Acute Cholecystitis

Early Versus Delayed Cholecystectomy, A Multicenter Randomized Trial (ACDC Study, NCT00447304)

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Objective: Acute cholecystitis is a common disease, and laparoscopic surgery is the standard of care.

Background: Optimal timing of surgery for acute cholecystitis remains controversial: either early surgery shortly after hospital admission or delayed elective surgery after a conservative treatment with antibiotics.

Methods: The ACDC ("Acute Cholecystitis—early laparoscopic surgery versus antibiotic therapy and Delayed elective Cholecystectomy") study is a randomized, prospective, open-label, parallel group trial. Patients were randomly assigned to receive immediate surgery within 24 hours of hospital admission (group ILC) or initial antibiotic treatment, followed by delayed laparoscopic cholecystectomy at days 7 to 45 (group DLC). For infection, all patients were treated with moxifloxacin for at least 48 hours. Primary endpoint was occurrence of predefined relevant morbidity within 75 days. Secondary endpoints were as follows: (1) 75-day morbidity using a scoring system; (2) conversion rate; (3) change of antibiotic therapy; (4) mortality; (5) costs; and (6) length of hospital stay.

Results: Morbidity rate was significantly lower in group ILC (304 patients) than in group DLC (314 patients): 11.8% versus 34.4%. Conversion rate to open surgery and mortality did not differ significantly between groups. Mean length of hospital stay (5.4 days vs 10.0 days; $P < 0.001$) and total hospital costs (€2919 vs €4262; $P < 0.001$) were significantly lower in group ILC.

Conclusions: In this large, randomized trial, laparoscopic cholecystectomy within 24 hours of hospital admission was shown to be superior to the conservative approach concerning morbidity and costs. Therefore, we believe that immediate laparoscopic cholecystectomy should become therapy of choice for acute cholecystitis in operable patients. (NCT00447304)

Keywords: cholecystitis, immediate vs delayed laparoscopic cholecystectomy, randomized trial

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Acute cholecystitis is one of the most significant diseases in the Western world and has a high socioeconomic impact. Mainly, patients with gallstones and older adults are affected. Because the risk of developing subsequent episodes of cholecystitis is high, laparoscopic cholecystectomy is usually recommended for acute cholecystitis. However, controversy exists about the best timing for surgery. Mainly 2 approaches are pursued: early surgery versus an initial conservative treatment with antibiotics for complete resolution of inflammation, followed by delayed laparoscopic cholecystectomy several weeks later.[1]

Delayed surgery is based on the assumption that affected inflammatory tissue is more vulnerable to surgical interventions and leads to an increased risk of surgical complications. Therefore, during its early years, laparoscopic cholecystectomy was contraindicated in acute cholecystitis.[2] In support of the delayed approach, a single-center cost-utility analysis favored conventional management of acute cholecystitis over early cholecystectomy because of lower incremental cost per quality-adjusted life year gained.[3] More recent studies do not support the necessity of the conservative pretreatment to overcome the acute inflammatory response.[4–6] In fact, the waiting period may be associated with higher morbidity.[7] Meta-analyses have shown that there is no difference between the 2 approaches in terms of bile duct injury, operation time, or conversion rate whereas total hospital stay is significantly shortened by early cholecystectomy.[1,8–11] The lately advocated immediate cholecystectomy within 24 hours has been compared with surgery after 24 hours in a single-center retrospective study, with no difference between the 2 approaches.[12]

In summary, despite numerous studies and analyses, the controversy regarding optimal timing of cholecystectomy is not yet resolved: (1) only a limited number of prospective, small-sized studies were available for meta-analyses; (2) in prospective and retrospective studies, the definition of early cholecystectomy and the methodology of surgery varied; (3) antibiotic regimens for the conservative

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approach were not standardized; and (4) the outcome parameters were often not well defined.

In clinical practice, acute cholecystitis is mostly not operated during the acute episode in many countries (eg, United States, United Kingdom, and Japan).[13–15] Specialization and/or preference of the physician at first patient contact seem to influence the treatment approach.[1,8]

To define best practice for the treatment of acute cholecystitis, the ACDC ("Acute Cholecystitis—early laparoscopic surgery versus antibiotic therapy and Delayed elective Cholecystectomy") study was designed as a multicenter, prospective, randomized trial to compare 75-day morbidity in patients with acute cholecystitis randomly assigned to immediate laparoscopic cholecystectomy (group ILC) or to the conservative approach with antibiotic treatment and subsequent elective laparoscopic cholecystectomy 7 to 45 days after enrollment (group DLC). In both groups, the third-generation fluoroquinolone moxifloxacin with a broad spectrum of activity and good penetration capabilities was used for therapy.[16–20] Each study center involved both surgeons and gastroenterologists.

METHODS

Study Design and Oversight

The study design has been reported in detail previously.[21] The study was approved both by the ethics committee of each participating hospital and by the Federal Institute for Drugs and Medical Devices of Germany (BfArM) as competent authority. The participating surgical departments were selected for their experience in laparoscopic cholecystectomy. Written informed consent was obtained from all patients. The random allocation sequence for patient randomization was generated by the Institut für Empirische Gesundheitsökonomie (Burscheid, Germany), using the SAS software. The sponsor of the study (University Hospital of Heidelberg) was fully responsible for the organization and conduct of the study, as for the statistical analysis and the interpretation of the data. Bayer Vital GmbH (Leverkusen, Germany) provided the antibiotic (moxifloxacin) used in this trial.

