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Early Versus Delayed Cholecystectomy for Acute Cholecystitis: A Meta-analysis of Randomized Controlled Trials

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Abstract

Purpose. We performed a meta-analysis of randomized controlled trials to determine the optimal timing of laparoscopic cholecystectomy and open cholecystectomy for acute cholecystitis.

Methods. We retrieved randomized controlled trials (RCTs) that compared early with delayed cholecystectomy for acute cholecystitis by systematically searching Medline and the Cochrane Library for studies published between 1966 and 2003. The outcomes of primary interest were mortality and morbidity.

Results. The ten trials we analyzed comprised 1014 subjects; 534 were assigned to the early group and 480 assigned to the delayed group. The combined risk difference of mortality appeared to favor open cholecystectomy in the early period (risk difference, –0.02; 95% confidence interval, –0.44 to –0.00), but no differences were found among laparoscopic procedures or among all procedures. The combined risk difference of morbidity showed no differences between the open and laparoscopic procedures. The combined risk difference of the rate of conversion to open surgery showed no differences in the included laparoscopic studies; however, the combined total hospital stay was significantly shorter in the early group than in the delayed group.

Conclusions. There is no advantage to delaying cholecystectomy for acute cholecystitis on the basis of outcomes in mortality, morbidity, rate of conversion to open surgery, and mean hospital stay. Thus, early cholecystectomy should be performed for patients with acute cholecystitis.

Kew words Meta-analysis · Cholecystectomy · Early · Delay

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Introduction

Open cholecystectomy was the standard treatment for acute cholecystitis for several decades. When laparoscopic cholecystectomy was first introduced in 1987, acute cholecystitis was a contraindication for this operation;[1–3] however, increased experience with this condition has led to laparoscopic cholecystectomy being equivalent to, or better than, open cholecystectomy for its treatment.[4] The specific purpose and timing of both open and laparoscopic cholecystectomy in the treatment of acute cholecystitis is a subject of some debate. Many clinicians still believe that inflammation, edema, and adhesions, which are commonly associated with cholecystectomy, make early surgery unsafe.

The benefits of both open and laparoscopic cholecystectomy have been substantiated by several randomized controlled trials (RCTs) showing that the early-operation strategy is associated with a shorter hospital stay without added morbidity.[5–11] However, other studies show an association between early procedures and an increase in morbidity.[12–14] Although several review articles and RCTs have addressed this issue, no meta-analyses of RCTs have been published.[5–16] In light of this, we performed a meta-analysis of RCTs to determine the optimal timing of laparoscopic cholecystectomy and open cholecystectomy for acute cholecystitis.

Methods

Search strategy

Retrieval of RCTs was based on the Cochrane Central Register of Controlled Trials (Cochrane Library, until issue 4, July 2003) and Medline (January 1966 to September 2003). The following search terms were used: “cholecystitis,” “cholecystectomy,” “early,” and "delayed." We supplemented electronic searches by hand searching reference lists and reviews. Trials in any language were taken into account.

Inclusion and Exclusion Criteria

This meta-analysis included studies that met the following four criteria: study design (randomized controlled trial), main purpose (comparing the effectiveness of early with delayed cholecystectomy), target population (patients with acute cholecystitis), and availability of mortality and morbidity data. We excluded studies that used cholecystectomy for cancer and those that were not RCTs. Each author first decided independently which reports should be included in the analysis. Then, any disagreement was settled by consensus among all investigators.

Data Collection

Data were collected independently by two investigators (SS and YN), with any disagreement resolved by a third reviewer (TF).

Outcome Measures

The outcomes of primary interest were mortality and morbidity related to cholecystectomy. Secondary outcomes were the rate of conversion to open surgery, hospital stay, operation time, and bleeding.

Quality Assessment of Primary Studies

We evaluated the quality of primary studies as described by Jadad et al.[17] This method assesses the description of randomization, appropriateness of randomization, description of double blinding, appropriateness of double blinding, and description of withdrawals or dropouts on a five-point scale. The minimum number of points possible was 0 and the maximum, 5.

