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Abdominal symptoms: do they disappear after cholecystectomy?

A systematic literature review

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Abstract
Objective: To evaluate the effect of cholecystectomy in patients with gallstones on preoperative abdominal symptoms.
Methods: A systematic search was made of the Medline database in combination with reference checking. Articles were excluded if patients aged <18 years, symptom relief rates could not be calculated, if follow-up after cholecystectomy was less than 1 month, or when the included patients were at extraordinary risk for a complicated outcome. Potential differences in relief rates due to patient selection, retrospective versus prospective design, duration of follow-up, or intervention were analyzed using logistic regression.
Results: The pooled relief rate for ''biliary pain'' was high 92% (95% confidence interval 86 to 96%). Symptom relief rates were consistently higher in studies that included acute cholecystectomies. For upper abdominal pain—without restrictions for intensity or duration—pooled relief rates ranged from 72% (66 to 77%) after elective cholecystectomy, to 86% (83 to 91%) after acute cholecystectomy. The relief rate of food intolerance was higher in studies with a follow-up ≤12 months (88%, 76 to 91%) compared to studies with a follow-up of more than 12 months (65%, 55 to 74%).
Conclusion: In almost all patients with gallstones biliary pain disappeared after cholecystectomy. There is insufficient evidence, however, that this relief was due to cholecystectomy. Relief rates of other isolated symptoms were low in patients with an elective cholecystectomy. A proper evaluation of the effectiveness of cholecystectomy in terms of abdominal symptom relief rates requires a randomized trial.

Key words: Abdominal symptoms — Cholelithiasis — Systematic review

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There is general agreement that symptomatic gallbladder stones should be treated [33]. Yet the decision whether abdominal symptoms are related to gallbladder stones remains a diagnostic challenge for the clinician. There seems to be little doubt that severe pain, located in the epigastrium or upper right abdominal quadrant, that occurs in attacks and lasts more than 15 to 30 minutes but no longer than 5 hours indicates gallbladder stones [40]. The evidence for this relation, however, is never systematically reviewed. Furthermore, controversy exits about a causal relation between gallbladder stones and other gastrointestinal symptoms. Although few clinicians will consider gallstones in a patient with only dyspeptic symptoms, the diagnosis of gallstones will become more likely when upper abdominal pain accompanies these symptoms.

The key questions are whether relief of symptoms after cholecystectomy can be predicted, and whether we may assume that these symptoms disappear as a result of cholecystectomy.

The aim of this study was to evaluate the effect of cholecystectomy on preoperative abdominal symptoms, ranging from the above-described biliary pain, to upper abdominal pain without restrictions of intensity or duration and other gastrointestinal symptoms. For this purpose we performed a systematic review of the literature.

Methods

Literature search

A systematic literature search was conducted in Medline (January 1966 to January 2000) of all English-, French-, Dutch- and German- language articles investigating the symptomatic outcome of cholecystectomy for gallstone disease. Combinations of the search keys 'cholelithiasis,' 'cholecystectomy,' 'abdominal pain,' and 'dyspepsia' as MeSH headings with 'symptom,' 'sign,' 'gallstone,' and 'gall stone' as (part of) text words were used. Additional references were obtained from the bibliographies of review articles and original papers. Titles and abstracts of identified published manuscripts were reviewed to

determine the relevance of the articles. Two reviewers (MYB, ToH) independently conducted this first eligibility screening.

Selection

In this review articles were excluded from further analyses according to the following criteria: (1) the follow-up after cholecystectomy was less than 1 month, (2) the included patients were younger than 18 years of age, (3) the included patients were at an extraordinary risk for a complicated outcome such as when the presence of diabetes mellitus was used as an additional criteria for inclusion, or (4) a comparison between pre- and postoperative results could not be made. Abstracts only, conference reports, and editorials were excluded. Criteria were applied independently by two reviewers (MYB, ToH) on the full text of all publications that had passed the first eligibility screening.