Study Population and Study Treatment

Adult patients with signs and symptoms of acute cholecystitis [at least 3 of the following: (1) abdominal pain in the upper right quadrant; (2) Murphy sign; (3) leukocytosis; or (4) rectal temperature above 38°C] were eligible for enrollment when cholecystolithiasis (stones/sludge) or sonographic signs of cholecystitis had been proven and when laparoscopic cholecystectomy was possible within 24 hours after presentation of the patient. The main exclusion criteria were as follows: ASA (American Society of Anesthesiologists) physical status IV and V, septic shock, perforation or abscess of the gallbladder, no possibility for laparoscopic surgery, life expectancy less than 48 hours, pregnancy or breast-feeding, and contraindications against the antibiotic (moxifloxacin) used in this trial.[21]

Eligible patients were randomly (block randomization with a block size of 4) assigned in a 1:1 ratio either to immediate laparoscopic cholecystectomy (group ILC) or to initial conservative treatment followed by elective laparoscopic cholecystectomy (group DLC) according to a sealed randomization envelope at each study center. In both groups, infection was treated with 400 mg of moxifloxacin once daily, over at least 48 hours intravenously, with the possibility to switch to oral moxifloxacin in patients who responded to therapy. Antibiotic treatment was discontinued when the patients responded clinically and inflammatory markers decreased to normal levels. Any additional measures such as endoscopic interventions were documented.

ILC patients underwent laparoscopic cholecystectomy within 24 hours of hospital admission. They were discharged as soon as possible after the first postoperative day depending on clinical presentation. The test-of-cure (TOC) visit was performed on day 75 after inclusion.

Patients randomized to conservative therapy (DLC) were treated with intravenous/oral moxifloxacin until fever was resolved and inflammatory markers had decreased to normal levels. Patients were discharged as soon as possible after day 3. Elective laparoscopic cholecystectomy was scheduled upon discharge for the time frame of 7 to 45 days after enrollment, using single-shot prophylaxis (400 mg of moxifloxacin intravenously). The TOC visit was also performed on day 75 after inclusion.

Outcomes

The primary endpoint was *morbidity*, defined as the occurrence of any of the clinically relevant complications out of a recently published morbidity score,[21] within 75 days after inclusion into the study, as assessed at the TOC visit. Secondary endpoints were as follows: (1) morbidity over the 75 days of study duration using a scoring system[21]; (2) rate of conversion from laparoscopic to open surgery; (3) change of antibiotic therapy due to nonresponse to or intolerance of moxifloxacin; (4) mortality within the 75 days of study duration; (5) costs and cost-effectiveness; (6) overall length of hospital stay; and (7) length of hospital stay after cholecystectomy.

Calculation of Costs and Cost-effectiveness

Costs were calculated on the basis of Diagnosis Related Group classification of Germany, using cost data from 2010. The cost-effectiveness ratio was calculated by dividing costs by success rate (1 − morbidity rate).

Statistical Analysis

The primary objective of the study was to compare morbidity between the 2 groups within 75 days after enrollment. A difference in morbidity of less than 10% was defined as equivalent. The null hypothesis was $|p_{M1} - p_{M2}| > 0.1$, where p_{Mi} was the morbidity rate of treatment group i. Under the assumption of a complication rate of 16% in each group, a β-error of 0.15 and an α-error of 0.05, 2-sided, 273 valid patients had to be enrolled per group. Assuming a validity rate of 85%, 322 patients were required per group, resulting in a total sample size of 644 patients.

The primary statistical analysis was to be performed on the per protocol (PP) population on a 2-sided significance level of 0.05. For the difference of morbidity rates, 95% 2-sided confidence intervals (CIs) were calculated using Mantel-Haenszel weights. The results of the intention-to-treat (ITT) population were planned to serve as the supportive evidence. Because superiority was demonstrated, the ITT results are primarily displayed. For the confirmatory analysis, the calculation of CIs was to be stratified by ASA physical status category (ASA $\leq$2, ASA $>$2, ASA not assessed). For the analysis of the morbidity score, the Mann-Whitney test was used. The analyses were performed using the SAS software (version 9.1.3; SAS Institute Inc), PASW Statistics 18 (SPSS Inc), Microsoft Excel, and Microsoft Access.

RESULTS

Recruitment and Follow-up

The trial was conducted at 35 study centers in Germany and Slovenia and lasted almost 4 years. The last patient was assessed on November 28, 2010. Of 642 screened patients, 618 were randomized into the study (ITT population): group ILC (immediate cholecystectomy), 304 patients; group DLC (initial conservative treatment with delayed cholecystectomy), 314 patients (Fig. 1). Twelve (group ILC) and 56 (group DLC) patients were excluded from the PP analysis.

