Preoperative Versus Postoperative Endoscopic Retrograde Cholangiopancreatography in Mild to Moderate Gallstone Pancreatitis
A Prospective Randomized Trial

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Objective
To determine whether endoscopic retrograde cholangiopancreatography (ERCP) and common bile duct (CBD) stone extraction should be performed routinely before surgery or selectively after surgery in patients with mild to moderate gallstone pancreatitis.

Summary Background Data
The role and timing of ERCP in mild to moderate gallstone pancreatitis remains controversial. Routine preoperative ERCP identifies persisting CBD stones but carries risks of complications and may delay definitive care. Selective postoperative ERCP, performed only if a CBD stone is seen on intraoperative cholangiography (IOC), avoids unnecessary ERCP but risks unsuccessful stone extraction.

Methods
A prospective, randomized study of consecutive patients with gallstone pancreatitis was conducted. Using previously determined criteria, patients with acute cholangitis or necrotizing pancreatitis were excluded. Patients considered at high risk for persisting CBD stones (CBD size ≥8 mm on admission ultrasound, serum total bilirubin ≥1.7 mg/dL, or serum amylase ≥150 U/L on hospital day 4) were randomly assigned to routine preoperative ERCP followed by laparoscopic cholecystectomy, or laparoscopic cholecystectomy with selective postoperative ERCP and endoscopic sphincterotomy with selective postoperative ERCP and endoscopic sphincterotomy only if a CBD stone was present on IOC. Primary end points were failure rates (failure of diagnostic ERCP and IOC, complications of ERCP and endoscopic sphincterotomy, and complications of surgery).

Results
One hundred fifty-four consecutive patients with gallstone pancreatitis were evaluated prospectively for study eligibility. Sixty patients met the randomization criteria. Thirty patients were randomized to routine preoperative ERCP and 29 patients to selective postoperative ERCP (1 patient refused). Age, admission laboratory values, and APACHE II and Imrie scores were similar in both groups. By protocol, ERCP was performed in all patients in the preoperative ERCP group. In the postoperative ERCP group, ERCP was necessary in only 7 of 29 patients (24%). Mean hospital stay was significantly longer in the routine preoperative ERCP group (11.7 days) than in the selective postoperative ERCP group (9.0 days). Mean total cost was higher in the preoperative ERCP group ($9,426) than in the postoperative ERCP group ($7,798). The combined treatment failure rate was 10% in both groups.

Conclusions
In patients with mild to moderate gallstone pancreatitis without cholangitis, selective postoperative ERCP and CBD stone extraction is associated with a shorter hospital stay, less cost, no increase in combined treatment failure rate, and significant reduction in ERCP use compared with routine preoperative ERCP.
The role of preoperative endoscopic retrograde cholangiopancreatography (ERCP) in the management of gallstone pancreatitis remains poorly defined. Fan et al\(^1\) recommended urgent ERCP and endoscopic stone removal in all patients with gallstone pancreatitis to reduce the incidence of biliary sepsis. However, we have previously found a low incidence of concomitant or subsequent cholangitis in this patient population, suggesting that routine use of urgent ERCP may be unnecessary.\(^2,3\) Neoptolemos et al\(^4,5\) recommended urgent ERCP in patients with predicted severe gallstone pancreatitis in an effort to reduce the overall complication rate. However, in an earlier study in our relatively youthful gallstone pancreatitis population, the mean APACHE II score was only 3, and only 3% had necrotizing pancreatitis.\(^3\) Thus, only a small subgroup of our patients would potentially benefit from urgent ERCP.

In the absence of concomitant cholangitis, controversy persists as to whether ERCP should be routinely performed before surgery in patients with gallstone pancreatitis with suspected persisting common bile duct (CBD) stones, or only after surgery in selected patients with CBD stones proven by intraoperative cholangiography (IOC). The purpose of this randomized prospective study was to compare the length of hospital stay, costs, complication rates, and clinical outcomes of routine preoperative elective ERCP followed by laparoscopic cholecystectomy versus laparoscopic cholecystectomy with IOC followed by selective postoperative ERCP for proven CBD stones. The study included only patients with a high suspicion of CBD stones based on criteria established by a previous retrospective study of our patient population.\(^2\) We hypothesized that performing selective postoperative ERCP for proven CBD stones would result in lower hospital costs.

