Gallstone Pancreatitis

Admission Versus Normal Cholecystectomy—a Randomized Trial (Gallstone PANC Trial)

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Introduction: Early cholecystectomy shortly after admission for mild gallstone pancreatitis has been proposed based on observational data. We hypothesized that cholecystectomy within 24 hours of admission versus after clinical resolution of gallstone pancreatitis that is predicted to be mild results in decreased length-of-stay (LOS) without an increase in complications.

Methods: Adults with predicted mild gallstone pancreatitis were randomized to cholecystectomy with cholangiogram within 24 hours of presentation (early group) versus after clinical resolution (control) based on abdominal exam and normalized laboratory values. Primary outcome was 30-day LOS including readmissions. Secondary outcomes were time to surgery, endoscopic retrograde cholangiopancreatography (ERCP) rates, and postoperative complications. Frequentist and Bayesian intention-to-treat analyses were performed.

Results: Baseline characteristics were similar in the early (n = 49) and control (n = 48) groups. Early group had fewer ERCPs (15% vs 29%, $P = 0.038$), faster time to surgery (16 h vs 43 h, $P < 0.005$), and shorter 30-day LOS (50 h vs 77 h, RR 0.68 95% CI 0.65 – 0.71, $P < 0.005$). Complication rates were 6% in early group versus 2% in controls ($P = 0.613$), which included recurrence/progression of pancreatitis (2 early, 1 control) and a cystic duct stump leak (early). On Bayesian analysis, early cholecystectomy has a 99% probability of reducing 30-day LOS, 93% probability of decreasing ERCP use, and 72% probability of increasing complications.

Conclusion: In patients with predicted mild gallstone pancreatitis, cholecystectomy within 24 hours of admission reduced rate of ERCPs, time to surgery, and 30-day length-of-stay. Minor complications may be increased with early cholecystectomy. Identification of patients with predicted mild gallstone pancreatitis in whom early cholecystectomy is safe warrants further investigation.

Keywords: cholecystectomy, gallstone pancreatitis, patient-reported outcomes, timing

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Pancreatitis is common in the United States, with a yearly incidence of 40 per 100,000 people. Pancreatitis leads to more than 300,000 inpatient admissions and 20,000 deaths annually, with costs exceeding $2.2 billion per year.[1] Thirty-five to 55% of pancreatitis cases are related to gallstones.[1] In patients with mild gallstone pancreatitis—characterized by the absence of organ failure, peripancreatic fluid collections or necrosis, and typical resolution within 1 week—evidence-based guidelines recommend cholecystectomy during index admission but do not specify further management recommendations.[2] The practice of waiting for clinical and laboratory resolution of acute gallstone pancreatitis stemmed from a 1980s randomized trial that showed higher morbidity and mortality with surgery performed prior to 48 hours after admission.[3] However, this practice is questioned based on recent data.[4–7]

Early cholecystectomy for mild gallstone pancreatitis has been reported in observational studies to be associated with reduced hospital length of stay (LOS) without increasing complications, even when performed in the subgroup of patients who have not had resolution of clinical symptoms and laboratory values.[4–7] In these studies, cholecystectomy was performed within 48 to 72 hours of admission. A recent randomized trial also showed that cholecystectomy within 48 hours of admission regardless of clinical and laboratory resolution led to shorter hospital LOS without increasing complications; however, this trial was terminated after interim analysis at 50% enrollment once the prespecified effect size was detected,[8] and trials stopped early for benefit typically overestimate treatment effects.[9]

Additional randomized trials are needed to confirm the safety and generalizability of early cholecystectomy for predicted mild acute gallstone pancreatitis. Furthermore, there are no prior randomized trials evaluating laparoscopic cholecystectomy within the first 24 hours of admission or in disadvantaged populations treated at safety-net hospitals.

The objectives of this pilot randomized trial were: 1) to determine the feasibility of early cholecystectomy within 24 hours of presentation regardless of symptoms or laboratory values for patients mild gallstone pancreatitis predicted to be mild on admission, and 2) to obtain unbiased estimates of the effect of early

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The trial was approved by the Institutional Review Board on December 2, 2015. The trial was registered on ClinicalTrials.gov on June 13, 2016. The first patient was randomized on June 27, 2016. The trial was stopped from May 18, 2017 to August 16, 2017 for analysis by the DSMB and modifications to the protocol (including on ClinicalTrials.gov). Enrollment resumed in August 2017, and was completed June 28, 2018. The ClinicalTrials.gov identifier for the trial is NCT02806297. All patients gave informed consent to participate in the study. The trial was approved by the Institutional Review Boards of the McGovern Medical School at the University of Texas Health Science Center and Harris Health System. (HSC-MS-15-0719).

LSK, KMM, SW, and KB had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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cholecystectomy on hospital LOS, complications, and patient-reported outcomes (PROs) in order to determine the need for further evaluation. The hypothesis was that early cholecystectomy during index admission for predicted mild gallstone pancreatitis is feasible and results in shorter 30-day total hospital LOS without an increase in complications.

METHODS

Design

A single-center, parallel-group randomized trial (NCT02806297) was performed comparing timing of laparoscopic cholecystectomy with intraoperative cholangiogram (IOC) during index admission among patients with predicted mild gallstone pancreatitis.[10] The trial compared cholecystectomy within 24 hours of presentation to cholecystectomy after clinical resolution on outcomes including 30-day hospital LOS, time to surgery, endoscopic retrograde cholangiopancreatography (ERCP) rates, complications, and PROs. Institutional Review Board approval was obtained.