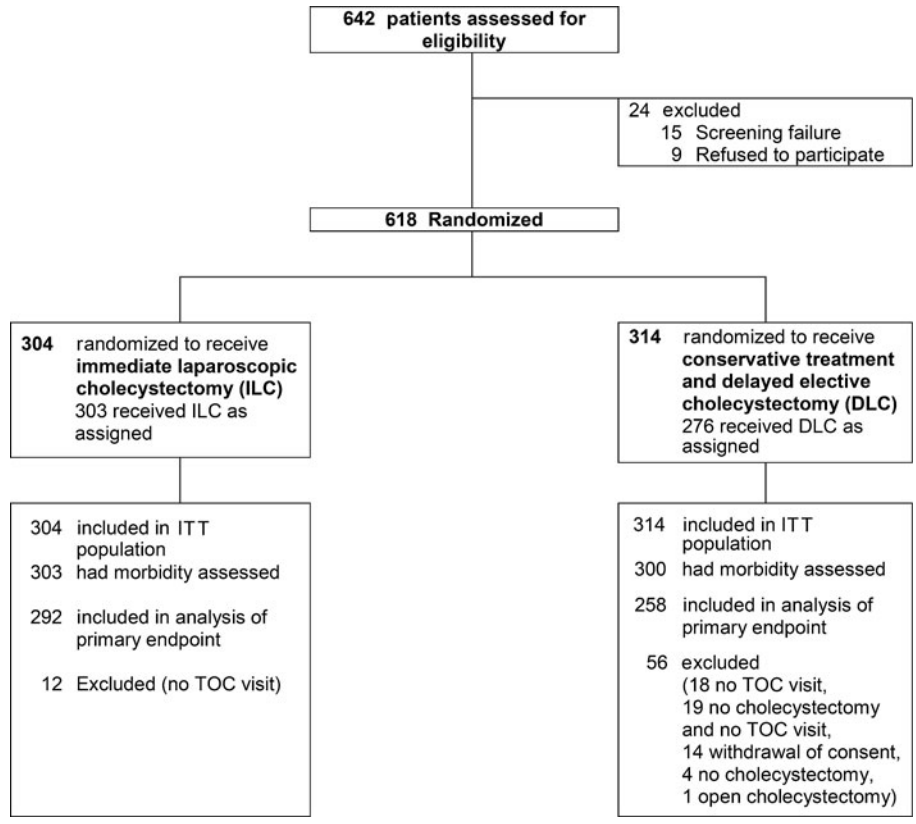

FIGURE 1. Flow of study participants in the ACDC trial.

In both groups, the main reason for exclusion was a lacking TOC assessment.

Patients, Study Drug, and Surgery

The baseline characteristics (ITT population) are summarized in Table 1. Because of the demography of disease, more female patients were enrolled. Severe comorbidities were generally rare in both groups.

A majority of patients (98.9%) received moxifloxacin for at least 2 days, with an overall exposure to moxifloxacin of 4.96 days in group ILC and 8.72 days in group DLC. At delayed cholecystectomy in group DLC, only 68.3% of patients received moxifloxacin as perioperative prophylaxis, which was defined as minor protocol violation not leading to exclusion from the PP analysis.

Cholecystectomy was performed at a mean of 0.6 days (median = 1.0; range = 0.0–4.0 days; surgery >3 days: 1 patient) in group ILC and at a mean of 25.1 days (median = 23.0; range = 1.0–99.0 days; surgery <4 days: 25 patients) in group DLC. The conversion rate from laparoscopic cholecystectomy to open surgery was similar in both groups (Table 2). The median operation time was 67 and 71 minutes.

TABLE 1. Baseline Characteristics by Treatment Group (ITT Population)

Characteristics	Group ILC (n = 304)	Group DLC (n = 314)
Female sex,* n (%)	191 (62.8)	172 (54.8)
Age, mean (SD), yr	55.6 (16.3)	56.8 (17.1)
Body mass index, mean (SD), kg/m^2	28.9 (5.8)	29.5 (6.6)
Body temperature, mean (SD), °C	37.2 (0.8)	37.3 (0.8)
Blood pressure,† mean (SD), mm Hg		
Systolic	134.9 (20.1)	136.9 (21.5)
Diastolic	78.5 (10.9)	79.3 (11.7)
Coexisting conditions, n (%)		
Renal insufficiency	5 (1.6)	8 (2.5)
Cancer*	2 (0.7)	11 (3.5)
Diabetes mellitus	29 (9.5)	46 (14.6)
Hypertension*	106 (34.9)	137 (43.6)
Respiratory insufficiency*‡	8 (2.6)	20 (6.4)
Congestive heart failure*	15 (4.9)	31 (9.9)
Previous intra-abdominal surgery	88 (28.9)	109 (34.7)
Biliary colic in medical history, n (%)	125 (41.1)	126 (40.1)
Cholecystolithiasis, n (%)	269 (88.5)	277 (88.2)

*$P < 0.05$ for the between-group comparison.
†Values are missing for 12 and 10 patients.
‡Mainly dyspnea under physical stress.