Data extraction

A standard form was used to extract pertinent data from the included articles (Table 1). Two reviewers (MYB, ToH) independently collected these data.

Quality assessment

The methodological quality of the studies was assessed using the following criteria [9]:

Was patient selection well described? Inclusion and exclusion criteria had to be described, as well as (mean) age and gender of the selected population.

Was there a possibility of recall bias? In a retrospective study design, where patients are asked postoperatively about their preoperative symptoms, symptom recall might be less accurate than in prospective studies, where the patients are asked before cholecystectomy about their actual symptoms.

Was the instrument to measure outcome adequately described? The methods used for evaluation of the presence of abdominal symptoms had to be described and validated.

Was there a sufficient duration of follow-up? The duration of follow-up was evaluated in order to preclude the "placebo" effect of cholecystectomy.

Were there losses to follow-up? Loss to follow-up might be due to factors related to the outcome of the study. This will give biased results. A loss to follow-up of more than 20% was considered to invalidate the results.

In case of disagreement about inclusion, the data extracted, or the assessment of quality criteria, the disagreement was resolved by a consensus meeting between the two reviewers (MYB and ToH). When disagreement persisted, third reviewer (AMB) was available to make the final decision. In all cases ($N = 5$), disagreement was solved by a consensus meeting between MYB and ToH.

Analysis

Relief rates after cholecystectomy were calculated for each symptom. The relief rate was defined as the number of patients in which the symptom had disappeared postoperatively, divided by the number of patients exhibiting the symptom preoperatively. We performed a sensitivity analysis of key components of study design rather than using quality scores as weights. Therefore we related the following quality criteria to the calculated relief rates [9]:

1. Studies that included only patients with an elective cholecystectomy were compared with studies that evaluated both patients with an acute and patients with an elective cholecystectomy.
2. Studies with a retrospective design were compared to studies with a prospective design.
3. Studies with a follow-up $\leq$12 months were compared with studies with a follow-up of more than 12 months.
4. Studies that reported a loss to follow-up of $\geq$20% were compared to studies that reported smaller losses to follow-up.

A quantitative analysis (statistical pooling) was conducted only in case of statistical and clinical homogeneity. As a measure for statistical heterogeneity the chi-square test statistic was used, with $n - 1$ degrees of freedom, n being the number of studies. To evaluate the effect of the quality criteria on heterogeneity in the results, univariate logistic regression was performed with the symptom relief rate as the dependent variable and the design features as the independent variables. All variables related to symptom relief with a p-value of 0.25 or lower were included in a multivariable analysis whenever the number of studies allowed this. Pooled estimates of the symptom relief rates with 95% confidence intervals were calculated according to the random effects model of Dersimonian and Laird [7]. All computations were performed with SPSS for Windows software, version 7.5 [43].

Results

The search in Medline yielded 543 titles and abstracts. After the first eligibility screening 27 articles were selected for further evaluation. Seven additional publications were identified from the reference lists. Of these 34 publications 11 articles had to be excluded: in 5 the presentation of the results precluded a comparison between pre- and postoperative symptoms [5, 22, 27, 36, 39]; in 3 the subject of the article was not related to the subject under study [12, 26, 35]; in 1 follow-up was restricted to patients with postoperative symptoms only [16]; and the data of 2 studies had already been presented in another included study [2, 18]. Thus, 23 articles were available for the analysis.

All identified studies, except one, were cohort studies. Plaisier et al. [30] performed a RCT comparing the effect of laparoscopic cholecystectomy with the effect of Electrocorporeal Schockwave Lithotripsy. We included the cholecystectomy arm in our analysis.

Quality assessment

The methodological quality of the studies was low. Inclusion and exclusion criteria were poorly or not described in 10 studies [3, 6, 10, 11, 14, 21, 38, 41, 42]; sex and age distribution were not described in 3 studies [34, 42, 47]. One study did not describe the intervention performed (open or laparoscopic cholecystectomy) [1]. In total 7 studies used a retrospective design for their study [13, 14, 17, 31, 34, 46, 47].