Setting

The trial was conducted at Lyndon Baines Johnson General Hospital (LBJGH), a 207-bed safety-net hospital in Houston, Texas. LBJGH is a part of the safety-net system for Harris County, Texas, which is the third most populous county in the United States. Approximately 1300 elective and nonelective cholecystectomies are performed per year. Operative capabilities are available 24 hours a day, 7 days a week. An on-call attending general surgeon is in house 24 hours a day along with a team of residents and operating room staff dedicated to perform around the clock nonelective general surgery procedures.

Study Population

From June 2016 through June 2018, patients $\geq$ 18 years of age with predicted mild gallstone pancreatitis who were planned to undergo laparoscopic cholecystectomy prior to discharge were screened for eligibility. Gallstone pancreatitis was defined as: 1) upper abdominal pain, nausea, vomiting, 2) absence of alcohol use disorder, 3) elevated plasma lipase level above the upper limit of normal ($\geq$370 U/L), and 4) imaging confirmation of gallstones or sludge.[11] Predicted mild pancreatitis was defined as a Bedside Index of Severity in Acute Pancreatitis (BISAP) score of 0 to 2 and no evidence of organ failure or local or systemic complications.[12,13]

A protocol change occurred in August 2017 which specified a 12-hour observational period between patient enrollment and randomization to ensure that there was no evidence of clinical deterioration from mild to more severe pancreatitis.[10] This change was prompted by 2 patients who were initially thought to have mild gallstone pancreatitis, but progressed to severe pancreatitis requiring intensive care within the first 12 hours of hospitalization. Neither patient received cholecystectomy prior to clinical deterioration. Patients were excluded if there were 2 strong or 1 very strong indicator for choledocholithiasis based on the American Society for Gastrointestinal Endoscopy (ASGE) guidelines (Fig. 1).[14] Patients with any very strong predictor of choledocholithiasis on admission were excluded because of a high likelihood of requiring preoperative ERCP as laparoscopic common bile duct explorations were not routinely performed at this institution. Additional exclusion criteria included pregnancy, developmental delay, severe preexisting medical comorbidities precluding surgery, chronic pancreatitis, native language other than English and Spanish, and patient refusal.

Study Protocol

CONSORT guidelines were followed.[15] Patients were randomized utilizing variable permuted blocks of 4, 6, and 8 using a computer-generated random sequence. Sequentially numbered, opaque, sealed envelopes containing the randomization cards were made by a research coordinator not involved in the study and kept in a locked surgery office. Prior to the protocol change, eligible patients were enrolled and randomized concurrently after admission. After

American Society for Gastrointestinal Endoscopy (ASGE) Guidelines for Risk of Choledocholithiasis	
Likelihood	**Predictors**
Very strong	Common bile duct stone on transabdominal ultrasound
	Clinical ascending cholangitis
	Bilirubin > 4 mg/dL
Strong	Dilated common bile duct (> 6 mm) on ultrasound
	Bilirubin level 1.8-4 mg/dL
Moderate	Abnormal liver biochemical test other than bilirubin
	Age older than 55 years
	Clinical gallstone pancreatitis

FIGURE 1. Presence of any very strong or both strong predictors suggests a high likelihood of choledocholithiasis. No predictors suggest a low likelihood, and all other patients have an intermediate likelihood.[25] By definition, all patients enrolled in this trial will have at least a moderate likelihood because of the clinical diagnosis of gallstone pancreatitis.

the protocol change, enrolled patients underwent delayed randomization after a 12-hour observational period if no clinical deterioration was noted. Patients were stratified based on intermediate (having only moderate predictors) versus high risk (having 1 strong predictor) for choledocholithiasis on admission using ASGE guidelines. While patients and the healthcare providers were not able to be blinded, postoperative PRO assessors and data analysts were blinded. In addition, a blinded adjudication committee reviewed the outcomes.

The intervention was laparoscopic cholecystectomy with IOC within 24 hours of presentation regardless of laboratory or clinical symptom resolution. The primary surgeon was allowed to refuse to perform cholecystectomy if the patient demonstrated worsening pancreatitis. The control was laparoscopic cholecystectomy with IOC once the patient had resolution of abdominal pain and downtrending laboratory values and was deemed appropriate for surgery by the clinical team. Patients received standardized postoperative care in both arms. Additional details of the study protocol along with a timeline of patient enrollment, randomization, interventions, and assessments have been previously published.[10]

Outcomes and Definitions

The primary endpoint was total 30-day hospital LOS in hours. The rationale for using 30-day LOS instead of hospital LOS was to capture any hospital readmissions within 30 days after treatment. Secondary endpoints included ERCP rates, complications (chosen *a priori*: unplanned transfusions, surgical site infections, pneumonia, bile duct injury, retained stone at 30 d, and bowel injury), Clavien-Dindo grading of complications,[16] readmissions within 30 days, exacerbation of pancreatitis, and conversion to open cholecystectomy. Additional outcomes evaluated timeliness of treatment including time from admission to cholecystectomy, index hospital LOS, number of procedures, and nighttime cholecystectomy. PROs were assessed by a short-term change in functional health status between admission and postoperative assessment at 1 month using the Gastrointestinal Quality-of-Life Index (GIQLI).[17,18] The GIQLI is a 36-question multiple choice survey; scores range from 0 to 144, with higher scores corresponding to fewer gastrointestinal symptoms and better quality of life.

