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Pain and Quality of Life in Patients with Symptomatic, Non-Complicated Gallbladder Stones: Results of a Randomized Controlled Trial

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Background: Cholecystectomy is intended to relieve symptoms of gallstones, but unfortunately some patients will experience postcholecystectomy symptoms, including pain. There is limited information in the literature on gallstone-related pain and its influence on quality of life. The aim of this study was to examine how pain and quality of life in patients with symptomatic, uncomplicated gallbladder stones were affected by observation of their condition compared with removal of the gallbladder. **Methods:** One-hundred and thirty-seven patients were randomized to observation (watchful waiting; $n = 69$) or cholecystectomy ($n = 68$) and answered questionnaires on pain, quality of life (PGWB index and NHP Part II) at randomization and fixed intervals (6, 12 and 60 months). All gallstone-related events (hospital admission for pain, complications of gallstone disease and cholecystectomy) and crossover between treatment groups were recorded. **Results:** Of patients randomized to observation, 35 of 69 patients (51%) eventually underwent a cholecystectomy. Significant improvements in quality of life and pain scores were detected regardless of surgical treatment. Patients that subsequently experienced gallstone-related events had significantly higher pain scores at randomization than patients that did not experience any subsequent events, and this difference was maintained throughout follow-up. **Conclusions:** Unexpectedly, in the majority of patients symptoms did abate without any significant differences between groups in pain and quality of life. Patients that had high intensity and frequency of pain at randomization had a higher risk of experiencing subsequent events.

Key words: Cholecystectomy; complications; pain; quality of life; randomized clinical trial; symptomatic gallstones

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Cholecystectomy is commonly recommended for symptomatic gallbladder stones (GBS) with the intention to relieve GBS-related pain and to alleviate the risk of GBS-related complications in the future. With the introduction of laparoscopy the cholecystectomy rate has increased, perhaps because of greater medical and lay interest in the perceived benefits of the technique compared with that of an open operation (1). However, cholecystectomy rates in patients with gallstones vary widely between countries in the Western world, from a low of 5% in Norway to a high of 50% in the United States (2), indicating that many factors contribute to the decision to operate.

Reports have indicated that 15% to 20% of patients will experience persistent pain postoperatively (3–6) but the increasing cholecystectomy rate has not been paralleled with a research interest in the ultimate outcome after cholecystectomy. Therefore, the nature of persisting symptoms and how they affect patients remain unknown. Together with the fact that not all patients with symptomatic gallstone are operated on (7, 8), the full clinical picture appears confusing. It also is largely unknown how non-operative (conservative) treatment affects the quality of life of those concerned.

Quality of life (QoL) measurements have been introduced in many clinical areas including gallstone surgery (9). QoL instruments measure parameters not normally assessed by routine clinical examinations and in traditional clinical research. The intention is to let the patient's own evaluation of the treatment be known through indirect questioning. So far, two studies have shown that non-invasive treatment of gallstones may be better for the patient's QoL than cholecystectomy (10, 11), whereas another study did not concur with this view (12). The most striking fact, which is in contrast to the high operation rates, is the paucity of QoL studies in GBS disease.

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In a previous study (13), we found that observation is a feasible option to routine cholecystectomy in symptomatic GBS patients. QoL studies in gallstone patients have never been carried out in such an experimental research design. The aim of our study was therefore to examine the frequency and intensity of pain attacks and QoL in patients with symptomatic, uncomplicated GBS treated with cholecystectomy or observation.

Materials and Methods

Patients

Three consultant surgeons from three hospitals recruited consecutive patients with symptomatic, uncomplicated GBS (Haukeland University Hospital in Bergen ($n = 73$), Rogaland Central Hospital in Stavanger ($n = 47$) and The Deacon's Hospital in Oslo ($n = 17$)) during a 39-month period from October 1991 to April 1994. The participating hospitals are first-line treatment centres for defined catchments areas.

