Prospective Randomized Trial of LC+LCBDE vs ERCP/S+LC for Common Bile Duct Stone Disease

Stanley J. Rogers, MD; John P. Cello, MD; Jan K. Horn, MD; Allan E. Siperstein, MD; William P. Schecter, MD; Andre R. Campbell, MD; Robert C. Mackersie, MD; Alex Rodas, CCRC; Huub T. C. Kreuwel, PhD; Hobart W. Harris, MD

Objective: To compare outcome parameters for good-risk patients with classic signs, symptoms, and laboratory and abdominal imaging features of cholecystolithiasis and choledocholithiasis randomized to either laparoscopic cholecystectomy plus laparoscopic common bile duct exploration (LC+LCBDE) or endoscopic retrograde cholangiopancreatography sphincterotomy plus laparoscopic cholecystectomy (ERCP/S+LC).

Design: Our study was a prospective trial conducted following written informed consent, with randomization by the serially numbered, opaque envelope technique.

Setting: Our institution is an academic teaching hospital and the central receiving and trauma center for the City and County of San Francisco, California.

Patients: We randomized 122 patients (American Society of Anesthesiologists grade 1 or 2) meeting entry criteria. Ten of these patients, excluded from outcome analysis, were protocol violators having signed out of the hospital against medical advice before 1 or both procedures were completed.

Interventions: Treatment was preoperative ERCP/S followed by LC, or LC+LCBDE.

Main Outcome Measures: The primary outcome measure was efficacy of stone clearance from the common bile duct. Secondary end points were length of hospital stay, cost of index hospitalization, professional fees, hospital charges, morbidity and mortality, and patient acceptance and quality of life scores.

Results: The baseline characteristics of the 2 randomized groups were similar. Efficacy of stone clearance was likewise equivalent for both groups. The time from first procedure to discharge was significantly shorter for LC+LCBDE (mean [SD], 55 [45] hours vs 98 [83] hours; P<.001). Hospital service and total charges for index hospitalization were likewise lower for LC+LCBDE, but the differences were not statistically significant. The professional fee charges for LC+LCBDE were significantly lower than those for ERCP/S+LC (median [SD], $4820 [1637] vs $6139 [1583]; P<.001). Patient acceptance and quality of life scores were equivalent for both groups.

Conclusions: Both ERCP/S+LC and LC+LCBDE were highly effective in detecting and removing common bile duct stones and were equivalent in overall cost and patient acceptance. However, the overall duration of hospitalization was shorter and physician fees lower for LC+LCBDE.

Trial Registration: clinicaltrials.gov Identifier: NCT00807729.


CME available online at www.jamaarchivescme.com and questions on page 7

Limited studies have prospectively compared LC plus laparoscopic common bile duct exploration (LC+LCBDE) with conventional ERCP/S followed by LC. We therefore conducted a randomized prospective controlled clinical trial comparing these techniques in good-risk patients with cholecystolithiasis and “likely” choledocholithiasis.
STUDY DESIGN

The study was a randomized controlled trial comparing preoperative ERCP/S followed by LC (ERCP/S+LC) with LC+LCBDE. The protocol and the consent form were approved by the Committee on Human Research of the University of California, San Francisco.

PATIENT POPULATION

Patients were selected from among a good-risk population (American Society of Anesthesiologists grade 1 or 2) with classic signs and symptoms of gallstone disease from San Francisco General Hospital, the central receiving hospital and trauma center for the city. Thus, patients who had clinical and/or laboratory data and/or radiographic imaging suggestive of cholecystitis, cholelithiasis, cholangitis, gallstone pancreatitis, choledocholithiasis, and/or cholecytitis and met the inclusion/exclusion criteria (Table 1) were approached by one of the investigators or a research assistant, who verified their eligibility and offered enrollment in the study after they had given fully informed written consent. Patients with suppurative cholangitis or clinically severe pancreatitis and others without an American Society of Anesthesiologists grade of 1 or 2 at the time of intended randomization were excluded as per protocol. Prior to enrollment, all patients received standard nonstudy treatments, including antibiotics, intravenous fluids, and modification of dietary intake. Participants received randomized treatment assignments according to serially numbered, sealed, opaque envelopes. These envelopes were held securely and separately at 1 site by the principal investigator (S.J.R.). Enrollment lasted 57 months (beginning on September 19, 1997, and ending on June 26, 2003).