The methods used for evaluation of the presence of abdominal symptoms were poorly described or lacked validity in 12 studies [1, 6, 10, 11, 13, 15, 21, 31, 32, 34, 38, 42]. One study did not report the duration of follow-up [42]. Mean follow-up was $\leq$ 12 months in 10 studies [1, 3, 6, 10, 11, 20, 23, 29, 31, 34, 41, 46]. Loss to follow-up was not reported or more than 20% in 5 studies [11, 32, 34, 38, 46].

Eight publications (35%) lacked three or more quality criteria [1, 6, 10, 11, 31, 34, 42, 46]. Four of these studies had been published before 1990 (Table 1).

The effect of the quality criteria on heterogeneity in the results

Compared to studies that included elective cholecystectomies only, symptom relief rates were consistently

Table 1. Characteristics of 23 studies included in the analysis of symptom relief after cholecystectomy

Author	Publication year	Intervention	Study design	Inclusion criteria	Exclusion criteria	Included patints (*n*)	Sex M/F	Mean age (years)	Measurement preoprative
Bouchier [6]	1968	Open	Pros	?	?	17	6/11	56 (34–68)	Non structured interview
Rhind [34]	1968	Open	Retro	Dyspepsia, biliary colic, hiatus hernia, elective	Peptic ulcer, CBDS*	56	?	?	None
Southam [42]	1968	Open	Pros	Gallstones and esophageal symptoms, elective	?	12	?	?	Non structured interview
Johnson [17]	1971	Open	Retro	Proven stones at operation, normal CBD**, elective	Peptic ulcer, pancreatitis, hiatus hernia, preoperative jaundice, exploration of CBD, sphincterotomy or other abdominal operation	108	35/73	50.7	None
Gunn [15]	1972	Open	Pros	Gallstones, elective	Pathologic conditions	107	19/88	47.5	Structured (?) interview
Kingston [21]	1975	Open	Pros	Gallstones and acute cholecystitis (52), elective and acute	?	100	25/75	53 (17–80)	Interview
Feretis [11]	1983	Open	Pros	?	?	47	11/36	46 (23–69)	?
Ross [38]	1987	Open	Pros	Gallstones, no emergency, elective	?	93	25/99	58 (39–76)	Questionnaire and interview
Gilliland [13]	1990	Open	Retro	Symptomatic gallstones, elective	Nonelective exploration of CBD	525	188/462	53 (16–86)	Medical records
Paul [29]	1991	Open	Pros	Symptomatic gallstones, elective	Gastrointestinal comorbidity	51	13/47	56 (21–78)	Structured interview
Jørgensen [20]	1991	Open	Pros	Symptomatic gallstones, elective	Asymptomatic gallstones	115	40/75	58 (18–86)	Structured interview
Bates [3]	1991	Open	Pros	Gallstones with upper abdominal pain or complications, elective and acute	?	278	82/196	53 (20–90)	Self-administered questionnaire
Vander Velpen [46]	1993	Open (80) Laparoscopic (80)	Retro	Symptomatic Gallstones?	CBDS	56 O 68 L	46/78	62 (32–87)	None
Qureshi [31]	1993	Laparoscopic	Retro	Biliary colic, chronic + acute cholecystitis, pancreatitis, elective and acute	Asymptomatic gallstones	100	23/77	47 ± 13.1	None
Rädecke [32]	1993	Open	Pros	Symptomatic gallstones acute + elective	Previous operation gallbladder, malignancy	80	33/47	56 (21–86)	History, not standardized
Scriven [41]	1993	Open	Pros	Gallstones, elective	?	75	?	?	Self-administered questionnaire
Plaisier [30]	1994	Open Laparoscopic (5)	Pros	Symptomatic gallstones, elective	Asymptomatic gallstones, complicated gallstone disease	22	6/20	49.8 ± 12.8	Pain diaries self-administered questionnaire.
Ure [45]	1995	Laparoscopic	Pros	Symptomatic gallstones, elective	> ‰ 60 pnt Talley-score, cancer of gallbladder, other laparoscopic surgery	468	111/357	50 (95% C.I. 47.7 to 52.3)	Self-administered questionnaire
Fenster [10]	1995	Laparoscopic	Pros	?	?	164	58/167	50 (12–79)	Interview, questionnaire
Luman [23]	1996	Laparoscopic	Pros	Gallstones, elective and acute	Open cholecystectomy	84	19/78	50.9 (19–85)	Standardized questionnaire, interview
Abu Farsakh [1]	1996	?	Pros	Gallstones, elective	Gastric surgery, severe illness	30	5/25	43.8 (22–70)	Interview
Gui [14]	1998	Open (35) Laparoscopic (57)	Retro	Symptomatic gallstones, elective	?	92	22/70	51.2 (24–84)	None
Victorzon [47]	1999	Laparoscopic	Retro	Symptomatic gallstones, CBDS, elective	Conversion to Open cholecystectomy	261	75/300	50.5 (17–88)	Self-administered questionnaire