Sample Size Calculation and Analysis

The sample size of 100 patients total was estimated based on a 1-day reduction in LOS (2-sided $\alpha = 0.05$, $\beta = 0.80$) from 3 to 2 with 10% nonadherence to protocol in each group. A negative binomial regression was used to compare 30-day LOS between the 2 groups including the stratifying variable as a covariate. Binary secondary outcomes were analyzed using chi-square tests. GIQLI scores pre- and postcholecystectomy were compared using the Wilcoxon signed-rank test for nonparametric data. The original planned analysis had included use of the Cochran–Mantel–Haenszel test for analysis of binary secondary outcomes. However complications and readmissions were rare and there were not enough occurrences per strata to perform the test. In addition to the frequentist analysis, a Bayesian analysis was also performed for the primary outcome and complication rates.[18] The Bayesian approach uses preexisting data (prior probability) combined with results of the study to generate posterior probabilities for various magnitudes of effect of the intervention.[19] Bayesian analyses allow for incorporation of uncertainty from what is already known or unknown based on prior studies, and report the results as probability of observing an outcome of some magnitude or greater. For example, if the posterior probability of the intervention in this trial is 50% for the primary outcome, it would be interpreted that early cholecystectomy has a 50% probability of reducing 30-day LOS as compared with control cholecystectomy, which would suggest that the intervention and control have a similar effect on the primary outcome. Given that most prior studies were observational and the early termination of Aboulian et al's randomized trial,[8] we chose a neutral prior probability distribution to estimate the posterior probability of reductions in 30-day LOS. An intention-to-treat analysis was performed.

RESULTS

Baseline Patient Characteristics

During the study period, 147 patients with gallstone pancreatitis were screened for eligibility. Of 100 consented patients (Fig. 2), 2 were excluded prior to randomization secondary to increasing pancreatitis severity. One patient was excluded after randomization due to unrecognized mild developmental delay at the time of enrollment. A total of 49 patients (50.5%) were randomized to early cholecystectomy, while 48 patients (49.5%) were randomized to control cholecystectomy. Two patients (2%) randomized to the control group were discharged prior to receiving cholecystectomy; they both received outpatient surgery. Both patients were analyzed in their randomized group in the intention-to-treat analysis.

Patients were predominantly female (75%), Hispanic (89%), middle-aged (median age of 40 yrs), and obese (median BMI of 31) (Table 1). Patients were similar in age, race/ethnicity, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, comorbid conditions, and duration of symptoms between treatment groups. Findings on ultrasonography, BISAP scores, and admission laboratory values were also similar between groups, with the exception of lipase, which was higher in the control group.

Procedural Characteristics

Of the 97 randomized patients, all received cholecystectomy. There were no conversions to open surgery. IOC was performed or attempted in 91% of cases in the early group and 83% of cases in the control group. Reasons for failure to perform IOC were not recorded. Patients who did and did not receive IOC had similar preoperative median total bilirubin (0.9, IQR 0.5–1.3 mg/dL in IOC vs 0.7, IQR 0.4–1.0 mg/dL in no IOC, $P = 0.3$) and similar median common bile duct diameter (4, IQR 3–5.8 mm in IOC vs 5, IQR 3.6–5.4 mm in no IOC, $P = 0.3$). Additionally, there were no differences in IOC rates in patients whose total bilirubin down trended or remained the same. ERCP was performed in 7 (15%) patients in the early group and 14 (30%) patients in the control group, with preoperative ERCP being performed in 1 (1%) case in the early group and 6 (6%) cases in the control group due to worsening laboratory values suggestive of choledocholithiasis. Overall, the early group had fewer ERCPs as compared with the control group (15% vs 30%, $P = 0.038$). There were no differences in rates of stone extraction during ERCP between groups. Five (38%) stones were retrieved in the intervention arm versus 8 (62%) stones retrieved in the control arm ($P = 0.35$). Two (25%) patients had only biliary sludge removed in the intervention arm versus 6 (75%) patients in the control arm ($P = 0.131$). Bayesian analysis showed that early cholecystectomy has a 93% probability of decreased ERCP use as compared with control cholecystectomy. Rates of intraoperative drain placement and operative duration were similar between groups (Table 2).

OUTCOMES

Total 30-day LOS was significantly shorter in the early group (median LOS 50 h, IQR 27–82 h) when compared with the control group (median LOS 77 h, IQR 52–111 h), with IRR of 0.68, 95% CI 0.65–0.71, $P < 0.005$ (Table 3). Readmission rates were low and similar between groups. Causes of readmission were related to the index procedure: 1) persistent right upper quadrant pain, 2) recurrent pancreatitis, and 3) cystic stump leak. Bayesian analysis showed that