Primary Outcome

Morbidity occurred in 35 ILC patients (12.0%) and 86 DLC patients (33.3%) of the PP population ($P < 0.001$) (Fig. 2A). In both groups, patients with an ASA status of more than 2 showed higher morbidity; a P value of 0.851 in the Breslow-Day test indicated no heterogeneity between the 2 ASA status defined groups (see Supplemental Digital Content Table 1, available at http://links.lww.com/SLA/A416). The 95% CI for the difference of morbidity rates, 12.8 to 26.5, was outside the defined limits of ±10%. The results for the ITT population (see Supplemental Digital Content Table 2, available at http://links.lww.com/SLA/A416) support the PP analysis: Morbidity rates were 11.6% (group ILC) versus 31.3% (group DLC), with a 95% CI of 12.5 to 25.7 (P value for the Breslow-Day test 0.952), when patients with unassessed morbidity status are excluded from

TABLE 2. Secondary Outcomes by Treatment Group (ITT Population)

Secondary Efficacy Outcomes	Group ILC (n = 304)	Group DLC (n = 314)	*P*
Morbidity score on day 75,* mean [95% CI]	0.53 [0.10–0.96]	1.12 [0.66–1.58]	<0.001
Conversion rate to open surgery, n (%) [95% CI]	30 (9.9) [6.5–13.2]	33 (11.9) [8.1–15.7]	0.44
Adverse events, n (%) patients [95% CI]	43 (14.1) [10.2–18.1]	127 (40.4) [35.0–45.9]	<0.001
Change of antibiotic treatment, n (%)	22 (7.2)	31 (9.9)	0.24
Mortality rate, n (%)	1 (0.3)	1 (0.3)	0.98
Total hospital stay, mean (interquartile range) [95% CI], d	5.4 (4–6) [5.08–5.71]	10.03 (7–12) [9.36–10.69]	<0.001
Duration of hospitalization after cholecystectomy, mean (interquartile range) [95% CI], d	4.68 (3–6) [4.36–5.00]	4.89 (3–6) [4.26–5.51]	0.57
Total hospital costs, mean (interquartile range) [95% CI], €	2919 (2651–2651) [2812–3026]	4262 (3021–4724) [4029–4494]	<0.001
Cost-effectiveness ratio,† mean, € per successful cholecystectomy	3300	6206	—

*Fifteen patients had a missing or implausible morbidity score.
†Ratio based on ITT population without patients with unassessed morbidity status.

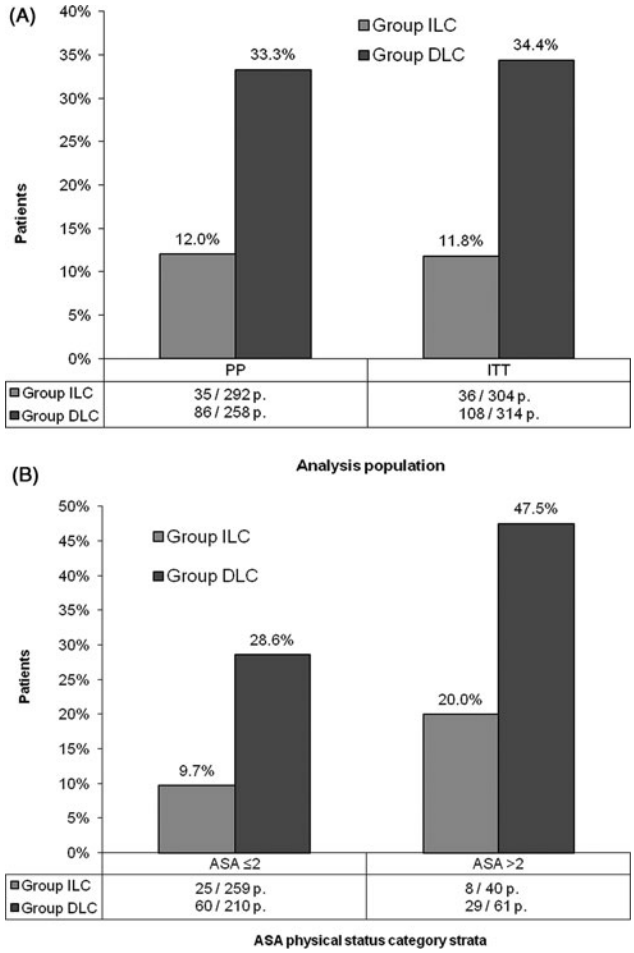

FIGURE 2. Rates of patients with relevant morbidities (as listed in Table 3) within 75 days after inclusion into the study. A, ITT population including 15 patients with unknown morbidity status at the TOC visit who were rated as having morbidity. 95% CI for the difference between groups: 12.8–26.5 (PP) and 12.9–26.2 (ITT). B, ITT population excluding patients with unknown morbidity status at the TOC visit. Patients with unassessed ASA status are not shown. 95% CI for the difference between groups: 11.4–26.0 (ASA status ≤2) and 9.9–45.2 (ASA status >2).

the analysis. When patients for whom morbidity was not assessed are rated as having morbidity, morbidity rates were 11.8% (group ILC) versus 34.4% (group DLC) and the 95% CI of 12.9 to 26.2. Likewise to the PP analysis, an ASA status of more than 2 was associated with higher morbidity in both treatment groups in the ITT population (Fig. 2B). Thus, regarding morbidity, it is statistically proven that immediate cholecystectomy is superior to conservative treatment followed by delayed surgery.

