Early Cholecystectomy for Mild to Moderate Gallstone Pancreatitis Shortens Hospital Stay

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BACKGROUND: The timing of cholecystectomy in gallstone pancreatitis remains controversial. We hypothesized that in patients with mild to moderate gallstone pancreatitis (three or fewer Ranson’s criteria), performing early cholecystectomy before resolution of laboratory or physical examination abnormalities would result in shorter hospitalization, without adversely affecting outcomes.

STUDY DESIGN: An observational study consisting of a retrospective and a prospective group was conducted. For the prospective group, a deliberate policy of early cholecystectomy (less than 48 hours from admission) was used. The primary end point was total length of hospital stay. Secondary endpoints were time from admission to definitive operation, need for endoscopic retrograde cholangiography, and major complications (organ failure and death).

RESULTS: Group I consisted of 177 patients retrospectively reviewed, and Group II was composed of 43 patients prospectively followed. There were no differences between the two groups with respect to demographics. With respect to admission laboratory values, there was a significant difference in median serum amylase, but there were no differences in median serum levels of lipase, total bilirubin, albumin, white blood cell count, or Ranson’s score. The median length of hospital stay was 7 days in Group I versus 4 days in Group II (p < 0.001). Median time from admission to cholecystectomy was 5 days in Group I versus 2 days in Group II (p < 0.0001). Complication rates were similar and there were no deaths in either group.

CONCLUSIONS: In patients with mild to moderate gallstone pancreatitis, a policy of early cholecystectomy resulted in a significantly reduced length of hospital stay with no increase in complications or mortality. (J Am Coll Surg 2007;205:762–766. © 2007 by the American College of Surgeons)

Calculous biliary disease remains the leading cause of acute pancreatitis in the US. The pathophysiology of gallstone pancreatitis is unclear, with several suggested theories. The “common channel” theory has led to the two most accepted explanations: reflux of duodenal juice into the pancreatic duct secondary to transient sphincter of Oddi dysfunction after stone passage or ductal hypertension secondary to sudden pancreatic duct obstruction. Removal of the gallbladder and clearance of calculi from the biliary tree are the cornerstones of treatment to prevent further attacks.

Current management of gallstone pancreatitis is laparoscopic cholecystectomy (LC) with intraoperative cholangiography (IOC), performed during the initial hospitalization. If common bile duct (CBD) stones are present on IOC, endoscopic retrograde cholangiography (ERC) with endoscopic sphincterotomy (ES) and stone removal can be performed postoperatively. Preoperative ERC is reserved for patients with evidence of concomitant cholangitis and is also advocated by some for patients with severe pancreatitis.

The timing of cholecystectomy is based not only on the severity of pancreatitis but also on physician preference. In the era of open cholecystectomy, Kelly and Wagner demonstrated that surgery for severe biliary pancreatitis (more than three Ranson’s criteria) was best delayed until resolution of the inflammatory process, but delaying operative intervention in mild to moderate (three or fewer Ranson’s criteria) cases was unnecessary. Despite this, Vitale stated, in a recent editorial, that his preferred approach in mild gallstone pancreatitis is to wait until enzymes and total bilirubin are normalizing before performing delayed cholecystectomy. This opinion is shared by other experienced pancreaticobiliary surgeons.

In the era of widespread use of LC for definitive management of biliary pancreatitis, there have been no prospective...
studies addressing timing and safety of early operative intervention. We hypothesized that early laparoscopic cholecystectomy within 48 hours in patients with mild to moderate gallstone pancreatitis would result in shorter hospitalization without adversely affecting outcomes, even in the absence of preoperative normalization of laboratory values and physical findings.

**METHODS**

A cohort study consisting of a retrospective (Group I) and a prospective group (Group II) with mild to moderate gallstone pancreatitis was conducted. For Group I, all charts from patients with discharge diagnoses of gallstone pancreatitis from 2003 through 2005 were reviewed. Patients with severe pancreatitis or concomitant acute cholangitis on admission were excluded. The prospective, observational Group II consisted of all patients admitted with a diagnosis of gallstone pancreatitis from July 2006 through February 2007. Patients with severe pancreatitis or acute cholangitis were excluded. At Harbor-UCLA Medical Center, the Trauma and Emergency Surgery service admits and manages these patients. The service consists of three teams, each with an attending surgeon, a chief or senior resident, a junior resident, and two interns. Institutional Review Board approval for the study was obtained from the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center.