Sensitivity Analysis

We performed a sensitivity analysis by excluding low-quality studies, defined as studies receiving a score of 2 or less on the Jadad scale, and assessed the impact of study quality.

Assessment of Publication Bias

The potential for publication bias was examined by the funnel plot method,[18] and the significance of differences was evaluated by the method of Begg and Mazumdar[19] and Egger et al.[20] A *P* value of publication bias less than 0.10 was considered significant.

Statistical Analysis

We calculated the risk difference for the outcomes of the trials and weighted pooled estimates for the data. The fixed-effect model weighted by the Mantel-Haenszel method was used for pooling the risk differences,[21] followed by a test of homogeneity. Homogeneity among studies was assessed using the χ-squared test (*Q* statistics).[22] *P* value of homogeneity less than 0.10 was considered significant. If the hypothesis of homogeneity was rejected, than the random-effect model using the DerSimonian-Laird method was used.[23] All statistical analyses were performed with the aid of STATA statistical software.[24] Results are expressed as means with 95% confidence intervals (CIs), unless otherwise indicated. A *P* value of less than 0.05 was considered significant.

Results

Trial Flow

Figure 1 shows the summary profile of the search. The database search yielded 141 articles, and the manual search of bibliographies in these articles yielded no further articles. Of the 141 articles selected, 14 met the inclusion criteria, but 4 of them were excluded because of multiple publication. Thus, the final analysis consisted of ten studies: four of laparoscopic cholecystectomy and six of open cholecystectomy. Our agreement on the selection of relevant articles was 100%.

Study Characteristics

The ten included trials comprised 1014 subjects. We assigned 534 to the early procedure group (early group) and 480 to the delayed procedure group (delayed group). The four studies on laparoscopic procedures (laparoscopic studies) comprised 363 subjects; 193 were assigned to the early group and 170 to the delayed group. The six studies on open procedures (open studies) comprised 651 subjects; 341 were assigned to the early group and 310 to the delayed group. Table 1 shows the baseline characteristics of the subjects in the included studies. The average age in the study by Chandler et al.,[5] 36/39 (early/delayed), was younger than that in the other studies, and the proportion of male subjects in the study by McArthur et al.,[13] 7%/18% (early/delayed), was much lower than in the other studies.

All primary studies met the inclusion criteria of patients with acute cholecystitis, but exclusion criteria and definitions of the terms "acute cholecystitis," "early operation," and "delayed operation" differed among the studies (Table 2).

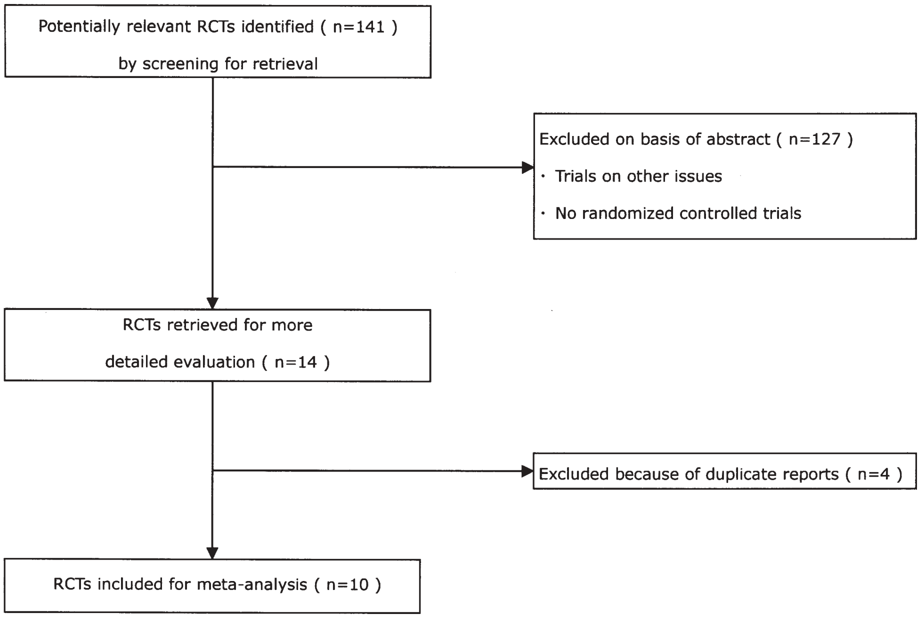

Fig. 1. Flow of randomized controlled trials through the process of retrieval and inclusion in the meta-analysis comparing early and delayed operations for acute cholecystitis. *RCT*, randomized controlled trial