STUDY INTERVENTIONS

Endoscopic Retrograde Cholangiopancreatography

All ERCPs were performed by one of us (J.P.C.), a full-time faculty member and gastroenterology fellowship instructor, in the presence and concurrence of the principal author/surgeon (S.J.R.). Patients randomized to ERCP/S+LC were scheduled to undergo the endoscopic procedure using fluoroscopy (9400; OEC Diasonics, Warsaw, Indiana) in the endoscopy suite under moderate sedation (principally intravenous midazolam and meperidine) prior to the intended laparoscopy. Duodenal atony during ERCP was routinely achieved using intravenous glucagon. If choledocholithiasis was detected or suspected at the time of ERCP, a sphincterotomy was undertaken so that gallstones could be extracted using a balloon catheter or retrieval basket. Small-bowel gas was aspirated endoscopically as much as possible at the conclusion of the ERCP. The LC was subsequently performed as soon as technically feasible (ie, following abdominal gas decompression) following the ERCP.

LC and Removal of Common Bile Duct Stones

Laparoscopic cholecystectomy plus LCBDE was performed in a routine fashion by 1 full-time faculty member (S.J.R.) with fellowship training in laparoscopy. Cholangiograms were obtained fluoroscopically using the same make and model fluoroscope (OEC Diasonics 9400) as used in ERCP by antegrade contrast flushing through the cystic duct. All fluoroscopy was performed by the principal author (S.J.R.) in the presence of and concurrence with the ERCP endoscopist (J.P.C.). When stones were detected or suspected by cholangiography, transpapillary exploration was undertaken by balloon or basket with associated balloon dilation of the sphincter of Oddi. A completion cholangiogram was obtained to confirm that all stones were removed. Once the LCBDE was completed, the cystic duct was ligated and the gallbladder removed.

A standardized short-form 36-item questionnaire (Outcomes Study 36-Item Short-Form General Health Survey) was given to all patients just before discharge from the hospital. The Karnofsky performance score was calculated for all patients at the first routine postoperative outpatient visit.

STUDY MEASURES

The primary end point was the efficacy of common bile duct stone clearance. Secondary end points were length of hospital stay, total cost of index hospitalization, professional fee charges, hospital charges, morbidity and mortality, and patient acceptability and quality of life scores. Hospital and professional charges were calculated using standard Medicare fee schedules.

STATISTICAL ANALYSIS

Primary and secondary outcome variables were compared between groups by using either Fisher exact test or a 2-tailed Mann-Whitney nonparametric test for independent samples. The Cox

Table 1. Inclusion and Exclusion Criteria for the Study

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Age &gt; 18 years</td>
<td>History of bleeding disorders, platelet count &lt; 100 000 × 10^9/L and/or prothrombin time &gt; 3 s over control</td>
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<td></td>
<td>Uremia as evidenced by a creatinine level &gt; 3 mg/dL and/or a blood urea nitrogen level &gt; 50 mg/dL</td>
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<td></td>
<td>Ultrasonographic or CT evidence of cirrhosis, intrahepatic gallbladder, liver mass or abscess, or periamputary neoplasm</td>
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<tr>
<td></td>
<td>Clinical or sonographic evidence of suppurative or necrotizing cholecystitis, gallbladder empyema, or perforation</td>
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<td></td>
<td>Insulin-dependent diabetes mellitus</td>
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<td></td>
<td>Multiple prior laparotomies</td>
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<td></td>
<td>Morbid obesity</td>
</tr>
<tr>
<td></td>
<td>Clinical, radiologic, and/or biochemical evidence of cirrhosis or portal vein thrombosis</td>
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<td></td>
<td>Pregnancy</td>
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</tbody>
</table>

Abbreviation: CT, computed tomography.