Study design: Pros, prospective; Retro, retrospective
Inclusion criteria: CBD, common bile duct; CBDS, common bile duct stones

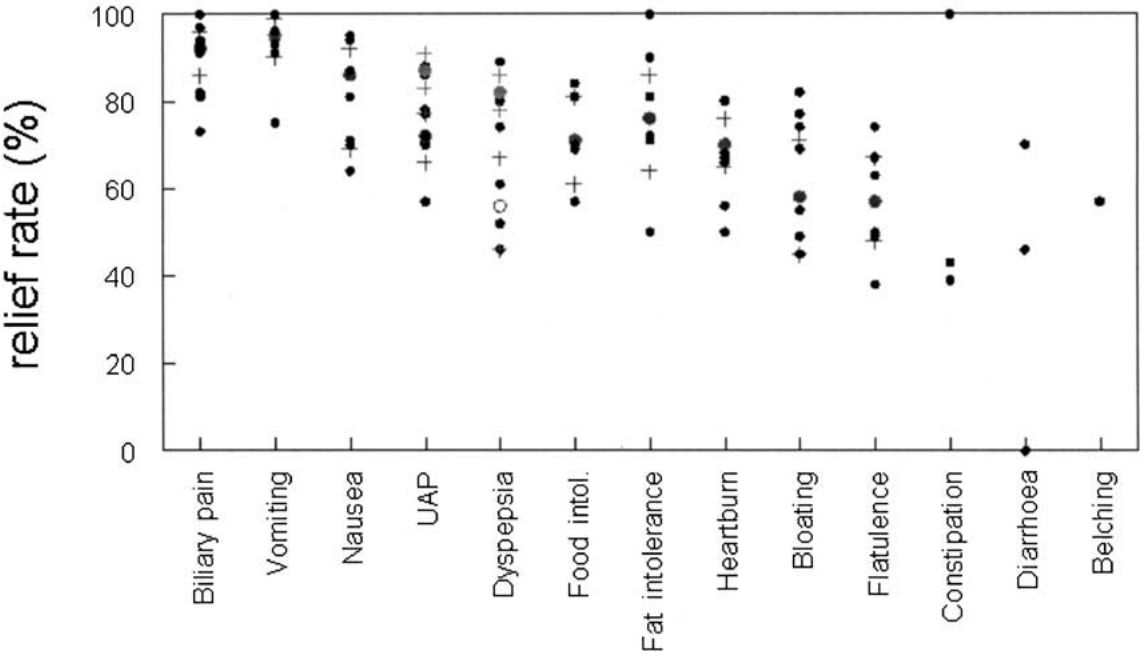

Fig. 1. Symptom relief rates as reported in published studies. Each dot represents the estimate of the symptom relief rate as reported in one article. The mean symptom relief rates are presented with 95% confidence intervals (+ ● +). For upper abdominal (UA) pain and dyspepsia, the mean relief rates and 95% CI are given separately for studies that included only elective cholecystectomies(+ ○ +) and for studies that also included acute cholecystectomies (+ ● +). References of included studies; Biliary pain [1, 10, 11, 14, 30, 32, 41, 45-47]; Vomiting [1, 14, 31, 45-47]; nausea [6, 10, 14, 15, 20, 23, 31, 32, 41, 45, 46]; UAP [6, 10, 14, 15, 20, 23, 31, 32, 34, 38]; dyspepsia [10, 11, 14, 17, 21, 31, 32, 34, 38]; food intolerance [29, 31, 32, 45, 47]; fat intolerance [1, 6, 14, 30, 41, 46]; Heartburn [1, 14, 32, 42, 46, 47]; Bloating [1, 14, 23, 30, 41, 45]; flatulence [14, 31, 32, 45, 46]; constipation [1, 14, 47]; Diarrhea [14, 23, 47]; belching [41].

higher in studies that also included acute cholecystectomies (Fig. 1). For food intolerance the duration of follow-up influenced the results: studies with a follow-up ≤ 12 months reported higher relief rates for food intolerance (relief rate of 88%, 95% c.i. 76 to 91%) compared to studies with a follow-up of more than 12 months (65%, 55 to 74%).

Symptom relief rates

The course of the symptom "biliary pain" could be evaluated in 10 studies (Fig. 1). The definition of "biliary pain" or "biliary colic" varied between the studies. In most studies the definition included a restriction to severe pain, located in the upper abdomen or epigastrium and lasting from 15 min to 5 h. One study included elective and acute cholecystectomies [32]. There was no statistically significant heterogeneity. The pooled symptom relief rate was 92% (86 to 96%).