Secondary Outcomes

Basically, the secondary outcomes (Table 2) support the primary outcome: The mean morbidity score was about twice as high in group DLC than in group ILC. A graph of the cumulative distribution of the morbidity score points (see Supplemental Digital Content Figure 1, available at http://links.lww.com/SLA/A416) shows that group ILC uniformly over all scores fared better than group DLC. Table 3 shows the rates of complications for the 2 groups in detail. Mean total length of hospital stay for group ILC versus group DLC was 5.4 days versus 10.0 days, whereas length of hospital stay after cholecystectomy was about the same in both groups, indicating that there is no major difference in surgical complications for early or delayed date of surgery. Change of antibiotic treatment occurred in 22 and 31 patients (7.2% and 9.9%; $P = 0.24$) but prevented premature surgery only in 14 cases of group DLC (4.6%). Costs were 46% higher in group DLC, mainly due to the longer total hospital stay. Cost-effectiveness ratio was better for group ILC than for group DLC.

A total of 58 adverse events were reported among 43 patients in group ILC and 179 adverse events among 127 patients in group DLC. Serious adverse events were reported among 28 (group ILC) and 85 (group DLC) patients. Most adverse events were associated with acute cholecystitis. Ten adverse events in 9 patients (group ILC) and 15 adverse events in 13 patients (group DLC) were classified as being related to the study drug moxifloxacin (mainly gastrointestinal disorders such as diarrhea, drug hypersensitivity, rash; each ≤2%). In group ILC, 47 of 58 adverse events (81%) were reported after cholecystectomy. In group DLC, 120 of 179 adverse events (67%) occurred before cholecystectomy or at the same day. In fact, adverse events were the main reason for premature surgery in group DLC.

Additional Measures

In 20 (group ILC) and 54 (group DLC) patients, 24 and 82 interventions were performed ($P < 0.001$; χ^2 test). The most frequent interventions (>2%) were endoscopic retrograde cholangiopancreatography (7 and 17 patients), esophagogastroduodenoscopy (3 and 14 patients), gastroscopy (1 and 12 patients), and ultrasonography of the upper abdomen (2 and 7 patients).

TABLE 3. Seventy-five-Day Morbidity Rates for Morbidity Score Items by Treatment Group (ITT Population)

Complications*	Score Points	Group ILC (n = 303/304),† n (%)	Group DLC (n = 300/314),† n (%)	*P*
Persistent abdominal pain >72 h	1	7 (2.3)	30 (10.0)	<0.001
Persistent fever >72 h	1	1 (0.33)	10 (3.33)	0.006
Persistently raised signs of infection >72 h	1	17 (5.6)	35 (11.7)	0.009
Wound-healing complication	2	6 (2.0)	8 (2.7)	0.59
Thrombosis	3	0	0	
Bleeding	3	1 (0.33)	1 (0.33)	0.99
Pneumonia	3	2 (0.66)	2 (0.67)	0.99
Cholangitis/cholecystitis	3	4 (1.32)	31 (10.33)	<0.001
Icterus	3	3 (0.99)	1 (0.33)	0.31
Abscess	3	1 (0.33)	2 (0.67)	0.57
Bile leak	3	3 (0.99)	1 (0.33)	0.31
Peritonitis‡	4	0	4 (1.33)	0.045
Pancreatitis	4	1 (0.33)	3 (1.0)	0.32
Embolic lung disease	4	0	0	
Renal failure	4	0	0	
Relaparotomy	5	3 (0.99)	4 (1.33)	0.71
Cerebral ischemia or bleeding	5	0	0	
Myocardial infarction	5	0	1 (0.33)	0.32
Septic shock	5	0	4 (1.33)	0.045
Death	63	1 (0.33)	1 (0.33)	0.98

*Patients could have more than 1 complication.
†Number of patients scored/total number of patients.
‡In 3 patients, peritonitis was due to gallbladder rupture.

Sensitivity Analyses

As shown in Table 1, female sex and some comorbidities were not balanced between groups. Several sensitivity analyses were performed to investigate whether these imbalances impacted the outcome, favoring group ILC. Results in Figure 3 show that only in patients with less common comorbidities such as respiratory insufficiency and heart failure, immediate cholecystectomy was not demonstrated to be superior to the conservative approach.

DISCUSSION

In this large, prospective, randomized trial, we compared immediate cholecystectomy within 24 hours of hospital admission versus conservative treatment and subsequent elective cholecystectomy 7 to 45 days later for the therapy of acute cholecystitis using standardized antibiotic treatment in both groups (moxifloxacin). In the primary analysis, which included patients in the PP population, and in the supportive ITT analysis, we found that immediate cholecystectomy is associated with statistically significant less morbidity, shorter hospital stay, and lower costs than the conservative approach. The mortality was 0.3% in both groups.