SI conversion factors: To convert platelet count to ×10^12/L, multiply by 1; bilirubin to micromoles per liter, multiply by 17.1; creatinine to micromoles per liter, multiply by 88.4; urea nitrogen to millimoles per liter, multiply by 0.357.
A proportional hazards model was used to test statistical hypotheses and analyze the effect of other possible covariates on outcome.

RESULTS

A total of 122 patients were randomized by serially numbered, sealed envelopes over the course of 57 months and had at least 24 months of follow-up review. Sixty-one patients were randomized to ERCP/S+LC and 61 patients were randomized to LC+LCBDE. Ten randomized patients were protocol violations and excluded from outcome analysis: 6 in the ERCP/S+LC arm and 4 in the LC+LCBDE arm. These patients had given written consent and were randomized, but then signed out of the hospital against medical advice before study procedures were completed. An additional 15 patients over the 57-month period were approached for randomization, declined to give informed consent to participate, and were not included in the study.

PATIENT CHARACTERISTICS

Demographic and clinical characteristics (Table 2) did not differ significantly between the study groups, except for fever and tachycardia, which were more common in the ERCP/S+LC group. Eighty percent of patients, disproportionately women, had right upper quadrant and/or epigastric abdominal pain together with nausea, vomiting, and intermittent biliary colic. Forty patients had an admission diagnosis of gallstone pancreatitis while 21 had clinical jaundice, the majority of whom presented with clinical cholangitis.

Laboratory diagnostic test results, aside from albumin level, did not differ significantly between the study groups (Table 2). Patients randomized to ERCP/S+LC had a significantly higher mean serum albumin level ($P < .05$). Both groups had modest leukocytosis, supporting a preprocedure suspicion of likely common bile duct calculi. Serum bilirubin, alkaline phosphatase, transaminase, and amylase levels were elevated in both groups but were not significantly different between the groups. As per the study protocol, cholecystolithiasis was detected by noninvasive imaging in all patients, principally ultrasonography and/or computed tomography. Dilated extrahepatic or intrahepatic bile ducts or both were noted by ultrasonography, computed tomographic scans, or both in 69 patients (32 in the ERCP/S+LC group and 37 in the LC+LCBDE group). In addition, noninvasive imaging studies identified likely common bile duct stones before direct cholangiography in 13 patients in the ERCP/S+LC group and 12 patients in the LC+LCBDE group. None of the laboratory and preprocedure radiological findings differed significantly between the groups.

### Table 2. Characteristics of Patients at the Time of Admission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ERCP/S+LC (n=61)</th>
<th>LC+LCBDE (n=61)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>55</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>44.6 (1.9)</td>
<td>39.9 (1.9)</td>
<td>.46</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>M</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>39</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>American Society of Anesthesiologists score, mean (SD)</td>
<td>1.9 (0.1)</td>
<td>1.9 (0.1)</td>
<td>.60</td>
</tr>
<tr>
<td>Right upper quadrant pain</td>
<td>49</td>
<td>49</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>43</td>
<td>41</td>
<td>.52</td>
</tr>
<tr>
<td>Nausea/emesis</td>
<td>40</td>
<td>38</td>
<td>.54</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>29</td>
<td>37</td>
<td>.25</td>
</tr>
<tr>
<td>Clinical pancreatitis</td>
<td>19</td>
<td>21</td>
<td>.84</td>
</tr>
<tr>
<td>Jaundice</td>
<td>11</td>
<td>10</td>
<td>.81</td>
</tr>
<tr>
<td>Fever, body temperature &gt;38.5°C</td>
<td>14</td>
<td>4</td>
<td>.01</td>
</tr>
<tr>
<td>Tachycardia, pulse &gt;100/min</td>
<td>11</td>
<td>1</td>
<td>.002</td>
</tr>
<tr>
<td>Hematocrit level, %, mean (SD)</td>
<td>41.0 (0.7)</td>
<td>40.1 (0.7)</td>
<td>.36</td>
</tr>
<tr>
<td>White blood cell count, /µL, mean (SD)</td>
<td>10 200 (600)</td>
<td>9200 (600)</td>
<td>.28</td>
</tr>
<tr>
<td>Bilirubin level, mg/dL, mean (SD)</td>
<td>2.8 (0.3)</td>
<td>2.4 (0.3)</td>
<td>.22</td>
</tr>
<tr>
<td>Alkaline phosphatase level, U/L, mean (SD)</td>
<td>226 (28)</td>
<td>269 (38)</td>
<td>.92</td>
</tr>
<tr>
<td>Aspartate aminotransferase level, U/L, mean (SD)</td>
<td>338 (33)</td>
<td>326 (43)</td>
<td>.82</td>
</tr>
<tr>
<td>Alanine aminotransferase level, U/L, mean (SD)</td>
<td>756 (211)</td>
<td>452 (139)</td>
<td>.22</td>
</tr>
<tr>
<td>Amylase level, U/L, mean (SD)</td>
<td>4.1 (0.1)</td>
<td>3.8 (0.1)</td>
<td>.03</td>
</tr>
<tr>
<td>Albumin level, g/dL, mean (SD)</td>
<td>32</td>
<td>37</td>
<td>.56</td>
</tr>
<tr>
<td>Dilated ductsa</td>
<td>13</td>
<td>12</td>
<td>.82</td>
</tr>
</tbody>
</table>