Disease definition

Episodic pain, commonly continuous in nature and located in the right subcostal or midline epigastric area lasting more than 30 min was classified as symptomatic disease in the presence of gallbladder stones confirmed by ultrasonography. Symptoms were categorized as severe, moderate or minimal based on frequency, intensity and whether they limited daily activities or social life. Patients with minimal or atypical pain were excluded and not randomized and patients with dyspeptic symptoms only were not assessed (14).

Eligibility, randomization and ethics

A total of 338 patients with symptomatic GBS were considered for participation in the study (14), of which 137 were randomized. The remaining 201 patients did not join the study as 45 were excluded according to predefined criteria and 102 patients had strong personal treatment preferences. Fifty-four patients had severe symptoms (pain) that made observation unethical. A detailed account on these patients has been reported elsewhere (13).

Patients confirmed their willingness to participate by signing a consent form and were randomized in blocks of five according to a computer program. Brown opaque, sealed and numbered envelopes were used.

Patients were randomized to surgery or observation (Fig. 1). Patients randomized to surgery were put on a regular waiting-list and operated on as soon as capacity permitted. The study was initiated after laparoscopic surgery was introduced in our country and only a minority of the patients had an open cholecystectomy.

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

Follow-up

Patients answered questionnaires on symptoms and QoL at the time of randomization and at 6, 12 and 60 months. Disease events after randomization (admission for pain, complications of GBS disease, cholecystectomy and causes of death) were recorded. Crossovers between treatment groups were expected and in the case of transfer from observation to cholecystectomy, or vice versa, this was a joint agreement between patient and surgeon, after an assessment of the presence or absence of symptoms or gallstone-related complications.

Outcome

Pain and QoL were major outcome measures and a comparison was made between the randomized groups and between actual treatment groups (operation versus observation).

Survey measures

The Psychological General Well Being (PGWB) index and the Nottingham Health Profile Part II (NHP) constituted the QoL instruments.

The PGWB index (15) is the sum of 22 general well-being questions split into six subscales (anxiety, depressed mood, positive well-being, self-control, general health and vitality). All items were scored using a six-step scale (Likert format). The range of the index is 22–132, and the higher scores indicate positive well-being. The PGWB index is a widely used QoL measure and has been extensively tested and validated (16).

NHP part II (17) consists of seven questions, which assess whether job of work, looking after the house, social life, home life, sex life, interests and hobbies or holidays are affected by the patient's health problem. All positive answers are given the value of 1 and summed up to a maximum of 7. The NHP has been extensively validated and tested (18).

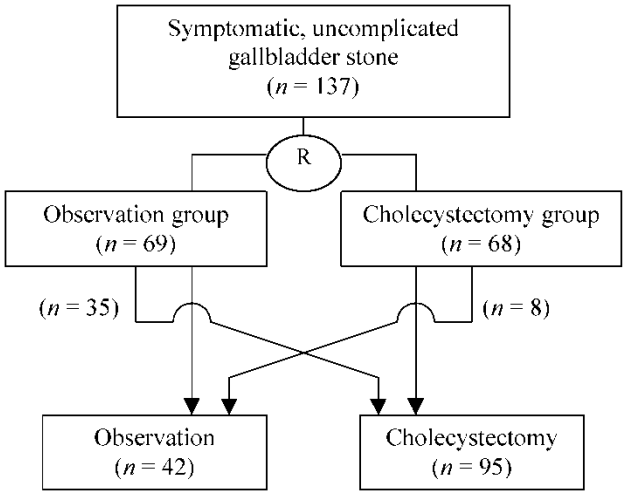

Fig. 1. Randomized groups and numbers of crossovers in the study populations.

Pain was registered using a pain score and a visual analogue pain scale (VAPS). The pain score was calculated as the sum of responses to four items related to gallstone pain (intensity of pain last week, duration of pain last week, frequency of pain in the past 6 months and use of analgesics in the past 6 months). All items were scored using a five-step scale (Likert format, 0–4) and the sum score ranged from 0 to 16, the higher range indicating frequent and severe pain attacks. VAPS represented intensity of pain during the previous week and was given by patients with a vertical mark on a 100 mm line ranging from no pain to unbearable pain.

