

# Early Cholecystectomy for Acute Cholecystitis

## A Prospective Randomized Study

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A randomized clinical trial was undertaken to compare early and delayed cholecystectomy for acute cholecystitis. Patients entering early (n = 83) or delayed (n = 82) surgery groups were comparable with regard to prandomization data. One patient in the early group and five in the delayed group refused surgery ( $p < 0.1$ ) and two misdiagnoses occurred in each group. (2.4%). There was no difference in the incidence of technical difficulty measured by operative complications and duration of operations between the two groups. The same number of patients with common duct stones and perforations of the gallbladder were in each group. There was one death in the delayed group and none in the early group. Post-operative morbidity was 13.8% in the early group and 17.3% in the delayed surgery group ( $p > 0.1$ ). Wound complications were slightly more common in the early surgery group ( $p > 0.1$ ). In the delayed surgery group 13% of the patients had to be operated on before the planned date of surgery because conservative management failed. In addition, 15% of the patients had clear recurrent symptoms. Early surgery reduced total hospital stay by a mean of 7.5 days and the period of the patient's incapacity for work by 14.4 days. The data suggest that in acute cholecystitis early surgery is preferable when performed by an experienced surgeon with adequate pre- and intraoperative aids. Besides lower costs it offers the advantage of avoiding recurrent attacks and emergency operations without increasing mortality or morbidity.

**I**N THE TREATMENT of acute cholecystitis both early surgery within a few days of onset<sup>3,13</sup> and delayed operation after the subsidence of acute symptoms<sup>1,9,12</sup> have supporters. Controversy concerning the preferable timing of surgery continues because of lack of comparable patient series treated with each modality. So far, the only controlled trial was reported by van der Linden and Sunzel in 1970.<sup>8</sup> Their data favored early surgery for acute cholecystitis, although not une-

quivocally. The present randomized study was undertaken to elucidate further the applicability of early definitive surgery compared with the traditional delayed surgery for acute cholecystitis.

### Patients and Methods

All the patients admitted to the Second Department of Surgery at the Helsinki University Central Hospital between February 1, 1976 and May 31, 1978, with a tentative clinical diagnosis of acute cholecystitis were candidates for the study. Those patients who after clinical, radiologic and laboratory examinations fulfilled the following criteria were considered eligible for the trial: 1) Acute abdominal pain of less than 7 days' duration; 2) Clear tenderness or muscular defense under the right costal margin; 3) Axillary temperature over 37.5 C and/or leukocytosis over  $10 \times 10^9/L$ ; 4) Intra-venous cholegraphy (or exceptional cholescintigraphy) supporting the diagnosis of acute cholecystitis.<sup>6,15</sup> Patients with a serum amylase level over 1000 units per liter entered another clinical trial and were excluded.

Forty-six (22%) of the 211 patients meeting the criteria were excluded before randomization because one or both of the treatment modalities were considered unsuitable. Of these, 28 had signs of spreading peritonitis and underwent emergency operation within 24 hours of admission without mortality. The remaining 18 patients either refused surgery or had severe contraindications warranting an operation on vital indications only. Five of these patients subsequently underwent emergency surgery, and one died.

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After these exclusions 165 patients were randomly allocated to early ( $n = 83$ ) or delayed ( $n = 82$ ) surgery groups by the method of supernumerary sealed envelopes. The control of comparability of the groups included age, sex, earlier history of biliary disease, duration of acute symptoms, liver function tests and presence of significant risk factors due to other diseases, such as severe cardiac or pulmonary disease or diabetes.

The supportive treatment was similar for the two groups. All patients received intravenous ampicillin (1g four times a day) or cephalothin (1–2g four times a day) for five to ten days during the acute stage. Fluid infusions and analgesics were used routinely and nasogastric suction was used in more severe cases. In an effort to achieve optimal conditions for surgery, chest x-ray, electrocardiogram, blood studies, electrolytes and urine sediment were examined at admission. Patients with estimated high risk of thromboembolic complications received low-dose heparin subcutaneously (5000 units three times a day) for five days from the day of surgery.