Gallstone pancreatitis was defined by appropriate history and physical examination (midepigastric or right upper quadrant or abdominal pain, nausea, vomiting, abdominal tenderness, and absence of ethanol use), elevated serum levels of amylase, lipase, or both, and evidence of gallstones on either ultrasound or CT. Mild to moderate gallstone pancreatitis was defined by three or fewer Ranson's criteria on admission and by the absence of concomitant cholangitis, as previously described.

Patient demographic data, including age, race, and medical comorbidities, were recorded. Presenting signs and symptoms, vital signs, and laboratory values on admission and at 24 hours were noted. Management variables concerning the use of preoperative ERC, timing of LC, the performance of IOC, need for postoperative ERC ± ES, and outcomes were collected. For the prospective group, a deliberate policy of early cholecystectomy (less than 48 hours from admission) with IOC was used. IOC was omitted if cystic duct cannulation was not feasible. In Group II, the use of preoperative ERC was restricted to patients with a persistently elevated total bilirubin of > 4.0 mg/dL on hospital day 2. This policy was based on our earlier study that demonstrated that the total bilirubin level on hospital day 2 was the best predictor of a retained CBD stone. Our routine when CBD stones are found on IOC is to administer intravenous glucagon and flush the extrahepatic biliary system liberally with saline. Retained CBD stones after this maneuver were managed intraoperatively only if the procedure had to be converted to an open operation. Postoperative ERC was reserved for patients with a CBD stone found on IOC that was unable to be cleared intraoperatively. The primary end point was total length of hospital stay (LOS). Secondary end points were time from admission to cholecystectomy, use of ERC, and major complications (organ failure and death).

**Data analysis**

A priori, we set the alpha level to 0.05 and the power at 0.9 to find a reduction in the absolute length of stay of 30% in the prospective cohort, assuming a 7-day total LOS (with standard deviation of 2 days) in the retrospective cohort. To achieve this power, it was determined that a minimum of 25 subjects with gallstone pancreatitis would need to be prospectively enrolled, given that 177 subjects existed in the retrospective cohort. The sample size calculations were performed using PASS 2002 (NCSS). We elected to enroll 43 patients in the prospective cohort to achieve even greater power. Data from both groups were entered into a Microsoft Excel spreadsheet (Microsoft Corp), and the combined database was translated into native SAS format using DBMS/Copy 8 (Data Flux Corporation).

Using SAS 9.2 (SAS Institute), we compared admission demographic variables, vital signs, and laboratory data. For variables with a normal distribution, a traditional t-test was used to compare mean scores; Satterthwaite’s approximate t-test was used to compare median scores and interquartile ranges for variables with unequal variances. For the baseline categorical variable of race, analysis of variance (ANOVA) was used to compare the two cohorts. Mantel-Haenszel chi-square odds ratios were used to compare differences in use of ERC, rates of organ failure, and mortality between the two cohorts; t-tests (or Satterthwaite’s approximate t-test) were used to compare the continuous variable outcomes: total length of hospital stay and days to cholecystectomy.

**Abbreviations and Acronyms**

- CBD = common bile duct
- ERC = endoscopic retrograde cholangiography
- ES = endoscopic sphincterotomy
- IOC = intraoperative cholangiography
- LC = laparoscopic cholecystectomy
- LOS = length of stay

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RESULTS

Patient demographics

Group I consisted of 198 patients. Twenty-one patients were excluded secondary to concomitant cholangitis or severe pancreatitis, leaving 177 patients. Group II consisted of 47 patients, 3 of whom were excluded secondary to evidence of cholangitis, and 1 for severe pancreatitis, leaving 43 patients. There were no significant differences between the groups with respect to median age (40 versus 40.5 years), female gender (73% versus 70%), ethnicity (83% versus 85% Hispanic), or medical comorbidities (18% versus 13%). Among the admission laboratory values, there were significant differences in median levels of serum amylase (1,155 mg/dL versus 682 mg/dL \(p = 0.003\)) and blood urea nitrogen (10 mg/dL versus 9.5 mg/dL \(p = 0.03\)) but no differences in lipase, total bilirubin, aspartateaminotransferase, alanine aminotransferase, albumin, creatinine, or white blood cell count (Table 1). There was no significant difference in the median admission Ranson’s score (0 versus 0).