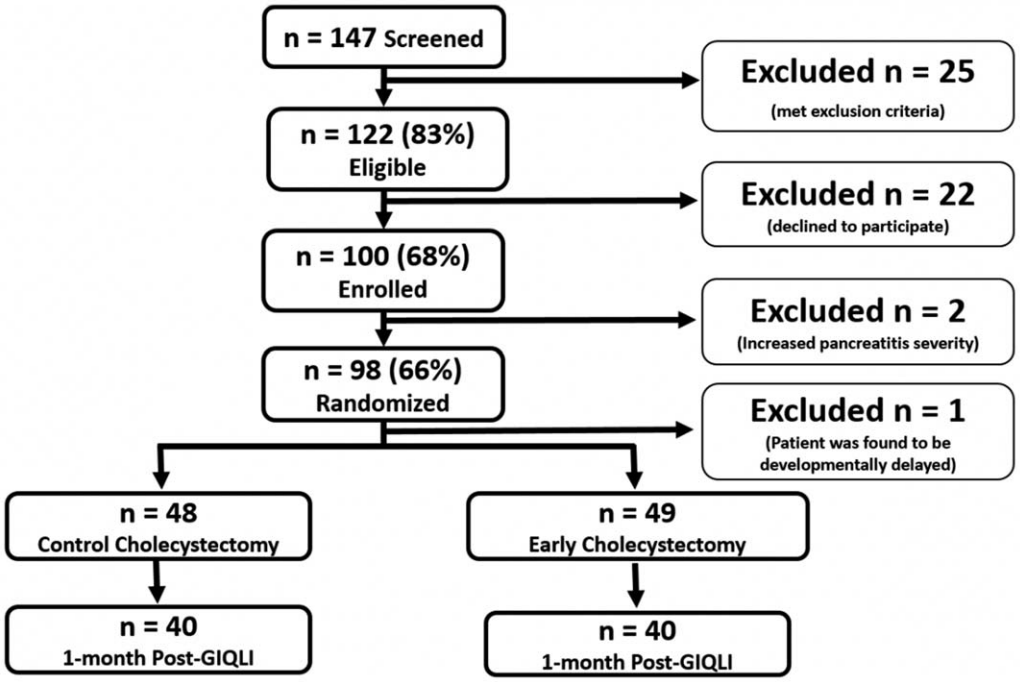

FIGURE 2. Patient Selection Flow Diagram: During the study period, 147 patients with gallstone pancreatitis were screened for eligibility. Forty-seven patients were excluded and 100 patients were enrolled in the study. After enrollment, 3 patients were excluded from the intention to treat analysis (2 patients excluded prior to randomization due to increasing pancreatitis severity; 1 patient excluded after randomization due to patient being developmentally delayed). A total of 48 patients were randomized to the control cholecystectomy group and 49 patients were randomized to the early cholecystectomy group. A total of 80 patients (40 from each group) were able to be reached for 1-mo postoperative GIQLI assessment.

early cholecystectomy has a 99% probability of reducing 30-day LOS as compared to control cholecystectomy.

Patients in the early cholecystectomy group had significantly shorter time from admission to surgery. The adjusted preoperative median LOS was 66% shorter in the early group (median LOS 16 h, IQR 13–21 h) than in the control group (median LOS 43 h, IQR 34–63 h). Median time to surgery was shorter within the early cholecystectomy group pre-protocol change as compared with post-protocol change, with median time to surgery being 13 (IQR 11–17) hours pre-protocol change versus 18 (IQR 15–22) hours post-protocol change ($P = 0.003$). Median time to surgery was similar pre- and post-protocol change in the control group, with median time to surgery being 43 (IQR 36–57) hours pre-protocol change versus 42 (IQR 33–66) hours post-protocol change ($P = 1.0$). No patients exhibited worsening pancreatitis during the 12 to 24-hour observational period after the protocol change. Postoperative LOS was similar between groups. Index hospital LOS was likewise shorter in the early group; the adjusted index hospital LOS was 33% shorter in the early group (median LOS 23 h, IQR 10–54 h) than in the control group (median LOS 19 h, IQR 11–43 h).

Complication rates were low in both groups (6% vs 2%, $P = 0.617$). Complications included recurrence/progression of pancreatitis (2 early vs 1 control) and 1 cystic duct stump leak in the early group. There were no differences in grades of Clavien–Dindo complications, with 10 (21%) patients having any Clavien–Dindo in the early group versus 4 (8%) patients in the control group ($P = 0.09$). There were no Clavien–Dindo grades higher than 3a, which only occurred in 1 (2%) patient in the early group (Table 4). On Bayesian analysis, early cholecystectomy had a 72% probability of increased minor complications as compared with control cholecystectomy.

Change in Functional Health Status

Preoperative GIQLI scores were obtained in all patients, and 81 patients (84%) completed a postoperative GIQLI survey at 1-month postoperative. Preoperative median GIQLI scores were 74 points (IQR 63–96) in early group versus 83 points (IQR 64–102) in the control group ($P = 0.284$). At 1-month postoperative follow-up, GIQLI scores were similar between treatment groups (108 points in early group vs 109 points in control group, $P = 0.869$). There was a significant improvement in GIQLI scores post-cholecystectomy at 1-month follow-up, as compared to pre-cholecystectomy [median GIQLI score 78 (IQR 63–97) pre-cholecystectomy versus 108 (IQR 95–117) post-cholecystectomy, $P < 0.001$]. The majority of patients had improvement in GIQLI scores after cholecystectomy, and degrees of improvement were comparable between treatment groups (29-point increase in early group vs 26-point increase in control group) (Table 5).