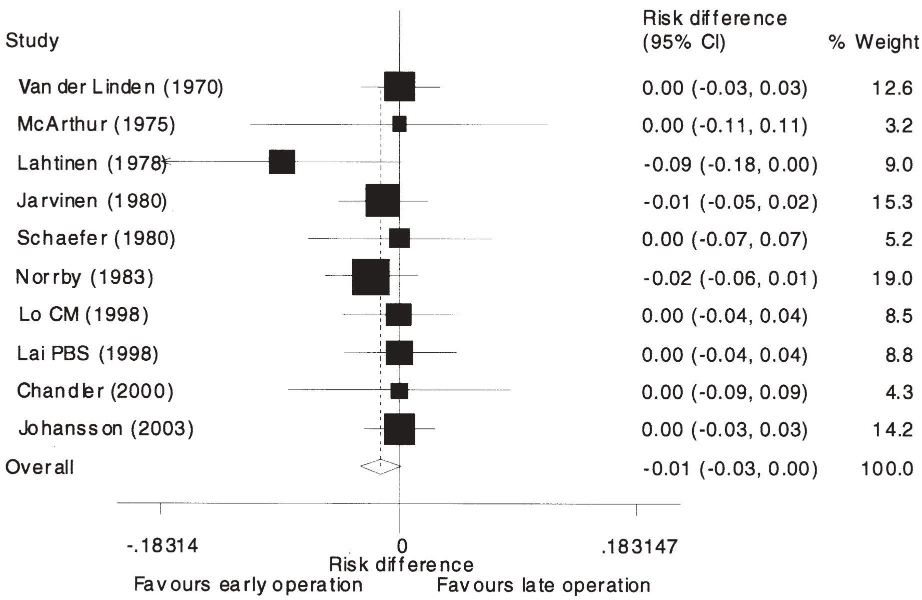

Fig. 2. Early versus delayed cholecystectomy: risk differences (95% confidence intervals) of mortality

Quality Assessment

The highest Jadad score was 3, the lowest was 1, and the average was 2.4 (Table 1). None of the studies met the requirements for description of double blinding or appropriateness of double blinding at all.

Mortality

Data on mortality were available in all included studies. No death was reported in the laparoscopic studies, but deaths were reported in three of the six open studies. The combined risk difference favored the open procedures, but no differences were noted among laparoscopic procedures or among all procedures. Heterogeneity between studies was not considered significant. (Fig. 2, Table 3).

Morbidity

Data on morbidity were available in all included studies. There was no combined risk difference among the open procedures, laparoscopic procedures, or all procedures. Heterogeneity between studies was considered significant, except in the laparoscopic procedures (Fig. 3, Table 3).

Table 1. Characteristics of the studies included for meta-analysis

Study (year)	Reference no.	Country	Jadad score	Early/Delayed: No. of patients	Mean age (yr)	Males (%)	Mean operation time (min)	Mean hospital stay (days)	No. of complications	No. of deaths
Open cholecystectomy										
van der Linden and Sunzel (1970)	14	Sweden	2	70/58	NR	NR	NR	10.1/18.9	10/2	0/0
McArthur et al. (1975)	13	U.K	3	15/17	49/50	7/18	NR	13.1/24.2	6/5	0/0
Lahtinen et al. (1978)	11	Finland	3	47/44	64/63	NR	77/98	13.0/25.0	14/39	0/4
Schaefer et al. (1980)	10	Germany	2	28/25	NR	NR	NR	12.0/22.0	8/9	0/0
Jarvinen and Hastbacka (1980)	9	Finland	3	80/75	58/57	50/48	93/85	10.7/18.2	11/13	0/1
Norrby et al. (1983)	8	Sweden	1	101/91	58/58	35/44	110/100	9.1/15.5	15/14	0/2
Laparoscopic cholecystectomy										
Lai et al. (1998)	7	China	3	53/38	59/61	43/29	123/107	7.6/11.6	5/3	0/0
Lo et al. (1998)	6	China	3	45/41	59/61	58/51	135/105	6.0/11.0	6/12	0/0
Chandler et al. (2000)	5	U.S.A	1	21/22	36/39	NR	115/125	5.4/7.1	2/2	0/0
Johansson et al. (2003)	12	Sweden	3	74/69	58/55	38/77	98/100	5.0/8.0	7/13	0/0

