Scandinavian Journal of Surgery 94: 34–39, 2005

QUALITY OF LIFE AND PAIN IN PATIENTS WITH ACUTE CHOLECYSTITIS

Results of a randomized clinical trial

M. Vetrhus[1], O. Søreide[2, 3], G. E. Eide[4], I. Nesvik[1], K. Søndenaa[1, 3]

[1] Department of Surgery, Stavanger University Hospital, Stavanger, Norway
[2] Department of Surgery, Haukeland University Hospital, Bergen, Norway
[3] Institute of Surgical Sciences, University of Bergen, Bergen, Norway
[4] Centre for Clinical Research, Haukeland University Hospital & Section for Epidemiology and Medical Statistics, Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway

ABSTRACT

Background: **Acute cholecystitis carries a higher risk of subsequent gallstone related events than symptomatic, non-complicated disease. However, it is largely unknown to what extent non-operative treatment will affect the patient's well-being as no trial has studied the possible consequences on pain and quality of life. Our aim was to study in a randomized trial how observational treatment (watchful waiting) compared to cholecystectomy.**

Methods: **Sixty-four patients with acute cholecystitis were randomized to observation or cholecystectomy. All gallstone related events were registered and patients answered questionnaires on quality of life (PGWB and NHP) and pain (Pain score and VAPS) at randomization and at 6, 12 and 60 months later.**

Results: **Patients were followed-up for a median of 67 months. Ten of 33 patients (30 %, 95 % CI 15 %–46 %) patients randomized to observation and 27 of 31 (87 %, 95 % CI 75 %–99 %) of patients randomized to operation had a cholecystectomy. Twelve of 33 (36 %, 95 % CI 20 %–53 %) patients in the observation group had a gallstone related event compared to 6 of 31 (19 %, 95 % CI 5 %–33 %) patients in the operation group, but the difference was not significant. When patients were grouped according to randomization or actual operative outcome (+/– cholecystectomy), we did not find any significant differences in pain or quality of life measurements.**

Conclusion: **Although conservative treatment of AC carried a certain but not significantly increased risk of subsequent gallstone related events, this did not influence the symptomatic outcome as assessed by quality of life and pain measurements. Thus, we argue that conservative (non-operative) treatment and observation of AC is an acceptable option and should at least be considered in elderly and frail patients.**

Key words: Acute cholecystitis; cholecystectomy; pain; quality of life; randomized clinical trial

Correspondence:
Morten Vetrhus, M.D.
Department of Surgery
Stavanger University Hospital
P.O. Box 8100
N - 4068 Stavanger, Norway
Email: mvetrhus@chello.no

INTRODUCTION

Acute cholecystitis (AC) is a complication of gallbladder stones, and carries a greater risk of subsequent gallstone related complications than non-complicated disease (1). Thus, the general opinion is that AC warrants cholecystectomy. A number of recent reports have been published on the subject but most focus on the timing of operation and rates of postoperative complications, length of hospital stay and cost (2–5). Ultrasonographic criteria for AC have been suggested (6) and the pain has been characterized by experimental (7) and clinical studies (8). Despite this, AC is not well defined in some other aspects, whether it is risk of later complications if treated conservatively or subsequent impact on patient's well-being.

In a recent report, we studied the feasibility of observation in AC in terms of risk of further episodes of gallstone disease (9). Not all patients underwent cholecystectomy even though non-operative, observational treatment carried a certain risk of subsequent gallstone related complications. In the same patient population, we also examined the possible impact on pain and quality of life, as it is a logical question whether such parameters would be worse in observed patients compared to those who had the gallbladder removed by surgery. QoL studies are particularly relevant in patients with a chronic disease when symptom control is a key outcome (10) and AC is a potentially chronic disease by way of recurrent pain attacks or cholecystitis.

Our aim was to study how pain and QoL was affected in patients with AC who were randomized to best medical treatment or surgery.

MATERIAL AND METHODS

PATIENTS

Consecutive patients with AC were recruited by two consultant surgeons in two hospitals (Haukeland University Hospital in Bergen (n = 38) and Rogaland Central Hospital in Stavanger (n = 26) from October 1991 to May 1994. The participating hospitals are first line treatment centres for defined catchments areas.

DISEASE DEFINITION, ACUTE CHOLECYSTITIS

AC was defined by three criteria: Acute abdominal pain in the right subcostal or midline epigastric area with a duration of more than 8 hours and tenderness on clinical examination in the right upper quadrant accompanied by signs of inflammation on ultrasonography (6) and in clinical biochemistry data (9).

