Selective Treatment of Symptomatic Gallstones

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The degree Doctor Medicinae (dr. med.)

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Contents

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List of papers

I. Vetrhus M, Søreide O, Solhaug JH, Nesvik I, Søndenaa K. Symptomatic, non-complicated gallbladder stone disease. Operation or observation? A randomized clinical study. Scand J Gastroenterol 2002; 37(7); 834-839.

II. Vetrhus M, Søreide O, Nesvik I, Søndenaa K. Acute cholecystitis: Delayed surgery or observation. A randomized clinical trial. Scand J Gastroenterol 2003; 38(9):985-990.

III. Vetrhus M, Søreide O, Eide GE, Solhaug JH, Nesvik I, Søndenaa K. Pain and quality of life in patients with symptomatic, non-complicated gallbladder stones: Results of a randomized controlled trial. Scand J Gastroenterol 2004; 39(3):270-276.

IV. Vetrhus M, Søreide O, Eide GE, Nesvik I, Søndenaa K. Quality of life and pain in patients with acute cholecystitis. Results of a randomized clinical trial. Scand J Surg 2005; 94(1):34-39.

V. Vetrhus M, Berhane T, Søreide O, Søndenaa K. Pain persists in many patients five years after removal of the gallbladder: observations from two randomized controlled trials of symptomatic, noncomplicated gallstone disease and acute cholecystitis. J Gastrointest Surg. 2005; 9(6):826-31.

Introduction

Historical note

The Babylonians and Assyrians considered the liver to be the seat of the soul, and inspected the liver of a sacrificed animal to divine the future. Although disease was considered to be of demonic origin, several texts describe what probably were pain attacks of gallstone and the poor prognosis of jaundice (1). Gallstones were found in the preserved gallbladder of an Egyptian mummy from circa 1500 B.C. (2) and Alexander Trallianus, a Greek physician from the 5th or 6th century AD wrote about concretions in the liver as a possible cause of obstruction (3).

Gallstone pathology and the recognition that it may lead to fatal complications was widely recognised during the renaissance and was discussed in several treatises (3). Some of the authors seem to have suspected that gallstones could give rise to recurrent pain attacks.

A report of the first known surgical treatment, cholecystotomy for empyema, was published in 1743 (4). Cholecystotomy and cholecystostomy gained popularity, but in order to avoid the problem of an external draining biliary fistula von Winiwarter invented cholecystocolostomy in 1880 (5).

Carl Langenbuch eventually performed the first cholecystectomy in 1882 after a series of experiments on cadavers (6), and a few years later Kummel reported another innovative procedure: the first common bile duct exploration (7). In 1911 Mayo stated “the innocent gallstone is a myth” (8). This has apparently influenced the treatment policy on gallstones for decades. In 1991 an estimated 600000 cholecystectomies were performed in the USA (9) and 3000 in Norway (1995) (10).

Definition of gallstone disease

Gallstones may be defined as asymptomatic and symptomatic, with or without complications.

The term symptomatic gallstone disease refers to pain attacks of a certain pattern that is thought to be elicited by the gallstones.

Acute cholecystitis is the most common complication of gallstones. Other complications of gallstones, e.g. gallbladder cancer, gallstone ileus, common bile duct stones and acute pancreatitis are not considered here.

Pathogenesis of gallstone disease

Symptomatic, uncomplicated gallbladder stone disease

The gallbladder and bile ducts are formed from an outgrowth of the foregut (11) and hence they share the same innervation. It is therefore likely that pain in uncomplicated and complicated gallbladder disease will broadly have the same characteristics and similar location. As the structures are derived from midline structures the visceral pain experienced is often referred and not easily differentiated from pain originating in other viscera by location, quality or intensity (12). A precise location specific for the biliary tract can not be expected unless the parietal peritoneum is affected by an inflammatory process.

The most likely theory why cholelithiasis should lead to pain is stone obstruction of the cystic duct leading to increased wall tension enhanced by gallbladder spasm and associated with inflammation (13), although this has not been confirmed by clinical studies. Nevertheless, increasing pressure in the gallbladder or increased wall tension are probably factors in the production of pain. In 1933, Zollinger (14) introduced a balloon in the gallbladder lumen after having done cholecystolithotomy in a number of patients. Later, when the balloon was inflated, the patients experienced epigastric pain similar to the pain they had experienced before the operation. Pain and nausea were also experienced if the balloon was placed in the common bile duct. An identical pain pattern was triggered by stimulating the bile duct with electric current (15). These findings have been supported by a recent clinical study on patients suffering from cholecystitis (13).

Acute Cholecystitis

In acute cholecystitis (AC) an impacted stone in the gallbladder neck is thought to cause cholestasis, chemical inflammation and subsequent bacterial super infection leading to luminal gallbladder swelling and wall thickening through inflammation and oedema (16, 17). However, CT may occasionally show a dilated gallbladder even in people with asymptomatic gallstones.

Clinically it has been observed that small fibrotic and chronically inflamed gallbladders harbouring stones may cause pain. It is common experience that most gallbladders with stones (96 %) show histological signs of inflammation (18). The significance of this finding is probably small as 33 - 82 % of gallbladders without stones exhibit similar features (19, 20).

Intravenous cholangiography without gallbladder filling (21) was once interpreted as an indirect evidence of AC. It has been observed, however, that the cystic duct is patent in 83 % of cases in cholangiograms performed soon after percutaneous gallbladder drainage for acute cholecystitis (22). Again, assumption, not evidenced based medicine, is the basis of the theories on development of AC.

Prevalence

The age-adjusted prevalence of gallstones in a Norwegian study from 1987 was 17.7 % in men and 21.2 % in women (23), which is of the same magnitude or higher than reported from other Scandinavian countries (24, 25).