**METHODS**

**Patient Selection**

All patients with gallstone pancreatitis admitted to Harbor–UCLA Medical Center from July 1994 through September 1996 were evaluated prospectively for study eligibility. Informed consent was obtained from patients before study participation. The study was approved by the Harbor–UCLA Human Subjects Committee.

The diagnosis of gallstone pancreatitis was based on the following criteria: upper abdominal pain and tenderness; serum amylase elevation greater than three times the upper limit of normal (≥330 U/L); documentation of gallstones on admission ultrasonography; and absence of alcohol abuse, hypercalcemia, hypertriglycerideremia, or medications known to cause pancreatitis.\(^2,3\)

Laboratory values obtained on admission and daily thereafter included complete blood count, amylase, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. APACHE II scores were calculated based on admission parameters. The severity of pancreatitis was also determined using the Imrie prognostic system.\(^6\)

Patients with cholangitis or necrotizing pancreatitis were excluded. Cholangitis was defined as a temperature >38.6°C, right upper quadrant pain and tenderness, and hyperbilirubinemia. Necrotizing pancreatitis was identified by computed tomography of the abdomen using bolus injection of intravenous contrast.

Patients who met any of the following three criteria for persisting CBD stone were eligible for randomization: CBD dilatation ≥8 mm on admission ultrasonography; elevation of the serum total bilirubin ≥1.7 mg/dL on hospital day 4; or serum amylase ≥150/L on hospital day 4.\(^2\) In addition, patients were randomized only if they demonstrated evidence of resolving pancreatitis, as determined by a decreasing serum amylase level and reduced abdominal pain.

**Randomization**

After obtaining consent, eligible patients were randomized into one of two groups using sealed envelopes on hospital day 4. Group I patients underwent preoperative ERCP with endoscopic sphincterotomy (ES) and stone extraction if a CBD stone was visualized. After ERCP, patients underwent laparoscopic cholecystectomy with IOC. IOC was obtained to confirm the results of ERCP and to delineate bile duct anatomy. Group II patients underwent laparoscopic cholecystectomy with IOC first. If a CBD stone was visualized on IOC, the patient was selected for postoperative ERCP and ES if a CBD stone was again visualized. If there was failure of IOC, the patient would undergo postoperative ERCP per protocol, with ES only if a CBD stone was visualized.

At our institution, cholecystectomy for gallstone pancreatitis is performed when the patient has demonstrated resolution of the pancreatitis as determined by relief of abdominal pain, a marked decrease in amylase, and absence of high fever. Based on our experience, this typically occurs between hospital day 4 and 6. Further, we routinely perform IOC during cholecystectomy to aid in the definition of bile duct anatomy, regardless of whether an ERCP has been performed before surgery. In the present study, we adhered to this institutional protocol. All data were analyzed on an intention-to-treat principle.

**Patient Management**

Patients were monitored throughout their hospital stay for the development of complications of pancreatitis (pancre-
actic abscess, pseudocyst, cholangitis, and organ failure), complications of ERCP (including pancreatitis, perforation, and bleeding), and complications of laparoscopic cholecystectomy (bile duct injury, bleeding, pneumonia, and organ failure). Failure of IOC (inability to visualize the bile duct), failure of ERCP (inability to visualize or cannulate the CBD), and failure of ES and stone extraction (inability to clear all CBD stones) were also noted.

