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Symptomatic, Non-Complicated Gallbladder Stone Disease. Operation or Observation?

A Randomized Clinical Study

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Background: Cholecystectomy has been recognized as the treatment of choice for symptomatic gallbladder stone disease. Not all patients are cured by an operation and the reason for having the gallbladder removed may rest on common practice rather than evidence-based medicine. The aim was to compare cholecystectomy with observation (watchful waiting) in patients with uncomplicated symptomatic GBS disease. Three-hundred-and-thirty-eight patients were considered for participation in the study; 45 patients were excluded according to predefined criteria and 156 did not join for other reasons. The remaining 137 were randomized to cholecystectomy ($n = 68$) or non-operative, expectant treatment ($n = 69$). **Methods:** Randomized patients were contacted regularly and followed for a median of 67 months. All gallstone-related hospital contacts were registered in both randomized and excluded patients. **Results:** Eight of the patients randomized to cholecystectomy did not undergo operation, while 35 of the patients randomized to observation later had their gallbladders removed. The cumulative risk of having a cholecystectomy seemed to level off after 4 years. Gallstone-related complications occurred in 3 patients in the observation group, 1 in the operation group and 5 of 201 excluded patients. After cholecystectomy, 16 of 222 patients had a major complication and 10 a minor. **Conclusions:** We found that non-operative expectant treatment carries a low risk of complications. Patients should be informed that watchful waiting is a safe option.

Key words: Cholecystectomy; complications; natural course; randomized clinical trial; symptomatic gallstones

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Nearly a hundred years ago, an authoritative surgeon postulated that all gallstones were potentially dangerous (1). Since then, this has dominated treatment policy, although epidemiological studies have shown that the majority of individuals with gallbladder stones (GBS) remain asymptomatic (2–4). In fact, the annual risk of developing symptoms or complications may be less than 1% (5). On the other hand, up to 20% of symptomatic patients are not cured of pain after cholecystectomy (6, 7).

Even though cholecystectomy rates have increased after the introduction of laparoscopic cholecystectomy without any parallel increase in disease incidence (8), prospective studies have not addressed the need for cholecystectomy in patients with GBS pain and no complications. Few studies have examined the natural course of untreated, symptomatic GBS disease and no controlled study has addressed the issue of watchful waiting in such patients (4, 9–12). Thus, based on the principles formulated for an evidence-based medicine, we

may argue that the indication for cholecystectomy in symptomatic GBS patients has never been properly investigated.

This study is a randomized clinical trial (RCT) comparing surgery with observation (watchful waiting) in patients with uncomplicated symptomatic GBS disease. The design of the study will provide information on the natural course of symptomatic GBS and will allow comparison between the rates of complications in observed patients and those undergoing cholecystectomy.

Patients and Methods

Patients

Consecutive patients with episodic abdominal pain attacks compatible with symptomatic, non-complicated GBS disease (see later) were recruited by 3 consultant surgeons in 3 hospitals during a 39-month period from October 1991 to
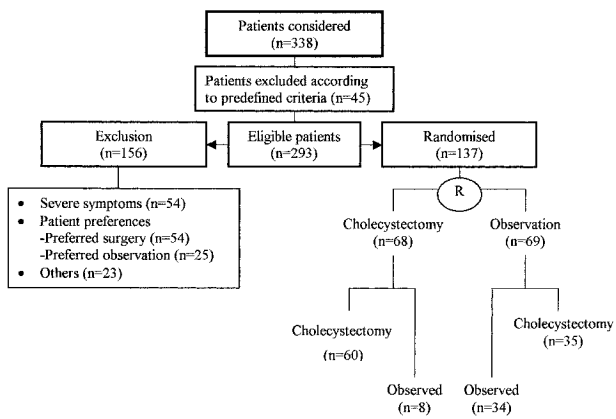
Fig. 1. Symptomatic, non-complicated gallstone disease study population.

April 1994. The participating hospitals (Haukeland University Hospital in Bergen ($n = 73$), Rogaland Central Hospital in Stavanger ($n = 47$) and the Deacon's Hospital in Oslo ($n = 17$)) are first-line treatment centres for defined catchments areas, and the study population was representative for patients being referred for surgical evaluation or treatment.

Symptom definition

Symptomatic disease was defined as episodes of pain, commonly continuous, in the right subcostal or midline epigastric area lasting more than 30 min, with ultrasonography (US) signs of GBS and no clinical or laboratory indication of other causes of their symptoms. Severe symptoms were defined as frequent and/or strong pain attacks limiting daily activities and/or social life. Pain of a less intense/frequent character that could be tolerated by patients and did not restrict their activities was defined as moderate.