Reviewing the development of laparoscopic cholecystectomy, it is obvious that earlier concerns to perform the operation in inflamed tissue[2] became less substantial with increasing experience and expertise. In more recent prospective studies, early laparoscopic cholecystectomy was shown to be safe and effective.[4,5] This result was confirmed by meta-analyses.[1,8–11] Mainly based on the Cochrane meta-analysis by Gurusamy and Samraj,[22] a cost-utility analysis was performed that showed that early laparoscopic cholecystectomy in acute cholecystitis is less costly (savings of £820 per patient) and results in better quality of life than the initial conservative treatment followed by delayed surgery.[23]

However, when analyzing the definition of early cholecystectomy, there seems to be a broad range: Often the threshold lies at 7 days. In addition, an assessment about the quality of randomized controlled trials for acute cholecystitis concluded that some important items of the CONSORT criteria are often not reported, making the evaluation of internal and external validity difficult.[24] On the basis of available evidence, the Tokyo guidelines for surgical treatment of acute cholecystitis advocate a different approach depending on the grade of severity.[25]

In a recent retrospective analysis of the optimal timing of emergency cholecystectomy in 4113 patients in Switzerland, immediate surgery was found to have statistically significant advantages in conversion/reoperation rates, postoperative complications, and length of postoperative hospital stay compared with delayed cholecystectomy 1 to 6 days after hospital admission.[26]

In comparison with the existing literature, our study is characterized by a randomized design and a sample size revealing differences between immediate and delayed cholecystectomy, by a better patient characterization including comorbidities, an effective antibiotic treatment (moxifloxacin), and standardized methods for the evaluation of primary and secondary outcome parameters. From our study results, it is obvious that patients with acute cholecystitis should be operated laparoscopically within 24 hours after admission—if their physical fitness (as measured by ASA status) allows surgery. The conservative approach is associated with a measurable risk that even using an effective antibiotic treatment, signs and symptoms of acute cholecystitis may not resolve or may recur shortly, eventually leading to prolonged or rehospitalization, surgery under more difficult conditions, and higher costs.

On the basis of the study design, several potential limitations have to be taken into account. (1) We compared 2 very distinct approaches in operable patients with acute cholecystitis: immediate surgery within 24 hours after hospital admission versus conservative treatment and elective surgery 7 to 45 days after admission. Indeed, in group ILC, the mean timing of surgery was 0.7 days after admission and the operation lasted 71 minutes. In group DLC, several patients were operated on before schedule because of persistent signs and symptoms. But we cannot make a statistically proven statement about the operation time in those patients because it was calculated including all patients (80 minutes). (2) It can be criticized that the

