

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

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After removal of the gallbladder, pain may persist in some patients. To study this condition, 124 patients from two randomized trials, including those with symptomatic noncomplicated gallbladder stones ($n = 90$) and acute cholecystitis ($n = 34$), were interviewed, while 139 patients (90%) excluded from both trials responded to a questionnaire 5 years after the operation. Thirty-four patients (27%) of those randomized had pain; 23 (18%) had diffuse, steady pain; and 11 (9%) had pain attacks resembling their preoperative symptoms. A significant dominance of diffuse pain occurred in women ($P = 0.024$), especially those younger than 60 years ($P = 0.004$). A tendency for the diffuse type to be dominant was also present in the group of female patients with symptomatic noncomplicated gallbladder stones ($P = 0.052$). Of the excluded patients, 18% (25/139) had pain, but 88% of them (96% of the men and 87% of the women) were satisfied with the result of the operation. The overall number of patients with postoperative pain was 22% (59/263). We conclude that persisting abdominal pain 5 years after the operation was mainly of a nonspecific type, found mostly in younger women who had had noncomplicated gallstone disease. Eighty-eight percent of the excluded patients declared themselves satisfied with the result of cholecystectomy. (J GASTROINTEST SURG 2005;9:826–831) © 2005 The Society for Surgery of the Alimentary Tract

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INTRODUCTION

Although cholecystectomy is considered to be the standard treatment for symptomatic gallstones, far from all patients are relieved of their pain following the procedure. It is still unclear if postcholecystectomy symptoms resemble the pain attacks that led to removal of the gallbladder and to what extent pain persists or occurs de novo postoperatively. According to a recent literature review,¹ 6% to 30% of patients experience the same type of pain after operation. No consistent pathophysiological substrate for such pain

has been documented, probably because of the diversity of the indications for cholecystectomy as well as the manner in which studies have been conducted.²

Unfortunately, most studies are retrospective, with follow-up periods commonly ranging from a few weeks to a couple of years.^{1,3} Additional problems have been lack of a distinct disease definition and separation of symptoms, and differences in the way patients have been examined.² Consequently, we will argue that more information on the magnitude and composition of pre- and postcholecystectomy pain is needed in order to gain a better understanding of

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the ability of the operation to cure the preoperative symptoms.

Our aim was to examine the incidence of pain after cholecystectomy in two randomized controlled trials (RCTs) with well-defined entry criteria,^{4,6} and to classify such symptoms in two main categories, one resembling acute gallstone attacks, the other a more diffuse type of pain.

MATERIAL AND METHODS

The two trials were carried out simultaneously and a combined follow-up was conducted. Therefore, patients who had undergone cholecystectomy in these trials were amalgamated for the single purpose of studying freedom of pain after removal of the gallbladder. The two RCTs comprised a population of 518 consecutive patients.^{4,5} At 5 years, 69% of patients with uncomplicated gallbladder stones (SGBS) and 58% of patients with acute calculous cholecystitis (AC), as well as 54% of all excluded patients, had undergone cholecystectomy. Twenty-four patients (8%) had died, but none of the deaths were the result of gallstone-related disease or postoperative complications. Overall, 278 patients, 124 randomized and 154 excluded patients, were eligible for follow-up.

Timing of Cholecystectomy

Because of our waiting list policy, patients with SGBS who were randomized to surgery had the procedure a median of 3 months (range 0–24 months) after randomization. Those randomized to observation but who dropped out and had cholecystectomy underwent surgery a median of 27 months (range 0–67 months) after randomization. AC patients who were randomized to surgery had the operation a median of 4 months (range 1–13) after randomization and those who were observed but later underwent cholecystectomy, had the procedure a median of 14 months (range 2–67 months) after randomization.

Excluded patients had surgery a median of 2 months (range 0–60 months) after exclusion.

Disease Definitions

The definitions of SGBS and AC and accounts of these two RCTs have been given in previous reports.^{4,5} The definition of SGBS pain included at least one of the following features: episodic pain, usually increasing gradually to a peak intensity, at which it normally was quite steady until it subsided similarly; location in the right subcostal or midline epigastric area lasting more than 30 minutes and up to 6 hours for uncomplicated disease; pain often referred to the

back in the region under the right shoulder blade; and pain usually accompanied by nausea and anorexia. Attacks appear relatively suddenly and are distinct from and stronger than any steady, continuous, or diffuse type of pain. Preoperative symptoms were defined as severe, moderate, or minimal according to frequency, intensity, and whether they limited daily activities or hampered social life.