Patient management

All patients in Group I underwent LC during their initial hospitalization. None required conversion to an open procedure. Forty-one (95%) patients in Group II underwent attempted LC during the index hospitalization. One patient was discharged without surgery secondary to concerns for bleeding because the patient was taking clopidogrel, and the other patient had surgery delayed because of developing respiratory and renal failure. One patient’s operation was converted to an open cholecystectomy because of unclear anatomy. An IOC was performed in 145 (82%) patients in Group I and 40 (93%) patients in Group II. One patient in Group II who underwent preoperative ERC with stone removal and sphincterotomy did not have an IOC performed secondary to an inability to cannulate the cystic duct, and two patients did not undergo surgery, so no IOC could be performed.

A total of 60 (34%) patients in Group I underwent ERC ± ES, 36 (60%) of which were performed preoperatively, and 24 (40%) were done postoperatively for CBD stones on IOC. Eleven patients (25%) in Group II required an ERC ± ES, 9 (82%) of which were done preoperatively and 2 (13%) postoperatively. There was no difference in overall ERC use \(p = 0.4\). There was a significant decrease in postoperative ERC use in Group II \(p = 0.04\), even though this group underwent operations earlier (a median of 2 days versus 5, \(p = < 0.0001\)).

Outcomes

The median LOS was 7 days in Group I versus 4 days in Group II \(p = < 0.0001\), Table 2). Median time from admission to cholecystectomy was 5 days in Group I versus 2 days in Group II \(p = < 0.0001\). The complication rate was 4.5% in Group I versus 4.8% in Group II \(p = 0.7\), Table 1). Specific complications are shown in Table 2.

DISCUSSION

This study investigated the optimal timing of LC in mild to moderate gallstone pancreatitis. A prospective group of 43

Table 1. Demographic and Management Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I, median (IQR), n = 198</th>
<th>Group II, median (IQR), n = 39</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>40 (28–54)</td>
<td>36.5 (29–59)</td>
<td>0.5</td>
</tr>
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<td>Amylase, mg/dL</td>
<td>1,155 (530–2,092)</td>
<td>682 (195–1,142)</td>
<td>0.003</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>10 (7–14)</td>
<td>9.5 (7–12)</td>
<td>0.03</td>
</tr>
<tr>
<td>Lactate dehydrogenase, mg/dL</td>
<td>261 (188–439)</td>
<td>201 (150–260)</td>
<td>0.004</td>
</tr>
<tr>
<td>Endoscopic retrograde cholangiography, %</td>
<td>34</td>
<td>28</td>
<td>0.4</td>
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</tbody>
</table>

Outcomes

<table>
<thead>
<tr>
<th>Days to operation, n</th>
<th>5 (3–7)</th>
<th>2 (1–3)</th>
<th>&lt; 0.0001</th>
</tr>
</thead>
<tbody>
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<td>Length of stay, d</td>
<td>7 (5–11)</td>
<td>4 (3–5)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Complication rate, %</td>
<td>4.5</td>
<td>4.8</td>
<td>0.7</td>
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<tr>
<td>Death rate, %</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

IQR, interquartile range; NA, not available.

Table 2. Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Bile leak</td>
<td>1</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
</tr>
</tbody>
</table>
patients was compared with a retrospective group of 177 patients. By using a protocol of early LC (less than 48 hours from admission) in the prospective group, without waiting for the normalization of enzymes or physical examination, the total LOS was significantly reduced from 7 to 4 days (p = < 0.001) without altering morbidity and mortality. Although laparoscopic CBD exploration was not performed in this study, such an approach certainly has the potential to further decrease length of stay by minimizing the need for postoperative ERC.

