence (n) of Organ Failure According to the Predicted Severity of the Attack

	EEI		ECM	
Organ Failure	Mild (n = 34)	Severe (n = 17)	Mild (n = 30)	Severe (n = 21)
On admission	1	6	0	4
New	0	5	1	5
Persisting	0	5	0	3

EEI indicates early endoscopic intervention; ECM, early conservative management. All *P* values are not significant.

TABLE 4. Changes in the CT Severity Index

	EEI	ECM	*P*
All attacks	(n = 51)	(n = 51)	
On admission	1.88 ± 1.86	1.84 ± 1.28	0.87
At day 7	1.76 ± 1.87	1.72 ± 1.74	0.90
Predicted severe attacks	(n = 17)	(n = 21)	
On admission	2.29 ± 1.89	2.19 ± 1.43	0.96
At day 7	2.47 ± 2.91	2.28 ± 2.36	0.71

CT indicates computed tomography; EEI, early endoscopic intervention; ECM, early conservative management. Data are means ± SD.

TABLE 5. Total Number of Complications

	EEI	ECM	Odds Ratio (95% confidence interval)	*P*
Organ failures*				
Respiratory	7	9	0.74 (0.25–2.17)	0.78
Renal	2	0		0.24
Coagulation	2	1	2.04 (0.17–23.2)	1.00
Cardiovascular	1	0		0.99
Central nervous system	1	0		0.99
Local complications				
Infected necrosis	2	2	1 (0.13–7.38)	0.99
Acute pseudocyst	1	1	1 (0.06–16)	0.99
Gallbladder perforation/ empyema	3	2	1.53 (0.24–9.57)	0.68

*Organ failures on admission were excluded.
EEI indicates early endoscopic intervention; ECM, early conservative management.

Elective Biliary Surgery

Ninety-two of the 102 study group patients underwent elective biliary surgery during the same hospital admission. Of the remaining 10 patients, 4 had previously undergone cholecystectomy, 4 refused operation, and 2 were considered to be poor surgical risks because of significant comorbidities. Of the 92 patients who underwent elective biliary surgery, 89 received laparoscopic cholecystectomy; in the remaining 3, an open procedure was deemed necessary because a concomitant necrosectomy was required. Intraoperative cholangiography disclosed main bile duct stones in 1 (2%) of 45 patients in the EEI group and 19 (40%) of 47 patients in the ECM group. Transcystic ductal stone clearance was successful in 11 of the 20 patients with choledocholithiasis. Of the remaining 9 patients, laparoscopic choledochotomy was successful in 7 and open choledochotomy was performed on 2 patients in the ECM group with concomitant infected necrosis. Overall, 3 (3%) of the 89 patients were converted to open procedure due to gross adhesion in the triangle of Calot. There was no statistically significant difference between the 2 groups in terms of mean total hospital stay (14.8 days in the EEI group vs. 14.4 days in the ECM group; $P = 0.80$).

DISCUSSION

Several authors support the concept that biliopancreatic obstruction not only initiates but also aggravates pancreatic inflammation.[1,4] Acosta et al[3] have claimed that persisting ampullary obstruction is the "single hit" that aggravates pancreatic inflammation, whereas Neoptolemos[4] has proposed a "multiple hit" model consisting of repeated episodes of pancreatic duct obstruction. Both ideas imply that there is a window of opportunity to relieve ductal obstruction before pancreatic inflammation evolves into a systemic disease affecting distant organs, and a local necrotizing process affecting the pancreas and peripancreatic tissues. Previous trials[7–9] have not specifically addressed the subgroup of patients with persisting biliopancreatic obstruction. These patients, however, are those theoretically most likely to benefit from EEI; indeed, a strong association between persisting bile duct stones and an increased complication rate has been reported in patients with either mild or severe attacks.[3,23] In the study reported by Neoptolemos et al,[23] the complication rate in patients with predicted mild attacks and persisting bile duct stones was higher than in those with predicted severe attacks and no bile duct stones, and almost as high as in those with bile duct stones in the predicted severe attack group. In the series by Acosta et al,[6] pancreatic necrosis developed in nearly all patients with bile duct stones persisting beyond 48 hours after onset of the attack.

Using inclusion criteria based on clinical parameters of biliary obstruction, we yielded, to our knowledge, the highest reported incidence of main bile duct stones at EEI (72%) in patients with acute gallstone pancreatitis. Likewise, patients in the ECM group exhibited an unusually high incidence of main bile duct stones at the time of elective biliary surgery (40%). Thus, our population provided a great opportunity to test the hypothesis that EEI limits the progression of pancreatic inflammation in patients with either mild or severe attacks.