AC was defined by acute abdominal pain, commonly in the right subcostal area, with a duration of more than 6 to 8 hours, and tenderness on clinical examination in the right upper quadrant accompanied by signs of inflammation on ultrasonography and in clinical biochemistry data.⁵

Follow-Up

In randomized patients, gallstone-related events were recorded consecutively. Patients answered questionnaires concerning pain patterns at randomization. All 124 eligible patients from the two RCTs were interviewed at a median of 61 months (range 3–91) after cholecystectomy using a structured interview designed to separate pain patterns.

Excluded patients were not followed-up routinely, but hospital notes were checked and all gallstone-related events recorded. These patients were sent a simple questionnaire in which they were asked about freedom from preoperative symptoms and patient satisfaction. Of the 154 excluded patients, 139 patients (90%) replied to the questionnaire at a median of 79 months (range 21–98 months) after surgery.

Consequently, data on the incidence of pain were available for 263 patients having had a cholecystectomy in the past.

Survey Measures

A self-composed, detailed questionnaire, based on the experience gained in the two RCTs and including all the clinical elements of pain attacks described, was used at follow-up. This questionnaire is currently being used in further prospective studies of gallstone disease. A visual analogue scale (VAS) pain score was included. The score point was crossed by the patients on a 100 mm straight horizontal unmarked line on which no pain and unbearable pain was indicated at the left and right ends, respectively.

Statistics

Fisher's exact test was used to compare frequency of pain between different subgroups of patients and a one sample binomial test to compare the different types of pain within a group of patients. A significance level of 0.05 was applied.

RESULTS

Patient Demographics

The demographics of the patients who were interviewed and responded to the questionnaires are given in Table 1.

Pain Incidence and Characteristics in Randomized Patients

The presence of abdominal pain for patients with SGBS and AC is shown in Table 2. Twenty-seven percent of the 124 patients (34/124) experienced pain, and 29% (29/101) of women. The diffuse type dominated in women ($P = 0.024$), especially those younger than 60 years ($P = 0.004$). Five men (22% of 23 patients) had pain but none of the two patterns dominated. Interestingly, although 8 women had pain attacks, 5 of these also had diffuse pain, meaning that only 3 women had pure pain attacks. Thus, 5% (6/124) of all patients had pure pain attacks. There were no significant differences between women and men for the two pain types (pain attacks, $P = 0.42$; diffuse pain, $P = 0.24$; combined, $P = 0.61$).

The duration of the history (more or less than 2 years), randomization outcome (operation vs. observation), and surgical method (open vs. laparoscopic surgery) made no significant impact.

Pain was located in the upper abdomen in 90% of women (26/29) and in all five men. The incidence of pain radiating to the back was equal among women ($n = 13$; 45%) and men ($n = 2$; 40%). The frequency of pain attacks per month was a median of 2.8 (range 1–8) for the eight women and 4.5 (range 1–8) for the three men.

When combined for both pain types, the VAS score was a median of 38 (range 2–100) for women and 42 (range 5–56) for men. Analgesic use according to symptomatic group is shown in Table 2. Thirteen of 29 women (45%) reported abdominal pain at follow-up, and 1 of 5 men (20%) used pain medication ($P = 0.38$). Preoperatively, 79% (98/124) of followed up patients had used analgesics. However, of the

group that was asymptomatic at follow-up, only 74% (67/90) had used analgesics preoperatively, compared with 91% (31/34) of the symptomatic patients.

Gallstone-Related Events in SGBS and AC Patients

A new gallstone-related event occurred after cholecystectomy in four patients (3%). Two patients (one early and one late) from the AC study had common bile duct (CBD) stones. One SGBS patient was admitted because of a pain attack without evidence of gallstone disease, and one had a CBD stone soon after the cholecystectomy.

Excluded Patients

The incidence of pain at follow-up is shown in Table 3. Twenty-five of 139 patients (18%) had pain. Despite these circumstances, 88% of all excluded patients (96% of the men and 87% of the women) were satisfied with the result of the operation. New gallstone-related events were noted in two patients: one patient had acute pancreatitis shortly after cholecystectomy and another had a CBD stone 2 years after surgery.

The majority of excluded patients who still reported pain (17/25) had originally refused randomization because they were experiencing severe symptoms or wanted an operation, while only two of the symptomatic patients had originally refused to be randomized because they did not want an operation.

Summary

A combined 22% (59/263) of the patients had pain at follow-up. There was no difference between randomized (34/124) and excluded (25/139) patients ($P = 0.076$). Of the 5 patients (2%) of 263 that had a CBD stone or acute pancreatitis following removal of the gallbladder, three were still suffering from pain.