Patients with suspected common bile duct stones and elevated liver function tests and/or a common bile duct cross-section diameter of > 6 mm at ultrasound, were investigated with ERCP.

ELIGIBILITY, RANDOMIZATION AND ETHICS

A total of 180 patients with AC were considered for participation in the study, eventually 64 patients were randomized. The remaining 116 patients did not join the study. Of these, 71 patients were excluded according to predefined criteria (age < 18 or > 80 years (n = 33), severe concomitant disease (n = 12), suspected common bile duct stone (n = 5), acalculous cholecystitis (n = 9) and patients with localized peritonitis suggestive of gallbladder perforation or gangrenous cholecystitis (n = 12). Of the remaining 45 patients, 30 had strong personal treatment preferences or were indecisive as whether to join the study and 15 patients had severe pain that precluded observation. A detailed account on these patients has been given in a previous report (9).

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

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

The study was approved by the Regional Ethics Committee (Health Region III) and the Norwegian Data Inspectorate.

FOLLOW-UP

Patients answered questionnaires on symptoms and QoL at the time of randomization and at 6, 12 and 60 months later. Disease events after randomization (admission for pain, complications of gallbladder stone disease, cholecystectomy and causes of death) were recorded. In the case of crossover from observation to cholecystectomy this was a joint agreement between patient and surgeon, based on symptoms or gallstone related complications. Some patients randomized to operation later decided not to have a cholecystectomy as their symptoms had abated.

OUTCOME

Pain and QoL were regarded as major outcome measures and a comparison was made between the two randomized

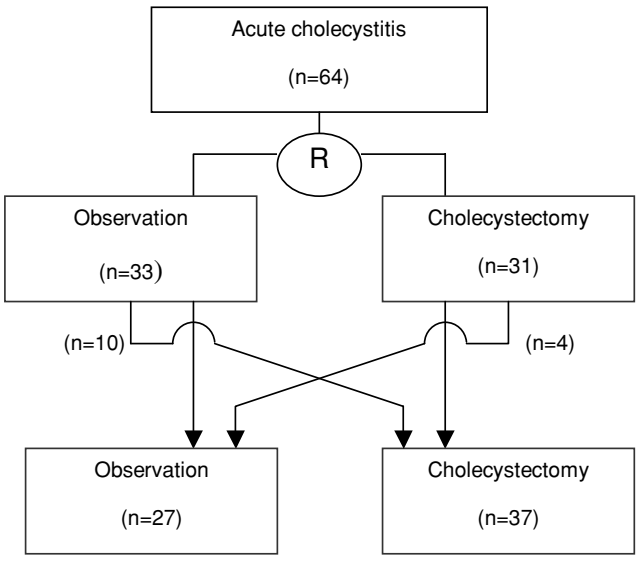

Fig. 1. Randomized groups and numbers of crossovers in the study populations.

groups and also with patients grouped according to final treatment outcome (operation versus observation).

SURVEY MEASURES

The Psychological General Well Being index (PGWB) and the Nottingham Health Profile part II (NHP) constituted the QoL instruments, both have been extensively tested and validated (11, 12).

The PGWB (13) is a widely used QoL measurement tool. The sum of 22 general well-being questions is 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 to 132, and the higher scores indicate a positive well being.

NHP part II (14) 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.

Pain was registered using a Pain score and a visual analogue pain scale (VAPS) score. The VAPS registered intensity of pain during the previous week and was given by patients with a vertical mark on a non-graded 100 mm line ranging from no pain to unbearable pain. 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 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 score ranged from 0 to16, the higher range indicated frequent and severe pain attacks.

STATISTICS

We assumed that 200 randomized patients would be sufficient, but no formal power calculation was performed, as data for such calculations were non-existing. The expected number was not achieved because a substantial number of patients were excluded according to the predefined criteria. The inclusion period was not extended beyond three years to avoid 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. In case of missing data in the NHP or VAPS no replacement was made and questionnaires that did not fulfil these criteria were excluded from the analysis.

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 and operative outcome as grouping factor.

Fisher's 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 characteristics of randomized patients are outlined in Table 1. The median age of patients was 58 (range 27–77) and 37 of 64 (58 %) patients were women. Eleven patients (17 %) had earlier been admitted to hospital for gallstone disease, including 6 patients for AC, and concomitant disease (heart disease, diabetes, obstructive lung disease) was present in 12 of 64 patients (19 %). No patient was lost to follow-up, but four patients died of unrelated disease after a median follow-up time of 45 (range 29–69) months. Median follow-up in the patients that completed the trial was 67 (range 56–98) months.