The results of our study, however, failed to support this hypothesis. EEI had no significant effect, neither on the change in organ failure scores nor on the progression of pancreatic and peripancreatic lesions. In addition, the overall morbidity and mortality rates were similar in both groups. Because 50% of patients with organ failure had organ failure on admission, our study lacked the power to evaluate the effect of EEI to prevent new organ failure. However, all of the 5 patients in the EEI group who developed new organ failure had undergone a successful ES within 48 hours of the onset of the attack, suggesting that early removal of main bile duct stones cannot prevent progression of systemic inflammation. Conversely, the small number of organ failure in conservatively managed patients with predicted mild and severe attacks casts doubt on the cause and effect relationship between persisting ductal obstruction and progressive pancreatitis. As already suggested,[24] the severity of the systemic and local inflammation seems to be predetermined at onset, and early removal of main bile duct stones does not by itself reduce the severity of the attack.

Two trials have claimed that EEI reduces morbidity in acute gallstone pancreatitis, especially in patients with predicted severe attacks.[7,8] The results of these trials, however, must be interpreted with caution because of methodologic weaknesses. First, both included patients with coexisting acute cholangitis, a condition usually refractory to supportive management and best managed by EEI.[25] In the Leicester trial,[7] of 20 patients with predicted severe attacks who underwent ERCP, 12 had main bile duct stones; of these, 5 (40%) had coexisting acute cholangitis. In addition, the diagnosis of acute cholangitis was not defined prospectively but was informed post hoc. In the Hong Kong trial,[8] 50% of patients with predicted severe attacks and main bile duct stones had acute cholangitis. Therefore, it remains unclear whether the clinical benefits observed in both trials were due to relief of pancreatic inflammation or to drainage of coexisting biliary sepsis. Second, although in both trials ERCP was performed within 72 hours of admission, the time elapsed from the onset of the attack to admission was not reported. The fact that in the Hong Kong trial[8] patients exhibited on admission levels of total serum bilirubin up to 37 mg/dL indicates that an unspecified number of patients presented with long-lasting biliary obstruction, a condition associated with neutrophil priming, myocardial dysfunction, and increased risk of sepsis.[26,27] In this setting, acute pancreatitis has usually subsided and the eventual benefit of endoscopic intervention may be ascribed to relief of biliary obstruction.[27] Third, gallstones were not the cause of acute pancreatitis in 34% of patients in the Hong Kong trial[8] and were not confirmed in 15% of patients in the Leicester trial.[7] Because we have focused on a very specific group of patients presenting within the parameters of biliary obstruction, our trial provided a more homogeneous population. Patients with acute cholangitis were excluded from our trial ab initio, as well as patients without biliary lithiasis. Because the delay from the onset of the attack to admission was less than 48

hours, patients with long-lasting biliary obstruction were also excluded.

The results of our study suggest that EEI has a very limited role in patients admitted within 48 hours of the onset of acute gallstone pancreatitis. This conclusion, however, may not hold true when extrapolating to populations from different geographic regions. The incidence of acute cholangitis in our entire cohort was 6 (2.5%) of 238 patients, similar to rates reported from Hispanic populations in the United States[28] but significantly lower than rates reported in previous studies from Europe and Asia (10%–20%).[7,8,29] Several factors have been found to be associated with acute cholangitis in patients with biliary lithiasis, including advanced age, pigment stones, and parasitic infections. None of these factors was present in our population. The median age of our patients was 47 years, compared with 64 years in the Leicester trial,[7] 63 years in the German trial,[9] and 65 years in the Hong Kong trial.[8] Pigment stones and ascaris within the bile ducts have been frequently found in Asian populations;[30] in the Hong Kong trial,[8] the incidence of acute cholangitis was 38% in patients with main bile duct stones, and ascaris protruding through the ampulla were found in 6% of patients who underwent EEI. Because it may be difficult to separate the inflammatory response due to pancreatic injury from that due to biliary sepsis, the diagnosis of coexisting acute cholangitis is not always straightforward and reliance on Charcot's triad may be insufficient. Thus, a conservative attitude in patients with acute gallstone pancreatitis and biliopancreatic obstruction may not be appropriate in populations with a high incidence of coexisting acute cholangitis. On the other hand, if ERCP and ES were completely safe, there would be no doubt in performing EEI on every patient with acute gallstone pancreatitis and biliopancreatic obstruction. Currently, however, the safety of EEI in acute pancreatitis has not been established. In previous studies, complications of EEI have included worsening of pancreatic inflammation,[31] hemorrhage,[9] respiratory insufficiency,[9] acute cholangitis,[9] severe cholecystitis,[7,9] and even lumbar osteitis.[7] Endoscopic expertise plays a major role in the outcome of EEI, but only a minority of endoscopists achieve an adequate volume of cases, and referral to specialized centers is usually not feasible. Therefore, indication of EEI in patients with acute gallstone pancreatitis requires an optimal balance between risk and benefit for the individual patient.

CONCLUSION

The present study failed to provide evidence that EEI benefits patients with acute gallstone pancreatitis and biliopancreatic obstruction. The persistence of main bile duct stones does not by itself contribute to worsening or persisting pancreatic inflammation. If acute cholangitis can be safely excluded, EEI is not mandatory and should not be considered a standard indication.

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