Table 1. Age and gender composition at 5-year follow-up

	Randomized patients (n = 124)		Excluded patients (n = 139)	
	SGBS (n = 90)	AC (n = 34)	SGBS (n = 111)	AC (n = 28)
Women (n = 214)				
No. of patients	78	23	97	16
Median age (range)	53 (26–84)	54 (33–84)	49 (21–88)	59 (34–82)
Men (n = 49)				
No. of patients	12	11	14	12
Median age (range)	55 (34–74)	65 (34–78)	63 (32–70)	75 (42–94)

SGBS = uncomplicated gallbladder stones; AC = acute calculous cholecystitis.

Table 2. Postcholecystectomy pain variables at a median of 61 months after removal of the gallbladder

Parameter	No. of patients (%)			Combined
	Pain attacks*	Diffuse pain	P values	
All patients (n = 124)	11 ⁵ (9)	23 (19)	0.058	34 (27)
Women (n = 101)	8 ⁵ (8)	21 (21)	0.024	29 (29)
Men (n = 23)	3 (13)	2 (9)	1.00	5 (22)
SGBS (n = 90)	7 ⁴ (8)	17 (19)	0.064	24 (27)
Women (n = 78)	6 ⁴ (8)	16 (21)	0.052	22 (28)
Men (n = 12)	1 (8)	1 (8)	1.00	2 (17)
AC (n = 34)	4 ¹ (12)	6 (18)	0.75	10 (29)
Women (n = 23)	2 ¹ (9)	5 (22)	0.45	7 (30)
Men (n = 11)	2 (18)	1 (9)	1.00	3 (27)
Age <60 (n = 86)	6 ³ (7)	20 (23)	0.009	26 (29)
Women (n = 71)	4 ³ (6)	18 (25)	0.004	22 (31)
Men (n = 15)	2 (13)	2 (13)	1.00	4 (27)
Pain medication (n = 14)	4 (36)	10 (43)	0.18	14 (41)

*Superscripts show the number of patients who had both pain attacks and diffuse pain.

DISCUSSION

Freedom from pain attacks is a major outcome measure after cholecystectomy and should consequently be assessed separately from other types of pain that might appear. Complete cure of biliary-type pain in contrast to persisting dull aching pain has been reported.⁷ Ure et al.⁸ found that biliary colic remained in only 8% of patients in contrast to noncolicky pain in 32%. In a prospective Danish study,⁹ 21% had persistent pain of the same character as before the operation. This is in agreement with a British randomized trial¹⁰ in which 19% of the patients experienced biliary pain five years after cholecystectomy. The reason for the discrepancies in outcome is not always clear.¹ The indication for surgery may have differed. Another problem may be that the medical community has not agreed completely on a useful definition of "true" biliary pain, as alluded to by Luman et al.² A confounding factor is that dyspepsia is often included in the postoperative assessment of satisfactory outcome, including such variables as nausea and vomiting, but these symptoms should be

considered part of the pain response elicited by gallstones. Studies of gallstone-elicited symptoms should preferentially be prospective with preoperative symptoms described accurately and in detail.¹

Ure et al.,⁸ who differentiated between colic and other types of pain, reported figures for postoperative pain quite similar to ours. They used a VAS for pain rating and found an average pain score of 68 in all patients with pain (representing 83% of total patients) before the operation. The average score was reduced to 43 in those who still experienced pain; however, they did not separate the results according to the two pain types. A similar result was obtained in another study,¹⁰ with a median score of 67 before and 45 at 5 years after treatment for those who still had pain. McMahan et al.³ found a lower VAS score of median 35 (range of 10–60), 1 year postoperative. This corresponded almost exactly to the VAS score recorded in our patients. Our median score value indicates moderate to severe pain.¹¹ Peterli et al.,¹² in a 12 to 25 month follow-up, found the incidence of analgesic use to be 16% in the open group and 15% in the laparoscopic group. This may seem to be in accordance with our figure of 11% at 5 years considering that the pain score decreased with time.⁶

How long after surgery the assessment of pain should take place may be a matter of debate. Patients were followed up from 10 to 25 years in two studies.^{13,14} No further gallstone events took place after 5 years in a study from Finland, and still the incidence of abdominal pain was 21% after 25 years.¹⁴ A Dutch study¹³ found a minimum of 15% of their patients had complaints at 10 years. In a study of quality of life,⁶ we found that the greatest improvement took place during the first 6 months. Bates et al.¹⁵ found