The course of the symptom "upper abdominal pain" without further restrictions to intensity or duration was evaluated in 13 studies (Fig. 1). The symptom relief rate could be calculated in 11 studies. The relief rate for upper abdominal pain ranged from 57% [41] to 88% [32]. For upper abdominal pain the relief rates showed statistical significant heterogeneity. In studies including only patients with an elective cholecystectomy the pooled relief rate for upper abdominal pain was significantly lower than in studies that also included patients with an acute cholecystectomy: 72% (66 to 77%) and 86% (83 to 91%), respectively.

Nine studies evaluated whether dyspepsia improved after cholecystectomy (Fig. 1). Dyspepsia was defined as the presence of three or more dyspeptic symptoms out of six or seven. These symptoms included belching, flatulence, nausea, intolerance to fatty food, bloating of the abdomen, epigastric discomfort, and acid regurgitation. Relief rates for dyspepsia were heterogeneous and ranged from 46% [10, 17] to 89% [32]. Most of the heterogeneity could be explained by differences in the selection of patients. In studies of patients that had undergone an elective cholecystectomy the pooled symptom relief rate was significantly lower than in studies that included also acute cholecystectomies, 56% (46 to 67%) versus 82% (78 to 86%), respectively. The symptom relief rates for all other abdominal symptoms studied are presented in Fig. 1. For belching ($n = 1$), diarrhea ($n = 3$), and constipation ($n = 3$), no pooled estimates of the relief rates are presented because of large clinical heterogeneity in small numbers of studies.

Discussion

In a systematic review of studies evaluating the effect of cholecystectomy in terms of the disappearance of preoperative symptoms, consistently high relief rates after cholecystectomy were reported for "biliary pain" defined as severe pain located in the upper abdomen or epigastrium lasting from 15 min to 5 h.