From the age group of 20 - 29 years to 60 - 69 years, the prevalence increased from 4.9 % to 37.0 % in men and 6.0 % to 41.3 % in women (23). A similar increase with age has been reported in other Scandinavian studies (24, 25).

Gallstones are more common in women than in men, in most studies approaching twice that of men (23 - 28). The male to female ratio increases in complicated disease and males may constitute up to 40 % of patients with cholecystitis (29, 30).

Apart from increasing prevalence with age, gallstones have been associated with high serum triglycerides, smoking, number of pregnancies and body mass index (31).

Natural history

Abdominal pain is frequent in a general population (32). The annual prevalence ranges from 38 % in men to 49 % in women and is most often located to the upper abdomen. An ultrasonographic screening study found that the frequency of abdominal symptoms was the same in patients with and without gallstones (33) and argued that the majority of gallstones are silent. Imaging will detect

gallstones in many patients with vague abdominal symptoms; the symptoms may be ascribed to the gallstones and lead to cholecystectomy. Pain is the cardinal symptom of gallbladder stone disease, but is not specific and it is sometimes difficult to distinguish between symptomatic and asymptomatic patients (34). Dyspepsia is usually not considered to be a symptom of gallbladder stone disease (23, 27, 35 - 38), but may be associated with gallstones (39). The relief of dyspepsia following cholecystectomy is unreliable (40).

In a follow-up study from 1960 of non-operated people with diagnosed gallstones it was found that very few remained asymptomatic. At least 1/3 developed severe symptoms and 1/5 developed complications. It was stated that “prophylactic removal of the gallbladder will prevent much future morbidity” (41). The same findings was supported by a contemporary study in which 35 % of the non-operated cases developed complications or such severe symptoms that cholecystectomy was performed (42).

More recent reports state that 2 - 4 % of asymptomatic patients will experience biliary pain annually, while the annual rate of gallstone complications is about 1 % (38, 43, 44). An Italian study found a higher risk (44): The cumulative probability of developing biliary colic was 11.9 % at 2 years, 16.5 % at 4 years and 25.8 % at 10 years. The risk of gallstone complication after 10 years was 3 % in asymptomatic patients. Another recent prospective study of 120 asymptomatic patients with gallstones found a 7.6 % cumulative 5 year risk of experiencing biliary colic or a complication of gallstone disease (45).

The risk of developing symptoms have been reported to decline after the first years of follow-up, and the majority of people with gallstones remain asymptomatic (33, 38, 43). Consequently, about 1/3 of patients with gallstones will experience pain caused by the stones or a stone related complication (28, 42, 46, 47)**.**

Patients with symptomatic, uncomplicated gallbladder stones (SGBS) have been found to have a higher risk of developing gallstone complications than asymptomatic patients (43), in one paper this risk was found to be 6.5 % after 10 years (44).

The general opinion is that the risk of recurrent complications of gallstone disease is high following AC. This is however based on data from the pre-ultrasonographic era where the risk of recurrent disease was found to be 32 – 36 % (48, 49). Recent reports are not available, but papers that compare early to delayed surgery state that the risk of recurrent AC while waiting for cholecystectomy ranges from 2% to 24% (50 - 54).

Treatment of gallstone disease, current trends and scientific basis

Symptomatic, uncomplicated gallstones

According to current opinion cholecystectomy should be offered to patients with gallstone pain attacks only. Dyspepsia is not considered a valid indication in the absence of pain (55). Some authors report cholecystectomy in patients with acalculous gallbladders and such non-defined entities as “biliary dyskinesia” and “chronic acalculous cholecystitis” (56, 57), but there is no solid scientific basis for such practice.

The recommendations are vague as to whether all patients with SGBS should be offered operation. Some authors argue that the available information is insufficient to make any conclusions about expectant management of symptomatic gallstones (47). Others state that watchful waiting may be tried (58). At the other extreme it has been argued that cholecystectomy does not extend life expectancy and should be offered to patients with debilitating symptoms (pain) only after a thorough preoperative selection bearing in mind that psychic vulnerability may predict a poor symptomatic outcome (59).

Laparoscopic versus open cholecystectomy

Following the introduction of laparoscopy a few papers have addressed symptomatic outcome (absence of biliary pain) in SGBS. So far there is no evidence to suggest that laparoscopic surgery is superior to open cholecystectomy in this regard. Outcome has been investigated in a retrospective fashion with 6 months follow-up (60) and in a prospective trial with 12 month follow-up (61) and was not affected by surgical access. In van der Velpen’s trial a satisfactory cosmetic outcome as appreciated by the patients were significantly more common in the laparoscopic group (60). A prospective trial that examined Quality of Life (QoL) after open and laparoscopic cholecystectomy found no significant differences between the two groups (62).

There is evidence that minimal invasive surgery is superior in terms of immediate postoperative pain. Similarly the length of hospital stay is significantly shorter after laparoscopic versus open cholecystectomy (57, 63). The same applies for return to full activity or work (60, 62).These findings

have been substantiated in other randomized clinical trials (RCT's) (64 - 66), but hospital stay and convalescence is known to be influenced by medical and cultural tradition (67).

Minilaparotomy cholecystectomy

Minilaparotomy cholecystectomy through a 5 - 10 cm incision was developed in the 1980's, but was soon overshadowed by laparoscopic cholecystectomy. The two techniques have been compared in RCT's (68, 69) and the only difference in outcome was operating time (laparoscopic cholecystectomy > minilaparotomy cholecystectomy) and time to return to normal activities (minilaparotomy cholecystectomy > laparoscopic cholecystectomy). One year after cholecystectomy, the symptomatic outcome was the same regardless of access (70).

Acute cholecystitis

A consensus document from 1993 stated that "Gallstone complications are all potentially life threatening and almost always merit prompt treatment", i.e. cholecystectomy (9). The statement reflects the present treatment policy (71 - 74).