Cost Analysis

Cost analysis was performed by comparing groups I and II with regard to hospital stay (intensive care unit [ICU] and ward), diagnostic ERCP, and therapeutic ERCP with ES and stone extraction. The costs of an ICU day and ward bed day proved difficult to determine at our public teaching hospital. An estimate of costs was obtained by multiplying hospital charges by the average percentage of these charges that were collected for a broad range of diagnoses. Based on this methodology, the average cost was $1,470 for an ICU day and $662 for a ward bed day. The costs of diagnostic ERCP ($638), therapeutic ERCP with ES and stone extraction ($954), and cholecystectomy with IOC ($784), without IOC ($731), and with CBD exploration ($911) were based on Medicare reimbursement rates. Anesthesia costs were not included in the calculation of costs.

End Points

The end points of the study were costs, length of hospital stay, and combined treatment failure rate (failure of IOC and diagnostic ERCP, complications of surgery, and complications of therapeutic ERCP with ES and stone extraction). These end points were compared between groups I and II.

Statistical Analysis

Continuous variables were compared using the Wilcoxon rank-sum test. Categorical variables were compared using the chi-square or Fisher’s exact test where appropriate. Odds ratios and associated 95% confidence intervals were also calculated. $P < .05$ was considered statistically significant, and no correction was made for multiple comparisons. All analysis were performed using SAS software (version 6.12, SAS Institute, Cary, NC).

RESULTS

A total of 154 patients were admitted to Harbor-UCLA Medical Center from July 1994 through September 1996 with a diagnosis of gallstone pancreatitis. Five (3.2%) patients with concomitant acute cholangitis underwent urgent ERCP with ES and stone extraction and were therefore excluded. Four (2.6%) patients with necrotizing pancreatitis were likewise excluded. An additional eight (5.6%) patients were excluded for the following reasons: six left against medical advice before any intervention, and two had other severe medical problems (unstable angina and severe pulmonary disease) that precluded performance of ERCP or IOC. The mean age of the remaining 137 patients was 36.8 years. Eighty-six percent were women and 14% were men. The mean APACHE II score was 2.87 (range 0–11).

Cholangitis developed in none of the remaining 137 patients while awaiting randomization. Sixty (43.8%) were eligible for the study based on meeting one or more of the randomization criteria for high risk of persisting CBD stone. Of the 60, 59 were randomized (1 refused participation) on hospital day 4 to either group I (n = 30) (routine preoperative ERCP followed by laparoscopic cholecystectomy) or group II (n = 29) (laparoscopic cholecystectomy followed by selective postoperative ERCP only if a CBD stone was found on IOC). As shown in Table 1, there were no differences in admission or interval parameters for group I versus group II patients.

<table>
<thead>
<tr>
<th>Table 1. COMPARISON OF GROUPS I AND II</th>
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<tbody>
<tr>
<td><strong>Group I</strong> (n = 30)</td>
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<tr>
<td><strong>Admission</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Amylase (U/L)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
</tr>
<tr>
<td>WBC</td>
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<tr>
<td>Alkaline phosphatase</td>
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<tr>
<td>APACHE II score</td>
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<tr>
<td>Imrie score</td>
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<tr>
<td>CBD ≥8 mm</td>
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<tr>
<td><strong>Hospital day 4</strong></td>
</tr>
<tr>
<td>Total bil. ≥1.7 mg/dL</td>
</tr>
<tr>
<td>Amylase ≥150 U/L</td>
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Group I patients were randomized on mean hospital day 4.2. All 30 (100%) group I patients underwent routine preoperative diagnostic ERCP. This was performed on a mean of 1.5 days after randomization. Persisting CBD stones were found in 12 of 30 patients (40%; 95% confidence interval [CI] 23%–59%). These 12 patients underwent therapeutic ERCP with ES and stone retrieval. In 1 of the 12 (8%), there was failure of complete duct clearance with ERCP and ES because one of six CBD stones could not be retrieved. Interval spontaneous passage of the residual CBD stone was subsequently confirmed by IOC. There was only one complication of preoperative ERCP and ES: in the same patient, post-ERCP pancreatitis developed (3% overall incidence); it resolved spontaneously.