Statistics

We assumed that 200 patients in each group would be sufficient, but no formal power calculation was performed, as data for such calculations did not exist. The expected number was not achieved because a substantial number of patients were excluded. The inclusion period was not extended beyond three years to avoid bias due to potential changes in management policy.

A maximum of one missing item in the pain score and in the different subcategories of the PGWB index was accepted and replaced by the mean of the patient's remaining responses. Missing data were not replaced in the NHP or VAPS.

A sum score was recorded for the PGWB index, NHP and pain score. A linear mixed model was used to analyse the survey measures (SPSS, version 11.0). Analyses were performed within groups (time effect) and between groups with the randomized groups, operative outcome and events as grouping factors.

The Fisher exact test was used to compare the frequency of events in the two randomized groups.

A significance level of 0.01 was applied throughout to adjust the overall type I error rate for multiple comparisons.

Results

Patient characteristics

The age and gender characteristics of randomized patients are outlined in Table I. The majority of patients were women (82%), and the median age of patients was 50 (range 20–79) years. Thirty patients (22%) had been admitted to hospital for gallstone disease earlier and concomitant disease (heart disease, diabetes, obstructive lung disease) was registered in 16 of 137 patients (12%). One patient was lost to follow-up after 30 months, and 8 patients died of unrelated disease after a median follow-up time of 54 (range 8–72) months. Median follow-up in patients that completed the trial was 67 (range 56–91) months.

Gallstone-related events, cholecystectomy and postoperative complications

Sixty of 68 patients (88%) randomized to cholecystectomy and 35 of 69 patients (51%) in the observation group eventually had a cholecystectomy (Fig. 1). The median time from randomization to surgery was 3 (range 0–24) months for patients randomized to surgery, and 27 (0–67) months in patients randomized to observation. Thus, at 6 months' follow-up, 7 of the 69 patients in the observation group had had a cholecystectomy.

Gallstone-related events after randomization (admissions for pain attacks or gallstone complications: acute cholecystitis, common bile duct (CBD) stone or acute pancreatitis) occurred in 15 out of 69 patients (22%) in the observation group and 3 of 68 patients (4%) in the surgery group (Table I), the difference was not significant (Fisher exact test, $P = 0.011$). One admission for a pain attack occurred in the operation group after cholecystectomy.

Ninety-five patients finally had a cholecystectomy (Table I). Eight patients (8%) suffered a major complication (infection, bile leak, etc.), including one patient in each group that had to be reoperated on for bile leak.

Pain and quality of life, randomized groups

PGWB mean values showed significant variation over time (Table II), but this variation was the same in the two randomized groups ($P = 0.069$). There were no differences between the randomized groups (Table III and Fig. 2). The time effect was mainly caused by changes in the PGWB from 0 to 6 months.

NHP mean values did not show significant variation over time, nor between the two randomized groups.

Table I. Patient characteristics and gallstone-related events (number of patients) following randomization in 137 patients with symptomatic, uncomplicated gallbladder stone disease

	Observation group		Cholecystectomy group	
	Women ($n = 57$)	Men ($n = 12$)	Women ($n = 55$)	Men ($n = 13$)
Median age (range)	48 (22–75)	60 (39–G79)	52 (20–77)	52 (27–74)
Gallstone complication	3	0	0	1
Admission for gallstone pain	10	2	2	0
Cholecystectomy (laparoscopic/open)	26/5	3/1	38/13	7/2
Major complications after cholecystectomy	3	2	3	0
Deaths (median follow-up 67 months)	3	1	3	1