About 70 years ago surgeons started debating which treatment was best for AC. Early surgery was more favoured in the USA, the arguments being that it reduced the risk of perforation and shortened the duration of the disease and the hospital stay. On the other hand, UK surgeons tended to be more conservative owing to the fact that the perforation rate was low (by some reported to be less than 1 %). Surgery carried a risk of biliary injury and other complications and in the majority of patients the disease settled on conservative management (75). Most reported that the risk of perforation was about 7 - 11 % (16, 48, 75) and the risk was at its highest 4 - 7 days after start of symptoms (16). In addition, cholecystectomy performed later than 7 days after onset of symptoms was found to be more challenging due to necrosis, abscesses in the gallbladder wall and fibrosis and thus carried a higher risk of septic and operative complications (16, 17).

In the interwar years, the trend in Scandinavia was to treat AC by delayed surgery or conservative treatment (48, 49, 76). Conservative treatment without subsequent cholecystectomy was not an uncommon treatment into the late 1950's (48). Generally, it was reported that ¾ of patients could be

treated successfully with or without antibiotics, emergency cholecystectomy being necessary in about 10 % (75).

Timing of operation

The first RCT comparing early to delayed cholecystectomy was published in 1970 (54). It was found that an erroneous diagnosis would sooner be rectified if an early operation was performed. Similarly patients waiting for delayed operation risked recurrent disease and had a longer overall hospital stay and absence from work.

Several prospective trials were published following this seminal paper. Two RCT's which both defined "early" surgery within 7 days of onset of symptoms and "late" at least two months following AC showed that conservative treatment failed in 9 – 13 % of patients. In the waiting time for deferred surgery up to 15 - 24 % of patients experienced renewed symptoms or recurrent AC (51, 52). None of the trials found any difference in intraoperative or postoperative complications between the two groups. Another non-randomized, prospective trial published in 1983 comparing early to delayed open cholecystectomy confirmed these findings (77).

A report from 1981 suggested that the trials comparing early to delayed operation were biased with regard to which of the two operations being the most challenging, and that the results simply reflected the pre-trial routine and selection in the respective hospitals (78).

New trials were carried out after the introduction of laparoscopic cholecystectomy and by this time (early 1980's) ultrasonography had become a widespread diagnostic tool. As in the earlier trials, conservative treatment failed in 14 – 26 % of patients randomized to delayed surgery and overall hospital stay was significantly shorter in early surgery (50, 53, 79).

Today, the professional consensus is that early operation is the treatment of choice as delayed surgery carries a risk of failure of conservative treatment, recurrent symptoms or AC while waiting for operation and a longer overall hospital stay and greater overall costs. A 2002 survey reported that 88 % of UK general surgeons prefer delayed cholecystectomy in AC (80). The situation in Norway is probably the same, although no corresponding survey has been performed.

Open versus laparoscopic cholecystectomy

Initially, laparoscopic surgery was considered to be contraindicated in acute AC (81). The procedure is more challenging in acute cholecystitis than in uncomplicated disease due to adhesions, inflammation and distortion of the normal anatomy.

In a prospective comparison of laparoscopic cholecystectomy in AC and SGBS, the risk of bile duct injuries was found to be 5.5 % in patients with AC and only 0.2 % in SGBS patients (82). A US review of 30211 cholecystectomies comparing open cholecystectomies from the pre-laparoscopic era with laparoscopic cholecystectomies found that the overall risk of bile duct injuries initially increased after the introduction of laparoscopy, but then decreased. Eventually no difference was detected between open and laparoscopic cholecystectomy. Despite this the risk of major bile duct injuries was increased in laparoscopy for complicated disease (AC and gallstone pancreatitis) and occurred in 0.51 % of patients, while the corresponding numbers in open surgery was 0.26 % (a statistically significant difference). The decrease in overall risk of bile duct injuries were attributed to increased surgeon experience (83).

A retrospective review of laparoscopic versus open cholecystectomy found a significantly higher risk of intraoperative complications in laparoscopy, while the risk of cardiopulmonary and gastrointestinal complications were significantly higher following open operations (57). Others have reported that there has been no change in the rate of complications (84 - 86) or operative mortality (63, 87) after the introduction of laparoscopy.

An evaluation of patients undergoing cholecystectomy for AC found that the need for conversion and postoperative complications were associated with the degree of inflammation and patient characteristics (88). They have suggested an individualized approach to early open or laparoscopic surgery, recommending open surgery in severe disease (severity determined by c-reactive protein (CRP), white blood cell count and duration of symptoms) or unfavourable circumstances (high age, sex (male) and low physical status classification). Much the same findings have been reported elsewhere (89). Conversion rates vary widely, from around 15 % to more than 40 % (53, 85, 86, 90, 91).

Percutaneous cholecystostomy

It has been reported that urgent or early cholecystectomy in old, high risk patients with complicated cholecystitis carries a high risk of mortality (>10 %) (92). This has also been reported in non-operative management of other types of gallstone complications (71). Percutaneous cholecystostomy has since it was introduced in 1980 (93) been shown to be an alternative to cholecystectomy in such patients as decompression reduces the risk of gallbladder rupture or gangrene. This treatment alternative seems to be superior to medical treatment alone in relieving symptoms and septicaemia with an acceptable rate of complications (0 – 12 %) (22, 94 - 96). The complications are mainly related to displacement of the catheter with or without bile leaks or haemorrhage. Some authors recommend deferred cholecystectomy following resolution of the acute disease (94, 95), although the necessity of this has been questioned by others as many of these patients are of high operative risk (22, 96, 97).