**Abbreviations:** ERCP/S+LC, preoperative endoscopic retrograde cholangiopancreatography sphincterotomy followed by laparoscopic cholecystectomy; LC+LCBDE, laparoscopic cholecystectomy plus laparoscopic common bile duct exploration.

**SI conversion factors:** To convert white blood cell count to $10^9$/L, multiply by 0.001; bilirubin to micromoles per liter, multiply by 17.104; alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and amylase to microkatals per liter, multiply by 0.0167; albumin to grams per liter, multiply by 10.

a By ultrasonography or computed tomography.
EFFICIENCY OF STONE CLEARANCE

Among the secondary outcomes, only duration between the first procedure until hospital discharge and overall professional fee charges differed significantly between the 2 groups (Table 4 and Table 5). Duration between the first procedure and hospital discharge was almost 2 days shorter in the LCBDE group (mean, 55 hours vs 98 hours for the ERCP/S + LC group; P < .001). Professional fees for the 2-procedure ERCP/S + LC arm were significantly higher than those for the single-procedure LCBDE arm (median [SD], $6139 [ $1583] vs $4820 [ $1637]; P < .001). Total hospitalization charges, patient acceptance, and quality of life scores were, however, not significantly different.

COMMENT

Our study demonstrates that LCBDE is equivalent in efficacy and safety to preoperative ERCP/S + LC for patients with “likely” common bile duct stones. However, common bile duct stones were more frequently reported during ERCP/S + LC than during LCBDE. This is likely because ERCP by technique allows fluoroscopic and endoscopic identification of small stones and sludge that would otherwise be immediately pushed clear when contrast is first injected during the antegrade cholangiography phase of LCBDE. Furthermore, ERCP with retrograde passage of occlusion balloons permits better detection and removal of proximal ductal stones. In short-term follow-up, however, no study patients returned with findings suggestive of residual stones. However, additional analysis of the long-term follow-up and consequences of either transcystic cholangiography or endoscopic sphincterotomy are necessary.

Several studies have been reported on the efficacy, safety, and efficiency of common bile duct stone removal whether by ERCP and/or LCBDE. In 2006, Martin et al23 in a meta-analysis of 8 trials and 760 patients comparing open laparotomy cholecystectomy and CBDE with preoperative ERCP/S + LC followed by cholecystectomy. Endoscopic retrograde cholangiopancreatoscopy sphincterotomy plus LC was less successful than the open surgery in bile duct clearance (odds ratio, 2.89; 95% confidence interval, 1.81-4.61).

Endoscopic retrograde cholangiopancreatoscopy with sphincterotomy has been available in most major medical centers around the world for nearly 30 years1-4,6,9 and is routinely used currently in conjunction with LC, rather than open cholecystectomy, to treat choledocholithiasis. The overall success rate of ERCP in experienced hands is well established at about 95%. However, the minimum number of ERCP procedures necessary for competency has been suggested by Jowell et al25 and Vitale et al26 to be between 102 and 185 procedures to achieve a success rate of 85% to 90%.