DISCUSSION

This is the first completed randomized trial that compared the timing of laparoscopic cholecystectomy before 24 hours of admission to later within the same admission for patients with predicted mild gallstone pancreatitis. The trial demonstrated that early laparoscopic cholecystectomy between 12 and 24 hours of admission is feasible at a busy safety-net hospital and decreased 30-day hospital LOS. Early cholecystectomy also decreased index hospital LOS, need for ERCP, and had similar improvements in patient reported

TABLE 1. Baseline Patient Characteristics

	All Patients, n = 97	Control Group, n = 48	Early Group, n = 49
Age, yrs (median, IQR)	40 (29–50)	38 (28–48)	44 (29–51)
Sex, female (%)	75.3 (73%)	40 (83.3%)	33 (67.3%)
Body mass index	31 (27–36)	33 (27–40)	30 (28–34)
Race/ethnicity, n (%)			
Caucasian	2 (2%)	2 (4%)	0 (0%)
Hispanic	86 (89%)	40 (83%)	46 (94%)
African American	8 (8%)	5 (10%)	3 (6%)
Other	1 (1%)	1 (2%)	0 (0%)
ASA Classification, n (%)			
1	16 (16%)	7 (15%)	9 (18%)
2	63 (65%)	30 (63%)	33 (67%)
3	18 (19%)	11 (23%)	7 (14%)
History of diabetes, n (%)	23 (24%)	8 (17%)	15 (31%)
History of hypertension, n (%)	16 (16%)	9 (19%)	7 (14%)
History of chronic kidney disease, n (%)	1 (1%)	1 (2%)	0 (0%)
History of liver disease, n (%)	2 (2%)	2 (4%)	0 (0%)
History of immune suppression, n (%)	3 (3%)	0 (0%)	3 (6%)
Duration of symptoms, d	2 (1–3)	2 (1–5)	2 (1–3)
ASGE risk of choledocholithiasis, n (%)			
Moderate	65 (67%)	32 (67%)	33 (67%)
Strong	32 (33%)	16 (33%)	16 (33%)
BISAP Score, n (%)			
0	70 (72%)	34 (71%)	36 (74%)
1	27 (28%)	14 (29%)	13 (27%)
Abdominal imaging obtained, n (%)			
Ultrasound only	82 (85%)	41 (85%)	41 (84%)
Ultrasound and CT Abdomen	13 (13%)	6 (13%)	7 (14%)
Ultrasound and MRCP	2 (2%)	1 (2%)	1 (2%)
Ultrasound findings, n (%)			
Immobile neck stone	14 (14%)	4 (8%)	10 (20%)
Peri-cholecystic Fluid	13 (13%)	4 (8%)	9 (18%)
Adenomyomatosis	2 (2%)	0 (0%)	2 (4%)
Polyp	1 (1%)	0 (0%)	1 (2%)
Hepatic Granulomas	1 (1%)	1 (2%)	0 (0%)
Gallbladder wall width, mm	2.6 (2.0–3.0)	2.7 (2.0–3.0)	2.6 (2.0–3.0)
Common bile duct width, mm	4.0 (3.0–5.8)	4.3 (2.5–6.0)	4.0 (3.0–5.4)
White blood cell count, 10^9/L	10.1 (8.4–13.1)	10.3 (8.7–13.6)	10.0 (8.0–12.3)
Total bilirubin, mg/dL	0.8 (0.5–1.3)	0.9 (0.5–1.2)	0.8 (0.5–1.4)
Lipase, IU/L	3581 (713–13,282)	5032 (760–17,621)	2066 (695–10,065)

ASA indicates American Society of Anesthesiologists; ASGE, American Society for Gastrointestinal Endoscopy; BISAP, Bedside Index of Severity in Acute Pancreatiti; CT, computed tomography; MRCP, magentic resonance cholangiopancreatography.

TABLE 2. Procedural Characteristics

	Control Group, n = 48	Early Group, n = 49	*P* Value
Intraoperative cholangiogram, n (%)			
Negative	30 (64%)	27 (57%)	
Positive, stones extracted	0 (0%)	3 (6%)	0.055
Positive, stones unable to be extracted	8 (17%)	6 (13%)	
Attempted/failed	1 (2%)	7 (15%)	
Not performed	8 (17%)	4 (9%)	
ERCP, n (%)			
Not indicated	34 (71%)	42 (86%)	
Preoperative	6 (13%)	0 (0%)	0.038
Postoperative	8 (17%)	7 (15%)	
ERCP with stone Extraction, n (%)	8 (17%)	5 (10%)	0.349
ERCP with sludge only, n (%)	6 (13%)	2 (4%)	0.131
Gallbladder fossa drain placement, n (%)	3 (6%)	1 (2%)	0.362
Conversion to open Cholecystectomy, n (%)	0 (0%)	0 (0%)	1.000
Nighttime Cholecystectomy, n (%)	17 (35%)	26 (53%)	0.103
Operative time, min (median, IQR)	72 (58–92)	76 (64–92)	0.489

ERCP indicates endoscopic retrograde cholangiopancreatography.

TABLE 3. Negative Binomial Regression for Length of Stay and Number of Procedures

	Control Group, n = 48	Early Group, n = 49	IRR	95% CI	*P* Value
Preoperative LOS, h	43 (34–63)	16 (13–21)	0.34	0.32–0.37	<0.005
Postoperative LOS, hours	19 (11–43)	23 (10–54)	0.99	0.93–1.05	0.641
Index Hospital LOS, h	77 (52–111)	45 (26–72)	0.67	0.64–0.70	<0.005
Number of procedures at 30 d, n	1 (1–1)	1 (1–2)	0.82	0.58–1.17	0.282
Total 30 d Length of stay, h	77 (52–111)	50 (27–82)	0.68	0.65–0.71	<0.005

Adjusted for American Society for Gastrointestinal Endoscopy Risk of Choledocholithiasis classification.