Postcholecystectomy pain

It is known that 10-20 % of patients have persistent symptoms following cholecystectomy (40, 60, 98 - 101), and this has resulted in the term “postcholecystectomy syndrome”. The “syndrome” is not well defined, and there is no consensus regarding its symptoms or cause(s). The term is applied to persisting or new abdominal pain following cholecystectomy. Even though new diagnostic tools (ultrasonography, ERCP) have been developed to improve the diagnostic accuracy, the rate of postcholecystectomy symptoms has been constant over the last 30 – 40 years.

In a review of 23 papers (mostly cohort studies), it was found that 92 % were relieved of “biliary pain” following cholecystectomy. The relief rate of non-specific upper abdominal pain ranged from 57 % - 88 %, while relief for dyspepsia ranged from 46 % - 89 % (102). Other retrospective trials do also report that following surgery, pain is cured more frequently than other symptoms (60, 100).

A follow-up of patients that underwent cholecystectomy for SGBS and AC found that patients with SGBS were more likely than AC patients to consider themselves cured or significantly improved after operation. The authors argue that if poor selection of patients is a cause of postcholecystectomy syndrome, the chances of cure should be higher after cholecystectomy for AC (103). Another paper with a prospective design came to an opposite conclusion (101).

Organic disease

There is a definitive, but small risk of biliary injury in cholecystectomy, but in most papers the risk is reported to be less than 1 % (104). Residual common bile duct stones are marginally more common (< 2 %) (61, 105). Disease in neighbouring organs may lead to biliary-like pain. Diettrich and co-workers did an interesting study in which upper endoscopy was performed in patients with symptomatic cholelithiasis awaiting cholecystectomy. Pathology was found in about 1/3 (including reflux oesophagitis, different degrees of gastritis, stomach and duodenal ulcer etc.) The findings resulted in cholecystectomy being cancelled in some patients (106). Similar findings have been reported in another paper that recommended that endoscopy should be performed in all patients scheduled for elective cholecystectomy even if it rarely (7 %) led to a change in treatment (107).

Dyspepsia

Although the general opinion is that dyspepsia is not, or only to a limited extent affected by cholecystectomy it has been shown that patients with functional dyspepsia have decreased vagal tone, larger antral volumes and dyspeptic symptoms induced by intake of meat soup when compared to healthy individuals. The same characteristics have been found in patients with symptomatic gallstones, suggesting a common pathogenic mechanism in functional dyspepsia and SGBS (108).

Sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction (SOD) has been put forward as one of the causes of postcholecystectomy symptoms. The aetiology is unknown and it is categorized as a functional disorder (109).

One study reported that all patients with SOD I or II were cured after spinchterotomy (110), but reality is probably more sober. Two RCT's have shown that spinchterotomy significantly improved symptoms in patients with an elevated sphincter of Oddi basal pressure (SOD I, > 40 mmHg), but has no apparent effect in patients with a normal basal pressure (SOD II - III) (111). It has been suggested SOD may be part of a generalized intestinal dysmotility (112, 113).

Psychological factors

Psychiatric medication is a predictor of persistent pain after laparoscopic cholecystectomy (101). Psychological factors influence outcome after cholecystectomy (114), and a plethora of different

theories have been set forth to explain this, whether it be psychic vulnerability (99), high levels of somatization and depression (113) or psychic vulnerability (115). One unifying theory suggests that positive coping resources negatively correlate with pain and vice versa (116).

Physiologic changes after cholecystectomy

Findings indicate that in some patients with duodenogastric reflux, the reflux increases significantly after cholecystectomy (117). It has been suggested that colonic passage is accelerated after cholecystectomy (118), but it is uncertain whether this leads to diarrhoea or other symptoms (119). It is unlikely that such changes can attribute to postcholecystectomy pain. There is indication that an impaired proximal gastric function is involved in gallstone disease as part of a motility disturbance (108).

Issues in the management of gallstone disease

Around 1990, when the present studies were planned, it was generally accepted that surgery was indicated in the majority of patients with symptomatic gallstones. Patients with non-complicated disease should undergo surgery after referral or admission and those with acute cholecystitis would benefit from early surgery. Non-operative treatment was not really considered to be an option, the consensus was that it led to unnecessary suffering due to persisting symptoms and recurrent, potentially life threatening complications. Still, trials that would aid the physician in giving qualified advice to his/her patient about the condition and the risk involved in non-operative treatment were lacking.

Without proper concern for these facts the international surgical community was responsible for increasing cholecystectomy rates after laparoscopic cholecystectomy gained popularity in the end of the 1980's (56, 57, 63, 87, 120, 121). In some centres the increase exceeded 50 %. The increase in cholecystectomy rates has apparently been driven by the novelty and fascination of a new technique.

The increase has been marked in young females with symptomatic, uncomplicated disease (57, 87), while the cholecystectomy rates of complicated disease has remained unchanged. A study from 43 US tertiary-care Veterans Administration medical centres found no increase in cholecystectomy rates as opposed to that reported in the private sector and questions the apparent change in indications in the private sector following introduction of laparoscopy (84).

In the Nordic countries the increase in numbers of procedures have been reported to be 20 to 30 % in Denmark and Sweden (55, 122, 123) and close to 50 % in Norway (124). The cholecystectomy rates range from 6.2 per 10000 in Norway to 14.2 per 10000 in Finland (10).

Unfortunately, the technical advances have not led to a similar surge in research on the clinical aspects of the diseases and a sound scientific basis for treatment. The indication for operation in complicated and non-complicated disease is still based on historical papers and dogma. Generally the risk of postcholecystectomy symptoms is not considered in the preoperative assessment of gallstone patients.

The time was overdue for the first ever randomized trials to compare observation to cholecystectomy in patients with symptomatic, uncomplicated gallstone disease and acute cholecystitis.

Aim of studies

The primary aim of the trials was to observe the natural course of symptomatic, non-complicated gallstone disease (pain attacks only) and acute calculous cholecystitis (complicated disease) and compare conservative treatment to cholecystectomy.