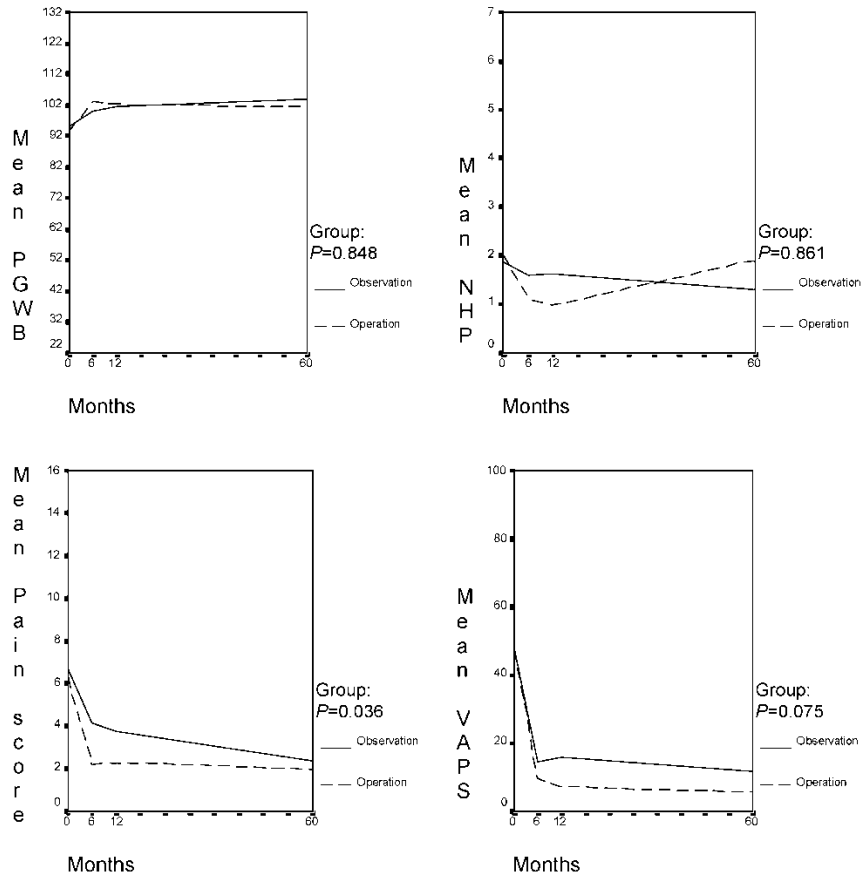

Fig. 2. Changes in quality of life (QoL) and pain with time. Mean results according to randomization group. NHP = Nottingham Health Profile Part II; PGWB = Psychological General Well-being Index; VAPS = Visual Analogue Pain Scale.

Pain score values showed significant variation over time but the variation was the same in the two randomized groups ($P = 0.012$) without differences between the groups. The time effect was mostly due to a decrease in pain score from 0 to 6 months.

VAPS values also showed significant variation over time; again, the variation was the same in the two randomized groups ($P = 0.591$), with no difference between them. The time effect was entirely caused by a decrease in VAPS from 0 to 6 months.

Further analyses showed that linear adjustment for age and gender did not alter the results for PGWB, pain score and VAPS. However, the NHP scores increased with age ($P = 0.007$).

Operation versus observation

The between-subjects analysis was also performed with operative outcome as the grouping factor, i.e. cholecystectomy or no cholecystectomy. No significant differences between the groups in any of the survey measures were found (*P* values: PGWB = 0.642; NHP = 0.065; pain score = 0.527; VAPS = 0.283). The variation over time was the same in both groups and age and gender did not influence the results significantly.

In non-operated patients, women had higher PGWB scores than men ($P = 0.01$), and older patients had higher scores than younger patients ($P = 0.004$).