The patients undergoing early surgery were operated on within seven days of the onset of acute symptoms, as a rule on the next schedule or after it in the afternoon. The mean interval between admission and operation was  $1.6 \pm 1.2$  days. The patients in the delayed surgery group were discharged as soon as the acute symptoms had subsided. They were readmitted for elective surgery two to four months later (mean  $2.6 \pm 0.7$  months). When possible, further attacks of acute cholecystitis during the interval were treated conservatively. If conservative treatment failed, operative intervention was performed before the planned date of surgery, but only on mandatory indications.

All operations were carried out by the same group of staff surgeons and senior residents. One of the authors attended 85% of the operations.

The surgical procedure was similar in the two groups. The abdomen was opened through a midline incision, and dissection of the gallbladder was started from the fundus. Operative needle cholangiography<sup>14</sup> was performed routinely. Choledochotomy was undertaken when indicated by the radiologic finding. Sphincterotomy with papilloplasty was used to remove tightly impacted ampullary stones. After choledochotomy, T-tube drainage was used. A postexploratory cholangiography was performed before wound closure, and repeated on the sixth to eighth postoperative day before extraction of the T-tube. The subhepatic space was always drained. The gallbladder was subjected to microscopic examination. Liver function tests and chest x-rays were repeated on the third postoperative day.

All patients were followed up for at least one month by personal examinations and laboratory tests.

Statistical methods employed were the frequencies, means  $\pm$  SD, and significance testing of the differences (chi square and Student's t-test).

## Results

One of the 83 patients in the early group and five of the 82 patients in the delayed surgery group refused surgery after randomization ( $p < 0.1$ ). There were four misdiagnoses (2.4%), two in both groups. All four patients had gallstones, but the acute symptoms proved to be due to a periappendicular abscess and liver cirrhosis in the patients of early surgery group and to a perforation of a duodenal ulcer and hydroponyonephrosis of the right kidney in the patients of the delayed surgery group. The patients of the delayed group underwent emergency operations on the third and sixth day after admission.

For all the other randomized patients cholecystectomy and operative cholangiography were successfully performed as planned, 80 in the early group and 75 in the delayed surgery group. Despite a slight excess of patients with "increased risk" in the early group, the two groups were statistically comparable with each other (Table 1).

### *Conservative Period of the Delayed Surgery Group*

The waiting period before the planned date of delayed operation was uneventful in 52 patients (69%), whereas operative intervention proved necessary before the scheduled date in ten patients (13%). Three of the latter patients developed signs of spreading peritonitis (two to three days after admission), five had increasing jaundice and cholangitis (4–18 days) and two an unresolving painful empyema (6–14 days). In addition, 11 patients (15%) undergoing delayed operation two to four months after the acute attack suffered from clear recurrent symptoms during the waiting period. Five of them had a recurrence of acute cholecystitis, two acute pancreatitis and four biliary colics. Nine patients had to be readmitted, but the symptoms soon subsided, and the patients were discharged and operated on delayed as planned. Furthermore, two cases of pneumonia occurred during the initial acute episode of cholecystitis.

### *Operative Findings*

There were five (3.2%) gallbladder perforations, three in the early and two in the delayed surgery group. Of the three early patients, two were free perforations and one

TABLE 1. Comparison of the Prerandomization Data in the Early and Delayed Surgery Groups

	Early Surgery (n = 80)	Delayed Surgery (n = 75)
Age (years)	57.8 ± 15.6	56.7 ± 15.9
Sex (males)	40 (50%)	36 (48%)
Previous history +	44 (55%)	34 (45%)
Duration of acute symptoms (days)	2.2 ± 1.5	2.3 ± 2.0
Increased risk	35 (44%)	23 (31%)*
Bilirubin over 21 mcmol/L	27 (34%)	23 (31%)
Transaminases over 40/45 units/L	25 (31%)	28 (37%)
Alkaline phosphatase over 280 units/L	16 (20%)	19 (25%)
U-amylase over 2500 units/L	6 (7.5%)	8 (11%)