All 30 (100%) group I patients underwent successful laparoscopic cholecystectomy and IOC. This was per-
formed a mean of 2.9 days (median 2) after ERCP. Three patients had a long delay in surgery. In the patient with post-ERCP pancreatitis, surgery was delayed by 10 days until the pancreatitis fully resolved. In two other patients, surgery was delayed 7 days in each due to persistent abdominal pain. No additional CBD stones were found on IOC.

There were no deaths. There was one postoperative complication (3%): pancreatitis that resolved without intervention over a protracted hospital stay.

**Group II Management Outcomes**

Group II patients were randomized on mean hospital day 4.1. All 29 (100%) group II patients underwent laparoscopic cholecystectomy and IOC without preoperative ERCP. This was performed a mean of 2.4 days after randomization. Three patients had long delays between randomization and surgery, ranging from 5 to 8 days, due to persistent abdominal pain in two instances and persistent fevers in one.

At surgery, IOC was technically unsuccessful in one patient, but the findings on a postoperative diagnostic ERCP were negative. Eight of 29 patients (28%; 95% CI 13%–47%) had CBD stones on IOC (P = .41 vs. group I). In one patient with a CBD stone, a choledochoduodenal fistula was also discovered on IOC, prompting conversion to open cholecystectomy with CBD exploration and stone removal. In the remaining seven (24%) patients with CBD stones, there was no attempt at intraoperative clearance of duct stones; rather, they underwent postoperative therapeutic ERCP with ES and stone extraction. This was performed a mean of 1.1 days after surgery.

All CBD stones were successfully removed. The number of CBD stones ranged from one to three. The CBD stone size ranged from 4 to 8 mm.

There were no deaths. The one complication of postoperative ERCP and ES was transient fever and hyperbilirubinemia that prompted a repeat diagnostic ERCP with normal findings. There was one postoperative complication (3%): bleeding from the gallbladder fossa that was confirmed by computed tomography and was managed without surgery.

**Group Comparisons**

For group I patients, the mean hospital stay was 11.7 ± 6.1 days (range 6–30, median 9.5, interquartile ratio [IQR] 8–12) and the mean ICU stay was 1.7 ± 1.9 days (range 0–8, median 1, IQR 0–3). The mean hospital stay for group II patients was 9.0 ± 3.2 days (range 6–20, median 8, IQR 7–10). This was significantly shorter than for group I (P = .042). The mean number of ICU days was 1.9 ± 2.7 (range 0–11, median 1, IQR 0–3), which was not statistically different from group I (P = .64).

There was a significant decrease in ERCP use from group I patients (100%) to group II patients (24%) (P < .0001).

Table 2. MEAN HOSPITAL COSTS

<table>
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<tr>
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<th>Group I</th>
<th>Group II</th>
<th>P Value</th>
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<tr>
<td>ICU</td>
<td>$2,548 ± 2,728</td>
<td>$2,788 ± 3,955</td>
<td>.63</td>
</tr>
<tr>
<td>Ward</td>
<td>$6,113 ± 3,454</td>
<td>$4,703 ± 2,492</td>
<td>.06</td>
</tr>
<tr>
<td>ERCP</td>
<td>$540 ± 764</td>
<td>$307 ± 485</td>
<td>.0003</td>
</tr>
<tr>
<td>Surgical</td>
<td>$784</td>
<td>$788</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$10,210 ± 3,839</td>
<td>$8,586 ± 3,520</td>
<td>.049</td>
</tr>
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There were no statistically significant differences between the groups with regard to combined failure rates of cholangiography, CBD stone retrieval, or morbidity rates for ERCP and surgery (3/30 [10%] for group I vs. 3/29 [10.3%] for group II, odds ratio 1.04, 95% CI 0.22–4.9).

**Cost Analysis**

The mean hospital costs are summarized in Table 2. There was a significant reduction in mean total costs for group II patients ($8,586) versus group I patients ($10,210); this was the result of lower ERCP costs and lower ward bed costs. Because IOC after ERCP may not have been necessary in group I patients, we also performed cost analysis by subtracting the cost ($53) of IOC for group I. The probability value for this analysis was .067.