NR, not reported

Conversion Risk

Data on the rate of conversion to open surgery were available in all laparoscopic studies. There was no combined risk difference in the included laparoscopic studies. The heterogeneity between studies was not considered significant (Table 3).

Other End Points

The combined total hospital stay was shorter in the early group than in the delayed group, at −2.7 days in the laparoscopic group and −10.2 days in the open group, which was significant. Data on operation time were available in only three studies on open cholecystectomy, and no difference was noted between the early group and the delayed group (Table 3). We were unable to perform an analysis of bleeding because data were available only in one laparoscopic study and one open study. The mean blood loss was 81 ± 12/299 ± 62 ml (early/delayed) in the laparoscopic study by Chandler et al.[5] and 420 ± 420/300 ± 270 ml (early/delayed) in the open study by Norrby et al.[9]

Exploring the Source of Homogeneity

The hypothesis of homogeneity was not rejected by using data of mortality, but it was rejected by using data of morbidity (χ^2 = 63.15, d.f. = 9, P = 0.00). Because morbidity in the study by Lahtinen et al.[11] was much higher than that in the other studies, a subgroup analysis was done by excluding this study. Homogeneity was noted among the remaining studies (χ^2 = 10.88, d.f. = 8, P = 0.21). Meta-regression analysis indicated that early cholecystectomy had a greater advantage in the study with higher morbidity in the delayed group (β coefficient; −4.16, P = 0.00).

Sensitivity Analysis

We performed a sensitivity analysis using the fixed-effect model by including only six high-quality studies, defined as those with a Jadad score of three or higher. According to our findings, the combined risk difference of mortality was 0.17 (−0.39, 0.00) and that of morbidity was −0.10 (−0.29, 0.87). These results were similar to the combined result of all studies.

Publication Bias

The funnel-plot, Begg's test, and Egger's test were used to evaluate the potential for publication bias associated with the mortality rate related to cholecystectomy. The funnel-plot did not show a symmetric pattern, whereas both of the statistical tests revealed

Table 2. Exclusion criteria and definitions employed in the studies included for meta-analysis