CHOLECYSTECTOMY, GALLSTONE RELATED EVENTS AND POSTOPERATIVE COMPLICATIONS

Of patients randomized to observation, 10 of 33 (30 %, 95% CI 15 %–46 %) eventually had a cholecystectomy (Figure 1) at a median of 14 months (range 2–67), while 27 of 31 patients (87 %, 95 % CI 75 %–99 %) randomized to operation underwent cholecystectomy at a median of 3.6 months (range 0.5–12.8) after randomization.

Gallstone related events (admissions for pain attacks or gallstone complications, i.e. acute cholecystitis, common bile duct (CBD) stone or acute pancreatitis) occurred in 12 of 33 patients (36 %, 95 % CI 20 %–53 %) in the observation group and in 6 of 31 patients in the operation group (19 %, 95 % CI 5 %–33 %). The difference was not significant (Fisher's exact test, p = 0.17). All events occurred before cholecystectomy except for one instance of CBD stone in each group, 14 and 37 months, respectively, after cholecystectomy.

Altogether four of 37 patients (11 %, 95 % CI 1 %–21 %) had a major postoperative complication (infec-

TABLE 1

Patient characteristics and events (number of patients) following randomization in 64 patients with Acute Cholecystitis.

	Observation group		Cholecystectomy group	
	Female (n = 20)	Male (n = 13)	Female (n = 17)	Male (n = 14)
Median age (range)	47 (29–71)	64 (29–73)	58 (27–77)	64 (41–77)
Gallstone complications after randomization	5	5	3	0
Admission for gallstone pain after randomization	1	1	2	1
Cholecystectomy (laparoscopic/open)	8/0	0/2	11/4	8/4
Major complication after cholecystectomy	0	1	1	2
Deaths (median follow-up 67 months)	0	0	1	3

tion, bile leakage, etc.), including a patient with bile duct injury that had a biliodigestive anastomosis two years later (Table 1).

PAIN AND QUALITY OF LIFE, RANDOMIZED GROUPS

PGWB mean values showed significant variation over time (Table 2), but this variation was the same in the two randomized groups (interaction p-value = 0.479), and there was no difference between them (Table 3). The time effect was mainly caused by changes in the PGWB from randomization to 6 months follow-up (Fig. 2).

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

Pain score mean values showed significant variation over time, but this variation was the same in the two randomized groups (interaction p-value = 0.055). There was no difference between the two randomized groups. The time effect was mostly due to a decrease in Pain score from randomization to 6 months follow-up (Fig. 2).

VAPS mean values showed significant variation over time. Again, the variation was the same in the two randomized groups (interaction p-value = 0.669). As for the other survey measures there was no difference between the two groups and the time effect was mostly due to a decrease in VAPS from randomization to 6 months follow-up (Fig. 2).

Further analyses showed that linear adjustment for age and gender did not alter the results for PGWB, NHP, Pain score and VAPS.

PAIN AND QUALITY OF LIFE, OPERATION VERSUS OBSERVATION

The between subjects analysis was also performed with operative outcome as grouping factor, i.e. whether the patients had had a cholecystectomy or not at the end of the study. We found no significant differences between the groups in any of the survey measures (p-values: 0.803 for PGWB, 0.986 for NHP, 0.365 for Pain score and 0.908 for VAPS). The variation over time was the same in both groups and adjustment for age and gender did not influence the results significantly.

DISCUSSION

Not much has been written on the presentation and natural history of AC during the last two decades. Available studies (2–5, 15) have mostly focused on the timing of operation with regard to safety and hospital costs. A common conclusion has been that in order to reduce hospital cost patients should be operated at first admission instead of having a deferred operation, but this policy has not been implemented in Norway. A previous report by our group looked at medical complications during observation and found that it did not jeopardize patient safety (9). In addition, this study is the first to longitudinally examine pain and QoL in AC, comparing observed with operated patients.