**Outcome of Nonrandomized Patients**

Seventy-seven patients did not meet randomization criteria, and one refused randomization. This latter patient requested preoperative ERCP. This was successfully performed with ES and retrieval of a CBD stone. Of the remaining 77 patients, none underwent preoperative ERCP, and cholangitis developed in none while awaiting cholecystectomy. All underwent laparoscopic cholecystectomy, and seven had CBD stones. In three patients, the CBD stones were successfully retrieved with postoperative ERCP and ES. In two patients, CBD stones had spontaneously cleared at the time of ERCP. In two other patients, CBD stones were retrieved by open CBD exploration because the operation had already been converted to open cholecystectomy for technical reasons.

There were five (6%) complications overall. Two patients required readmission within 30 days for elevated liver chemistries and abdominal pain. The findings on ERCP in both patients were normal. One patient had a postoperative minor bile leak that resolved spontaneously. One patient had an anesthetic-induced arrhythmia that forced postponement of surgery. There was one failure of IOC, for which a postoperative ERCP was performed; the results were normal. There were no postoperative deaths.
Confirmation of Utility of Randomization Criteria

Of the 60 patients who met the randomization criteria (including the 1 patient who refused randomization), 21 had CBD stones (35%; 95% CI 23%–48%). Of the 77 patients who did not meet the randomization criteria, only 7 (9%; 95% CI 3.8%–18%) had CBD stones (P = .0003). A more detailed analysis of the utility of the randomization criteria has been reported previously.3

DISCUSSION

This prospective randomized study of ERCP in patients with mild to moderate gallstone pancreatitis demonstrated a significant reduction in total hospital costs and length of hospital stay when selective ERCP was performed after surgery for CBD stones documented on IOC as compared to routine preoperative ERCP. Further, the utilization rate of ERCP was significantly reduced from 100% in the routine preoperative ERCP group to 24% in the selective postoperative ERCP group (P < .0001). The timing of ERCP (routine preoperative vs. selective postoperative) did not affect clinical outcomes (combined treatment failure rate). The combined treatment failure rate was acceptable (10%) (95% CI 4%–21%), further supporting the use of selective postoperative ERCP.

Our study differs from prior randomized ERCP trials for gallstone pancreatitis in several respects. We excluded patients who had evidence of concomitant cholangitis at presentation. Patients with cholangitis underwent urgent ERCP with ES and CBD stone extraction. Only 3% of our patients with gallstone pancreatitis had concomitant cholangitis,3 an incidence similar to those previously reported by others.7 We also excluded patients with necrotizing pancreatitis (2.6% of our population). Although such patients have been postulated to benefit from urgent ERCP with ES and CBD stone extraction4,5, we chose conservative initial management for these patients. In fact, a recent study has demonstrated no benefit from early ERCP and ES in patients with gallstone pancreatitis in the absence of concomitant obstructive jaundice.8 The present study therefore focused on patients with uncomplicated mild to moderate gallstone pancreatitis. This was confirmed by the low APACHE II and Imrie system scores. Randomization was delayed until hospital day 4. This allowed time for the pancreatitis to resolve. It also provided the opportunity to apply our previously reported criteria for predicting persisting CBD stones in gallstone pancreatitis to maximize the yield of ERCP.

The utility of these criteria (persistent hyperbilirubinemia ≥1.7 mg/dL and persistent hyperamylasemia ≥150 U/L) have recently been prospectively confirmed, although on multivariate analysis the single best predictor of CBD stones proved to be a serum total bilirubin >1.35 mg/dL on hospital day 2.3 We plan to use this revised criterion henceforth.