TABLE 4. Complications After Control Versus Early Cholecystectomy

	Control Group, N = 48	Early Group, N = 49	*P* Value
Any complication, n (%)	1 (2%)	3 (6%)	0.617
Complications, n (%)			
Common bile duct injury	0 (0%)	0 (0%)	
Biloma or bile leak	0 (0%)	1 (2%)	0.513
Retained stone	0 (0%)	0 (0%)	
Surgical site infection	0 (0%)	0 (0%)	
Exacerbation of pancreatitis	1 (2%)	2 (4%)	
Bleeding requiring Transfusion	0 (0%)	0 (0%)	
Bowel injury	0 (0%)	0 (0%)	
Pneumonia	0 (0%)	0 (0%)	
Clavien–Dindo Classification, n (%)			0.357
0	43 (91%)	38 (79%)	
1	3 (6%)	7 (15%)	
2	1 (2%)	2 (4%)	
3a	0 (0%)	1 (2%)	
Readmissions, n (%)	1 (2%)	3 (6%)	0.617

TABLE 5. One Month Outcomes, Early Versus Control Operation

	Control Group, N = 48	Early Group, N = 49	*P* Value
Completed one Month follow-up, n (%)	41 (85%)	40 (82%)	0.616
Preoperative GIQLI Score	83 (64–102)	74 (63–96)	0.284
Postoperative GIQLI score	109 (93–118)	108 (96–117)	0.869
Change in GIQLI Score	26 (10–40)	29 (11–47)	0.337
	Precholecystectomy N = 92	Postcholecystectomy N = 80	*P* value
GIQLI Score (median, IQR)	78 (63–97)	108 (95–117)	<0.001

GIQLI indicates Gastrointestinal Quality of Life Index (given in median and interquartile range). Higher GIQLI scores indicate better quality of life.

quality of life after surgery as compared with control cholecystectomy. The trial's findings are similar to those of Aboulian et al's randomized trial which reported decreased hospital LOS with early cholecystectomy within 48 hours of admission regardless of symptoms or laboratory values.[8] However, by narrowing the window for early cholecystectomy to within 24 hours, the mean time to cholecystectomy in the early group (17.8 vs 35.1 h) and index LOS (2.5 vs 3.5 d) were shorter in the present trial.

In addition to decreasing LOS, early cholecystectomy has the potential to improve patient-centered outcomes. An unpublished qualitative study performed at LBJGH suggested that effective and timely resolution of symptoms is important among patients with gallstone disease such as acute cholecystitis.[20] However, despite an increasing interest in PROs after surgery, PROs after biliary surgery are rarely measured,[21] particularly after acute pancreatitis. The Gallstone PANC trial utilized the GIQLI which was used to measure PROs after acute pancreatitis in 1 of 16 studies included in a systematic review and meta-analysis.[22] The study showed that the GIQLI did demonstrate differences between patients with acute cholecystitis as compared to age-matched controls (mean GIQLI score 104 ± 3 after pancreatitis vs 126 ± 1 in controls).[23] In the present study, both groups showed a significant improvement in 1-month post-cholecystectomy GIQLI scores as compared with pre-cholecystectomy, and the 1-year postoperative GIQLI scores are in the process of being collected. Further evaluation is required of other patient-centered outcomes that may be improved by early cholecystectomy and shorter hospital LOS.

Despite evidence-based recommendations, opponents to early cholecystectomy, even when defined as within index admission, cite concern for increased risk of surgical complications due to severity of inflammation or to unrecognized pancreatic necrosis. Although worsened outcomes with unrecognized necrosis at the time of same admission cholecystectomy have been reported,[24] the literature is limited to small retrospective cohort studies that are subject to selection bias. However, a high complication rate is not supported by higher quality evidence. Based on systematic reviews of randomized trials of same admission versus post-discharge cholecystectomy for mild gallstone pancreatitis, same admission cholecystectomy results in an approximately 7% complication rate.[25,26] In the present trial, the complication rates were 2% and 6% in the control and early groups, respectively. Furthermore there were no major complications (ie, Clavien–Dindo IV or V) in either group. From a Bayesian perspective, there is a 72% probability that early cholecystectomy led to increased complications, the majority of which were minor complications (Clavien–Dindo grade 1 or 2). Thus, larger trials are necessary to evaluate the risks of postoperative cholecystectomy and to validate the benefits across a broad range of hospitals.

Another potential barrier to early cholecystectomy is the difficulty in accurately predicting the severity of pancreatitis, as evidenced by the need to change the protocol to allow for 12 hours of observation prior to randomization. Several studies have compared both clinical and radiologic scoring systems for the prediction of severity of pancreatitis.[27–30] Comparators included Ranson's criteria, Acute Physiology and Chronic Health Evaluation (APACHE) II, and Modified CT Severity Index (MCTSI). These studies all suggested that BISAP is accurate for risk stratification. In addition, it is easy to use and correlates with mortality and ICU admission.[27,28] A 2015 systematic review and meta-analysis of 10 studies suggested that a BISAP score ≥ 3 had a sensitivity of 51% and a specificity of 91% for severe acute pancreatitis,[31]suggesting that the BISAP score is useful in ruling in severe pancreatitis but not in ruling it out. Thus, despite the advantages of the BISAP score, there is still significant possibility of inaccurately predicting severity of acute pancreatitis. Unfortunately, no current scoring system is entirely accurate in ruling out severe acute pancreatitis at admission, which is one of the reasons that the trial protocol was changed to include a 12-hour observation window. Furthermore, the grading of severity of acute pancreatitis at admission is not granular enough to identify predictors of complications with early cholecystectomy. Therefore, more research is needed to determine which patients would truly benefit from cholecystectomy within 24 hours for mild acute gallstone pancreatitis.