\*  $p > 0.05$ , in all other variables  $p > 0.1$ .

was a cholecystoduodenal fistula; the two late patients had concealed perforations. Microscopic examination of the gallbladder wall revealed gangrenous changes in 22 early and in seven delayed group specimens (Table 2). Histopathologic signs of acute inflammation were seen in 11 delayed group cases while seven early group cases had chronic changes only, although there was no doubt of the diagnosis at operation.

### Operative Procedures

In addition to cholecystectomy and operative cholangiography, common duct exploration was performed for 17 patients in the early and 15 patients in the delayed surgery group. Common duct stones were present in 15 (18.8%) and 12 (16.0%) instances, respectively ( $p > 0.1$ , mean: 17.4%). In four delayed operations transduodenal sphincterotomy was necessary for the removal of an impacted ampullary stone.

Coincidental findings in the early surgery group were one renal carcinoma, two incisional hernias and one case of polycystic liver; right nephrectomy and closure of hernias were performed at the primary operation. Similarly, one appendix, one Meckel's diverticulum and one hepatoma were removed and one umbilical hernia repaired in delayed operations.

TABLE 2. Histopathologic Findings in Gallbladder Specimens in Early and Delayed Surgery Groups

	Early Surgery (n = 80)	Delayed Surgery (n = 75)
Acute gangrenous cholecystitis	22	7
Acute cholecystitis	39	4
Acute and chronic cholecystitis	12	7
Chronic cholecystitis	7	57

### Technical Difficulty

In neither of the groups were there patients with intraoperative blood loss indicating correction by transfusions, although anemia present before surgery was occasionally compensated with blood. Three minor intraoperative complications occurred in early and two in elective delayed operations. The former included a tear of the duodenal stump and a bleeding of the portal vein in patients with earlier partial gastrectomy and one case of minor bile leak at the cystic duct junction needing a stitch. Two lesions of the latter type occurred in the delayed surgery group. All lesions were easily corrected without any later consequences.

The operation times for simple cholecystectomy were  $93 \pm 27$  minutes in the early and  $85 \pm 33$  minutes in the delayed surgery group ( $p > 0.1$ ) while operations with common duct exploration took  $139 \pm 44$  minutes and  $147 \pm 37$  minutes ( $p > 0.1$ ), respectively.

### Postoperative Morbidity and Reoperations

There was no mortality after early surgery, whereas one patient (1.3%) of the delayed surgery group died of postoperative thrombosis of the superior mesenteric artery, despite reoperation and resection of the small intestine two days later. This 68-year-old woman coincidentally had a hepatoma 2 cm in diameter at the border of the right liver lobe, and this was removed by a wedge resection at the primary operation.

The total number of postoperative complications showed no statistical difference between the two groups (Table 3). Wound complications were, however, slightly more common in the early surgery group ( $p > 0.1$ ), and other abdominal complications were more common in the delayed surgery group ( $p < 0.1$ ). Besides re-sutures and the case of intestinal resection mentioned already, one drainage operation was needed in each group because of intra-abdominal abscesses. All patients with postoperative ileus responded to conservative measures in a few days.

Retained common duct stones were encountered in two cases (1.3% of all and 6.3% of patients with common duct exploration), one in each group. The patient in the early surgery group was reoperated on, while the stone in the delayed group case passed spontaneously.

### Hospital Stay and Patient's Incapacity for Work

The total hospital stay was 7.5 days fewer in the early surgery group than in the delayed surgery group. The difference was 14.4 days in the case of insurance payment for the loss of working capacity (paid for all gainfully employed people under the age of 65 in Finland).

The difference was highly significant in both instances (Table 4). The average time spent in hospital for conservative treatment, including the management of recurrences, was 6.2 days in the delayed surgery group and time required during operative admission was 12.0 days.