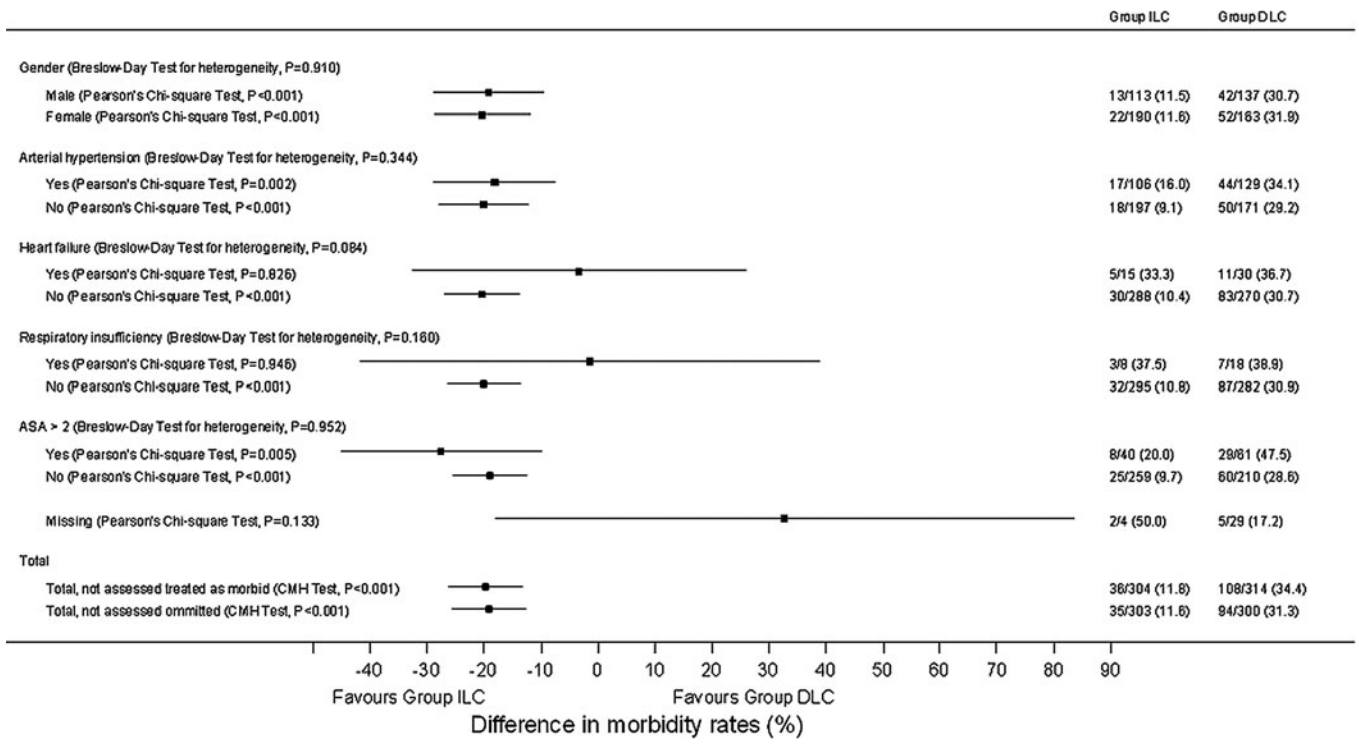

FIGURE 3. Forest plot of sensitivity analyses testing for potential interactions between sex or specific comorbidities and the primary outcome at the TOC visit. CMH indicates Cochran-Mantel-Haenszel.

onset of symptoms in the individual patients was not recorded. However, from our experience, the onset of acute attack is rather difficult to define and capture because patients have a varying perception of signs and symptoms. Therefore, we used the comprehensive criterion "hospital admission," which reflects clinical practice. (3) Although patients were randomized in each center, distribution of some rare comorbidities was not balanced between treatment groups. Monitoring did not reveal any systematic randomization errors. To test for a potential influence of this imbalance on outcome, we performed sensitivity analyses showing that the superiority of group ILC was not driven by the imbalance in comorbidities. Therefore, the result favoring immediate cholecystectomy seems to be robust.

The results of all previous prospective studies, retrospective analyses, and our randomized trial taken together suggest that the question about the optimal timing for laparoscopic cholecystectomy is now answered for those patients with acute cholecystitis whose general status and comorbidities allow surgery. A cholecystectomy within 24 hours is optimal. Postponement due to logistical reasons seems to be feasible, although the earliest possible time should be aimed for. From our point of view, hospitals should reevaluate their approach to treating acute cholecystitis with their laparoscopic surgeons and their gastroenterologists and should secure the availability of surgical expertise, appropriate equipment, and operating theatres for laparoscopic surgery. Hospitals should organize the internal referral pathway in their emergency department to ensure that operable patients with acute cholecystitis are referred to the surgical department.

CONCLUSIONS

Our study represents the largest prospective, randomized study comparing immediate cholecystectomy with conservative antibiotic treatment and elective surgery 7 to 45 days later in patients with acute cholecystitis. Our results show that immediate cholecystectomy within 24 hours of hospital admission is the therapy of choice and should be implemented as treatment algorithm for this condition.

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Author contributions*: Drs Gutt and Encke contributed equally to the study. Drs Büchler, Encke, and Gutt had full access to all the data and take responsibility for the integrity and the accuracy of the data analysis.* Study concept and design: *Drs Gutt, Encke, Köninger, Weigand, Stremmel, and Büchler and Mr Daniel.* Acquisition of data: *Drs Gutt, Encke, Köninger, Harnoss, Weigand, Kipfmüller, Schunter, Götze, Golling, Menges, Klar, Feilhauer, Zoller, Ridwelski, Ackmann, Baron, Schön, Seitz, Stremmel, and Büchler.* Analysis and interpretation of data: *Drs Gutt, Encke, Harnoss, and Büchler and Mr Daniel.* Drafting of the manuscript: *Drs Gutt, Encke, Harnoss, and Büchler and Mr Daniel.* Critical revision of the manuscript for important intellectual content and final approval of the version: *Drs Gutt, Encke, Köninger, Harnoss, Weigand, Kipfmüller, Schunter, Götze, Golling, Menges, Klar, Feilhauer, Zoller, Ridwelski, Ackmann, Baron, Schön, Seitz, Stremmel, and Büchler and Mr Daniel.* Statistical analysis: *Drs Gutt, Encke, and Büchler and Mr Daniel.* Administrative, technical, or material support: *Drs Gutt, Encke, Köninger, Weigand, and Büchler.* Study supervision: *Drs Gutt, Encke, and Büchler.*

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DISCUSSANTS

A.L. Warshaw (Boston, MA):

Your findings convincingly showed that laparoscopic cholecystectomy for uncomplicated acute cholecystitis can be accomplished within 24 hours of presentation with the same conversion rate, morbidity, postoperative complication rate, mortality, and hospital length of stay when compared with delayed cholecystectomy.

Furthermore, immediate cholecystectomy led to a 50% reduction in total hospital days, obviously that is due to not waiting to perform the operation, and a 33% reduction in hospital costs is achieved again because the time is better spent. The findings are predictable because the preoperative hospital days are largely eliminated.

Particularly noteworthy is that the adverse events or morbidity that you point out were 3 times higher in the delayed group, including persistent cholecystitis, cholangitis, peritonitis, and abscess.

Also, 67% of these events precipitated an operation before it was intended, indicating the importance of source control by eliminating the inflamed gallbladder. There is no doubt in my mind that immediate cholecystectomy was superior to delayed cholecystectomy in this patient population.

You excluded patients considered poor medical candidates for operation. Only uncomplicated, essentially stable patients were included. Can you extrapolate your findings to a broader, sicker population?