Laparoscopic CBDE has been developed over the past 2 decades as a means of dealing with common bile stones discovered incidentally during the course of LC.10-24 In a retrospective review by Paganini and Lezoche16 of 284 patients undergoing LCBDE, an overall success rate of 94.6% was reported. No data exist as to the minimum number of procedures for competency in CBDE when proficiency in routine LC has been demonstrated.

A handful of retrospective studies have compared ERCP/S + LC with LCBDE for common bile duct stones. Liberman et al19 reported that total hospital charges and total costs were significantly less for the LCBDE group, while length of hospitalization was also significantly lower in the single operative procedure group. Heili et al22 in a retrospective review, compared patients who underwent ERCP following LC with patients undergoing the single laparoscopic procedure. They reported a significant reduction in the length of hospital stay and overall morbidity in patients receiving the single operative procedure compared with those in the ERCP group. The total costs of hospitalization were also lower, but not significantly so, in the LCBDE group compared with the group receiving the preoperative ERCP.

Cuschieri et al20 reported in 1999 the results of a multicenter prospective randomized trial comparing preoperative ERCP/S + LC with LC + LCBDE. Cholangiography in their hands was successfully accomplished in 93%...
of the ERCP group and 99% of the LCBDE group. Complications and mortality were not significantly different between the groups. However, they reported a significant difference in duration of hospitalization, with a median hospital stay of 6 days in the ERCP group compared with 9 days in the LCBDE group (P < .05).

Sgourakis and Karaliotas\textsuperscript{21} published in 2002 a second randomized trial of preoperative laparoscopic ERCP/S+LC (36 patients) vs LCBDE (42 patients). Stone detection and clearance were equivalent between the groups (24 of 28 stones [86%] cleared by ERCP/S+LC vs 27 of 32 stones [84%] cleared by LCBDE). They noted, however, an 18% morbidity and 1% mortality in each group, with median hospital durations of 7.4 and 9.0 days, respectively.

In our study, stone clearance by LCBDE (88%) was nearly identical to that reported in the Sgourakis and Karaliotas article\textsuperscript{21}; however, our ERCP/S clearance rate (98%) was higher. There is, of course, a possibility of a type II error in our study and other studies. We can estimate that given our overall study size with stones detected in 31 of 55 ERCP/S+LC patients and in 17 of 57 LC+LCBDE patients, the power to detect a significant difference (α = .05) in CBDE clearance would be approximately 0.82.

The time from the first procedure to hospital discharge was significantly less for patients undergoing the single operative procedure (LCBDE). Although professional fees were significantly less for patients in the LCBDE arm, total hospital charges and overall charges were basically equivalent. This was likely due to higher operating room charges associated with longer anesthesia time and higher equipment expenses in the LCBDE arm compared with comparable time and equipment for moderate sedation in the endoscopy suite in the ERCP/S+LC study group. Patient satisfaction and quality of life scores were equivalent in both groups using standardized scoring.

In conclusion, our study shows that both ERCP/S+LC and LC+LCBDE were highly effective in detecting and removing common bile duct stones and were equivalent in overall cost and patient acceptance. However, the overall duration of hospitalization was shorter for LC+LCBDE. Laparoscopic CBDE eliminates the potential risks of ERCP-associated pancreatitis and the need for another procedure and the associated risks of anesthesia. As surgical skill with laparoscopic exploration of the common bile duct increases, the need for routine preoperative ERCP will likely decrease, except in unique high-risk situations. Therefore, a single surgical procedure for common bile duct stone disease is feasible, cost-effective, and ultimately should be available for most patients.

Accepted for Publication: February 10, 2009.
Correspondence: Stanley J. Rogers, MD, 3A Surgical Service, San Francisco General Hospital, 1001 Potrero Ave, San Francisco, CA 94110 (stan.rogers@ucsfmedctr.org).

Author Contributions: Dr Rogers had full access to all the data in the study and takes responsibility for the accuracy and integrity of the data analysis. Study concept and design: Rogers, Cello, Horn, Siperstein, Schecter, Campbell, and Mackersie. Acquisition of data: Rogers, Cello, Mackersie, Rodas, and Harris. Analysis and inter-
REFERENCES