Kelly and Wagner9 previously addressed the appropriate timing of open cholecystectomy for acute biliary pancreatitis in a prospective randomized study. The study spanned 12 years, from 1975 to 1988, and randomized 165 patients, all during the era before LC. In patients with 3 or fewer Ranson’s criteria, early operation (within 48 hours) resulted in a 6.7% morbidity and a 3.3% mortality, versus a 3.1% morbidity and a 0% mortality in the delayed group; the differences were not significant. With severe pancreatitis, early operation was associated with high morbidity and mortality rates of 82.6% and 47.8%, respectively. By comparison, there was a 17.6% morbidity rate and an 11% mortality rate with delayed surgery (p < 0.001). As a result of this study, delayed open cholecystectomy for severe gallstone pancreatitis became the accepted approach.

Although delay in surgery remains the standard of care for severe gallstone pancreatitis, the timing of cholecystectomy for mild to moderate gallstone pancreatitis remains controversial. There has been a paucity of studies addressing this issue in the laparoscopic era, and none has been prospective or randomized. Tang and colleagues8 retrospectively demonstrated that early surgery (more than 48 hours but less than 1 week from admission) was safe in mild gallstone pancreatitis, leading to a decreased mean length of stay of 4.2 days. But they recommended operation after biochemical and clinical resolution of pancreatitis. In another retrospective study, Taylor and Wong7 compared the approaches of two surgeons. Surgeon 1 preferred to delay operation until normalization of amylase and complete resolution of abdominal tenderness; surgeon 2 proceeded to LC as soon as the amylase was decreasing and the abdominal pain was improving. The complication rate was 10% for surgeon 1 and 11% for surgeon 2 (p = 0.12). Hospital stay was 4.7 days for surgeon 1’s patients and 3.7 days for surgeon 2’s patients (p = 0.01).

The role of preoperative ERC for gallstone pancreatitis is also controversial and is another contributor to the delay in definitive cholecystectomy. In a prospective, randomized study, Fan and associates16 demonstrated that routine early (less than 24 hours from admission) ERC resulted in a decreased rate of biliary sepsis, without any significant differences in local or systemic complications or mortality. But a criticism of the study was that patients with cholangitis may have been randomized to the nonurgent ERC group.

Folsch and coworkers11 demonstrated that, in the absence of cholangitis, there was no benefit from early ERC and ES. In a prospective randomized study from our institution, patients with mild to moderate gallstone pancreatitis without cholangitis were randomized to preoperative ERC versus postoperative ERC if CBD stones were seen on intraoperative cholangiography.12 There was no difference in complication rate, but length of stay and costs were significantly less in the postoperative ERC group. In a separate prospective study, biochemical markers were followed daily to determine the best predictor of retained CBD stones in gallstone pancreatitis.7 A serum total bilirubin greater than 1.35 mg/dL on hospital day 2 had a sensitivity of 90.5% and a specificity of 60% for predicting the presence of a common duct stone; a serum bilirubin greater than 4.0 mg/dL on day 2 had a sensitivity and specificity of 40% and 85%, respectively. A recent metaanalysis of three randomized controlled trials comparing early CBD decompression versus conservative management in patients with gallstone pancreatitis demonstrated a significant decrease in complications if ERC ± ES was performed early in patients with severe biliary pancreatitis.15 Conversely, this metaanalysis did not demonstrate any decrease in morbidity or mortality when early decompression was used for mild gallstone pancreatitis. So our current approach for mild to moderate pancreatitis is to limit ERC to patients with suspected cholangitis or persistent elevation of total bilirubin above 4.0 mg/dL on hospital day 2. In this study, there was no difference in the use of ERCP in Groups I and II. These prospective findings support the judicial use of ERC in patients with mild biliary pancreatitis.

Patients with mild to moderate gallstone pancreatitis can safely undergo early LC without waiting for the normalization of laboratory values or resolution of symptoms. A policy of early LC resulted in a significantly reduced LOS. The approach did not result in an increased need for ERC or an increased complication or mortality rate. We have currently submitted a proposal for a prospective randomized study protocol, to further address the timing of cholecystectomy that will include a cost analysis. This protocol currently awaits approval from our IRB.

Author Contributions
Study conception and design: de Virgilio
Acquisition of data: Rosing, Yaghoubian, El Masry
Analysis and interpretation of data: de Virgilio, Rosing, Kaji
Drafting of manuscript: Rosing
Critical revision: de Virgilio, Stabile
REFERENCES