### Discussion

One argument against early surgery in acute cholecystitis is the possibility of an erroneous diagnosis.<sup>2,4</sup> In the present series only four patients (2.4%) were misdiagnosed; they were distributed evenly between the two groups. Of these four patients, all of whom had gallstones, three required emergency surgery in any case. Further examinations would probably have been unsuccessful or even hazardous. Usually, adequate clinical and radiologic evaluation can be made within 24–48 hours of admission.<sup>3,8,13</sup> Intravenous cholecography, as used in the present study, has proved a valuable diagnostic aid,<sup>6</sup> but other radiologic measures, such as cholescintigraphy, infusion tomography of the gallbladder, ultrasound and even oral cholecystography can also be considered.<sup>6,7,15</sup>

Another issue of controversy is the claimed technical difficulty of performing cholecystectomy during the acute phase of cholecystitis.<sup>11,12</sup> The evaluation of this problem is always subjective and no generally accepted criteria exists.<sup>8</sup> However, in none of the cases of the present series was cholecystectomy technically impossible. Furthermore, both operation times and the incidence of minor operative complications were equal in the two groups. In all stages of acute cholecystitis, however, cholecystectomy may be considerably more difficult than elective operations for uncomplicated cholelithiasis. In operations for acute cholecystitis the need for surgical experience is to be emphasized.

Common duct stones were equally frequent in the two groups of the present series, on average 17.4%. The low rate of retained stones in our series suggests that they present no special problems when routine intraoperative cholangiography is used. However, if conservative treatment is practiced, common duct stones carry an increased risk of cholangitis and impaction at the sphincter of Oddi. Furthermore, conservative treatment involves a threat of gallbladder gangrene and perforations, complications that were observed in both groups of the present study.

Postoperative mortality and morbidity were equal in the two groups. However, wound complications were somewhat more frequent in the early surgery group. A similar, and actually statistically significant difference was encountered in the series of van der Linden and Sunzel.<sup>8</sup>

TABLE 3. Postoperative Complications in the Early and Delayed Surgery Groups

	Early Surgery (n = 80)	Delayed Surgery (n = 75)
Pneumonia	1	2
Wound infection/hematoma	3*	—
Wound dehiscence	3***	1*
Incisional hernia	1	1
Intra-abdominal abscess	1*	1*
Ileus	1	3
Mesenteric thrombosis	—	1*†
Pancreatitis	—	2
Cardiac infarction	—	1
Transient psychosis	1	1
	11 (13.8%)	13 (17.3%)

\* Reoperation.

† Death.

In the group of delayed surgery, 13% of the patients required emergency surgery before the planned date of operation, as also observed in the preliminary report by McArthur et al.<sup>10</sup> In addition, 15% of the patients experienced clear recurrent symptoms during the waiting period. Even though no severe surgical complications occurred in the present closely monitored trial, it seems clear that in routine clinical work such patients present a greater risk characterized even by enhanced mortality.<sup>5,16</sup>

In conclusion, the present study did not reveal any arguments against early cholecystectomy in acute cholecystitis. The results of the early and delayed treatment regimens were similar both diagnostically and technically, as well as with regard to postoperative morbidity and mortality. However, conservative treatment often failed and had to be interrupted with emergency surgery in a complicated situation, which is prone to increase the risks of the delayed surgery regimen. Furthermore, the socioeconomic benefits of the one-week shorter hospital stay and two-weeks

TABLE 4. Total Hospital Stay and Insurance Payment for the Loss of Working Capacity

	Hospital Stay (days)	Insurance Payment (days)
Early surgery group (n = 80)	10.7 ± 4.9	40.0 ± 4.4 (n = 33)
Delayed surgery group (n = 75)	18.2 ± 8.6	54.4 ± 8.8 (n = 35)
Difference	7.5 (p < 0.001)	14.4 (p < 0.001)

reduction in loss of working capacity of patients treated with early surgery are obvious.

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