Limitations

This trial has several limitations. First, results may not be generalizable to other hospitals. The population consists primarily of low socioeconomic status and racial/ethnic minority patients, namely Hispanic patients who are known to present at an earlier age and with milder disease than non-Hispanic patients.[32] Additionally, LBJGH is capable of performing cholecystectomies 24 hours a day, 7 days a week, due to the presence of in-house faculty, which may not be possible in other hospitals across the country. However, hospitals with an acute care surgery model may have similar capacity. Second, the trial did not incorporate laparoscopic common bile duct exploration which is commonly performed at other institutions and which may have an effect on the results. Third, as noted, the inability to accurately predict the severity of acute pancreatitis soon after admission may limit implementation, particularly given the possibility of increased complications noted on Bayesian analysis. These limitations are best addressed by planning a future multicenter trial to confirm the findings of decreased LOS, to provide more precision in determining the risk of complications, and to ascertain generalizability to other centers. Such a trial could include less strict timing criteria (ie, early cholecystectomy within 12–36 h), enroll patients at centers that routinely practice laparoscopic common bile duct explorations, and prospectively track patients who worsen after enrollment to identify better predictive criteria.

CONCLUSIONS

In patients with predicted mild gallstone pancreatitis, cholecystectomy within 24 hours of admission significantly reduced rate of ERCPs, time to surgery, and 30-day length-of-stay. However, early cholecystectomy may increase the risk of Clavien–Dindo Grade I–III complications suggesting caution should be employed in applying the results of this trial. Identification of patients with mild gallstone pancreatitis in whom early cholecystectomy is safe given limitations in current prediction models of disease severity warrants further investigation.

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DISCUSSANTS

Dr Nathaniel J. Soper (Chicago, IL):

Thank you very much. I have no relevant disclosures. I would like to thank the Association for the opportunity to discuss this excellently presented and nicely done study. We all know how difficult it is to do prospective randomized trials, so we thank you for this submission. I will not summarize the data you have just presented to avoid redundancy.

This was a relatively small trial in a hospital staffed for 24/7 surgical coverage. Although the length of stay was less in the group undergoing early surgery, there was a trend towards more complications in this group. Therefore, what should the next step be? Should we all be performing these early cholecystectomies or should a multicenter trial be performed to confirm these results?

Second, the institution was safety–net hospital. What factors in this setting created barriers or, conversely, facilitated the performance of the trial? In an unfunded investigator-initiated trial such as this, what type of infrastructure is necessary to be successful?

Third, despite excluding patients with severe pancreatitis and those with a high likelihood of choledocholithiasis, the group undergoing more delayed cholecystectomy underwent ERCP significantly more often. Why do you think this was the case, as I would think the reverse would be true due to stones passing into the CBD during the waiting interval.

Fourth, when common duct stones were demonstrated by cholangiography, only 3 of 17 were able to be extracted. Do you have an active simulation program to teach trainees how to perform laparoscopic common bile duct exploration? At Northwestern, we have developed such a simulator and have shown the ability to train the residents and faculty to a mastery level while significantly decreasing the need for perioperative ERCP. Also, nearly a quarter of the patients undergoing early lap chole did not have cholangiography. Could that have influenced the results?

Finally, I have to admit my ignorance regarding Bayesian analysis. What are the potential advantages of this type of analysis compared to the more traditional frequentist analysis? Further, how do we compare the Bayesian probabilities to the traditional *P* values?

Again, congratulations on a very well-done study and great presentation. I am appreciative to the Association for the opportunity of the floor.

Dr Krislynn Mueck

Thank you so much for your questions. With regards to the question of whether we should start implementing the findings of this trial, our answer is no, not on this trial alone would we recommend implementation of earlier operation. Our complication rate was low, reasonably on par with rates otherwise seen in the literature, but the study was small, as you mentioned, and underpowered to accurately evaluate complications. Additionally, the results of our Bayesian analysis did suggest that there was a predicted increase in minor complications. Furthermore, within the first 50 patients, there were 2 that despite meeting all of our criteria for mild disease (having an appropriate BISAP score and being admitted to a floor bed) still had clinical deterioration to severe pancreatitis, which calls into question our ability to appropriately risk stratify.

I think the next step is a multicenter trial. We've already been in talks about that. One of the goals of such a trial would be to try to develop a model to better predict severity and to better stratify patients in whom earlier cholecystectomy would be appropriate versus those who are likely to deteriorate. We'd like to incorporate machine learning, but all of this is still currently in the works. Please contact us if you're interested in participating in a future multicenter trial.

As far as barriers at the safety net hospital, I think one of the largest ones is we're dealing with a very vulnerable population. Certainly, throughout the trial but most explicitly at the beginning, patients were very suspicious of being involved in research or being experimented upon. Some of that improved with standardization of the way we presented the trial to patients and the way we discussed it with them. But, still, 22 declined. I think that one of the other large barriers was the lack of 24/7 coordinator availability in order to enroll randomized patients. A large amount of the legwork (as this was unfunded, resident developed and largely resident run) was residents taking call to be able to screen and enroll patients, which was a large burden to them. Actually, after implementing the period of observation of 12 hours, some of the burden to residents coming in at night was decreased because of daytime availability of research assistants.