The need for cholecystectomy, rate of gallstone related events (gallstone related complications and admissions for biliary pain) and postoperative complications were the primary outcome measures.

The secondary aim was to assess the impact of the diseases by comparing symptoms (pain) and quality of life by multiple longitudinal observations, including a survey of postcholecystectomy pain.

Patients and methodological concerns

Design of study

During the planning stages for the trials, one of the major problems was to estimate sample size. At that time only limited available numerical information was available on the risk of subsequent gallstone related complications in SGBS if not treated by cholecystectomy. Most of the papers on this subject were written in the era before ultrasonography and ERCP and could therefore not form a reliable basis for estimation of number of patients required.

Our secondary aim was to compare symptomatic relief in the two groups of patients, and from earlier reports on postcholecystectomy pain 80 % of the patients were expected to be free of pain after cholecystectomy. To the best of our knowledge the symptomatic results after non-operative treatment had until recently never been reported (24).

The same questions had to be addressed for AC. As for SGBS, little information existed on QoL or pain, but it was generally accepted that the risk of gallstone related complications were higher after conservative treatment of AC. Several studies comparing early to delayed surgery or reporting on conservative treatment of AC have shown that up to 36 % of patients will have recurrent AC or another type of gallstone related event (48 - 54) .

For these reasons no formal power calculations were performed, but it was assumed that 200 patients with SGBS and 200 with AC would be sufficient to draw reliable conclusions.

There were some concerns as to how long follow-up period was needed. Theoretically a 6-12 month period would be sufficient to observe a difference in symptoms, but a longer period was clearly needed to assess potential differences in risk of gallstone complications. In the end it was agreed that a 5-year follow-up period was sufficient.

Number of patients randomized

The number of patients included in the two trials never reached the optimistic aim of 400 patients. A high number of patients were excluded; in all 317 of 518 patients (61 %). One-hundred-and-thirty-seven of 338 SGBS patients (41 %) and 64 of 180 AC patients (36 %) were randomized. Such a high

number of exclusions is a weakness. However, similar problems have been noted by other authors reporting from a RCT in gallstone patients (125). Nor is it uncommon for papers not to state the numbers of exclusions (126, 127).

About one third of the exclusions were due to predefined criteria (116 of 317 (37 %)), but higher in AC than in SGBS as complications were more common (localized peritonitis, suspected CBD stone, acalculous cholecystitis) and the patients were generally older (> 80 years of age). In the SGBS group, patients with minimal or no symptoms were not assessed. One-hundred-and-two of 317 (32 %) excluded patients had rather unexpectedly strong treatment preferences, especially the patients in the SGBS group were favouring operative treatment. Altogether 69 patients (22 %) had such severe symptoms that randomization was considered unethical.

The number of patients randomized could have been increased by making the inclusion period longer, but for practical purposes and to avoid changes in treatment policy the period was not extended beyond 2.5 years.

Distribution of and response to survey measures

The original intention was to distribute all the QoL (Psychological general well-being index (PGWB) and Nottingham health profile part II (NHP)) and pain questionnaires (Visual analogue pain scale (VAPS) and an ad hoc pain score) to the patients at 6, 12 and 60 months following randomization, and the pain questionnaires at 24 months as well. As a number of patients were expected to crossover between the randomized groups, it was also intended to redistribute the questionnaires to these patients at 6, 12 and 24 months following cholecystectomy. Unfortunately, this had to be abandoned quite early in the course of the trial as limited resources restricted the use of auxiliary staff to keep track of replies and to make repeated requests to patients not returning the questionnaires. Thus, the questionnaires were distributed at 6, 12, and 60 months following randomization only.

With hindsight, one may argue that three forms (PGWB, NHP and pain score) and a VAPS were too much of a burden for patients to fill out on at least four occasions. Patient interest dwindled over time, on the other hand getting patients to attend the outpatient clinic at the closing of the trial hardly

posed any problems and only one patient was lost to follow-up. The percentage of questionnaires returned by patients remained fairly high throughout the trial. A regular and more direct contact between patient and physician would probably have resulted in even higher numbers. It has been noted by others that patients do not tolerate repeated questionnaires, especially longer ones (128). If the questionnaire is self-administered an even lower response rate may be expected (129).

Quality of life and pain surveys

Quality of life

Traditionally the impact of illness has been measured by clinical and laboratory indicators. QoL surveys were introduced in the early 1970s to incorporate the patients own perspective (128). The simplest definition of quality of life is subjective well-being (130), but includes numerous dimensions such as “love and affection, self-respect and self-satisfaction, challenge and stimulation, social acceptance, achievement and job satisfaction, individuality, involvement and participation, comfort, economic well-being and good health, novelty and change, dominance, superiority, independence and privacy” (131). The five essential features of a quality of life instrument are face validity, reliability, responsiveness (sensitivity to change), appropriateness and practicality. (132).

Although the wider definition differs between authors most incorporate the following: 1) Quality of life is a subjective phenomenon. 2) Although quality of life can be defined in terms of global happiness or satisfaction, this global perception is influenced by numerous dimensions of life such as those described above. 3) Satisfaction or happiness with life is determined by the difference between one’s perceived needs or expectations in each domain compared to what one actually possesses or achieves in that domain (133). Obviously QoL assessment is complex and the patient’s response to components may not only change due to a perceived change in QoL but also through adaptation, coping, and expectations (128).

The idea is to measure health related quality of life as opposed to global QoL. QoL can be measured by a generic or a disease specific instrument. No gallstone specific instrument was available at the start of our trial. A disease specific instrument was published in 1996, but to our knowledge it has never been widely accepted and applied (134). A disease specific instrument is more responsive to change, with the main disadvantage that it makes comparisons across diseases impossible.