The location and characteristics of pain in AC was investigated in an experimental fashion 70 years ago (16) and have been confirmed by a more recent study (7). Because it usually has a longer duration and often displays distinct ultrasonographic signs and laboratory findings, the inflammatory process of AC should be clinically distinguishable from other conditions which may be located in the right upper quadrant of the abdomen. A few uncontrolled (8) or retrospective (17) studies have shown that cholecystectomy gives pain relief in both symptomatic, uncomplicated gallbladder stones and AC. On the other hand, up to twenty percent of patients are not relieved of their preoperative type of pain (8, 18, 19)

In the analyses we did not find any significant differences in pain between the groups for any of the survey measures. If anything, the figures indicate

TABLE 2

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

Survey measure	Observation group *P* values	Operation group *P* values
PGWB	< 0.0001	< 0.0001
NHP	0.074	0.12
Pain score	< 0.0001	< 0.0001
VAPS	< 0.0001	< 0.0001

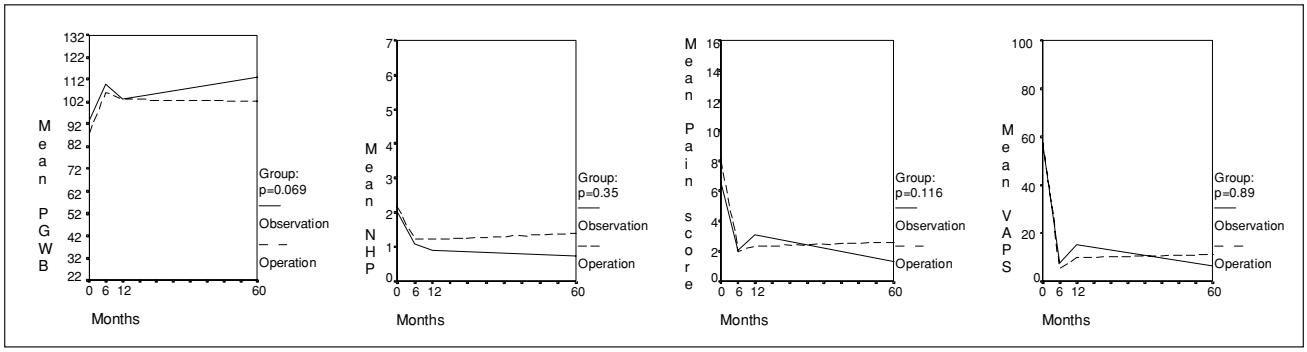

Fig. 2. Changes in QoL and pain with time. Mean results according to randomization group.

TABLE 3

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

Group		Randomization	6 months	12 months	60 months
PGWB	Observation	94.2 (n = 31)	110.2 (n = 33)	103.1 (n = 32)	112.0 (n = 30)
	Operation	88.1 (n = 31)	106.2 (n = 25)	103.2 (n = 25)	102.5 (n = 25)
NHP	Observation	2.0 (n = 29)	1.1 (n = 25)	0.9 (n = 22)	0.7 (n = 27)
	Operation	2.2 (n = 28)	1.2 (n = 18)	1.2 (n = 18)	1.4 (n = 23)
Pain score	Observation	6.6 (n = 33)	2.1 (n = 31)	3.1 (n = 32)	1.3 (n = 31)
	Operation	8.1 (n = 31)	2.0 (n = 27)	2.4 (n = 25)	2.6 (n = 24)
VAPS	Observation	57.1 (n = 31)	8.1 (n = 30)	15.1 (n = 31)	6.2 (n = 31)
	Operation	57.7 (n = 31)	5.4 (n = 24)	9.9 (n = 24)	11.3 (n = 24)

that the pain in patients in the observation group tended to return to normal sooner than in the operation group, even though a higher, but not significant, proportion in the observation group had a gallstone related event. However, all events except one in each group, took place before cholecystectomy. Nonetheless, all major changes in pain were reported 6 months after randomization with only minor changes thereafter. At this time 3 of 31 patients (10 %, 95 % CI 0 %–20 %) in the observation group and 23 of 31 patients (74 %, 95 % CI 59 %–90 %) in the operation group had had a cholecystectomy. Contrary to that found in patients with symptomatic, uncomplicated gallbladder stones (20), gallstone related complications were more prevalent then admissions for pain.

Both groups of patients reported a high intensity of pain at randomization with a mean VAPS of 57 (Table 3) which corresponds to severe pain (21). The Pain score was somewhat lower; the mean in the observation group was 6.6 and in the operation group 8.1 out of a maximum of 16. The Pain score recorded a mixture of intensity and frequency of pain, and scores in the lower half coupled with a high VAPS indicated that the pain had been of rather short duration, which would be understandable in the case of an acute episodic disease such as AC.