Study (year)	Reference no.	Exclusion criteria	Definitions: Acute cholecystitis	Definitions: Early operation	Definitions: Delayed operation
Open cholecystectomy					
van der Linden and Sunzel (1970)	14	Presenting with peritonitis, elderly	NR	Performed on the next routine operating list	6 to 10 weeks
McArthur et al. (1975)	13	Presenting with peritonitis or jaundice, Symptoms >1 week, elderly >80 years	Acute RUQ tenderness and guarding, pyrexia with , tachycardia a neutrophil leukocytosis	NR	NR
Lahtinen et al. (1978)	11	Suspicion of diffuse peritonitis, Cardiac or respiratory disorder	(1) Pain in the right hypochondrium, (2) tenderness or palpable GB, (3) abnormal X-ray of the GB, (4) duration <7 days, (5) BT >37.5°C or WBC >10×10^9	Performed on the next operating list	8 to 10 weeks
Schaefer et al. (1980)	10	Symptoms >1 week	NR	Within 48h or onset	6 to 8 weeks
Jarvinen and Hastbacka (1980)	9	Spreading peritonitis, refusal of operation, severe contraindi cations, amy >1000U	(1) Acute abd. pain <7 days, (2) tenderness at RUQ, (3) BT >37.5°C or WBC >10×10^9	Within 7 days of onset	2 to 4 months
Norrby et al. (1983)	8	Elderly >75 years, refusal of operation, pancreatitis risk of perforation, symtoms >1 week, or anesthetic risk.	NR	Within 7 days of onset	After initial conservative therapy
Laparoscopic cholecystectomy					
Lai et al. (1998)	7	(1) Symptoms >1 week, (2) Previous upper abd surgery, (3) Coexisting CBD stones	Acute RUQ pain, 37.5°C, WBC >10×10^9, and US findings of AC	Within 24h of randomization	6 to 8 weeks
Lo et al. (1998)	6	Spreading peritonitis or uncertainty of diagnosis, previous upper abd surgery, absolute contraindication, concomitant malignant disease, or pregnancy.	(1) Acute upper abd. pain (2) BT >37.5°C, WBC >10×10^9 (3) US finding of AC	Within 72h of admission	8 to 12 weeks
Chandler et al. (2000)	5	A history of peptic ulcer disease, evidence of GB perforation, or uncertainty of diagnosis.	GBS, thickened GB wall, pericholecystic fluid, or ultrasonic Murphy's sign	Within 72h of admission	After the resolution of symptoms or after 5 days of treatment
Johansson et al. (2003)	12	(1) Bil >3.5mg/dl, (2) Symptoms >1 week, (3) Patient could not understand the study, (4) elderly >90yr	(1) Acute tenderness in RUQ and US findings of AC, or (2) acute tenderness in RUQ and US after randomization findings of GBS	Within 48h	6 to 8 weeks

NR, not reported; Abd, abdominal; AC, acute cholecystitis; CBD, common biliary duct; US, ultrasound; RUQ, right upper quadrant; GB, gallbladder; GBS, gallbladder stones

Table 3. Results of weighted pooled analysis and tests for homogeneity

Outcome	No. of trials	Risk difference (95% CI)	*Q* value	*P* value of test for homogeneity
Mortality				
Laparoscopic	4	0.00 (–0.22, 0.22)	0.00	1.00
Open	6	–0.02 (–0.44, –0.00)	4.98	0.42
All	10	–0.01 (–0.03, 0.00)	5.92	0.75
Morbidity				
Laparoscopic	4	0.00 (–0.07, 0.07)	5.16	0.16
Open	6	–0.09 (–0.28, 0.11)*	56.8	<0.01
All	10	–0.06 (–0.17, 0.06)*	63.2	<0.01
Conversion to open surgery	4	–0.40 (–0.13, 0.49)	1.76	0.62
Hospital stay (days)				
Laparoscopic	2	–2.73 (–4.97, –0.49)*	8.61	<0.01
Open	3	–10.23 (–13.42, –7.04)*	14.6	<0.01
Operation time (hours)				
Open	3	–1.65 (–25.54, 22.24)*	51.5	<0.0001