The relief rates for upper abdominal pain and dyspepsia showed more heterogeneity. The finding that

higher relief rates for upper abdominal pain were reported in studies that also included acute cholecystectomies may indicate a dose-response-like relation between these symptoms and gallstones. The more extensive the disease, the stronger the association between the stones and these symptoms will be. For dyspepsia, however, this is not a plausible conclusion. Dyspepsia, defined as at least three abdominal symptoms out of seven, is a syndrome rather than a symptom. Talley et al. reported a placebo response in functional dyspepsia (that is, dyspepsia without a biochemical or structural explanation) of almost 70% [44]. This is comparable to the pooled relief rate for dyspepsia in the studies including elective cholecystectomies only: 56% (46 to 67%). In contrast, dyspeptic symptoms, most likely nausea and vomiting, may accompany upper abdominal pain in cases of extended gallstone disease.

The finding that studies with a short follow-up period reported higher relief rates for food intolerance compared to studies with a follow-up of more than 12 months can be explained by a placebo effect of the operation [8]. Patients expect food intolerance to improve because of the explicit relation that is often claimed between gallstones and food intolerance. Our finding weakens the evidence for this putative relation.

The methodological quality of the cohort studies included in this review was low: 35% of the included studies lacked information about three important characteristics of study design. This might have influenced the results of the individual studies in an unpredictable way. Only the selection of the patients turned out to consistently affect the symptom relief rate after cholecystectomy. Therefore we think poor methodology will mainly have influenced the precision of the measurements. We did not identify randomized, placebo- controlled trials evaluating the effect of cholecystectomy on preoperative abdominal symptoms. This will be due to the ethical dilemmas incorporated in all surgical RCTs asking for sham operations. But this finding should be kept in mind while interpreting the results of this review. A comparison of abdominal symptoms before and after cholecystectomy makes it difficult to attribute improvement exclusively to the surgical procedure. It is known that upper abdominal pain, presented at a general practitioner, disappears without intervention within 1 year in about 70% of the patients [25]. The natural history of a nonrelated gastrointestinal disease such as functional dyspepsia [44] may well explain improvement. And although the relief rates for biliary pain were found to be high in this review, Jørgensen [19] reported that in patients presenting with biliary pain, upper abdominal pain (from mild to severe) persisted in 6–41% after cholecystectomy. Furthermore, in a systematic review of the predictive value of abdominal symptoms on the presence of gallbladder stones, it was found that 80% of the patients with gallbladder stones were referred with other abdominal symptoms than "biliary pain" [4]. These findings could indicate that not only gallstones cause "biliary pain" but also that "biliary pain," might not be the only symptom of gallstone disease. Both interpretations question the effect of cholecystectomy on "biliary pain."

Whereas the indication for emergency cholecystectomy is to treat or avoid potentially fatal peritonitis, thousands of (elective) cholecystectomies are performed on a daily basis, in order to prevent "biliary pain" and other abdominal symptoms in patients with gallbladder stones.

We feel that the statement that symptomatic gallstones should be treated remains a sledgehammer argument as long as it is unknown which symptoms are likely to improve after cholecystectomy, as a result of this surgical procedure. A proper evaluation of the effectiveness of cholecystectomy in terms of abdominal symptom relief rates requires a randomized trial, comparing outcomes in patients after cholecystectomy with patient outcome after watchful waiting [28]. The research question might be "Is early elective cholecystectomy better than watchful waiting?" rather than: "Is cholecystectomy better than watchful waiting?" The former question is a relevant clinical question that may overcome the necessity of a sham operation in the control group. Obviously for the first question cholecystectomy is part of the "treatment package" for the control group. Concern remains, however, about the blinding of patients and investigators, particularly where it is known that surgery has a significant placebo effect. To reduce the possibility of this bias, follow-up should be at least 1 year [24].

Another important direction for further research should be the evaluation of the additional value in predicting the clinical outcome of cholecystectomy of findings on ultrasound, such as the number and size of the stone [37], stone impaction, and thickness of the gallbladder wall [14].

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