A theoretical concern with performing ERCP after surgery is failure to achieve CBD stone clearance, with a subsequent need for surgical reexplotation. This concern may be heightened in gallstone pancreatitis, where the ampulla of Vater may be edematous and difficult to cannulate. We previously reported a 100% CBD stone retrieval rate with postoperative ERCP, although the study was retrospective and the number of patients small.2 In one review of patients who underwent laparoscopic cholecystectomy for various indications, all symptomatic and asymptomatic CBD stones were cleared in 123 of 127 (97%) patients.9 In a more recent study of laparoscopic CBD exploration versus postoperative ERCP for symptomatic CBD stones, the postoperative ERCP duct clearance rate was 93%.10 This study was not limited to gallstone pancreatitis, however, and endoscopic CBD stone clearance is typically easier for other indications. To our knowledge, no previous randomized trial comparing preoperative and postoperative ERCP has focused exclusively on patients with isolated gallstone pancreatitis. In the present study, all CBD stones were successfully retrieved or passed spontaneously without the need for reoperation.

A theoretical problem in patients with gallstone pancreatitis is the development of cholangitis while awaiting ERCP. In the present study, cholangitis did not develop in any patients while awaiting randomization or treatment. The reported complication rates from ERCP vary widely, depending on the indication for ERCP and the expertise of the endoscopist.11 In a large multicenter study of 2,347 patients undergoing ERCP for various indications, 9.8% had complications, consisting primarily of pancreatitis (5.4%) and hemorrhage (2%).10 Complication rates were highest when the procedure was performed for sphincter of Oddi dysfunction (21.7%) and lowest when the indication was removal of CBD stones within 30 days of laparoscopic cholecystectomy (4.9%).11 Endoscopists who performed more than one sphincterotomy per week had lower rates of complications (8.4% vs. 11.1%).11 In the present study, 2 of the 59 randomized patients (3.4%) had complications of ERCP (pancreatitis and fever with hyperbilirubinemia in one patient each).

This study has several limitations. First, the limited sample size precluded a more precise comparison of the combined failure rates between the two treatment approaches. This is reflected in the relatively wide 95% CI for the odds ratio comparing these rates (0.22–4.9). Thus, although we have demonstrated no difference, we cannot exclude the possibility that the combined failure rate is higher with one treatment approach or the other. The number of patients randomized was limited because only patients considered at high risk for a persisting CBD stone were included. As noted, of the 77 patients who did not meet the randomization criteria, only 7 (9%) had persisting CBD stones, and all were detected on IOC at surgery. Had these 77 patients been randomized, the costs of diagnostic ERCP would have increased substantially, with only a very small increase in the number of CBD stones retrieved. Despite the relatively small sample size, there were significant reductions in costs.
and hospital stay in the selective postoperative ERCP group, as well as in the ERCP utilization rate.

Another limitation of the study was the inability to obtain actual costs of all aspects of patient care. We relied on Medicare reimbursement rates and did not consider anesthesia costs. Also, our policy is to perform IOC routinely during laparoscopic cholecystectomy, even if an ERCP has already been performed, to identify the ductal anatomy. If we excluded the cost of IOC for group I, there was still a trend toward cost savings in favor of group II.

In the present study, using a management protocol for gallstone pancreatitis that is followed at our institution, we were able to reduce the percentage of patients undergoing ERCP from 100% in group I to 24% in group II without compromising the clinical outcome. It would seem intuitive that subjecting most patients to only one procedure (cholecystectomy) would be less expensive and more expeditiously accomplished than performing two procedures (ERCP and cholecystectomy) in all patients. Nevertheless, this study attempted to address this issue in a prospective randomized fashion. Rather than subject all patients with gallstone pancreatitis to randomization, only the patients at high risk for CBD stones were included. Also, the study was limited to patients with mild to moderate gallstone pancreatitis who did not have cholangitis. From this study, we conclude that such patients can safely undergo laparoscopic cholecystectomy without preliminary ERCP. ERCP and stone retrieval can be performed after surgery in selected patients with CBD stones on IOC, provided an experienced endoscopist is available. Patients treated in this manner had lower costs, a shorter hospital stay, and a less frequent need for endoscopic intervention without any increase in the combined treatment failure rate.

References