A review paper published in 2001 found after searching Medline only 20 papers that measured QoL in a valid fashion in randomized surgical trials. Five of the papers were design studies that did not report results. In altogether 10 of the 20 papers the QoL results were determined important enough to affect clinical practice (135). QoL is important for measuring the impact of chronic disease. The goal of QoL measures is to differentiate between people with better or worse QoL and to measure change over time (129).

The few trials that have studied QoL or pain in gallstone patients have to our knowledge only investigated QoL or pain at two points, before and after treatment. A few RCT's exist, covering symptomatic outcome (ESWL vs. laparoscopic.cholecystectomy (136), ESWL vs. open cholecystectomy (137), laparoscopic vs. minilaparotomy cholecystectomy (postoperative assessment only) (70), and early vs. delayed laparoscopic cholecystectomy in AC (preoperative assessment not complete) (126). The remaining non-randomized papers covers symptomatic outcome (40, 60, 98 – 101, 105, 138, 139) or QoL outcome (62, 82, 114, 140 - 144) after cholecystectomy in a controlled or non-controlled fashion. Not all of these papers have preoperative assessments of pain or QoL and the follow-up is, with few exceptions, generally short.

The PGWB index (145) and NHP (146) (see later) were introduced in the mid 1980's and both have been widely used. Since the start of our trials they have been replaced by newer instruments: the generic Medical Outcomes Study Short-Form 36 (SF-36) in 1992 (147) and the GastroIntestinal Quality of Life Index (GIQLI) in 1995 (148), both being the two most widely used today. Individualised measures, where patients specify and score important areas of life are receiving more attention, but it has been noted that due to the individual nature the analysis is more complex (149).

PGWB

Most generic QoL measures investigate several domains: physical, psychological, social, somatic, and spiritual (150), but the PGWB is centred on psychological domains. The following domains are covered: anxiety, depressed mood, positive well-being, self-control, general health, vitality. The score ranges from 22 to 132, with higher ranges indicating high quality of life. The PGWB has been translated to several languages and has been found to have good reproducibility, internal consistency, validity and responsiveness (151).

NHP

Nottingham Health Profile is a generic health-related QoL measure. We only used part II which consisted of seven questions on how disease affected job of work, looking after the house, social life, home life, sex life, interests and hobbies or holidays. NHP II covers areas that the PGWB does not, namely physical impact of disease. NHP has been translated to several European languages and has been extensively tested (152).

Pain

Pain is one of the most important determinants of quality of life (150) and is the cardinal symptom of gallstone disease. Unidimensional tools, like VAPS have been shown to be sensitive to differences in pain intensity (153) and earlier trials have found it to have a high degree of reliability (154). The limitation is that some patients find the concept too abstract, and ratings across groups of patients may be affected as individuals interpret the scale differently (155).

Multidimensional tools have been developed, including the Brief Pain inventory (BPI) (156) introduced in the late 1980s. This is a recognised pain measurement tool that records information on history, intensity, location and quality of pain, but unfortunately, this and others had until recently not been validated in Norwegian (157). For this reason, we used an ad Hoc multidimensional pain measurement tool which consisted of four items related to gallstone pain: intensity of pain last week, duration of pain last week, frequency of pain past 6 months and use of analgesics past 6 months). All items were scored by the use of a five-step scale (Likert format, 0 – 4) and the sum ranged from 0 – 16, the higher range indicated frequent and severe pain attacks. The tool has not been formally validated, but was found to have a fair internal consistency (Table I) and correlated well to the VAPS (Table II).

Table I. Internal consistency of the survey measures at randomization.

	Cronbach's alfa	Number of items
PGWB *(n=192)*	0.9497	22
NHP *(n=160)*	0.7870	7
PAIN SCORE *(n=197)*	0.7617	4

Table II. Correlation (construct validity) of survey measures at randomization using Pearson's correlation coefficient.

		PGWB*	NHP	Pain score
VAPS *(n = 195)*	Pearson correlation	-0.437	0.216	0.722
	p-value	<0.0001	0.007	<0.0001
	n	*187*	*159*	*195*

* PGWB scores opposite of the other survey measures.

Statistics

In the papers we have used Fisher's exact test to compare the difference in events and postoperative complications between the randomized groups. Fisher's exact test for categorical data is assumed to be more suitable for use with small expected frequencies than the chi square test.

Reciprocal Kaplan-Meier survival curves were used to visualize the cumulative probability of having a cholecystectomy in the randomized groups of SGBS and AC patients. A log-rank test (Mantel-Cox) was used to compare the groups.

When comparing the frequencies of two types of pain within a group (paper V), we used the one-sample binomial test which measures whether the proportion of two categorical variables significantly differs from a hypothesized proportion (0.5).

The linear mixed-effects model

The analysis of multiple measures as in the QoL and pain surveys is complex and few models are available, most are dependent on balanced data. The linear mixed-effects model has not the same restrictions and can handle unpaired responses and cases with missing data.

It is a flexible tool for estimating linear models for a continuous response variable from data sampled from normal distributions. In this model response from a subject are thought to be the linear sum of so-called fixed and random effects, hereby the term 'mixed'. If an effect, such as treatment group or time in our case, affects the population mean, it is fixed. If an effect is associated with a sampling procedure (e.g. subject effect), it is random. In the mixed-effects model, random effects contribute only to the covariance structure of the data. The presence of random effects, however, often introduces correlation between observations as well. Though the fixed effects are the primary

interest here, it is necessary to adjust for the covariance structure between repeated measurements in the same subject. In our analyses we have assumed a first-order covariance structure between a subject's responses (on QoL, pain) at the four time points (0, 6, 12 and 60 months from randomization). Estimates were obtained applying the restricted maximum likelihood (REML) method, and the assumption of normality assumed to be approximately fulfilled.