In addition, because this seems to have been a study conducted under surgical auspices of your group, do your internists and gastroenterologists now accept this pathway for their patients, especially considering the fact that they are often the first physicians to see these patients and make the primary decisions regarding mode of treatment?

Consequently, although your conclusions are impressive for this selected population, will you succeed in convincing your emergency department physicians to refer these patients to the surgical service, which will provide better care? I hope so.

Response From M.W. Büchler:

We have excluded patients with high morbidity. In answer to your question about how to extrapolate the findings to these patients, I do not know for sure at this moment, but it might be that patients with high morbidity take advantage from a preoperative improvement of their conditions. Therefore, I think, in patients with high morbidity, it might be better to treat them for 1 to 2 days by providing with antibiotics and other kinds of care to make them fit for surgery.

How do we convince our internists to refer these patients immediately? This will take a long time, at least in Germany, because many such patients are referred to the internists primarily, and whether they will refer them to the surgeons immediately is an open question. Such kinds of data are not sufficient to convince not just the surgeons.

How do we convince the emergency physicians? That will be much easier, I think, because the emergency physicians work more closely with the surgeons than the internists.

DISCUSSANTS

S.M. Steinberg (Columbus, OH):

We conducted a similar study about 10 years ago, and although it was retrospective, we came to the same conclusions. However, there was one finding in your study that I find very curious and I would like you to try to address it. You indicate that the hospital length of stay after cholecystectomy was the same in both groups, but there was a significant reduction in complications in the early cholecystectomy group. Most other studies link postoperative complications to an increased length of stay. How do you explain this finding?

Response From M.W. Büchler:

I think that the hospital stay in Germany is completely different from the hospital stay in your country. You saw that we have a postoperative hospital stay of 5 days. I would expect that in the United States to be 1 or 2 days. Therefore, here we speak about different conditions. In Germany, we keep the patients longer in the hospital than you are used to doing.

Now, the question is whether these patients stayed for the same length of time in the hospital, and this is not explained by the higher morbidity rate in the group with delayed cholecystectomy. I would explain this by the fact that when you compare the total hospital stay, this was double in the delayed cholecystectomy group, namely, 10 days versus 5 days. So, this explains the higher morbidity rate in the delayed cholecystectomy group.

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O.C. Kirton (Hartford, CT):

I would say that early laparoscopic cholecystectomy is a fairly well-accepted process and approach here in this country. I was intrigued with the conversion rate that there was a similarity of conversion between early and delayed laparoscopic cholecystectomy. I wonder whether in the delayed group, these conversions were clustered between day 3 and days 5 to 14 versus the period of time from 14 onward, where you would think that adhesions and the difficulty would be greatest. Was this the case in your study when you broke down where these conversions occurred?

Response From M.W. Büchler:

I do not have data about the conversion rate when we operated on days 6, 7, 9, 10, 35, etc. We were also surprised, because we expected that the conversion rate would be higher in the delayed cholecystectomy group, but this was not the case, which tells us that the surgeons doing the job have now learned to do the job laparoscopically even in a difficult situation. This is one explanation for me.

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E.M. Copeland (Gainesville, FL):

Randomized trials that result in "pathway medicine" are flawed because clinical acumen may be bypassed. The proper time to perform cholecystectomy for acute cholecystitis has been debated since I finished my residency in 1969. I expect that your study was conducted in centers with highly qualified laparoscopic surgeons. This article, however, will be published in *Annals of Surgery* and will become a pathway for this procedure for all hospitals, possibly even for payment purposes.

There are patients with cholecystitis who should have their procedures delayed for any number of reasons, but at some hospitals, these patients will be rushed to the operating room, their belly opened, and the gallbladder impossible to remove because of the inflammatory reaction at the hilum.

I think your study is probably excellent for the patients within the study. However, how long were your patients ill before reporting to the hospital? A 2-week illness may be quite different from a 36-hour illness when analyzing your data.

Response From M.W. Büchler:

You are absolutely right that this study has been conducted in study centers that are used to knowing what to do regarding following the pathways, and many other hospitals would not be able to follow pathways such as immediate laparoscopic cholecystectomy. So, I agree with you that this study is applicable in centers that can simply apply the pathways we have worked out.

On the one hand, I think that data are convincing that you prevent morbidity, you save costs, and you save hospital stay. Therefore, it should also be applied in other hospitals. On the other hand, we have chosen the centers as experienced laparoscopic centers, and this is a limitation of the study.

We do not have data about prehospital symptoms. The patients were randomized after coming into the hospital, but in Germany you can expect that when patients have an illness such as acute cholecystitis with fever and pain, they go to the hospital. So, we do not expect patients will have suffered 10 days and only then come to the hospital.

DISCUSSANTS

F.L. Greene (Chapel Hill, NC):

In your study, did you see less intraoperative cholangiography in patients with acute cholecystitis, which seems to be prevalent in this country, and what is the philosophy where you practice about intraoperative cholangiography?

Response From M.W. Büchler:

In Germany, intraoperative cholangiography is very rarely used because this is our standard of care. It is used only when there is a very good reason for it, such as jaundice etc. Practically all of the jaundice cases are referred to preoperative endoscopy.