Gallstone-related events

Patients that experienced gallstone-related events after randomization had a significantly higher pain score and VAPS (Fig. 3) than patients with no events, but the variation over time was the same in the groups (interaction *P* values: VAPS = 0.486; pain score = 0.055). No corresponding sig-

Table II. Survey measures, time effect within group. Stratified according to randomization

Survey measure	Observation group *P* values	Operation group *P* values
PGWB	0.011	0.001
NHP	0.53	0.007
Pain score	<0.0001	<0.0001
VAPS	<0.0001	<0.0001

PGWB = Psychological General Well-Being Index; NHP = Nottingham Health Profile Part II; VAPS = Visual Analogue Pain Scale.

Table III. QoL and pain survey measures, mean values and numbers of responders

	Group	Randomization		6 months		12 months		60 months		*P* values
PGWB	Observation	95.2	(*n* = 67)	99.9	(*n* = 59)	101.8	(*n* = 60)	104.1	(*n* = 55)	0.848
	Operation	93.7	(*n* = 63)	103.3	(*n* = 54)	102.3	(*n* = 57)	101.6	(*n* = 56)	
NHP	Observation	1.8	(*n* = 53)	1.6	(*n* = 44)	1.6	(*n* = 46)	1.3	(*n* = 47)	0.861
	Operation	2.0	(*n* = 50)	1.1	(*n* = 43)	1.0	(*n* = 43)	1.9	(*n* = 52)	
Pain score	Observation	6.7	(*n* = 66)	4.1	(*n* = 63)	3.7	(*n* = 61)	2.4	(*n* = 56)	0.036
	Operation	6.3	(*n* = 67)	2.2	(*n* = 57)	2.3	(*n* = 58)	2.0	(*n* = 56)	
VAPS	Observation	48.1	(*n* = 65)	14.7	(*n* = 61)	15.7	(*n* = 60)	11.5	(*n* = 56)	0.075
	Operation	47.2	(*n* = 67)	9.4	(*n* = 57)	7.0	(*n* = 55)	5.5	(*n* = 55)	

QoL = quality of life; PGWB = Psychological General Well-Being Index; NHP = Nottingham Health Profile Part II; VAPS = Visual Analogue Pain Scale.

nificant difference was found for the PGWB score ($P = 0.20$) or for the NHP score ($P = 0.015$). Linear adjustment for age and gender did not alter these results, and neither the PGWB nor the NHP scores were significantly influenced by age and gender.

Discussion

It was unexpected that patients, regardless of randomization or treatment group (i.e. operation or observation), experienced a significant reduction in pain and an increase in QoL with time. In all groups of patients the major changes in the survey measures were, without exception, observed 6 months after randomization. The median time from randomization to cholecystectomy in the observation group was 27 months; thus, at 6 months, only 7 of the 69 patients in this group had had a cholecystectomy. At the time of inclusion patients were invariably at a high level of disease activity that prompted referral or admittance to the hospital, with the probability that the intensity and frequency of symptoms would persist over time was unlikely. Therefore, regression towards the mean may be the reason for this change in pain and QoL. Later in the follow-up period (12 and 60 months), only minor changes were found in the VAPS, pain score and QoL indices.

Cholecystectomy was considered in patients randomized to observation if recurrent, intolerable pain and/or gallstone-related complications occurred. Few gallstone-related complications were encountered in patients randomized to observation (Table II) and consequently pain was the indication for operation in these patients. Eventually, 35 of 69 patients (51%) in the observation group underwent a cholecystectomy, signifying that far from all patients experienced pain attacks of such severity that the health services were contacted during the 5-year follow-up period. No significant differences were found between patients having a cholecystectomy and those that were only being observed. This finding was unexpected, and we have no valid explanation for this improvement in symptoms and QoL in both observed and surgically treated patients. The question remains whether symptomatic gallstone disease may have a more benign natural course than previously surmised. Theoretically, the patients may also have answered the survey measures in a favourable fashion or, as mentioned, a regression towards the mean may have been observed.