At inclusion the mean PGWB was 94 in the observation and 88 in the operation group, and as for the pain scores no differences were found between groups for PGWB or the other QoL scale: NHP. The figures for PGWB represent a minor reduction in general well-being compared to that of controls where a score of around 105 would have been expected (13). The NHP scores showed little variation over time. The PGWB index and NHP have been shown to be reliable tools to assess QoL (11, 12), but as discussed by others NHP might be too insensitive to differentiate between minor ailments (22). In fact, gallstone disease may not be suitable for QoL measurements because of the episodic nature of the disease (23).

An unknown number of crossovers were expected between the groups as persistent pain and eventual complications would make patients in the observation group want to have a cholecystectomy and not all patients in the operation group were expected to turn up for cholecystectomy. In the end, 30 % of patients randomized to observation and 87 % of patients randomized to operation had a cholecystectomy. It was expected that observed patients would be more troubled with pain and reduced QoL than operated patients. For this reason the analyses were also performed with the actual outcome (observation vs. operation) as grouping factor, but surprisingly this did not change the results.

With time, a reduction in the intensity of pain and an improvement in QoL were expected in all groups. As discussed in symptomatic, non-complicated gallbladder stone disease (20), patients were assessed at a time of high disease intensity and a regression towards the mean would be expected even in the case of more chronic pain. This problem should be addressed in any study comparing pain and QoL in a longitudinal fashion, but particularly in non-controlled studies (8, 24). A new QoL index for gastrointestinal disease which was introduced in 1995 (24), showed that patients had an improved QoL after removal of the gallbladder. The study was without any control group and a very short follow-up of six weeks. It has also been shown that the QoL gain is higher in symptomatic patients than in asymptomatic patients after cholecystectomy (25). Studies in patients with chronic gastrointestinal diseases like chronic pancreatitis (26) and gastroesophageal reflux (27) have shown a marked reduction in QoL. The reduction in QoL is not always proportionate to the severity of disease as a reduced QoL has been shown in both inflammatory bowel disease and irritable bowel syndrome, but the difference between the two groups was indiscernible (28).

Observation after AC carries a certain risk of subsequent gallstone related complications. However, in our study the difference in complications between the observation and operation group was not significant and no gallstone or procedure related deaths occurred in the two groups. Nevertheless, a number of patients randomized to cholecystectomy developed gallstone related complications while waiting for operation, and one may speculate if the difference between the groups would have been significant had early surgery been performed.

Unexpectedly, we found no significant differences in symptomatic outcome between the randomized groups or when the grouping was according to final operative outcome (observed versus operated patients). It can be argued that the groups were small

and that larger groups would have shown differences in favour of operative treatment, but all figures except NHP showed a tendency towards better QoL and less pain in the observation group. In view of this we argue that observation is an acceptable option in AC, at least in elderly and frail patients, and does not lead to lower QoL or expose the patients to unnecessary pain.

ACKNOWLEDGEMENTS

The study was supported by a scholarship from the Centre for Clinical Research, Haukeland University Hospital. Financial support was given by The Research Council of Norway, The Research Committee of Rogaland Central Hospital, The University of Bergen, Helga Semb's Foundation and Karla and Arne Oddmar's Foundation. We acknowledge the supportive collaboration of the staff at the participating hospitals.