Results and discussion

Symptomatic, non-complicated gallbladder stone disease, papers I & III

Events and complications

When the study was planned the natural history of symptomatic, uncomplicated gallstone disease was largely unknown (46). Our findings indicate that non-operative treatment carries a low risk of complications, confirming the results of non-controlled studies (35, 38, 43, 44). We found a significant difference in events (admissions for pain or gallstone-related events; observation group 15/69, operation group 3/68) between patients randomized to observation or operation (P = 0.0043). Only 3 out of the 15 events in the 69 patients randomized to observation were gallstone complications, the rest were admissions for pain. If analysed with gallstone complications as endpoint, the results show no significant difference between the two groups (observation group 3/69, operation group 1/68, Fisher's exact test; P = 0.62).

One may argue that to get a total view of the burden on the patients, it would be more sensible to include events and postoperative complications in the analysis. Such a setup is outlined in the last column in Table III. An analysis of this yields a significant difference between the groups randomized to observation or operation with more events in the observation group (P = 0.007, Fisher's exact test). Again, the admissions for pain in the group randomized to observation constitute the majority of the difference between the two groups.

We expected a number of patients to withdraw from the two randomized groups. In the end eight of the patients randomized to cholecystectomy (12 %) did not undergo operation while 35 of patients randomized to observation (51 %) later had their gallbladders removed. The cumulative risk of having a cholecystectomy levelled off after four years and we found a significant difference in the cholecystectomy rate in the two groups (log-rank test (Mantel-Cox) P < 0.0001).

Quality of life and pain

Although there was a significant difference in events (mainly admissions for pain) and numbers of cholecystectomies between the two randomized groups, we found no differences in QoL and pain. Significant improvements in quality of life and pain scores were detected regardless of treatment,

with the marked positive changes found 6 months after randomization. The results did not change if the patients were grouped according to actual outcome (observation or operation). In this regard, the findings are not unlike those reported in trials comparing ESWL to cholecystectomy that found marked improvement in pain in both groups following treatment (136, 137).

Interestingly, the patients that subsequently experienced gallstone related events scored significantly higher on pain at randomization than patients that did not experience any later events. A similar observation was noted in a paper published in 1968 (158). The difference in pain was maintained throughout the follow-up period. Intuitively, one would expect persisting pain in patients treated in a non-operative fashion, but most of these patients later had a cholecystectomy. At randomization, sixty-seven of all 137 patients reported a VAPS equal to or in excess of 50. Of these, 50 patients (75 %) eventually had a cholecystectomy. In patients with persisting chronic pain one may speculate if this was due to neuropathic pain caused by prolonged preoperative damage to the gallbladder. This may complicate the decision making and as warned by others preoperative prediction of outcome after cholecystectomy is uncertain (40). More research is needed to develop a prognostic scoring system that can be employed in routine use.

Table III. Number of patients with gallstone events and postoperative complications and cumulative risk of events and postoperative complications.

Randomization	Preoperative events	Postoperative events	Operated	Major postoperative complications	All events and major postoperative complications
	No.	No.	No. (%)	No.	No (%)
Observation *(n=69)*	15	0	35 (51)	5	19 (28)*
Operation *(n=68)*	2	1	60 (88)	3	6 (9)
Excluded *(n=201)*	25	0	127 (63)	8	30 (15)**

*) One patient with preoperative event and major postoperative complications. **) Three patients with preoperative events and major postoperative complications.

Conclusion

Symptomatic patients with uncomplicated gallstone disease have a low risk of subsequent gallstone related complications. Operation is not warranted just to further reduce this risk. According to our findings symptoms vary and may improve with time. Therefore a wait-and-see policy appears safe. Patients with initially high intensity and frequency of pain are more likely later to experience gallstone pain. Persisting pain following cholecystectomy is not uncommon, and we did not find any significant effect of cholecystectomy on QoL and pain.

Acute cholecystitis, papers II and IV

Events and complications

In AC, randomized trials have focused on early versus delayed surgery (53), concluding that surgery is warranted in order to avoid further complications of gallstone disease. We found no significant difference in gallstone related events between the two randomized groups (P = 0.16). Contrary to the findings in the SGBS group, the events were mainly gallstone complications (16 out of 23 events in 18 patients; 12/33 patients in the observation group and 6/31 in the operation group). It may be argued that it is well known that patients waiting for delayed surgery are at risk of recurrent symptoms or disease (50, 53) This risk may theoretically be eliminated if the design of the trial had been early as opposed to delayed cholecystectomy. However, not all patients scheduled for early operation will eventually have a cholecystectomy (79).

As for patients with SGBS, the two randomized groups were analysed in an alternative fashion including all gallstone related events and major postoperative complications, as outlined in the last column of Table IV. We found no significant difference between the two groups (Fisher's exact test, P = 0.42).

As noted by others (77, 159), some patients eventually refused delayed surgery, probably due to minimal symptoms. Twenty-seven of 31 patients (87 %) randomized to operation had a cholecystectomy at a median of 3.6 months after randomization. Ten patients randomized to observation later had their gallbladders removed, leaving 70 % (23 of 33) with an intact gallbladder.

The difference in number of operations between the two groups was significant (log-rank test (Mantel-Cox), P < 0.0001)).

Quality of life and pain

There was a significant improvement in both QoL and pain six months following randomization. There was no significant difference between the two randomized groups, nor when patients were grouped according to the final operative outcome (+ / - cholecystectomy).

The improvement in QoL and pain was the same in patients with AC and SGBS and we believe that this may partly be explained by a genuine improvement and partly by regression towards the mean. Regression towards the mean is a problem in serial measurements, making natural variation in repeated data look like real change. Extreme measurements tend to be followed by measurements that are closer to the mean (160).