Patients with infrequent and/or minimal pain that needed only very occasional medication were not randomized. Patients with abdominal symptoms previously attributed to GBS (dyspepsia, flatulence, nausea, etc.) were not assessed (13).

Diagnostic criteria

The clinical diagnosis was confirmed by US. Criteria for GBS were an echo with an acoustic shadow in a visible gallbladder, or an echo with positional change and size ≤3 mm or, alternatively no demonstrable gallbladder but a strong echo with an acoustic shadow in the position of the gallbladder (14).

Patients with increased liver function tests (bilirubin, alkaline phosphatase, gamma glutamyl-transferase or alanine aminotransferase) suggestive of common bile duct (CBD) obstruction or a CBD diameter of >6 mm at US were investigated further with ERCP to detect CBD stones.

Eligibility, randomization and ethics

Patients were considered for the study after the work-up was completed and the diagnosis made (13). Those with defined exclusion criteria (age <18 or >80 years, pregnancy, serious concomitant disease and suspected CBD stone; $n = 45$) were treated at the discretion of the surgeon.

Eligible patients ($n = 293$) were asked to join the study. Of the 156 patients who did not join, 79 (51%) had personal preferences regarding choice of treatment. Other reasons for exclusion are given in Fig. 1. The remaining 137 were then randomized in blocks of 5 according to a computer program using brown opaque, sealed and numbered envelopes. Participation was confirmed by the patient with a signed agreement form.

Sixty-eight patients were randomized to cholecystectomy and 69 to observation (Fig. 1). Patients randomized to surgery were put on a regular waiting list and operated on as soon as capacity permitted. Those randomized to observation were given information about the nature of their disease, and were advised to avoid food that from experience they knew provoked abdominal pain or discomfort. Strict dietary restriction concerning fat was not advocated.

The study was approved by the Regional Ethics Committee (Health Region III) and the National Surveillance Bureau of Data Registries in Norway.

Follow-up

Eight patients died before completion of the trial. One dropped out of the study after 30 months, the rest were followed for a median of 67 months (range 56–91 months). Patients were given the opportunity to contact the local study coordinator or the hospital at any time if needed, and they answered questionnaires on symptoms and quality of life at the time of randomization and later at regular intervals (6, 12, 24 and 60 months).

Excluded patients were not followed routinely. After 60 months, hospital notes were checked and relevant new events (hospital admittance for abdominal pain, complications of gallstone disease, cholecystectomy, etc.) were recorded. Patients who had moved to other parts of the country were contacted and hospital notes in neighbouring hospitals were examined. Official population registries were searched to record time and cause of death for deceased patients. With the exception of one patient with psychosocial problems, follow-up in randomized patients was 100%. Hospital notes for seven of the excluded patients were missing.

Statistics

When the study was designed it was found difficult to calculate the number of patients required to permit meaningful comparisons between an operated and non-operated group. The choice of end-points and the paucity of studies addressing the time dependency of such end-points made sample size and power calculations difficult. As an example, a conventional end-point like freedom of pain was assumed to be achieved in more than 80% of operated patients shortly

Table I. Patient characteristics

	Randomized patients		Excluded patients	
	Cholecystectomy	Observation	Cholecystectomy	Observation
Women				
No. of patients	55	57	107	57
Median age (range)	52 (20–77)	48 (22–75)	43 (14–80)	70 (19–99)
Men				
No. of patients	13	12	20	17
Median age (range)	52 (27–74)	60 (39–79)	58 (25–78)	69 (17–86)

after operation, whereas information on re-occurrence of pain particularly related to time was not found in the literature.

Secondly, the number of potential crossovers (withdrawals) from the observation group was also unknown, since a similar study had never been done before. The number of patients who had to be excluded and the number of withdrawals due to treatment preferences were other unknown elements.

Pragmatically, therefore, we settled for 100 patients in each arm (group) as this would be sufficient for valid analysis. To avoid potential changes in management policy over time, an inclusion period of 2 years was set.

The results are given by calculations of frequency distributions and cross-tabulations. The cumulative probability of having a cholecystectomy was studied using time-to-event analysis and presented as the reciprocal of the Kaplan-Meier survival analysis plot. A log-rank test (Mantel-Cox) was performed to compare the cholecystectomy rates in the two groups.

Results

Patient characteristics

Gender, age and disease characteristics for randomized and excluded patients are given in Tables I and II. One-hundred-and-twelve of 137 randomized patients (82%) were women. One-hundred-and-twenty-seven of 137 randomized patients (93%) had past symptoms compatible with gallstones and only 10 patients joined the study after their first pain attack. The median duration of symptoms at randomization was 22 months (range 0–623). Two patients had not taken any pain relief medication during GBS pain. Twelve percent of patients had concomitant heart disease, diabetes or obstructive lung disease. Median follow-up in randomized patients was 67 months.