REFERENCES

1. Ransohoff DF, Gracie WA: Treatment of gallstones. Ann Intern Med 1993;119(7 Pt 1):606–619
2. Lo CM, Liu CL, Lai EC, Fan ST, Wong J: Early versus delayed laparoscopic cholecystectomy for treatment of acute cholecystitis. Ann Surg 1996;223(1):37–42
3. Lahtinen J, Alhava EM, Aukee S: Acute cholecystitis treated by early and delayed surgery. A controlled clinical trial. Scand J Gastroenterol 1978;13(6):673–678
4. Johansson M, Thune A, Blomqvist A, Nelvin L, Lundell L: Management of acute cholecystitis in the laparoscopic era: results of a prospective, randomized clinical trial. J Gastrointest Surg 2003;7(5):642–645
5. Chandler CF, Lane JS, Ferguson P, Thompson JE, Ashley SW: Prospective evaluation of early versus delayed laparoscopic cholecystectomy for treatment of acute cholecystitis. Am Surg 2000; 66(9):896–900
6. Marton KI, Doubilet P: How to image the gallbladder in suspected cholecystitis. Ann Intern Med 1988;109(9):722–729
7. Middelfart HV, Jensen P, Hojgaard L, Funch-Jensen P: Pain patterns after distension of the gallbladder in patients with acute cholecystitis. Scand J Gastroenterol 1998;33(9):982–987
8. Jorgensen T, Teglbjerg JS, Wille-Jorgensen P, Bille T, Thorvaldsen P: Persisting pain after cholecystectomy. A prospective investigation. Scand J Gastroenterol 1991;26(1):124–128
9. Vetrhus M, Soreide O, Nesvik I, Sondenaa K: Acute cholecystitis: delayed surgery or observation. A randomized clinical trial. Scand J Gastroenterol 2003;38(9):985–990
10. Guyatt GH, Feeny DH, Patrick DL: Measuring health-related quality of life. Ann Intern Med 1993;118(8):622–629
11. Wiklund I, Karlberg J: Evaluation of quality of life in clinical trials. Selecting quality-of-life measures. Control Clin Trials 1991;12(4 Suppl):204S–216S
12. Wiklund I, Dimenas E: Svensk version av Nottingham Health Profile. Frågeformular mäter hälsorelaterad livskvalitet. Lakartidningen 1990;87(18):1575–1576
13. Dupuy HJ: The psychological general well-being (PGWB) Index. In: Assessment of quality of life in clinical trials of cardiovascular therapies. Eds. N.K. Wenger, M.E. Mattson, C.D. Furburg, J. Elinson. Le Jacq Publications, New York, USA, 1984, pp. 170–183
14. Hunt SM, McEwen J, McKenna S: Measuring health status. Crom Helm Publishers, London, UK, 1986
15. Jarvinen HJ, Hastbacka J: Early cholecystectomy for acute cholecystitis: a prospective randomized study. Ann Surg 1980; 191(4):501–505
16. Zollinger R: Observations following distension of the gallbladder and common duct in man. Proc Soc Exp Biol Med 1933; 30:1260–1261
17. Middelfart HV, Kristensen JU, Laursen CN, Qvist N, Hojgaard L, Funch-Jensen P, Kehlet H: Pain and dyspepsia after elective and acute cholecystectomy. Scand J Gastroenterol 1998; 33(1):10–14
18. Vander Velpen G, Shimi SM, Cuschieri A: Outcome after cholecystectomy for symptomatic gall stone disease and effect of surgical access: laparoscopic v open approach. Gut 1993;34(10):1448–1451
19. Bates T, Ebbs SR, Harrison M, A'Hern RP: Influence of cholecystectomy on symptoms. Br J Surg 1991;78(8):964–967
20. Vetrhus M, Soreide O, Eide I, Solhaug JH, Nesvik I, Sondenaa K: Pain and quality of life in patients with symptomatic, noncomplicated gallbladder stones: results of a randomized controlled trial. Scand J Gastroenterol 2004;39(3):270–276
21. Collins SL, Moore RA, McQuay HJ: The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain 1997;72(1–2):95–97
22. Jenkinson C, Fitzpatrick R, Argyle M: The Nottingham health profile: an analysis of its sensitivity in differentiating illness groups. Soc Sci Med 1988;27(12):1411–1414
23. Boerma D, Rauws EA, Keulemans YC, Janssen IM, Bolwerk CJ, Timmer R, Boerma EJ, Obertop H, Huibregtse K, Gouma DJ: Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones: a randomised trial. Lancet 2002;360(9335):761–765
24. Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmulling C, Neugebauer E, Troidl H: Gastrointestinal quality of life index: development, validation and application of a new instrument. Br J Surg 1995;82(2):216–222
25. Quintana JM, Arostegui I, Cabriada J, Lopez dT, I, Perdigo L: Predictors of improvement in health-related quality of life in patients undergoing cholecystectomy. Br J Surg 2003;90(12): 1549–1555
26. Wehler M, Reulbach U, Nichterlein R, Lange K, Fischer B, Farnbacher M, Hahn EG, Schneider T: Health-related quality of life in chronic pancreatitis: a psychometric assessment. Scand J Gastroenterol 2003;38(10):1083–1089
27. Glise H, Hallerback B, Johansson B: Quality of life assessments in the evaluation of gastroesophageal reflux and peptic ulcer disease before, during and after treatment. Scand J Gastroenterol Suppl 1995;208:133–135
28. Pace F, Molteni P, Bollani S, Sarzi-Puttini P, Stockbrugger R, Porro GB, Drossman DA: Inflammatory bowel disease versus irritable bowel syndrome: a hospital-based, case-control study of disease impact on quality of life. Scand J Gastroenterol 2003; 38(10):1031–1038

Received: July 19, 2004
Accepted: November 22, 2004