CI, confidence interval
*, DerSimonian-Laird method

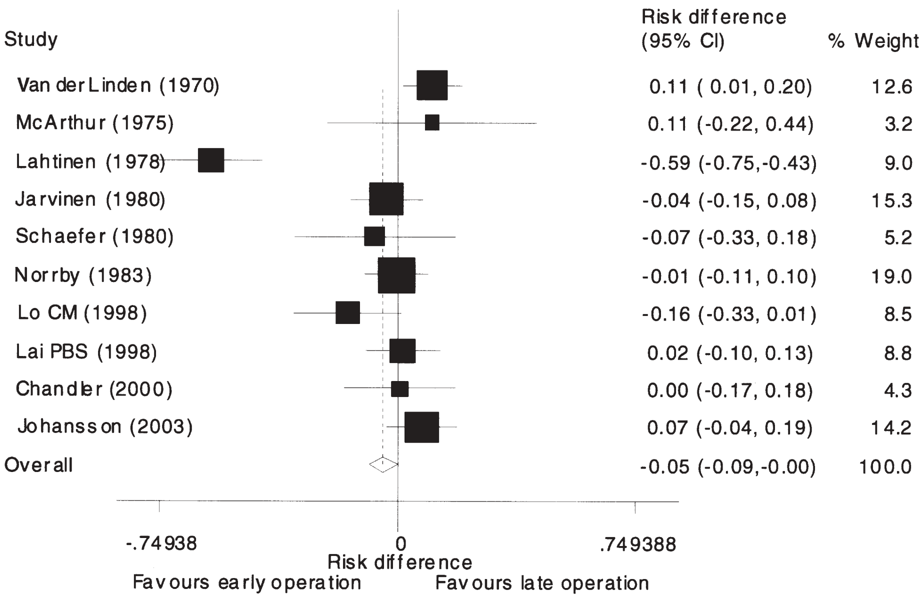

Fig. 3. Early versus delayed cholecystectomy: risk differences (95% confidence intervals) of morbidity

significant publication bias (Begg's test, $P = 0.004$; Egger's test, $P = 0.000$).

Discussion

A recent review article, based entirely on nonrandomized and retrospective studies, lent support to the use of early laparoscopic cholecystectomy to treat acute cholecystitis.[16] However, no meta-analyses of RCTs have addressed this issue. Thus, with the aim of providing better insight into whether early laparoscopic cholecystectomy is valid for treating patients with acute cholecystitis, we conducted a meta-analysis of ten RCTs to assess and clarify early versus delayed laparoscopic and open cholecystectomy for acute cholecystitis.

Summary of Outcomes

Our findings reveled no risk difference between early and delayed surgery on the basis of outcomes in mortality, morbidity, and rates of conversion. The mean total hospital stay was shorter in the early group than in the delayed group, and there was no difference in operation time between the two groups. As mentioned in our Results section, in exploring the source of homogeneity, we found that the study by Lahtinen et al.[11] reported much higher mortality and morbidity than the other studies. In their study, four patients died in the delayed group, two of pulmonary embolism and coronary events during medical treatment. High morbidity was caused by a high rate of recurrence (11/44) and wound infections (8/44).

Meta-regression Analysis

Meta-regression analysis indicated that the advantage of early cholecystectomy was more apparent in studies with higher morbidity. This result suggests that performing an early operation is better for serious and advanced disease. According to Rattner et al.[25] and Singer and McKeen,[26] as the inflammatory process progresses, the risks of induration, hypervascularity, abscess, and necrosis of the gallbladder increase. These late inflammatory changes are therefore seen as factors that can cause difficulty in gallbladder retraction and lead to problems with visualization of vital anatomic structures.

Quality Assessment

The quality of studies included in this meta-analysis should be considered in the interpretation of our findings. None of the trials reported adequate comprehensive blinding of outcome assessment; however, in light of this being an inevitable and common problem among surgical trials, we evaluated the studies of high quality with Jadad scores of 3 and not 5. Sensitivity analysis of high-quality studies showed no change in results for all studies.

Limitations

Our study has several limitations. First, the quality of the individual RCTs included in our analysis was not necessarily high, as stated above. Second, the included studies provided different definitions of the terms, "acute cholecystitis," "early operation," and "delayed operation," and the exclusion criteria also varied. Third, although statistical tests revealed that there was publication bias, it is difficult to evaluate the potential for such bias because of the small number of included studies. Thus, the evaluation of future RCTs by another meta-analysis may produce different results.

Conclusions

Our meta-analysis clarified that there is no advantage in delaying cholecystectomy for acute cholecystitis on the basis of outcomes in mortality, morbidity, rate of conversion to open surgery, and mean hospital stay. Based on these findings, we surmise that performing early surgery is more appropriate for patients with serious and advanced cholecystitis. Taking into consideration medical expenses and prolonged suffering, we conclude that early cholecystectomy should be performed for patients with acute cholecystitis.

Emergency surgery is mandatory for patients with sings of spreading peritonitis, as a matter of course. Early scheduled laparoscopic cholecystectomy after percutaneous transhepatic gallbladder drainage was recently shown to be a safe and appropriate therapeutic option for severe acute cholecystitis.[27] This finding is consistent with the results of our meta-regression analysis.

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