Outcome

Altogether, 95 of 137 randomized patients (69%) eventually underwent cholecystectomy. Eight of 68 patients (12%) randomized to cholecystectomy did not undergo operation, while 35 of 69 (51%) randomized to observation later had their gallbladders removed (Fig. 1). The cumulative proportion of patients in each group (cholecystectomy versus observation) having a cholecystectomy is illustrated in Fig. 2. The risk of having a cholecystectomy levelled off after 3–4 years. A log-rank test (Mantel-Cox) showed a significant difference in cholecystectomy rates in the two groups ($P < 0.0001$).

Of the 293 eligible patients, 207 (71%) had a cholecystectomy, while 86 (29%) were managed conservatively (Fig. 1 and Table IV). Eight patients (15%) of the 54 who were eligible, but excluded from randomization because of severe symptoms, did not have a cholecystectomy.

Events during follow-up

Table III gives GBS-related events in randomized and excluded patients. Twelve of 69 patients (17%) in the observation group, 2 of 68 (3%) in the operation group and 20 of 201 excluded patients (10%) were admitted because of

Table II. Disease characteristics in randomised patients

|	Treatment group	
Variable	Cholecystectomy $n = 68$	Observation $n = 69$
Prior hospitalization for gallbladder stone disease	14	16
Current episode first symptom	4	6
No. (%) of patients with gallbladder stone symptoms in the past	64 (94%)	63 (91%)
Median months (range) of symptoms at randomization	26 (0–622)	20 (0–533)
Pain attacks, frequency	60 of 68	60 of 69
0–5/year	23	23
6–11/year	6	5
1–5/month	25	25
>5/month	6	7

One Minus Survival Functions

MONTHS
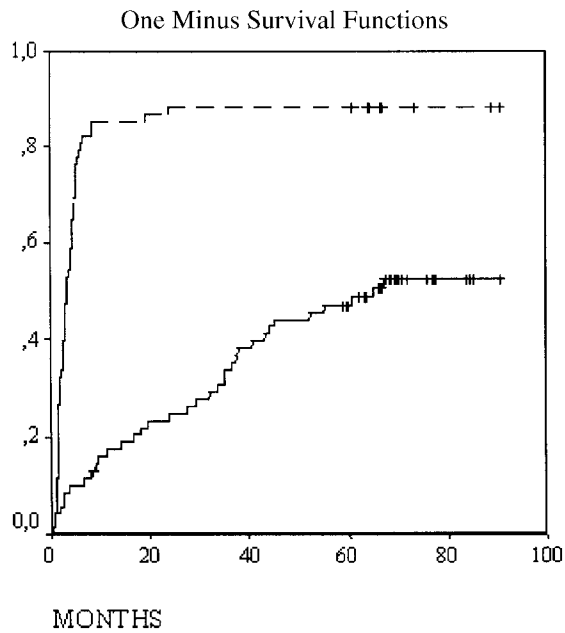
Fig. 2. Cumulative risk of having a cholecystectomy (---- operation group, — observation group, + censored).

biliary pain during the follow-up time. GBS complications (acute cholecystitis, CBD stone or acute pancreatitis) occurred in 3 of 69 patients (4%) in the observation group, 1 of 95 in the operation group (1%) and in 5 of 201 excluded patients (2%).

Complications after cholecystectomy in 222 patients are given in Table V. Sixteen patients (7%) had a major complication and 10 (5%) a minor. Two patients (2%) had to be re-operated. There was no mortality related to cholecystectomy or GBS disease. However, 8 randomized (6%) and 25 excluded (12%) patients died of other causes.

Discussion

The aim of this RCT was to study the natural course of symptomatic, non-complicated GBS disease even though we realized that this could be difficult (13) owing to patients' treatment preferences and dominant treatment preferences commonly expressed by the medical profession. Thus, even if

only 47% of eligible patients were randomized we would argue that the study adds important and new information.

Fifty-one percent of patients randomized to observation underwent cholecystectomy during a follow-up period of up to 90 months (Fig. 2). Twelve percent of patients randomized to cholecystectomy did not undergo the scheduled operation. The cumulative risk of having a cholecystectomy seemed to level off after about 4 years, as shown in Fig. 2, and may indicate that symptoms are of an episodic nature or abate over time. Comparative studies are lacking, although a similar trend regarding all events (symptoms and complications) has been noted by others (3). Thus, although a follow-up period of 5 years may seem short in view of the fact that the median age of patients was 49 years, the cumulative risk estimates (Fig. 2) combined with the fact that there is no indication in the literature that symptoms or complications are more common in the elderly, strongly suggest that the follow-up data are relevant.