Randomization is the best way to separate the genuine effect of treatment from the effect of regression towards the mean (161). A few trials have compared QoL in symptomatic and asymptomatic patients following cholecystectomy and concluded that the gain is higher in symptomatic patients (143, 144), but both of these trials were uncontrolled. A randomized trial by Johansen et al. comparing pain and QoL in patients with AC randomized to early or delayed operation (126), reported a non-significantly higher QoL one month following delayed operation, but paradoxically this group of patients had significantly more abdominal symptoms. A major weakness of the trial is that it is a postoperative survey only.

Although SGBS patients that subsequently experienced gallstone related events scored significantly higher on pain at randomization than patients that did not experience any events, no such corresponding difference were found in patients with AC (p-values Pain score: 0.35; VAS: 0.484; PGWB 0.027; NHP: 0.012).).

Table IV. Number of AC patients with gallstone events and postoperative complications and cumulative risk of events and postoperative complications.

Randomization	Preoperative events	Postoperative events	Operated	Major postoperative complications	All events and major postoperative complications
	No.	No.	No. (%)	No.	No. (%)
Observation *(n=33)*	11	1	10 (30)	1	12 (36)*
Operation *(n=31)*	5	1	27 (87)	3	8 (26)*
Excluded *(n=116)*	16	3	43 (37)	6	23 (20)**

*) One patient in each group with postoperative event and major postoperative complication. **) Two patients with preoperative events and major postoperative complications.

Conclusion

We found that conservative, non-operative treatment of AC carried a non-significant risk of a subsequent gallstone related event, but this did not influence the symptomatic outcome as assessed by QoL and pain measurements. Patients should receive information on the risks of conservative management and cholecystectomy need not be compulsory after AC.

Postcholecystectomy pain, paper V

All patients considered for participation in the two trials were interviewed concerning their symptoms. Pain was categorised mainly according to its localisation (right subcostal region) and whether it was accompanied by referred pain (shoulder, back) or other symptoms (dyspepsia, nausea etc.). It soon became apparent that the symptoms needed to be addressed in a more thorough and systematic fashion and a new questionnaire was developed for the five-year follow-up. This questionnaire included detailed information on accompanying dyspepsia, factors that may provoke pain, and the duration, localisation and intensity of pain.

During interviews with patients, we found that two patterns of pain existed: pain attacks and a more diffuse type of pain. Both types of pain were located in the right subcostal or midline epigastric area. Pain attacks were episodic, usually increasing gradually to peak intensity where it normally was quite

steady until it subsided similarly. It lasted more than 30 minutes and up to six hours and was usually accompanied by nausea and anorexia. The pain attacks were often referred to the back in the region under the right shoulder blade. The diffuse type of pain was steady, persisting and of lower intensity.

The questionnaire was used in the five-year follow-up consultation. The incidence of postcholecystectomy abdominal pain was 27 % in our series (34 / 124). Although this is not the first series with a five-year follow-up (162), most other series report shorter follow-up (24 - 36 months) (105;138). It is interesting that pain persisted for such a long period of time following surgery (median 61 months (range 3 - 91)). The majority of patients were women (78 / 124), but we found no difference in incidence of pain between the sexes. Interestingly, the diffuse type of pain was significantly more common than pain attacks in women, especially in younger women (< 60 years of age). Similar findings and characteristics of pain have been reported by others (105, 138). Although it has been established that not all patients are cured of pain after cholecystectomy, few studies have tried to identify preoperative factors that may predict the outcome after surgery. A Danish study concluded that the presence of psychic vulnerability and dyspepsia, high frequency of pain attacks and a long history of gallstone pain indicated higher risk of poor symptomatic outcome after cholecystectomy (139).

Conclusion

All our patients were thoroughly assessed on inclusion, and no patients with dubious symptoms (dyspepsia or vague pain, only) were entered in the trails. Thus, despite a very careful selection of patients it is disappointing that the frequency of postoperative pain was the same as reported by others. In order to decipher postcholecystectomy pain, we suggest that preoperative pain needs further classification and comparison with postoperative complaints.

Summary

I. The risk of gallstone complications was low in patients with SGBS and the prevention of complications should not in itself be an indication for operation.

II. SGBS patients with high frequency and intensity of pain at randomization were more likely later to experience gallstone events than other patients. Throughout follow-up, these patients had a persisting higher level of pain than other patients even though most of them eventually had a cholecystectomy.

III. In patients with SGBS we found no difference in symptomatic outcome (QoL and pain) between the randomized groups, or when analysed according to final outcome (observation versus operation). In most patients, the symptoms varied and waned over time. Thus, a wait-and-see policy may be a reasonable option to cholecystectomy.

IV. In AC, observation carried a higher (although non-significant) risk of gallstone events than operation, and there was no mortality in any group. Almost all events in AC were complications of gallstone disease as opposed to what found in patients with SGBS where most events were admissions for pain. As the risk of gallstone complications is moderate, conservative treatment and observation may be an option in AC.

V. The symptomatic outcome (QoL and pain) in AC was the same regardless of randomization group and final outcome (observation or operation).

VI. Postcholecystectomy symptoms and its causes are still an enigma. We suggest that preoperative gallstone pain needs further classification and comparison with postoperative complaints.

Errata

Paper II:

Page 988, first column, first paragraph under *Events during follow-up*: P = 0.13 is incorrect and should read P = 0.061. The analysis in the second paragraph is correct (P = 0.16).

Page 988, second column, first paragraph. The analysis of major complications is correct (P = 1.00), but the analysis of minor complications (P = 0.66) is incorrect and should be replaced by P = 0.4.

Paper III:

Page 272, second column, second paragraph under *Gallstone-related events, cholecystectomy and postoperative complications*. The stated P is incorrect (P = 0.011) and should read P = 0.0043, thus there is a significant difference between the two groups (see page 35 in thesis, Events and complications, first paragraph).

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