At inclusion the VAPS score reported by patients varied widely in the two randomized groups. A mean VAPS score of 48 indicated moderate to severe pain (19), while the pain score was in the mid-range (mean 6.7 out of maximum 16). This suggests that even though the pain was of high intensity, the frequency of pain attacks was lower. To our knowledge, a

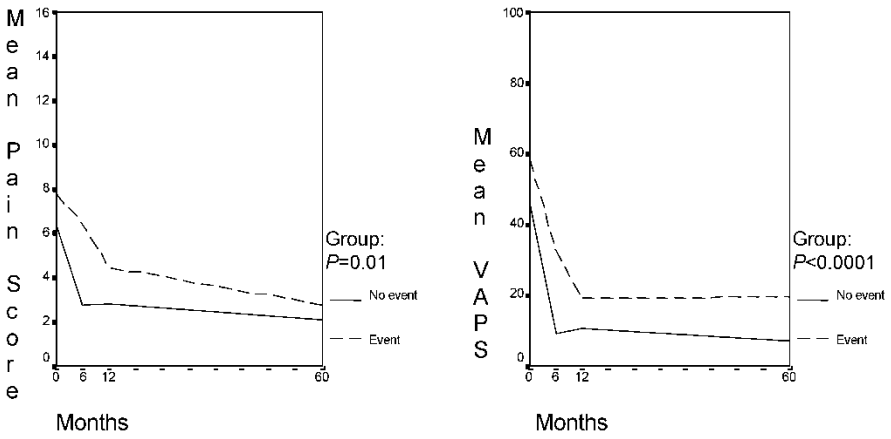

Fig. 3. Mean pain score and visual analogue pain score (VAPS) in patients with symptomatic gallbladder stones with or without gallstone-related events after randomization.

similar assessment of pain has not been carried out in gallstone patients before. Patients with GS-related events had significantly higher pain scores and VAPS than patients without events (Fig. 4). The scores differed from the time of randomization and patients with pain of higher frequency and intensity had a greater risk over time of experiencing more events than patients with less pain. This corresponds to results reported in an earlier paper (20).

The mean PGWB score at inclusion was 94. Such values correspond to those reported in patients suffering from other upper gastrointestinal disorders such as gastro-oesophageal reflux (21) and peptic ulcer disease (22, 23). These figures represented a minor reduction in general well-being compared with that of controls, in whom a score of around 105 would be expected (15). The NHP scores showed little variation over time.

The PGWB index was developed in 1984 (15) and has been shown to be a reliable instrument in the assessment of QoL (16). This global QoL instrument has been used extensively in upper gastrointestinal diseases (21, 24, 25). A disease-specific survey would theoretically be preferable and a survey of this kind has been developed for gallstone disease (26). This instrument has, however, never been accepted and used as widely as the PGWB index and in any case was not available when our study was planned.

As mentioned earlier, we found a minor reduction in the PGWB scores. One might ask whether the impact of gallstone disease is significant enough to be measured in QoL instruments. It may also be that the existing instruments do not differentiate well enough between disease states or categories (27). Results of trials in patients with CBD stones (28) and CBD injuries (29) may support this notion. Three studies were carried out to investigate how QoL was affected by cholecystectomy compared to extra corporeal shock-wave lithotripsy (10, 11), including a randomized trial (12) in which cholecystectomy was found to be the superior approach. The set-up and findings are not directly comparable with those of our study but, as we have observed, many patients had strong personal treatment preferences (12).

NHP has also been extensively tested (16), but may be insensitive to minor ailments (30). The NHP was the survey measure that provoked the greatest number of non-responders. Since a significant number of patients had retired from work, the work situation question was of little relevance. It is also to be expected that elderly people might be reluctant to answer questions about whether their sexual activities are affected by their health problems.

We conclude that irrespective of treatment groups, patients experienced a rapid decline in pain score and improved QoL indices after randomization, but patients with a higher frequency and intensity of pain at randomization seemed to stand a higher risk of subsequent gallstone-related events. The pain of symptomatic gallstone disease fluctuated with time, and this suggests that far from all patients will need to undergo cholecystectomy.

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