A third of eligible excluded patients reported severe symptoms precluding randomization, but only 85% (46 of 54) of these actually had an operation. More interestingly, 27% (79 of 293) of eligible patients had strong treatment preferences as two-thirds of them favoured surgery. Seen together with the final outcome (Table IV), this demonstrated that patients with symptomatic GBS are a heterogeneous group for which it may be difficult to establish a single correct treatment strategy although the professional community most often will recommend surgery for symptomatic patients. The heterogeneity in symptom severity is also probably the reason why so many patients changed treatment group.

An additional interesting feature is the skewed gender distribution in the study population, as 82% were women. This is disproportionate to the male versus female distribution rate found in a US screening study in the area from where the majority of patients were recruited (15). We do not know whether the difference in distribution was caused by a varying symptom pattern in women and men, nor do we know whether the threshold for referral differs between genders. One may assume that professional judgment bias—based on old maxims like 'female, fair, fat, fertile, forty'—may result in such a gradient.

The indication for cholecystectomy or the intensity of symptoms may not be identical in different age groups. This is

Table III. Gallstone-related complications after randomization

	Observation group		Cholecystectomy group		
	Observation only (n = 34)	Cholecystectomy (withdrawal) (n = 35)	Cholecystectomy (n = 60)	Observation (withdrawal) (n = 8)	Excluded patients (n = 201)
Admission due to pain	6	9	2[1]	—	20
Acute pancreatitis	—	—	1	—	1
Common bile duct stone(s)	—	2	—	—	2
Acute cholecystitis	—	1	—	—	2

[1] One patient admitted after cholecystectomy.

Table IV. Final outcome in 293 eligible patients

| Patients | Randomized | Excluded patients | | | Total |
		Severe symptoms	Patient preferences	Other	
Cholecystectomy	95	46	55	11	207
Observation	42	8	24	12	86

Table V. Complications in 222 patients undergoing cholecystectomy

| | Excluded patients | Randomized patients | | Total |
		Cholecystectomy group	Observation group	
No. of patients undergoing cholecystectomy	127	60	35	222
Laparoscopic/open / converted cholecystectomy	93/ 26/ 8	45/ 15/ —	29/ 2/ 4	167/ 43/ 12
Complications—major				
Intra-abdominal infection / bile leakage	2 ⎫	2 ⎫	3 ⎫	7 ⎫
Wound infection / dehiscence	2 ⎬ 8	1 ⎬ 3	1 ⎬ 5	4 ⎬ 16
Common bile duct stone / stenosis / pancreatitis	4 ⎭	— ⎭	1 ⎭	5 ⎭
Complications—minor	4	6	—	10
No. of re-operations	—	1	1	2

clearly demonstrated when examining the median age in the different treatment groups. Patients excluded and later observed were 20–30 years older than those operated on (Table I); this may indicate that pain attacks interfering with social life are felt more inconvenient in younger age groups or that barriers to surgery are more pronounced in the elderly.

Importantly, the frequency of GBS-related complications in the group randomized to observation is small indeed. During follow-up, 12 of 69 patients in the observation group were re-referred because of pain. A GBS-related complication occurred in only 4% of observed and 2% of excluded patients. As discussed before, it can be argued that the observation period was too short. A few other follow-up studies exist, most from the pre-ultrasonographic area. These studies have a longer observation period and a marginally higher annual complication rate of 1–2% (10–12). The most recent study had only a small number of symptomatic patients and reported a somewhat lower annual rate of complications at 0.7% (4).

The potential risks in patients observed must be weighed against observed complications in patients undergoing cholecystectomy. Firstly, in those randomized to cholecystectomy, GBS-related complications were few (Table III). Considering all the 222 patients that had a cholecystectomy (Table V), 16 (7%) had a major complication and 10 (4%) a minor (e.g. pneumonia, urinary infection). Two patients had to be re-operated, whereas no deaths occurred in 222 operated patients. Our findings do not differ significantly from what others have found (16). These figures therefore show a complication rate after cholecystectomy that exceeds GBS-related complications in observed patients.

Despite the heterogeneity of the study population and the problems of patients' treatment preferences which compli-

cated this study, expectant treatment (watchful waiting) appears to be a feasible option. GBS complications in this group were few and less frequent than postoperative complications in patients randomized to surgery. Pain did lead to a number of re-referrals, but far from every patient with symptomatic disease will need a cholecystectomy. In fact, only 51% of patients randomized to observation had a cholecystectomy. Therefore, we recommend that patient guidance should include the information that watchful waiting may be a safe option.

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