Table 3. Postcholecystectomy pain in 139 excluded patients* at median 79 months after removal of the gallbladder

Parameter	Women	Men	All patients
	n = 113	n = 26	n = 139
Symptomatic patients	23 (20%)	2 (8%)	25 (18%)
Satisfied with outcome	97 (86%)	25 (96%)	122 (88%)

*Symptomatic uncomplicated gallbladder stones, n = 111; acute cholecystitis, n = 28.

that slightly more patients were affected by postcholecystectomy pain at 1 year follow-up than 1 year further on. Ahmed et al.¹⁰ observed that the severity of postcholecystectomy pain decreased slightly from 1 to 5 years following surgery. These results are in agreement with our study; the total number of noncomplicated gallstone disease patients affected by abdominal pain fell from the first to the fifth year, when 27% were affected by abdominal pain.⁶ A simple explanation for this may be that postoperative pain symptoms, for whatever reason, improve gradually over time. Coincidentally, it has been reported that 70% of unspecific abdominal pain encountered in general practice will go away after 1 year.¹⁶

Severity of preoperative symptoms³ or degree of inflammation seen at histology² has been inversely linked to better outcome. There was a tendency toward more reported pain of the diffuse type in uncomplicated disease compared with AC. Thirty-nine percent of patients with AC in our study had only one episode of pain before randomization.⁵ Ros and Zambon⁷ found that the longer the preoperative history, the higher the frequency of mild postcholecystectomy symptoms. In one study,² there was a tendency for a better outcome with a history shorter than 6 months. However, although our patients with a history of less than 2 years had almost significantly more diffuse pain, the total number of patients with pain was unaffected by the preoperative duration of the disease.

Sex did not reach statistical difference in the study of Jørgensen et al.,⁹ but there was a tendency for more women to have pain. Others have found that sex matters in disfavor of women when it comes to patient satisfaction,^{12,17} or, to the contrary, that it does not matter.^{3,13} Konsten et al.¹³ also found that age did not influence outcome. Old age, with 50 years the cutoff point, was not important in one study,⁹ whereas the opposite was found when 55 years was used.¹⁵ In contrast to these studies, we found that women under the age of 60 years had significantly more pain of the diffuse, more continuous type that is also described in functional dyspepsia. Among excluded patients, more men than women reported a satisfactory outcome. Patients with psychic instability or disorders have been found to have more postoperative complaints.^{2,9,18,19} A recent retrospective study²⁰ found this to be more prominent in women.

No difference has been found in outcome between open and laparoscopic surgery in terms of persistent pain.^{3,12} Does some other biliary pathology explain postcholecystectomy symptoms? With a follow-up of 10 years, Konsten et al.¹³ found a CBD stone incidence of 2%. These were discovered by a combination of clinical and other signs and not by routine

blood tests alone. Similar figures have been reported after more than 1 year of follow-up.^{8,12} Two percent of all our patients had been treated for CBD stones, but this occurred some time before the 5-year follow-up.

Sphincter of Oddi dysfunction (SOD), types I and II, has been held responsible by several investigators as a cause of persistent postoperative pain after cholecystectomy. However, consistent evidence for this connection has not been readily produced.^{21,22} In SOD type III, duodenal-specific visceral hyperalgesia by distension has been found as a possible cause for pain.¹⁹ There is experimental and clinical evidence that both gallbladder disease itself and cholecystectomy may increase duodenogastric reflux.^{7,23} Excessive duodenogastric reflux after cholecystectomy is associated with a high incidence of chronic gastritis.²⁴ Apparently, the gastric mucosa is vulnerable to bile injury in some but not most persons.²⁵ Although gastritis or duodenal hypersensitivity may be to blame for some symptoms in patients with gallstones, convincing studies linking duodenogastric reflux to postcholecystectomy pain have not been reported.

Eighteen percent of all excluded patients admitted to having postoperative symptoms. In spite of these figures, 88% were satisfied with the operation. This is in accordance with others who have reported 93% satisfaction after removal of the gallbladder.^{3,12,26} This has been independent of surgical approach.²⁶ Because of the long follow-up, our figures should express true complaints in contrast to a demonstrated placebo effect concerning dyspeptic symptoms that has been seen up to 1 year after treatment.¹

What remains to be examined in future prospective studies is the reason for "biliary" pain attacks even 5 years after cholecystectomy, especially in female patients with a history of noncomplicated gallstone disease given a proper indication for the operation.

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