As far as generalizability and implementation, I think that our facility is a very specific one. We were uniquely positioned to perform a trial like this because we have operative capabilities 24/7. It's hard to imagine that that is globally available throughout the country, but hospitals that have developed an acute care surgery model may have the ability to perform this as well. I think certainly in order to succeed in any environment with a trial like this, you need absolute leadership support, especially to complete the trial on a very fast timeline. You need surgeon champions in order to help you develop and run the trial, and certainly a dedicated and tireless research team available all the time.

In reference to more ERCPs in the control group, we don't know for certain why that is true. Some of the thoughts that we had had include: in the longer wait, perhaps there was more time for sludge and stones to pass into the ducts but were not actually passed beyond the ampulla. It's also possible that there was an imbalance by chance alone. It's possible that there are faculty that are more or less aggressive at trying to clear the stones in the operating room, though I can tell you that no laparoscopic common bile duct explorations were performed on any of these patients. I think we need further studies in order to know for sure.

We do not, at our institution, that I am aware of, have any simulated training for laparoscopic common bile duct exploration. We do have some minimally invasive surgeons who like to give presentations about it and talk about it whenever they have these cases to demonstrate to us. But I'm not sure that we have any simulations quite yet.

As far as a decrease in the use of cholangiography, as far as that affecting the results and the rates of ERCP, it's certainly true that if for some reason that was not performed and the concern is that you hadn't cleared the duct and labs were continuing to maintain at a certain level or increase, that could certainly have increased the postoperative ERCP rate.

As far as Bayesian analyses, we have actually moved quite a bit to including them in addition to our frequentist analyses for many of our research projects for several reasons. The first is that it tends to complement the frequentist analysis. We know that *P* values are commonly misinterpreted, and, generally speaking, the results of a Bayesian analysis seem to be more approachable, especially for those of us who are not very statistically evolved. It also gives us a nice estimate of treatment effects, even when the frequentist analysis does not give us significant results. Bayesian probabilities potentially could be used to design a future multicenter trial. The other aspect that I like about it quite a bit is that it gives us the opportunity to iteratively update our assessments of treatment effect based on new information that we gain, new information in the literature, which I think is also more in the way that we think. Thank you.

Dr Pierre Clavien (Zurich, Switzerland):

I have no disclosure relating to this paper. Dr Mueck, I first would like to congratulate you and the team for this RCT. Undoubtedly, if your results were to be replicated in a larger RCT involving other centers, it would change the practice. To validate the study, both the etiology and the prediction of severity must be established. I have 2 questions related to this.

First, how did you secure the etiology of gallstone pancreatitis, or conversely, exclude an alcoholic etiology? How would you label a ''suspicion'' of sludge with some alcohol consumption? I would be interested to know how many cases of pancreatitis were not from a biliary origin during the study period?

Secondly, while designing the next multicentric RCT, would you consider a CT scan to secure the diagnosis, and perhaps, the severity of the pancreatitis, although not routinely indicated in this population?

Again, I congratulate you on this paper.

Dr Krislynn Mueck

Thank you very much for your questions. For the first one, regarding accurate diagnosis of biliary pancreatitis as opposed to colic and in dealing with stones versus sludge or both, I think that the way in which we classified the diagnosis of biliary pancreatitis was fairly specific. They had to have stones or sludge or both on ultrasound. Some patients did receive a CT scan, but that was not on the basis of needs for the trial. That was within the scope of usual care.

I think we did a fairly good job of taking out other etiologies of pancreatitis including in relation to alcohol use. People that had a history of chronic pancreatitis still had to have stones or sludge. And I think that there are certainly limitations to any of this without further imaging studies such as the CT scan that you talked about. Certainly in our pilot trial, outside of usual care, it would have been challenging to incorporate a CT scan for all patients to verify a diagnosis of pancreatitis. But I think that information would be very, very interesting and something to consider for future multicenter trials.

Dr Michael Brunt (St. Louis, MO):

No disclosures. Congratulations on a very nicely presented paper. I applaud you for incorporating intraoperative cholangiography in your trial. I think that's something that we don't utilize enough in patients undergoing cholecystectomy in the US.

It's not surprising that the earlier you operate on gallstone pancreatitis you might see a few more stones at operation. My question relates to the preoperative assessment. It's not unusual to have a bump in transaminases as you pass a stone.

My question is, those patients that were found to have stones at early operation, did you see any difference in the LFT profile between those who did and those who did not? What were the reasons for failure of management of those laparoscopically at operation? It relates a little bit to Dr Soper's question. And did all those patients get an ERCP or did you observe some of them and wait for them to pass?

Dr Krislynn Mueck

Thank you so much for your questions. As far as LFTs, we looked at them on admission and compared them as part of the baseline comparison between groups, but we did not make any comparisons of them further in their trajectory within the hospitalization, but I think that would be very interesting to look into in the future.

As far as IOC and its use in the operating room, there were a few patients in which IOC was attempted but due to the viability of the duct was unable to be completed. I think that as far as more aggressive management of stones and positive IOCs within the operating room, it's fairly common for staff to incorporate the use of glucagon and saline flushing, but there are only a few of our staff that would routinely do a common bile duct exploration, two really that I can think of most commonly. No common duct explorations were utilized in the trial. I think that would also be something nice to incorporate whenever we have additional centers with additional surgeons and variability in their practice patterns.